EU RISK MANAGEMENT PLAN FOR YORVIPATH (PALOPEGTERIPARATIDE)

RMP Version to Be Assessed as Part of This Application:

RMP Version Number:	0.4
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Rationale for Submitting an Updated RMP:	Not applicable due to this is an initial marketing authorisation application submission
Summary of Significant Changes in This RMP:	Not applicable
Other RMP Versions Under Evaluation:	Not applicable
Details of the Currently Approved RMP:	Not applicable
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TABLE OF CONTENTS

PART I: PRODUCT(S) OVERVIEW

Table Part I.1 – Product(s) Overview

Active Substance(s) (INN or common name)	Palopegteriparatide
Pharmacotherapeutic Group(s) (ATC Code)	Pharmacotherapeutic group: Calcium homeostasis, parathyroid hormones and analogues ATC code: H05AA (Subject to final ATC code)
Marketing Authorisation Holder	Ascendis Pharma Bone Diseases A/S
Medicinal Products to which this RMP refers	One
Invented Name(s) in the European Economic Area (EEA)	Yorvipath
Marketing Authorisation Procedure	Centrally authorised
Brief Description of the Product	Chemical class: Peptide
	Summary of mode of action Palopegteriparatide is a prodrug, consisting of PTH(1-34) transiently conjugated to a methoxypolyethylene glycol (mPEG) carrier via a proprietary TransCon Linker. At physiological conditions, parathyroid hormone (PTH) is released from palopegteriparatide in a sustained manner to maintain a continuous systemic exposure to PTH. Endogenous PTH maintains extracellular calcium and phosphate homeostasis by increasing serum calcium and decreasing serum phosphate. These effects are mediated by stimulating bone turnover to mobilise calcium and phosphate from bone, by promoting renal calcium reabsorption and phosphate excretion and by facilitating synthesis of active vitamin D, in turn increasing intestinal absorption of calcium and phosphate. Similar to endogenous PTH, PTH released from palopegteriparatide exerts these effects through its main receptor, PTH1R, which is highly expressed on osteoblasts, osteocytes, and tubular cells of the kidney, and in several other tissues, including the intestinal tract, heart, and central nervous system.
	Important information about its composition Yorvipath consists of PTH(1-34) transiently conjugated to an inert carrier via a TransCon Linker. The carrier is a branched 40 kDa (2×20 kDa) mPEG moiety.
Hyperlink to the Product Information	European Summary of Product Characteristics (EU SmPC)
Indication(s) in the EEA	**Current:** Yorvipath is a PTH replacement therapy indicated for the treatment of adults with chronic hypoparathyroidism
	Proposed: Not applicable.

Dosage in the EEA	Current: Dose recommendations of Yorvipath refer to micrograms of PTH(1-34). The dose should be individualised based on serum calcium. The optimal dose after titration is the minimum dose required to prevent hypocalcaemia. Generally, this is the dose that maintains serum calcium within the normal range without the need for active forms of vitamin D or calcium supplementation beyond recommended nutritional supplementation for the general population (generally less than 600 mg per day). Doses of active forms of vitamin D and calcium supplements will need to be adjusted when using Yorvipath. Patients receiving the maximum Yorvipath dose of 60 mcg per day who experience ongoing hypocalcaemia may require co-administration of therapeutic calcium and/or active forms of vitamin D. The recommended starting dose is 18 mcg once daily. The dose can be adjusted in 3 mcg increments thereafter. The dose range is 6 to 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. Optionally, calcium supplementation sufficient to meet daily dietary requirements may be continued. Measure serum calcium and 25(OH) vitamin D as per standard of care once a maintenance dose is achieved.
	Proposed: Not applicable.
Pharmaceutical Form(s) and Strengths	Current: Solution for injection. Yorvipath 168 mcg/0.56 mL solution for injection in pre-filled pen Each prefilled pen contains palopegteriparatide equivalent to 168 mcg of PTH(1-34) in 0.56 mL of solvent*. The concentration based on PTH(1-34) is 0.3 mg/mL. Yorvipath 294 mcg/0.98 mL solution for injection in pre-filled pen Each prefilled pen contains palopegteriparatide equivalent to 294 mcg of PTH(1-34) in 0.98 mL of solvent*. The concentration based on PTH(1-34) is 0.3 mg/mL. Yorvipath 420 mcg/1.4 mL solution for injection in pre-filled pen Each prefilled pen contains palopegteriparatide equivalent to 420 mcg of PTH(1-34) in 1.4 mL of solvent*. The concentration based on PTH(1-34) is 0.3 mg/mL. *The strength indicates the quantity of the PTH(1-34) moiety without consideration of the mPEG-linker.
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Indication

Yorvipath is a PTH replacement therapy indicated for the treatment of adults with chronic hypoparathyroidism.

Incidence and Prevalence

Hypoparathyroidism is a rare endocrine disease of PTH insufficiency resulting in abnormal calcium and phosphate homeostasis, neuromuscular symptoms, and impaired quality of life.

Several different causes for chronic hypoparathyroidism exist. In adults, the most common cause, up to 75% of cases, is as a complication after anterior neck surgery, where an estimated 0.12 to 4.6% of such surgeries are associated with inadvertent removal or injury to the parathyroid glands (Brandi 2016, Clarke 2016). Of these, up to 30% result in chronic (versus transient) hypoparathyroidism, defined as features of hypoparathyroidism lasting more than 6 months after the surgery (Mannstadt 2013, Brandi 2016, Shoback 2016). Other causes of chronic hypoparathyroidism include genetic, autoimmune, or infiltrative disease (e.g., hemochromatosis, thalassemia). Some cases without clearly defined aetiology are deemed idiopathic (Brandi 2016, Clarke 2016). The prevalence of hypoparathyroidism in the United States (US) is estimated to range from 60,000 to 115,000, thus qualifying as an orphan disease (Brandi 2016).

In the European Union (EU), the best prevalence estimate (2020) for non-surgical hypoparathyroidism is 1.2/10,000 and for postsurgical hypoparathyroidism 2.1/10,000. Combining these numbers yields a total EU prevalence of hypoparathyroidism of 3.2/10,000 (95% CI: 2.4 to 4.1 per 10,000; addition discrepancy due to rounding) which can be expected to rise to 3.5/10,000 (95% CI: 2.7 to 4.2 per 10,000) by the year 2030 (Astor 2016, Cianferotti 2019, Clarke 2011, Powers 2013, Underbjerg 2013, Underbjerg 2015, Vadiveloo 2018).

Demographics of the Population in the Proposed Indication – Age, Gender, Racial and/or Ethnic Origin and Risk Factors for the Disease

Females are twice as likely to develop primary hypoparathyroidism than males. Hypoparathyroidism can develop at any age, but in females in the United Kingdom it is most often diagnosed between the ages of 50 and 60 (National Institute for Health and Care Excellence, www.nice.org.uk).

Main Existing Treatment Options

Conventional therapy of hypoparathyroidism includes calcium and oral active vitamin D (calcitriol or its analogue alfacalcidol) as the endogenous production of calcitriol is insufficient in the context of PTH deficiency. While conventional therapy can be successful at prevention of certain short-term neuromuscular symptoms, it comes at the cost of iatrogenic long-term co-morbidities and is thus considered a therapeutic compromise. Conventional therapy increases the filtered load of calcium in the kidneys and has been reported to be associated with more than a 4-fold risk of nephrolithiasis, nephrocalcinosis, and chronic kidney disease (Mannstadt 2017). Conventional therapy likewise fails to restore normal rates of bone turnover; and has failed to alleviate the burdens of diminished quality of life (Mitchell 2012, Bilezikian 2011). Although conventional therapy can improve hypocalcaemia, it does not reduce the elevated serum phosphate characteristic of hypoparathyroidism. Consequent increases in the serum calcium ×

phosphate product predispose to ectopic calcifications in the renal parenchyma, eye, central nervous system (particularly the basal ganglia) and vasculature (Abate 2017).

