

5.13 PALOPEGTERIPARATIDE,

**Solution for subcutaneous injection 168 mcg in
0.56 mL pre-filled pen,**

**Solution for subcutaneous injection 294 mcg in
0.98 mL pre-filled pen,**

**Solution for subcutaneous injection 420 mcg in
1.4 mL pre-filled pen,**

Yorvipath[®]

Specialised Therapeutics Pharma Pty Ltd.

1 Purpose of submission

- 1.1 The Category 1 submission requested General Schedule – Authority Required (telephone/online) PBS listing for palopegteriparatide, a prodrug of parathyroid hormone (PTH), for the treatment of adult patients with chronic hypoparathyroidism (HPT) who are inadequately controlled on conventional therapy (active vitamin D and calcium supplements).
- 1.2 Listing was requested on the basis of a cost-utility analysis versus conventional therapy. The components of the overall clinical claim addressed by the submission are summarised in Table 1.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	<p>Patients with chronic hypoparathyroidism due to postsurgical, auto-immune, genetic, or idiopathic causes for (> 12 months), who have been treated with calcitriol \geq 0.5 mcg/day in addition to elemental calcium \geq 800 mg/day for at least 12 weeks and who are inadequately controlled on conventional therapy, where inadequately controlled is defined based on meeting any one of the following criteria:</p> <ul style="list-style-type: none"> • calcium serum levels < 2.0 mmol/L or prior emergency room/urgent care visits related to hypoparathyroidism (in the previous 6 months), or prior hospitalisations related to hypoparathyroidism (in the previous 6 months), or • serum phosphate > 1.5 mmol/L (4.5 mg/dL), or • history of nephrolithiasis, or • history of nephrocalcinosis, or • eGFR < 60 mL/min/1.73 m² or • 24-hour urinary calcium level > 7 mmol/24 hours.
Intervention	<p>18 mcg once daily, as a subcutaneous injection (pre- filled pen), with dose adjustments in 3 mcg increments thereafter every 7 days. The dosing range is 6–60 mcg per day; the maintenance dose should be the dose that achieves serum calcium within the normal range, without the need for active vitamin D or therapeutic doses of calcium.</p>
Comparator	<p>Continuing conventional therapy, consisting of active vitamin D and calcium</p>
Outcomes	<p><u>Primary endpoint</u> Response defined as the proportion of participants at Week 26 who achieved all of the following:</p> <ul style="list-style-type: none"> • albumin-adjusted serum calcium in the normal range (2.07–2.64 mmol/L), • independence from active vitamin D, • independence from therapeutic doses of elemental calcium (> 600 mg/day) and • no increase in study drug drug within 4 weeks prior to Week 26 visit. <p><u>Secondary endpoints</u></p> <ul style="list-style-type: none"> • active vitamin D doses, pill burden, serum calcium, serum phosphate, serum calcium-phosphate product, bone mineral density, HPES, EQ-5D, SF-36. <p><u>Other endpoints</u></p> <ul style="list-style-type: none"> • Post-hoc analysis of change from baseline in eGFR. <p><u>Safety</u></p> <ul style="list-style-type: none"> • TEAEs, serious TEAEs, TEAEs related to hyper or hypocalcaemia, TEAEs leading to discontinuation, 24-hour urinary calcium, death.
Clinical claim	<p>Palopegteriparatide is superior relative to conventional therapy with respect to efficacy, based on response, health-related quality of life and kidney function, non-inferior with respect to safety in the short term, and expected to be superior in the longer term owing to the independence from conventional therapy.</p>

Source: Table 1 pp6-7 of the submission.

eGFR = estimated glomerular filtration rate, EQ-5D = EuroQoL 5 Dimension, HPES = Hypoparathyroidism Patient Experience Scale, SF-36 = Short Form Survey 36 questionnaire, TEAE = treatment emergent adverse effects.

2 Background

Registration status

2.1 Palopegteriparatide received orphan drug designation in April 2024. At the time of PBAC consideration, palopegteriparatide was listed on the Australian Register of Therapeutic Goods for the treatment of chronic hypoparathyroidism in adults.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

Public Summary Document - March 2025 PBAC Meeting

MEDICINAL PRODUCT medicinal product pack	DPMQ	Max. qty packs	Max. qty units	No. of Rpts	Available brands
Palopegteriparatide					
Palopegteriparatide 168 mcg/0.56 mL solution for injection, pre-filled pen	Published: \$ [REDACTED] Effective: \$ [REDACTED]	1	2	6	Yorvipath
Palopegteriparatide 294 mcg/0.98 mL solution for injection, pre-filled pen	Published: \$ [REDACTED] Effective: \$ [REDACTED]	1	2	6	Yorvipath
Palopegteriparatide 420 mcg/1.4 mL solution for injection, pre-filled pen	Published: \$ [REDACTED] Effective: \$ [REDACTED]	1	2	6	Yorvipath
Episodicity:	Chronic				
Severity:	–				
Condition:	Hypoparathyroidism				
PBS indication:	Patients with hypoparathyroidism				
Treatment phase:	Initial treatment				
Restriction:	<input checked="" type="checkbox"/> Authority Required –Telephone				
Treatment criteria:	Must be treated by an endocrinologist				
Clinical criteria:	<p>Patient must have been diagnosed with chronic hypoparathyroidism due to postsurgical, auto-immune, genetic, or idiopathic causes for (> 12 months), established based on presence of persistent hypocalcaemia in the setting of inappropriately low serum parathyroid hormone (PTH) levels (PTH levels at or below the median value of the reference range at the laboratory)</p> <p>AND</p> <p>Patient must have been treated with calcitriol ≥ 0.5 mcg/day in addition to elemental calcium ≥ 800 mg/day for at least 12 weeks</p> <p>AND</p> <p>Patient must have calcium serum levels < 2.0 mmol/L, or prior emergency room/urgent care visits related to hypoparathyroidism in the previous 6 months, or prior hospitalisations related to hypoparathyroidism in the previous 6 months</p> <p>OR</p> <p>Patient must have had serum phosphate > 1.5 mmol/L</p> <p>OR</p> <p>Patient must have a history of nephrolithiasis, or a history of nephrocalcinosis, or eGFR < 60 mL/min/1.73m² (estimated glomerular filtration rate)</p> <p>OR</p> <p>Patient must have had 24-hour urinary calcium level > 7 mmol/24 hours</p> <p>AND</p> <p>Patient must not receive more than 26 weeks of treatment under this restriction.</p>				
Population criteria:	Patient must be ≥ 18 years old				

Treatment phase:	Continuing treatment – first continuing treatment
Restriction:	<input checked="" type="checkbox"/> Authority Required –Telephone
Treatment criteria:	Must be treated by an endocrinologist
Clinical criteria:	<p>Patient must have received this drug as their most recent course of PBS-subsidised treatment for this condition</p> <p>AND</p> <p>Patient must have demonstrated an adequate response to treatment with this drug</p> <p>An adequate response to treatment is defined as:</p> <p>An albumin-adjusted serum calcium in the normal range AND Without concomitant use of active vitamin D AND Without concomitant use of elemental calcium at a dose of > 600 mg/day AND The dose of this drug must be stable over the last four weeks.</p>
Population criteria:	Patient must be ≥ 18 years old

Treatment phase:	Continuing treatment – subsequent continuing treatment
Restriction:	<input checked="" type="checkbox"/> Authority Required – Telephone
Treatment criteria:	Must be treated by an endocrinologist OR Must be treated by a general practitioner experienced in the management of hypoparathyroidism in consultation with an endocrinologist
Clinical criteria:	Patient must have received this drug as their most recent course of PBS-subsidised treatment for this condition
	AND
	Patient must be undergoing regular biochemistry serum/urine testing
Population criteria:	Patient must be ≥ 18 years old

- 3.1 The submission requested a Special Pricing Arrangement (SPA) with an effective price that is █████% less than the published price.
- 3.2 The proposed PBS restriction, which restricts use to patients with chronic HPT which persists for more than 12 months and are inadequately controlled on conventional therapy, is narrower than the TGA indication.
- 3.3 The submission proposed 3 pre-filled pens which deliver different doses for PBS listing. These doses were consistent with the Product Information and the clinical data presented.
 - 168 mcg/0.56 mL solution for injection in pre-filled pen (each pre-filled pen delivers doses of 6, 9, or 12 mcg of PTH (1-34));
 - 294 mcg/0.98 mL solution for injection in pre-filled pen (each pre-filled pen delivers doses of 15, 18, or 21 mcg of PTH (1-34)) and
 - 420 mcg/1.4 mL solution for injection in pre-filled pen (each pre-filled pen delivers doses of 24, 27, or 30 mcg of PTH (1-34)).
- 3.4 The PBS restriction defines chronic HPT as having had a diagnosis of HPT for > 12 months. All patients in the PaTHway trial had HPT for > 12 months.
- 3.5 For initial treatment, the PBS restriction outlines a list of criteria for inadequate control of HPT, of which at least one needs to be met for the patient to be eligible for PBS subsidised palopegteriparatide. The criteria for inadequate control were based on the Hypoparathyroidism Summary Statement and Guidelines from the Second International Workshop (Khan International Guidelines)¹ and by consultation with 9 endocrinologists.
- 3.6 The criteria for inadequate control in the proposed restriction were not aligned with the trial inclusion criteria. The submission therefore performed a *post-hoc* subgroup analysis for efficacy to provide evidence for palopegteriparatide in patients who were inadequately controlled, as per the proposed restriction criteria. However, the definition of inadequate control used to define the subgroup was inconsistent with

¹ Khan et al., 2022. Evaluation and Management of Hypoparathyroidism Summary Statement and Guidelines from the Second International Workshop. J Bone Miner Res, 37(12):2568-2585.

the proposed PBS restriction in that it did not include patients who had inadequately controlled serum calcium (i.e. < 2.0 mmol/L), as one of the PaTHway inclusion criteria specified they must have normal serum calcium levels (i.e., albumin-adjusted serum calcium 7.8-10.6 mg/dL (or 1.95-2.64 mmol/L) or ionised serum calcium 4.40-5.29 mg/dL (or 1.10-1.32 mmol/L)). The Product Information also specifies patients should have serum calcium in the normal range or slightly below the normal range before starting treatment.

- 3.7 The clinical biochemistry cut-offs proposed for inadequate control for serum calcium, serum phosphate and 24-hour urinary calcium as listed above were appropriate and aligned with Australian pathology reference ranges and agreed upon by the 9 endocrinologists who work in the treatment of HPT. The submission did not provide any evidence to support the criterion for prior emergency room/urgent care visit/hospitalisation for hypoparathyroidism in the previous 6 months as an indication of inadequate control as it was not included as an inclusion criterion in the PaTHway clinical trial. It is possible that some patients will have had an emergency room/urgent care visit/hospitalisation in the previous 6 months, then subsequently have been adequately controlled on conventional therapy. Under the proposed PBS restriction, these patients would be eligible for palopegteriparatide despite being adequately controlled on conventional therapy. The ESC and DUSC noted this was likely to apply to a small number of patients and considered that it would be unlikely that an endocrinologist responsible for the care of such a patient would change treatment based on this criterion. Additionally, the ESC noted that the presence of nephrocalcinosis and renal calculi does not necessarily indicate current inadequate control of serum calcium and an estimated glomerular filtration rate (eGFR) < 60mL/min/1.73 m² could be due to many other potential causes. Therefore, the ESC and DUSC considered these requirements should be removed from the proposed restriction. The pre-PBAC response requested that the criteria requiring a history of nephrolithiasis and a history of nephrocalcinosis be included.
- 3.8 The ESC noted that palopegteriparatide has not been studied in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m²). Therefore, the ESC considered the inclusion of the following clinical criterion be appropriate "Patient must not have an eGFR of less than or equal to 30 mL/min/1.73 m²". The pre-PBAC response stated that this was a reasonable inclusion.
- 3.9 The PBS restriction is restricted to patients ≥ 18 years which is aligned with PaTHway. The submission did not discuss the treatment of HPT in patients aged < 18 years. The ESC considered that it may be appropriate for the restriction to be age agnostic.
- 3.10 The first continuing treatment restriction required patients to have demonstrated an adequate response to treatment, defined as an albumin-adjusted serum calcium in the normal range, AND without concomitant use of active vitamin D, AND without concomitant use of elemental calcium at a dose of > 600 mg/day, AND the dose of this drug must be stable over the last four weeks, to continue treatment. The ESC noted that the subsequent continuing treatment restriction does not require patients to

meet any specific response criteria to continue treatment. The ESC and DUSC considered that the defining factors confirming an adequate response to treatment in the first continuing treatment were reasonable and aligned with the clinical trial. The ESC and DUSC considered that the subsequent continuing restriction should also require patients to have demonstrated an adequate response to treatment (defined as per the first continuing restriction).

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 HPT is characterised by impaired or inadequate levels of PTH. PTH is responsible for calcium and phosphate homeostasis via bone resorption, kidney transport of calcium and phosphorus and intestinal calcium absorption. As a result, people with HPT experience low serum calcium, high urinary calcium and increased serum phosphate.
- 4.2 HPT is associated with a spectrum of clinical manifestations, ranging from few, if any, symptoms when hypocalcaemia is mild, to life-threatening seizures, refractory heart failure, or laryngospasm if it is severe. Chronic manifestations of the disease (and potentially from treatment with calcium and vitamin D) may include chronic kidney disease (CKD), soft tissue calcification (e.g. basal ganglia), neuromuscular symptoms such as seizures, tetany and muscle stiffness, above average bone mineral density (BMD), cataracts and cardiovascular symptoms such as cardiomyopathy, congestive heart failure and ischaemic heart disease. A large Danish study² found no difference in survival compared to the general population after 22 years of follow-up of Danish patients with postsurgical HPT due to surgery for non-malignant diseases treated between 1988 and 2012 (688 HPT cases compared to 2,064 control patients).
- 4.3 Current first line management of HPT is calcium and active vitamin D. Patients who achieve normal serum calcium levels with conventional therapy may still experience symptoms of the condition itself, such as renal insufficiency, hypercalciuria and have impaired quality of life. Patients who are inadequately controlled on conventional therapy experience significant burden of illness because of the symptoms of HPT such as physical fatigue, muscle cramps, heaviness in limbs, tingling which affects the ability to exercise, sleep and work. Prolonged use of high dose calcium and active vitamin D may increase the risk of hypercalciuria, renal stones, renal calcinosis, impaired renal function and ectopic soft tissue calcification.
- 4.4 HPT can develop as a result of surgery (75% of all cases) or non-surgical (e.g. autoimmune, idiopathic or genetic). In post-surgical HPT, incidence may be acute/transient or chronic.

