20 November 2023
EMA/OD/0000140073
EMADOC-1700519818-1182486
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Yorvipath (palopegteriparatide)
Treatment of hypoparathyroidism
EU/3/20/2350

Sponsor: Ascendis Pharma Bone Diseases A/S

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted

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1. Product and administrative information

Product	
Designated active substance(s) (CAS name)	Poly(oxy-1,2-ethanediyl), alpha-hydro-omega-methoxy, ether with N-[[[2-[[6-[[1-[3-[[3-(2,3-dihydroxypropoxy)propyl]amino]-3-oxopropyl]-2,5-dioxo-3-pyrrolidinyl]thio]hexyl]amino]ethyl]amino]carbonyl]-2-methylalanyl-teriparatide (2:1)
Other name(s)	TransCon PTH
International Non-Proprietary Name	Palopegteriparatide
Tradename	Yorvipath
Orphan condition	Treatment of hypoparathyroidism
Sponsor's details:	Ascendis Pharma Bone Diseases A/S Tuborg Boulevard 12 2900 Hellerup Hovedstaden Denmark
Orphan medicinal product designation procedural history	
Sponsor/applicant	Ascendis Pharma Bone Diseases A/S
COMP opinion	10 September 2020
EC decision	19 October 2020
EC registration number	EU/3/20/2350
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Martina Weise / Maria Concepcion Prieto Yerro
Applicant	Ascendis Pharma Bone Diseases A/S
Application submission	12 November 2022
Procedure start	1 December 2022
Procedure number	EMEA/H/C/005934
Invented name	Yorvipath
Proposed therapeutic indication	Yorvipath is a parathyroid hormone (PTH) replacement therapy indicated for the treatment of adults with chronic hypoparathyroidism. Further information can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Yorvipath
CHMP opinion	14 September 2023
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Vallo Tillmann / Joao Rocha
Sponsor's report submission	10 May 2023
COMP discussion	5-7 September 2023
COMP opinion	5 October 2023

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2020 designation was based on the following grounds:

"Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing poly(oxy-1,2-ethanediyl), alpha-hydro-omega-methoxy, ether with N-[[[2-[[6-[[1-[3-[[3-(2,3-dihydroxypropoxy)propyl]amino]-3-oxopropyl]-2,5-dioxo-3-pyrrolidinyl]thio]hexyl]amino]ethyl]amino]carbonyl]-2-methylalanyl-teriparatide (2:1) was considered justified based on clinical data in patients with the condition which showed sustained normalisation of calcium and phosphate serum levels;
- the condition is chronically debilitating due to neuromuscular symptoms, cognitive impairment, abnormal calcium and phosphate metabolism, and reduced bone turnover. The condition may be life-threatening due to risk of hypocalcaemia that may lead to seizures, cardiac arrhythmias, cardiomyopathy and laryngeal spasm if untreated;
- the condition was estimated to be affecting approximately 3.2 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing poly(oxy-1,2-ethanediyl), alpha-hydro-omega-methoxy, ether with N-[[[2-[[6-[[1-[3-[[3-(2,3-dihydroxypropoxy)propyl]amino]-3-oxopropyl]-2,5-dioxo-3-pyrrolidinyl]thio]hexyl]amino]ethyl]amino]carbonyl]-2-methylalanyl-teriparatide (2:1) will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate a reduction or elimination of standard of care involving the use of vitamin D supplementation. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled."

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Hypoparathyroidism is an endocrine disorder characterised by hypocalcaemia due to deficient parathyroid hormone (PTH) and is typically associated with hyperphosphataemia, hypercalciuria, and reduced concentrations of 1,25-dihydroxyvitamin D. Clinical features of the disease include symptoms of hypocalcaemia, such as perioral numbness, paresthaesias, and carpal/pedal muscle spasms. Laryngeal spasm, tetany, and seizures are serious and potentially life-threatening complications of the condition (Cusano et al., 2012).

