14 September 2023
EMA/439682/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Yorvipath

International non-proprietary name: palopegteriparatide

Procedure No. EMEA/H/C/005934/0000

Note

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

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List of abbreviations

1,25-(OH)2D3	calcitriol, also known as 1,25-dihydroxyvitamin D, the active hormonal form of vitamin D
25(OH)D3	calcifediol, also known as calcidiol, 25-hydroxycholecalciferol, or 25-hydroxyvitamin D3
ADA	anti-drug antibody
AE(s)	adverse event(s)
AESI(s)	adverse event(s) of special interest
ANCOVA	analysis of covariance
AUC0-∞ or AUC0-inf	Area under the concentration-time curve from time zero to infinity
AUC0-t	Area under the concentration-time curve from time zero to the last quantifiable concentration
BID	twice daily
BMD	bone mineral density
BMI	body mass index
BSAP	bone specific alkaline phosphatase
BTM(s)	bone turnover marker(s)
CaSR	calcium-sensing receptor
CNS	Central nervous system
CGIS	Clinical Global Impression of Severity
CSR(s)	Clinical study report(s)
CV%	coefficient of variation
Cmax	maximum observed concentration
CTx	C-terminal telopeptide of type I collagen
DXA	dual-energy x-ray absorptiometry
ECG(s)	Electrocardiogram(s)
FDA	Food and Drug Administration
FECa	fractional excretion of calcium
Free PTH(1-34):	Free PTH(1-34) is PTH(1-34) released from palopegteriparatide
Free PTH(1-33)	Free PTH(1-33) is PTH(1-34) metabolized to PTH(1-33) in the prodrug or after PTH(1-34) is released
Free PTH	The sum of active PTH (Free PTH(1-34) and Free PTH(1-33))
HPES	Hypoparathyroidism Patient Experience Scale
ISR(s)	injection site reaction(s)
ITT	Intent-to-treat
LLN	lower limit of normal
LS	least squares
mPEG	methoxypolyethylene glycol
MAD	multiple ascending dose
NDA	New Drug Application
NTx	N-terminal telopeptide
OLE	open-label extension
P1NP	procollagen type 1 amino-terminal propeptide
PD	pharmacodynamics
PEG	polyethylene glycol
PK	pharmacokinetics

PGI	Patient Global Impression
PT(s)	preferred term(s)
PTH, also PTH(1-34)	parathyroid hormone
PTH1R	parathyroid hormone 1 receptor
PRO(s)	patient-reported outcome(s)
PRN	pro re nata (as needed)
QoL	quality of life
QTc	corrected Q-T interval
QSP	quantitative systems pharmacology
RI	renally impaired or renal impairment
SAD	single ascending dose
SAE	serious adverse events
SC	subcutaneous
SD	standard deviation
SE	standard error
SF-36	Short Form-36
TBS	trabecular bone score
TEAE	treatment-emergent adverse event
TESAE(s)	treatment-emergent serious adverse event(s)
Tmax	time to maximum observed concentration
ULN	upper limit of normal

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Ascendis Pharma Bone Diseases A/S submitted on 12 November 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Yorvipath, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 May 2021.

Yorvipath, was designated as an orphan medicinal product EU/3/20/2350 on 19 October 2020 in the following condition:

> Treatment of hypoparathyroidism.

The applicant applied for the following indication:

> Palopegteriparatide, a prodrug providing sustained-release of parathyroid hormone (PTH(1-34)), is a PTH replacement therapy indicated for the treatment of hypoparathyroidism in adults.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Yorvipath as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website:

https://www.ema.europa.eu/en/medicines/human/EPAR/Yorvipath

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0021/2022 on the agreement of a paediatric investigation plan (PIP).

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's request(s) for consideration

1.5.1. New active substance status

The applicant requested the active substance palopegteriparatide contained in the above medicinal product to be considered as a new active substance in comparison to teriparatide previously authorised in the European Union as Forsteo, and rhPTH(1-84)/parathyroid hormone previously authorised in the European Union as Natpar, as the applicant claimed that palopegteriparatide differs significantly in properties with regard to safety and/or efficacy from the already authorised active substance.

1.6. Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
29 May 2019	EMA/CHMP/SAWP/277942/2019	*Dr Walter Janssens and Dr Juha Kolehmainen*

The Protocol assistance pertained to the following non-clinical aspects:

- Agreement was sought that no carcinogenicity study is warranted.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Martina Weise Co-Rapporteur: Maria Concepcion Prieto Yerro

The application was received by the EMA on	12 November 2022
The procedure started on	1 December 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	27 February 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	9 March 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	7 March 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	30 March 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	18 May 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	26 June 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to	6 July 2023

CHMP during the meeting on	
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	20 July 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	10 August 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	4 September 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Yorvipath on	14 September 2023

2. Scientific discussion

2.1. Problem statement

Ascendis Pharma Bone Diseases A/S is submitting this dossier in support of a new Marketing Authorisation Application for palopegteriparatide (also known as TransCon PTH), a prodrug providing sustained-release of parathyroid hormone (PTH[1-34]). Palopegteriparatide is a PTH replacement therapy indicated for the treatment of chronic hypoparathyroidism in adults and is designed as a once-daily subcutaneous (SC) injection.

2.1.1. Disease or condition

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

The symptoms, manifestations, and complications of hypoparathyroidism affect multiple organ systems. Neuromuscular irritability is often the most prominent feature affecting day-to-day life, with symptoms ranging from paresthesias and muscle cramps to life-threatening laryngospasm, bronchospasm, seizures, and arrhythmias. Patients with hypoparathyroidism are more likely to report pain, fatigue, "brain fog", anxiety, and depression. Additional complications include propensity for infections, heart failure, renal failure, ectopic calcifications (e.g., of the basal ganglia, and lenses), and abnormal skeletal dynamics (Shoback 2008). Insufficient production of PTH leads to reduced bone turnover with a consequent accumulation of unremodeled bone reflected in increased bone mass and density. Intestinal absorption of calcium and phosphate are both impaired in the setting of insufficient PTH (Brandi 2016, Clarke 2016, Shoback 2016, Mannstadt 2013). Low PTH levels impair renal reabsorption of calcium while decreasing phosphate excretion. The chronic hypercalciuria in patients with hypoparathyroidism is associated with a greater than 4-fold increase in risk of kidney stones and renal insufficiency (Mannstadt 2017). Among patients with postsurgical chronic hypoparathyroidism, the risk of death over approximately a 4-year follow-up is 2-fold higher compared to patients without chronic hypoparathyroidism (Almquist 2018).

2.1.2. Epidemiology

In the European Union, the best prevalence estimate (2020) for non-surgical HP is 1.2/10,000 and for post-surgical HP to 2.1/10,000. Combining these numbers yields a total EU prevalence of HP in 2020 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).

2.1.3. Aetiology

There exist several different causes for chronic hypoparathyroidism. In adults, the most common cause (up to 75% of the time) 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 etiology or associations are deemed idiopathic (Brandi 2016, Clarke 2016).

2.1.4. Management

The goal of current treatment is to relieve symptoms and improve biochemistries (i.e., normalize calcium and phosphate levels) and to prevent neuromuscular sequelae via administration of calcium supplements, active vitamin D, and, in some cases, magnesium supplements if normalization of magnesium levels is indicated. Conventional therapy of hypoparathyroidism includes oral calcitriol (or its analogue alfacalcidol)—as its endogenous production is insufficient in the context of PTH deficiency—and oral calcium. While conventional therapy can be successful for the 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 QoL (Mitchell 2012, Bilezikian 2016). Although conventional therapy can improve hypocalcemia, it does not reduce the elevated serum phosphate characteristic of hypoparathyroidism. Consequent increases in the serum calcium×serum phosphate product predispose patients to ectopic calcifications in the renal parenchyma, eye, central nervous system (CNS) (particularly the basal ganglia) and vasculature (Abate 2017).

Recombinant human (rh) PTH(1-84) (Natpara/Natpar) was approved as an adjunct to active vitamin D and calcium by the Food and Drug Administration (FDA) in 2015 and by the European Medicines Agency (EMA) in 2017. It was subsequently recalled in the US in September 2019 due to incidences of rubber particulate formation. Approximately 55% of subjects taking Natpar in their pivotal trial were able to reduce conventional therapy by 50% while maintaining serum calcium levels at 7.5 to 10.6 mg/dL (Natpara USPI), thereby partially reducing pill burden; other clinically important changes were not observed. Additionally, Natpar did not reduce the incidence of adverse events (AEs) referable to hypo- or hypercalcemia, and neither normalized nor significantly reduced urinary excretion of calcium (Mannstadt 2013).

Once-daily administration of short-lived PTH analogues results in a "bolus effect" with wide hormone fluctuations characterized by an initial supraphysiological PTH level (maximum observed concentration [Cmax]) followed by a rapid decline to subtherapeutic levels. Investigations using twice daily (BID) administration of another short-lived PTH analogue, PTH(1-34), have shown better calcaemic control than daily administration, with still better control achieved by continuous infusion via a subcutaneous pump (Winer 1998, Winer 2008, Winer 2012, Winer 2018). The wide fluctuations in PTH levels and intermittent supraphysiologic PTH concentrations seen with short-lived administration are avoided by this continuous infusion. In addition to normalizing both serum calcium and serum phosphate, therapy with continuous infusion of PTH(1-34) was associated with fewer serum calcium fluctuations, a reduction in urine calcium, and normalized bone turnover compared to BID administration. These improvements were achieved while requiring a 65% lower cumulative dose of PTH(1-34) compared with BID dosing (Winer 2012). Although PTH(1-34) is currently only approved for osteoporosis (Forteo USPI, Forsteo EPAR), these studies provided proof of concept for use in hypoparathyroidism and demonstrate the importance of a treatment that provides active PTH within the normal range for 24 h (hours) per day.

2.2. About the product

Yorvipath (palopegteriparatide) consists of PTH(1-34), i.e. teriparatide, conjugated to an inert mPEG-carrier via a cleavable proprietary linker (TransCon Linker). The sequence of teriparatide is identical to the first 34 amino acids of endogenous PTH(1-84), i.e. parathyroid hormone. After SC injection, the

prodrug releases the active moiety as either PTH(1-34) or PTH(1-33) by first-order kinetics to provide continuous exposure within the physiological range over 24 hours. According to a signal transduction study that evaluated PTH(1-31), PTH(1-34), and PTH(1-30), it is the initial 31 residues of the amino-terminus that are required for PTH1R binding and full activation (Takasu 1998, Morley 1999). Additionally, PTH(1-34) displays the same receptor-mediated activity at bone and kidney as PTH(1-84) (Habener 1984, Lee 1995). Further, it has been demonstrated that PTH(1-34) and PTH(1-33) bind to PTH1R with the same affinity as endogenous PTH(1-84) (Drechsler 2011); and that PTH(1-33) is equipotent to PTH(1-34) (Morley 1999).

Palopegteriparatide is administered as a once-daily SC injection. After SC injection, autocleavage of the linker was stated to occur in a controlled manner by first-order kinetics. The released active PTH acts through PTH1R to regulate calcium and phosphate homeostasis and facilitate the synthesis of active vitamin D.

2.3. Quality aspects

2.3.1. Introduction

The active substance palopegteriparatide is a synthetic peptide with 34 amino acids transiently conjugated to a branched mPEG carrier via a TransCon Linker and a prodrug.

The finished product is presented as solution in a 1.5 mL cartridge containing 300 µg/mL of palopegteriparatide as active substance.

Other ingredients are: succinic acid, mannitol, metacresol, sodium hydroxide, hydrochloric acid, water for injections.

The product is available in a cartridge (type 1 glass) with a plunger (halobutyl) and a laminate rubber sheet (halobutyl/isoprene) contained in a pre-filled multidose disposable pen made of polypropylene. The pre-filled pen contains 0.56, 0.98 or 1.4 mL solution for injection.

2.3.2. Active Substance

General Information

Palopegteriparatide consists of PTH(1-34) transiently conjugated to a carrier via a TransCon Linker. The molecular formula is $C_{209}H_{340}N_{60}O_{59}S_3$ + 2 × $(C_2H_4O)n$, where n is between approximately 450 and 500. PTH(1-34) is identical to the first 34 amino acids, from Ser to Phe, of the full length, 84 amino acid human parathyroid hormone (PTH) possessing a modified N-terminus and a free carboxyl group at the C-terminus. The N-terminus modification consists of the TransCon Linker is attached to the carrier (a branched 40 kDa (2 × 20 kDa) mPEG succinimide derivative).

The structure of palopegteriparatide is detailed in Figure 1 below:

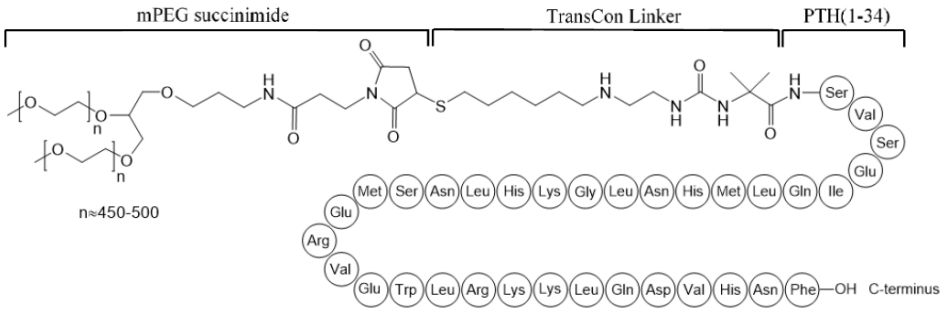


Figure 1 structure of palopegteriparatide

The applicant confirms that the active substance is manufactured by chemical synthesis without materials of biological origin and that the mPEG-carrier intermediate and the peptidic intermediate are manufactured by chemical synthesis, the latter by solid phase synthesis.

Information on the drug substance's appearance, solubility, hygroscopicity and optical rotation characteristics has been provided.

Palopegteriparatide is monomeric and the secondary structure analysis of palopegteriparatide demonstrate a spectrum consistent with the published far-UV circular dichroism spectrum for PTH(1-34).

Manufacture, characterisation and process controls

The sites employed in manufacture of the active substance and intermediates are detailed in the submission dossier.

Ascendis Pharma A/S Tuborg Boulevard 12, 2900 Hellerup, Denmark is responsible for batch release.

A QP declaration has been provided, confirming that the active substance is manufactured in accordance with the detailed guideline on good manufacturing practice for active substances used as starting materials.

Description of the manufacturing process

The description of the manufacturing process is presented separately for intermediates and palopegteriparatide. The applicant has discussed the manufacturing development from the early batches (manufactured in 2016) to the PPQ batches manufactured in 2021.

Palopegteriparatide is manufactured in a synthetic multiple steps process using well-defined starting materials and with acceptable specifications.

Palopegteriparatide active substance is manufactured by conjugation of the peptidic intermediate and the mPEG-carrier intermediate, followed by purification, filtration and final lyophilisation. The manufacturing process has been described in sufficient detail.

Control of materials

Starting materials

The evaluation of starting materials for the manufacturing process of palopegteriparatide active substance has been performed according to the principles described in ICH Q11. The justifications for the selected starting materials are acceptable.

Raw materials

A list of the raw materials used for the manufacture of the intermediates is presented. Specifications have been provided.

The specifications for the reagents, solvents and auxiliary materials of the active substance are presented and are acceptable.

Control of critical steps and intermediates

The number of critical steps and in-process controls is rather limited. Justification of non-criticality of manufacturing process steps and parameters is provided.

Characterisation data and specifications for the peptidic intermediate and the mPEG-carrier intermediate have been provided including justifications. All analytical methods have been described in the dossier and a summary of validation data has been provided for the in-house methods. Analytical data for PPQ batches have been provided. The applicant commits to re-evaluate the limit for total impurities by HPLC in the specification for the peptidic intermediate when data from 20 batches are available.

Stability studies have been performed and stability data have been provided.

Process validation

Process performance and qualification (PPQ) campaigns were conducted, comprising three consecutive batches of intermediates and palopegteriparatide active substance. The process validation fulfilled all pre-set requirements, and the acceptance criteria defined in the validation protocols were met. The processes are maintained in a validated state through the product lifecycle by continued process verification. A summary of the data has been provided in the dossier.

Manufacturing process development

This section of Module 3 briefly covers active substance manufacturing history, including manufacturing quality, scale and usage of the batches. Process optimisations have been adequately described and justified and information on the control strategy has been provided.

Elucidation of structure and other characteristics

The elucidation of structure and other characteristics was performed on active substance (three PPQ batches).

The structure of the active substance was analysed. The determined primary and secondary structure of the active substance comprise with expectations and monomeric behaviour was shown for active substance in solution. Structural analysis of chemically released PTH(1-34) by peptide mapping, ESI-MS, N-terminal amino acid sequencing and far-UV CD indicated that the chemical release procedure does not have structural impact on PTH(1-34). . While biological activity in a cell-based assay of active substance could not be determined due to it being a prodrug, the Hek293-PTH1R cell-based assay with PTH(1-34) released from finished product resulted in activities comparable to PTH(1-34) standard material.

Further characteristics investigated for the active substance are provided in the dossier.

Impurities

The impurity thresholds for impurities applied by the Applicant are the Ph. Eur. 2034 thresholds. The potential related impurities from starting materials and intermediates are discussed in the respective sections.

Potential peptide-related impurities are discussed. It is indicated that these can be considered non-clinically and clinically qualified. Related impurities can for example stem from the different starting

materials. In Section 3.2.S.2.3, the impurities in and control of these starting materials are described and assessed. Specifications are set to ensure that the resulting impurity will have no impact on the quality of the active substance. Potential related impurities originating from the intermediates and their control are described in Section 3.2.S.2.4. The respective impurities are controlled in the specifications to ensure that the resulting impurities in the active substance will be below the identification threshold in the active substance. Generation, prevention and prevalence for most impurity types are described in sufficient detail. Acceptable justification for control of impurity groups as specified or unspecified impurities in the intermediates or active substance specification is provided.

In response to the Major Objection on nitrosamines, a detailed risk assessment for nitrosamine impurities was provided, summarising the risk within the manufacturing process for drug substance and drug product, including the risk assessment of the manufacturing processes for all intermediates, starting materials, reagents, solvents, and other raw materials. In summary, no medium nor major risk for nitrosamine contamination has been identified.

The 3.2.P.5.5 Nitrosamines Risk Assessment has been updated (the detailed risk assessment for drug substance and drug product has been added in Appendix 1) and submitted.

All current qualified suppliers have been evaluated in combination with the associated risk assessment for nitrosamine impurities.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

Overall, a good understanding of the structure and the impurity profile of the active substance is demonstrated. The intermediates were included in the analyses as appropriate and the correlation between the structures and impurities were elucidated. Detailed investigation of related impurities was performed including those originating from starting materials, intermediates, manufacture and degradation. Non-peptide-related impurities were investigated and are controlled mainly by release data which is acceptable.

Specification

Control of active substance

The specification proposed for the active substance includes tests for appearance, identification, assay, water, residual solvents, bacterial endotoxins, total aerobic microbial count, and total yeasts and moulds count.

CQAs for the active substance have been presented and reflect the active substance specification. The selection of test parameters is acceptable overall.

Batch release data were the basis for setting of acceptance criteria together with analytical variation and requirements for finished product manufacturing. Release and stability data were used for calculation of tolerance intervals, widened by analytical variation calculated as SD from stability data. If a change was observed during long-term storage, an Allen contribution was additionally introduced to compensate this. Limits for residual solvents and TAMC/TYMC are based on ICH Q3C and

pharmacopoeial guidance, respectively, and acceptable. The acceptance criterion for bacterial endotoxins is justified in sufficient detail.

All non-compendial methods are described briefly without providing details on the equipment (besides applied columns) and the procedure (e.g. number and order of samples). Sample preparation, system suitability test (SST) parameters, formulae for result calculation and exemplary chromatograms are provided as applicable. Performance of the methods is acceptable.

Validation data is provided for all non-compendial methods. All relevant parameters were validated for the respective methods. Overall, the information provided on method validation is acceptable. It is indicated that all pharmacopoeial methods have been verified.

Batch release data for GMP, technical and post-PPQ (GMP) batches manufactured between 2016 and 2022 is provided. The batches were tested according to the specification in force at time of release. Nevertheless, the specification proposed for the early development batches was very similar to the current specification. All respective specification criteria are met.

The control strategy for the active substance has been summarised and contains overviews on the following elements: control of input materials, validation of manufacturing process for the active substance, specifications and stability testing. References to the relevant sections in the dossier are provided. The overall approach for the control strategy is reasonable.

Reference standards or materials

The active substance reference standards used during development are described.

Container closure system

The active substance will be packed in amber glass bottles (in compliance with Ph. Eur. 3.2.1. Glass containers for pharmaceutical use).

Acceptable specifications for the container closure system are presented. Suitability of the container closure system is demonstrated by reference to stability studies.

Stability

Palopegteriparatide drug substance stability studies were performed on one supportive GMP batch produced in pilot scale, three primary batches produced in production scale and three PPQ batches. Since only minor optimization was performed before production of the PPQ batches, all stability batches can be considered representative. The applicant indicates that smaller size containers and closures than commercial are used, but that they simulate the proposed for commercial. The applicant also indicates that the ratio of headspace volume to material volume applied in the stability studies is worst-case ratio. The studies are designed according to ICH Q1A. The selection of parameters is supported by the forced degradation studies presented. The applicant commits to continue the stability studies throughout the retest period and to place one batch per year on long-term stability. It is confirmed that in the case of negative stability results or out of specification events during on-going or post-approval stability studies the relevant authorities will be informed. Testing will be performed for similar parameters as the on-going stability studies.

Stability data are provided for the supportive batch (all supportive studies are completed.); for two primary batches; for one primary batch and for all three PPQ batches. All available results were within acceptance criteria at long-term and accelerated conditions. Forced degradation studies investigated the influence of temperature, moisture and light exposure on the solid active substance as well as stability of the drug in aqueous solution alone or upon acid, oxidation or base stress.

The retest period is based on the available long-term stability data of the primary stability batches and pilot batch and considered acceptable.

2.3.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Palopegteriparatide prefilled pen is a drug-device combination product. The product consists of a solution in a 1.5 mL cartridge assembled in a single-patient-use pen injector intended for daily subcutaneous injection. CE-marked Injection needles are provided co-packed in the secondary packaging.

Palopegteriparatide finished product is a sterile, colourless, and clear solution for injection, with a nominal concentration of 0.3 mg PTH(1-34)/mL, in a 1.5 mL cartridge. Three different volumes of palopegteriparatide compounded solution are filled into the cartridges, providing palopegteriparatide finished product containing 0.56, 0.98 and 1.4 mL solution for injection, respectively. alopegteriparatide finished product cartridges are each filled with an overfill.

The three pen presentations are designed to deliver doses of 6-12 µg (168 µg/0.56 mL), 15-21 µg (294 µg/0.98 mL) or 24-30 µg (420 µg/1.4 mL) in 3 µg increments. The pens differ by the colour of the push button.

The finished product solution contains the prodrug palopegteriparatide, water for injections, succinic acid , mannitol, metacresol, sodium hydroxide and hydrochloric acid (for pH adjustment). The description and composition of the finished product is detailed in the dossier and in the SmPC section 6.

Pharmaceutical development

Formulation studies were executed to identify the optimal finished product composition with regard to stability and patient convenience (suitability for s.c. injection). The company has considered factors such as physiological pH, tonicity, historical use of excipients and compendial requirements, stability during shelf-life and stability during use.

Only minor formulation adjustments have been introduced during the development of palopegteriparatide finished product. The excipients have not been changed throughout the entire clinical development program. The composition of the finished product and the primary container closure system used during Phase 2 and Phase 3 clinical trials are identical to the ones intended for the market.

The prodrug palopegteriparatide consists of PTH(1-34) transiently conjugated to an inert carrier via a cleavable proprietary linker (TransCon Linker). At physiological pH and temperature, active PTH(1-34) is released from the prodrug via an auto-cleavage reaction. Biological activity of released PTH(1-34) has been demonstrated by a cell-based bioassay (PTH1R-expressing HEK293 cells) in comparison to the WHO international reference standard.

The selected excipients are widely used. No novel excipients or material from animal or human origin are used for finished product manufacture. The function, type and quantity of excipients have been well justified and are acceptable.

Manufacturing process changes occurring throughout development are transparently described, and comparability of the finished product is sufficiently demonstrated. Problems and resolutions of it are clearly explained without important modification of the formula or of the manufacturing process during the time. Criticality of process parameters and controls is described in the dossier.

The suitability of the primary packaging components has been sufficiently demonstrated.

The finished product manufacturing process and its control strategy ensures that the finished product is sterile. Container closure integrity (CCI) and sterility have been confirmed during primary stability studies until end of shelf-life.

The functional secondary packaging, the single-use pen, was a platform-based pen device and the 31G x 5mm pen needles. The needle is sterilized, single use, made of stainless-steel, complies with applicable standards and is suitable for use with pen injectors for self-administration of injection liquid. Suitability of the pen device(s) for the intended purpose is confirmed by the respective NBOp included in the dossier.

Compatibility of the finished product solution with the pen device and the co-packaged needles is confirmed by the NBOp.

Manufacture of the product and process controls

Ascendis Pharma A/S (Tuborg Boulevard 12, DK-2900 Hellerup, Denmark) is responsible for batch release.

Proof of GMP compliance for all manufacturing and testing sites has been provided.

The components of the finished product are compounded, sterile filtered and aseptic filled. The cartridges are then finally assembled into the pen devices, before secondary packaging.

The manufacturing process for the prefilled pen is detailed in the dossier.