Recombinant human PTH(1-84) was approved as an adjunct to oral active vitamin D and calcium by the Food and Drug Administration (FDA) in the US (Natpara®) in 2015 and in the EU in 2017 (Natpar®). It was subsequently recalled in the US in September 2019 due to incidences of rubber particulate formation. In the pivotal trial, approximately 53% of subjects taking Natpar were able to reduce conventional therapy by 50% while maintaining serum calcium levels at 7.5 to 10.6 mg/dL (Natpar EPAR 2017), thereby partially reducing pill burden; other clinically important changes were not observed. Additionally, Natpar did not reduce the incidence of adverse events (AEs) attributed to hypo- or hypercalcaemia, and neither normalised nor significantly reduced urinary excretion of calcium (Mannstadt 2013). Of relevance, the marketing authorisation holder of Natpar/Natpara recently announced that manufacturing of this medicinal product will be globally discontinued at the end of 2024 due to unresolved supply issues (Takeda Statement 2022).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

As PTH is required for renal 1α-hydroxylation of calcidiol to calcitriol (1,25-dihydroxyvitamin D, or active vitamin D), PTH deficiency results in downstream deficiency of calcitriol. Under normal conditions, PTH and calcitriol act on bone, kidney and the intestines to control serum calcium and phosphate homeostasis.

This two-hormone deficiency results in a serious disease associated with a significant burden of morbidity and mortality and a substantial impact on daily functioning. It is characterised by neuromuscular symptoms, impaired quality of life, and the potential for life threatening complications including seizures and laryngospasm. Insufficient production of PTH leads to reduced bone turnover with a consequent accumulation of unremodelled, hypermineralised bone reflected in increased bone mass and density. Low PTH levels impair renal reabsorption of calcium while decreasing phosphate excretion. Intestinal absorption of calcium and phosphate are both impaired in the setting of insufficient PTH (Brandi 2016, Clarke 2016, Shoback 2008, Mannstadt 2013). Cognitive and behavioural deficits such as an inability to concentrate, dubbed “brain fog”, are common complaints (Mannstadt 2017). Significantly greater incidences of both epilepsy and cataracts have also been reported (Vadiveloo 2018).

Perhaps most significantly, available data indicate a markedly increased risk of mortality in this disease, with a greater than twofold increase in the risk of death seen in post-thyroidectomy patients complicated by chronic hypoparathyroidism than in post-thyroidectomy patients with preserved parathyroid function (Almquist 2018).

Important Co-Morbidities

NPS Pharma conducted a quantitative burden of illness study in hypoparathyroidism patients in conjunction with the Hypoparathyroidism Association and the Mayo Clinic, in which 374 patients with hypoparathyroidism were surveyed (Hadker 2014). Overall, 69.3% of respondents reported experiencing comorbidities since the time of diagnosis. The comorbidities included: heart arrhythmias (66%), kidney stones (35.5%), elevated bone mineral density ([BMD], 22%), decreased BMD (20%), seizures/convulsions/fits (18%), and bone fractures (16%) (Hadker 2014).

Clarke (2011) also compared the prevalent comorbid conditions among 54 hypoparathyroidism cases to 108 controls. The cases were limited to those still residing locally in 2009, and comorbid conditions were identified from 2006 through 2008, using the Rochester (Minnesota) Epidemiology Project data resources. The authors found that although hypoparathyroidism is relatively rare, patients with this disorder have a substantial burden of comorbidities compared to controls. A few of these comorbidities include neoplasms, endocrine/nutritional/metabolic /immune disorders, congenital anomalies, infectious/parasitic diseases, and diseases of the respiratory system, genitourinary system, and skin/subcutaneous (SC) tissue.

Mitchell (2012) studied 120 hypoparathyroidism patients who were seen at a Boston tertiary care hospital system between 1988 and 2009. The mean age at the end of the observation period was 52±19 years, the cohort was 73% female, and the mean duration of hypoparathyroidism was 17±16 years; the mean length of follow-up was 7.4±5.1 years. Rates of chronic kidney disease stage 3 or higher were 2- to 17-fold greater than age-appropriate norms. The authors concluded that their analysis showed a high rate of complications in patients with hypoparathyroidism, even though serum calcium levels were within the targeted range 88% of the time. These complications included symptomatic episodes of both hypocalcaemia and hypercalcaemia and significant rates of renal calcification and impairment.

Underbjerg (2013) evaluated patients with postsurgical hypoparathyroidism to evaluate their risks of renal complications and cardiovascular disease in relation to their disease and its treatment. The prevalence of postsurgical hypoparathyroidism was 22/100,000. The average age at diagnosis was 49 years (range 17 to 87 years), and 88% were women. Sixteen percent of all patients had neck surgery prior to the operation causing hypoparathyroidism. Compared with controls, patients with hypoparathyroidism had an increased risk of renal complications (Hazard Ratio [HR] 3.67); 95% confidence interval [CI] 2.41 to 5.59) and hospitalisation due to seizures (HR 3.82; 95% CI, 2.15 to 6.79), whereas there was no increased risk of cardiac arrhythmias (HR 1.11; 95% CI, 0.79 to 1.57), or cardiovascular disease or death (HR 0.89; CI, 0.73 to 1.09).

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

The prodrug, palopegteriparatide, as well as products generated after auto-cleavage (i.e., PTH(1-34) and the TransCon Linker attached to mPEG) and the main metabolite PTH(1-33) were assessed in the non-clinical development programme, which included a range of in silico, in vitro and in vivo studies in the selected non-clinical species (Sprague Dawley rats, cynomolgus monkeys of Mauritian origin and New Zealand White rabbits).

Toxicity

- **Acute and Repeat-Dose Toxicity Studies**

Palopegteriparatide was administered SC daily in repeat-dose toxicity studies for up to 26 weeks at dose levels of 2, 5, 10 and 20 µg PTH(1-34)/kg in rats and 0.2, 0.5 and 1.5/1.0[1] µg PTH(1-34)/kg in monkeys. The no observed adverse effect level (NOAEL) for SC daily administrations of palopegteriparatide for up to 26 weeks was 10 µg PTH(1-34)/kg in rats and 0.5 µg PTH(1-34)/kg in monkeys.

No off-target effects were observed in the non-clinical studies, and adverse findings related to palopegteriparatide were solely related to the expected, albeit exaggerated, pharmacological effects of continuous exposure to supraphysiological levels of PTH in animals. Consistent with PTH's mode of action, hypercalcaemia was observed in rats and, in a dose-dependent manner, resulting in premature death/euthanasia, clinical signs, body weight loss and adverse soft tissue mineralisation, mainly in the kidneys. Dose-dependent hypercalcaemia was also observed in

[1] 1 5 µg were reduced to 1.0 µg PTH (1-34)/kg on Day 25/26 as a preventive measure.

monkeys and may have contributed to the death of one monkey but did not result in soft tissue mineralisation. In rats only, adverse findings were observed in the growth plate (dysplasia and increased thickness). As PTH1R is present in the growth plate and plays an essential role in long bone growth (Iwamoto 1994, Chen 2008, Qiu 2015), these findings were also considered exaggerated pharmacological effects and were reversible. An adverse finding of degenerative joint disease was observed in one female monkey receiving 1.5/1.0 µg PTH(1-34)/kg and although a relation to palopegteriparatide could not be excluded, this finding was considered incidental.

Considering the intended use of palopegteriparatide, maintaining circulating PTH within the physiological range in patients with hypoparathyroidism, the adverse and exaggerated pharmacological effects in the non-clinical studies were not considered of relevance to hypoparathyroid patients treated with therapeutic doses of palopegteriparatide.

- **Reproductive/Developmental Toxicity**

The conducted developmental and reproductive toxicity (DART) studies identified adverse maternal effects at the highest dose levels (30 µg PTH(1-34)/kg/day in rats and 6 µg PTH(1-34)/kg/day in rabbits). The maternal effects were related to exaggerated pharmacology of palopegteriparatide, similar to those observed in the repeat-dose toxicity studies. No palopegteriparatide-related adverse effects on fertility, early embryonic development or embryo-foetal development were observed. In addition, an in silico assessment of the TransCon Linker identified no structural alerts for DART. In alignment with advice received from health authorities, a pre- and postnatal development study has not been conducted prior to submission of the marketing authorisation application.

- **Genotoxicity**

No genotoxicity risk has been identified for palopegteriparatide or its components in the standard genotoxicity battery. Furthermore, no structural alerts were identified for genotoxic potential in the in silico assessment of the TransCon Linker.