Acquired hypoparathyroidism is most commonly the result of inadvertent removal or irreversible damage to the parathyroid glands, usually to their blood supply, during thyroidectomy, parathyroidectomy, or radical neck dissection. Definitions of permanent postsurgical hypoparathyroidism vary, but the definition is generally accepted to be insufficient PTH to maintain normocalcaemia 6 months after surgery (Shoback, 2008). Autoimmune destruction of the parathyroid glands, and rarely, congenital syndromes of parathyroid dysgenesis such as DiGeorge syndrome, can also be causes of hypoparathyroidism. The diagnosis of hypoparathyroidism is readily made by the concurrence of hypocalcaemia and markedly reduced or absent PTH levels (Cusano et al., 2012).

The COMP continues to designate hypoparathyroidism as an orphan condition.

The approved therapeutic indication "Yorvipath is a parathyroid hormone (PTH) replacement therapy indicated for the treatment of adults with chronic hypoparathyroidism" falls within the scope of the designated orphan condition "treatment of hypoparathyroidism".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by CHMP's positive benefit/risk assessment, see EPAR.

Chronically debilitating and/or life-threatening nature

Most clinical symptoms of the disease are due to hypocalcaemia and include weakness, fatigue, muscle cramps, abnormal sensations such as tingling, burning and numbness (paraesthesia) of the hands, excessive nervousness, anxiety, loss of memory, mood swings, hoarseness, wheezing and dyspnoea, headaches and uncontrollable cramping muscle movements of the wrists and feet, and hypomagnesaemia, hypokalaemia, and alkalosis (e.g., hyperventilation), which worsen signs and symptoms of hypocalcaemia.

Chronic hypocalcaemia, as observed in primary hypoparathyroidism, is also associated with ocular cataracts, abnormal dentition, and dry, puffy, coarse skin. Prolongation of the QT interval may be observed in severe cases on electrocardiogram (ECG), and congestive heart failure (reversed with correction of the hypocalcaemia) may occur.

Laryngeal spasm, tetany, and seizures are serious and potentially life-threatening complications of hypoparathyroidism (Cusano et al., 2012). Since the available treatment with calcium supplements, often in high doses, and active vitamin D analogues does not replace PTH, it may itself result in severe adverse health outcomes. A two-fold to 17-fold increased risk of chronic kidney disease stage 3 with renal calcifications in 31% of patients has been reported for post-surgical hypoparathyroidism (Underbjerg et al., 2013). Risks of ischaemic heart disease and of cataract are increased in non-surgical hypoparathyroidism, but not among patients with post-surgical hypoparathyroidism (Underbjerg et al., 2013).

The COMP concluded that hypoparathyroidism continues to be a chronically debilitating and life-threatening condition.

Number of people affected or at risk

The prevalence estimate is based on a literature search conducted by the sponsor. MEDLINE (PubMed), EMBASE (Scopus), and the Cochrane Central trials register were used to identify literature by applying the following search criteria: hypoparathyroidism; DiGeorge syndrome; hypocalcaemia and incidence; prevalence; epidemiology or statistics and numerical data. A total of 398 studies published were flagged for review. All population-based European prevalence studies were collected as well as studies from the US due to similar demographics and the potential for large population cohorts. A single recent study (Swartling 2022) met these criteria for inclusion, in addition to the seven identified in the original submission in 2020.

The two US Studies were included in the study overview table as examples only of studies returned in the literature search with similar demographics and the potential for large population cohorts.

The single UK study (Vadiveloo 2018) was removed for the purpose of calculating the prevalence of the condition.

Below is the overview of prevalence from different sources of included and excluded studies (Table 1).