The equipment is described with the relevant level of detail, as is the preparation of the primary packaging. Critical and non-critical process parameters and controls are stated and overall adequately described. The manufacturing process of the finished product is well described and sufficiently detailed, including appropriate flow-charts and process control parameters.

Criticality of process parameters (PP) and in-process controls (IPC) was established based on a risk assessment. The overall control strategy is explained and the data to underpin the proven acceptable ranges (PAR) are presented. The classification of process parameters and in-process controls according to their criticality is deemed acceptable. Holding times are indicated as applicable and supported by respective validation data. Overall, the finished product manufacturing process and its control are satisfactorily described.

Process validation comprises validation of the aseptic manufacturing, manufacture of PPQ batches at the commercial site and continued process verification. A bracketing approach was applied for the PPQ batches, which is deemed acceptable as the finished product solution is identical for the three presentations.

Validation of the Millipore Durapore PVDF membrane filters was performed, including microbial retention, viability studies (a modified finished product solution with a higher pH and without metacresol was used), membrane compatibility, product specific bubble point and extractables. Respective data is considered sufficient. Additionally, the aseptic manufacturing is validated/revalidated by performing media fills, covering worst-case conditions.Shipping is sufficiently supported by a shipping simulation study.

Product specification

Finished product release and shelf-life specifications are presented in the dossier.

The finished product specification is considered comprehensive and covering the main quality aspects: Identity, content of palopegteriparatide, impurities related to palopegteriparatide, release of PTH(1-34), impurities of released PTH(1-34), appearance, contaminants, pH, osmolality, sub-visible particles and dose accuracy.

The applicant justified the omission of purity acceptance limits by the fact that main peak and impurity peaks sum up to 100%, thus defining purity by default as 100%-sum of impurities.

Biological activity was agreed not to form part of the finished product specification. The applicant argued that correlation is well established for PTH(1-34) and physicochemical properties which in turn are adequately controlled at release and during storage.

Extractable volume is not part of the finished product specification. The applicant justified omission of this test by the fact that fill volume is controlled for each cartridge by the correct plunger position which is acceptable since the respective correlation is transparently described.

Nitrosamines, elemental impurities and residual solvents are not included in the finished product specification based on respective risk assessments. This is acceptable based on the respective risk assessments that have been provided.

A characterization study has been performed to identify the related impurities generated during manufacture and storage of palopegteriparatide finished product. The study has shown that the impurity profiles of palopegteriparatide active substance and finished product batches are comparable, and no new impurities are formed during the finished product manufacturing process.

The proposed finished product release acceptance limits for impurities take into account both batch release data and stability data where applicable, analytical variability and statistical evaluation of the data. As the composition of the finished product solution is identical for all three presentations, their data across the presentations were pooled for statistical analysis which is deemed acceptable.

The analytical procedures for finished product quality control are adequately described. SST criteria are defined and example chromatograms and spectra (as applicable) included.

The tests for sterility and bacterial endotoxins have been validated in accordance with the Ph. Eur.

Release data have been submitted and confirm compliance with the finished product specifications in place at time of release.

Reference standards

For palopegteriparatide reference standard(s), reference is made to the section S.5.

Container Closure System (CCS)

The palopegteriparatide finished product is filled in glass cartridges, closed with a rubber stopper and a double layer disc-seal with an aluminium crimp cap. The description of the container closure system for the finished product is clear and sufficiently detailed (for Medical Device issues, please see below).

Compliance with the relevant Ph. Eur. requirements is stated to be given for type I glass and the rubber components.

The cartridges are inserted in disposable, multi-dose pens. Three different types of pen are used in order to meet the requirements for all types of posology. The three different pens can be distinguished by differently coloured push buttons. The description of the pen components, their sub-assembly and final assembly is sufficiently detailed in the dossier.

The pre-filled pens are packed together with CE marked needles.

Stability of the product

The applicant claims stability of the finished product for 36 months at 2-8°C, with an in-use period of 14 days at up to 30°C. The results from the primary, supportive and PPQ batches show no difference in stability profiles thus justifying that the primary stability data can be used to set the shelf-life for all presentations.

To support this claim, primary stability studies were performed in line with ICH Q1A (R2) using finished product in cartridges for 36 months at the recommended storage condition . A bracketing approach was selected, including the lowest and the highest fill volumes (0.58 and 1.4 mL). This is acceptable as the finished product composition is identical for all three presentations.

It could be demonstrated that the pen assembly does not impact on the stability of the finished product solution, thus the data of unassembled cartridges are deemed representative. For all stability studies, the primary packaging components as intended for the commercial process were used.

In both the primary and the supportive stability study, all acceptance criteria of the finished product shelf-life specification were met, generally supporting the Applicant's shelf-life claim.

Comprehensive in-use stability data using finished product of various ages are presented and support the Applicant's claim for 14 days in-use stability at up to 30°C.

Photostability studies according to ICH Q1B show that palopegteriparatide is light-sensitive and that the prefilled pen must be stored in the inner carton box to be sufficiently protected against light during shelf life. The pen with the pen cap on provides sufficient protection during in-use storage. This and the in-use stability claim are adequately reflected in the SmPC.

The applicant's shelf-life claim (36 months at 2-8°C, plus 14 days in-use stability at 30°C) is satisfactorily supported by data and can be agreed.

Ascendis Pharma commits to continue the monitoring of the stability of palopegteriparatide finished product primary and PPQ batches through the proposed shelf life in accordance with the stability protocols for primary and PPQ batches. Ascendis Pharma commits to annually place one batch of palopegteriparatide finished product alternating different presentations into the on-going stability program.

Medical Device Issues

A NBOp confirms compliance of the pen device with the relevant GSPR. In addition, stability of the pen for 3 years has been confirmed. This period is sufficient to cover the intended shelf-life of the fixed drug-device combination.

Information substantiating pen functionality taking into account potential storage prior to assembly has been provided. It supports storage of the pen sub-assemblies for 24 months prior to assembly.

The co-packaged needles bear a CE mark. An EC certificate confirming the compliance of the needle manufacturer's quality system with Directive 93/42/EEC on Medical Devices (MDD) is presented. This is acceptable, as this certificate remains valid until end of the transition period (according to FAQ – MDR Transitional provisions issued by the CAMD).

Adventitious agents

No materials of human or animal origin are used.

2.3.4. Discussion and conclusions on chemical and pharmaceutical aspects

Overall, the quality dossier is well structured and informative.

The active substance palopegteriparatide is a synthetic PTH(1-34) transiently conjugated to a carrier via a TransCon Linker. From the prodrug palopegteriparatide, PTH(1-34) is released under physiological conditions by auto-cleavage of the TransCon Linker. PTH(1-34) is identical to the first 34 amino acids of the full length, 84 amino acid human parathyroid hormone (PTH). The N-terminus modification consists of the TransCon Linker attached to the carrier (a branched 40 kDa (2 × 20 kDa) mPEG succinimide derivative).

The finished product is a fixed drug-device combination, consisting of a finished product solution in a cartridge, assembled in a pre-filled pen. Three different presentations are foreseen, containing the identical formulation at different fill volumes. The finished product solution is compounded, sterile filtered and aseptically filled into cartridges. The manufacture and control of the finished product is adequately described. The control strategy is well justified and it could be demonstrated that the finished product manufacturing process leads to finished product of consistent quality. In response to an MO raised on its absence, a satisfactory risk assessment for all possible sources of nitrosamines has been provided and considered acceptable.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3.6. Recommendations for future quality development

Not applicable.

2.4. Non-clinical aspects

2.4.1. Introduction

Palopegteriparatide consists of PTH(1-34) conjugated to a methoxypolyethylene glycol inert carrier (mPEG) via a Linker designed as a subcutaneous (SC) once daily replacement therapy to provide continuous parathyroid hormone (PTH) exposure for 24 h in adult patients with hypoparathyroidism. The recommended starting dose of palopegteriparatide is 18 µg PTH(1-34)/day. Based on the concentration of serum calcium in the systemic circulation, the dose level can be adjusted in increments of 3 µg PTH(1-34)/day within the dose range from 6 µg PTH(1-34)/day and up to the maximum recommended human dose (MRHD) of 60 µg PTH(1-34)/day.

PTH(1-34) is identical to the first 34 amino acids of the full length, 84 amino acid, human PTH, and is essentially inactive when connected to the carrier. The carrier is a branched 40 kDa (2×20 kDa) methoxypolyethylene glycol (mPEG) moiety. At physiologic pH and temperature, active PTH is released from the prodrug via auto-cleavage to maintain a continuous exposure to PTH in the systemic circulation.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

Endogenous PTH exerts its action through binding to PTH receptor 1 (PTH1R). As only amino acid residues 1-31 are required for full PTH1R activation, amino-terminally truncated PTH variants such as PTH(1-34) and PTH(1-33) bind to the receptor with the same affinity as full length PTH.

Palopegteriparatide itself was shown to have a low affinity for PTH1R. In contrast, PTH(1-34) released from palopegteriparatide had a similar affinity for PTH1R as the PTH(1-34) reference standard as shown by surface plasmon resonance.

According to the literature (Cheloha et al. 2014), sequence homology of human PTH(1-34) compared to rat, rabbit and cynomolgus monkey PTH(1-34) is 85%, 79% and 100%, respectively. The sequence of rat, rabbit and monkey PTH1R has also a great degree of homology to human PTH1R. In line with these findings, comparable binding affinity and biopotency of human PTH(1-34) for rat and human PTH1R was observed. Thus, rats, rabbits and monkeys are considered pharmacologically relevant species for the non-clinical evaluation of palopegteriparatide.

PTH is a major regulator of calcium and phosphate homeostasis. While calcium levels are determined almost solely by PTH, serum phosphate is additionally regulated by fibroblast growth factor 23 (FGF23). Therefore, quantification of the circulating calcium was considered the primary pharmacodynamic endpoint. The secondary pharmacodynamic parameters included in the evaluation were serum and urinary phosphate and urinary calcium.

No clear dose-related effects on blood calcium or blood phosphate levels were observed after a single intravenous or subcutaneous administration of TransCon PTH to normal Sprague-Dawley rats at 10 µg PTH(1-34)/kg or 30 µg PTH(1-34)/kg. Although all animals were exposed to PTH, the exposure was apparently not sufficient to elicit a pharmacodynamic response.

In normal male cynomolgus monkeys, subcutaneous and intravenous administration of 1 µg PTH(1-34)/kg led to an increase in plasma calcium levels, at the dose of 5 µg PTH(1-34)/kg calcium concentrations exceeded the historical range. Therefore, the primary pharmacodynamic endpoint was achieved in monkeys as a dose-related increase in plasma calcium could be demonstrated.

The effect on urinary calcium is less convincing. The applicant reported an increase in urinary calcium/urinary creatinine following treatment with palopegteriparatide at 1 and 5 µg PTH(1-34)/kg intravenously . No clear trend was noted after subcutaneous administration of 1 µg PTH(1-34)/kg. Generally, great variability in urinary calcium concentrations was observed making any conclusions regarding the effect of palopegteriparatide on urinary calcium unreliable. The applicant explains that the large variability in the urinary calcium in this study represents both intraindividual variability in addition to the interindividual variability as the same animals were administered palopegteriparatide subcutaneously and and 1 µg PTH(1-34)/kg intravenously. The applicant acknowledges that no meaningful conclusions on urinary calcium excretion can be drawn from the results of this study.

A proof-of-principle for palopegteriparatide was evaluated in the thyroparathyroidectomised (TPTx) Sprague Dawley rat model. In TPTx rats, the parathyroid glands are excised together with the thyroid glands followed by thyroxin substitution. As the rat parathyroid glands are very small, identification and excision of these glands alone is difficult and does not produce reliable data on postoperative concentrations of endogenous PTH and/or calcium. Therefore, the TPTx model routinely used to evaluate the potential biological effects of PTH analogues was considered suitable to assess the pharmacological activity of palopegteriparatide. The applicant selected only female animals for the proof-of-principle study as most patients with hypoparathyroidism are female. Sex-related PK and PD

differences were investigated in toxicology studies. Taking into account the 3R principles, including only female animals in the proof-of-principle study is justified. Next to the vehicle-treated TPTx control group, a sham-operated vehicle-treated group was included as euparathyroid control.

Compared to sham controls, TPTx control animals were characterised by suppressed serum vitamin D levels as a direct consequence of the absent PTH production consistent with low serum calcium and high serum phosphorus concentrations, and low urinary phosphorus/creatinine levels. Urinary excretion of calcium was comparable to sham-operated control rats possibly due to the low filtered calcium and lack of calcium and active vitamin D supplementations. Resulting from the distorted calcium and phosphorus homeostasis, TPTx rats had a low bone turnover as was clear from low levels of both the bone formation (P1NP) and resorption (CTx) markers and an increase in trabecular bone mass and trabecular bone mineral density. These are all representative hallmarks of human hypoparathyroidism.

TPTx rats were then subcutaneously administered either vehicle, palopegteriparatide at 5, 10 or 30 µg PTH(1-34)/kg/day or 70 µg rhPTH(1-84)/kg/day over 28 days. Recombinant hPTH(1-84), with the same amino acid sequence as in Natpar, served as a comparator at the pharmacologically active dose. On a molar basis, 70 µg rhPTH(1-84)/kg/day is similar to the highest dose of palopegteriparatide (30 µg PTH(1-34)/kg/day).

rhPTH(1-84) treatment produced a small and transient increase in serum calcium. Serum phosphate levels were comparable to TPTx and higher than in sham controls. No effects on urinary calcium or phosphorus were noted. Circulating active vitamin D concentrations were higher than in TPTx controls and comparable to sham controls. The increased bone mineral density observed due to the thyroparathyroidectomy procedure alone was further augmented by rhPTH(1-84) as evident from the markers of bone turnover.

In contrast, palopegteriparatide at 5 or 10 µg PTH(1-34)/kg/day led to a sustained increase in serum calcium and sustained decrease in serum phosphorus. Urinary calcium initially increased, probably representing the increased filtered load of calcium, which at first overruled the calcium conserving property of PTH. Such an increase is consistent with the expected enhanced intestinal absorption of calcium combined with increased mobilisation of calcium from the skeleton upon reestablishment of PTH1R signalling. The latter is likely to result from excessive calcium stored in hypermineralised bones of TPTx rats. Later in the course of the study, urinary calcium declined and was comparable to TPTx and sham controls by the end of the study. This result is in agreement with the expected PTH-induced effects on renal calcium reabsorption. At the study end, more long-term compensatory mechanisms to avoid hypercalcemia, such as reduced gastrointestinal absorption of calcium, may have been activated as supported by low levels of the active vitamin D. Urinary phosphate excretion increased in palopegteriparatide-treated TPTx rats relative to TPTx controls but was comparable to sham controls at the end. Circulating levels of active vitamin D remained below LLOQ in almost all animals administered palopegteriparatide at 5 or 10 µg PTH(1-34)/kg/day. Low concentrations of vitamin D may reflect a compensatory mechanism to the sustained increase in circulating calcium and/or PTH. In line with this interpretation, low active vitamin D has been described in hyperparathyroidism. It is likely related to either inhibited synthesis or accelerated catabolism of active vitamin D induced by high circulating calcium or FGF23 released from osteocytes upon excessive PTH signalling. This points out at a possible exaggerated pharmacological effect of palopegteriparatide already at 5 or 10 µg PTH(1-34)/kg/day.

The biochemical markers of bone turnover also improved dose-dependently after administration of palopegteriparatide. Circulating P1NP, a marker of bone formation, increased to a level comparable to that in sham controls whereas urinary CTx, a marker of bone resorption, markedly exceeded sham control levels. As bone resorption apparently exceeded bone formation, trabecular bone mineral density and content were decreased at both 5 and 10 µg PTH(1-34)/kg/day compared to both TPTx and sham controls. The applicant attributes this effect to exaggerated pharmacology and argues that

the extent of this effect is a hallmark feature of the TPTx rat since bone turnover markers in patients normalised after initial peaking.

At the highest dose of palopegteriparatide (30 µg PTH(1-34)/kg/day), the death of two rats was noted. Signs of soft tissue mineralisation were found in the aorta, heart, kidneys, stomach and pancreas. The applicant considers soft tissue mineralisation an expected exaggerated pharmacological effect of palopegteriparatide, which is agreed. Nevertheless, the Applicant is of the opinion that the observed effects of persistent hypercalcemia are related to exaggerated pharmacology of palopegteriparatide in animals and are thus not clinically relevant. Hypercalcemia was observed in clinical trials but proved to be manageable. The aim in a clinical setting is to find an individual dose of Yorvipath that normalises serum calcium. Hereafter, serum calcium is continuously monitored in the patient along with signs and symptoms of hypercalcaemia and hypocalcaemia. Persistent hypercalcemia is therefore only of clinical relevance in the extreme, but very unlikely, clinical scenario consisting of continuous overdosing, with a lack of monitoring of serum calcium levels as well as signs and symptoms of hypercalcaemia.

2.4.2.2. Secondary pharmacodynamic studies

As no secondary pharmacodynamic effects of palopegteriparatide or the products of its cleavage were noted in non-clinical studies, the absence of dedicated secondary pharmacodynamics studies is acceptable.

2.4.2.3. Safety pharmacology programme

Subcutaneous administration of palopegteriparatide to Sprague-Dawley rats had no effects on central nervous or respiratory system up to and including 60 µg PTH(1-34)/kg. At this dose, exposure (AUC) to free PTH was 7.3-fold the observed clinical exposure at a dose similar to MRHD. Transient increase in serum calcium levels was noted at doses from 30 µg PTH(1-34)/kg.

Subcutaneous injection of palopegteriparatide to cynomolgus monkeys had no effect on cardiovascular parameters, calcium and phosphorus levels up to and including 1.5 µg PTH(1-34)/kg, which corresponds to 0.98-fold the predicted clinical exposure at the MRHD based on Cmax after repeated administration, which is the proposed clinical schedule.

2.4.2.4. Pharmacodynamic drug interactions

Palopegteriparatide is a prodrug releasing PTH(1-34), which in turn binds PTH receptor 1 with high specificity. No pharmacodynamic effects of the remaining mPEG-based TransCon linker were detected in non-clinical studies. Therefore, the absence of pharmacodynamic drug interaction studies is agreed.

2.4.3. Pharmacokinetics

The pharmacokinetics of palopegteriparatide was investigated in single-dose PK/PD studies in Sprague-Dawley rats and cynomolgus monkeys. PTH release from palopegteriparatide was studied in vitro. Metabolism in rats, monkeys and humans was assessed in vitro and ex vivo.

The bioanalytical methods to be used in pharmacokinetic and toxicokinetic studies were developed and successfully validated. In many methods, the acceptance criteria for the validation parameters were set wider than recommended by the EMA guideline on bioanalytical method validation EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2 due to method complications. Nevertheless, the criteria are in line with those described in the scientific literature, which is acceptable.

The release of PTH from palopegteriparatide has been shown to be faster with increasing temperature and increasing pH. The half-life of the linker cleavage at 37 °C and pH 7.4 was around 2.5 days. In vivo PK data from monkeys confirmed this estimation. The absorption of palopegteriparatide after single dose subcutaneous and intravenous administration was characterised in Sprague-Dawley rats and cynomolgus monkeys. In both species, exposure was dose-proportional. The terminal half-life was substantially long in both species. In monkeys, the bioavailability of Total PTH was higher (73 – 78 %) than that of Total PTH(1-34) (51 – 54 %) indicating a faster and/or additional C-terminal peptide degradation in subcutaneous tissue. No gender comparison has been done as the studies were performed only in male animals. This is, however, acceptable since toxicokinetic evaluation included both sexes. Toxicokinetic measurements showed higher exposure to Total PTH in female rats, whereas no gender differences were reported for Free PTH.

Palopegteriparatide is a prodrug designed for slow release of PTH, a naturally occurring hormone that specifically binds the PTH receptor 1. Therefore, the absence of protein binding and distribution studies is acceptable. Due to the presence of high molecular weight mPEG part, membrane diffusion and thus distribution is limited to highly vascularised organs and palopegteriparatide mainly stays in circulation.

PTH(1-34) is metabolised to PTH(1-33) by proteolytic cleavage. In vitro, metabolism was most pronounced in monkey plasma (11.3%), followed by rat plasma (6.9%) and human plasma (2.3%). The same order was observed in non-clinical species in vivo. In cynomolgus monkeys, around 60% of palopegteriparatide was converted to PTH(1-33), in rats it were only about 20%. These findings suggest a low degree of metabolism in humans in vivo.

PTH(1-34) released from palopegteriparatide is likely to be excreted via renal route. Another part of palopegteriparatide, mPEG, is also excreted in urine with a minimal contribution of hepatic clearance. The linker has been shown to remain attached to mPEG after cleavage (plasma concentrations of mPEG and mPEG-linker were similar) and is therefore eliminated together with mPEG.

Drug interaction potential of palopegteriparatide is considered to be low as it is a peptide-based therapeutic aimed to release a naturally occurring hormone.

2.4.4. Toxicology

The toxicity profile of palopegteriparatide was characterized in repeat-dose toxicity studies in rats and cynomolgus monkeys, up to 4- and 26-weeks duration, respectively. The choice of these species was justified by the highly conserved amino acid sequences of PTH and its primary receptor PTH1R across rats, rabbits, monkeys and humans. Further, palopegteriparatide was shown to be pharmacologically active in these species. Palopegteriparatide was administered by SC injection in all in vivo toxicity studies. This is the same administration route as the intended clinical route.

2.4.4.1. Single dose toxicity

No single dose toxicity studies have been conducted which is considered acceptable.

2.4.4.2. Repeat dose toxicity

The majority of treatment-related findings in repeat-dose studies in rats and monkeys were the result of an exaggerated pharmacology of the drug, a dose-dependent and reversible increase in serum calcium and a dose-dependent and reversible decrease in serum phosphate levels.

As mentioned above, repeat dose toxicity assessment has been analysed in 4- and 26-week studies in rats and monkeys. Although the duration is acceptable according to ICH M3 guideline in the EU, a 39-

week study in the non-rodent species should have been considered, especially when dose levels selected in monkeys were below the MHRD. The limitation of the maximum dose level in monkeys (treatment at 1.5 µg PTH(1-34)/kg/day resulted in one death animal (one out of four)) makes it difficult to consider this species for anticipating toxicity in humans. In this regard, limited toxic effects have been reported in toxicity studies in monkeys (4- and 26-week).

Also in the 4-week toxicity studies in rats, findings in physis and bone were reported (≥30 µg PTH(1-34)/kg/day). These findings were further confirmed in the chronic repeat dose toxicology in rats, when a long-term administration/observation is necessary to identify significant changes in bone turnover.

In the 4-week rat study, two female animals died after administration of the highest dose tested, 60 µg PTH(1-34)/kg/day. These deaths were the result of the adverse effects of mineralization of kidney and associated tubular findings in the kidney and/or mineralization of the myocardium. Soft tissue mineralization was also observed in the aorta, adrenal gland, liver, lungs, pancreas, stomach and small and/or large intestines in rats at the highest dose tested, but not in monkeys.

Deaths of animals also occurred during the 26-week rat study. However, in contrast to the moribund animals in the 4-week study, 6 of these deaths were considered to be not treatment-related; only one cause of death could not be determined since no abnormal clinical signs were noted prior to its death and no body weight changes noted. Thus, the cause of death may be treatment-related but seems unlikely.

Effects on investigated parameters mainly reflected the exaggerated pharmacological effects including bone formation, decrease in bone marrow spaces, extramedullary hemaopoiesis and increases in serum calcium. An increase in urinary calcium was not observed in the repeat-dose studies but in the pharmacology studies. In both rat studies, an increase in ALP values was noted. No equivalent changes in ALP were found in monkeys; and biochemical markers (PINP and CTx) were evaluated in the 26-week monkey study.

Further to the effects on bone formation, reversibly increased thickness of the physis and physeal dysplasia in long bones occurred. The latter was only present in the 26-week rat study but not in the 4-week rat study. The observed thickening of the physis at high dose levels may reflect PTH-induced retention of chondrocytes in the proliferative and less differentiated state. The changes observed in the physis are not considered relevant for patients since the physis are closed in mature patients and the effects occurred only at doses which are above the intended physiological range. No equivalent changes were found in monkeys. The absence of changes in the studies in monkeys (4- and 26-week) can be attributed to the treatment duration along with limited dose level (exposure margin below 1), which make it difficult to detect significant changes relevant to humans in bone turnover or physis thickening. These changes need longer treatment duration and higher doses to be detected, so the information obtained from monkey studies could be considered as limited.

The anabolic effect on bones was overall more pronounced in male rats whereas the catabolic effect was evident in female rats. Such sex differences have already been reported in mice where continuous exposure to PTH favored a bone catabolic effect in females. The net anabolic bone effect was generally considered to occur during the first 13/14 weeks of dosing (as males showed a similar magnitude of increases in pQCT values in Weeks 13/14 and 25/26, but a higher increase in histomorphometrical BV/TV in Week 26 than Week 4).

The net catabolic effect (increases in cortical and trabecular BMD) in the 26-week rat study at the end of the recovery period in conjunction with increases in ALP and the lack of effect on PINP were interpreted in that way that continuous exposure to PTH increased the commitment of progenitor cells to an osteoblast fate, but remained at the pre-osteoblast stage. The net catabolic bone effect was considered to occur during the first 4 weeks of dosing (females showed a similar magnitude of

decrease in histomorphometrical BV/TV in Weeks 4 and 26 and had stable pQCT values in Weeks 13/14 and 25/26).