² Underbjerg, L., Sikjaer, T., Mosekilde, L. and Rejnmark, L., 2013. Cardiovascular and renal complications to postsurgical hypoparathyroidism: A Danish nationwide controlled historic follow-up study. *J Bone Miner Res*, 28: 2277-2285.

- 4.5 Palopegteriparatide is a PTH replacement therapy. It is a prodrug of PTH, PTH (1-34), thereby returning PTH levels within the normal range across a 24-hour dosing period and returning calcium homeostasis.
- 4.6 Palopegteriparatide is administered once daily via subcutaneous injection with sustained release of PTH. The starting dose of palopegteriparatide is 18 mcg once daily, increasing by 3 mcg every 7 days to the maintenance dose. The maintenance dose is defined as the dose which achieves serum calcium in the normal range without the need for active vitamin D or therapeutic doses of calcium (> 600 mcg daily).
- 4.7 This is the first time the PBAC has considered a drug for the treatment of chronic HPT. *For more detail on PBAC's view, see section 7 PBAC outcome.*

5 Comparator

- 5.1 The submission nominated conventional therapy as the comparator. Conventional therapy consists of large doses of calcium and active vitamin D taken several times a day. The submission stated that the average patient takes approximately 6.7 pills per day. The recommended dose of calcium is in the range of 500-3000 mg three times a day. The submission defined therapeutic doses of calcium as > 600 mg/day and supplemental doses of calcium as ≤ 600 mg/day. The recommended dose of vitamin D is 0.25-3.0 mcg per day. Some patients also receive thiazide diuretics if they develop hypercalciuria.
- 5.2 The main arguments provided in support of this nomination were:
- There are no PTH replacement therapies listed on the PBS or registered for use in HPT in Australia.
 - The choice of conventional therapy as the comparator was confirmed by Australian endocrinologists.
- 5.3 The ESC considered that the choice of conventional therapy as the comparator for palopegteriparatide was appropriate. *For more detail on PBAC's view, see section 7 PBAC outcome.*

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician noted the high clinical need for additional treatments for patients who were inadequately controlled with conventional therapies. The clinician noted that for some patients, HPT was difficult to treat and that the balance between acceptable calcium levels and symptom control whilst avoiding complications such as hypercalciuria was difficult to maintain, affecting patients' quality of life.
- 6.2 The clinician noted the clinical effectiveness of palopegteriparatide, stating that the PaTHway trial demonstrated that palopegteriparatide was associated with

improvements in serum calcium levels, reduced doses of conventional therapy and improved 24-hour urine calcium excretion. Further, it was noted that palopegteriparatide was associated with improvements in downstream symptoms of HPT including eGFR and quality of life outcomes.

- 6.3 The clinician also described that, for patients in the conventional therapy arm of the PaTHway trial with normal serum calcium levels, placebo was required to be maintained whilst calcium and vitamin D levels were titrated downwards. The clinician stated that the titration protocol was designed to maintain the double-blind aspect of the trial and to minimise the risk of treatment bias. The clinician stated that although this lacked real world representativeness, there was a high level of clinical supervision (weekly visits) and that it reflected the difficulties in managing HPT in clinical practice, which is to maintain serum calcium in the lower range of normal using the lowest possible dose to avoid long-term complications. The clinician noted that adjusted serum calcium levels were maintained in the clinically targeted lower range of normal throughout the double-blind period.

Consumer comments

- 6.4 The PBAC noted and welcomed the input from individuals (14), health care professionals (46) and organisations (5) via the Consumer Comments facility on the PBS website. The comments from individuals described the debilitating symptoms of HPT including, but not limited to, daily fatigue, parathesis, tetany, muscle and joint pain, brain fog, ectopic heart beats, unsteady gait and kidney stones. The individuals also described the burden of constant conventional therapy and hospitalisations due to high or low calcium levels. Individuals stated that the availability of palopegteriparatide on the PBS would be life changing, as it would reduce calcium level fluctuations, reduce symptoms, prevent the decline of renal function and improve quality of life.
- 6.5 The clinicians stated that HPT is a chronic condition that requires regular pathology monitoring, intermittent 24-hour urinary calcium monitoring, large doses of conventional therapy and strict dietary changes to manage the condition. The clinicians stated that unstable patients require very frequent monitoring and adjustment of medications to avoid symptomatic hypocalcaemia, hypercalciuria, hypercalcaemia and nephrocalcinosis, all of which cause complications and recurrent hospital admissions. Clinicians noted that as palopegteriparatide treats the hormone deficiency, rather than treating the downstream effects of low calcium, it has the potential to improve the health of those affected by treating the cause of the condition and allowing a more comprehensive management of the complications of HPT.
- 6.6 The PBAC noted the input from the Endocrine Society of Australia, which supported the submission. The Endocrine Society stated that palopegteriparatide would potentially provide adequate control of HPT in patients who are not currently controlled with conventional therapy and would potentially reduce the serious

consequences of treatment including nephrolithiasis, nephrocalcinosis and brain calcification.

- 6.7 Input was also received from the Australian and New Zealand Bone and Mineral Society, the Australian Thyroid Foundation and Healthy Bones Australia. The Australian and New Zealand Bone and Mineral Society stated that palopegteriparatide was more likely to maintain normal mineral homeostasis and reduce complications compared to conventional therapy. The Society noted that this would result in improved quality of life and kidney function. The Australian Thyroid Foundation noted the current equity issues due to the cost of palopegteriparatide. Health Bones Australia supported the submission, noting the significant burden of disease associated with HPT and the benefits of palopegteriparatide in terms of quality of life, physical functioning and wellbeing.

Clinical trials

- 6.8 The submission was based on 2 head-to-head randomised controlled trials (RCTs) comparing palopegteriparatide to conventional therapy (+placebo), PaTHway and PaTH Forward. PaTHway was the primary evidence presented in the submission and used to support the efficacy and safety claim. PaTH Forward was presented to support the long-term safety of palopegteriparatide.
- 6.9 The submission claimed that, compared to conventional therapy, palopegteriparatide was superior in terms of efficacy based on response, health-related quality of life (HRQoL), and kidney function (as measured by the eGFR), and non-inferior in terms of safety in the short term and expected to be superior with respect to safety in the longer term owing to the independence from conventional therapy. The submission used a multi-component outcome to represent response which was defined as albumin-adjusted serum calcium in the normal range (2.07–2.64 mmol/L [8.3–10.6 mg/dL]), independence from active vitamin D, independence from therapeutic doses of elemental calcium (> 600 mg/day) and no increase in study drug within 4 weeks prior to Week 26 visit.
- 6.10 PaTHway was a phase 3, double-blind, randomised controlled trial (RCT) in which patients commenced treatment at 18 mcg/day, which is aligned with the Product Information and proposed PBS restriction. Patients in PaTHway had their dose of study drug (placebo or palopegteriparatide), calcium and active vitamin D titrated based on the PaTHway treatment algorithm, as described in the Clinical Study Report (see paragraph 6.15). After 26 weeks patients were assigned to open-label treatment. Patients in the treatment arm during the 26-week blinded period remained on treatment and patients in the placebo arm during the double-blind period were then switched to palopegteriparatide. The submission presented the results of the 52-week and 104-week follow-up to support the long-term efficacy and safety of the drug. The open-label extension (OLE) period of the study is planned for 156 weeks; the study was expected to be completed in December 2025.

6.11 PaTH Forward was a phase 2 trial designed to assess the safety, tolerability and efficacy of palopegteriparatide in adult patients with chronic HPT. The PaTH Forward trial investigated 3 different starting doses, 15 mcg/day (n=14), 18 mcg/day (n=15) and 21 mcg/day (n=15), compared with placebo (n=15). The trial was double-blinded for 4 weeks, after which patients were assigned to open-label treatment during which time all patients received palopegteriparatide. The submission presented the results of the 110-week follow-up to support the long-term safety of the drug.

6.12 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
PaTHway	PaTHway TRIAL: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Trial, with an Open-Label Extension, Investigating the Safety, Tolerability and Efficacy of TransCon PTH Administered Subcutaneously Daily in Adults with Hypoparathyroidism	Clinical Study Report
	Khan et al. (2023). Efficacy and Safety of Parathyroid Hormone Replacement with TransCon PTH in Hypoparathyroidism: 26-Week Results from the Phase 3 PaTHway Trial	Journal of bone and mineral research 38(1): 14-25
	Khan, A. (2022). Phase 3 PaTHway Trial: participants Treated with TransCon PTH Achieved Independence from Conventional Therapy While Maintaining Normal Serum Calcium	Journal of the Endocrine Society 6: A802-A803 (conference abstract)
	Schneider, M., et al. (2023). TransCon PTH enables independence from conventional therapy while maintaining normal serum calcium in adults with chronic postsurgical hypoparathyroidism: results from a sub-analysis of the pathway phase 3 trial.	Thyroid 33: A15 (conference abstract)
	Nct (2021). A Trial Investigating the Safety, Tolerability and Efficacy of TransCon PTH Administered Daily in Adults with Hypoparathyroidism.	https://clinicaltrials.gov/ct2/show/NCT04701203 .
	Euctr, H. U. (2020). PaTHway TRIAL: a Clinical Trial to Investigate the Safety and Effectiveness of TransCon PTH Administered as an Injection Under the Skin in Adults with Hypoparathyroidism.	Clinical trial record
	Tsourdi et al (2024) Improved Skeletal Dynamics in Adults Treated with Palopegteriparatide for Hypoparathyroidism: 52-Week Analysis of Phase 3 PaTHway Trial. Osteologie 33,2:113.	Osteologie 33,2:113 (conference abstract)
	Rejnmark et al (2024) Palopegteriparatide Treatment Improves Renal Function in Adults with Chronic 1 Hypoparathyroidism: 1-Year Results from the Phase 3 PaTHway Trial	Adv Ther (2024) 41:2500–2518
	Clarke, B., et al. (2023). Long-term Efficacy and Safety of Transcon PTH in Adults With Hypoparathyroidism: 52-week Results From The Open-label Extension Of The Phase 3 Pathway Trial.	Journal of the Endocrine Society 7: A303-A304 (conference abstract)
	Schwarz et al (2024). Sustained Improvement in Renal Function with Palopegteriparatide in Adults with Chronic Hypoparathyroidism: 2-Year Results from the Phase 3 PaTHway Trial.	ECE 2024, Stockholm Sweden (conference abstract draft)
PaTH Forward	PaTH Forward: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Trial with an Open-Label Extension, Investigating the Safety, Tolerability	Clinical Study Report

Trial ID	Protocol title/ Publication title	Publication citation
	and Efficacy of TransCon PTH Administered Subcutaneously Daily in Adults with Hypoparathyroidism	
	Khan, A. A., et al. (2022). PaTH Forward: A Randomized, Double-Blind, Placebo- Controlled Phase 2 Trial of TransCon PTH in Adult Hypoparathyroidism.	Journal of clinical endocrinology and metabolism 107(1): E372-E385.
	Ahmed, I., et al. (2022). The PaTH Forward Trial: efficacy and Safety of TransCon PTH Through Week 84 for Adults with Hypoparathyroidism.	Journal of the Endocrine Society 6: A193. (conference abstract)
	Clarke, B., et al. (2023). Abstract #1408044: Long-term Efficacy and Safety of TransCon PTH from Phase 2 PaTH Forward Trial in Adults with Chronic Hypoparathyroidism.	Endocrine practice 29(5): S58. (conference abstract)
	Rubin et al (2023) Indices of Skeletal Remodelling in 2-Year Analysis of Phase 2 PaTH Forward Trial with TransCon PTH in Adults with Hypoparathyroidism	JBMR Plus Vol 7 (conference abstract)
	Euctr, D. K. (2019). PaTH Forward: a study to investigate the safety and efficacy of TransCon PTH administered as an injection under the skin daily in adults with hypoparathyroidism.	Clinical trial record
	Hofbauer, L., et al. (2022). Efficacy and safety with TransCon PTH for adults with hypoparathyroidism through week 84 in the PaTH Forward trial.	Bone reports 16 (conference abstract)
	Khan, A., et al. (2020). Results of the PaTH Forward Phase 2 Trial Demonstrating Potential of TransCon PTH as a Replacement Therapy for Hypoparathyroidism.	Journal of bone and mineral research 35(SUPPL 1): 46 (conference abstract)
	Nct (2019). A Trial Investigating the Safety, Tolerability and Efficacy of TransCon PTH in Adults with Hypoparathyroidism.	https://clinicaltrials.gov/show/NCT04009291 .
	Rejnmark, L., et al. (2021). Week 26 results from the PaTH Forward Open-Label Extension Trial Support TransCon PTH as a potential hormone replacement therapy for patients with hypoparathyroidism.	Bone reports 14 (conference abstract)
	Rubin, M. R., et al. (2021). TransCon PTH as a Hormone Replacement Therapy for Patients with Hypoparathyroidism: 6-Month Update from the PaTH Forward Open-Label Extension.	Journal of the Endocrine Society 5: A253 (conference abstract)

Source: Table 13 p34 of the submission.

PTH = parathyroid hormone.

6.13 The key features of the RCTs are summarised in Table 3.

Table 3: Key features of the included trials

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Palopegteriparatide versus placebo						
PaTHway	84	Phase 3, R, DB, PC, PG with OLE	Low	Adults with chronic HPT for ≥ 26 wks and have been treated with calcitriol ≥ 0.5 mcg/d or alfacalcidol ≥ 1.0 mcg/d in addition to calcium ≥ 800 mg/d for at least 12 wks prior.	Primary: response based on albumin-adjusted serum calcium in the normal range, independence from active vitamin D and independence from therapeutic doses of calcium (> 600 mg/d) with no increase in study drug over the 4 weeks prior. Secondary: HRQoL, active vitamin D dose, calcium dose, daily pill burden, serum calcium, serum phosphate, serum calcium/phosphate product, BMD, 24-hour urine calcium.	Primary outcome applied at the end of Cycle 1. Proportion of patients in CKD stages applied at baseline and the end of Cycle 1. Baseline EQ-5D-5L and change from baseline applied for the duration of the model.
PaTH Forward	59	Phase 2, MC, R, DB, PC, PG, with OLE	Low	Adults with chronic HPT for ≥ 26 wks and have been treated with calcitriol ≥ 0.5 mcg/d or alfacalcidol ≥ 1.0 mcg/d in addition to calcium ≥ 800 mg/d for at least 12 wks prior.	Primary: The proportion of patients who achieved albumin-adjusted serum calcium in the normal range, SPOT AM FEC within normal range, independence from active vitamin D, independence from therapeutic doses of calcium (≤ 1000 mg/day) with no increase in study drug over 4 wks prior. Secondary: Active vitamin D doses, calcium doses, daily pill burden, serum calcium	Not used

Source: Table 14 p36 of the submission.