Table 1. Overview of hypoparathyroidism prevalence from different sources

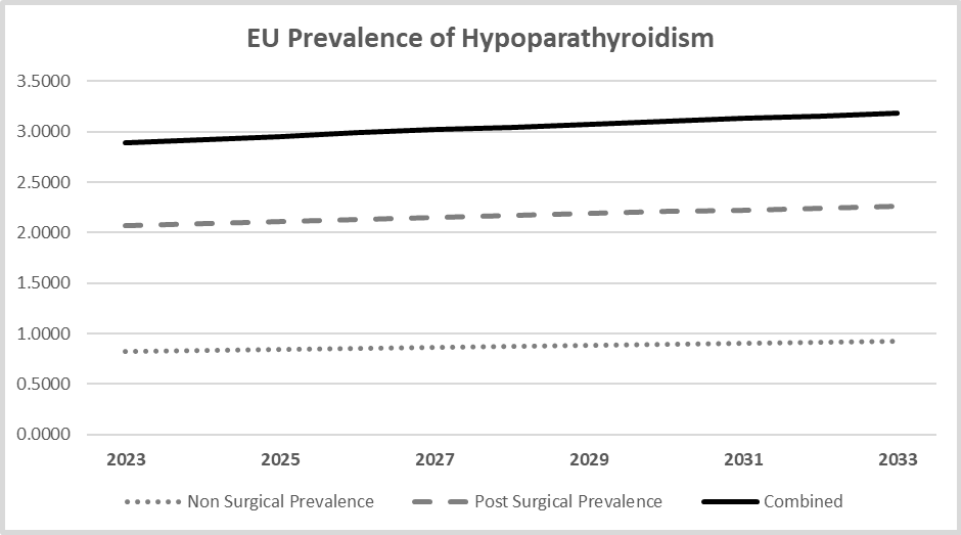
Source	Country	EU	Total Cases* (per 10K pop)	Non-surgical Cases* (per 10K pop)	Post-surgical Cases* (per 10K pop)	Identified via ICD9 codes	Identified via treatment patterns
Included Studies							
Swartling 2022	Sweden	✓	2.16	0.61	1.55	✓	✓
Cianferotti 2018	Italy	✓	3.17	1.04	2.13	✓	✓
Underbjerg 2013	Denmark	✓	*n/s*	*n/s*	2.51	✓	✓
Excluded Studies *(Outside of EU Region)*							
Vadiveloo 2018*	UK		3.51	1.50	2.01		✓
Powers 2013	USA		2.92	0.97	1.95	✓	
Clarke 2011 (Abstract Only)	USA		4.28	0.99	3.29	✓	
Excluded Studies *(Incomplete Patient Identification)*							
Astor 2016	Norway	✓	1.39	0.45	0.94	✓	
Underbjerg 2015	Denmark	✓	*n/s*	0.37	*n/s*	✓	✓

*Prevalence estimates reported in the literature were standardised to 2023 using the trend over time data available in Vadiveloo 2018. Vadiveloo 2018 provided the trend for both non-surgical and post-surgical rates between 1988 and 2015.

With the UK-based study removed from the analysis, this results in a slightly lower overall prevalence estimate of 2.9/10,000 in 2023.

With the removal of the Vadiveloo study, the updated prevalence estimate for non-surgical hypoparathyroidism in the EU was 0.83/10,000 (95% CI: 0.40-1.3 per 10,000) and the updated prevalence estimate for post-surgical hypoparathyroidism in the EU was 2.1/10,000 (95% CI: 1.5-2.7 per 10,000). These estimates are still in line with the non-surgical and post-surgical estimates provided at the time of designation.

Figure 1. Expected EU hypoparathyroidism prevalence over time, overall and by subtype



Taking the estimates from the most robust studies available in addition to trends over time, it is apparent that the combined EU prevalence of hypoparathyroidism currently (year 2023) approximates 2.9/10,000 (95% CI: 1.9-3.9 per 10,000) and can be expected to rise to 3.2/10,000 (95% CI: 2.1-4.2 per 10,000) by the year 2033 (Figure 1). These prevalence estimates are slightly lower than the estimate provided in the orphan maintenance report due to removal of the UK based paper that had a higher non-surgical estimate.