The applicant concluded a net anabolic or catabolic bone effect, occurred after an exaggerated pharmacological effect. It is agreed that bone remodelling is a continuous process between catabolic and anabolic effects, which in turn depends on several factors such as species, sex or time point of measurement. Given that many parameters have been recorded in chronic rat study, and the effects on some of them look contradictory, it is difficult to anticipate the actual effect in humans after administration of palopegteriparatide. Likewise, bone effects (trend towards a decrease in cortical BMD have been also observed in monkeys, although remaining parameters related to bone turnover were unaffected. Thus, a direct translation to humans should be determined in clinical practice.

Again, information from chronic monkey study is considered limited due to low dose levels tested.

In the 26-week monkey study, TransCon PTH (ACP-014) was administered daily sc at doses of 0.2, 0.5, 1.5/1.0 µg PTH(1-34)/kg/day. 1 female monkey administered 1.5 µg PTH(1-34)/kg/day was found dead on day 24. The cause of poor clinical condition and death was changes in liver, kidney, brain and ovary. The histopathological findings were mainly reflective of the markedly increased serum calcium levels. No deaths occurred in the 4-week monkey study.

Bone mineral density content was analysed and a trend towards a decrease in cortical bone mineral density (BMD) was observed at the highest dose level in the 26-week repeat-dose toxicity study in monkeys. Other indices of bone turnover were unaffected in monkeys.

Vacuoles related to palopegteriparatide in choroid plexus epithelial cells or in any other tissue or organ, were not demonstrated at the histopathological evaluations in any toxicity studies in rats and monkeys.

Finally, the NOAEL values for chronic studies were established at 10 and 0.5 µg PTH(1-34)/kg/day for rat and monkey, respectively. In the case of rat chronic study, adverse physeal dysplasia was observed at 20 µg PTH(1-34)/kg/day (also observed at 10 µg PTH(1-34)/kg/day with less severity). In monkeys, preterminal death occurred at 1.5 µg PTH(1-34)/kg/day, marked sustained increases in sCa levels and potentially TransCon PTH (ACP-014)-related severe degenerative joint disease were observed bilaterally in one animal at 1.5/1.0 µg PTH(1-34)/kg/day.

The main findings reported in the repeat dose toxicity studies are included in the SmPC, section 5.3.

2.4.4.3. Genotoxicity

A standard battery of in vitro and in vivo genotoxicity tests was performed with palopegteriparatide and its associated cleavage products. To investigate the potential genotoxicity of the products generated by in vivo auto-cleavage of palopegteriparatide, the two in vitro genotoxicity studies were conducted using palopegteriparatide incubated beforehand under physiological conditions. Thereby the test article contained palopegteriparatide, PTH(1-34) and mPEG attached to the TransCon Linker.

Cleaved palopegteriparatide was negative in three bacterial strains in the Ames test but reported to be slightly positive (~2-fold increase in revertants or outside historical control data) at the two highest concentrations with S9-mix in strains TA98 and TA100. Published studies indicate that rat liver homogenate is able to cleave PTH(1-34) and generate histidine or fragments with a terminal histidine moiety (Liao, 2010). As indicated in ICH S2(R1), histidine is known to produce false positive results in the Ames test. This is substantiated by the fact that PTH(1-34) has previously been shown to produce false positives by bacterial overgrowth in Ames tests (Thompson, 2005). Reassuringly, cleaved palopegteriparatide was negative in an in vitro chromosome aberration assay and an in vivo

micronucleus test in rats at sufficiently high exposures. In addition, in silico assessment of the TransCon linker in line with ICH M7(R1) revealed no concern for genotoxicity and carcinogenicity.

Overall, it can be concluded that palopegteriparatide and its cleavage products show no genotoxic potential in vitro and in vivo.

2.4.4.4. Carcinogenicity

No carcinogenicity studies have been performed with palopegteriparatide. Instead, a thorough discussion has been provided by the Applicant. Overall, the arguments presented are supported. Short-lived PTH analogues lead to intermittent supra-physiological exposure to PTH, resulting in a net anabolic bone effect in rats and as consequence to osteosarcomas. Albeit so far no increased osteosarcoma incidences have been reported in patients, the SmPCs of those compounds still contain the information of osteosarcoma findings in rats with unknown but probably minor consequences for patients due to species differences in bone physiology of rats and humans. In contrast, palopegteriparatide as a replacement therapy provides physiological PTH levels and thus normalizes bone turnover and has not been shown to lead to a net anabolic effect on the long term in patients. In addition, the TransCon Linker did not flag concerns about genotoxicity and carcinogenicity in in silico analyses. Therefore, the lack of carcinogenicity studies is considered acceptable.

The lack of carcinogenicity studies is adequately addressed in section 5.3 of the SmPC. Further information of the physeal dysplasia and net anabolic/catabolic effects reported in the chronic rat study, as well as the exposure ratio established in the non-clinical studies is also included in section 5.3 of the SmPC.

2.4.4.5. Reproductive and developmental toxicity

Palopegteriparatide has been investigated in a range of ICH S5 compliant reproductive and development toxicity studies after daily subcutaneous administration. These included fertility and early embryonic development toxicity studies separately conducted in male and female rats as well as preliminary and definitive embryo-foetal development toxicity studies in rats and rabbits. The definitive studies were performed in accordance with GLP. No pre-and postnatal development toxicity studies have been performed with palopegteriparatide.

No separate reproductive and developmental studies have been conducted with the TransCon Linker attached to mPEG or the single components (mPEG and TransCon Linker). This is acceptable given that potential effects of the TransCon Linker attached to mPEG on foetal development and maternal function were addressed by exposing the animal until GD 17 in rats and GD 19 in rabbits in EFD studies conducted with palopegteriparatide and that it is considered unlikely that PTH(1-34) and TransCon Linker attached to mPEG will cross the placenta or will be excreted in breast milk (please also refer to the assessment of section 4.5.3). *In silico* assessment of the 4 structures of the TransCon Linker, with and without the branching point for mPEG, identified no structural alerts for DART or genotoxicity.

In fertility and early embryonic development (FEED) studies male and female rats treated subcutaneously with 0, (vehicle), 2, 6 or 20 µg PTH(1-34)/kg/day, no effects on parental performance (number of days to mating, mating and fertility indices and conception rate), male reproductive investigations (sperm motility, count and morphology, organ weights and testicular histopathology) or on early embryonic development were observed. Pharmacologically related increased serum calcium levels were observed in males and females administered 20 µg PTH(1-34)/kg/day, in addition to

transient body weight loss with no effect on food consumption. All palopegteriparatide-treated animals were exposed to Total PTH for the entire dosing period.

20 µg PTH(1-34)/kg/day was considered to be the NOAEL for male and female toxicity and fertility and the no observed effect level (NOEL) for early embryonic development. At the NOAEL and NOEL, steady state exposure ($AUC_{0\text{-}24h}$ and $C_{max,}$ extrapolated from repeat dose studies in rats) to Free PTH was 3.7 and 8.9-fold, respectively, and to Total PTH 3.9 and 7.4-fold, respectively the predicted exposure at the MRHD.

Embryo-foetal development toxicity (EFD) studies were performed with palopegteriparatide in rats and rabbits in preliminary studies and definitive GLP-compliant studies. TK evaluations of Total and Free PTH were performed in all EFD studies, except for the GLP-compliant EFD study in rats where only proof of exposure to Total PTH was evaluated. In rabbits, anti-PTH antibodies were evaluated in the GLP-compliant EFD study.

In the EFD-studies in rats, palopegteriparatide were investigated at doses of 0 (vehicle), 2, 10 or 30 µg PTH(1-34)/kg/day for the preliminary study and 0 (vehicle), 2, 8 or 30 µg PTH(1-34)/kg/day for the definitive study from GDs 6 to 17.

At 30 µg PTH(1-34)/kg/day, there was pharmacologically related, but adverse, increase in serum calcium at the high dose of 30 µg PTH(1-34)/kg/day on GD 9 associated with transient clinical signs of suspected dehydration and hunched posture, an initial body weight loss and a lower body weight gain (GDs 6 to 12) correlating with decreased food consumption. Non-adverse increased calcium levels and lower body weight gains were seen at lower dose levels.

There was no evidence of embryo-lethality, foetotoxicity or dysmorphogenesis at any dose level in the EFD studies in rats. Continuous exposure to Total PTH was demonstrated in the EFD studies in rats. Based on the results of the GLP-compliant study, the NOAEL for maternal toxicity was 8 µg PTH(1-34)/kg/day and the NOEL for EFD toxicity was 30 µg PTH(1-34)/kg/day in rats. At the NOAEL for maternal toxicity, exposure ($AUC_{0\text{-}24h}$ and C_{max} extrapolated from repeat dose studies in rats) to Free PTH was 1.6 and 3.0-fold, respectively and to Total PTH 2.6 and 2.8-fold, respectively, the predicted exposure at the MRHD. At the NOEL for EFD, extrapolated exposure ($AUC_{0\text{-}24h}$ and C_{max}) to Free PTH was 7.9 and 13.3-fold, respectively, and to Total PTH 10.1 and 11.2-fold, respectively, the predicted exposure at the MRHD.

In the EFD studies in rabbits, palopegteriparatide was administered at doses of 0 (vehicle), 1, 3, or 10 µg PTH(1-34)/kg/day for the preliminary study and 0 (vehicle), 1, 3, or 6 µg PTH(1-34)/kg/day for the definitive study. The preliminary study also included a DRF toxicity-phase prior to the EFD-phase in non-pregnant female rabbits with doses of 0 (vehicle), 1, 5, 10 or 20 µg PTH(1-34)/kg/day.

In the preliminary study, the highest dose resulted in treatment-related preterminal euthanasia in the first week of dosing generally following a period of no/reduced food intake, body weight loss, increased calcium and phosphate levels and deteriorating clinical condition in addition to soft tissue mineralization and/or necrosis in many organs.

In the definitive study at 6 µg PTH(1-34)/kg/day, there was an initial (GDs 7-13) body weight loss and a lower body weight gain accompanied with decreased food consumption. Pharmacologically related dose-dependent increase in serum calcium appeared on GD 7 which at 6 µg PTH(1-34)/kg/day remained increased up to GD 19.

There was no evidence of embryo-lethality, fetotoxicity or dysmorphogenesis at any dose level in the preliminary and GLP-compliant EFD studies.

There was a dose-dependent increase of the liver variation "Lobe supernumerary" of 0/0.71/1.36/2.89 % in foetuses and 0/5.0/5.0/17.6 % in litters in the Control-, 1, 3, or 6 µg PTH(1-34)/kg/day dose

group, respectively. The incidences on the foetal basis were within the historical control ranges and the litter incidences at the highest dose group were slightly above the historical control range. Since the increased incidence of supernumerary liver lobes was not statistically significant and there were no associations with any other malformations or adverse findings (such as dam body weight, occurrence of anti-drug antibodies, exposure, number of resorptions, gross observations, live or dead foetuses and foetal uterine position, sex, or body weight), this finding is unlikely to be related to the palopegteriparatide treatment.

Systemic exposure to Total PTH was demonstrated in all pregnant rabbits after 13 daily doses. Exposure to Free PTH(1-34) was confirmed in all females administered 3 and 6 µg PTH(1-34)/kg/day, but not in animals administered 1 µg PTH(1-34)/kg/day as exposure was below the lower limit of quantification (LLOQ). On GD 19, anti-PTH antibodies were detected in all palopegteriparatide dose groups in 3, 9, and 8 animals at 1, 3, and 6 µg PTH(1-34)/kg/day, respectively resulting in a systemic exposure (C_{max} and AUC_{0-24h}) 0.6 fold lower for Total PTH and 3- to 8-fold higher for Free PTH(1-34) compared to anti-PTH antibody negative females. In view of the lack of increase in serum calcium concomitant to Free PTH increase, the anti PTH antibodies are likely neutralizing. Maternal and EFD data from females and their litters with and without detectable anti-PTH antibodies were comparable. Therefore, the anti-PTH antibodies were considered not to have impacted the overall validity and conclusion of the study.

Based on the results of the GLP-compliant EFD study in rabbits, the NOAEL for maternal toxicity was 3 µg PTH(1-34)/kg/day and the NOEL for EFD toxicity was proposed to be 6 µg PTH(1-34)/kg/day. Exposure margins at the MRHD to Total and Free PTH were calculated by the applicant based on the AUC_{0-24h} and C_{max} levels at the NOAEL/NOEL obtained from anti-PTH antibody negative animals. At the NOAEL for maternal toxicity, exposure to Free PTH to be 2.7 and 3.2-fold, respectively, and to Total PTH 2.6 and 2.7-fold, respectively, the predicted exposure at the MRHD. At the currently proposed NOEL for EFD, exposure (AUC_{0-24h} and C_{max}) to Free PTH was 6.6 to 7.6-fold and to Total PTH 5.1 to 5.4-fold the predicted exposure at the MRHD. Regarding the exposure margins for Total PTH, calculation of exposure margins to the MRHD for Total PTH Using AUC_{0-24h} and C_{max} levels from anti-PTH antibody positive and negative animals should be used. Based on such calculation, the exposure margins to the MRHD are 2.1- and 2.3- fold, respectively at 3 µg PTH(1-34)/kg/day and 4.5- and 4.1-fold, respectively at 6 µg PTH(1-34)/kg/day. Nevertheless, the overall conclusion is that exposure margins to the MRHD at the NOAEL/NOEL of the rabbit EFD are low.

No pre-postnatal developmental toxicity (PPND) study has been conducted with palopegteriparatide at time of marketing authorization submission. Based on pharmaco-chemical properties, palopegteriparatide, PTH(1-34) and the TransCon Linker attached to mPEG are expected to have negligible transplacental transfer and are not or only minimally excreted into breast-milk. The most dose limiting effect in PPND studies with palopegteriparatide in animals would be the well-known PTH-treatment associated maternal hypercalcemia, as also shown in the EFD studies in rats and rabbits, which compromises administration of higher doses. In addition, some experience with use of pegylated products and PTH-products during pregnancy are also available. Therefore, a PPND study conducted with palopegteriparatide will not provide additional information of value to the risk assessment of palopegteriparatide in pregnant women with hypoparathyroidism.

It is recommended that the use of palopegteriparatide during pregnancy should only be considered after risk-benefit assessment. 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..

Furthermore, due to the risk for development of severe hypercalcaemia during treatment with Yorvipath and the known foetal and neonatal complications associated with maternal hypercalcaemia, a

recommendation should be given to closely monitor maternal serum calcium levels if treatment with Yorvipath during pregnancy or lactation is necessary.

Since palopegeriparatide is a new active substance and in consideration of the low safety margins to human exposure at the MRHD, the main findings from the EFD studies in rats and rabbits and the respective safety margins to human at the MRHD based on the exposures at the NOAELs/NOELs were added to section 5.3. In addition, the lack of a PPND study with palopegteriparatide is mentioned in section 5.3 of the SmPC.

Studies in juvenile animals have not been conducted with palopegteriparatide and are not warranted based on the intended indication of Yorvipath for treatment of adults with hypoparathyroidism.

2.4.4.6. Toxicokinetic data

Margins of exposure for Total as well as for Free PTH between NOAELs in repeated dose toxicity studies and intended human clinical exposure (MRHD 60 µg PTH(1-34)/day) are small (rat) or non-existent (monkeys): Free PTH: for the rat C_{max} based (26 week study) 7.6/8.4 for males/females, AUC based (same study) 4.8/4.7 for males/females; for monkeys C_{max} based (26 week study) 0.4 (combined value males and females), AUC based (same study) 0.3 (combined value males and females).

2.4.4.7. Local tolerance

Local tolerance was assessed as part of repeat-dose toxicity studies in rats and monkeys and in DART studies in rats and rabbits.

2.4.4.8. Other toxicity studies

Antibodies specific for PTH were detected in the 26-week repeat-dose toxicity study in rats and monkeys. However, the frequency of antibody formation was low (4 out of 320 rats; 2 female animals at 5 µg at the end of recovery and 2 females at 20 µg predosing and 1 out of 6 monkeys at the highest dose tested). Thus, from the results provided an immune response seems unlikely.

Potential phototoxicity of the TransCon Linker was assessed in silico (QSAR), resulting negative in the analysis performed.

The impurity profile of the batches used in the pivotal studies (26-week in rats) as well as the batches used in the clinical trials are considered by the applicant representative for commercial batches. Regarding the specifications, clinical qualification has been provided in Phase II and III Clinical Trials.

2.4.5. Ecotoxicity/environmental risk assessment

The active substance PTH(1-34) as released from palopegteriparatide has an identical structure to the first 34 amino acids of human PTH (Parathyroid hormone, PTH(1-84). According to the guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Corr 2), the applicant is therefore exempted from the need to provide an ERA as this naturally occurring hormone is unlikely to pose a risk to the environment.

Nevertheless, the Applicant provided an ERA Phase I. The PEC_{sw} of palopegteriparatide refined with prevalence's resulted in a value of 0.0001 µg/L that does not exceed the action limit of 0.01 µg/L.

In conclusion and due to its nature, palopegteriparatide, is unlikely to result in a significant risk to the environment following the prescribed use of palopegteriparatide drug product Yorvipath.

Table 1. Summary of main study results

Substance (INN/Invented Name): Palopegteriparatide (with the active moiety Teriparatide (PTH(1-34))			
CAS-number (if available): 2222514-04-8			
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surfacewater, refined (prevalence's, orphan designation)	0.0001	µg/L	> 0.01 threshold (N)

2.4.6. Discussion on non-clinical aspects

The action of endogenous PTH is directed to PTH1R. Since only amino acids 1 to 31 are required for full PTH1R activation, the potency of PTH(1-34), its metabolite PTH(1-33) and the full length PTH(1-84) is similar. Palopegteriparatide has a low affinity for PTH1R. In contrast, released PTH(1-34) and PTH(1-33) exhibited comparable affinity as the standard PTH(1-34).

PTH and its receptor show a great deal of homology across species (rat, rabbit, monkey and human). The released PTH(1-34) has been demonstrated to be metabolised to PTH(1-33) in rat, monkey and human plasma. Therefore, rats, rabbits and monkey were considered pharmacologically relevant species for the non-clinical evaluation of palopegteriparatide.

The primary pharmacodynamic endpoint in the pharmacology studies was serum calcium levels. Serum phosphorus, urinary calcium and urinary phosphorus were considered secondary pharmacodynamic endpoints. In normal cynomolgus monkey, palopegteriparatide administration resulted in the dose-dependent increase in serum calcium.

A non-clinical proof-of-principle was investigated in thyroparathyroidectomised (TPTx) rat model. This model demonstrated characteristic features of human hypoparathyroidism and is considered suitable. The applicant selected only female animals as most patients with hypoparathyroidism are female. Sex-related PK and PD differences were investigated in toxicology studies. Taking into account the 3R principles, including only female animals in the proof-of-principle study is justified. A comparator compound rhPTH(1-84) with the same amino acid sequence as in the approved product Natpar induced only a transient increase in serum calcium levels. The increased bone mineral density manifested in the TPTx rat was further augmented by rhPTH(1-84). In contrast, similar and lower doses of palopegteriparatide (based on molar equivalents) resulted in sustained increase in serum calcium, sustained decrease in serum phosphorus and improved bone turnover as seen from the reduced bone mineral density. Already at lower doses, palopegteriparatide showed signs of exaggerated pharmacological effects. In the high dose group, two animals were found dead. The deaths were attributed to soft tissue mineralisation, a result of exaggerated pharmacology. Nevertheless, the Applicant is of the opinion that the observed effects of persistent hypercalcemia are related to exaggerated pharmacology of palopegteriparatide in animals and are thus not clinically relevant. In a clinical setting, an individual dose of Yorvipath that normalises serum calcium is set for each patient following dose titration. Persistent hypercalcemia is therefore only of clinical relevance in the extreme clinical scenario of continuous overdosing with a lack of monitoring, which is very unlikely.

Effects of palopegteriparatide injected subcutaneously to cynomolgus monkeys on cardiovascular parameters were investigated up to 1.5 µg PTH(1-34)/kg, which corresponds to 0.98-fold the predicted

clinical exposure at MRHD based on Cmax after repeated daily administration, which is the proposed clinical schedule.

Absorption of palopegteriparatide was investigated in PK studies with male rats and cynomolgus monkeys. The use of only male animals is acceptable because both sexes were included in toxicokinetic evaluation. In both species, exposure was dose-proportional. The release of PTH(1-34) is faster at higher temperature and higher pH. The half-life at 37 °C and pH 7.4 is around 2.5 days. After cleavage, the linker remains attached to the mPEG carrier. Toxicokinetic evaluation revealed higher exposure to Total PTH in female rats, but no sex differences were noted for Free PTH.

In repeat-dose toxicity studies with palopegteriparatide in rats and monkeys, no off-target effects were observed. While it could be questioned whether a study duration of up to 26-weeks was long enough, especially given that the dose levels used in the monkey studies were below the MHRD, and the fact that the dose limitations in the monkey studies make it difficult to extrapolate the observed adverse events to humans, the studied conducted and data provided by the applicant are considered acceptable.

In the long-term studies, the main effect reported in rats was related to physis and bone, which were not entirely appreciated in monkeys perhaps because of the low dose level tested. Nevertheless, it is obvious that the observed effects were due to exaggerated pharmacology of palopegteriparatide (agonism of PTH1R) and the anabolic effect was more pronounced in rats than in monkeys. However, a robust conclusion that can be translated to clinical practice could not be found, as in many parameters related to bone turnover, contradictory results were obtained. Effects of palopegteriparatide observed in the repeat-dose toxicology studies are incorporated in section 5.3 of the SmPC.

Tissue mineralisation of the kidney and myocardium were the cause of death of 2 rats in the 4-week repeat-dose study. One female monkey at the highest dose tested was found dead, and serum calcium levels were markedly elevated in this animal, which may be the cause of death. Mineralisation of organs was only seen in rats, not in monkeys. However, dose dependent hypercalcaemia was also observed in monkeys and may have contributed to the death of one monkey. Mineralisation due to hypercalcaemia is unlikely to occur in patients, having in mind the intended use of palopegteriparatide as replacement therapy.

An increase in bone turnover occurred predominantly in rats, whereas in monkeys only a decrease in cortical BMD at the highest dose tested was seen. The observed species differences are in line with scientific literature. However, only ALP values as marker for bone turnover were determined, no other markers such as cholecalciferol or TRAP were determined. Instead, biochemical bone markers such as PINP and CTx were evaluated in the 26-week monkey study.

Margins of exposure at the human equivalent dose for Free and Total PTH based on AUC and Cmax were low (rats) or not existent (monkeys).

Palopegteriparatide and its cleavage products show no genotoxic potential in vitro and in vivo.

Therefore, the lack of carcinogenicity studies is considered acceptable. Information has been included in section 5.3 of the SmPC with regard to the lack of carcinogenicity studies with palopegteriparatide, and the rationale for the waiver considering also the physeal dysplasia and net anabolic/catabolic effects reported in the chronic rat study, as well as the exposure ratio established in the non-clinical studies, because other PTH analogues have produced osteosarcomas in rat carcinogenicity studies albeit with probably minor relevance for patients with hypoparathyroidism.

In the reproductive and developmental toxicity studies, pharmacologically related increased serum calcium levels were observed, in addition to transient body weight loss sometimes accompanied by reduced food consumption.

In fertility and early embryonic development toxicity studies male and female rats, no effects on parental performance (number of days to mating, mating and fertility indices and conception rate), male reproductive investigations (sperm motility, count and morphology, organ weights and testicular histopathology) or on early embryonic development were observed.

In the embryo-foetal developmental toxicity studies in rats and rabbits, there was no evidence of embryo-lethality, foetotoxicity or dysmorphogenesis.

In rabbits, there was a dose-dependent increase of the liver variation "Lobe supernumerary" of 0/0.71/1.36/2.89 % in foetuses and 0/5.0/5.0/17.6 % in litters in the Control-, 1, 3, or 6 µg PTH(1-34)/kg/day dose group, respectively. The incidence was within the historical control ranges or only slightly above (litters at the highest dose group). Since, the increased incidence of supernumerary liver lobes was not statistically significant and there were no associations with any other malformations or adverse findings, this finding is unlikely to be related to palopegteriparatide treatment.

In rabbits, anti-PTH antibodies were detected at GD19 in all palopegteriparatide dose groups in 3, 9, and 8 animals at 1, 3, and 6 µg PTH(1-34)/kg/day, respectively resulting in a systemic exposure (C_{max} and AUC_{0-24h}) 0.6 fold lower for Total PTH and 3- to 8-fold higher for Free PTH(1-34) compared to anti-PTH antibody negative females. In view of the lack of increase in serum calcium concomitant to Free PTH increase, the anti-PTH antibodies are likely neutralizing. Maternal and EFD data from females and their litters with and without detectable anti-PTH antibodies were comparable. Therefore, the anti-PTH antibodies were considered not to have impacted the overall validity and conclusion of the study.

The exposure margins to the human exposure at the MRHD at the NOEAL/NOEL from the reproductive and the developmental toxicity studies were low.

For the rabbit study, the exposure margins to the MRHD for Total and Free PTH were calculated based on AUC_{0-24h} and C_{max} levels from anti-PTH antibody negative animals. For Total PTH calculation of exposure margins to AUC_{0-24h} and C_{max}, levels from anti-PTH antibody positive and negative animals seems to be more appropriate and should be used. Based on such calculation, the exposure margins to the MRHD are 2.1- and 2.3- fold, respectively at 3 µg PTH(1-34)/kg/day and 4.5- and 4.1-fold, respectively at 6 µg PTH(1-34)/kg/day. Nevertheless, the overall conclusion that exposure margins to the MRHD at the NOAEL/NOEL of the rabbit EFD are low is not impacted.