BMD = bone mineral density, CKD = chronic kidney disease, d = day, DB = double-blind, EQ-5D-5L = EuroQoL-5D-5L, HPT = hypoparathyroidism, HRQoL = health-related quality of life, MC = multicentre, OLE = open label extension, PC = placebo controlled, PG = parallel group, R = randomised, SPOT AM FEC = spot morning fractional excretion of calcium, wks = weeks.

6.14 Key differences between the PaTHway trial and the proposed PBS criteria include:

- During the screening period (prior to randomisation), adjustments to doses of active vitamin D, calcium and magnesium were made so that patients achieved serum calcium in the normal range prior to treatment. This was not consistent with the intended PBS use. The proposed PBS restriction includes patients who have a serum calcium < 2.0 mmol/L. The evidence regarding the use of palopegteriparatide in patients who have serum calcium < 2.0 mmol/L was absent. However, this was not a mandatory requirement of the proposed PBS eligibility, and the ESC considered that it was highly likely that clinicians would correct metabolic disturbances, particularly hypocalcaemia, prior to commencement on palopegteriparatide. It is also possible that some patients with a serum calcium < 2.0 mmol/L may meet one or more of the other PBS criteria such as hypercalciuria.

- PaTHway required patients to have magnesium, vitamin D and thyroid stimulating hormone (TSH) within the normal range, and thyroid replacement therapy normalised before starting palopegteriparatide. This has not been specified in the proposed PBS restriction. The implications of this were not discussed in the submission.
- 6.15 All patients in PaTHway received conventional therapy and study drug (either palopegteriparatide or placebo). The trial used a dose titration algorithm as described in the Clinical Study Report to titrate the doses of conventional therapy and study drug based on serum calcium levels. This meant that patients in the comparator arm who had normal serum calcium levels received dose reductions to their conventional therapy, while their dose of placebo was unchanged. The ESC agreed with the evaluation that this approach is not representative of standard management of these patients, and therefore the comparator arm in the trial was an inaccurate representation of standard of care for patients with normal serum calcium levels. Patients who had low serum calcium after 7 days of treatment had the dose of the study drug increased, which for placebo patients meant an increase in placebo rather than the dose of conventional therapy. Again, the ESC considered this is not representative of standard management. The implications of changes to conventional therapy in the comparator group on the outcomes observed in the trial were not discussed in the submission.
- 6.16 PaTHway was not restricted to patients who were inadequately controlled on conventional therapy. Given that the eligibility criteria of PaTHway were not aligned with the proposed PBS restriction, the submission conducted a *post-hoc* subgroup analysis in patients who mostly aligned with the PBS criteria (see paragraph 3.6). The results of the subgroup analysis were aligned with the results of the wider trial population. The subgroup analysis did not include patients with serum calcium < 2.0 mmol/L. However, it is possible that patients with serum calcium < 2.0mmol/L are likely to meet the other criteria for inadequate control.

Comparative effectiveness

- 6.17 The results of the multi-component primary efficacy outcome are shown in Table 4. For this endpoint the submission presented the results of the 26-week blinded period and the 52-week and 104-week OLE periods. At Week 104, 76 (93%) patients remained in the trial.

Table 4: Results of response in PaTHway at Week 26 (blinded period), Week 52 (OLE) and Week 104 (OLE), ITT population

	Week 26 (blinded)		Week 52 (OLE)		Week 104 (OLE)
	PPT (N=61)	Placebo (N=21)	PPT (N=59)	Placebo / PPT (N=19)	Placebo / PPT (N=76)
Primary endpoint, n (%)	48 (78.7%)	1 (4.8%)	48 (81.3%)	15 (78.9%)	NR
95% CI	66.3, 88.1	0.1, 23.8	69.1, 90.3	54.4, 93.9	NR
P-value (PPT vs PBO)	<0.0001		NR		NR
Albumin-adjusted serum calcium within the normal range, n (%)	49 (80.3%)	10 (47.6%)	50 (84.7%)	17 (89.5%)	62 (81.6%)
Independence from active vitamin D, n (%)	60 (98.3%) ^a	5 (23.8%)	59 (100%)	19 (100%)	76 (100%)
Independence from therapeutic doses of calcium, n (%)	57 (93.4%)	1 (4.8%)	57 (96.6%)	17 (89.5%)	74 (97.4%)
No increase in prescribed study drug, n (%)	57 (93.4%)	12 (57.1%)	NR	NR	NR

Source: Table 25, p61 of the submission.

CI = confidence interval, ITT = intention to treat, n = number of participants with event, N = total participants in group, NR = not reported, OLE = open-label extension, PBO = placebo, PPT = palopegteriparatide.

^a the remaining 1 patient achieved independence from vitamin D at Week 8 but died thereafter from a cardiac arrest that was deemed unrelated to study drug by the investigator.

Bold represents a significant result.

- 6.18 At the end of the 26-week blinded period, more patients in the palopegteriparatide arm met the multicomponent primary outcome, as well as each individual criteria within it, when compared to the comparator arm. As patients in the placebo arm switched to palopegteriparatide in the OLE, at 52 weeks the proportion of patients who achieved the primary outcome, and each individual criterion within it, increased. Results for the primary outcome were not presented at the 104-week OLE time point. However, all patients achieved independence from vitamin D and the majority of patients reported albumin-adjusted serum calcium within normal range and independence from therapeutic doses of calcium.
- 6.19 While the primary outcome in PaTHway demonstrates that patients can have their conventional therapy reduced when using palopegteriparatide, it may not inform a comparison of palopegteriparatide with standard of care. The primary outcome required patients to achieve independence from active vitamin D and therapeutic doses of calcium whilst maintaining a normal serum calcium; the ESC considered this was less likely to be accomplished in patients in the placebo arm, given they had their doses of calcium and vitamin D reduced (and dose of placebo increased) even in the presence of normal serum calcium, to maintain the double-blinded nature of the trial. While all patients in the placebo arm had normal serum calcium in a steady state at the start of the trial, over half (52.4%) had developed abnormally low serum calcium levels by Week 26 and the mean serum calcium level in the placebo population was 2.05 mmol/L, which was below the lower limit of normal. The primary outcome therefore favours the palopegteriparatide arm.
- 6.20 The submission did not provide any longer-term evidence to suggest that achievement of this primary (surrogate) outcome would lead to improvements in long term

complications of HPT such as renal function, although the ESC did note that renal function (eGFR) improved at 26 weeks in the palopegteriparatide arm compared to the placebo arm. The submission referenced the RELAY trial which investigated the use of recombinant human parathyroid hormone (rh-PTH). In the RELAY trial the primary efficacy endpoint was reductions in calcium supplementation to ≤ 500 mg/day and in calcitriol to ≤ 0.25 mcg/day, while maintaining serum calcium levels between 1.875 mmol/L and the upper limit of normal. No further analysis or discussion regarding the surrogate endpoint was supplied. While there is a known link between HPT and CKD, the exact mechanism is not clear but likely related to the formation of calcium crystals in the nephrons (nephrolithiasis and nephrocalcinosis). The submission stated that prolonged use of calcium and active vitamin D may additionally increase the risk of hypercalciuria, renal stones, renal calcinosis, impaired renal function and ectopic soft tissue calcification³. However, the submission did not describe the biological relationship between the primary outcome and any long-term clinical outcome, as per Appendix 5 of the PBAC Guidelines. The ESC considered that while there exists a biological rationale for lowering urinary calcium in patients with kidney damage due to hypercalciuria to mitigate further kidney damage, whether that outcome can be achieved as a result of treatment with palopegteriparatide or conventional therapy was not made clear, noting thiazide diuretics are currently used in clinical practice to reduce urine calcium levels and protect kidney function in patients with HPT on conventional therapy.

6.21 The results for secondary endpoints are presented in Table 5.

³ Brandi M, Bilezikian J, Shoback D, et al., 2016. Management of Hypoparathyroidism: Summary Statement and Guidelines. *J Clin Endocrinol Metab*, 101(6):2273-2283.

Table 5: Results of other secondary endpoints in PaTHway at Week 26 (ITT population)

	Palopegteriparatide (N=61)			Placebo (N=21)			Difference in LS means (95% CI)	P-value (PPT vs PBO)
	Baseline	Week 26	Change from baseline ^a	Baseline	Week 26	Change from baseline ^a		
	Mean (SD)	Mean (SD)	LS mean (SE)	Mean (SD)	Mean (SD)	LS mean (SE)		
Calcium (mg) dose	1,748 (904)	274 (1372)	-1,177 (218)	2,105 (1382)	1,847 (1326)	324 (359)	-1,501 (-2,238, -765)	0.0003
Active vitamin D (mcg)	0.99 (0.74)	0 (0.00)	-0.99 (0.06)	0.94 (0.62)	0.61 (0.73)	-0.37 (0.09)	-0.62 (-0.80, -0.44)	<0.0001
Daily pill burden	6.69 (2.20)	0.45 (1.66)	-5.61 (0.28)	6.74 (2.99)	5.42 (3.22)	-0.54 (0.74)	-5.08 (-6.61, -3.55)	<0.0001
Serum phosphate (mg/dL)	4.22 (0.59)	3.80 (0.57)	-0.35 (0.08)	3.91 (0.80)	3.88 (0.90)	-0.13 (0.16)	-0.23 (-0.57, 0.12)	0.19
Serum calcium (mg/dL) ^b	8.80 (0.69)	8.94 (0.67)	0.31 (0.11)	8.63 (0.64)	8.22 (0.53)	-0.39 (0.144)	0.69 (0.40, 0.99)	<0.0001
Serum calcium-phosphate product	37.05 (5.68)	33.89 (4.76)	-1.84 (0.76)	33.67 (6.73)	31.66 (6.41)	-2.77 (1.28)	0.93 (-1.68, 3.55)	0.4711

Source: Table 30 p74, Table 31 p78 of the submission.

ANCOVA = analysis of covariance, CI = confidence interval, ITT = intention to treat, LS = least squares, PBO = placebo, PPT = palopegteriparatide, SD = standard deviation, SE = standard error.

^a calculated from ANCOVA model.

^b the normal range for albumin-adjusted serum calcium was 8.3 to 10.6 mg/dL (2.07 to 2.64 mmol/L).

Bold represents a significant result.

- 6.22 At the end of Week 26, patients in the palopegteriparatide arm had their mean daily dose of calcium reduced to a supplemental dose (≤ 600 mg/day). Patients in the placebo arm did not. At baseline the active vitamin D doses and mean daily pill burden in both arms were similar (6.69 and 6.74 tablets); however, by the end of Week 26, all patients in the palopegteriparatide arm had stopped taking their active vitamin D tablets and the mean daily pill burden for patients using palopegteriparatide had reduced to 0.45 tablets. The difference in the least square (LS) means between the palopegteriparatide arm and the placebo arm was significant for change in calcium dose, active vitamin D dose and daily pill burden.
- 6.23 With respect to biochemistry results, the mean serum calcium levels were in the normal range for the palopegteriparatide arm at baseline and Week 26. Patients in the placebo arm experienced a numerical decrease in mean serum calcium level at Week 26, with it falling to just below the normal range. The difference in the LS means was significant. These results need to be interpreted in the context of the trial titration algorithm, as patients in the placebo arm with normal serum calcium levels had their calcium and active vitamin D doses reduced.
- 6.24 Results related to key secondary outcomes i.e., changes from baseline in hypoparathyroidism experience scales (HPES) and SF-36 are presented in Table 6. The HPES is a disease-specific patient-related outcome that was developed and validated

by the Sponsor in a different study⁴ to assess relevant patient reported symptom and disease impacts. A decrease in HPES scores and an increase in SF-36 scores indicates an improvement in HRQoL.

Table 6: Results of key secondary outcomes and EQ-5D-5L scores in PaTHway at Week 26 (ITT population)

Instrument (Domain/subscale)	Palopegteriparatide (N=61)			Placebo (N=21)			Difference in LS means (95% CI)	P-value (PPT vs PBO)
	Baseline	Week 26	Change from baseline ^a	Baseline	Week 26	Change from baseline ^a		
	Mean (SD)	Mean (SD)	LS mean (SE)	Mean (SD)	Mean (SD)	LS mean (SE)		
Key secondary endpoints								
HPES symptoms (physical)	41.39 (22.79)	21.65 (15.14)	-21.01 (2.20)	47.72 (25.93)	41.78 (25.93)	-4.81 (5.02)	-16.20 (-26.61, -5.79)	0.0038
HPES symptoms (cognitive)	39.34 (28.41)	18.05 (16.40)	-20.49 (2.59)	38.33 (24.00)	32.63 (25.30)	-6.16 (4.71)	-14.33 (-24.00, -4.66)	0.0055
HPES impact (physical functioning)	35.90 (25.70)	17.29 (17.67)	-18.29 (2.65)	40.71 (27.54)	38.68 (29.34)	-1.01 (5.49)	-17.28 (-28.66, -5.89)	0.0046
HPES impact (daily life)	31.28 (24.76)	13.91 (15.98)	-17.65 (2.37)	34.61 (28.21)	34.21 (30.80)	-0.36 (5.68)	-17.29 (-29.08, -5.49)	0.0061
SF-36 physical functioning subscale	46.31 (9.33)	51.58 (7.08)	5.29 (0.91)	44.37 (11.33)	44.40 (12.73)	0.122 (2.29)	5.16 (0.41, 9.92)	0.0347
Other secondary endpoints								
EQ-5D index score (UK algorithm)	0.71 (0.19)	0.79 (0.17)	0.08 (0.02)	0.66 (0.24)	0.66 (0.30)	-0.03 (0.06)	0.11 (-0.01, 0.22)	0.0615
EQ-5D index score (Australian algorithm)	0.85 (0.17)	0.92 (0.12)	0.08 (0.02)	0.78 (0.25)	0.76 (0.32)	-0.04 (0.03)	0.12 (0.04, 0.20)	0.0044
EQ-5D VAS	67.7 (17.62)	76.0 (16.57)	8.3 (2.67)	62.6 (24.51)	65.2 (24.28)	-0.0 (4.37)	8.3 (-0.7, 17.3)	0.0706

Source: Table 26 p63, Table 29 p71, Attachment 4 of the submission.

ANCOVA = analysis of covariance, CI = confidence interval; EQ-5D = EuroQol-5D, HPES = hypoparathyroidism patient experience scale, ITT = intention to treat, LS = least squares, PBO = placebo, PPT = palopegteriparatide, SD = standard deviation, SE = standard error. VAS = visual analogue scale.

^a calculated from ANCOVA model.

Bold indicates a significant result.