- **Carcinogenicity**

A carcinogenicity weight of evidence assessment supported that palopegteriparatide, PTH(1-34) and the TransCon Linker attached to mPEG will not pose a carcinogenic risk.

Based upon the occurrence of osteosarcomas in non-clinical carcinogenicity studies in rats, the market authorisation holders of the short-lived PTH analogues have an obligation to conduct postauthorisation studies to evaluate the occurrence of osteosarcomas (Forsteo EPAR 2005, Natpar EPAR 2017). There is no evidence, however, that osteosarcoma is induced by PTH in any other species and osteosarcomas have not been observed as a consequence of long-term exposure to supraphysiological levels of PTH, as occurs e.g., in chronic hyperparathyroidism (Jimenez 2005, Cinamon 2006). Likewise, osteoporotic patients treated with Forsteo for up to 2 years do not have an increased incidence of osteosarcoma (Andrews 2012, Cipriani 2012, Nishikawa 2016, Gilsenan 2018, Gilsenan 2021a, Gilsenan 2021b, Kellier-Steele 2022, Forteo Patient Registry 2022).

All effects of palopegteriparatide in bone in the non-clinical studies were considered to result from exaggerated pharmacological effects of continuous exposure to supraphysiological levels of PTH.

The Phase 2 and 3 clinical trials (TCP-201, TCP-304) with palopegteriparatide demonstrated no net anabolic effect, but rather an initial phase of increased bone turnover with the balance between bone resorption and formation favouring resorption. After this initial phase, biochemical markers of bone turnover trended downwards towards the age- and sex-matched norms. In accordance, BMD mean Z-scores decreased towards age- and sex-expected norms consistent with reversal of the hypermineralised and hypermature bone state characteristic of chronic hypoparathyroidism. Thus, in addition to PTH(1-34) alone not posing a risk of osteosarcomas in humans, palopegteriparatide providing physiological PTH levels and normalising bone turnover, provides further reassurance against a higher risk of osteosarcoma beyond that expected in the general population.

In general, long-term (chronic) use of PEGylated proteins containing high molecular weight PEG in animals and humans has, to date, not indicated any safety concerns (Webster 2007, Ivens 2015, Stidl 2018, Zhu 2021) and PEG is neither mutagenic nor carcinogenic (Webster 2007, Palombo 2014). Hence, the mPEG carrier in palopegteriparatide is not considered to pose a risk of carcinogenicity.

Furthermore, no structural alerts for potential carcinogenicity were identified in the in silico assessment of the TransCon Linker. In addition, toxicokinetic evaluations in rats and monkeys indicated that the linker molecule, as intended, remained attached to the mPEG-carrier following auto-cleavage of palopegteriparatide. Therefore, the carcinogenicity assessment of mPEG is considered to support the conclusion that the TransCon Linker is not considered to pose a risk of carcinogenicity.

Accordingly, and in alignment with advice received from Committee for Medicinal Products for Human Use and FDA (US), a rodent carcinogenicity study with palopegteriparatide was not conducted.

Safety Pharmacology

Palopegteriparatide did not induce adverse functional effects on the central nervous, respiratory and cardiovascular systems in rats and cynomolgus monkeys in the core battery of safety pharmacology studies (ICH S7A). Also, there were no adverse effects on cardiovascular function after repeat dosing for up to 26 weeks in monkeys. Furthermore, no structural alerts were identified for cardiotoxic potential in the in silico assessment of the TransCon Linker.

Due to the size of palopegteriparatide (47.4 kDa) and the highly targeted nature of PTH(1-34), in vitro evaluation of inhibition of the rapidly activating delayed rectifier potassium current (I_{Kr}) was not deemed relevant. Large molecules generally have limited intracellular penetration and hence are not expected to reach the binding site in the channel protein encoded by the human ether-a-go-go-related gene (hERG) (Vargas 2008). In addition, palopegteriparatide is considered a highly targeted molecule as PTH has been reported to bind only to PTH specific receptors (Murray 2005).

- **Other Toxicity- Related Information or Data**

A comprehensive in silico analysis (quantitative structure-activity relationship [QSAR]) concluded that the TransCon Linker was negative (ICH M7 Class 5) for potential bacterial mutagenicity and negative for potential genotoxic and nongenotoxic carcinogenicity, geno-, hepato-, renal-, cardiotoxicity, DART and systemic toxicity including phototoxicity.

Summary of Non-Clinical Data

No off-target effects were observed in the non-clinical development programme. No effects related to palopegteriparatide were observed on local tolerance, genotoxicity or DART. Adverse findings related to palopegteriparatide, observed at high dose levels in repeat-dose toxicity studies and in maternal animals in DART studies, were considered exaggerated pharmacological effects expected with continuous exposure to supraphysiological levels of PTH in animals. Considering the intended use of Yorvipath, designed and demonstrated to maintain the circulating PTH levels within the physiological range, the adverse findings associated with persistent supraphysiological PTH levels were not considered clinically relevant hypoparathyroid patients treated with therapeutic doses of palopegteriparatide.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Five clinical trials have been conducted as part of the palopegteriparatide clinical development programme: three Phase 1 trials in healthy adults (CT-103 [TransCon PTH-Phase 1 single ascending dose and multiple ascending dose], TCP-104 [included renally-impaired {RI} subjects without hypoparathyroidism, referred to as "healthy subjects with RI" for conciseness], and TCP-105 [Phase 1 Ethnobridging Trial]), one Phase 2 trial (TCP-201, PaTH Forward), and one Phase 3 trial (TCP-304, PaTHway). The double-blind portions of TCP-201 and TCP-304 have both been completed; the open-label extension (OLE) periods of both trials, planned for up to 210 weeks (4 years) for TCP-201 and 156 weeks (3 years) for TCP-304, are ongoing.

Table SIII.1 Duration of Exposure to Palopegteriparatide

Duration of Exposure	Subjects
>0 and <26 weeks	207
≥26 and <52 weeks	60
≥52 and <84 weeks	6
≥84 weeks	52
Total	**325**

Table SIII.2: Cumulative Subject Exposure to Palopegteriparatide in the Development Programme (Age Group and Sex)

Age group	Subjects	
	Male	**Female**
<18	0	0
≥18 to <65	133	163
≥65	11	18
Total	**144**	**181**

Table SIII.3: Cumulative Subject Exposure to Palopegteriparatide from Ongoing and Completed Clinical Trials by Race

Ethnic/Race Origin	Subjects
Asian	38
Black	7
Caucasian	271
Other	6
Multiple	2
Unknown	1
Total	**325**

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Trials Within the Development Programme

Exclusion Criterion	Reason for Exclusion	Missing information?	Rationale
Pregnant or lactating women	Ethical consideration in order to protect these subjects.	Yes	
Paediatric subjects	Ethical consideration in order to protect these subjects. Need to first establish safety in adults before considering clinical development with paediatric subjects.	No	Indication population is limited to adults
Impaired responsiveness to PTH (pseudohypoparathyroidism) which is characterised as PTH-resistance, with elevated PTH levels in the setting of hypocalcaemia	Pseudohypoparathyroidism is a different disease state and treatment with PTH will not be successful in this disease.	No	Language in current SmPC states the indication of palopegteriparatide is for hypoparathyroidism, not pseudohypoparathyroidism.
Any disease that might affect calcium metabolism or calcium-phosphate homeostasis or PTH levels other than hypoparathyroidism.	To avoid confounding the assessment of the efficacy of palopegteriparatide.	No	The use of the product for other diseases that affect calcium or PTH levels other than hypoparathyroidism can be predicted to result in hypercalcaemia or hypocalcaemia. Hypercalcaemia is a risk in the safety profile of the drug. The safety profile of the drug and hypocalcaemia is part of the underlying disease state.
High risk thyroid cancer within 2 years, requiring suppression of TSH <0.2 mIU/L	Hyperthyroidism / suppressed TSH can result in bone loss and would confound assessment of bone related endpoints.	No	Use in this population is not predicted to be associated with additional risks of clinical significance.
Use of loop diuretics, phosphate binders (other than calcium supplements), digoxin, lithium, methotrexate, biotin >30 µg/day, or systemic corticosteroids (other than as replacement therapy)	Loop diuretics can exert independent effects on serum calcium with the potential in causing safety AEs of hypocalcaemia and interfere with effects of treatment with palopegteriparatide.	No	The use of the product with loop diuretics can be predicted to result in hypocalcaemia.
Use of thiazide diuretic within 4 weeks prior to the 24-hour urine collection scheduled to occur within 1 week prior to Visit 1	Thiazide diuretics can exert independent effects on serum calcium with the potential in causing safety AEs of hypercalcaemia and interfere with effects of treatment with palopegteriparatide.	No	The use of the product with thiazide diuretics can be predicted to result in hypercalcaemia. Hypercalcaemia is a risk in the safety profile of the drug.