The COMP accepted the prevalence estimate of 2.9 in 10,000 for the purpose of review for the Maintenance of the Orphan Designation and recommended maintaining the orphan designation.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The main treatments for individuals with hypoparathyroidism are calcium supplements and active vitamin D.

There are also two products which are authorised for use in Europe.

Table 2.

Tradename(s)	INN	Member State(s) Where Authorised	Authorization Holder	Authorised Indication
Natpar	Parathyroid hormone	EU	Shire Pharmaceuticals Ireland Ltd	Adjunctive treatment of adult patients with chronic hypoparathyroidism who cannot be adequately controlled with standard therapy alone.
Forsteo	Teriparatide	EU	Eli Lilly Nederland B.V.	Treatment of osteoporosis

The main supplemental form of vitamin D used for individuals with hypoparathyroidism is calcitriol or alfacalcidol (also referred to as active vitamin D), that appears specifically authorized for the condition in some EU countries. Another form of vitamin D that may be used is ergocalciferol or cholecalciferol. Long-term therapy with calcium supplements and with vitamin D and its analogues and metabolites (like calcitriol) carries a risk of serious side effects including calcium deposits accumulating in the kidneys (nephrocalcinosis), the development of kidney stones and, ultimately, improper function of the kidneys if blood tests are not carefully monitored.

Some individuals with severe hypoparathyroidism that do have a high urinary calcium level may be treated with thiazide diuretics.

There are clinical guidelines in Europe: Clinical Practice Guideline for chronic hypoparathyroidism which has published in 2015 (Bollerslev J et al European Journal of Endocrinology (2015) 173, G1-G20). Recently a new publication has been released at the international level: Evaluation and Management of Hypoparathyroidism Summary Statement and Guidelines from the Second International Workshop. Journal of Bone and Mineral Research, Vol. 37, No. 12, December 2022, pp 2568–2585. Please see Table 3.

Table 3. Conventional therapy for hypoparathyroidism

Medication	Dose	Comments/half-life
Calcium carbonate or calcium citrate	Ranges from 500–3000 mg three times daily preferably with meals to enhance phosphate binding effects	Calcium citrate preferred in presence of Proton Pump Inhibitor (PPI) use
Vitamin D3 (cholecalciferol)	1000 IU/day to 100,000 IU/day based on 25-hydroxy vitamin D level	4–6 hours plasma half-life
Vitamin D2 (ergocalciferol)	50,000 IU weekly to daily based on 25-hydroxyvitamin D levels	4–6 hours plasma half-life
Calcitriol	0.25–3 µg /day total dose administered in divided doses	5–8 hours plasma half-life
Alfacalcidol	0.5–6 µg/day	3–6 hours plasma half-life
Thiazide diuretics	25–100 mg/day	6–12 hours plasma half-life

Conventional therapy consists of oral calcium and active vitamin D. In patients with low PTH levels following total thyroidectomy (<10 pg/mL (1.05 pmol/L)), medical therapy is advised with 2–3 g of elemental calcium daily and 0.5–1.5 µg calcitriol/day. Approximately 70%–80% of individuals with postoperative parathyroid failure will recover within a month following thyroidectomy, and medical therapy can be gradually withdrawn with close monitoring. Cholecalciferol or ergocalciferol is also often required to maintain the 25-hydroxyvitamin D level within the normal range. Recommendations for management are derived from case series, consensus statements, guidelines, and standards of care.

Thiazide diuretics can be utilized to lower urine calcium losses as they enhance distal tubular renal calcium reabsorption when paired with low salt intake.

Natpar is indicated as adjunctive treatment of adult patients with chronic hypoparathyroidism who cannot be adequately controlled with standard therapy alone. NatPar is not considered a satisfactory method as it does not cover the same broad patient population as Yorvipath.