No pre-postnatal developmental toxicity study has been conducted with palopegteriparatide at time of marketing authorization submission. Based on pharmaco-chemical properties, palopegteriparatide, PTH(1-34) and the TransCon Linker attached to mPEG are expected to have negligible transplacental transfer and are not or only minimally excreted into breast-milk. The most dose limiting effect in PPND studies with palopegteriparatide in animals would be the well-known PTH-treatment associated maternal hypercalcemia, as also shown in the EFD studies in rats and rabbits, which compromises administration of higher doses. In addition, some experience with use of pegylated products and PTH-products during pregnancy are also available. Therefore, a PPND study conducted with palopegteriparatide will not provide additional information of value to the risk assessment of palopegteriparatide in pregnant women with hypoparathyroidism.

No separate reproductive and developmental studies have been conducted with the TransCon Linker attached to mPEG or the single components (mPEG and TransCon Linker). This is acceptable given that potential effects of the TransCon Linker attached to mPEG on foetal development and maternal function were addressed until GD 17 in rats and GD 19 in rabbits in EFD studies conducted with palopegteriparatide and that it is considered unlikely that PTH(1-34) and TransCon Linker attached to mPEG will cross the placenta or will be excreted in breast milk. *In silico* assessment of the 4 structures of the TransCon Linker, with and without the branching point for mPEG, identified no structural alerts for DART or genotoxicity.

As detailed in section 4.6 of the SmPC, the use of palopegteriparatide during pregnancy should only be considered after risk-benefit assessment. 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..

Furthermore, due to the risk for development of severe hypercalcaemia during treatment with Yorvipath and the known foetal and neonatal complications associated with maternal hypercalcaemia, a recommendation has been added in section 4.6 of the SmPC to closely monitor maternal serum calcium levels if treatment with Yorvipath during pregnancy or lactation is necessary.

Since palopegteriparatide is a new active substance and in consideration of the low safety margins to human exposure at the MRHD, the main findings from the EFD studies in rats and rabbits and the respective safety margins to human at the MRHD based on the exposures at the NOAELs/NOELs are included in section 5.3 of the SmPC. In addition, the lack of a PPND study with palopegteriparatide is adequately mentioned in section 5.3 of the SmPC.

The active substance PTH(1-34) as released from palopegteriparatide is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. In addition, palopegteriparatide PEC $_{surfacewater}$ value is below the action limit of 0.01 μg/L. Therefore, palopegteriparatide is not expected to pose a risk to the environment.

2.4.7. Conclusion on the non-clinical aspects

The CHMP considers the pharmacology, pharmacokinetics and toxicology of palopegteriparatide have been well characterised.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Phase/ Trial Design	Treatment and Duration	Trial ID No. of Site Locations	Primary/ Secondary Objectives	Trial Population	No. of Subjects Included in Analysis
Phase 3/ Multi-center, randomized, double-blind, placebo-controlled, parallel-group trial with open-label extension (OLE)	Subjects randomized 3:1 to starting dose of palopegteriparatide 18 µg/day or Placebo. Dose was individually and progressively titrated to an optimal dose in increments of 3 µg/day (to 6 to 60 µg/day). After 26 weeks of blinded treatment, Placebo subjects crossed over to OLE. Subjects then received	TCP-304 21 sites Canada, Denmark, Germany, Hungary, Italy, Norway, United States	Efficacy and Safety	Adult subjects (≥18 years of age) with hypoparathyroidism	84 (3:1): 63 subjects randomized to palopegteriparatide and 21 subjects randomized to placebo

	individualized dosing of 6-60 µg/day and were followed up to 156 weeks. Blinded Period (Weeks 0 to 26) completed; OLE period ongoing.				
Phase 2/ Multi-center, randomized, double-blind, placebo-controlled, parallel-group trial with OLE	Subjects randomized 1:1:1:1 to 3 fixed doses of palopegteriparatide (15, 18, and 21 µg/day) or Placebo. After 4 weeks of blinded treatment, subjects in placebo group crossed over to palopegteriparatide in the OLE. All subjects then received individualized doses of 6-60 µg/day palopegteriparatide and are followed up to 210 weeks. Blinded Period (Weeks 0 to 4) completed; OLE period ongoing.	TCP-201 12 sites Canada, Denmark, Germany, Italy, Norway, United States	Efficacy and Safety	Adult subjects (≥18 years of age) with hypoparathyroidism	59 (1:1:1:1): 14, 15, 15, and 15 subjects randomized to palopegteriparatide 15, 18, and 21 µg/day or placebo, respectively
Phase 1/ Randomized, double-blind trial with SAD and MAD parts/ 10 days	SAD: 7 cohorts. In each cohort, subjects were randomized to a single dose of palopegteriparatide (3.5, 12, 32, 48, 72, 100, or 124 µg) or placebo. MAD: 6 cohorts. In each cohort, subjects were randomized to multiple doses of palopegteriparatide (3.5, 7, 12, 16, 20, or 24 µg/day) or placebo, and treated for 10 days.	CT-103 1 site Australia	Safety and Tolerability, PD and PK	Healthy subjects (18 to 60 years of age)	Total:132 randomized SAD: 69 (56 palopegteriparatide vs 13 placebo) MAD: 63 (50 palopegteriparatide vs 13 placebo)
Phase 1/ Open-label, single-dose, parallel-group trial	Single dose of 50 µg palopegteriparatide in all 4 groups: Group 1 (normal renal function), Group 2 (mild renal impairment), Group 3 (moderate renal impairment), Group 4 (severe renal impairment)	TCP-104 4 sites Germany, Hungary, Moldova, Romania,	PK Safety and Tolerability	Healthy subjects (18 to 65 years of age) including renal impaired subjects	Total: 38 (palopegteriparatide only): Group 1: 13 Group 2: 9 Group 3: 8 Group 4: 8
Phase 1/ Randomized, double-blind, parallel, single-dose, ethno-bridging trial	Single dose of palopegteriparatide at 3 dose levels (50, 75, 100 µg). Each level with 2 cohorts: subjects with Japanese ancestry vs. non-Japanese. In each cohort, subjects were randomized 7:1 to single dose palopegteriparatide vs placebo.	TCP-105 1 site United States	PK, PD, Safety, and Tolerability	Healthy subjects (18 to 65 years of age) including subjects of Japanese descent and non-Japanese	Total: 48 (42 palopegteriparatide, 6 placebo) 6 cohorts: 8 subjects/cohort

Abbreviations: MAD = multiple ascending dose; OLE = open-label extension; PD = pharmacodynamics; PK = pharmacokinetics; SAD = single ascending dose; vs = versus. Dose of palopegteriparatide refers to micrograms PTH(1-34).

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Palopegteriparatide is a sustained-release prodrug for once daily SC injection which consists of PTH(1 34) (also called teriparatide) conjugated to an inert carrier via a TransCon Linker. PTH(1-34) is identical to the C-terminal first 34 amino acids of human PTH, and is essentially inactive when connected to the branched 40 kDa (2×20 kDa) mPEG carrier. While still attached to the carrier, a part of PTH(1-34) is metabolized to PTH(1-33) in vivo, meaning that in the systemic circulation the prodrug releases both PTH(1-34) and the fully active metabolite PTH(1-33).

It is emphasized that in all clinical studies the investigated doses of palopegteriparatide are always expressed in terms of corresponding micrograms of the active moiety of PTH(1-34), i.e. teriparatide, and do not include the additional amount of mPEG plus TransCon-linker.

The clinical pharmacology program to evaluate pharmacokinetics and pharmacodynamics of palopegteriparatide included 5 clinical studies, 3 in healthy volunteers and 2 in patients.

For this application, a full PK documentation is necessary, considering that for therapeutic proteins, in accordance with the recommendations of the relevant EMA Guideline on the clinical evaluation of the pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004), a reduced programme is appropriate, as e.g. no specific DDI studies are required.

Absorption

Bioequivalence

Bioequivalence trials were not regarded necessary by the applicant and consequently not conducted.

Palopegteriparatide has been developed for the market as a prefilled pen in three presentations: 168 µg PTH(1-34)/0.56 mL, 294 µg PTH(1-34)/0.98 mL and 420 µg PTH(1-34)/1.4 mL. During clinical development, formulations were manufactured as liquid solutions filled into vials and cartridges. The same excipients were used throughout the entire clinical development program, except for a decrease in the amount of metacresol with compensatory increase of mannitol and a change in the drug product concentration of active ingredient after conduct of the initial phase I study.

While the three phase I studies utilised syringe and needle for injection into abdomen, palopegteriparatide was injected via prefilled pens into the left and right thighs and left and right abdomen in the Phase II and III clinical trials (TCP-201 and TCP-304); herein, it was recommended to rotate the 4 injection sites. According to the applicant, it was not possible to assess injection site as a covariate in the population PK analysis due to the sparse PK sampling. Upon request, concentration data were provided from patients in study TCP-201 separated by site of injection and compared to phase I study CT-103 data. Both, the comparison with the information of study CT-103 and the comparison between injection sites suggest that exposure with regard to Total PTH and Free PTH(1-34) is similar independent of injection site.

Bioavailability

The absolute bioavailability of SC injection of palopegteriparatide has not been determined.

The **Phase I study CT-103** included 7 single dose cohorts and 6 multiple dose (10 days administration) cohorts in healthy males and females.

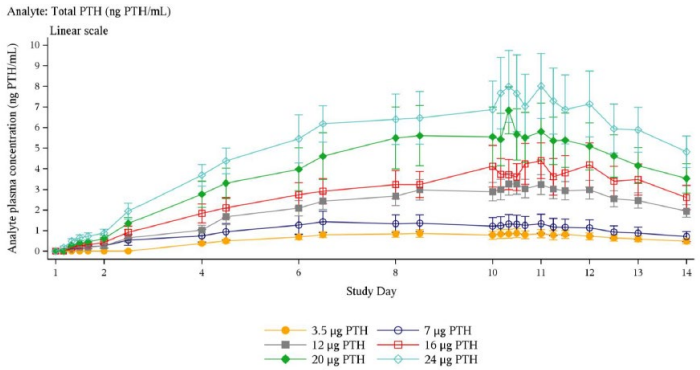
In healthy subjects, a dose-dependent increase in Free PTH was observed. Median Free PTH Tmax ranged from 4 - 8 h postdose, with individual values from 2 - 60 h postdose. Plasma concentrations declined steadily after Tmax after SD administration.

Total PTH (as a surrogate measure of the prodrug) concentration-time profiles were characterized by a slow rise to peak concentrations, with a median Tmax across doses ranging from 48 - 72 h postdose.

For Free PTH, Free PTH(1-34) and Free PTH(1-33), trough concentrations appeared to be approaching steady state by Day 8 - 10 of dosing. Steady state was not achieved for Total PTH and Total PTH(1-34) after 10 days of once daily dosing (Figure PK 1).

Figure 2. Arithmetic mean (±SE) plasma concentrations after multiple doses in HV (study CT-103)

(A) Total PTH

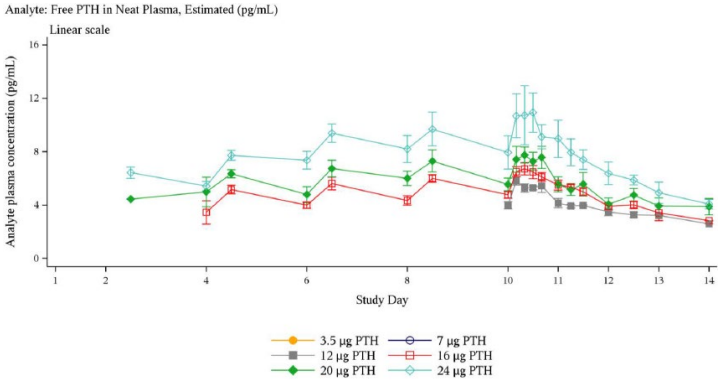


Note: Negative SE bars less than 0 are shown as 0
Reference: Table 14.2.1-6

Total PTH	Dose of TransCon PTH											
	3.5 µg PTH (N=8)		7 µg PTH (N=8)		12 µg PTH (N=8)		16 µg PTH (N=8)		20 µg PTH (N=8)		24 µg PTH (N=8)	
Parameter	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10
AUC_{0-t} (h*ng PTH/mL)	NC [0]	25.7 (33.1) [6]	6.74 (33.4) [4]	29.3 (156.7) [6]	5.85 (64.0) [4]	84.9 (14.8) [7]	6.50 (89.7) [5]	80.2 (80.2) [7]	9.44 (54.1) [6]	147 (44.1) [6]	9.87 (94.3) [8]	172 (42.9) [3]
C_{max} (ng PTH/mL)	NC [2]	1.18 (31.1) [6]	0.490 (30.1) [4]	1.35 (144.0) [6]	0.291 (72.9) [6]	3.95 (14.9) [7]	0.427 (79.0) [6]	3.87 (92.0) [6]	0.590 (89.3) [7]	6.82 (44.5) [6]	0.709 (88.3) [8]	7.78 (40.2) [3]
C_{24h} (ng PTH/mL)	NC	1.09 (30.9) [6]	NC	1.21 (187.8) [6]	NC	3.68 (11.3) [7]	NC	3.69 (83.8) [7]	NC	6.25 (48.1) [6]	NC	7.68 (38.4) [3]
T_{max}[a] (h)	NC (23.50-23.50) [2]	24.00 (12.00-36.00) [6]	23.55 (23.25-23.68) [4]	18.02 (0-24.03) [6]	23.08 (23.05-23.48) [6]	8.13 (4.00-30.02) [7]	23.33 (12.00-23.33) [6]	24.02 (12.03-48.00) [6]	23.52 (23.50-23.60) [7]	12.02 (0-24.00) [6]	23.45 (8.00-23.50) [8]	24.00 (12.00-24.00) [3]
$t_{1/2}$ (h)	NC	83.6 (22.0) [6]	NC	79.7 (37.4) [5]	NC	94.4 (44.2) [7]	NC	79.7 (73.2) [4]	NC	100 (39.3) [6]	NC	NC [2]
AR_{AUC}	NC	NC [0]	NC	7.49 (31.7) [4]	NC	15.0 (50.2) [4]	NC	17.5 (132.3) [5]	NC	15.0 (35.6) [5]	NC	18.3 (46.6) [3]
AR_{Cmax}	NC	NC [1]	NC	4.62 (20.4) [4]	NC	12.5 (64.7) [5]	NC	12.0 (142.7) [4]	NC	10.5 (52.3) [6]	NC	10.4 (42.0) [3]
Peak to trough	NC	1.08 (7.4) [6]	NC	1.11 (18.2) [6]	NC	1.07 (5.3) [7]	NC	1.06 (7.2) [7]	NC	1.09 (8.2) [6]	NC	1.01 (2.2) [3]

Source: Table 14.2.1-4

(B) Free PTH



Note: Negative SE bars less than 0 are shown as 0
Reference: Table 14.2.1-6

Free PTH in Neat Plasma, Estimated	Dose of TransCon PTH			
	12 µg PTH (N=8)	16 µg PTH (N=8)	20 µg PTH (N=8)	24 µg PTH (N=8)
Parameter	Day 10	Day 10	Day 10	Day 10
$AUC_{0-\tau}$ (h*pg/mL)	122 (13.4) [5]	152 (9.4) [5]	165 (21.7) [6]	231 (24.2) [3]
C_{max} (pg/mL)	6.24 (13.1) [6]	6.87 (16.8) [7]	8.30 (21.4) [6]	11.1 (27.6) [3]
C_{24h} (pg/mL)	4.09 (19.2) [5]	5.44 (14.9) [5]	5.39 (25.8) [6]	8.76 (25.7) [3]
T_{max} [a] (h)	4.00 (4.00-16.02) [6]	8.00 (4.00-12.00) [7]	6.08 (4.03-16.05) [6]	7.88 (4.00-12.00) [3]
$t_{1/2}$ (h)	64.8 (39.2) [4]	60.0 (20.3) [4]	51.7 (44.5) [5]	69.0 (22.3) [3]
AR_{AUC}	NC [0]	NC [0]	NC [0]	NC [0]
AR_{Cmax}	NC [0]	NC [0]	NC [0]	NC [0]
Free PTH:Total PTH (AUC_{0-t})	0.000897 (15.6) [5]	0.000902 (44.0) [5]	0.000694 (23.6) [5]	0.00102 (50.6) [3]
Peak to trough	1.55 (12.0) [5]	1.37 (6.0) [5]	1.54 (10.3) [6]	1.27 (4.4) [3]

Source: Table 14.2.1-4

Plasma concentrations of mPEG peaked at the end of the dosing interval (24 h postdose) on Day 1, and, for all dose levels, appeared to be increasing after the end of the dosing interval on Day 10; therefore, steady-state had not been achieved during the 10 days of once daily administration.

In HV moderate to high between-subject variability was noted for Total PTH(1-34) AUC0-t and Cmax, with values ranging from 29 to 131% and 38 to 99% CV, respectively. The 124 µg PTH dose level was an exception to this with low between-subject variability for AUC0-t and Cmax, at approximately 17% for both.

In patients in study TCP-201 variability to Free PTH, Total PTH and mPEG ranged from low (0.6-3%) to medium/high (54.9-112.2%), with mainly ~40% for Total PTH and mPEG.

Distribution

Distribution was estimated in the population PK modelling analysis. However, as the volume of distribution estimates were correlated with absorption and dissociation rate estimates, these estimates should be interpreted with caution. An apparent central volume of distribution V/F of 4.8 L for Total PTH and mPEG was estimated for the reference subject (a female, Phase I subject of 70 kg). For subjects in Phase 2 and Phase 3, the apparent central volume of distribution V/F was estimated to be 1.4-fold (β = 0.338) compared to a Phase 1 subject, i.e., 6.8 L. The apparent volume of distribution for Free PTH(1-34) and Free PTH(1-33) V_{PTH}/F was estimated to 8.7 L for all subpopulations.

Elimination

The mean apparent half-life t½ for Free PTH was similar across the 72 - 124 µg PTH(1-34) doses, with values ranging from 51 - 56 h. For Total PTH, plasma concentrations declined slowly and the terminal phase was not well defined for the majority of subjects in study CT-103 due to the short sampling time

postdose (up to 96 h). Hence, all estimates of t1/2 were calculated over a period of <2 times the resultant half-life.

PK parameters estimated from popPK for absorption and elimination rates per day showed that the elimination rate of palopegteriparatide is ~3-fold slower compared to its absorption rate. In contrast, the elimination rate of Free PTH is about 1000-fold faster than the absorption of and linker release (t½ of approximately 60 h) from palopegteriparatide which are therefore the controlling and rate-limiting steps (flip-flop kinetics).

PTH(1-34) is considered to be excreted via the kidneys like endogenous PTH(1-84). Clearance of PEG molecules occurs primarily through glomerular filtration and excretion in urine. With a MW of palopegteriparatide of about 44 kDa, hepatic clearance is assumed to be minimal. Higher MW PEGs are retained longer in the blood and the increase in half-life is most dramatic when the PEG MW is greater than 30 kDa. The linker is expected to be excreted together with the mPEG.

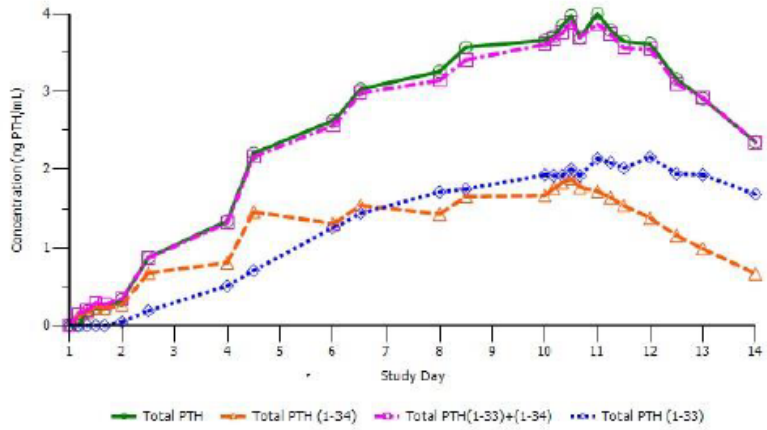
In the population PK analysis, the apparent clearance of mPEG and prodrug was estimated to 0.583 L/day. The Free PTH elimination rate could not be estimated independently from the volume of distribution for Free PTH, and the half-life was therefore fixed to 5 min (kPTH = 200/day) in the model. However, as some of the estimated parameters were correlated, the individual estimates need to be interpreted with care.

Metabolism

At physiologic pH and temperature, active PTH is released from the prodrug via auto-cleavage of the linker; however, while still attached to the linker, a part of PTH(1-34) is metabolized to PTH(1-33) *in vivo*, meaning that in the systemic circulation the prodrug releases both PTH(1-34) and the fully active metabolite PTH(1-33).

In study CT-103, metabolism was investigated in an exploratory PK analysis which showed negligible differences between the sum of Total PTH(1-34) plus Total PTH(1-33) plasma concentrations and the corresponding C_{max} and AUC values compared to those for Total PTH, indicating systemic exposure to Total PTH was solely comprised of Total PTH(1-34) and Total-PTH(1-33). Total PTH(1-33) accounted for approximately 60% of Total PTH exposure (Figure 2).

Figure 3. Mean plasma concentration-time profiles of Total PTH, Total PTH(1-33), Total PTH(1-34), Total PTH(1-33)+(1-34) - MAD cohort on 12µg palopegteriparatide for 10 days



Source: Figure 11.20, CT-103 Exploratory metabolism report

Dose proportionality and time dependencies

Exposure to Total PTH following single and multiple dosing appeared to increase in a proportional manner. Dose proportionality for Free PTH following single and multiple dosing and mPEG following multiple dosing appeared as slightly less than proportional.

The popPK analysis MODPTH03 suggested that in the phase III patient population there was an indication that Free PTH(1-33) concentrations were potentially slightly overproportional at low doses, particularly at 9 and 12 µg/day. Across the most used dose levels of 15 to 27 µg/day, however, the dose-normalized concentrations had a high degree of overlap.

Accumulation of Total PTH in plasma after 10 days was observed, with mean accumulation ratios, based on AUC0-τ and Cmax, between 7.49 - 18.3 (individual range: 6.00 - 102) and 4.62 - 12.5 (individual range: 4.01 - 57.9), respectively, and for mPEG Cmax 9.2-19.4-fold. On Day 10 the peak:trough ratios of Total PTH and mPEG were consistent about 1.0-1.2-fold over the dosing interval at the investigated doses.

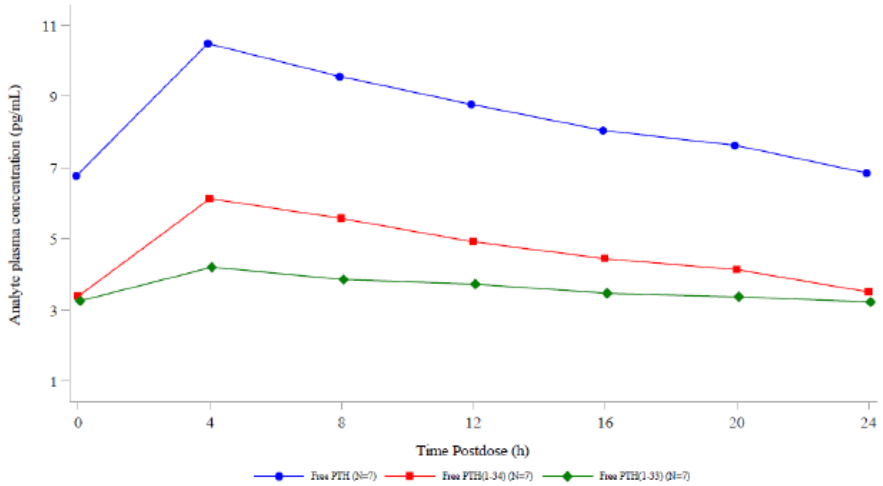
For Free PTH(1-34), accumulation ratio on Day 10 for AUC and C_{max} were 2.0-2.2-fold and 1.8-2.0-fold, respectively. Peak:trough ratio was 1.4-1.8-fold.

The observed concentrations of Total PTH and Free PTH remained stable throughout the study periods in patients with hypoparathyroidism.

Pharmacokinetics in the target population

In the **Phase II study TCP-201,** steady-state of Free PTH and Total PTH was approached after ~1 and 2 weeks, respectively, after initial dosing. The PK sub-study (n = 12) after week 58 dosing confirmed continuous exposure of PTH released from palopegteriparatide over 24 h post dose. The highest concentration was observed at 4 h post dose followed by a slow decline for the remaining 20 h and with a small peak:trough ratio (Figure 3).

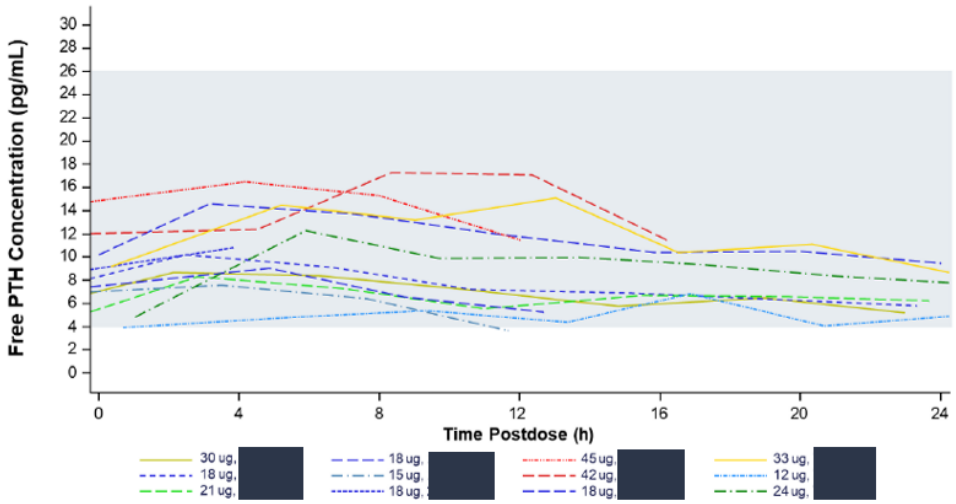
Figure 4. Mean Free PTH, Free PTH(1-34), and Free PTH(1-33) (TCP-201, PK/PD sub-study, n = 7)



Source: OLE Figure 14.5.1.4.
Note: Timepoint 0 = time of palopegteriparatide dose. Subgroup analysis set of the PD/PK substudy population is defined as all subjects that had a pre-dose PK sample collected within 30 minutes prior to dosing. The subjects included in the summary display received the following doses of study treatment: 12 ug/d (N=1), 18 ug/d (N=2)x, 21 ug/d (N=1), 24 ug/d (N=1),30 ug/d (N=1), and 33 ug/d (N=1). Subjects with a value less than LLOQ in a time point were not included in the mean calculation for that time point.