Exclusion Criterion	Reason for Exclusion	Missing information?	Rationale
Use of PTH-like drugs (commercially available or through participation in an investigational trial), including PTH(1-84), PTH(1-34), or other N-terminal fragments or analogues of PTH or PTH-related protein, within 4 weeks prior to screening	To avoid confounding the assessment of the efficacy of palopegteriparatide.	No	The use of the product with other PTH-like products can be predicted to result in hypercalcaemia. Hypercalcaemia is a risk in the safety profile of the drug.
Use of osteoporosis therapies known to influence calcium and bone metabolism, i.e., bisphosphonate (oral or intravenous), denosumab, raloxifene, or romosozumab therapies within 2 years prior to screening	To avoid confounding the assessment of the efficacy of palopegteriparatide and bone related endpoints.	No	SmPC contains language addressing use of osteoporosis therapies known to influence calcium metabolism.
Non-hypocalcaemic seizure disorder with a history of a seizure within 26 weeks prior to screening	To avoid confounding the assessment of the safety of palopegteriparatide with symptoms from unrelated disorders.	No	Seizures are a potential consequence of hypocalcaemia which is part of the disease state.
Increased risk for osteosarcoma, such as those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, hereditary disorders predisposing to osteosarcoma, or with a prior history of substantial external beam or implant radiation therapy involving the skeleton	Short-lived PTH analogues approved for human use are contraindicated in patients at increased risk of osteosarcoma (section 4.3 Natpar SmPC).	No	A carcinogenicity weight of evidence assessment supported that palopegteriparatide, PTH(1-34), and the TransCon Linker attached to mPEG will not pose a carcinogenic risk (Part II: Module SII – Non-Clinical Part of the Safety Specification). Patients at increased risk of osteosarcoma are listed under warnings/precautions in the SmPC.
Disease processes that adversely affect gastrointestinal absorption, including but not limited to short bowel syndrome, significant small bowel resection, gastric bypass, tropical sprue, active celiac disease, active ulcerative colitis, active Crohn's disease, gastroparesis and autoimmune regulator gene mutations with malabsorption	To avoid confounding the assessment of the safety and efficacy of palopegteriparatide with symptoms from unrelated disorders.	No	Gastrointestinal diseases that result in malabsorption independently contribute to potential for hypocalcaemia.
Chronic or severe cardiac disease within 26 weeks prior to screening including but not limited to congestive heart failure, myocardial infarction, severe or uncontrolled arrhythmias, bradycardia (resting heart rate <48 beats/minute,	To avoid confounding the assessment of the safety and palopegteriparatide with symptoms from unrelated disorders.	No	Yorvipath helps control hypoparathyroidism by exerting the same physiological effects as the native hormone and reduce the need for supplements. Serum PTH and serum calcium levels are maintained

Exclusion Criterion	Reason for Exclusion	Missing information?	Rationale
unless chronic and asymptomatic), symptomatic hypotension or systolic BP <80 mm Hg or diastolic <40 mm Hg, or poorly controlled hypertension (systolic BP >165 mm Hg or diastolic >95 mm Hg). In the absence of a prior history of hypertension, an isolated BP >165/95 in the setting of white coat hypertension/anxiety may not be exclusionary and a measurement can be repeated prior to randomization.			within the normal range, which is anticipated to be beneficial to patients with severe and chronic cardiovascular disease.
Cerebrovascular accident within 5 years prior to Screening	To avoid confounding the assessment of the safety and palopegteriparatide with symptoms from unrelated disorders.	No	Use in this population is not predicted to be associated with additional risks of clinical significance.
Within 26 weeks prior to Screening: acute colic due to nephrolithiasis, or acute gout. Subjects with asymptomatic renal stones are permitted.	To avoid confounding the assessment of the safety of palopegteriparatide with symptoms from unrelated disorders.	No	Use in this population is not predicted to be associated with additional risks of clinical significance.
Use in subjects with severe and chronic renal impairment (Subjects with an eGFR <30mL/min/1.73 m^2 during screening were excluded).	To avoid confounding the assessment of the safety of palopegteriparatide with symptoms from unrelated disorders.	Yes	
Use in subjects with severe or chronic hepatic impairment	To avoid confounding the assessment of the safety of palopegteriparatide with symptoms from unrelated disorders.	No	Palopegteriparatide is expected to be primarily renally cleared.
Known allergy or sensitivity to PTH or any of the excipients [metacresol, mannitol, succinic acid, sodium hydroxide/hydrochloric acid]	Ethical consideration in order to protect these subjects.	No	SmPC contains language addressing known allergy or sensitivities to PTH.

AE=adverse event; BP=blood pressure; eGFR=estimated glomerular rate; mPEG= methoxypolyethylene glycol; PTH=parathyroid hormone; SmPC=summary of product characteristic; TSH=thyroid stimulating hormone

SIV.2 Limitations to Detect Adverse Reactions in Clinical Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table SIV.2: Exposure of Special Populations Included or Not in the Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development programme.
Lactating women	
Subjects < 18 years of age	
Subjects with severe and chronic hepatic disease	
Subjects with severe and chronic renal impairment	Phase 1 Trial TCP-104 evaluated the effect of palopegteriparatide on subjects with normal healthy renal function (n=13), and mild (n=9), moderate (n=8), and severe renal insufficiency (n=8). Four of 38 (10.5%) subjects experienced a total of five TEAEs; all in the mild or moderate renal insufficiency group (n=2 each). All TEAEs were mild, and most were considered related to palopegteriparatide by the investigator. No safety signals were detected (TCP-104 CSR, Section 12). No modification in starting dose or titration algorithm is warranted for subjects with impaired renal function. There is not sufficient exposure data available in subjects with hypoparathyroidism and severe and chronic renal impairment.

CSR=clinical study report; TEAE=treatment-emergent adverse event

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1.1 Post-authorisation Exposure

Not applicable. As of the data lock point of this report, palopegteriparatide is not approved for marketing in any country.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for Misuse for Illegal Purposes

Palopegteriparatide has no specific effects likely to induce a potential for misuse for illegal purposes. Palopegteriparatide is not structurally or pharmacologically related to any drug known to induce abuse potential.

Part II: Module SVII - Identified and Potential Risks SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not all adverse reactions are necessarily considered a risk for the medicinal product in a given therapeutic context and not all risks qualify as important to be included in the list of safety concerns for the purpose of risk management planning.

The information available for palopegteriparatide has been analysed and those risks which are not considered important for inclusion in the list of safety concerns in the risk management plan (RMP) (along with the reason of not including) are detailed below:

Reason for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Risks with minimal clinical impact on subject (in relation to the severity of the indication treated):

- Hypocalcaemia (disease effect, not a direct drug effect)
- Fatigue
- Headache
- Muscle spasms
- Injection site reactions (Injection site erythema, Injection site pain, Injection site pain, Injection site rash, Injection site swelling)
- Arthralgia
- Myalgia
- Peripheral oedema
- Pruritus
- Skin rash

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- None

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised):

- Dizziness
- Orthostatic hypotension
- Syncope/Presyncope
- Palpitations
- Postural orthostatic tachycardia syndrome
- Paraesthesia

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk:

Hypercalcaemia

Risk-Benefit Impact:

Palopegteriparatide increases serum calcium levels. Therefore, transient hypercalcaemia may occur in subjects treated with palopegteriparatide. Symptomatic hypercalcaemia occurred almost exclusively early on in trials (during the blinded periods and during the most active titration phase). Subjects with hypercalcaemia are often asymptomatic. Severe hypercalcaemia can be a life-threatening emergency. Symptomatic hypercalcaemia is managed by palopegteriparatide being temporarily held or completely discontinued.