6.25 Across all the secondary endpoints for HPES, patients in the palopegteriparatide arm experienced a greater improvement in the domain/subscale scores (decrease in HPES scores) at Week 26 compared to the placebo arm. The difference from baseline in the HPES key secondary outcomes met the pre-defined minimum clinically important difference (MCID) of a 13 to 15-point difference for the palopegteriparatide arm.

6.26 For the SF-36, patients in the palopegteriparatide arm experienced a greater improvement (increase in SF-36 score) and the difference in the LS means were significant for all domains and component summaries except for the role emotional

⁴ Brod, M. *et al.* (2021) 'Psychometric validation of the Hypoparathyroidism Patient Experience Scales (HPES)', Journal of Patient-Reported Outcomes, 5(1). doi:10.1186/s41687-021-00320-2.

domain, mental health domain, mental health component summary and bodily pain domain. The submission did not propose an MCID for this endpoint.

- 6.27 The difference in the change from baseline in the LS means between the palopegteriparatide and placebo arms for the EQ-5D VAS and EQ-5D-5L utility score using the UK value set was not significant at Week 26. The EQ-5D-5L index scores using the Australian value set⁵ is utilised in the economic model and is included in Table 6 above. Using the Australian algorithm, the change from baseline in the LS means between the palopegteriparatide and placebo arms for EQ-5D-5L utility score was significant at Week 26.
- 6.28 The submission claimed superiority of palopegteriparatide compared to placebo based on changes in BMD. At baseline the mean BMD and Z-scores were above the age- and sex-matched reference ranges for both arms. By Week 26 the palopegteriparatide arm reported a reduction in their mean Z-scores for 4 out of the 5 locations reported. While these Z-scores were still above age- and sex-matched reference ranges, they were trending toward normalisation. The placebo arm did not report similar reductions in Z-scores. The difference in the LS means for change from baseline to Week 26 in Z-scores was significant for all regions except forearm/radius 1/3 distal. The submission did not present an MCID for a change in BMD in patients with HPT.

eGFR results

- 6.29 The submission also claimed superiority of palopegteriparatide compared to conventional therapy based on a *post-hoc* analysis of eGFR at 26 weeks as a measure of renal function. The submission also presented the results of the 52-week and 104-week follow up. The Pre-Sub-Committee Response (PSCR) provided results of the 156 week follow up. These are presented in Table 7 below.

⁵ Norman R, Mulhern B, Lancsar E, et al., 2023. The Use of a Discrete Choice Experiment Including Both Duration and Dead for the Development of an EQ-5D-5L Value Set for Australia. *Pharmacoeconomics*. 41(4):427-438.

Table 7: eGFR results for patients in PaTHway at Week 26, Week 52, Week 104 and Week 156 (ITT population)

	Double-blind period		Open-label period			
	26 weeks		52 weeks		104 weeks	156 weeks
	PPT (N=61)	Placebo (N=21)	PPT (N=61)	Placebo/PPT (N=21)	PPT and placebo/ PPT (N=82)	PPT and placebo/PPT (N=74)
Baseline						
Mean (SD)	67.5 (13.8) ^a	72.7 (14.6)	-	-	77.8 (14.8)	-
Change from baseline at follow up						
Mean (SD)	7.9 (10.4)	-1.9 (8.6)	9.3 (11.7)	7.6 (8.7)	9.0 (10.3)	8.8 (11.9)
Change From baseline (ANCOVA)						
Difference in LS Means SE)	8.8 (2.5)		-	-	-	
P-value (PPT vs PBO)	0.0007		-	-	-	

Source: Table 33 p80 of the submission, Table 3 p7 Khan et al. 2023, PaTHway_eGFR_156wks provided in PSCR.

ANCOVA = analysis of covariance, ITT = intention to treat, PBO = placebo, PPT = palopegteriparatide, SD = standard deviation, SE = standard error.

n = 60 for palopegteriparatide arm at Week 26 and n = 59 at Week 52. N = 19 for placebo arms at Week 26 and Week 52.

^a Sourced from Khan 2023

Bold indicates a significant result.

6.30 At Week 26 there was a statistically significant improvement in eGFR for patients receiving palopegteriparatide compared with placebo. Patients initially randomised to placebo experienced an initial decline in eGFR at Week 26, followed by an improvement in eGFR at Week 52 after switching to open label palopegteriparatide. The changes from baseline to Week 52 for both arms met the predefined MCID of 5 mL/min/1.73 m² difference at 12-months. However, the MCID proposed by the submission for change in eGFR was established in patients with end-stage renal disease who had undergone deceased donor kidney transplantation and was a means of predicting subsequent death-censored graft failure⁶. In that setting, a difference in eGFR of 5 mL/min/1.73 m² is likely to be clinically significant and may represent a delay and/or reduction in the need for dialysis. However, these patients are not aligned with those in the PaTHway trial, where the average baseline eGFR was 67.5 to 72.7 mL/min/1.73 m² and where a difference in eGFR of 5 mL/min/1.73 m² at 12 months is unlikely to be clinically meaningful. Thus, the ESC considered the applicability to patients with chronic HPT of the MCID for eGFR proposed by the submission was not justified. The ESC noted the improvement of 9.81 mL/min/1.73 m² at Week 156 relative to baseline in patients treated with palopegteriparatide only. The improvement in all patients, including patients that received placebo for the first 26 weeks and subsequently switched to open-label treatment with palopegteriparatide, was 8.8 mL/min/1.73 m². The change from baseline to Week 156 met the predefined MCID of 5 mL/min/1.73 m²; however, as discussed, there was insufficient evidence to support this MCID in patients with chronic hypoparathyroidism. The pre-PBAC response stated that it was important to consider not only the magnitude of the benefit in terms of the difference, but also the direction of change in the respective

⁶ Mayne et al., 2021. Defining a minimal clinically meaningful difference in 12-month estimated glomerular filtration rate for clinical trials in deceased donor kidney transplantation. Clin Transplant. 2021;35(7): e14326.

treatment arms. It noted that conventional therapy resulted in worsening of kidney function consistent with the natural history of HPT (rate of decline in eGFR = 2 to 3 mL/min/1.73 m² per year), whereas palopegteriparatide continued to preserve/improve eGFR.

- 6.31 The submission performed a *post-hoc* subgroup analysis to inform the relative efficacy and safety of palopegteriparatide in patients who are inadequately controlled as per the PBS criteria, noting that the subgroup did not entirely match the PBS restriction. Seventy-two (87.8%) patients were included in the subgroup.
- 6.32 The submission presented the results of the primary outcome, the key secondary outcomes for HPES domain scores, and eGFR for the subgroup. The submission also presented the results of the complement group i.e., patients in PaTHway who did not meet the subgroup criteria; however, the number of patients in the complement group was small (n=10).
- 6.33 Results for the primary outcome and change from baseline in eGFR are presented in Table 8 and Table 9.

Table 8: Results of the primary outcome at Week 26 in PaTHway (PBS subgroup and ITT population)

Population	Trial ID	Palopegteriparatide n/N (%)	Placebo n/N (%)	RR (95% CI)	RD (95% CI)
Whole trial population	Primary efficacy endpoint at Week 26	48/61 (78.7)	1/21 (4.8)	NR ^a	NR ^a
PBS subgroup	Primary efficacy endpoint at Week 26	43/56 (76.8)	1/16 (6.3)	12.37 (1.84, 83.13)	0.71 (0.55, 0.87)
Complement of subgroup	Primary efficacy endpoint at Week 26	5/5 (100)	0/5	5.07 (0.81, 31.57)	1 (1.00, 1.00)
Subgroup interaction p-value	0.9621				

Source: Table 47, p103 of the submission

CI = confidence interval, ITT = intention to treat, n = number of participants reporting data, N = total participants in group, PBS = Pharmaceutical Benefits Scheme, RD = risk difference, RR = relative risk.

^a Estimate of effect was not generated for the primary efficacy endpoint as initially outlined in the protocol given the placebo group had only 1 responder (p80 of the CSR).

Note that the sub-group results presented in Table 8 are derived from post-hoc analyses conducted by the Sponsor specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for the PaTHway study. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Table 9: Change in eGFR from baseline to Week 26 in PaTHway (PBS subgroup and ITT population)

	Baseline		Week 26			Palopegteriparatide vs. Placebo Difference in LS-Mean (95 %CI) p-value	Subgroup interaction p-value	
	n/N	Mean (SD)	n/N	Mean (SD)	Change from baseline LS-Mean (SE)			
Whole trial population								
Palopegteriparatide	61/61	67.5 (13.8)	60/61	75.6 (14.5)	NR	8.8 ^a P=0.0007	NA	
Placebo	21/21	72.7 (14.6)	19/21	70.8 (13.4)	NR			
PBS subgroup								
Palopegteriparatide	55/56	66.97 (13.50)	55/56	75.03 (14.64)	7.14 (1.76)	9.62 (3.92, 15.32) P=0.0013	P=0.5532	
Placebo	15/16	70.96 (16.46)	15/16	68.43 (12.88)	-2.48 (2.81)			
Complement								
Palopegteriparatide	5/5	75.06 (17.32)	5/5	81.44 (12.75)	2.77 (3.41)	6.12 (-5.13, 17.38) P=0.2207		
Placebo	4/5	79.03 (9.75)	4/5	79.45 (4.16)	-3.36 (4.62)			

Source: Table 33 p80, Table 49 p106 of the submission, Table 3 Khan 2023 et al. 2023.

CI = confidence interval, ITT = intention to treat, LS = least squares, NA = not applicable, NR = not reported, PBS = pharmaceutical benefits scheme, PPT = palopegteriparatide, SD = standard deviation, SE = standard error.

^a 95% CI not reported.

Note that the sub-group results presented in Table 8 are derived from post-hoc analyses conducted by the Sponsor specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for the PaTHway study. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.34 For all outcomes, the PBS subgroup experienced similar improvements as when compared to the whole trial results. The subgroup interaction p-value demonstrated that there was no significant difference between the PBS population and the complement population, noting again the small size of the complement group and the post-hoc nature of the analysis.

Comparative harms

6.35 To support the safety claim, the submission presented the results of the 26-week blinded period, the 52-week OLE and the 104-week OLE from PaTHway, and the long-term safety results from PaTH Forward. TEAEs for PaTHway are reported in Table 10 and Table 11.

Table 10: Overview of treatment emergent adverse effects in PaTHway at Week 26, Week 52 and Week 104 (safety analysis set)

	Double-blind period		Open-label period	Open-label period
	26 weeks		52 weeks	104 weeks
	Palopegteriparatide (N=61) n (%)	Placebo (N=21) n (%)	Palopegteriparatide (N=80) n (%)	Palopegteriparatide (N=80) n (%)
TEAEs	50 (82.0)	21 (100.0)	72 (90.0)	75 (93.8)
Serious TEAEs	5 (8.2)	3 (14.3)	8 (10.0)	14 (17.5)
Severity				
Grade 1	27 (44.3)	11 (52.4)	37 (46.3)	36 (45.0)
Grade 2	21 (34.4)	9 (42.9)	27 (33.8)	29 (36.3)
Grade 3	1 (1.6)	1 (4.8)	7 (8.8)	9 (11.3)
Grade 4	1 (1.6)	0	1 (1.3)	1 (1.3)
Related TEAE	30 (49.2)	8 (38.1)	42 (52.5)	44 (55.0)
Serious related TEAE	1 (1.6)	0	2 (2.5)	2 (2.5)
TEAE related to hyper- or hypocalcaemia leading to ER/urgent care visit and/or hospitalisation	4 (6.6)	2 (9.5)	6 (7.5)	6 (7.5)
TEAE leading to discontinuation of study drug	1 (1.6)	2 (9.5)	1 (1.3)	NA
TEAE leading to discontinuation of trial	1 (1.6)	1 (4.8)	NR	1 (1.3)
TEAE leading to death	1 (1.6)	0	1 (1.3)	1 (1.3)
TEAE of special interest	8 (13.1)	0	NR	NR

Source: Table 34 p84, Table 38 p88, of the submission.

ER = emergency room, n = number of participants with event, N = total participants in group, TEAE = treatment emergent adverse effect.

6.36 A greater proportion of patients in the placebo arm experienced a related TEAE compared to placebo (49% vs 38%) and serious TEAEs at the 26-week blinded period. The ESC noted that this may be, at least partly, explained by the fact that placebo patients with normal serum calcium levels had their HPT treatments reduced and replaced by placebo injections, and that hypocalcaemia was considered a TEAE rather than a symptom of the underlying condition.

6.37 Frequently reported TEAEs are presented in Table 11.

Table 11: Frequently occurring TEAEs in PaTHway at Week 26 (safety analysis set)

System Organ Class Preferred Term	26 weeks	
	Palopegteriparatide (N=61), n (%)	Placebo (N=21), n (%)
Subjects with at least one TEAE	50 (82.0)	21 (100.0)
General disorders and administration site conditions	33 (54.1)	8 (38.1)
Injection site reaction	19 (31.1)	0
Fatigue	9 (14.8)	5 (23.8)
Nervous system disorders	26 (42.6)	5 (23.8)
Headache	13 (21.3)	2 (9.5)
Paraesthesia	11 (18.0)	3 (14.3)
Dizziness	4 (6.6)	0
Musculoskeletal and connective tissue disorders	21 (34.4)	6 (28.6)
Muscle spasms	7 (11.5)	3 (14.3)
Arthralgia	6 (9.8)	3 (14.3)
Gastrointestinal disorders	20 (32.8)	5 (23.8)
Nausea	7 (11.5)	2 (9.5)
Diarrhoea	6 (9.8)	1 (4.8)
Constipation	4 (6.6)	1 (4.8)
Metabolism and nutrition disorders	12 (19.7)	9 (42.9)
Hypocalcaemia	6 (9.8)	9 (42.9)
Hypercalcaemia	6 (9.8)	0
Investigations	9 (14.8)	3 (14.3)
Blood thyroid-stimulating hormone decreased	2 (3.3)	2 (9.5)
Psychiatric disorders	7 (11.5)	1 (4.8)
Insomnia	4 (6.6)	1 (4.8)
Respiratory, thoracic and mediastinal disorders	8 (13.1)	0
Oropharyngeal pain	4 (6.6)	0

Source: Table 34 p84, Table 38 p88, of the submission.

n = number of participants with event, N = total participants in group, TEAE = treatment emergent adverse effect.