Based on the considerations that PTH(1-34) and PTH(1-33) comprise about 40% of the molecular mass of PTH(1-84) and the normal range for PTH(1-84) is 10-65 pg/mL, exposure to Free PTH was within the calculated normal range (~4-26 pg/mL for PTH(1-34)) (Figure 4).

Figure 5. Individual Free PTH concentrations over 24 hours (TCP-201, PK/PD sub-study)



Source: Derived from Figure 14.5.1.5 and including calculated physiological range (4-26 pg/mL)
Dose of palopegteriparatide refers to dose of PTH(1-34)/day administered

A dose-related increase in Total PTH and mPEG concentrations was observed with no relevant change in steady state exposure over the 84 weeks dosing period. The mean concentrations of Total PTH were in the range from 0.175 - 13.2 ng PTH/mL and of mPEG up to 1010 ng/mL.

Through simulations with the population PK model, missed doses were predicted to temporarily reduce median Free PTH C_{trough} by 20 and 40% for 1 or 2 consecutive missed doses, and 60 and 80%, respectively, for 4 or 7 consecutive missed doses. For 7 missed doses, the median exposure was predicted to return to steady state within 1-2 weeks.

Further, the effect of fever on PK was modelled because the linker release half-life was known to be temperature- and pH sensitive. Mild hypothermia (35°C) to moderate fever (41°C) alter Free PTH levels to a degree that would not be expected to be clinically notable in comparison to the underlying pathophysiologic state. The same conclusions are evident for pH alterations across the range compatible with life (pH 7.0-7.6).

Population pharmacokinetic analysis

Two different population PK analysis were conducted. The first one including data from Phase 1 and Phase 2 studies and the second analysis including data from Phase 1, Phase 2 and Phase 3 studies.

Population PK of TransCon PTH in healthy and in subjects with hypoparathyroidism in trials CT-103, TCP-104, TCP-105 and TCP-201

The population PK analysis was based on a pooled dataset from 4 studies, which includes data of Palopegteriparatide (TransCon PTH) in healthy volunteers (Phase 1 Studies CT-103 and TPC-105), in healthy volunteers with different degree of renal impairment (Phase 1 Study TCP-104) and patients with hypoparathyroidism (Phase 2 Study TCP-201). The objective was to develop a population PK model that describes the pharmacokinetics of mPEG, Total PTH, Total PTH(1-34), Free PTH(1-34) and Free PTH(1-33) in those populations.

TransCon PTH PK was described using a 1-compartmental model with first-order absorption rates ka (TransCon PTH and PEG) and kaPTH (PTH) from a subcutaneous tissue depot compartment and linear clearance CL/F (TransCon PTH and mPEG) and KPTH (PTH) from the central compartment. KPTH was fixed to 5 minutes based on data of the recombinant PTH analog Forteo uspi. As part of the assumptions the rapid appearance of the metabolite TransCon PTH (1-33) after the first administration was modelled as part of the administered TransCon PTH (1-Fm).

IIV was high for some parameters Ka (94%) and KaPTH (76%), and moderate-high for some parameters Cl/F (52%) and Kmetab (54%). Structural model parameters were estimated with relatively good precision (RSE <21%).

The inclusion of body weight and sex on clearance was justified by the Applicant. Individual post-hoc estimates for apparent mPEG and Total PTH volume of distribution (V/F) versus individual body weight and sex for Phase I and Phase II PK analysis and Phase III analysis showed that effects of sex and body weight on V/F were not duplicated. On the other hand, the inclusion of Phase 2 trial as a covariate on KPTH, V/F and Kdiss is controversial since a temperature-dependency of the linker release was detected and justified by the Applicant, but differences due to disease status may also contribute to explain the difference in those PK parameters.

Model evaluation of the initial analysis confirmed the adequacy of the overall framework to describe the data based on the graphical and numerical assessment. The current model over-estimates the inter-individual variability across the different analytes and studies as a consequence of the large number of inter-individual random effects associated to the model structure. However, its regulatory implication is of low relevance due to the detailed and well characterized description at the structural level of the PK processes involved. The implication may be relevant when there are extrapolation studies to minority population groups, where the selection of the dosing regimen is based on model predictions and little/null experimental evidence. In these cases, establishing the dosage regimen based on the simulations can lead to selecting/discarding schemes that may have therapeutic relevance.

The population PK model structure is able to simultaneously characterize the PK longitudinal data of mPEG, Total PTH, Total PTH(1-34), Free PTH(1- 34) and Free PTH(1-33) in healthy subjects, subjects with varying degrees of renal function and in patients with hypoparathyroidism. The modelling strategy is endorsed, since the Applicant developed the current mathematical framework using data from Phase I (healthy volunteers) and Phase II (patients) studies and thereafter, a model re-evaluation was conducted using data from a Phase III study. Modelling assumptions are endorsed based on the level of evidence collected and the mechanistic description of the PK processes involved in the metabolism/dissociation of the parent drug at the absorption and central compartments.

Population PK of TransCon PTH in healthy and in subjects with hypoparathyroidism in trials CT-103, TCP-104, TCP-105, TCP-201 and TCP-304

The population PK analysis was based on a pooled dataset from 5 studies, which includes data of Palopegteriparatide (TransCon PTH) in healthy volunteers (Phase 1 Studies CT-103 and TPC-105), in healthy volunteers with different degree of renal impairment (Phase 1 Study TCP-104) and patients with hypoparathyroidism (Phase 2 Study TCP-201 and Phase 3 Study TCP-304). The objective was to develop a population PK model that describes the pharmacokinetics of mPEG, Total PTH, Total PTH(1-34), Free PTH(1-34) and Free PTH(1-33) in those populations. From the phase 3 trial TCP-304, only Free PTH(1-34) and Free PTH(1-33) concentration data were available.

The analysis contained 281 subjects (178 healthy subjects and 103 patients with hypoparathyroidism) and a total of 11.165 observations (excluding Free PTH observations). PK samples below limit of

quantification (BLQ) of total PK observations were 13 % and were included in the population PK analysis using the censored methodology available with Monolix.

The population PK of TransCon PTH described by mPEG, Total PTH, Total PTH(1-34), Free PTH(1- 34) and Free PTH(1-33) was adapted to further characterize data from an ongoing phase 3 trial in adults with hypoparathyroidism investigating daily SC administration of TransCon PTH with a 26-week blinded dosing period and an open label extension. A pooled data approach was conducted, fitting simultaneously all experimental data available (phase 1, 2, and 3). The structural definition of the PK model together with the identified covariates in the previous analysis was adapted to the current experimental evidence. A covariate analysis was conducted to further evaluate whether additional covariates could be statistically relevant. Two additional covariates were identified: Sex covariate on prodrug and mPEG clearance Cl/F and Phase 2/3 trial covariate on the mPEG and prodrug absorption rate ka. The high number of selected covariates is expected considering the complexity of the model and the number of analytes analyzed simultaneously.

IIV was very high for some parameters Ka (127%), KaPTH (81%), and moderate-high for some parameters Cl/F (52%), V/F (50%), and Kmetab (53%). Structural model parameters were estimated with relatively good precision (RSE <25%).

The model evaluation step of the final model demonstrates the adequacy of the PK structure to characterize the longitudinal data across the different analytes and studies with an over-estimation of the inter-individual random effects previously mentioned.

A forest plot has been provided to assess the clinical relevance of the covariates selected based on the change on the exposure (C_{avg}). The impact of disease condition (Phase 2/3) vs healthy volunteers (Phase 1) suggests a 40% increase in V/F, 43% increase in kpth, and 25% decrease in Kdiss in patients vs healthy volunteers. This may be a consequence of a higher exposure of Free PTH in the Phase 2/3 vs. 1 studies. The explanation of temperature changes in the analysis of the samples is ambiguous and, as mentioned above, additional mechanisms due to disease conditions may alter the PK properties of PTH and PEG. The applicant explained that no differences due to disease status could affect the PK of palopegteriparatide and the study effect was confounded by additional elements and general between-trial variations. However, since no additional information has been provided regarding additional factors affecting Study 2 and 3 vs Phase 1 studies, the factors involved in the PK behavior are highly uncertain and it is highly unlikely to be clarified with the available information.

The clinical relevance assessment demonstrated clinically relevant changes in Free PTH, Free PTH (1-33), and Free PTH (1-34) due to disease status (previously mentioned) and 5th percentile of CrCL. Predicted fold-change of average concentration of Free PTH of subjects with different degrees of renal capacity reveal a significant increase in exposure in patients with CrCl= 15 mL/min . The SmPC states that no dose adjustment is required in patients with glomerular filtration rate >30 mg/min/1.73m2 and that Yorvipath has not been studied in patients with severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m2). Taking into account the results from the simulation exercise and the results from the single dose dedicated RI study (Study TCP-104), the SmPC reflects that Yorvipath should be used with caution in patients with severe renal function.

Special populations

Impaired renal function

Study TCP-104 evaluated the PK in subjects with mild, moderate, or severe renal impairment after a single SC injection of 50 µg PTH(1-34).

Mean C_{max} and $AUC_{0\text{-}tlast}$ for Total PTH and mPEG were similar and had similar variability for the mild, moderate, and severe RI groups compared to the normal renal function group, indicating that RI did not affect exposure to these analytes. No clinically relevant differences were observed.

Mean Free PTH(1-34) C_{max}, $AUC_{0\text{-}tlast}$, and associated ranges were similar between the mild and moderate RI groups compared to the normal renal function group, no clinically relevant differences were observed.

Subjects with severe RI had a higher apparent exposure (C_{max} and $AUC_{0\text{-}tlast}$) to Free PTH(1-34) than subjects with normal renal function and reasons for the high Free PTH(1-34) observations were discussed by the applicant:

- In severe RI patients, there are alterations in PTH metabolism. Both the hepatic clearance of endogenous PTH(1-84) and the kidney clearance of the C-terminal fragment are impaired. Thus, the elevated blood levels of PTH in CKD are due to both increased secretion and impaired degradation. Therefore, the target levels of endogenous PTH are varied based on the CKD Stage. 5 of 8 subjects in the severe RI group had higher than their respective target range of endogenous PTH(1-84) (70 to 110 pg/mL) with baseline levels ranging from 186.5 - 286.8 pg/mL. C_{max} and $AUC_{0\text{-}tlast}$ values (and where available, t1/2 and $AUC_{0\text{-}\infty}$) of Free PTH(1-34) were higher for the 5 subjects with higher than target range baseline endogenous PTH(1-84) levels compared to the 3 subjects that had within target range endogenous PTH(1-84) levels. This indicated an association between higher endogenous PTH(1-84) levels and the higher apparent exposure to Free PTH(1-34).
- The bioanalytical report indicated interference from endogenous compound or matrix (plasma) in the assay.Variability was observed between the original and reanalyzed samples of the severe RI group, indicating that cleavage of PTH(1-84) to PTH(1-34) fragments was occurring during sample collection and sample preparation in the analytical runs. Although, PTH(1-34) is not one of the PTH fragments normally found in circulation, it can be formed by cleavage of endogenous PTH(1-84) by enzyme cathepsin-D, which is active in acidic conditions. The plasma samples were made acidic during sampling to avoid release of PTH from the prodrug after collection of the sample. The assay used to measure Free PTH(1-34) in this study, cannot distinguish between PTH(1-34) released from the prodrug and that cleaved from endogenous PTH(1-84). The high Free PTH(1-34) concentrations detected in the severe RI subjects are the sum of Free PTH(1-34) released from the prodrug and the cleaved PTH(1-34) of the high levels of endogenous PTH(1-84).

As a consequence, it was not possible to determine if there was any effect of severe RI on the Free PTH(1-34) released from palopegteriparatide.

The relationship between baseline creatinine clearance and drug exposure was also explored in the population PK covariate analysis. A clinically relevant rise in Free PTH was seen with baseline creatinine clearance of 15 mL/min. However, the increased concentrations of Free PTH could be due to *ex vivo* processing of endogenous PTH(1-84), as described above.

Trial TCP-304 included subjects with hypoparathyroidism with eGFR ≥30 mL/min/1.73m² and included subjects with mild and moderate RI (mean eGFR 68.9; range 38.7 – 107.6 mL/min/1.73m²). The subjects with RI were administered the same starting doses as those with normal renal function, with no safety signals identified by the applicant.

Impaired hepatic function

That effect of hepatic impairment on the PK of palopegteriparatide has not been assessed.

Race

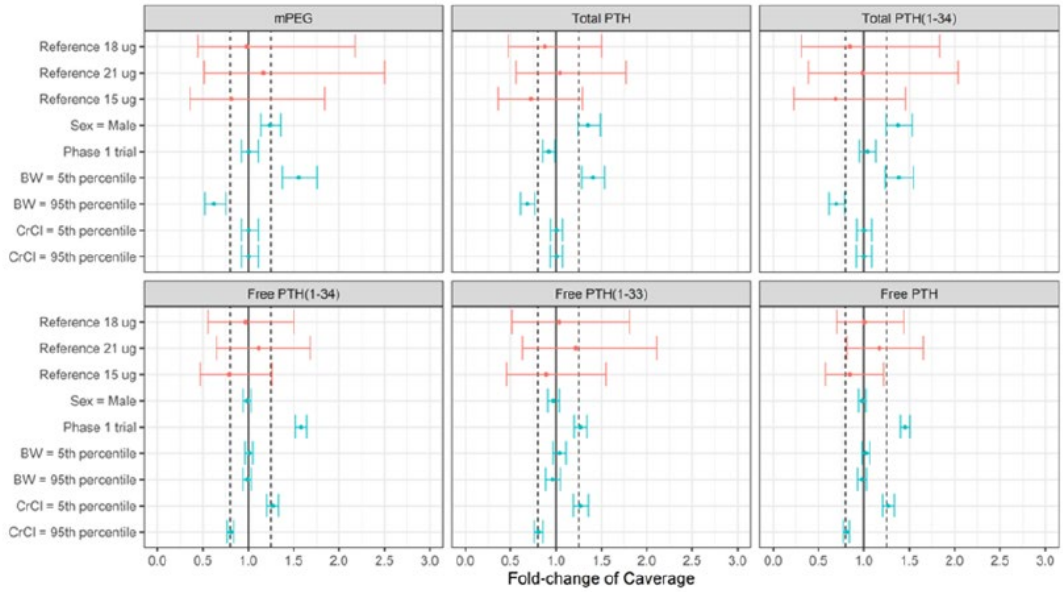
Study TCP-105 evaluated the PK of Japanese vs. non-Japanese subjects. No clinically relevant difference was observed in systemic exposure of Free PTH(1-34), Total PTH, mPEG, and Free PTH (100 µg PTH(1-34)) between Japanese and non-Japanese subjects after a single dose administration of ~50 µg, 75 µg or ~100 µg PTH(1-34).

In the popPK analysis MODPTH03, no differences in exposure could be found by comparing the two race groups, White (N=43) and Other (N=4), and the two ethnicity groups, Not Hispanic or Latino (N=43) and Other (N=4). Hence, due to the low number of subjects in the respective groups categorized as "Other", race and ethnicity were not included in the population PK covariate analysis. No conclusion could be drawn on the influence of race and ethnicity on the PK of palopegteriparatide, based on the available data.

Gender, Weight

The impact of sex, phase 1 trial, body weight and creatinine clearance on the steady-state $C_{average}$ of mPEG, Total PTH and Free PTH are shown in Figure 5. With females as the reference, a tendency for higher exposure was observed in males for mPEG, and for Total PTH and Total PTH(1-34). Higher exposure of mPEG and Total PTH and Total PTH(1-34) was also seen with low body weight, and correspondingly lower exposure with high body weight. However, the exposure of Free PTH(1-34) and Free PTH(1-33) was not influenced, meaning that the effect of these two covariates were not considered clinically relevant.

Figure 6. Predicted fold-change of $C_{average}$ at steady-state relative to reference



Source: Report MODPTH03 Figure 39

In conclusion, the same starting dose is recommended for females and males and for all patients across the range of baseline body weights.

Elderly

The effect of age on exposure of Free PTH(1-34) and Free PTH(1-33) in trial TCP-304 was explored graphically in MODPTH03, and no differences in exposure could be found by comparing quartiles of the population based on age at baseline. Age was also tested as a potential continuous covariate in the population PK covariate analysis and was found not to improve the model fit. In conclusion, the same starting dose was recommended across all age groups.

Exposure relevant for safety evaluation

Steady state C_{max} and AUC_{τ} levels for the different analytes in the adult target population for dose levels of 18 and 60 µg/day were simulated. Table 2 shows the predicted mPEG, Total PTH, Total PTH(1-34), Free PTH(1-34) and Free PTH(1-33) in patients with hypoparathyroidism at Day 84.

Table 2. Predicted Day-84 Cmax and AUC per dose and analyte

Dose group	Analyte	Mean (5th – 95th percentile)	
		C_{max}	AUC_{day-84}
18 µg/day	Total PTH (ng PTH/mL)	5.18 (2.62 - 8.65)	124 (62.6 - 207)
	Total PTH(1-34) (ng PTH/mL)	2.40 (0.796 - 4.54)	56.9 (19.0 - 108)
	Free PTH (pg PTH(1-34)/mL)	6.92 (4.70 - 9.66)	152 (103 - 213)
	Free PTH(1-34) (pg/mL)	4.08 (2.37 - 6.19)	85.4 (47.9 - 130)
	Free PTH(1-33) (pg/mL)	2.74 (1.31 - 4.51)	64.5 (30.9 - 107)
	mPEG (ng/mL)	324 (129 - 599)	7'760 (3'090 – 14'400)
60 µg/day	Total PTH (ng PTH/mL)	16.8 (8.43 - 27.8)	401 (202 - 664)
	Total PTH(1-34) (ng PTH/mL)	7.90 (2.65 - 15.4)	187 (62.7 - 362)
	Free PTH (pg PTH(1-34)/mL)	22.8 (15.6 - 31.5)	502 (343 - 694)
	Free PTH(1-34) (pg/mL)	13.6 (8.11 - 20.5)	284 (165 - 435)
	Free PTH(1-33) (pg/mL)	8.93 (4.26 - 14.9)	210 (100 - 351)
	mPEG (ng/mL)	1'050 (444 – 2'000)	25'100 (10'600 – 48'000)

2.5.2.2. Pharmacodynamics

Mechanism of action

Endogenous PTH acts through the parathyroid hormone 1 receptor (PTH1R) to maintain calcium and phosphate homeostasis by mobilizing calcium and phosphate from the skeleton and by promoting renal calcium reabsorption and phosphate excretion. Furthermore, endogenous PTH promotes gastrointestinal absorption of calcium through the synthesis of active vitamin D. As PTH1R-mediated activities require only the N-terminal 31 amino acids of full length PTH, PTH(1-33), PTH(1-34) and PTH(1-84) have comparable affinity to and activation of this receptor.

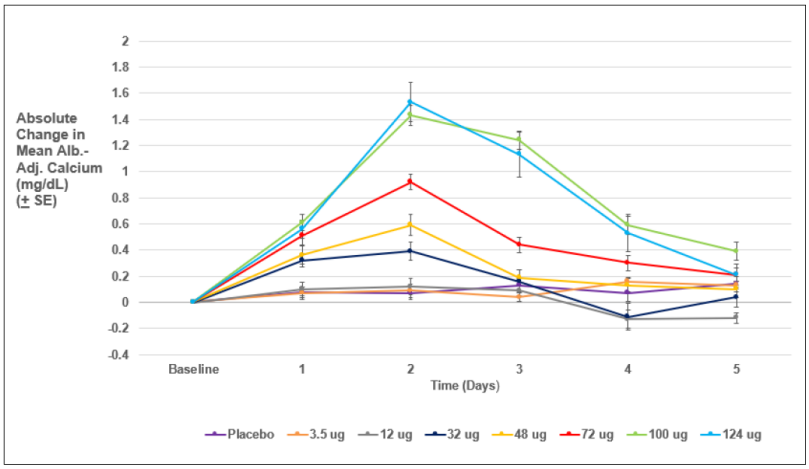
Hypoparathyroidism is a rare endocrine disease characterized by insufficient PTH production. The condition is characterized by insufficient endogenous PTH in the circulation and lack of its downstream hormone active vitamin D. Hypoparathyroidism is thus a two-hormone deficiency resulting in disturbed calcium and phosphate homeostasis characterized by hypocalcemia, hyperphosphatemia and hypercalciuria, the latter due to the inability to conserve filtered calcium. Patients with hypoparathyroidism also suffer from low bone turnover.

Palopegteriparatide is proposed as a subcutaneous once-daily replacement therapy to provide continuous exposure to active PTH within the physiological range for 24 h in patients with hypoparathyroidism. Several PD biomarkers, serum and urine analysis and bone turnover markers, were measured and monitored to identify efficacy and safety of palopegteriparatide in the clinical studies.

Primary and Secondary pharmacology

In the single dose cohorts in **healthy volunteers** of study CT-103, a dose-dependent increase in albumin-adjusted **serum calcium** was observed (Figure 6). Subjects dosed with 100 µg or 124 µg PTH(1-34) demonstrated sustained mild hypercalcemia (albumin-adjusted serum calcium levels of 10.4 to 12.1 mg/dL over about 3 days; average 10.8 and 11.0 mg/dL on Day 2).

Figure 7. Change from baseline in albumin-adjusted serum calcium (SAD cohorts)



Source: CSR CT-103, Figure 5

A similar increase after single dose of 50µg was observed in the renal impairment study TCP-104, where no significant difference was observed for the mild and moderate renally impaired subjects, neither for the severe RI group.

Multiple dose administration resulted in a continuous, dose-dependent increase in albumin-adjusted serum calcium over 10 days with mean peak increases in the range of 0.46-1.16 mg/dL. Inter-subject variability was low. Doses <12 µg PTH(1-34)/day did not produce significant increases compared to placebo or baseline whereas subjects dosed with ≥20 µg PTH/day showed sustained mild hypercalcemia.

Endogenous PTH(1-84) decreased in a dose-dependent manner for each single dose treatment group. Mean change from baseline over the 48 hours ranged from -11.2 pg/mL in the 3.5 µg group to -25.9 pg/mL in the 124 µg group. Palopegteriparatide doses ≥72 µg PTH(1-34) appeared to completely suppress endogenous PTH(1-84) to ≤10 pg/mL, the detection limit, likely due to the increased serum calcium in these cohorts.

After multiple dose, mean change from baseline after 10 days of treatment ranged from -9.8 pg/mL in the 3.5 µg/day group to -31.1 pg/mL in the 20 µg/day group.

In the renal impairment study, decreases from baseline in endogenous PTH(1-84) were observed on Day 2 for all groups. Decreases from baseline were similar between the normal renal function and mild and moderate RI groups. In the severe RI group, decrease of endogenous PTH(1-84) was stronger and levels were highly variable.

Mean spot **Fractional Excretion of Calcium** (FECa) remained stable after a single and multiple SC injection of palopegteriparatide in HV. At Day 12, the change from baseline in mean spot FECa ranged from -0.11% in the 7 µg/day group to 0.88% in the 20 µg/day group. Results indicated a sustained effect of palopegteriparatide on tubular reabsorption of calcium, driven by continuous exposure to active PTH.

In healthy subjects in study CT-103 after multiple dose, **1,25-Dihydroxyvitamin D** decreased slightly from baseline in a dose-dependent manner. In the RI study TCP-104 the greatest mean decrease was observed for the normal renal function group (Day 4) and smaller decreases from baseline in the mild, moderate, and severe RI groups.

In healthy subjects, mean **serum phosphate** remained stable after single doses. A trend towards a reduction compared to placebo was observed with increasing palopegteriparatide doses after multiple doses, though remained within the normal range.

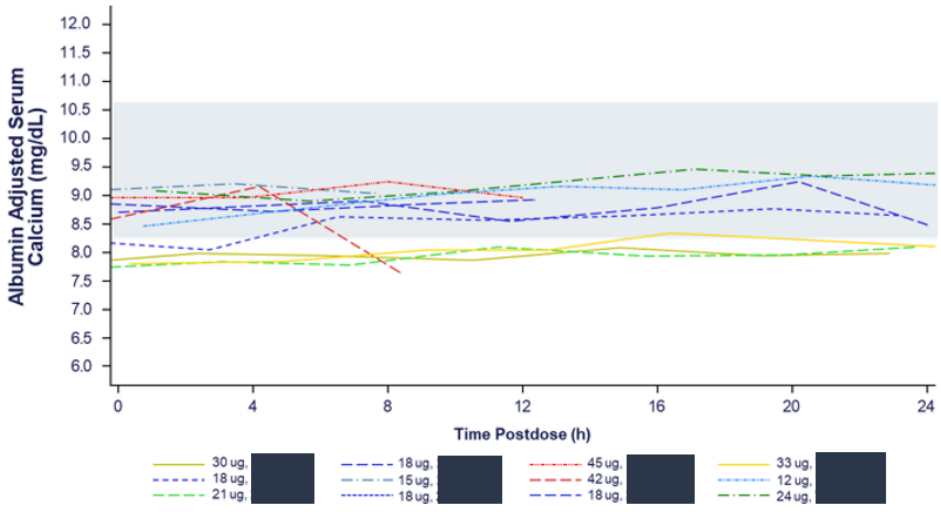
The **bone turnover markers** C-terminal telopeptide of type 1 collagen (CTx), Type I Collagen N-Telopeptides (NTx), Procollagen type 1 amino-terminal propeptide (P1NP), and Bone Specific Alkaline Phosphatase (BSAP) were evaluated in study CT-103.