Standard of care consists of oral calcium and active vitamin D, the therapeutic indications are wide enough to cover the same target patient population as the one indicated for Yorvipath, therefore, they are considered satisfactory treatments and need to be addressed in the significant benefit section below.

Significant benefit

The therapeutic indication is: Yorvipath is a parathyroid hormone (PTH) replacement therapy indicated for the treatment of adults with chronic hypoparathyroidism.

The sponsor did not request a question on significant benefit at the time of protocol assistance.

The sponsor claims that their product offers significant benefit over the current standard of care for adult patients with hypoparathyroidism. Data from the Phase II (TCP-201) and Phase III study (TCP-304) have been used to support this claim.

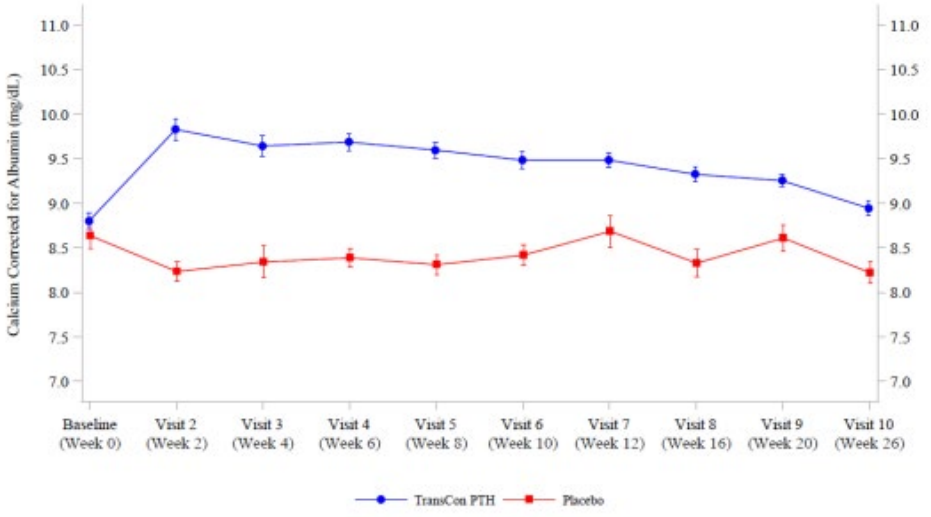
The pivotal TCP-304 clinical trial was designed to assess the efficacy and safety of palopegteriparatide as PTH replacement therapy for adults with hypoparathyroidism. The 26-week double-blind, placebo-controlled period of the clinical trial included subjects randomised (3:1) to palopegteriparatide at a starting dose of 18 µg/day or placebo, co-administered with conventional therapy. Randomisation was stratified by aetiology of hypoparathyroidism, i.e., postsurgical vs all other causes. 82 subjects received at least one dose of study drug. Study drug and conventional therapy were subsequently titrated according to a dosing algorithm guided by albumin-adjusted serum calcium levels. All pre-specified primary and secondary endpoint analyses were performed at Week 26. After Week 26, all subjects who completed the 26-week blinded phase were eligible to continue in the open label extension (OLE) and receive palopegteriparatide for 156 weeks. The double-blind (DB) period in the TCP-304 trial was completed as of the data cut-off date for this trial of 12 January 2022; the OLE period in the TCP-304 trial is ongoing.

The ongoing TCP-201 trial randomised 59 adults with hypoparathyroidism in a 1:1:1:1 ratio to receive either once-daily palopegteriparatide (15, 18 or 21 µg/day) or placebo for a 4-week blinded period. Participants then entered an OLE period for a total of 214 weeks, during which palopegteriparatide and conventional therapy were titrated according to a dosing algorithm. The DB period in the TCP-201 trial has been completed and the OLE period is ongoing with 84 of 214 planned weeks completed and 58 of 59 subjects are ongoing as of the data cut-off date of 24 September 2021.