Important Potential Risk: None

Missing Information:

Use in pregnant and breastfeeding women

Risk-Benefit Impact:

Pregnant and lactating women were excluded from the clinical programme. The current non-clinical data package for palopegteriparatide indicated no risk of impaired fertility, embryo-lethality, foetotoxicity, or dysmorphogenesis. Due to the molecular size, no or minimal exposure to palopegteriparatide, PTH(1-34) and the TransCon linker attached to mPEG is expected via placental transfer to the foetus or after ingestion of milk by the infant. As there is no or very low oral bioavailability of PTH (Leone-Bay 2001, Hwang 2016), possible excretion of PTH into the milk is considered to result in no or negligible exposure in the infant. No transfer of PEG to breast milk was observed in lactating mothers receiving certolizumab pegol and observations in the infants were consistent with those seen in infants of similar age in the general population (Clowse 2018). Since the TransCon Linker is attached to mPEG in the systemic circulation, it can be deduced that the TransCon Linker attached to mPEG will not be excreted in breast milk. No indications of malformations have been observed in more than 1300 pregnant women exposed to Cimzia® (a PEGylated (40 kDa anti-TNFα biologic approved for the treatment of rheumatoid arthritis and Crohn's disease (Mahadevan 2013, Mariette 2018, Clowse 2018, Cimzia EPAR 2023). Future evaluation of data during routine pharmacovigilance may improve the understanding of safety in pregnant and breast-feeding women.

Missing Information:

Use in patients with severe and chronic renal impairment

Risk-Benefit Impact:

Palopegteriparatide has been administered to subjects with hypoparathyroidism with an estimated glomerular filtration rate >30mL/min/1.73 m² in long-term clinical trials without the need for dose adjustment beyond the trial titration algorithm. No clinical trials were conducted in severe renally impaired subjects with hypoparathyroidism or subjects on dialysis. In a trial where palopegteriparatide was administered as a single dose to non-hypoparathyroid subjects with renal impairment, exposure to palopegteriparatide and resulting serum calcium levels were similar in subjects with mild, moderate, and severe renal impairment as compared to subjects without renal impairment. No dose adjustment is necessary in subjects with mild to moderate renal impairment (estimated glomerular filtration rate 30 to 80 mL/min/m2). Future evaluation of data during routine pharmacovigilance activities may improve the understanding of safety in patients with severe and chronic renal impairment.

Missing Information

Long-term safety (including long-term effects on bone health and adverse drug reactions potentially related to mPEG exposure)

Risk-Benefit Impact

Based on available clinical data, no safety concerns related to bone health have been identified; however, information on long term effects on bone health will be collected and reviewed routinely via long-term extension studies currently in progress. Future evaluation of data during routine pharmacovigilance may improve the understanding of safety of long-term effects on bone health.

In the clinical development programme, there was no evidence of AEs that could be attributed to mPEG exposure. Additionally, no safety issues potentially related to mPEG have been identified in the ongoing trials. Future evaluation of data during routine pharmacovigilance may improve the understanding of safety of long-term mPEG exposure.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable as this is the first submission of the RMP.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: Hypercalcaemia

Potential mechanisms: PTH is the principal regulator of plasma calcium homeostasis. In the kidney, PTH increases tubular reabsorption of calcium while decreasing phosphate reabsorption and furthermore increases the synthesis of active vitamin D, in turn increasing intestinal calcium and phosphate absorption. In addition, PTH stimulates bone turnover to mobilise calcium and phosphate. The net effect of PTH is therefore an increase in serum calcium.

Evidence source(s) and strength of evidence**:**

In the clinical development programme, hypercalcaemia has been reported with the use of palopegteriparatide with symptomatic episodes occurring almost exclusively during the first three months of treatment.

Characterisation of the risk:

Clinically symptomatic hypercalcaemia occurred almost exclusively early on in trials (during the blinded periods and during the most active titration phase). In palopegteriparatide-treated subjects, hypercalcaemia was one of the most common treatment-emergent adverse events (TEAEs) associated with abnormal calcium laboratory values in palopegteriparatide-treated subjects; all considered related to trial treatment (9.8% [6/61] in TCP-304 and 6.8% [4/59] in TCP-201). In palopegteriparatide-treated subjects in TCP-304, clinically symptomatic hypercalcaemia occurred only during the first three months of the blinded period, generally during the first month. This finding is consistent with the observation that serum calcium initially increased during study drug titration before returning to within baseline levels.

One TEAE of Grade 1 hypercalcaemia occurred in a subject in TCP-201 during the OLE period likely from a special situation of overdose. This subject reported that an additional dose may have been taken on a single day in error.

Four of 61 (6.6%) palopegteriparatide-treated subjects experienced TEAEs related to hypercalcaemia which led to an emergency room/urgent care visit and/or hospitalisation in the blinded treatment period in TCP-304. There were no TEAEs related to hypercalcaemia that led to an emergency room/urgent care visit and/or hospitalisation reported in study TCP-201.

One treatment-related serious adverse event of Grade 3 hypercalcaemia was reported in palopegteriparatide-treated subject in TCP-304 in the blinded treatment period. No treatment-emergent serious adverse event of hypercalcaemia was reported in TCP-201. No persistent, severe hypercalcaemia were reported.

Risk factors and risk groups:

Hypercalcaemia occurred almost exclusively early during treatment. This is consistent with the observation that serum calcium initially increased during study drug titration before returning to baseline levels.

Patients at higher risk for hypercalcaemia include elderly patients with renal insufficiency, patients with a disease predisposing to hypercalcaemia (e.g., active neoplasia, multiple myeloma, granulomatous disease, endocrinopathy), and patients taking concomitant medications that affect serum calcium levels such as thiazide diuretics. (Powers 2013, Clarke 2011, Mitchell 2012, Underbjerg 2013).

Thiazide diuretics are sometimes used in patients with hypoparathyroidism to increase urinary calcium reabsorption at the distal tubule and induce osteoblast differentiation which will contribute to increasing serum calcium levels. In patients with a history of calcium stones, thiazide diuretics are prescribed to reduce recurrent calcium stones (Li 2020). Thus, the concomitant treatment of thiazide diuretics and palopegteriparatide is likely to reduce the adverse renal effects (including nephrolithiasis, nephrocalcinosis) but can augment the risk for transient hypercalcaemia. It is therefore recommended to monitor serum calcium when adding or changing the dose of thiazide diuretics in patients treated with palopegteriparatide.

Preventability:

For any drug that affects serum calcium levels (lithium, thiazide diuretics), the patient's serum calcium levels should be monitored especially during treatment start or dose adjustment. Hypercalcaemia can be minimised by following the recommended dosing and monitoring information in the Summary of Product Characteristics (SmPC). Symptomatic hypercalcaemia is managed by palopegteriparatide being temporarily held or completely discontinued.

Impact on the risk-benefit balance of the product:

As most cases of hypercalcaemia have been mild in severity, the impact on the individual patient is expected to be low. Mild hypercalcaemia is often asymptomatic. In general, clinical manifestations of chronic hypercalcaemia affect the neuromuscular, gastrointestinal, renal, skeletal, and cardiovascular systems. Neuromuscular effects include impaired concentration, confusion, corneal calcification, fatigue, muscle weakness, nausea, abdominal pain, anorexia, constipation, and, rarely, peptic granulomatous disease, and endocrinopathies. Elderly patients are more likely to be symptomatic from moderate elevations of serum calcium levels.

Public health impact:

None

Important Potential Risk:

None

SVII.3.2. Presentation of the Missing Information

Missing Information: Use in pregnant and breastfeeding women:

Evidence source:

Hypoparathyroidism during pregnancy is associated with maternal morbidity and foetal loss. There are limited case reports and no established management guidelines. Physiological adaptations to maternal calcium homeostasis occur during pregnancy and lactation to e.g., facilitate mineralisation of the foetal skeleton and ensure adequate calcium in breast milk, whilst maintaining normal maternal serum calcium levels (Kovacs 2011). Inadequate management of hypoparathyroidism during pregnancy can result in miscarriage (Eastell 1985), stillbirth (Callies 1998), preterm labour, and acute neonatal morbidity such as respiratory distress syndrome (Kaneko 1999).