Palopegteriparatide did not increase P1NP or BSAP, and the applicant concluded that by producing a flat-infusion-like profile within the calculated normal range the study drug is not anabolic.

Palopegteriparatide did modestly increase CTx, peaking between 7 and 9 days and returning to baseline after Day 14, that was less than that seen in published data with short-lived PTH and did not show a meaningful increase in NTx. The applicant concluded that these data are similar to published literature illustrating the effects of continuous PTH administration.

In **patients with hypoparathyroidism** in study TCP-201, **serum calcium** increased from baseline to Week 4. Daily administration of palopegteriparatide led to consistent serum calcium concentrations to just below or within the normal range (8.3-10.6 mg/dL) over 24h (Figure 7). The Week 84 serum calcium was 8.52 mg/dL (range 7.30 to 9.50 mg/dL).

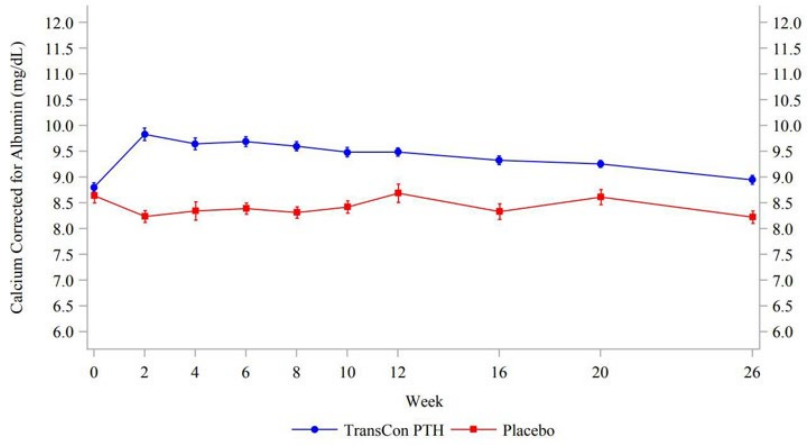
Figure 8. Individual albumin-adjusted serum calcium concentrations after daily SC injections of palopegteriparatide (TCP-201, PK/PD sub-study)



Source: TCP-201 CSR Figure 14.100.6, Derived from Figure 14.5.1.15 and including normal range
Dose of palopegteriparatide refers to dose of µg PTH(1-34)/day administered
Five of the sub-study subjects took their daily dose at different times. The shaded area in the figure depicts the normal range for albumin-adjusted serum calcium defined in this study is 8.3-10.6 mg/dL (2.07-2.64 mmol/L).

In the pivotal study TCP-304, serum calcium increased promptly after initiation of palopegteriparatide, peaking at Week 2 during initial titration to individualized optimal doses. Serum calcium values subsequently decreased from this initial peak and remained above baseline and within the normal range through Week 26.

Figure 9. Mean albumin-adjusted serum calcium concentrations after daily SC administration of palopegteriparatide (study TCP-304)

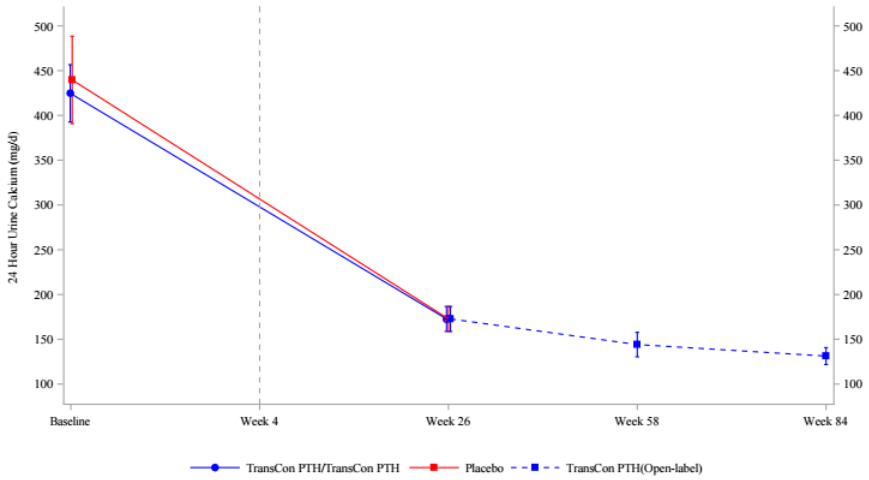


Excretion of Calcium

After Week 8, mean **spot AM FECa** values steadily decreased for pooled subjects to approximately 1.1% (range 0.15 - 4.46%; normal ≤2%) at Week 84. While the mechanism of continued decline in FECa from Week 8 is not entirely clear, it may be related to sustained renal exposure to active PTH over time, as well as normalization of bone metabolism after initial increase in bone turnover with exposure to PTH.

Trends in mean **24 h urine calcium excretion** were similar to spot FECa. Mean 24 h urine calcium fell from 428 mg/24 h (high) at baseline to 178, 149, and 134 mg/24 h (normal <250 mg/24 h) at Weeks 26, 58, and 84, respectively, showing normalization by Week 26.

Figure 10. Mean 24h urine calcium



In study TCP-201, a decrease in mean **serum phosphate** values was observed in patients as early as Week 2 to 3.40 mg/dL (range 2.26 - 4.60 mg/dL) with a nadir at Week 4 (3.29 mg/dL [range 2.40 - 4.61 mg/dL]), thereafter increasing slightly and stabilizing for the remainder of 84 weeks. Consistent results were observed in study TCP-304, where serum phosphate decreased from baseline after initiation of treatment and remained below baseline and stable within the normal range thereafter.

1,25-Dihydroxyvitamin D decreased after treatment initiation and returned to baseline levels during treatment.

In study TCP-304, **bone turnover marker P1NP** increased in palopegteriparatide-treated subjects over the first 12 weeks of the blinded period, followed by a slight increase through Week 26.

Under treatment, the mean **CTx** values for all patients in TCP-201 reached a peak at Week 12 of 804 ng/L (range 230 to 2540 ng/L) and then gradually decreased to 533 ng/L (range 80 to 2170 ng/L) at Week 58.

Impact on PK and serum calcium has only been observed for subjects with an anti-PEG **antibody** treatment boost. Clearance of both the prodrug and mPEG was increased in the presence of anti-PEG antibodies only when a treatment boost occurred.

QSP model

The exposure-efficacy was evaluated implementing a previously developed QSP model to describe the calcium and phosphate homeostasis, which served as the framework to mechanistically substantiate the physiologic and pharmacologic responses to palopegteriparatide administration in subjects with hypoparathyroidism.

Observations from Phase 1 subjects receiving palopegteriparatide were used to further refine the model to match clinical measurements. During model evaluation, the results demonstrate adequate characterization of serum calcium, serum phosphate, urine calcium and serum active vitamin D with the proposed approach across the different dose levels evaluated in patients, demonstrating an adequate description of the median tendency on both efficacy endpoints.

Subsequently, the Applicant has evaluated the impact that missed doses of PTH would have on the efficacy markers. The results show that periods of more than 2 days without dose could have an impact on serum calcium levels.

2.5.3. Discussion on clinical pharmacology

Pharmacokinetics

The proposed medicinal product is a prodrug for injection with a suitable pen device into subcutaneous tissue. The prodrug palopegteriparatide contains a mPEG-part connected with a linker to teriparatide, i.e. PTH(1-34). Both the prodrug and its cleavage product teriparatide are released into the circulation where both can be metabolised to PTH(1-33).

It is noted that the applicant usually shortened the "name" for description of various moieties and drug contents in the dossier, e.g.: the presentation says 168µg PTH(1-34)/0.56ml which does not include the TransCon-linker and the large mPEG-moiety. This naming of PTH(1-34) can make difficult the distinction between prodrug ("Total" - unreleased as the prodrug) and active drug ("Free" - cleaved from the linker), considering also that both can also be metabolised to PTH(1-33).

It is also emphasized that in all clinical studies the investigated doses of palopegteriparatide were always expressed in terms of micrograms of the active moiety of PTH(1-34), i.e. teriparatide, and do not include the additional amount of the mPEG plus TransCon-linker,. This approach is also proposed for the SmPC, where all dose recommendations are given as the corresponding PTH(1-34)/teriparatide amount. This approach seems clinically useful because all study results are referring to micrograms of teriparatide, the product information has been revised to reduce any inconsistencies with regard to product name and expression of strengths in order to minimise dosing errors.

The pharmacokinetics of palopegteriparatide were investigated in 3 phase I studies in healthy volunteers and 2 studies in patients with hypoparathyroidism. Single dose and multiple dose evaluation and dose finding with full PK sampling was only performed in one phase I study. One study in subjects with renal impairment and one for comparison with a Japanese population was performed.

Three bioanalytical procedures were developed and validated to investigate the PK of palopegteriparatide and its metabolites. Besides the prodrug palopegteriparatide, Free PTH(1-33) and Free PTH(1-34), as well as Total mPEG are analysed. Free PTH is present at very low concentrations (pg/mL range) and it has to be analysed in presence of much higher concentrations of the prodrug (ng/mL range), which is analytically challenging. As a consequence, the acceptance criteria for several parameters (accuracy, precision, selectivity) were widened, which is deemed acceptable.

The applicant provided comprehensive analytical procedure validation reports, covering all relevant aspects. All analytical procedures were validated with respect to precision, accuracy, matrix effect (selectivity) in normal, haemolysed and lipemic plasma, sample stability in plasma, freeze-thaw stability, stability in whole blood and carry-over. The analytical procedures are overall considered suitable for their intended use. However, due to the very low concentrations of Free PTH(1-33) and Free PTH(1-34), analytical limitations exist that are adequately considered upon data analysis.

The method to sample and correctly quantify Free PTH included a vital acidification and cooling step immediately after blood drawl, critical to minimize further ex vivo release of Free PTH from the prodrug. As further discussed for the dedicated renal impairment study below, also in the pivotal phase 3study the results of the Free PTH plasma concentrations of all patients from 4 investigational sites had to be excluded from the PK analyses.

The most relevant for evaluation of release from the prodrug is to analyse the Total PTHs and for PD/efficacy is to evaluate the Free PTHs.

PK results indicated that LLOQ was obviously too high for adequate analysis of Free PTH released from low concentrations. In addition, though sampling times were mostly considered sufficient to characterise the PK of palopegteriparatide and its metabolites, it is noted that plasma sampling for 96 hours postdose was not optimal to describe the elimination phase and subsequently, elimination related parameters were only estimated in the popPK model.

Two population PK models were developed, one on Phase 1 and 2 data and this model was updated to also describe Phase 3 data. Identified covariates were considered either too uncertain or clinically not relevant. The model was not used for potential dose adjustment.

In addition, an existing QSP model was updated to the given conditions. This model confirmed the mechanistic understanding of the effects of palopegteriparatide and was used to investigate the effect of missed doses.

Two different formulations were used during the clinical development. The first one was used in the Phase I study CT-103 and the second one in the rest of studies. Compared to the first formulation, the amount of metacresol was decreased in the second formulation with a compensatory increase in mannitol and the concentration of the active ingredient was reduced from 0.4 to 0.3 mg PTH(1-34)/mL. Furthermore, different devices were used, syringe and needle in phase I studies and prefilled pens in phase 2 and 3 studies. In Phase 2 and Phase 3 clinical trials, palopegteriparatide injection was rotated between the left and right thigh and left and right abdomen, however, in the early phase 1 studies, it was administered as an abdominal injection. The applicant did not formally compare exposure to PTH(1-34) after administration of palopegteriparatide at different injection sites, although it is known from other PTH products (e.g. for Forsteo, see EPAR) that the BA may differ between abdominal and thigh injections.

Taken together, from the submitted data there was insufficient clinical information on potential impact of concentrations (i.e. different viscosity), injection volume (i.e. size of and diffusion characteristics from the SC administration), injection sites (i.e. abdomen and thigh) and device (i.e. use of syringe or pen) on the bioavailability (autocleavage and release) of Total PTH, Free PTH and mPEG for a final conclusion on bioequivalence of early and final formulation. The applicant's biopharmaceutical development was considered incomplete in this aspect because the most relevant PK data were obtained with the early formulation using only one injection site and not using the final device. The applicant argued that BE studies would not be necessary considering the low contribution of one single dose to the total exposure at steady-state because of the long half-life, in contrast to short-half-lived PTH products, which can be agreed to.

From the plasma concentrations obtained from the phase I study CT-103 in HV, it had been derived that the different volumes of injected drug (acc. to CSR volumes of 10-400 µL were to be injected subcutaneously) did not relevantly affect the bioavailability, because a roughly dose proportional, though slightly less than proportional exposure was observed with single and multiple doses. On the other hand, the lowest dose given to patients had the highest dose-normalised exposure which might indicate "faster diffusion" out of the smaller depot than for highest doses. Exposure data from patients in study 201 were separated by injection site and compared to study CT-103. Results suggest that injections site does not have a relevant impact on exposure to Total and Free PTH.

In summary, no further BE study to compare sites is considered necessary. The recommendations in the PI to rotate the injection sites between left/right abdomen and thighs are thus considered sufficiently justified.

Study CT-103 in healthy volunteers was the main and only full sampling study to evaluate the PK of palopegteriparatide for the prodrug and its cleaved active metabolites Free PTH(1-34) and (1-33) after single and multiple doses.

Acknowledging that the release from the prodrug is sustained, from the PK data it cannot be derived whether a lag-time may be seen, because the analytical methods were not sensitive enough to reliably detect total and especially Free PTH levels at low doses and early after dosing. At least, what can be derived from the concentration curves is that no obvious unexpected bursts were detectable.

Overall, dose-related increases in exposure over the dose range studied (3.5-142 µg) were observed. Absorption of the prodrug palopegteriparatide following subcutaneous abdominal administration was slow with median Tmax of 48-72 h after SD and 8-24 h after MD. The absorption of mPEG was similarly slow. The release of the active free PTH(1-34) by cleavage from the linker reached maximum concentrations after about 4-8 h after SD and MD, whereas the metabolism to PTH(1-33) was slower (6-12 h after MD).

PK parameters for absorption and elimination rates per day derived from popPK modelling showed that the elimination rate of palopegteriparatide (0.067/day) was ~3-fold slower compared to its absorption rate (0.213/day). In contrast, the elimination rate of free PTH (285/day) was about 1000-fold faster than the absorption of (0.213/day) and linker release from (0.277/day) palopegteriparatide which are therefore the controlling and rate-limiting steps (flip-flop kinetics).

In healthy volunteers, increase in plasma concentrations of Total PTH as well as Free PTH seemed to follow a somehow pulsatile manner as shoulders are observable about every 12 hours. As, according to the quality assessment, no "non-linear" release was observed in vitro, it is unclear whether the clinical profiles are due to the release characteristics of palopegteriparatide drug product at the depot conditions and/or due to interfering physiological parathyroid function in HV. According to the applicant, the observation of shoulders or additional peaks may be seen as artefacts resulting from individual variation and handling matters for Free PTH.

After the 10 days' administration, period steady-state was not yet achieved for the prodrug and mPEG, while it was reached for the released Free PTH after approximately 8 days. Due to the slow elimination, accumulation was large, especially for the prodrug and mPEG up to 20-fold. Free PTH accumulated only ~2-fold.

The peak:trough-ratio for Free PTH after multiple dosing was ~1.4-1.8-fold which indicated that the exposure of the active Free PTH could be regarded relatively constant after multiple daily dosing. Accumulation of Total PTH $AUC_{0-\tau}$ and C_{max} was 7.5-18-fold and 4.6-12.5-fold, respectively and for mPEG C_{max} 9.2-19.4-fold. Peak:trough ratios were also small and consistent at all doses tested with 1.0-1.2-fold. Variability for all analytes was moderate to high.

From the phase I study, a roughly dose-proportional increase of C_{max} and AUC was derived, though slightly less than proportional. PopPK from the phase III study in patients indicated that after SC injection of lower doses an overproportional exposure was observed. It is unclear if this is related to any of the discussed variables to be considered also for BE.

V/F was only estimated via popPK modelling. For Total PTH and mPEG V/F was 4.8 L and for Free PTH it was 8.7 L. This is considered comparable to Natpar with 5.35 L after IV dosing.

No mass balance study was performed and none is necessary, because elimination of a protein is usually via proteolytic catabolism and reabsorption as amino acids and incorporation into general proteins.

No specific metabolism studies have been perform in humans. An exploratory metabolism study was carried out as part of the phase 1 CT-103 study Part 1 (SAD), Cohort 6, 100 µg PTH Part 2 (MAD), Cohort 3, 12 µg PTH. The metabolism was only studied at the prodrug level due to limitations in the Free PTH assay. The results showed that the sum of each analyte (Total PTH(1-33 and PTH(1-34)) nearly overlap with the Total PTH plasma exposure. This indicates that there were no other metabolites.

In accordance with general guidance in the EMA Guideline on therapeutic peptides, no specific studies were performed to evaluate excretion; except for the dedicated renal impairment study relevant for protein lower than MW 50kDa.

Elimination was generally very slow (60 h plus), so that in study CT-103 all of the calculated $T_{1/2}$ values are regarded unreliable, because the applicant did not perform blood sampling for long enough (96 h postdose), both after single dose and the 10^{th} of the multiple dose scheme. Therefore, the applicant did not calculate further elimination-related parameters, such as CL/F and Vz/F, although this was planned in the PKAP. This is considered an oversight in study planning.

Considering respective requirements of the EMA MR-GL, from the elimination-related PK results it cannot be derived for most of the analytes, especially mPEG, after SD and MD, how plasma concentrations would decrease after the last dose. This is deemed relevant information because there may be patients who have to withdraw from the treatment and it is unknown how exposures would decrease; even acknowledging that the SmPC recommends to measure calcium levels at interruption or withdrawal. Therefore, new simulations were performed for patients stopping palopegteriparatide 21µg at day 84. Results show that concentrations of Total PTH and Free PTH would decline and approach zero within the following 3 weeks. In contrast, mPEG was simulated to remain at measurable (LLOQ 5ng/ml) concentrations for the following 10 weeks, but would take even longer for complete elimination. The currently unknown long-term effects of mPEG exposure were included in the RMP.

PK results in patients with hypoparathyroidism in studies TCP-201 and 301 were in line with results obtained from HV: concentrations of Total PTH, mPEG and Free PTH increased with doses and steady-

state was achieved after about 2 and 1 weeks, respectively. Over the study periods investigated the peak:trough-ratio was small which supported the slow release of Free PTH.

The applicant calculated a normal range for free PTH levels on basis of the physiological normal range of endogenous PTH(1-84) (10-65 pg/ml) and their molecular mass relation (40%). By this calculation the applicant proposed a normal range for the active peptides of ~4-26 pg/ml. This approach can be followed.

The impact of missed doses on the exposure of the various analytes was modelled and revealed that for up to 2 missed doses the Free PTH concentrations would remain in the usual variability ranges. With longer time off dose return to steady-state Free PTH levels would need 1-2 weeks. The information about missing doses included in the PI is considered adequate.

Fever, hypothermia and pH alterations were modelled to have no clinically relevant effect on release and exposure of Free PTH.

Special populations

Impaired renal function

The dedicated RI study indicated for Total PTH and mPEG no relevant difference in plasma exposure between normal and renally impaired subjects of any grade.

The impact of renal impairment on Free PTH (1-34) exposure levels was evaluated by statistical analysis, where AUC increases of 42% and 34%, respectively, were observed in patients with mild and moderate renal impairment. The changes observed in the statistical analysis on C_{max} are of minor relevance, which is expected due to the mechanism of PTH elimination.

These changes in exposure were evaluated on the different analytes (mPEG, Total PTH, Total PTH (1-34), Free PTH, Free PTH (1-33) and Free PTH (1-34)) by forest-plot on the C_{ave} exposure marker. In addition, the Applicant has explored changes in renal function on Free PTH levels, showing that clinically relevant changes in exposure are to be expected from CrCL<60 mL/min. These results partially agree with the statistical analysis, which indicates that the selected dosage regimen maintains levels of Free PTH exposure similar in patients with mild renal impairment to the levels observed in patients with normal renal function. Patients with moderate renal insufficiency could present important changes (>1.5-fold) in Free PTH exposure. However, an exploratory comparison of total and free PTH demonstrated no significant accumulation of those analytes in patients with mild or moderate renal impairment for the median and the minimum-maximum range.

Free PTH(1-34) results for the severe RI group were significantly different with more than 3-fold increases in AUC exposure to the mild and moderate groups, as levels did not decrease over the 4-weeks-postdose sampling period.

The applicant discussed that methodological constraints with sample handling and preparation in combination with the medical history of the subjects in the severe RI group probably resulted in the unreliable and obviously unexpectedly high Free PTH(1-34) values. In addition to no immediate cooling and acidification, the applicant argues that the samples had been compromised by a potential cleavage of endogenous PTH to Free PTH(1-34) by the endogenous enzyme cathepsin-D in the sample that occurred in acidic conditions. It remains to be speculated if such cleavage by catepsin could have been suspected and maybe an enzyme inhibitor could have been added to the samples.

Regarding study entrance criteria, it may be speculated whether the sponsor wanted to be able to also include and investigate subjects who develop secondary hyperparathyroidism from severe RI; although under consideration of the sought hypoparathyroidism indication, a "hypo"-patient with severe RI developing hyperparathyroidism seems somewhat arbitrary. As such, the sponsor has not further

narrowed the CSP exclusion criterion 7 that excluded primary or tertiary active hyperparathyroidism (beside others). Hence, for 2 subjects enrolled, the medical history specifically lists secondary hyperparathyroidism, but BL PTH levels do indicate such condition also for additional 3 subjects.

While the bioanalytical problems of (non-)acidified/cooled plasma are one aspect in the correct determination of the free PTH(1-34) PK, it is acknowledged that the feasibility to include subjects with severe RI may be challenging. 7 of 8 severe RI subjects were included at one site while the 8th subject with severe RI was from a different site. That single subject had "target" baseline endogenous PTH levels and its individual concentration-time-profile for Free PTH(1-34) was decreasing as probably expected and so this "pre-selection" of enrolment may have added to the unreliable Free PTH(1-34) results due to probably incorrect sample handling at the site level and the high endogenous PTH(1-84) concentrations.

While it still remains unclear in how far severe RI would have an impact on the elimination of Free PTH, the data provided is nevertheless supportive that the C_{max} and AUC_{last} values for the few (3) subjects with lowest PTH(1-84) were in a comparable range as for those with moderate RI or better renal stages. Exposure to Total PTH and mPEG was similar for the normal subjects and for the mild and moderate RI groups.

In phase III study patients with low baseline eGFR, the filtration rate even dropped further during the initial 2-6 weeks of treatment. Patients with eGFR < 45 ml/min also showed increases in serum calcium levels during this period. As a consequence, the applicant added a warning on PI covering the need for more frequent monitoring of serum calcium levels in patients with impaired renal function at treatment initiation.

Dose adjustments for mild and moderate RI are not proposed and not regarded necessary based on the study results.

Impaired hepatic function

No information has been provided by the Applicant regarding the impact of hepatic impairment on the PK exposure metrics of mPEG and PTH due to the lack of data. The SmPC section 4.2 states "No study in patients with severe hepatic impairment has been performed" and "Yorvipath has not been studied in patients with severe hepatic impairment and should be used with caution in these patients."

Gender

According to the Population PK analysis, there is a clear effect of covariate (sex=men) on the KaPTH, the apparent clearance and on the apparent volume of distribution. The forest plot analysis showed an increased in Total PTH exposure and Total PTH 1-34 in male patients compared to women. However, since no relevant differences in free fractions (Free PTH(1-34), Free PTH(1-33) and Free PTH) was detected, the impact of gender differences in the exposure are considered of minor relevance.

Race

No relevant race effects were detected due to the low level of experimental evidence collected. Therefore, it seems premature to establish any dose recommendation in non-White patients.

Weight

The impact of body weight has been evaluated using the forest plot analysis. The results suggest that an impact on Total PTH levels is expected in patients with different body weight, but it is recognized that those differences do not affect the exposure of Free PTH, possibly due to differences in the

distribution of Total PTH in adipose tissue after its administration. The uncertainties regarding how the higher exposure is transmitted to the free fraction have been solved, since no differences in steady-state exposure are expected due to body weight.

Children

The PK properties in children have not been characterized. No indication is sought for paediatric population.

Overall, except for the exposure in severe renally impaired subjects, PK in special population is considered sufficiently investigated. Based on these data including popPK, no specific dose adjustments are necessary for hepatic impairment, race, gender, weight, and age, especially because palopegteriparatide will be titrated under monitoring of serum calcium levels in clinical practice.

Pharmacokinetic interactions studies

No formal drug-drug interaction studies have been conducted with Palopegteriparatide and none are required for a therapeutic protein.

PTH and mPEG are not expected to induce or inhibit the major drug metabolizing cytochrome P450 pathways.