- 6.38 The ESC noted that approximately one-third of patients in the palopegteriparatide arm experienced injection site reactions compared to none in the placebo arm. The pre-PBAC response stated that injection site reactions associated with palopegteriparatide were transient. During the blinded period treatment compliance was > 90% for both arms.
- 6.39 The ESC noted that a greater proportion of patients in the placebo arm experienced hypocalcaemia, which could be explained by the fact that patients in the placebo arm had their calcium and active vitamin D doses titrated in the presence of serum calcium in the normal range. This could also explain why a greater proportion of patients in the placebo arm had an emergency room/urgent care visits/hospitalisation that was related to hypocalcaemia. No patients in the placebo arm experienced hypercalcaemia, while it was experienced by 9.8% of patients in the palopegteriparatide arm. Hypercalcaemia was reported only in the first 3 months of the blinded period, suggesting that serum calcium increased initially during study drug titration before returning to baseline levels.
- 6.40 The submission presented the results of the 84-week and 110-week OLE follow up for PaTH Forward to support the long-term safety claim. Within that study, the proportion of patients who experienced a TEAE steadily increased over time, from 40.0% after the

4-week double-blind period, to 94.9% at the 110 OLE period. The majority of TEAEs were Grade 1 or Grade 2. At 110 weeks about one-third (28.8%) of patients experienced a Grade 3 TEAE and 6.8% experienced a Grade 4 TEAE. There were no TEAEs leading to discontinuation of study drug, withdrawal or death. The most commonly reported TEAEs (occurring in $\geq 5\%$ of patients) were headache (22.0%), fatigue (11.9%), muscle spasms (11.9%), paraesthesia (10.2%), hypertension (10.2%) and nausea (10.2%). The remaining TEAEs occurred in 5 or fewer patients.

Benefits/harms

6.41 A summary of the comparative benefits and harms for palopegteriparatide versus placebo is presented in Table 12.

Table 12: Summary of comparative benefits and harms for palopegteriparatide and placebo

Trial	PPT n/N	Placebo n/N	RR (95% CI)	Event rate/100 patients		RD (95% CI)
				PPT	Placebo	
Benefits						
Achieving the primary endpoint (response to treatment) at 26 weeks						
PaTHway	48/61	1/21	16.52 (2.43, 112.4)	78.7	4.8	0.74 (0.60, 0.88)
Harms at 26 weeks						
	PPTn/N	Placebo n/N	RR (95% CI)	Event rate/100 patients		RD (95% CI)
				PPT	Placebo	
Serious TEAEs						
PaTHway	5/61	3/21	0.57 (0.15, 2.20)	8.2	14.3	-0.06 (-0.23, 0.10)
TEAE related to hyper- or hypocalcaemia leading to ER/urgent care visit and/or hospitalisation						
PaTHway	4/61	2/21	0.69 (0.14, 3.49)	6.6	9.5	-0.03 (-0.17, 0.11)
Hypercalcaemia						
PaTHway	6/61	0/21	4.61 (0.27, 78.57)	9.8	0	0.10 (0.02, 0.17)

Source: Table 34 p84, Table 38 p88, of the submission.

CI = confidence interval, ER = emergency room, PPT = palopegteriparatide, RD = risk difference, RR = relative risk, TEAE = treatment emergent adverse effect.

6.42 On the basis of direct comparative evidence presented by the submission, for every 100 patients treated with palopegteriparatide in comparison with placebo over a 26-week period:

- Approximately 74 additional patients will achieve the primary endpoint i.e., achieve a response to treatment based on serum calcium within the normal range, reduction in calcium dose (to ≤ 600 mg/day), cessation of active vitamin D dose and no increase in study drug within the 4 previous weeks.
- Approximately 10 more patients would experience hypercalcaemia.

Clinical claim

6.43 The submission described palopegteriparatide as superior in terms of effectiveness compared with conventional therapy.

6.44 The ESC noted that the trial demonstrated that most patients who commenced palopegteriparatide were able to achieve independence from active vitamin D and therapeutic doses of calcium while maintaining normal serum calcium levels (as measured by the primary outcome of the trial). However, the ESC considered the

submission did not provide sufficient clinical evidence that supported the use of this outcome as a surrogate for efficacy. There is uncertainty with translating this into longer-term mortality, morbidity and quality of life improvements, particularly as compared with conventional therapy. The pre-PBAC response stated that the primary outcome in the PaTHway trial is a multi-component efficacy endpoint whereby being a responder means a patient achieves normocalcaemia independent of treatment with conventional therapy, which is consistent with the goal of HPT management. Further, current research demonstrates that patients on conventional therapy have an increased risk of nephrolithiasis, nephrocalcinosis and impaired renal function. Hence, the pre-PBAC response stated that being independent of conventional therapy will have beneficial effects on a patient's kidney function over time. The pre-PBAC response stated that the PaTHway trial provides direct evidence informing the clinical therapeutic conclusion in the target population in terms of response, quality of life, biochemistry and kidney function.

- 6.45 The ESC noted that patients in the placebo arm who achieved normal serum calcium levels had their active vitamin D and calcium supplements reduced which did not represent standard of care for patients with normal serum calcium levels. The ESC further noted that this was associated with an increase in hypocalcaemia and TEAE's.
- 6.46 The ESC noted that the interpretation of the ITT results is subject to qualification given the small sample size in the placebo arm (n=21). Further, the evidence for the use of palopegteriparatide in patients who were inadequately controlled on conventional therapy, as per the proposed PBS restriction, was based on a *post-hoc* subgroup analysis, which was further limited by the number of patients in the placebo arm (n = 16). While results of the subgroup were similar to the wider trial results, the ESC considered that the results should be interpreted with caution.
- 6.47 Overall, the ESC considered that the claim that palopegteriparatide was superior in terms of effectiveness was supported by the evidence presented in the submission; however, the magnitude of the benefit was highly uncertain due to the reasons outlined above.
- 6.48 The PBAC considered that the claim that palopegteriparatide was superior in terms of effectiveness compared to conventional therapy was reasonable.
- 6.49 The submission described palopegteriparatide as non-inferior in terms of safety compared to conventional therapy. The ESC considered that this claim was not adequately supported by the evidence presented. The ESC noted that (i) injection site reactions were higher in the palopegteriparatide arm compared to the placebo arm; (ii) gastrointestinal adverse events were more common in the palopegteriparatide arm and (iii) the incidence of hypercalcaemia was more common on the palopegteriparatide arm. The ESC also felt that the claim of superior safety in the long-term was not supported as the OLE periods of PaTHway were non-comparative. The pre-PBAC response stated that the injection site reactions associated with palopegteriparatide were transient in nature.

6.50 The PBAC considered that the claim that palopegteriparatide was non-inferior in terms of safety compared to conventional therapy was not adequately supported given the differences outlined, the small numbers of patients and the lack of long-term comparative data. Overall, the PBAC considered that palopegteriparatide was likely comparable to conventional therapy.

Economic analysis

6.51 The submission presented a stepped economic evaluation and a cost-utility analysis comparing palopegteriparatide with conventional therapy in patients with chronic HPT. The economic evaluation used data from the PaTHway trial and published literature to extrapolate the clinical outcomes beyond the study duration to estimate the costs and benefits of treatment over time in both arms. The outcomes presented in the model were CKD and end-stage kidney disease (ESKD).

6.52 The ESC noted that the model did not assess all outcomes associated with HPT deemed important by clinicians and patients. Other potential patient relevant long-term effects of HPT include basal ganglia calcification (prevalence of 12%), neuromuscular manifestations including seizures, tetany and muscle stiffness (prevalence of 40% - 60%) and cataracts (prevalence of 17%). The pre-PBAC response stated that the model structure explicitly captured two patient relevant treatment benefits demonstrated in PaTHway, improved quality of life and improved kidney function. The pre-PBAC response also stated that, whilst the model does attribute quality of life gains to comparative effectiveness in kidney function, it also captures the benefits of palopegteriparatide on HPT symptoms via treatment specific utility values. Further, the pre-PBAC response stated that whilst it is conceivable that palopegteriparatide could reduce the rate of other patient relevant long-term effects of HPT, inclusion of additional outcomes would require the economic model to depart from the underlying evidence base.

6.53 The model structure is summarised in Table 13.

Table 13: Summary of model structure, key inputs and rationale

Element	Description
Treatments	Palopegteriparatide vs conventional therapy (calcium and vitamin D supplements)
Time horizon	51 years in the model base case versus 26 weeks in the PaTHway trial. Given the trial duration (26 weeks vs 51-year time horizon) and the lack of direct evidence on kidney function and mortality, the ESC considered that this was optimistic and favoured palopegteriparatide.
Outcomes	LYs and QALYs
Methods used to generate results	Markov cohort model
Health states	Health states: <ul style="list-style-type: none"> •On PPT: CKD 1/2; CKD 3; CKD 4; CKD 5 (CM). •On CT: CKD 1/2; CKD 3; CKD 4; CKD 5 (CM). •CKD 5 (dialysis) •CKD 5 (post-transplant) •Death
Cycle length	6 months (26 weeks)

Element	Description
Transition probabilities	<p>11 health states.</p> <ul style="list-style-type: none"> •CKD 1 to CKD 5 transitions <ul style="list-style-type: none"> ○ Cycle 1: PaTHway trial. <ul style="list-style-type: none"> ○ CKD 1/2 to CKD 1/2 risk per cycle. CT: 100%, PPT: 100%. ○ CKD 1/2 to CKD 3 risk per cycle. CT: 0%, PPT: 0%. ○ CKD 3 to CKD 1/2 risk per cycle. CT: 0%, PPT: 61%. ○ From Cycle 2: published natural history studies (Rejnmark 2022⁷; Gosmanova 2021a⁸). <ul style="list-style-type: none"> ○ CKD1/2 to CKD 3 risk per cycle (Rejnmark 2022). CT: 3.6%, PPT: 1.7% (HR PPT vs CT = 0.47). ○ CKD 3 to CKD 4 and CKD 4 to CKD 5 risks per cycle (Gosmanova 2021a). CT: 3.8%, PPT: 2.4% (HR PPT vs CT = 0.63). •Uptake of dialysis or transplant: AIHW Chronic Kidney Disease: Australian facts. An age-based risk of renal replacement therapy was applied. •Distribution of dialysis and transplant: ANZDATA 46th Annual Report 2023. Dialysis: 97.3%, transplant: 2.7%. •Transition from dialysis to transplant: ANZDATA 46th Annual Report 2023. Age-based transitions were applied. •Probability of death given CKD health state: CDC Kidney Disease Surveillance System. <p>The ESC noted that several transitions were derived from the literature with uncertain applicability to the intended population.</p>
Health related quality of life	<ul style="list-style-type: none"> •Baseline utility values from the PaTHway trial. •Treatment specific utility decrement/increment sourced from the PaTHway trial and applied for the model duration. •CKD stage related utility decrements were sourced from a Deloitte (2023) report of chronic kidney disease in the Australian population. <p>Cycle 1 all utilities for all health states were: 0.831 From Cycle 2: On PPT: CKD 1/2 = 0.906 On PPT: CKD 3 = 0.856 On PPT: CKD 4 = 0.796 On PPT: CKD 5 (CM) = 0.596 On CT: CKD 1/2 = 0.788 On CT: CKD 3 = 0.738 On CT: CKD 4 = 0.678 On CT: CKD 5 (CM) = 0.478</p> <p>The submission assumed that treatment effects are sustained while on treatment.</p>

Source: Table 52, p121, Table 78, p149 and Table 82, p150, Table 94, p164 of the submission.

AIHW = Australian Institute of Health and Welfare, ANZDATA = Australia and New Zealand Dialysis and Transplant Registry, CDC = Centre for Disease Control, CKD = chronic kidney disease, CM = conservative management, CT = conventional therapy, HR = hazard rate, LYs = life years, PPT = palopegteriparatide, QALYs = quality adjusted life years.

6.54 The submission presented a Markov cohort analysis of palopegteriparatide compared with conventional therapy. Patients began the model with various levels of renal impairment (CKD 1/2 or CKD 3). During each cycle of the Markov model, patients could

⁷ Rejnmark, L., Ayodele, O., Lax, A., Mu, F., Swallow, E. and Gosmanova, E.O., 2023. The risk of chronic kidney disease development in adult patients with chronic hypoparathyroidism treated with rhPTH (1-84): A retrospective cohort study. *Clinical Endocrinology*, 98(4), pp.496-504.

⁸ Gosmanova, E.O., Chen, K., Rejnmark, L., Mu, F., Swallow, E., Briggs, A., Ayodele, O., Sherry, N. and Ketteler, M., 2021. Risk of chronic kidney disease and estimated glomerular filtration rate decline in patients with chronic hypoparathyroidism: a retrospective cohort study. *Advances in therapy*, 38, pp.1876-1888.

remain in their current health state, experience progression/regression of renal impairment (among CKD 1/2, CKD 3, CKD 4 or CKD 5 (conservative management [CM]), initiate dialysis or transplantation, or die. Transition probabilities among CKD 1/2, CKD 3, CKD 4 and CKD 5 (CM) were treatment specific.

- 6.55 In Cycle 1 transition probabilities were based on PaTHway. These data were derived from patients with eGFR data for CKD staging available at baseline and Week 26. From Cycle 2 transition probabilities in both the palopegteriparatide arm and conventional therapy arm were based on published literature, with uncertain applicability to the intended population. Patients initiating dialysis/transplantation transitioned to a corresponding chronic disease state in the next cycle. Patients in the palopegteriparatide arm could discontinue treatment in any cycle and adopt the same risks/utilities as the conventional therapy arm.
- 6.56 The model structure relied on the assumption that HPT symptoms and the side effects of conventional therapy (i.e., calcium and vitamin D) are captured via CKD stage related health states. The reported estimated prevalence of CKD in HPT patients varies widely. A systematic review reported that across 8 included studies in HPT, the prevalence of CKD ranged from 5.0% to 41.0%⁹. The ESC considered that the wide range of estimated rates and the confounders present across the studies made it difficult to accurately describe the relationship between HPT and CKD.
- 6.57 The economic model relied on the claim presented by the submission that palopegteriparatide had superior effectiveness in kidney function compared to conventional therapy. Although the PaTHway trial demonstrated a statistically significant improvement in eGFR for patients using palopegteriparatide compared with placebo (conventional therapy arm), the ESC considered that this claim was uncertain for several reasons. Firstly, the PaTHway trial was small, and comparative data was only available for 26 weeks. Secondly, the magnitude of any improvement is uncertain, given that the comparator arm in the trial was an inaccurate representation of standard of care. Thirdly, the change from baseline in eGFR was assessed in PaTHway based on a *post-hoc* analysis and on the change over a single cycle (i.e. 26 weeks). Although the submission's nominated MCID was met, this MCID was not relevant to the population in the PaTHway trial. Therefore, the clinical relevance of the change in eGFR was uncertain. Finally, the submission did not provide a study translating the primary composite endpoint of PaTHway to kidney function. The plausibility of the results of the model relied on the assumption that any benefits of palopegteriparatide are sustained in the long-term. The ESC considered that this was not supported by the clinical evidence provided by the submission which provided open-label data up to 104 weeks (and up to 156 weeks in the PSCR).