Summary of relevant efficacy results:

Palopegteriparatide was effective at maintaining normocalcaemia while permitting independence from conventional therapy. In the pivotal Phase 3 TCP-304 trial, 78.7% (48/61) of the subjects in the palopegteriparatide (treatment) arm met the composite primary endpoint (achieving serum calcium levels within the normal range (2.07-2.64 mmol/L or 8.3 – 10.6 mg/dL), independence from therapeutic levels of calcium (≤ 600 mg/day), receiving no standing active vitamin D, and no increase in prescribed study drug within 4 weeks prior to the Week 26 visit), compared to 4.8% (1/21) of subjects in the placebo arm (p-value for difference between arms = < 0.0001).
From baseline, mean albumin-adjusted serum calcium increased and remained within the normal range for palopegteriparatide-treated subjects (Figure 2).

Figure 2. Mean (+/-SE) Albumin-Adjusted Serum Calcium (mg/dL) by Visit (Study TCP-304)

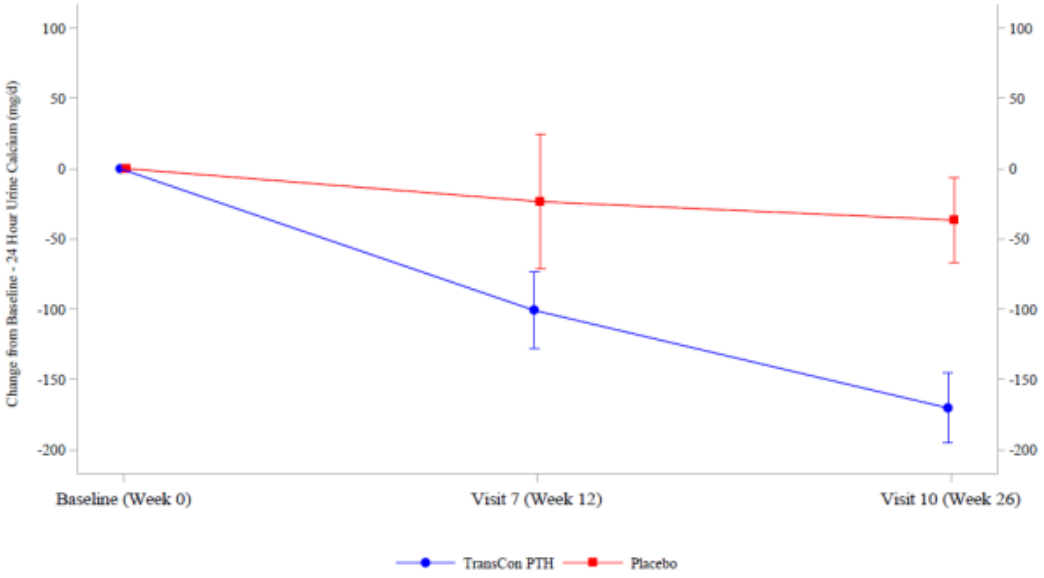


Normalises Mineral Ion Handling in the Renal Tubules

Palopegteriparatide treated subjects in TCP-304 had a significant decrease in the mean 24-h urine calcium excretion into the normal range, from 390 mg/24 h at baseline to 220 mg/24 h at Week 26 (Figure 5), compared to the placebo arm, decreasing from 329 mg/24 h to 292 mg/24 h. Despite a higher mean serum calcium at Week 26, there was a significant decrease in 24-h urine calcium from baseline for the treatment arm compared to the control arm (p-value = 0.0085).

A significantly greater proportion of subjects treated with palopegteriparatide achieved normal 24-h urine calcium excretion at Week 26 than those receiving placebo: 60.7% (37/61) vs. 28.6% (6/21) (p-value = 0.0213) (Figure 3). For the purposes of this study, normal urine calcium was defined as ≤ 250 mg/day.