The interactions with drugs that may act on calcium/phosphate metabolism such as to bisphosphonates, denosumab, romosozumab, thiazide and loop diuretics, systemic corticosteroids, and lithium were added in the SmPC. Monitoring patients treated concomitantly with these drugs for changes in serum calcium is recommended.

The pharmacodynamics interaction with digoxin and the need of signs and symptoms of toxicity monitoring has also been reflected in the SmPC.

At a dose of 18µg/day palopegteriparatide, which is the proposed starting dose for titration and was within the most commonly used dose range (15-24µg/day) in the phase III study target population, the safety relevant concentration of Free PTH was estimated as 6.92pg/ml (4.7-9.7pg/ml) for Cmax and 152pg/ml*h (103-213) for AUC in steady-state. For the highest dose of 60µg used, the safety relevant concentration of Free PTH was estimated as 22.8pg/ml (15.6-31.5 pg/ml) for Cmax and 502pg/ml*h (343-694 pg/ml*h) for AUC in steady-state.

As only dose-response data were provided, "exposure relevant for safety evaluation" seemed an open issue. Nonetheless, the applicant explained that a definite Total and Free PTH exposure relevant for safety and efficacy cannot be established because response and responsiveness to external hormone substitution are highly individually affected e.g. by physical activity, dietary calcium intake, intercurrent illness or environmental changes and also depending on the severity of the underlying disease. It is acknowledged that, at least, the to-date known short-term side effects of palopegteriparatide-related PTH-substitution can be diminished by close monitoring and maintenance of serum calcium levels within the (low-)normal range.

TWith regard to mPEG, according to simulations, the concentration of mPEG at a daily dose of 18µg was estimated with up to 600 ng/ml and at a 60µg dose up to 2000 ng/ml. It was assessed that this mPEG dose and systemic exposure would be 45- and 95-fold lower, respectively, than the thresholds established by the CHMP Safety working party.

The presented QSP model describes the relation between PTH, in particular, the PTH released from TransCon PTH following administration to patients with hypoparathyroidism, calcium, vitamin D, FGF23 and Phosphate. The model is quite complex and the quality of its predictive performance is different for the varying components but it can be considered to support the principles of the mechanistic understanding of the activity of the active substances.

Pharmacodynamics

In healthy subjects, a circadian rhythm of PTH secretion and associated serum calcium and phosphate levels is known since decades (cf. e.g. Jubitz et al. 1972). Similar to other hormones, endogenous PTH secretion is characterized by tonic and pulsatile components with the majority of PTH being secreted in a tonic fashion with superimposed low-amplitude and high-frequency bursts occurring every 10–20 min, which is thought to modulate target organ responsiveness (Chiavistelli et al. Bone Res 2015).

Hypoparathyroidism results in hypocalcemia, hyperphosphatemia and hypercalciuria, the latter due to the inability to conserve filtered calcium. Also, low bone turnover is a relevant marker of hypoparathyroidism. Palopegteriparatide was shown to provide continuous exposure to PTH(1-34) in patients with deficient endogenous PTH. Based on the clinical data, similar to GH replacement therapy, a low-amplitude pulsatile secretion does not appear to be necessary for effective PTH replacement therapy in addition to tonic continuous PTH levels. Palopegteriparatide is a prodrug, which is a peglylated form of PTH(1-34), i.e. teriparatide. Teriparatide is slowly released from the mPEG-(plus linker)-part into the system and is active at the target PTH1 receptor similar to endogenous PTH(1-84).PTH(1-33) has the same activity as PTH (1-34).

During development in phase I in healthy subjects several serum, urine and bone-related pharmacodynamic markers were evaluated, such as serum calcium, phosphate, endogenous PTH(1-84), 1,25 dihydroxyvitamin D, fractional excretion of calcium and bone turnover markers (BSAP, P1NP, CTx, NTx).

In HV after single (3.5-124 µg) and multiple (3.5-24 µg) palopegteriparatide injections, dose-related increases or decreases of the measured PD parameters could be observed mainly at palopegteriparatide doses equivalent to ≥12µg teriparatide. These responses showed that the relevant PTH-dependent pathways were targeted by the injection of palopegteriparatide and reacted accordingly. After multiple doses return to baseline after the final 10^{th} dose was observed.

However, administration of single doses of palopegteriparatide in HV seemed to result in endogenous PTH(1-84) levels to re-increase after about 16 hours as all doses except the lowest of 3.5µg showed a peak at that timepoint. Similarly, 24-hours fluctuating serum phosphate levels were seen in the MAD study at any dose. As, comparably, peaks and/or shoulders were observable both for PD, it is suspected that the functioning parathyroid loops in HV seem to react to the external administration of the hormonal substitution. Therefore, the study results from healthy volunteers can be seen as confirmative for the general proof-of-concept, however, PD effects are vital to be investigated in the target hypoparathyroidism population.

From the PD data obtained in subjects with various degrees of renal impairment (study TCP-104), increase in albumin-adjusted serum calcium, suppression of endogenous PTH(1-84) or slight decrease from baseline 1,25-(OH)2D3 was observed similarly as for normal subjects. Serum phosphate remained at BL levels for moderate and severe RI subjects. However, it has to be kept in mind that some of the severe RI subjects (5 of 8 cases) had a medical history of secondary hyperparathyroidism with high endogenous BL PTH levels so that means with error bars cannot be regarded as fully reliable.

It is pointed out that in the Phase 2 and 3 clinical trials only those patients with hypoparathyroidism were treated whose serum calcium and 25(OH)-vitamin D levels were adequately adjusted to the target range prior to first dose of palopegteriparatide. Therefore, baseline levels for all patients were comparable. Up-titration of palopegteriparatide concurrently with down-titration and withdrawal of oral calcium and vitamin D supplements was to be performed in line with specific treatment algorithms stipulated in the CSPs. Therefore, one can expect the PD marker levels to change only over time.

In general, PD marker evaluation in patients confirmed: serum calcium levels increased and returned to normal ranges without additional oral calcium. Within 24 hours, levels could be maintained stable in the normal range without significant peak-trough fluctuation; high urinary excretion of calcium decreased and returned to normal ranges; high serum phosphate levels dropped early after treatment initiation, re-increased to less than baseline values and stabilised in normal ranges; active vitamin D levels initially dropped after withdrawal of oral intake but over time levels increased to normal ranges indicating the possibility to produce this hormone again; and bone turnover marker also adjusted.

For none of the PD markers an exposure-response relationship was submitted. The applicant re-iterated that exposure-response analyses for safety and efficacy were not possible for palopegteriparatide and active Free PTH because response and responsiveness are so individual. With regard to mPEG, they argued that no PEG-related AEs were observed why no such E-R analyses were performed. This is considered acceptable.

In addition, the applicant was asked to discuss ERR of palopegteriparatide in comparison to the approved PTH products Natpar and Forsteo that have shorter half-lives. With simulated plasma PK profiles, the applicant compared PTH exposures from Yorvipath with those after a daily teriparatide injection. It was shown that plasma levels are highly fluctuating with the latter, in contrast to palopegteriparatide.

With regard to exposure-response, published literature was referenced. Especially the QSP model of Khurana et al., 2019, provides further assurance how serum calcium levels probably develop after different dosing schemes and formulations of PTH, i.e. the peak:trough ratios of PTH and the PD marker serum calcium decline significantly with a slower release formulation.

Pre-existing anti-PEG and anti-TransCon PTH antibodies were considered to impact the exposure of Free PTH or serum calcium. An effect on PK and serum calcium has only been observed for patients with an anti-PEG-antibody treatment boost. Then, clearance of both the prodrug and mPEG was increased in the presence of anti-PEG antibodies.

2.5.4. Conclusions on clinical pharmacology

The clinical development and pharmacokinetic evaluation for this product with a peptidic drug substance for subcutaneous injection should follow the EMA requirements as laid down in the respective guidelines for modified release products (EMA/CHMP/EWP/280/96 Rev1) and therapeutic proteins (CHMP/EWP/89249/2004). Based on these and knowledge from other marketed PTH products regarding the fact that different injection sites may have relevant effects on distribution volume or absorption rate, the biopharmaceutical development was considered incomplete, as aspects that relate to bioequivalence, especially the effect of different injection sites, were not investigated. However, comparison of exposure data separated by injection sites suggest that BA is largely independent of administration site and rotation of injection sites is considered sufficiently justified.

No final conclusions could be drawn for PK in subjects with severe renal impairment because most samples for Free PTH(1-34) were obviously impaired by inadequate sample handling and the patient studies did not include patients with eGFR below 30ml/min. Based on review of available patient PK and safety data, the SmPC was amended to advise that more frequent serum calcium level monitoring is necessary in patients with eGFR <45ml/min.

PK in patients is considered only incompletely investigated. The limited data available, at least, showed that the exposure to the active moieties could be adequately maintained in the targeted normal range with only low fluctuation.

Initial and extensive PD evaluation was performed in HV and the results supported dose-related changes as of e.g., the serum levels of calcium, phosphate, active vitamin D, bone turnover markers as well as urinary excretion of calcium, both after single and multiple doses. Observations that are probably related to endogenous PTH(1-84) levels and functioning PTH loops in healthy subjects raise the question whether healthy volunteers could be regarded the correct population to study PD effects of such hormone replacement.

In the patient studies, only sparse sampling for PD was performed except from a few patients where serum calcium and phosphate levels and urinary excretion were evaluated over 24 hours. While these data confirmed the stable calcium levels in the targeted normal range after 58 weeks of treatment, other PD markers were not obtained and thus cannot be correlated to PK.

An exposure-response relationship for safety and efficacy was not provided and it was argued as being unreliable due to response and responsiveness being very individual. This is acceptable since individual treatment monitoring via the PD parameter serum calcium is obligatory.

The pharmacodynamics of palopegteriparatide can be considered generally understood and investigated. The product is mimicking the effects of the missing endogenous hormone and will be titrated under continuous monitoring of serum calcium levels. By this, any clinically relevant changes in PD parameters may be observed at short notice and corrected by dose adjustment or oral calcium supplement in clinical practice.

It is concluded that PK and PD results are supportive for the applicant’s claims that a hormonal substitution can be achieved by daily palopegteriparatide injections.

2.5.5. Clinical efficacy

The clinical development program aimed to support the following indication:

“Yorvipath is a parathyroid hormone (PTH) replacement therapy indicated for the treatment of adults with chronic hypoparathyroidism .”

The following table lists efficacy studies submitted to support this application:

Table 3. Clinical efficacy studies in adult patients with hypoparathyroidism

Phase/ Trial Design	Treatment and Duration	Trial ID No. of Site Locations	Primary/ Secondary Objectives	Trial Population	No. of Subjects Included in Analysis
Phase 3/ Multi-center, randomized, double-blind, placebo-controlled, parallel-group trial with open-label extension (OLE)	Subjects randomized 3:1 to starting dose of palopegteriparatide 18 µg/day or Placebo. Dose was individually and progressively titrated to an optimal dose in increments of 3 µg/day (to 6 to 60 µg/day). After 26 weeks of blinded treatment, Placebo subjects crossed over to OLE. Subjects then received individualized dosing of 6-60 µg/day and were followed up to 156 weeks. Blinded Period (Weeks 0 to 26) completed; OLE period ongoing.	TCP-304 21 sites Canada, Denmark, Germany, Hungary, Italy, Norway, United States	Efficacy and Safety	Adult subjects (≥18 years of age) with hypoparathyroidism	84 (3:1): 63 subjects randomized to palopegteriparatide and 21 subjects randomized to placebo
Phase 2/ Multi-center, randomized, double-blind, placebo-controlled, parallel-group trial with OLE	Subjects randomized 1:1:1:1 to 3 fixed doses of palopegteriparatide (15, 18, and 21 µg/day) or Placebo. After 4 weeks of blinded treatment, subjects in placebo group crossed over to palopegteriparatide in the OLE. All subjects then received individualized doses of 6-60 µg/day palopegteriparatide and are followed up to 210 weeks. Blinded Period (Weeks 0 to 4) completed; OLE period ongoing.	TCP-201 12 sites Canada, Denmark, Germany, Italy, Norway, United States	Efficacy and Safety	Adult subjects (≥18 years of age) with hypoparathyroidism	59 (1:1:1:1): 14, 15, 15, and 15 subjects randomized to palopegteriparatide 15, 18, and 21 µg/day or placebo, respectively

2.5.5.1. Dose response study(ies)

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

Methods

TCP-201 was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel group, 4-week trial with an Open-label Extension (OLE) period of 210 weeks of daily palopegteriparatide (TransCon PTH) in male and female adults with either postsurgical hypoparathyroidism or autoimmune, genetic, or idiopathic hypoparathyroidism for at least 26 weeks, treated with a stable dose of active vitamin D (≥0.25 µg twice daily calcitriol or ≥1.0 µg/day alfacalcidol) and ≥400 mg twice daily calcium for at least 12 weeks prior to Screening. The randomized and placebo controlled 4-week main study compared three dose levels of palopegteriparatide administered once daily (15 µg PTH(1-34)/day, 18 µg PTH(1-34)/day, 21 µg PTH(1-34)/day) to placebo.

Main study:

Screening:

The Screening Period consisted of determining eligibility, documenting baseline status, and optimizing vitamin D and magnesium levels, and doses of standard of care (SOC; active vitamin D and calcium) prior to study drug dosing to achieve the following target levels:

- 25(OH) vitamin D: 30-70 ng/mL (75-175 pmol/mL)
- Magnesium: within the normal range
- Serum calcium: within the lower half of the normal range

4-Week Blinded Treatment (Visits 1-3; Weeks 0-4):

At Visit 1, subjects were randomized into one of 4 treatment groups (1:1:1:1): palopegteriparatide 15 µg PTH(1-34)/day, 18 µg PTH(1-34)/day, 21 µg PTH(1-34)/day (dose of palopegteriparatide refers to dose of PTH(1-34) administered, i.e., 15 µg/day, 18 µg/day, or 21 µg/day PTH(1-34)), or placebo.

Subjects were to remain on the same dose of study treatment throughout the 4-week Blinded Period; however, SOC doses of active vitamin D and calcium were optimized or discontinued based on serum calcium remaining within ≥lower limit of normal (LLN) and ≤upper limit of normal (ULN).

Open-Label Extension (Visits 3-21; Weeks 4-214):

At Visit 3, subjects were enrolled into the OLE:

• If on active vitamin D: Started palopegteriparatide 15 µg/day and SOC titrated as per the Blinded Period

• If not on active vitamin D: Maintained same dose of palopegteriparatide as during the Blinded Period.

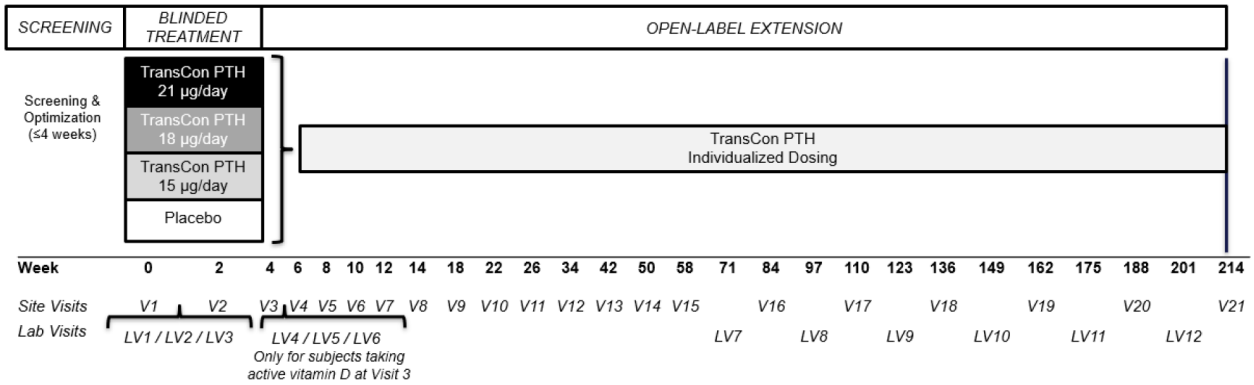
At every clinic visit (every 2 weeks) up to and including Visit 8, the palopegteriparatide dose was to be increased by 3 µg/day if the serum calcium level was <LLN or the subject was experiencing persistent hypocalcemic symptoms.
If a subject not taking SOC experienced persistent hypercalcemic symptoms in the setting of an elevated serum calcium value, the palopegteriparatide dose was decreased by 3 µg/day; the dose range during the OLE was expected to be 6 to 60 µg/day.

Starting at Visit 9, palopegteriparatide, active vitamin D, and calcium doses were expected to remain stable but dose adjustments were allowed as needed based on serum calcium and other indicators.

Rescue doses of active vitamin D and/or calcium were permitted throughout the OLE.

The figure below illustrates the Main Study Design including OLE period:

Figure 11. TCP-201 Main Study Design and OLE



Study Participants

As outlined in the Clinical Study Protocol (Amendment 3 dated 10 March 2021), patients must meet the following conditions:

- Estimated glomerular filtration rate (eGFR) >30 mL/min/1.73m^2 during Screening
- Thyroid-stimulating hormone (TSH) within normal laboratory limits within the 12 weeks prior to Visit 1; if on suppressive therapy for thyroid cancer, TSH level must be ⩾0.2 µIU/mL
- If treated with thyroid hormone replacement therapy, the dose must have been stable for at least 12 weeks prior to Visit 1

- Was able to perform daily subcutaneous self-injections of study drug (or have a designee perform injection) via a pre-filled injection pen
- Meets the requirements of all in- and exclusion criteria to be eligible for the main study

Inclusion criteria

1. Male or female aged ≥18 years

2. Subjects with postsurgical chronic hypoparathyroidism or auto-immune, genetic, or idiopathic hypoparathyroidism for at least 26 weeks. Diagnosis of hypoparathyroidism is established based on hypocalcemia in the setting of inappropriately low serum parathyroid hormone (PTH) levels.

3. On a stable dose* for at least 12 weeks (US only: or 4 weeks if on Natpara as of September 2019) prior to Screening of:
− ≥0.25 µg BID of calcitriol (active vitamin D) or ≥0.5 µg BID or ≥1.0 µg daily of alfacalcidol (active vitamin D) and
− ≥400 mg BID calcium citrate or carbonate
− If subject had a history of hypercalcemia on such doses, subject could have taken <0.25 µg BID of calcitriol, <0.5 µg BID or <1.0 µg daily of alfacalcidol, or <400 mg BID of calcium citrate or carbonate, with approval of the Medical Monitor/Medical Expert

*Did not preclude occasional (<3/week) rescue doses of active vitamin D and/or calcium for symptomatic hypocalcemia

4. Optimization of supplements prior to randomization to achieve the target levels of:
− 25(OH) vitamin D levels of 30-70 ng/mL (75-175 pmol/mL) and
− Magnesium level within the normal range* and
− Albumin-adjusted or ionized serum calcium level in the lower half of the normal range

*If subject had a history of inability to be successfully managed within the normal range for magnesium level, a level slightly below the normal range was acceptable with approval of the Medical Monitor/Medical Expert

5. Body mass index (BMI) 17-40 kg/m^2 at Visit 1

6. If ≤25 years of age, radiological evidence of epiphyseal closure based on x-ray of non-dominant wrist and hand

7. Provided written, signed, informed consent

Exclusion criteria

1. Known activating mutation in the calcium-sensing receptor (CaSR) gene

2. Impaired responsiveness to PTH (pseudohypoparathyroidism) which was characterized as PTH-resistance, with elevated PTH levels in the setting of hypocalcemia

3. Any disease that could have affected calcium metabolism or calcium-phosphate homeostasis or PTH levels other than hypoparathyroidism, such as active hyperthyroidism; Paget's disease; hypomagnesemia; type 1 diabetes mellitus or poorly controlled type 2 diabetes mellitus; severe and chronic cardiac, liver, or renal disease; Cushing syndrome; rheumatoid arthritis; multiple myeloma; active pancreatitis; malnutrition; rickets; recent prolonged immobility; active malignancy (other than low-risk well differentiated thyroid cancer or basal cell skin cancer); parathyroid carcinoma within 5 years prior to Screening; acromegaly; multiple endocrine neoplasia types 1 and 2

4. Use of loop diuretics, phosphate binders (other than calcium carbonate/calcium citrate), digoxin, lithium, methotrexate, or systemic corticosteroids (other than replacement therapy)

5. Use of thiazide diuretic within 4 weeks prior to the Screening 24-h urine collection or the first dose adjustment of SOC during Screening

6. Use of PTH-like drugs (whether commercially available or through participation in an investigational trial) including PTH(1-84), PTH(1-34), or other N-terminal fragments or analogs of PTH or PTH-related protein within 12 weeks (US only: 5 weeks) prior to Visit 1

7. Use of other drugs known to influence calcium and bone metabolism, such as calcitonin, fluoride tablets (>0.5 mg/day), strontium, or cinacalcet hydrochloride within 12 weeks prior to Visit 1

8. Use of bisphosphonates (oral or IV) or denosumab within 2 years prior to Visit 1

9. Non-hypocalcemic seizure disorder with a history of a seizure within 26 weeks prior to Visit 1
NOTE: History of seizures that occurred in the setting of hypocalcemia was not exclusionary

10. Increased risk for osteosarcoma, such as those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, open epiphyses, hereditary disorders predisposing to osteosarcoma, or with a prior history of substantial external beam or implant radiation therapy involving the skeleton

11. Pregnant or lactating women.
NOTE: Highly effective contraception was required for sexually active women of childbearing potential during the trial and for 2 weeks after the last dose of study drug, and pregnancy testing was performed throughout the trial. Sexually active women of childbearing potential who were unwilling to use highly effective contraception were to be excluded from the trial.

12. Diagnosis of drug or alcohol dependence within 3 years prior to Visit 1

13. Disease processes that may have adversely affected gastrointestinal absorption including, but not limited to, short bowel syndrome, bowel resection, gastric bypass, tropical sprue, active celiac disease, active ulcerative colitis, gastroparesis, AIRE gene mutations with malabsorption, and active Crohn's disease

14. Chronic or severe cardiac disease within 26 weeks prior to Visit 1 including, but not limited to, congestive heart failure, myocardial infarction, QTcF>430 msec (males) or >450 msec (females), severe or uncontrolled arrhythmias, bradycardia (resting heart rate <50 beats/minute), symptomatic hypotension, systolic BP <80 mm Hg or diastolic <40 mm Hg, or poorly controlled hypertension (systolic BP >150 mm Hg or diastolic >95 mm Hg)

15. Cerebrovascular accident within 5 years prior to Visit 1

16. History of renal colic or acute gout within 52 weeks prior to Visit 1

17. Any disease or condition that, in the opinion of the investigator, may have made the subject unlikely to fully complete the trial, or any condition that presented undue risk from the investigational product or procedures, including treated malignancies that were likely to recur within the approximate 1-year duration of the trial

18. Known allergy or sensitivity to PTH or any of the excipients [metacresol, mannitol, succinic acid, NaOH/(HCl)]

19. Participation in another clinical trial in which receipt of investigational drug or device occurred within 8 weeks (or at least 5.5 times the half-life of the investigational drug) prior to Visit 1

20. Was likely to have been non-compliant with respect to trial conduct

21. Any other reason that in the opinion of the investigator could have prevented the subject from completing participation or following the trial schedule

Treatments

Palopegteriparatide or placebo control (vehicle only) was to be injected SC daily into the upper or lower abdomen or anterior thigh.

Screening Period (Supplement Dose Adjustments):

During the Screening Period, adjustments to doses of hypoparathyroidism-related supplements (SOC, magnesium, vitamin D) were made to achieve the following laboratory levels:

• 25(OH) vitamin D: 30 to 70 ng/mL (75 to 175 pmol/mL)

• Magnesium: within the normal range

– If a subject had a history of inability to be successfully managed within the normal range for magnesium level, a level slightly below the normal range was acceptable with approval of Medical Monitor/ Medical Expert.

• Serum calcium: within the lower half of the normal range

Main Study (Blinded Treatment Period):

At Visit 1, subjects were randomized (1:1:1:1) to one of the following:

• Palopegteriparatide 15 µg/day

• Palopegteriparatide 18 µg/day

• Palopegteriparatide 21 µg/day

• Placebo for palopegteriparatide (sub-randomized 1:1:1)

– Mimicking dose of 15 µg/day

– Mimicking dose of 18 µg/day

– Mimicking dose of 21 µg/day

Subjects were to remain on the same dose of study drug throughout the Blinded Treatment period.

Active vitamin D and/or calcium doses were optimized. The investigator could adjust SOC in a different manner than as outlined in the protocol with prior approval by the Medical Monitor/Medical Expert (CSP Appendix 1).

Open-label Extension Period:

At Visit 3, subjects were assigned to open-label treatment as follows:

• If taking active vitamin D: Palopegteriparatide was started at a dose of 15 µg/day and undergo titration of SOC as performed during the 4-week Blinded Treatment period.

• If not taking active vitamin D: Palopegteriparatide was started at the same dose of study drug taken during the Blinded Treatment period. Exception could have been made if hypo- or hypercalcaemic symptoms were present at Visit 3, in which case palopegteriparatide dose could have been adjusted by 3 µg/day.

At every clinic visit (every 2 weeks) up to and including Visit 8, the palopegteriparatide dose was to be increased by 3 µg/day if the serum calcium level was <LLN or the subject was experiencing persistent hypocalcemic symptoms. However, if a subject not taking SOC experienced persistent hypercalcaemic symptoms in the setting of an elevated serum calcium value, the palopegteriparatide dose was decreased by 3 µg/day; the dose range during the OLE was expected to be 6 to 60 µg/day. Starting at Visit 9, palopegteriparatide, active vitamin D, and calcium doses were expected to remain stable but dose adjustments were allowed as needed based on serum calcium and other indicators. Rescue doses of active vitamin D and/or calcium were permitted throughout the OLE.