⁹ Gosmanova, E.O., Houillier, P., Rejnmark, L., Marelli, C. and Bilezikian, J.P., 2021. Renal complications in patients with chronic hypoparathyroidism on conventional therapy: a systematic literature review: renal disease in chronic hypoparathyroidism. *Reviews in Endocrine and Metabolic Disorders*, 22(2), pp.297-316.

- 6.58 The submission stated that the lifetime horizon (51 years) was used to capture the long-term downstream implications of treatment with palopegteriparatide compared to conventional therapy in chronic HPT and the impact of the treatments on the long-term progression to ESKD and mortality. The submission stated that, given the trial duration of 26 weeks was too short to observe most effects of the treatment, it was necessary to extrapolate effects to a longer time horizon. However, the ESC considered the modelled effectiveness of palopegteriparatide was perpetuated over the long time horizon without supportive clinical evidence and this biased the results in favour of palopegteriparatide.
- 6.59 In Cycle 1 of the model, transitions were derived from patients in PaTHway with eGFR data for CKD staging available at baseline and Week 26 (3 patients had missing CKD staging at baseline). The model allowed for 61% of patients in the palopegteriparatide arm to improve from CKD 3 to CKD 1/2 at Week 26. 100% of patients in CKD 1/2 at baseline remained in CKD 1/2 at Week 26. In the conventional therapy arm, all patients remained in their respective health states between baseline and Week 26. These data were based on individual patient data not presented in the Clinical Study Report and were unable to be verified. While the proportion of CKD 3 patients who improved to CKD 1/2 at Week 26 was 61%, this was based on 11/18 patients with CKD 3 at baseline. The ESC considered that the modelled improvement was highly uncertain.
- 6.60 After Cycle 1, the risk of CKD progression from CKD 1/2 to CKD 3 in both the palopegteriparatide and conventional therapy arms was based on Rejnmark (2022)⁷. Rejnmark (2022) evaluated the incidence of CKD in HPT patients treated with recombinant human (rh) PTH (1-84) (n=118) compared to those treated with calcium and vitamin D supplementation (n=497) using regression models. This was a retrospective study with significant differences in baseline characteristics between the two groups, almost all favouring the rhPTH group. The rhPTH cohort were all clinical trial participants, while the comparator 'standard treatment' group was drawn from real world U.S. patient data. Further, the applicability of this study is uncertain given no comparative studies have been reported comparing rhPTH (1-84) with palopegteriparatide.
- 6.61 The submission applied a risk per cycle (for CKD 1/2 to CKD 3 progression) for the duration of the model, based on the estimated 5-year risk of CKD from Rejnmark (2002)⁷. This was not consistent with Figure 2 of Rejnmark (2022)⁷ which showed a plateauing from approximately 2 years in the percentage of patients developing CKD (i.e. transitioning from CKD 1/2 to CKD 3). There are no long-term estimates to support the application of the risk of CKD for the duration of the model and therefore this assumption was uncertain and may overestimate the number of patients progressing to CKD 3 in the model. Application of the hazard rate (0.47) from Rejnmark (2022)⁷ to the palopegteriparatide arm (CKD 1/2 to CKD 3) of the model also assumes treatment effects are sustained over the model time horizon. This assumption was not supported by the clinical evidence presented in the submission. Removing the modelled benefit (hazard rate = 1) increased the ICER to \$115,000 to < \$135,000/QALY gained.

- 6.62 The transition probabilities from CKD 3 to CKD 5 (CM) health states were based on Gosmanova (2021a)⁸. The submission stated that this was because Rejnmark (2022)⁷ was limited to the incidence of CKD (stages 3-5), whereas Gosmanova (2021a)⁸ reported time to CKD progression (among stages 3-5). Gosmanova (2021a)⁸ was a retrospective cohort study with 5-year follow-up of 8,097 adults with chronic HPT and 40,485 adults without HPT. The submission applied a risk per cycle of CKD 3 to CKD 4 or CKD 4 to CKD 5 (CM) progression based on the 5-year risk of CKD in the historical cohort and then applied a hazard rate to derive the risk per cycle of progression from CKD 3 to CKD 4 or CKD 4 to CKD 5 (CM) in the palopegteriparatide arm. Given Gosmanova (2021a)⁸ compared HPT patients with controls who did not have HPT the application of this hazard rate was not appropriate and infers that patients treated with palopegteriparatide are effectively cured (in terms of outcomes captured in the model). The ESC considered this was implausible and greatly increased the uncertainty associated with the model. Further, this was a retrospective study with significant differences in baseline characteristics between the two groups, which may have confounded the resultant hazard rate.
- 6.63 ESKD treatment distribution and ESKD transitions were derived from the overall kidney disease population rather than the HPT population. The ESC noted that this likely overestimated the burden of disease, as most ESKD has significant comorbid associations, such as advanced diabetes or cardiovascular disease. The submission did not provide any evidence to suggest a significant proportion of HPT patients progress to dialysis or transplant due to HPT alone. The proportion of HPT patients receiving dialysis or transplant may differ from the overall kidney disease population given thiazides are commonly administered when hypercalciuria persists and HPT patients may experience differing rates of comorbidities. Other large studies on the long-term effect of HPT on CKD have found no risk of developing ESKD in HPT patients compared to control patients^{10, 11}. The model was not sensitive to the uptake of renal replacement therapy (RRT), the treatment distribution of dialysis/transplant amongst RRT initiators or dialysis to transplant transitions.
- 6.64 Mortality hazard rates were derived from the overall kidney disease population, which had uncertain applicability to the HPT population. The submission did not provide any evidence to demonstrate that there is an increased mortality risk associated with HPT. Underbjerg (2013)¹¹ found no difference in survival after 22 years of follow-up of 688 Danish patients with post-surgical HPT, compared to 2,064 controls. A recent meta-

¹⁰ Luk, Y., Fung, M.M.H., Lui, D.T.W., Liu, X., Li, L., Wong, C.K.H. and Lang, B.H.H., 2024. Long-term kidney outcomes in patients with permanent hypoparathyroidism after total thyroidectomy for benign disease: A population-based study. *Surgery*.

¹¹ Underbjerg, L., Sikjaer, T., Mosekilde, L. and Rejnmark, L., 2013. Cardiovascular and renal complications to postsurgical hypoparathyroidism: a Danish nationwide controlled historic follow-up study. *Journal of Bone and Mineral Research*, 28(11), pp.2277-2285.

- analysis also found no effect on mortality risk due to HPT¹². A further study found that only non-surgical HPT is associated with increased mortality¹³.
- 6.65 Baseline utility was applied to all patients in the first cycle of the model, based on the mean baseline utility from PaTHway using results from the EQ-5D-5L. EQ-5D-5L data were transformed to utility values using the Australian value set⁵. The mean baseline utility across the trial was 0.831. Treatment specific utilities were applied based on EQ-5D-5L data from the PaTHway trial from Cycle 2 onwards. An ANCOVA model on results at Week 26 resulted in least square mean change from baseline utilities of 0.075 in the palopegteriparatide arm and a decrement of -0.043 in the conventional therapy arm. The ESC noted that this meant that palopegteriparatide patients in CKD 1/2 from Cycle 2 were applied a utility value of 0.906 (0.831+0.075), which is higher than population norms of 0.86 (standard deviation 0.19) for Australia^{14,14}.
- 6.66 The submission applied the utility values to each cycle, therefore it was assumed that the treatment specific increment and decrement were constant and that the treatment effects are sustained while on treatment. This likely overestimated the benefits in the palopegteriparatide arm and was not supported by the clinical evidence provided by the submission. Since the HRQoL data was based on a short time period of 26 weeks, it may not have been reasonable to assume that a constant increment would be sustained for the duration of the model, noting that there is no long-term data available. Further, the observed decrement in the conventional therapy arm may be, at least in part, a result of the dose titration algorithm applied in PaTHway. The ESC also noted that the utility increments/decrements were based on small number of patients (59 in PPT arm; 19 in CT arm). Further as EQ-5D is a generic quality of life instrument, the increment/decrement may be driven by changes in health outcomes not related to kidney function, such as neuromuscular manifestations.
- 6.67 The submission also applied a disutility to each cycle related to the CKD health stages 3-5. These disutility values were based on Deloitte (2023)¹⁵, that based its estimates on a systematic literature review¹⁶ of health state utility weights for different stages

¹² Hadedeya, D., Kay, J., Attia, A., Omar, M., Shalaby, M., Youssef, M.R., Shama, M., Toraih, E. and Kandil, E., 2021. Effect of postsurgical chronic hypoparathyroidism on morbidity and mortality: a systematic review and meta-analysis. *Gland Surgery*, 10(10), p.3007.

¹³ Vadiveloo, T., Donnan, P.T., Leese, C.J., Abraham, K.J. and Leese, G.P., 2019. Increased mortality and morbidity in patients with chronic hypoparathyroidism: a population-based study. *Clinical endocrinology*, 90(2), pp.285-292.

¹⁴ Redwood, L., Currow, D., Kochovska, S. and Thomas, S.J., 2024. Australian population norms for health-related quality of life measured using the EQ-5D-5L, and relationships with sociodemographic characteristics. *Quality of Life Research*, 33(3), pp.721-733.

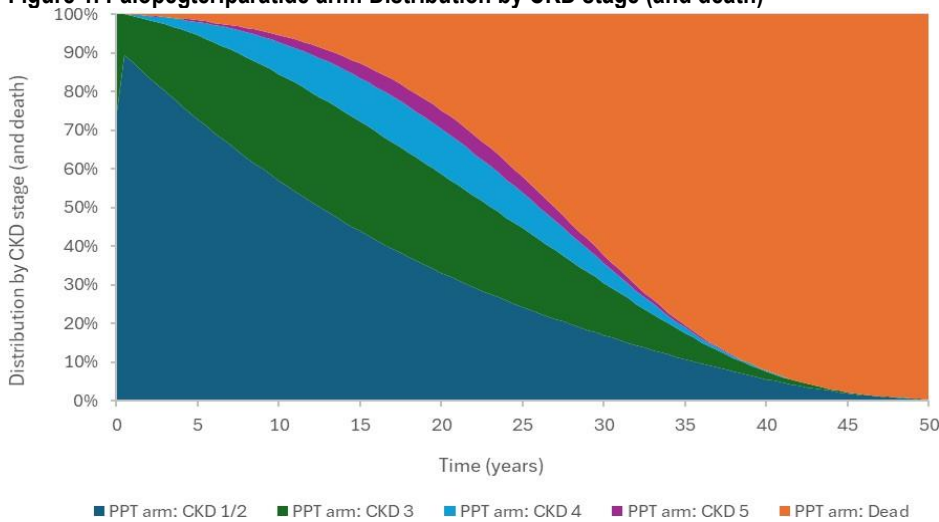
¹⁵ Deloitte Access Economics. 2023. Changing the chronic kidney disease landscape: The economic benefits of early detection and treatment.

¹⁶ Cooper, J.T., Lloyd, A., Sanchez, J.J.G., Sörstadius, E., Briggs, A. and McFarlane, P., 2020. Health related quality of life utility weights for economic evaluation through different stages of chronic kidney disease: a systematic literature review. *Health and Quality of Life Outcomes*, 18(1), p.310.

of CKD, renal replacement therapy and complications. The model was not sensitive to the CKD stage related utility decrements.

6.68 The submission presented traces from the economic model displaying the time spent in each of the health states over 50 years. The traces for palopegteriparatide and conventional therapy are presented in Figure 1 and Figure 2, respectively. According to the traces, half of the patients who started in CKD 1/2 health state would remain in that health state at approximately 20 years in the palopegteriparatide arm and approximately 12 years in the conventional therapy arm. The figures demonstrate that more time was spent in the CKD 4 and CKD 5 health states in the conventional therapy arm compared to palopegteriparatide arm. This is driven by both the Cycle 1 transitions derived from PaTHway and the transitions for CKD health stages for Cycle 2 onwards derived from the literature. The ESC noted that the outcomes in the model are based on less than 1% (= 0.5 year / 51 years) of the trial data compared to the extrapolated period. The ESC considered that the health state distributions were highly uncertain and favoured palopegteriparatide.

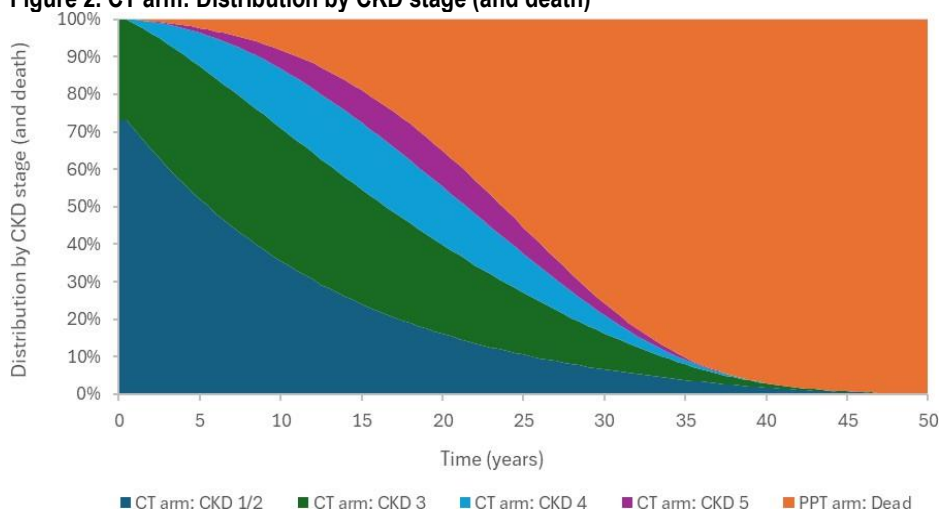
Figure 1. Palopegteriparatide arm: Distribution by CKD stage (and death)



Source: Figure 41, p177 of the submission.

CKD= chronic kidney disease, PPT = palopegteriparatide.

Figure 2. CT arm: Distribution by CKD stage (and death)



Source: Figure 42, p177 of the submission.

CKD = chronic kidney disease, CT = conventional therapy.