Anticipated risk/consequence of the missing information:

There are limited amount of data from the use of Yorvipath in pregnant females. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. However, a risk to the pregnant female or developing foetus cannot be excluded. A decision to initiate or discontinue treatment with Yorvipath during pregnancy should take into account the known risks versus benefits for the pregnant female. It is recommended to closely monitor serum calcium levels in pregnant females with hypoparathyroidism, including if treated with Yorvipath.

It is recommended to closely monitor maternalserum calcium levels in breast-feeding females with hypoparathyroidism, including if treated with Yorvipath. It is unknown whether Yorvipath is excreted in human milk. As Yorvipath is not orally absorbed, Yorvipath potentially excreted in the milk is unlikely to adversely affect the breast-fed child. A decision to discontinue breast-feeding or Yorvipath therapy should take into account the benefit of breast-feeding for the child and the benefit of therapy for the female.

Missing Information: Use in patients with severe and chronic renal impairment:

Evidence source:

Palopegteriparatide is primarily renally metabolised and excreted. Patients with hypoparathyroidism typically have abnormally high urine calcium levels, which may increase the risk for nephrolithiasis, nephrocalcinosis, and chronic kidney disease. No dose adjustment is indicated in patients with mild to moderate renal impairment (creatinine clearance 30 to 80 mL/min). Yorvipath has not been studied in subjects with hypoparathyroidism and severe renal impairment (estimated glomerular filtration rate < 30 mL/min). No studies were conducted in patients on renal dialysis. Data in non-hypoparathyroid subjects with renal impairment, does not suggest dose adjustment, across mild to severe renally impaired patients (30-15 mL/min).

Population in need of further characterisation:

There is very limited data to evaluate the effects of palopegteriparatide on patients with severe and chronic renal impairment.

Missing Information: Long-term safety (including long-term effects on bone health and adverse drug reactions potentially related to mPEG exposure):

Evidence source:

PTH stimulates bone turnover as part of maintaining calcium homeostasis (Langdahl 2016, Martin 2000). Accordingly, bone turnover is low in patients with hypoparathyroidism (Rubin 2008, Langdahl 2016). This reduced skeletal turnover leads to an accumulation of hypermineralised bone as reflected by above average BMD in both cortical and trabecular compartments (Rubin 2008). After initiation of Yorvipath treatment, bone turnover increased as reflected by increased concentrations of markers of bone resorption and formation. These markers peaked before or at Week 26 and then trended downwards toward age and sex-appropriate norms. Accordingly, BMD decreased from above normal at baseline with the largest decrements taking place within the first 26 weeks of treatment followed by BMD trending towards age- and sex appropriate norms. This is in line with the expected effects of continuous PTH exposure within the physiological range facilitating physiologic mobilisation of calcium from the skeleton followed by formation of new mineralised bone in its place. Based on the evaluation of short- and medium- term safety data from the clinical studies, no safety concerns related to bone health have been identified. Considering that the changes in bone turnover and thus bone mass appeared more pronounced within the first 26 weeks of treatment, no additional safety concerns with regard to bone health are expected with long-term follow-up.

In general, long-term (chronic) use of PEGylated proteins containing high molecular weight PEG in animals and humans has, to date, not indicated any safety concerns (Webster 2007, Palombo 2014, Ivens 2015, Stidl 2018, Zhu 2021). Based on available clinical data with Yorvipath, short and medium-term exposure to mPEG has not identified any safety concerns.

Population in need of further characterisation:

Long-term safety in patients treated with palopegteriparatide: There continues to be a need to further evaluate and monitor the long-term safety of the molecule and the effects on the targeted population.

Currently long-term safety data of palopegteriparatide is limited for up to 84 weeks of follow up. TCP-201 and TCP-304 currently have ongoing OLE to further assess long-term safety (including long-term effects on bone health and adverse drug reactions potentially related to mPEG exposure). Based on the evaluation of safety data from the clinical studies, no safety concerns have been identified. Long-term safety of the molecule will continue to be monitored.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risk(s)	Hypercalcaemia
Important potential risks	None identified
Missing information	• Use in pregnant and breastfeeding women • Use in patients with severe and chronic renal impairment • Long-term safety (including long-term effects on bone health and adverse drug reactions potentially related to mPEG exposure)

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

All safety concerns will be monitored via routine pharmacovigilance activities including the following:

- Systems and processes that ensure that information about all suspected adverse reactions that are reported to Ascendis Pharma are collected and collated in an accessible manner.
- The preparation of reports for regulatory authorities: Expedited AE Reports, Period Benefit Risk Evaluation Reports.
- Continuous monitoring of the safety profile of approved products including signal detection, issue evaluation, updating of labelling, and liaison with regulatory authorities.

All pharmacovigilance activities are fully described in the Pharmacovigilance System Master File.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

There are no routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.

Specific adverse reaction follow-up questionnaires for safety concerns:

A. Pregnancy follow-up form.

B. Renal Impairment follow-up form

Other forms of routine pharmacovigilance activities for safety concerns:

Not applicable.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Two long term extension studies are ongoing. Analysis of data from the studies includes review of calcium laboratory data from TCP-201 and TCP-304 on a quarterly basis.

Subjects in trials TCP-201 and TCP-304 undergo annual bone mineral density and trabecular bone score by dual-energy X-ray absorptiometry and bone turnover marker assessment (procollagen type 1 amino-terminal propeptide [P1NP] and c-telopeptide of type 1 collagen [CTx]) to monitor bone health.

Analysis comparing long-term AEs (>1 year exposure to Yorvipath) against short-term AEs (<1 year exposure), and comparing AEs year by year (<1 year exposure, 1 to 2 years exposure, 2 to 3 years exposure once these timepoints and sufficient amount of data are reached).

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
TCP-201: PaTH Forward: A Phase 2, 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 Ongoing open label extension	To assess the effectiveness of daily TransCon PTH on serum and urine calcium levels (FECa) and active vitamin D and calcium doses at 4 weeks of treatment To assess the safety and tolerability of daily TransCon PTH To assess the effectiveness of daily TransCon PTH on serum and urine calcium levels (FECa) and active vitamin D and calcium doses during the Extension Period To assess the treatment effect of daily TransCon PTH on daily pill burden (active vitamin D and calcium) To assess the treatment effect of daily TransCon PTH on serum phosphate, serum magnesium, and calcium x phosphate product (sCa x sP product) To assess the treatment effect of daily TransCon PTH on hypocalcaemia and hypercalcaemia symptoms, emergency room (ER) visits, and hospitalisations To assess anti-PTH and anti-PEG antibody responses	Hypercalcaemia Long-term safety (including long-term effects on bone health and adverse drug reactions potentially related to mPEG exposure)	Interim Analysis	See footnote
			Final report	Projected March 2025

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
TCP-304: PaTHway: 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 Ongoing	To assess the treatment effect of daily TransCon PTH on PD markers (including sCa) and active vitamin D and calcium doses To assess the treatment effect of daily TransCon PTH on sP, CxP (albumin-adjusted sCa x sP product) and sMg To assess anti-PTH, anti-TransCon PTH and anti-PEG antibody responses To assess the treatment effect of daily TransCon PTH on − BMD and trabecular bone score (TBS) by DXA − Bone turnover markers (serum P1NP and CTx)	Hypercalcaemia Long-term safety (including long-term effects on bone health and adverse drug reactions potentially related to mPEG exposure)	Interim analysis	See footnote
			Final report	Projected January 2026

Note: Interim analyses will include 1) Yearly measurement of bone mineral density (BMD) and trabecular bone score (TBS) by dual energy X-ray absorptiometry (DXA) and bone turnover markers (serum procollagen type 1 amino-terminal propeptide [P1NP] and C-telopeptide of type 1 collagen [CTx]). 2) Comparison of long-term AEs (>1 year exposure to Yorvipath) against short-term AEs (<1 year exposure). 3) When appropriate, comparison of AEs year by year (<1 year exposure, 1-2 years exposure, 2-3 years exposure etc.).