Figure 3. Mean (+/- SE) Change from Baseline 24-Hour Urine Calcium (mg/day) (Study TCP-304)



Improves Health-Related Quality of Life

In TCP-304, the 5 key secondary endpoints concerning QoL were tested sequentially to control the overall significance level at 0.05. Hypoparathyroidism experience scale (HPES) measures are disease specific patient reported outcomes that were developed and validated to assess the relevant patient perspective. The SF-36 survey is a general measure of patient reported outcome. Statistically significant improvement in all key secondary endpoints for QoL was achieved in the treatment arm: HPES-Symptom - Physical domain score (p-value = 0.0038); HPES-Symptom - Cognitive domain score (p-value = 0.0055); HPES-Impact - Physical Functioning domain score (p-value = 0.0046); HPES-Impact - Daily Life domain score (p-value = 0.0061); and SF-36 - Physical Functioning subscale score (p-value = 0.0347) CHMP; However, based on the comparison to a potentially suboptimal SOC treatment in the Placebo arm, results on PROs and a comparison of rates of ADRs related to hypocalcaemia should not be mentioned in section 5.1 of the SmPC.

The COMP considered that the QoL data was interesting although not essential in establishing significant benefit but could be considered supportive. Concerns with regards to the optimal dose of SOC in the placebo arm also limits the reliability of these data (see EPAR for detailed discussion).

The sponsor has provided Phase III data from study TCP-304 which confirms the clinically relevant advantage of using their product in combination with standard of care versus placebo and standard of care (Calcitriol ≥0.5 µg/day or alfacalcidol ≥1.0 µg/day (active form of vitamin D) and Elemental calcium ≥800 mg/day).

The results of the primary efficacy analysis of the main study TCP-304 demonstrate a statistically compelling and clinically relevant effect of Yorvipath in patients with HP. The primary composite endpoint was consistently favourable for Yorvipath across the primary and all sensitivity analysis and in subgroup analyses. In addition, the results from a series of secondary endpoints support patient benefit. Supportive efficacy data come from the dose-finding study TCP-201. The efficacy results can therefore be considered robust.

By normalising the serum calcium and urinary calcium, complications associated with abnormal levels of calcium are reduced or stopped. Complications associated with calcaemic abnormalities are chronic kidney disease (CKD), skeletal mineralisation complications, cardiovascular complications (hypocalcemia can lead to electrocardiographic abnormalities, cardiomyopathy and congestive heart failure), cataracts, basal ganglia calcifications, neuropsychiatric complications and infections.

The COMP accepted this data to support the basis of significant benefit at the time of review for the maintenance of the orphan designation.

4. COMP list of issues

NA

5. COMP position adopted on 5 October 2023

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of hypoparathyroidism (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 2.9 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to neuromuscular symptoms, cognitive impairment, abnormal calcium and phosphate metabolism, and reduced bone turnover. The condition may be life-threatening due to risk of hypocalcaemia that may lead to seizures, cardiac arrhythmias, cardiomyopathy and laryngeal spasm if untreated;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union for all the patients covered by Yorvipath, the assumption that Yorvipath may be of potential significant benefit to those affected by the orphan condition still holds. In the clinical trials Yorvipath was shown to be effective in clinically relevant endpoints and was also able to do so without the need for adjunctive administration of calcium and activated vitamin D. The COMP considered this to be a clinically relevant advantage.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Yorvipath, Poly(oxy-1,2-ethanediyl), alpha-hydro-omega-methoxy, ether with N-[[[2-[[6-[[1-[3-[[3-(2,3-dihydroxypropoxy)propyl]amino]-3-oxopropyl]-2,5-dioxo-3-pyrrolidinyl]thio]hexyl]amino]ethyl]amino]carbonyl]-2-methylalanyl-teriparatide (2:1); palopegteriparatide for treatment of hypoparathyroidism (EU/3/20/2350) is not removed from the Community Register of Orphan Medicinal Products.