- 6.69 To derive the dose distribution applied in the economic model, the submission applied a normal distribution to the mean daily dose (21.4 mcg/day) at 26 weeks in PaTHway, a minimum dose of 9 mcg/day and a maximum dose of 39 mcg/day from PaTHway. Based on the dose distribution estimated by the submission and the volumes dispensed across the range of possible doses the submission estimated that each PBS item will cover 30.08 days of treatment (equivalent to 6.07 PBS items per cycle). The submission also estimated a compliance rate of 96.4%, based on exposure in PaTHway.
- 6.70 The submission included anniversary price reductions every 5 years until Year 15 (5%, 5% and 30% at years 5, 10 and 15 respectively). The ESC considered that this was not reasonable. Excluding the anniversary price reductions increased the ICER from the base case of \$95,000 to < \$115,000 /QALY gained to \$95,000 to < \$115,000 /QALY gained.
- 6.71 The submission sourced the cost of health states from a Deloitte (2023) report on the economic cost of CKD in Australia in 2021. The report estimated a health system cost for CKD in Australia in 2021.
- 6.72 A summary of the key drivers of the model is presented in Table 14.

Table 14: Key drivers of the model

Description	Method/Value	Impact Base case: \$█ ¹ /QALY gained.
Utilities	Treatment specific utility increments/decrements from PaTHway applied for the duration of the model	High, favours palopegteriparatide. Removing utility increment/decrement for PPT and CT after Cycle 2 increased the ICER to \$█ ² /QALY gained.
Time horizon	51-year time horizon in the base case	High, favours palopegteriparatide. Reducing the time horizon to 10-years increased the ICER to \$█ ² /QALY gained.
Transition probabilities	Cycle 2 onwards: CKD 1/2 to CKD 3 transitions (base case: Rejnmark 2022)	High, favours palopegteriparatide. Removing modelled benefit (HR = 1) of palopegteriparatide increased the ICER to \$█ ³ /QALY gained.
Baseline CKD distribution	Baseline CKD health state distribution: 73.2% CKD 1/2; 26.8% CKD 3	Moderate, favours palopegteriparatide. Assuming all patients started in CKD 1/2 increased the ICER to \$█ ⁴ /QALY gained.

Source: Compiled during evaluation.

CKD = chronic kidney disease, CT = conventional therapy, HR = hazard rate, ICER = incremental cost effectiveness ratio, PPT = palopegteriparatide, QALY = quality adjusted life years.

The redacted values correspond to the following ranges:

¹ \$75,000 to < \$95,000

² \$155,000 to < \$255,000

³ \$115,000 to < \$135,000

⁴ \$95,000 to < \$115,000

6.73 The results of the stepped economic evaluation are presented in

6.74 Table 15: Results of the stepped economic evaluation

	Costs (\$)			Health outcomes			ICER
	PPT	CT	Increment	PPT	CT	Increment	
Step 1A: Trial setting PaTHway, Time horizon: 26 weeks Outcome: response Cost: treatment only	\$█	\$214	\$█	0.787 response	0.048 response	0.739	█ ¹ per responder
Step 1B: Trial setting PaTHway, Time horizon: 26 weeks Outcome: eGFR Cost: treatment only	\$█	\$214	\$█	7.9 mL/min/1.73m ²	-1.9 mL/min/1.73m ²	9.8 mL/min/1.73m ²	█ ² per 1 mL/min/1.73 m ² improvement in eGFR.
Step 2. Translation of outcomes to QALY Cost: treatment only	\$█	\$214	\$█	0.427 QALYs	0.401 QALYs	0.025 QALYs	█ ³ per QALY
Step 3: Extrapolate data to lifetime horizon (51 years) Cost: treatment only	\$█	\$5,508	\$█	12.027 QALYs	10.058 QALYs	1.969 QALYs	█ ⁴ per QALY
Step 4: Lifetime horizon Costs: all costs	\$█	\$92,247	\$█	12.027 QALYs	10.058 QALYs	1.969 QALYs	█ ⁵ per QALY
With anniversary price reductions removed	\$█	\$92,247	\$█	12.027 QALYs	10.058 QALYs	1.969 QALYs	█ ⁶ per QALY

Public Summary Document - March 2025 PBAC Meeting

Source: Table 109 of the submission.

CT = conventional therapy, PPT = palopegteriparatide, eGFR = estimated glomerular filtration rate, ICER = incremental cost effectiveness ratio; QALY = quality adjusted life years.

The redacted values correspond to the following ranges:

¹ \$15,000 to < \$25,000

² \$0 to < \$5,000

³ \$455,000 to < \$555,000

⁴ \$95,000 to < \$115,000

⁵ \$75,000 to < \$95,000

6.75 ⁶ \$95,000 to < \$115,000. The base case results were based on the proposed effective price of palopegteriparatide.

Table 15: Results of the stepped economic evaluation

	Costs (\$)			Health outcomes			ICER
	PPT	CT	Increment	PPT	CT	Increment	
Step 1A: Trial setting PaTHway, Time horizon: 26 weeks Outcome: response Cost: treatment only	\$█	\$214	\$█	0.787 response	0.048 response	0.739	█ ¹ per responder
Step 1B: Trial setting PaTHway, Time horizon: 26 weeks Outcome: eGFR Cost: treatment only	\$█	\$214	\$█	7.9 mL/min/ 1.73m ²	-1.9 mL/min/ 1.73m ²	9.8 mL/min/ 1.73m ²	█ ² per 1 mL/min/ 1.73 m ² improvement in eGFR.
Step 2. Translation of outcomes to QALY Cost: treatment only	\$█	\$214	\$█	0.427 QALYs	0.401 QALYs	0.025 QALYs	█ ³ per QALY
Step 3: Extrapolate data to lifetime horizon (51 years) Cost: treatment only	\$█	\$5,508	\$█	12.027 QALYs	10.058 QALYs	1.969 QALYs	█ ⁴ per QALY
Step 4: Lifetime horizon Costs: all costs	\$█	\$92,247	\$█	12.027 QALYs	10.058 QALYs	1.969 QALYs	█ ⁵ per QALY
With anniversary price reductions removed	\$█	\$92,247	\$█	12.027 QALYs	10.058 QALYs	1.969 QALYs	█ ⁶ per QALY

Public Summary Document - March 2025 PBAC Meeting

Source: Table 109 of the submission.

CT = conventional therapy, PPT = palopegeteriparatide, eGFR = estimated glomerular filtration rate, ICER = incremental cost effectiveness ratio; QALY = quality adjusted life years.

The redacted values correspond to the following ranges:

¹ \$15,000 to < \$25,000

² \$0 to < \$5,000

³ \$455,000 to < \$555,000

⁴ \$95,000 to < \$115,000

⁵ \$75,000 to < \$95,000

⁶ \$95,000 to < \$115,000

6.76 The results of key univariate sensitivity analyses are summarised in Table 16. During the evaluation additional univariate and multivariate analyses were conducted. Multivariate sensitivity analyses assumed shorter time horizon (20 years), excluded anniversary price reductions and removed the treatment specific utility increment/decrement after Cycle 2.

Table 16: Sensitivity analyses

Analyses	Incremental cost (\$)	Incremental QALY	ICER
Base case		1.969	¹
Model structure			
Discount rate (base case % costs and outcomes)			
• % costs and outcomes		2.452	¹
• % costs and outcomes		4.572	²
Time horizon (base case 51 years)			
• 30 years		1.784	³
• 20 years		1.371	⁴
• 10 years ^a		0.791	⁵
PPT pricing (base case: anniversary price cuts included)			
• Anniversary price cuts excluded		1.969	³
Baseline CKD health state distribution (base case: 73.2% CKD 1/2; 26.8% CKD 3)			
• 100% CKD 1/2		1.700	³
Cycle 1: CKD 3 to CKD 1/2 transitions (base case: PaTHway, 61%)			
• No patients transition from CKD 3 to CKD 1/2 in Cycle 1 ^b (0%)		1.558	⁴
Long-term: CKD 1/2 to CKD 3 transitions (base case: Rejnmark 2022)			
• Rejnmark 2022 for CT, no modelled benefit of PPT (i.e. HR = 1) ^c		1.462	⁴
Long-term: CKD 3 to CKD 4 and CKD 4 to CKD 5 transitions (base case: Gosmanova 2021)			
• Gosmanova 2021 (b) for CT, no modelled benefit of PPT (i.e. HR = 1) ^d		1.850	³
HPT-related utilities (base case: On PPT: 0.075; On CT: -0.043)			
• Halved (On PPT: 0.038; On CT: -0.022)		1.480	⁴
• Doubled (On PPT: 0.150; On CT: -0.086)		2.948	²
• Removing utility increment after Cycle 2 for PPT (On PPT: 0; On CT: -0.043) ^e		1.342	⁴
• Removing utility decrement after Cycle 2 for CT (On PPT: 0.075; On CT: 0) ^f		1.665	³
• Removing utility increment/decrement after Cycle 2 for PPT and CT (On PPT: 0; On CT: 0) ^g		1.038	⁵
Multivariate analysis conducted during evaluation			
• Time horizon of 20 years and excluding anniversary price cuts ^h		1.371	⁴
• Time horizon of 20 years, excluding anniversary price cuts and removing utility increment/decrement after Cycle 2 for PPT and CT (On PPT: 0; On CT: 0) ⁱ		0.530	⁶

Analyses	Incremental cost (\$)	Incremental QALY	ICER
Multivariate analysis conducted during ESC			
<ul style="list-style-type: none"> Time horizon of 30 years, excluding anniversary price cuts and halving the HPT-related utility increment/decrement from Cycle 2 for PPT and CT (On PPT:0.038; On CT: -0.022)ⁱ 		1.310	7

Source: Table 113, p183; Table 114, p184; Table 115, pp184-185; Table 116, p185; Table 117, p186 of the submission.

CKD = chronic kidney disease, CT = conventional therapy, HPT = hypoparathyroidism, HR = hazard rate, ICER = incremental cost-effectiveness ratio, PPT = palopegteriparatide; QALY = quality-adjusted life year.

^a to estimate the ICER the value in worksheet 'Model inputs', in cell C10 was changed to 10.

^b to estimate the ICER the values in worksheet 'Model inputs', in cell C110 was changed to 73.2%, and in Cell D110 to 26.8%.

^c to estimate the ICER the value in worksheet 'Model inputs', in cell D127 was changed to 1.

^d to estimate the ICER the value in worksheet 'Model inputs', in cell C132 was changed to 1.

^e to estimate the ICER, the base case model utility values in cycle 2 were hardcoded in Trace_PPT worksheets in rows: AC15:AL15 and in Model inputs worksheet the value in worksheet 'Model inputs' in cell E203 was replaced equal zero (original value 0.075).

^f to estimate the ICER, the base case model utility values in cycle 2 were hardcoded in Trace_CT worksheets in rows: AG15:AL15 and in Model inputs worksheet the value in worksheet 'Model inputs' cell E204 was replaced equal zero (original value -0.043).

^g to estimate the ICER the action described in notes ^f and ^g were combined.

^h to estimate the ICER the value in worksheet 'Model inputs', in cell C10 was changed to 20, and values in Cells D62 to F62 were set to 0.

ⁱ to estimate the ICER the action described in notes ^g and ^h were combined.

The redacted values correspond to the following ranges:

¹ \$75,000 to < \$95,000

² \$55,000 to < \$75,000

³ \$95,000 to < \$115,000

⁴ \$115,000 to < \$135,000

⁵ \$155,000 to < \$255,000

⁶ \$255,000 to < \$355,000

⁷ \$135,000 to < \$155,000

6.77 The results from the sensitivity analyses demonstrated that the ICER was sensitive to variations in:

- the time horizon. A 10-year time horizon increased the ICER to \$155,000 to < \$255,000 QALY/gained. The ESC noted that the mean age of PaTHway patients was 48.6 years, the ESC considered that a 30-year time horizon may be more reasonable.
- varying utility increment for palopegteriparatide and decrement for conventional therapy. These utilities are applied to every cycle from Cycle 2 until the end of treatment. The ESC noted that, although a utility benefit for the treatment arm might be warranted due to independence from calcium and vitamin D treatment, the effect size was uncertain due to the unsupported claim of non-inferior safety, small patient numbers informing the analysis and the use of a generic health-related quality of life instrument for a multifaceted disease.
- transition probabilities for CKD health states. The ICER was highly sensitive to the transition probabilities for CKD 1/2 to CKD 3 transitions from Cycle 2. The ESC considered that the distribution of patients in the health states was highly uncertain.
- patient distribution at baseline across CKD 1/2 and CKD 3. The more patients with CKD 1/ 2 receiving treatment with palopegteriparatide, the higher the ICER.

6.78 The ESC considered that the application of the trial-based utility increment/decrement for the entire model time horizon, in combination with the uncertainty surrounding the estimated incidence/prevalence of CKD, meant that the base case ICER was optimistic and highly uncertain.

Palopegteriparatide cost/patient/year

Table 17: Drug cost per patient for proposed and comparator drugs

	Palopegteriparatide			Conventional therapy		
	Trial dose and duration	Model	Financial estimates	Trial dose and duration	Model	Financial estimates
Mean dose / day	21.4 mg	22.92 ^a mg	0.47 doses per week	Calcium: 1,8479 mg Calcitriol: 0.612 mcg	Calcium: 1,750 mg ^e Calcitriol: 0.50 mcg ^e	Calcium: 2,400 mg ^f Calcitriol: 1.00 mcg ^f
Days of treatment	34 ^b	30.08 ^a days per pack	30.08 days per script	Ongoing daily	Ongoing daily	Ongoing daily
Packs per cycle (26 weeks)	5.37 ^b	6.07	12.10 ^d scripts per year	Calcium: 9.37 Calcitriol: 4.51	Calcium: 8.88 Calcitriol: 3.65	Calcium: 6.01 Calcitriol: 3.64
Cost per pack	\$■■■■ (DPMQ)	\$■■■■ (DPMQ)	\$■■■■ (DPMQ)	Calcium: \$11.99 (60 * 600 mg tablets) Calcitriol: \$29.58 (100 * 0.25 mcg capsules)	Calcium: \$11.99 (60 * 600 mg tablets) Calcitriol: \$29.58 (100 * 0.25 mcg capsules)	Calcium: \$19.03 (item 4082W) (120 * 600 mg tablets), Calcitriol: \$45.71 (13457G) (200 * 0.25 mcg capsules)
Cost/patient/cycle	\$■■■■ ^c	\$■■■■ ^c	-	Calcium: \$112.37 Calcitriol: \$133.54 Total: \$245.90	Calcium: \$106.44 Calcitriol: \$108.04 Total: \$214.48	Calcium: \$114.37 Calcitriol: \$166.38 Total: \$281.83
Cost/patient/year (chronic)	\$■■■■	\$■■■■	\$■■■■ ^c	\$492	\$429	\$564

Source: Compiled during the evaluation.

DPMQ = dispensed price for maximum quantity.