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable as no post-authorisation efficacy studies are planned or ongoing.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Hypercalcaemia (Important Identified Risk)	Routine risk communication: *SmPC Sections 4.2, 4.4 and 4.8.* *Corresponding PL sections* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Dosing schedule, Section 4.2* *Routine lab tests and monitoring (Ca levels)* *Special warnings and precaution, Section 4.4 to minimise hypercalcaemia by following recommended dosing, the monitoring information, and asking patients about symptoms.* *Treatment recommendation if severe hypercalcaemia occurs.* *Drug interactions that affect serum calcium Section 4.5* *Overdose, Section 4.9* Other routine risk minimisation measures beyond the Product Information: *None* Legal status: *Restricted medical prescription.*
Use in pregnant and breastfeeding women (Missing Information)	Routine risk communication: *SmPC Section 4.6* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Fertility, pregnancy and lactation are discussed in Section 4.6* Other routine risk minimisation measures beyond the Product Information: *None* Legal status: *Restricted medical prescription.*
Use in patients with severe and chronic renal impairment (Missing Information)	Routine risk communication: *SmPC Sections 4.2, 4.4 and 5.2* *Corresponding PL sections* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Description of requirements in cases of severe renal impairment provided in Section 4.2* *Warnings and precautions for patients with severe renal impairment in Section 4.4* *PK properties regarding renal impairment discussed in Section 5.2* Other routine risk minimisation measures beyond the Product Information: *None* Legal status: *Restricted medical prescription.*

Safety Concern	Routine Risk Minimisation Activities
Long-term safety (including long-term effects on bone health and adverse drug reactions potentially related to mPEG exposure) (Missing Information)	Routine risk communication: *None.* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: *None* Legal status*: Restricted medical prescription.*

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table Part V.3: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Hypercalcaemia (Important Identified Risk)	Routine risk communication: *SmPC Sections 4.2, 4.4 and 4.8* *Corresponding PL sections* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Dosing schedule, Section 4.2* *Routine lab tests and monitoring (Ca levels)* *Special warnings and precaution, Section 4.4 to minimise hypercalcaemia by following recommended dosing, the monitoring information, and asking patients about symptoms.* *Treatment recommendation if severe hypercalcaemia occurs.* *Drug interactions that affect serum calcium Section 4.5.* *Undesirable effects, Section 4.8* *Overdose, Section 4.9* Other routine risk minimisation measures beyond the Product Information: *None* Legal status: *Restricted medical prescription.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *Open label extension studies TCP-201 and TCP-304.*

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in pregnant and breastfeeding women (Missing Information)	Routine risk communication: *SmPC Section 4.6* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Fertility, pregnancy and lactation are discussed in Section 4.6* Other routine risk minimisation measures beyond the Product Information: *None* Legal status: *Restricted medical prescription.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Follow-up questionnaire* Additional pharmacovigilance activities: *None*
Use in patients with severe and chronic renal impairment (Missing Information)	Routine risk communication: *SmPC Sections 4.2, 4.4 and 5.2* *Corresponding PL sections* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Description of requirements in cases of renal impairment provided in Section 4.2* *Warnings and precautions for patients with severe renal impairment in Section 4.4* *PK properties regarding renal impairment discussed in Section 5.2* Other routine risk minimisation measures beyond the Product Information: Legal status: *Restricted medical prescription.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Follow-up questionnaire* Additional pharmacovigilance activities: *None.*
Long-term safety (including long-term effects on bone health and adverse drug reactions potentially related to mPEG exposure) (Missing Information)	Routine risk communication: *None* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: *None* Legal status: *Restricted medical prescription.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *Open label extension studies TCP-201 and TCP-304.*

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Yorvipath (Palopegteriparatide)

This is a summary of the Risk Management Plan (RMP) for Yorvipath. The RMP details important risks of Yorvipath, how these risks can be minimised, and how more information will be obtained about the risks and uncertainties (missing information).

The summary of product characteristics (SmPC) and package leaflet give essential information to healthcare professionals and patients on how Yorvipath should be used.

This summary of the RMP for Yorvipath should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report.

Important new concerns or changes to the current risks will be included in updates of Yorvipath RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Yorvipath is authorised as a parathyroid hormone replacement therapy indicated for the treatment of chronic hypoparathyroidism in adults (see SmPC for the full indication). It contains palopegteriparatide as the active substance and it is given by subcutaneous route of administration.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Yorvipath, together with measures to minimise such risks and the proposed studies for learning more about the risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Yorvipath is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Yorvipath are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Yorvipath. Potential risks are where an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Summary of Safety Concerns	
Important identified risks	Hypercalcaemia
Important potential risks	None identified
Missing information	Use in pregnant and breastfeeding women Use in patients with severe and chronic renal impairment Long-term safety (including long-term effects on bone health and adverse drug reactions potentially related to mPEG exposure)

II.B Summary of Important Risks

Important Identified Risk: Hypercalcaemia	
Evidence for linking the risk to the medicine	Clinical trials and literature
Risk factors and risk groups	Hypercalcaemia occurred almost exclusively during early treatment. This is consistent with the observation that serum calcium initially increased during study drug titration before returning to baseline levels. Patients at higher risk for hypercalcaemia include elderly patients with renal insufficiency, subjects with a disease predisposing to hypercalcaemia (e.g., active neoplasia, multiple myeloma, granulomatous disease, endocrinopathy), and persons taking concomitant medications that affect serum calcium levels such as thiazide diuretics (Powers 2013, Clarke 2011, Mitchell 2012, Underbjerg 2013). For any drug that affects serum calcium levels (lithium, thiazide diuretics), the patient's serum calcium levels should be monitored especially during treatment start or dose adjustment. Thiazide diuretics are sometimes used in patients with hypoparathyroidism to increase urinary calcium reabsorption at the distal tubule and induce osteoblast differentiation which will contribute to increasing serum calcium levels. In patients with a history of calcium stones (Li 2020), thiazide diuretics are prescribed to reduce recurrent calcium stones. Thus, the concomitant treatment of thiazide diuretics and palopegteriparatide is likely to reduce the adverse renal effects (including nephrolithiasis, nephrocalcinosis) but can augment the risk for transient hypercalcaemia. It is therefore recommended to monitor serum calcium when adding or changing the dose of thiazide diuretics in patients treated with palopegteriparatide.

Important Identified Risk: Hypercalcaemia	
Risk minimisation measures	Routine risk communication: *SmPC Sections 4.2 , 4.4 and 4.8* *Corresponding PL sections* Other routine risk minimisation measures beyond the Product Information: Legal status: *Restricted medical prescription.*
Additional pharmacovigilance activities	Open label extension studies TCP-201 and TCP-304

Important Potential Risk: None identified	
Evidence for linking the risk to the medicine	Not Applicable
Risk factors and risk groups	Not Applicable
Risk minimisation measures	Not Applicable
Additional pharmacovigilance activities	Not Applicable

Missing Information: Use in Pregnant and Breastfeeding Women	
Risk minimisation measures	Routine risk communication: *SmPC Section 4.6* Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Follow-up questionnaire* Other routine risk minimisation measures beyond the Product Information: *None* Legal status: *Restricted medical prescription*
Additional pharmacovigilance activities	None

Missing Information: Use in Patients with Severe and Chronic Renal Impairment	
Risk minimisation measures	Routine risk communication: *SmPC sections 4.2, 4.4 and 5.2* *Corresponding PL sections* Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Follow-up questionnaire* Other routine risk minimisation measures beyond the Product Information: Legal status: *Restricted medical prescription*
Additional pharmacovigilance activities	None

Missing Information: Long-term safety (including long-term effects on bone health and adverse drug reactions potentially related to mPEG exposure)	
Risk minimisation measures	Routine risk communication: *None* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: *None*

Missing Information: Long-term safety (including long-term effects on bone health and adverse drug reactions potentially related to mPEG exposure)	
	Legal status: *Restricted medical prescription*
Additional pharmacovigilance activities	Open label extension studies TCP-201 and TCP-304

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Yorvipath.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Yorvipath.

PART VII: ANNEXES

Annex 1 – EudraVigilance Interface

Annex 2 – Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Programme

Annex 3 – Protocols for Proposed, on-Going and Completed Studies in the Pharmacovigilance Plan

Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms

Annex 5 – Protocols for Proposed and on-Going Studies in RMP Part IV

Annex 6 –Details of Proposed Additional Risk Minimisation Activities (if applicable)

Annex 7 – Other Supporting Data (including referenced material)

Annex 8 – Summary of Changes to the Risk Management Plan Over Time

Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms

A) Postmarketing pregnancy report follow-up form.

ascendis pharma	**Yorvipath (palopegteriparatide)** **Post Marketing Pregnancy Surveillance Form**

Patient ID		**Country**	

Initial report ☐	Follow-up report ☐	Follow up no.:	Ascendis Pharma Case ID:

Patient Demographics		
Initials:	**Date of Birth:**	
Age:	**Height:** ☐ cm ☐ in	**Weight:** ☐ kg ☐ lb
Ethnic Origin: ☐ Asian ☐ Black ☐ Caucasian ☐ Hispanic ☐ Other: _____		

Yorvipath Therapy Information

Dose / Frequency	Route	Indication	First dose DD-MMM-YYYY	Last dose DD-MMM-YYYY	Ongoing
					☐

Relevant Maternal Past Medical History
(especially gravidity, parity and abortus, endocrinological problems, gynecological infections, infertility, menstrual disorders)

	Condition / Disease	Start Date DD-MMM-YYYY	Stop Date DD-MMM-YYYY	Ongoing
1.				☐
2.				☐
3.				☐
4.				☐
5.				☐

Other Relevant Maternal History			
Alcohol consumption	Yes ☐ No ☐	Since:	
Tobacco consumption	Yes ☐ No ☐	Since:	
Previous Pregnancies	Yes ☐ No ☐		
No. of full-term births:	No. of preterm births:	No. of miscarriages:	No. of elective abortions:

Maternal Medication History *(including contraceptive methods used & recreational drugs)*

	Medication/ Generic Name	Dose / Frequency	Route	Indication	Start Date DD-MMM-YYYY	Stop Date DD-MMM-YYYY
1						
2						
3						
4						
5						
6						

Yorvipath (palopegteriparatide)
Post Marketing Pregnancy Surveillance form

Pregnancy Information	
Pregnancy Confirmation date	(DD-MMM-YYYY)
Last menstrual period date	(DD-MMM-YYYY)
Presumed conception date	(DD-MMM-YYYY)
Estimated delivery date	(DD-MMM-YYYY)

Was contraception used? Yes ☐ No ☐

If yes, form of contraception:

Contraception start / stop date: (DD-MMM-YYYY)/(DD-MMM-YYYY) or Ongoing ☐

Pregnancy Follow Up	
Has the patient already been referred to an Obstetrician/gynecologist?	Yes ☐ No ☐
If yes, please provide Obstetrician/gynaecologist contact details	
Description of Pregnancy (e.g.,abnormal findings, premature termination)	

Outcome Of Pregnancy

☐ Full Term
☐ Premature Birth
☐ Spontaneous miscarriage (Date occurred:)
☐ Elective Termination:
Was the elective termination caused by any medical reason? Yes ☐ No ☐
If yes, please provide details:

Any significant complications during pregnancy, at delivery or post-partum? Yes ☐ No ☐
If yes, please provide details:

Details Of Birth *please complete an additional Safety Report Form in case of acquired disease/congenital anomaly/Birth Defect*

ascendis pharma	**Yorvipath (palopegteriparatide)** **Post Marketing Pregnancy Surveillance form**

☐ Healthy newborn
☐ Acquired diseases (e.g., infection, trauma, etc.), please specify
☐ Congenital anomaly/Birth Defect, please specify
☐ Still birth

Date of Birth: Sex: ☐ M ☐ F

APGAR Score: 1 min 5 min 10 min

Additional section to report further information not mentioned on the previous pages

Was there clinically significant hypocalcaemia or hypercalcaemia observed during the pregnancy?
Yes ☐ No ☐
If Yes, please provide Lab results (with dates):

Symptoms (if any):

Is the mother breastfeeding the baby? Yes ☐ No ☐

Please provide any other relevant information:

Reporter Information:
Reporter is a) Healthcare Professional ☐ b) Consumer ☐

Reporter's Name:	Reporter's Signature:
Reporter's Occupation:	

Please submit your response to: drug.safety@ascendispharma.com

B) Renal Impairment follow-up form

ascendis pharma	**Follow-Up Form for Patients with Renal Event or Medical History of Renal Impairment during treatment with YORVIPATH**

Some data fields from the initial Adverse Event report has been pre-populated in the below. Ascendis Pharma is kindly asking you to fill in this Form and return it to: drug.safety@ascendispharma.com

Local case ID:	
Ascendis Pharma case ID:	
Latest receive date:	

1. Patient demographics

Age	Gender	Weight (kg)	Initials
	☐ Male ☐ Female		

Ethnic origin ☐ Asian ☐ Black ☐ Caucasian ☐ Hispanic ☐ Other:_____

2. Reporter details

Name	Occupation

3. Reported adverse event

Adverse event, as initially reported	Description

4. Suspected medications

	Medication/ Generic Name	Indication	Dose/unit	Frequency	Route of administration	Start Date DD / MMM / YYYY	Stop Date / Ongoing DD / MMM / YYYY
1						__/___/____	__/___/____
2						__/___/____	__/___/____
3						__/___/____	__/___/____

5. Concomitant medications *(not including the Suspected medications listed above)*

	Medication/ Generic Name	Indication	Dose/unit	Frequency	Route of administration	Start Date DD / MMM / YYYY	Stop Date / Ongoing DD / MMM / YYYY
1						__/___/____	__/___/____
2						__/___/____	__/___/____
3						__/___/____	__/___/____
4						__/___/____	__/___/____
5						__/___/____	__/___/____
6						__/___/____	__/___/____
7						__/___/____	__/___/____
8						__/___/____	__/___/____

Page 1 of 3

ascendis pharma	**Follow-Up Form for Patients with Renal Event or Medical History of Renal Impairment during treatment with YORVIPATH**

6. Provide details of relevant past medical history (Diabetes, hypertension, bone disease, anemia etc). Also include childhood and relevant family history.

	Condition / Disease	Start Date DD / MMM / YYYY	Stop Date (DD / MMM / YYYY)	Ongoing
1		__/___/____	__/___/____	☐
2		__/___/____	__/___/____	☐
3		__/___/____	__/___/____	☐
4		__/___/____	__/___/____	☐
5		__/___/____	__/___/____	☐

7. Exposure to risk factors for the patient Yes ☐ No ☐

If yes, please specify	Yes/No	Start Date DD / MMM / YYYY	Stop Date DD / MMM / YYYY
Risk factors for kidney disease If yes, please specify:	☐ Yes ☐ No		
Smoking If yes, please specify pack years: _____ _____ _	☐ Yes ☐ No	__/___/____	__/___/____
Alcohol use _____ _	☐ Yes ☐ No	__/___/____	__/___/____
Chemical exposure _____ _	☐ Yes ☐ No	__/___/____	__/___/____
Chemotherapy exposure (specify): _____ _	☐ Yes ☐ No	__/___/____	__/___/____
Others, please specify: _____ _	☐ Yes ☐ No	__/___/____	__/___/____

8. Details of patient's kidney disease

1	Did the patient have kidney disease prior to starting therapy with Yorvipath? Yes ☐ No ☐
2	When was the patient diagnosed with kidney disease (DD-MMM-YYYY)?
3	What is the specific kidney disease diagnosis?
4	If chronic kidney disease has been diagnosed, what stage CKD does the patient currently have (CKD stage 1-5)?
5	How was this diagnosis determined (e.g. laboratory studies, clinical symptoms); please provide the dates (DD-MMM-YYYY) if possible?

ascendis pharma	**Follow-Up Form for Patients with Renal Event or Medical History of Renal Impairment during treatment with YORVIPATH**

6	What past medical history or comorbid conditions may contribute to the patient's chronic kidney disease?
7	What treatment for chronic kidney disease or predisposing medical conditions is the patient receiving now?
8	Is the patient on renal replacement therapy? Please provide details.
9	What is the patient's most recent serum calcium level with date (DD-MMM-YYYY) if available. Please provide baseline, and at the time of event, and at event resolution, if available.
10	Please provide details including dates (DD-MMM-YYYY) of the most recent laboratory tests relevant to the diagnosis of chronic kidney disease (e.g. eGFR, Serum creatinine (sCr), Urine albumin-creatinine ratio (uACR), BUN). Please include values at baseline, at the time of the event, and at the event resolution, if available. Attach test results, if possible.

9. Additional Information (use this space to provide details on the current and/or past conditions mentioned above)

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Not applicable.