^a normal distribution estimated on the mean dose (21.4 mg/day) in PaTHway to estimate the dose distribution in the model.

^b Individual patient data on dose distribution not presented by the submission, days of treatment calculated using the mean dose/day, rounded up to the next daily dose (24mcg).

^c based on compliance rate of 96.4% (PaTHway trial), applied when estimating cost per cycle.

^d based on 364 days (52 weeks * 7 days)

^e median dose at Week 26 in PaTHway.

^f the submission assumed 4 tablets per day of calcitriol and vitamin D.

6.79 The average cost of treatment of palopegteriparatide per patient per year was estimated by the economic model to be \$■■■■ (= \$■■■■ (cost per cycle) x 2) based on the dispensed price of \$■■■■ per pack and compliance rate of 96.4%. The cost of conventional therapy per patient per year was estimated to be \$429.

Estimated PBS usage & financial implications

6.80 This submission was considered by the DUSC.

6.81 The submission used an epidemiological approach to estimate utilisation. Details of the key inputs for the financial estimates are presented in Table 18.

Table 18: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Prevalent patients: Adults with chronic HPT	Prevalence of 37.2 per 100,000 population based on DUSC data on calcitriol utilisation.	The DUSC considered the prevalence rate was at the higher end of the average pooled global estimate and higher than real-world examples provided in submission. Average pooled global data suggested an incidence of 25-37 per 100,000 population.
Proportion of patients who are inadequately controlled as per the proposed PBS criteria	34.52% based on a survey conducted by the submission of 69 Australian endocrinologists.	-
Uptake rate	█% in Year 1, increasing to █% in Year 6, based on a survey of 69 Australian endocrinologists.	The DUSC considered that this was uncertain. The DUSC considered that the uptake rates in early years may be overestimated.
Number of patients responding to treatment with PPT after 26 weeks	Based on the response rate of treatment (78.69%) from PaTHway.	The DUSC considered that this was uncertain, and likely overestimated. The DUSC considered that the real-world population would be broader than the trial population and the response rate was likely to be lower.
Discontinuation rate	Assumed 5% discontinuation rate after first 26 weeks (1 cycle, that applied a stopping rule based on response to treatment).	The DUSC considered that this was reasonable but uncertain, noting that a discontinuation rate of 3.6% was observed in the PaTHway trial.

Source: Compiled during the evaluation.

DUSC = Drug Utilisation Sub Committee, HPT = hypoparathyroidism, PBS = Pharmaceutical Benefits Scheme.

A summary of the estimated use and financial implications is presented in

Table 19.

Table 19: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients on palopegteriparatide	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of scripts dispensed ^a	█ ²	█ ²	█ ²	█ ³	█ ³	█ ³
Estimated financial implications of palopegteriparatide						
Cost to PBS/RPBS less copayments	█ ⁴	█ ⁵	█ ⁶	█ ⁶	█ ⁶	█ ⁷
Estimated financial implications for conventional therapy						
Cost to PBS/RPBS less copayments	█ ⁸	█ ⁸	█ ⁸	█ ⁸	█ ⁸	█ ⁸
Net financial implications						
Net cost to PBS/RPBS	█ ⁴	█ ⁵	█ ⁶	█ ⁶	█ ⁶	█ ⁶

Source: Table 139, p202 of the submission.

PBS = Pharmaceutical Benefits Scheme, RPBS = Repatriation Pharmaceutical Benefits Scheme.

^a Estimation based on 7 scripts (in first 6 months of first year of treatment) for initiating patients on palopegteriparatide, and 4.79 scripts (in second 6 months in the first year of treatment) for responding initiating patients and 11.67 scripts per year for continuing patients in following years.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 20,000 to < 30,000

³ 30,000 to < 40,000

⁴ \$40 million to < \$50 million

⁵ \$50 million to < \$60 million

⁶ \$60 million to < \$70 million

⁷ \$70 million to < \$80 million

⁸ net cost saving

- 6.82 Based on the effective price of palopegteriparatide the cost to the PBS/RPBS of listing palopegteriparatide was estimated to be \$60 million to < \$70 million in Year 6, with a total of \$300 million to < \$400 million over the first 6 years of listing.
- 6.83 The DUSC noted that the estimate of prevalent patients (37.2 per 100,000 population), which was based on PBS calcitriol usage, was higher than international comparisons, with average pooled global data suggesting a prevalence of 25-37 per 100,000 population. The DUSC considered the inclusion of the streamlined authority code for the use of calcitriol for hypocalcaemia in estimating the prevalent population was not appropriate, as it was specific for patients with hypocalcaemia due to renal disease, not HPT. The DUSC noted that a reanalysis of patient numbers between 2018 and 2023 for the PBS listing of calcitriol which only used the streamlined authority codes for HPT and excluded the code for hypocalcaemia resulted in a lower average prevalence of HPT of 30.1/100,000.
- 6.84 The DUSC noted that the uptake rate was based on the high clinical need in this population and based on a survey of Australian endocrinologists (n=69) conducted by the submission. The clinicians reported on the proportion of inadequately controlled patients receiving conventional therapy that they would commence treatment with palopegteriparatide. The average estimate was █% (IQR: █% to █%). Based on these data the submission estimated an uptake of █% in Year 1, increasing to █% in Years 5 and 6. The DUSC considered that initial uptake will most likely be

lower than assumed in the submission. This may be due to reluctance for patients to start a daily injection, initial lack of experience and potentially slow adoption of the drug amongst endocrinologists, and the likelihood that many patients may not be reviewed by an endocrinologist more often than every 6 to 12 months.

Quality Use of Medicines

- 6.85 The submission did not include any information under the quality use of medicines. The TGA Delegate noted uncertainties around the long-term safety and efficacy of palopegteriparatide and recommended post-market submission of trial data and a post-market pharmacovigilance plan (p64, palopegteriparatide, TGA Delegate's Overview, November 2024).

Financial Management – Risk Sharing Arrangements

- 6.86 The submission stated that the sponsor is willing to enter a risk-sharing arrangement related to any uncertainties that require mitigation.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC did not recommend palopegteriparatide for the treatment of patients with chronic hypoparathyroidism (HPT) who are inadequately controlled on conventional therapy (i.e. active vitamin D and calcium supplements). The PBAC considered that palopegteriparatide was superior compared to the nominated comparator of conventional therapy in terms of efficacy and likely comparable in terms of safety. However, the PBAC considered that the economic model presented in the submission was highly uncertain and may not be suitable for decision making, given its reliance on chronic kidney disease (CKD) outcomes and, at the price proposed in the submission, that palopegteriparatide was not cost-effective. The PBAC considered that the estimated utilisation was likely overestimated and considered that a risk sharing arrangement (RSA) would be required to mitigate the risk of usage in the first line setting.
- 7.2 The primary reason for this outcome was due to the economic evaluation.
- 7.3 The PBAC noted the consumer input which was in support of the submission. The PBAC noted the debilitating symptoms of HPT, and the burden associated with conventional therapy. The PBAC noted that palopegteriparatide was likely to improve HPT control and reduce complications in patients who are inadequately controlled on calcium and vitamin D supplements.
- 7.4 The PBAC considered that the proposed place in therapy, as a second-line treatment for patients who are inadequately controlled on conventional therapy, was reasonable. The PBAC considered that the nomination of conventional therapy, consisting of active vitamin D and calcium supplements, as the comparator was appropriate.

- 7.5 In terms of the proposed restrictions, the PBAC considered that the Authority Required (telephone/online) listing was reasonable. The PBAC advised that the following amendments to the proposed restrictions should be considered:
- The restriction should align with the PaTHway trial and exclude patients with an eGFR of less than or equal to 30 mL/min/1.73 m²;
 - The initial and first continuing restrictions should require treatment by an endocrinologist, or a specialist experienced in the treatment of HPT;
 - The restriction should be age agnostic; and
 - The subsequent continuing treatment restriction should include the response criteria currently described in the first continuing treatment restriction.
- 7.6 The PBAC noted that the primary efficacy and safety evidence presented in the submission was from the PaTHway trial, a randomised controlled trial that compared palopegteriparatide to conventional therapy (N = 84) over 26 weeks, followed by an open-label extension study. Additional long term follow-up safety data was presented from the PaTH Forward trial (N = 59).
- 7.7 The PBAC noted that response was represented by a multi-component outcome which was defined as albumin-adjusted serum calcium in the normal range (2.07-2.64 mmol/L), independence from active vitamin D, independence from therapeutic doses of elemental calcium (< 600 mg/day) and no increase in study drug. The PBAC noted that the dose titration algorithm in the PaTHway trial meant that patients in the comparator arm who had normal serum calcium levels received dose reductions to their conventional therapy, while their dose of placebo was unchanged or increased. Whilst noting that this was not representative of standard management, the PBAC accepted that the dose protocol was required to maintain the double-blind aspect of the trial.
- 7.8 The PBAC noted that, at the end of the 26-week blinded period of the PaTHway trial, significantly more patients in the palopegteriparatide (78.7%) arm met the multicomponent primary outcome compared to patients in the conventional therapy arm (4.8%) in the intention to treat (ITT) population. The PBAC noted that the outcome was maintained with palopegteriparatide in the open-label extension study (see Table 4). The results from the *post hoc* subgroup analysis of patients who better matched the proposed PBS criteria were similar to the ITT population at Week 26.
- 7.9 The PBAC noted that the pill burden was significantly reduced for patients in the palopegteriparatide arm (mean number of daily pills reduced from 6.7 to 0.45 from baseline to Week 26). For patients in the conventional therapy arm, the mean daily pill burden reduced from 6.7 at baseline to 5.4 at Week 26. The PBAC also noted that the mean calcium dose, mean active vitamin D dose and mean serum calcium were significantly reduced in the palopegteriparatide arm compared to the conventional therapy arm at Week 26 (see Table 5). Further, the PBAC noted that palopegteriparatide was associated with improvements in health-related quality of

life scores (see Table 6).

- 7.10 The PBAC noted that a *post hoc* analysis demonstrated that palopegteriparatide was associated with a statistically significant improvement in estimated glomerular filtration rate (eGFR) compared to conventional therapy after 26 weeks (see Table 7). The PBAC noted that the improvement was maintained in the open-label extension study, in which all patients received palopegteriparatide. The results from the *post hoc* subgroup analysis of patients who better matched the proposed PBS criteria were similar to the ITT population at Week 26.
- 7.11 The PBAC considered that palopegteriparatide was superior compared to standard of care in terms of effectiveness; however, noted that the magnitude of the benefit was uncertain as the trial population was small, the surrogate trial outcomes were not directly related to morbidity or mortality and the dose titration algorithm for the conventional therapy arm was not representative of standard clinical management.
- 7.12 In terms of safety, the PBAC noted that palopegteriparatide was associated with injection site reactions but considered that these were transient in nature. Overall, the PBAC considered that palopegteriparatide was likely comparable to standard of care in term of safety.
- 7.13 The PBAC noted that the submission presented a cost utility analysis model which assumed that palopegteriparatide had superior effectiveness in kidney function compared to conventional therapy. The PBAC noted that, although palopegteriparatide was associated with improved eGFR, this claim was uncertain given the small sample size of the PaTHway trial, the *post-hoc* nature of the analysis and as comparative data were only available for 26 weeks (Cycle 1), with literature-based inputs, which were not representative of the Australian clinical context, applied from Cycle 2. The PBAC noted that the model structure relied on the assumption that HPT symptoms and the side effects of conventional therapy were captured by the CKD stage-related health states. The PBAC, noting that that the prevalence of CKD varied considerably in patients with HPT (see paragraph 6.56), considered that the relationship between CKD and HPT was uncertain.
- 7.14 The PBAC considered that the time horizon of 51 years applied in the model was long compared to the 26 weeks of comparative evidence from the PaTHway trial. The PBAC noted that that the modelled effectiveness of palopegteriparatide was perpetuated over this period, biasing the results in favour palopegteriparatide.
- 7.15 The PBAC also considered that the application of treatment specific utility increments and decrements from Cycle 2 was inappropriate. The PBAC noted that the application of the utility increment resulted in patients in the palopegteriparatide arm with CKD Stages 1/2 having a higher utility that the general population (see paragraph 6.65), likely overestimating the benefits in the palopegteriparatide arm.
- 7.16 The PBAC noted that the submission inappropriately included anniversary price reductions in the base case incremental cost effectiveness ratio (ICER). The PBAC

noted that the base case ICER, when the anniversary price reductions were removed, was \$95,000 to < \$115,000 per quality adjusted life year (QALY).

- 7.17 The PBAC considered that a more reasonable base case would apply a time horizon of 30 years and halve the utility increment/decrement from Cycle 2 in both the palopegteriparatide and conventional therapy arms. Noting the uncertainties associated with the reliance on CKD outcomes, the derivation and application of utilities, and the lack of comparative data to inform the inputs, the PBAC considered that palopegteriparatide would be cost effective at an ICER of \$45,000 to < \$55,000/QALY (with anniversary price reductions removed). The PBAC advised that all other model inputs should remain the same.
- 7.18 The PBAC considered that the methods used to derive the utilisation and financial estimates was mostly reasonable. However, the PBAC considered that overall, the utilisation was overestimated as:
- The prevalence rate applied of 37.2 per 100,000 was likely overestimated. The PBAC considered that the DUSC estimate of prevalence of 30.1 per 100,000 population was more reasonable (see paragraph 6.83);
 - The uptake rate applied, which assumed an uptake of █████% in Year 1, increasing to █████% in Years 5 and 6 was high. The PBAC considered that more reasonable estimates would be uptake of █████% in Year 1, increasing to █████% in Year 6 due to the likelihood that many patients may not be reviewed by an endocrinologists more often than every 6 to 12 months (see paragraph 6.84).
- 7.19 The PBAC considered that an RSA, with a rebate of █████% for use above the expenditure caps would be required to mitigate the risk of usage in the first line HPT population who are adequately controlled on conventional therapy.
- 7.20 The PBAC considered the outstanding issues could be easily resolved in a simple resubmission for palopegteriparatide using the early re-entry pathway. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation.
- A revised restriction that incorporates the changes suggested in paragraph 7.5;
 - A price reduction for palopegteriparatide that results in an ICER of no more than \$45,000 to < \$55,000/QALY, as per paragraph 7.17;
 - Revised utilisation and financial impact estimates that incorporate the revised price of palopegteriparatide and the changes suggested in paragraph 7.18; and
 - An RSA, as per paragraph 7.19.

The early re-entry resubmission must be lodged by Week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early re-entry timing is not acceptable, a standard re-entry pathway is available.

7.21 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

Specialised Therapeutics is committed to working with the PBAC to ensure timely access to palopegteriparatide for patients with HPT in Australia.