Objectives

Primary:

• To assess the effectiveness of daily palopegteriparatide on serum and urine calcium levels (FECa) and active vitamin D and calcium doses at 4 weeks of treatment

Secondary:

• To assess the safety and tolerability of daily palopegteriparatide

• To assess the effectiveness of daily palopegteriparatide on serum and urine calcium levels (FECa) and active vitamin D and calcium doses

• To assess the treatment effect of daily palopegteriparatide on daily pill burden (vitamin D and calcium)

• To assess the treatment effect of daily palopegteriparatide on serum phosphate, serum magnesium, and serum calcium × serum phosphate product (serum calcium×serum phosphate)

• To assess the treatment effect of daily palopegteriparatide on hypocalcemia and hypercalcemia symptoms, emergency room (ER) visits, and hospitalizations

Outcomes/endpoints

The following efficacy endpoints were to be investigated:

Primary efficacy variables:

Four efficacy variables were used to define the criteria for determination of a responder to treatment, the primary efficacy variable. The proportion (%) of responders to treatment, the primary efficacy endpoint, was analysed as described in the section on statistical methods.
A responder to treatment was defined as a subject who met the following 4 criteria:

- Serum calcium (albumin adjusted) within the normal range and
- Spot morning fractional excretion of calcium (spot AM FECa) within normal range (≤2%) or a reduction by at least 50% from baseline and
- Not taking active vitamin D supplements and
- Taking ≤1000 mg/day of calcium supplements (≤500 mg/day of calcium supplements was used as the criteria for the key secondary endpoint).

Secondary efficacy variables:

Other efficacy variables were measured at predefined timepoints during the Blinded Period and over the OLE.

- Calcium and active vitamin D doses
- Number of SOC supplements (pill burden)
- Spot AM FECa
- Serum phosphate
- Serum magnesium
- The serum calcium×serum phosphate product, including the proportion of subjects with serum calcium×serum phosphate product ≤55 mg^2/dL^2, ≤52 mg^2/dL^2, and ≤44 mg^2/dL^2
- Serum calcium (albumin adjusted)

At predefined timepoints over the OLE:

- 24-h urine calcium excretion

Safety and tolerability variables:

The following safety variables were assessed for both the Blinded Period and OLE:

• Serum chemistry, hematology, and spot urine parameters

• Incidence of AEs, AEs of special interest/situations (collection of AESIs added starting with Amendment 3 during the OLE), and serious adverse events (SAEs)

• Clinical events of hypo- or hypercalcemia (emergency room/urgent care visits and hospitalizations) and progression of vascular calcifications, nephrocalcinosis, and nephrolithiasis

• Injection site tolerability (based on Local Tolerability Scale and AEs)

• Evaluation of anti-PTH and anti-PEG antibody response

• Physical examinations, including vital signs

Exploratory variables:

At Week 4 of the Blinded Period, the following assessments were made:

• Patient-Reported Outcome (PRO) measures

• Bone turnover markers (serum P1NP and CTx)

• Device usability questionnaire

Throughout the OLE, the following assessments were made:

• BMD and TBS by DXA at 26, 58, 110, 162, and 214 weeks

• 24-h urine calcium excretion at 26, 58, 84, 110, 136, 162, 188, and 214 weeks

• Clinical outcome assessments (COAs) at 6, 8, 12, 26, 58, 110,162, and 214 weeks

• Bone turnover markers (serum P1NP and CTx) at 8, 12, 26, 58, 110, 162, and 214 weeks

• Serum calcium (albumin adjusted), magnesium, phosphate, and serum calcium×serum phosphate product at 8, 18, 26, 42, 58, 84, 110, 136, 162, 188, and 214 weeks

Sample size

Based on clinical experience, the proportion of subjects on SOC meeting the primary endpoint will be rare and close to 0. According to simulation data from the FDA, 66% of subjects with continuous infusion of PTH will have normal sCa. The phase 1 study data predict that a large proportion of HP subjects, around 90%, on TransCon PTH will have normal FECa. Assuming that TransCon PTH has the same profile as PTH by continuous infusion, the proportion of subjects able to discontinue active vitamin D and require less than 1000 mg/day of supplemental calcium is estimated to be at least 70%. This translates to an estimate of the proportion of TransCon PTH-treated subjects meeting the primary endpoint at more than 40%. With 10 subjects per arm, the statistical power to detect a significant treatment difference is calculated in the following table.

Power calculation for 10 subjects per arm with alpha level at 0.05 and 0.10 (two-sided).

Table 4. Clinical efficacy studies in adult patients with hypoparathyroidism:

Proportion for TransCon PTH	Proportion for Placebo	Power	
		α=0.05 (2-sided)	α=0.10 (2-sided)
40%	1%	40.7%	53.2%
50%	1%	58.8%	70.4%
60%	1%	74.8%	83.8%
80%	1%	94.7%	97.3%

Randomisation and blinding (masking)

During the Blinded Treatment period, subjects were randomized into 4 treatment groups (1:1:1:1) and assigned to a treatment sequence group via an Interactive Web Randomization System (IWRS). The placebo group was further sub-randomized into 3 groups (1:1:1) to mimic the active treatment group.

There were no stratification factors for randomization in this trial.

To reduce the potential for bias in the study, subjects were randomized to receive palopegteriparatide or placebo, and placebo subjects were further randomized into 3 placebo dose subgroups to mimic the 3 palopegteriparatide doses. In addition, treatment for all subjects was double-blind; the subject, study site personnel, Sponsor, and its representatives involved in the conduct and/or management of the study remained blinded to treatment until database lock.

The TransCon PTH delivery system consisted of a multi-use cartridge integrated into a modified Ypsomed UnoPen Fix using 31G, 5 mm needles. The cartridge contained a liquid formulation of TransCon PTH or placebo for TransCon PTH sufficient for 14 doses. Each study drug administration was in a volume ≤100 µL and was to be self-administered.

For the Blinded Treatment period, both TransCon PTH and placebo for TransCon PTH were provided in the mid-dose pen allowing for doses of 15, 18, and 21 µg/day.

Statistical methods

Efficacy analyses were based on the Full Analysis Population (subjects who received at least one dose of study drug, analysed as randomized) by study period. Safety analyses were performed based on the Safety Analysis Population (subjects who received at least one dose of study drug) by study period. PK analyses were performed based on the PK Population (subjects who received any amount of study drug and for whom the plasma concentration data were considered sufficient and interpretable).

The following study periods were used for the purpose of summarizing study data:

• Blinded Period: Week 0 (Day 1) through Week 4 (Day 28, prior to open-label dosing) of placebo-controlled treatment.

• Open-Label Extension: Week 4 (Day 28 after open-label dosing) through Week 214 (Day 1498) of open-label palopegteriparatide treatment.

• TransCon PTH Period: The total period of exposure to palopegteriparatide. The TransCon PTH Period for subjects randomized to palopegteriparatide at enrollment was the time from the first dose of

blinded palopegteriparatide until data cut-off in the OLE. The TransCon PTH Period for subjects randomized to placebo at enrollment was the time from first exposure to palopegteriparatide, i.e., at the time of cross-over from placebo, until data cut-off in the OLE.

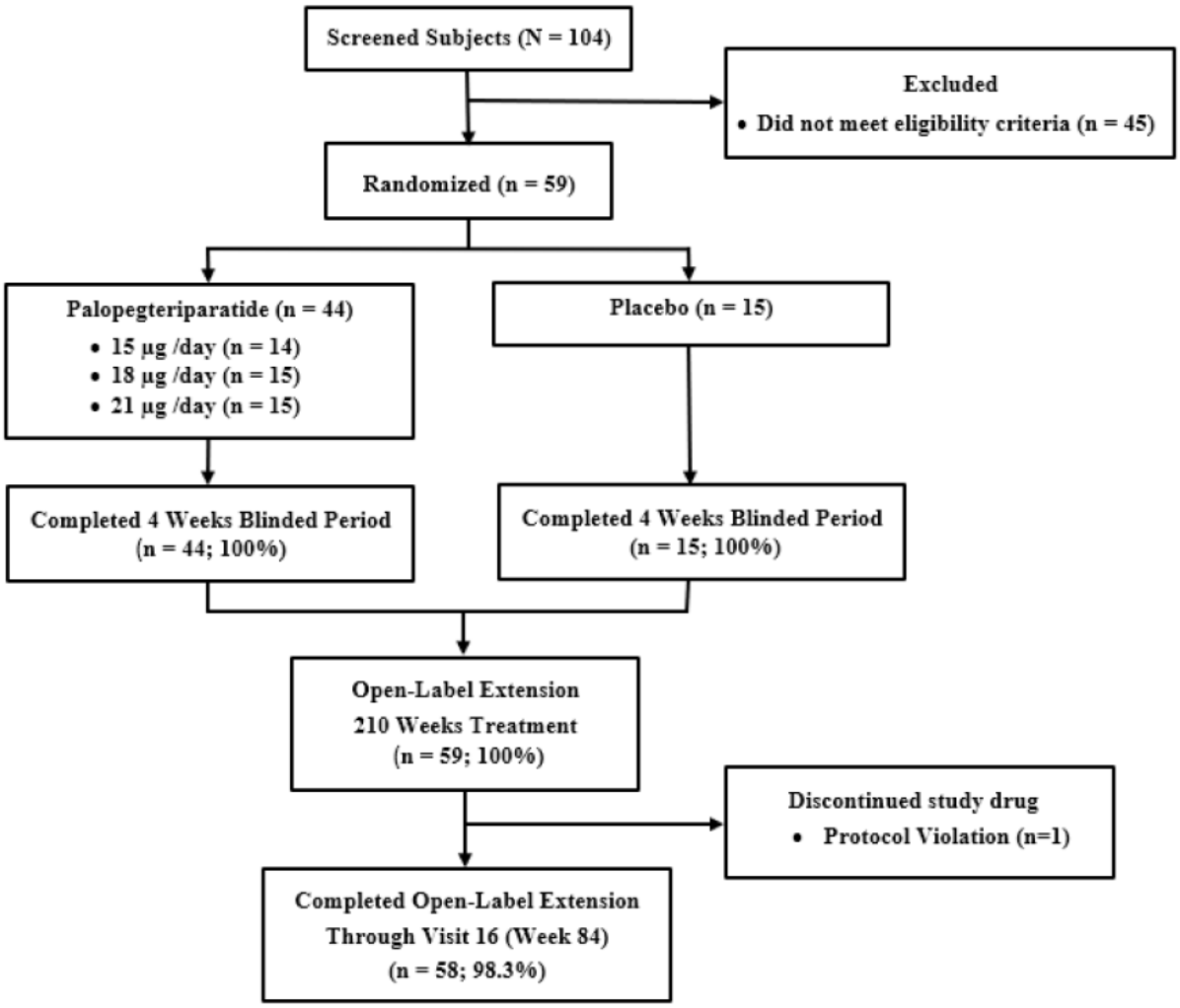
In general, variables were summarized descriptively. The primary efficacy analysis compared the proportion (%) of responders between palopegteriparatide-treated subjects overall and at each individual dose level with the pooled placebo-treated subjects, based on the Full Analysis Population. Treatment differences were compared using Fisher's exact test. The key secondary efficacy endpoint was analysed in the same manner as for the primary efficacy endpoint.

All statistical tests were two-sided and tested at a significance level of α=0.05. Confidence intervals were 2-sided 95% confidence intervals (CIs), unless stated otherwise.

Results

Participant flow

Figure 12. ***Subject Disposition (All Subjects)***



Abbreviations: n, N = number of subjects; µg/day = micrograms per day.

A total of 104 subjects were screened and 59 of these met eligibility criteria and were enrolled into the study. The applicant outlined that enrolment above the planned number of subjects (approximately 40) was due to an unanticipated increase in screening activity at the end of the screening period. Subjects were randomized to either fixed doses of palopegteriparatide 15 µg/day (n=14), 18 µg/day (n=15), 21 µg/day (n=15), or placebo (n=15); all initially co-administered with conventional therapy (active vitamin D and calcium supplements).

Table 5. ***Disposition of Patients (Blinded Period and Open-Label Extension (All Subjects))***

	TransCon PTH					
	PTH 15 µg/day n (%)	PTH 18 µg/day n (%)	PTH 21 µg/day n (%)	All PTH Subjects n (%)	Placebo[a] n (%)	Overall N (%)
Randomized	14	15	15	44	15	59
Full Analysis Population[b]	14 (100)	15 (100)	15 (100)	44 (100)	15 (100)	59 (100)
Safety Analysis Population[c]	14 (100)	15 (100)	15 (100)	44 (100)	15 (100)	59 (100)
PK Population[d]	14 (100)	15 (100)	15 (100)	44 (100)	15 (100)	59 (100)
Completed Blinded Period (Visit 3)	14 (100)	15 (100)	15 (100)	44 (100)	15 (100)	59 (100)
Discontinued Treatment During Blinded Period	0	0	0	0	0	0
Withdrawal by Subject	0	0	0	0	0	0
Entered Open-Label Extension				44 (100)	15 (100)	59 (100)
Discontinued Treatment During the Extension Period				0	1 (6.7)	1 (1.7)
Protocol Violation				0	1 (6.7)	1 (1.7)
Discontinued Trial During the Extension Period				0	1 (6.7)	1 (1.7)
Protocol Violation				0	1 (6.7)	1 (1.7)
Completed Through Visit 16 / Week 84				44 (100)	14 (93.3)	58 (98.3)

Abbreviations: PK = pharmacokinetics; TransCon PTH = palopegteriparatide; µg = microgram(s)
Note: Percentages were calculated based on the number of subjects randomized.
a Pooled placebo dose groups.
b Full Analysis Population defined as all subjects who were randomized and received at least 1 dose of study drug.
c Safety Analysis Population defined as all subjects in the randomized population who received at least 1 dose of study drug.
d PK Population defined as all subjects who received any amount of study drug and for whom the plasma concentration data were considered sufficient and interpretable.

All 59 (100%) subjects completed 4 weeks of treatment in the Blinded Period and entered the OLE period. Subject 26000-007 (placebo) discontinued treatment and discontinued the trial after Visit 4 in the OLE period due to a protocol violation of non-compliance with contraception requirements. Overall, 58 (98.3%) subjects completed treatment through Visit 16/Week 84, and 57 (96.6%) subjects completed treatment through Visit 17/Week 110. One subject discontinued study treatment and trial within this 120-day safety update due to withdrawal by subject.

Recruitment

The first subject was screened on 30 July 2019 (FPFV). The last study patient completed the blinded 4 weeks period on 06 March 2020 (LPLV main study). At 24 September 2021, the last patient completed the OLE period Week 84 timepoint.

Conduct of the study

Compliance with study drug and co-administered conventional therapy

Compliance of both study drug and hypoparathyroidism-related supplements (SOC, magnesium, vitamin D) were assessed based on review of the daily diary and returned pens at every clinic visit.

Subjects in all treatment and dose groups in the 4-week Blinded Period had ≥95.7% compliance and received the intended doses. There were 2 subjects in the 21 µg/day dose group who had ≤80% treatment compliance. Treatment compliance during the TransCon PTH Period was 99.8%. There were no subjects who had ≤90% treatment compliance during the TransCon PTH Period.

Study Protocol Amendments

The original study protocol was approved on 16 January 2019. The study began when the first subject was screened on 30 July 2019. There have been 3 major protocol amendments and 2 region-specific addendums. Brief summaries of the key changes were listed in the study report.

Baseline data

Demographic characteristics

The main demographic characteristics (FAS) are summarised in the table below:

Table 6. ***Demographics and Baseline Characteristics – Blinded Period (Full Analysis Population)***

	TransCon PTH				
	PTH 15 µg/day N=14	**PTH 18 µg/day N=15**	**PTH 21 µg/day N=15**	**All PTH Subjects N=44**	**Placebo[a] N=15**
Age (years)					
Mean	47.03	46.58	53.67	49.14	51.80
SD, SE	13.230, 3.536	11.157, 2.881	11.287, 2.914	12.075, 1.820	12.345, 3.188
Median	44.00	44.50	55.50	45.95	51.50
Min, Max	26.4, 71.5	25.4, 63.5	38.6, 76.4	25.4, 76.4	28.5, 68.6
Age Group (years) – n (%)					
<30	1 (7.1)	1 (6.7)	0	2 (4.5)	1 (6.7)
>=30 - <65	11 (78.6)	14 (93.3)	13 (86.7)	38 (86.4)	13 (86.7)
≥65	2 (14.3)	0	2 (13.3)	4 (9.1)	1 (6.7)
Sex at Birth – n (%)					
Female	12 (85.7)	12 (80.0)	12 (80.0)	36 (81.8)	12 (80.0)
Male	2 (14.3)	3 (20.0)	3 (20.0)	8 (18.2)	3 (20.0)

[...]

Geographic Region					
North America	7 (50.0)	12 (80.0)	10 (66.7)	29 (65.9)	9 (60.0)
Europe	7 (50.0)	3 (20.0)	5 (33.3)	15 (34.1)	6 (40.0)
Middle East and North Africa	0	0	0	0	0
Oceania	0	0	0	0	0
Height (cm)					
n	14	15	15	44	15
Mean	166.92	166.71	165.37	166.32	164.07
SD, SE	8.806, 2.353	8.385, 2.165	10.961, 2.830	9.270, 1.398	10.368, 2.677
Weight (kg)					
n	14	15	15	44	15
Mean	76.58	80.04	72.26	76.29	76.43
SD, SE	22.479, 6.008	11.279, 2.912	18.621, 4.808	17.823, 2.687	14.256, 3.681
Body Mass Index (kg/m²)					
n	14	15	15	44	15
Mean	27.08	28.76	26.12	27.33	28.30
SD, SE	5.723, 1.530	3.148, 0.813	4.647, 1.200	4.626, 0.697	3.775, 0.975

[...]
Max = maximum; Min = minimum; n, N = number of subjects; SD = standard deviation; SE = standard error
Note: Percentages were calculated based on the number of subjects in the FAS.
a Consists of pooled dosage placebo groups.

Most subjects were female (>80%, the majority of whom were premenopausal) and White (≥80%), and non-Hispanic/Latino (>90%).

The high proportions of female to male reflects the prevalence found in hypoparathyroidism (Powers 2013, Clarke 2016, Vadiveloo 2018) and are similar to a study of the treatment of hypoparathyroidism (Mannstadt 2013).

Table 7. Hypoparathyroidism Disease Characteristics and History – Blinded Period (Full Analysis Population)

	TransCon PTH				
	PTH 15 µg/day N=14	PTH 18 µg/day N=15	PTH 21 µg/day N=15	All PTH Subjects N=44	Placebo[a] N=15
Cause of Hypoparathyroidism					
Acquired from neck surgery	10 (71.4)	12 (80.0)	12 (80.0)	34 (77.3)	13 (86.7)
Autoimmune disease	1 (7.1)	0	0	1 (2.3)	0
Intrinsic genetic defects of the parathyroid glands	0	0	0	0	0
Magnesium deficiency	0	0	0	0	0
Idiopathic disease	3 (21.4)	3 (20.0)	3 (20.0)	9 (20.5)	2 (13.3)
Other	0	0	0	0	0
Duration of Hypoparathyroidism (years)					
n	14	15	15	44	15
Mean	12.4	9.3	12.3	11.3	13.5
SD, SE	12.35, 3.3	7.41, 1.91	7.65, 1.97	9.23, 1.39	9.26, 2.39
Median	9.0	7.0	10.0	8.5	13.0
Min, Max	1, 39	2, 29	3, 25	1, 39	3, 30
Prior Treatment with PTH Therapy Within 6 Month Prior to Screening[b]					
Yes	3 (21.4)	3 (20.0)	3 (20.0)	9 (20.5)	3 (20.0)
No	11 (78.6)	12 (80.0)	12 (80.0)	35 (79.5)	12 (80.0)

Abbreviations: Max = maximum; Min = minimum; n, N = number of subjects; SD = standard deviation; SE = standard error; mg = milligram; TransCon PTH = palopegteriparatide; µg = micrograms
a Consists of pooled dosage placebo groups.
b Six (6) subjects on Natpara, 6 subjects on PTH (1-84) (source: DB Listing 16.2.4.3). Ten of the subjects that received Natpara within 6 months of Screening were likely impacted by the Natpara US withdrawal on May 9, 2019.

c From electronic data capture.

Table 8. Hypoparathyroidism Disease Characteristics and History – Blinded Period (Full Analysis Population)

	TransCon PTH				
	PTH 15 µg/day N=14	PTH 18 µg/day N=15	PTH 21 µg/day N=15	All PTH Subjects N=44	Placebo[a] N=15
Renal Insufficiency History					
Yes	1 (7.1)	3 (20.0)	1 (6.7)	5 (11.4)	0
No	13 (92.9)	12 (80.0)	14 (93.3)	39 (88.6)	15 (100.0)
Kidney Stones History (Nephrolithiasis)					
Yes	2 (14.3)	1 (6.7)	1 (6.7)	4 (9.1)	4 (26.7)
No	12 (85.7)	14 (93.3)	14 (93.3)	40 (90.9)	11 (73.3)
Ectopic Calcifications History					
Yes	0	0	1 (6.7)	1 (2.3)	0
No	14 (100.0)	15 (100.0)	14 (93.3)	43 (97.7)	15 (100.0)
Vascular Calcifications History					
Yes	0	0	0	0	0
No	14 (100.0)	15 (100.0)	15 (100.0)	44 (100.0)	15 (100.0)
Brain Calcification History					
Yes	0	0	0	0	0
No	14 (100.0)	15 (100.0)	15 (100.0)	44 (100.0)	15 (100.0)
Cataract History					
Yes	0	0	0	0	0
No	14 (100.0)	15 (100.0)	15 (100.0)	44 (100.0)	15 (100.0)
Seizure History					
Yes	1 (7.1)	0	0	1 (2.3)	1 (6.7)
No	13 (92.9)	15 (100.0)	15 (100.0)	43 (97.7)	14 (93.3)

Abbreviations: Max = maximum; Min = minimum; n, N = number of subjects; SD = standard deviation; SE = standard error; mg = milligram; TransCon PTH = palopegteriparatide; µg = micrograms
a Consists of pooled dosage placebo groups.
b Six (6) subjects on Natpara, 6 subjects on PTH (1-84) (source: DB Listing 16.2.4.3). Ten of the subjects that received Natpara within 6 months of Screening were likely impacted by the Natpara US withdrawal on May 9, 2019.

c From electronic data capture.

Hypoparathyroidism Supplements at Baseline

Table 9. Hypoparathyroidism Disease Characteristics and History – Blinded Period (Full Analysis Population)

	TransCon PTH				
	PTH 15 µg/day N=14	PTH 18 µg/day N=15	PTH 21 µg/day N=15	All PTH Subjects N=44	Placebo[a] N=15
Hypoparathyroidism Supplements at Baseline[c] – Calcium Citrate or Carbonate Total Daily Dose (mg)					
n	13	14	12	39	13
Mean	1538	2153	2387	2020	1490
SD, SE	998.8, 277.0	1837.4, 491.1	1132.5, 326.9	1403.4, 224.7	786.9, 218.2
Median	1200	1316	2699	1550	1200
Min, Max	500, 4000	963, 8000	500, 4000	500, 8000	800, 3200

Calcitriol (Active Vitamin D) Total Daily Dose (mg)[c]					
n	5	11	9	25	6
Mean	0.700	0.711	0.849	0.759	0.542
SD, SE	0.4472, 0.2000	0.2717, 0.0819	0.4741, 0.1580	0.3793, 0.0759	0.2923, 0.1193
Median	0.500	0.500	0.750	0.500	0.500
Min, Max	0.50, 1.50	0.50, 1.25	0.50, 2.00	0.50, 2.00	0.25, 1.00
Alfacalcidol (Active Vitamin D) Total Daily Dose (µg)[c]					
n	2	3	2	7	3
Mean	2.50	3.00	2.50	2.71	0.83
SD, SE	0.000, 0.000	1.000, 0.577	0.707, 0.500	0.699, 0.264	0.289, 0.167
Median	2.50	3.00	2.50	2.50	1.00
Min, Max	2.5, 2.5	2.0, 4.0	2.0, 3.0	2.0, 4.0	0.5, 1.0
Cholecalciferol (Vitamin D3) Total Daily Dose (µg)[c]					
n	9	8	7	24	9
Mean	52	64	59	58	53
SD, SE	34.1, 11.4	34.5, 12.2	31.8, 12.0	32.5, 6.6	39.2, 13.1
Median	40	63	70	50	38
Min, Max	14, 123	22, 107	11, 100	11, 123	15, 125
Magnesium Total Daily Dose (mg)[c]					
n	6	4	5	15	6
Mean	344	1064	489	584	487
SD, SE	226.3, 92.4	1518.2, 759.1	582.4, 260.5	838.3, 216.5	216.5, 88.4
Median	325	332	300	330	500
Min, Max	43, 720	250, 3340	40, 1503	43, 3340	143, 720
Hypoparathyroidism Supplements at Baseline from eDiary Data					
Calcitriol (Active Vitamin D) Total Daily Dose (µg)					
n	10	12	13	35	11
Mean	1.025	0.792	0.750	0.843	0.614
SD, SE	0.8032, 0.2540	0.2984, 0.0861	0.4208, 0.1167	0.5254, 0.0888	0.2820, 0.0850
Median	0.625	0.750	0.500	0.750	0.500
Min, Max	0.50, 3.00	0.50, 1.25	0.50, 2.00	0.50, 3.00	0.25, 1.00

	TransCon PTH				
	PTH 15 µg/day N=14	**PTH 18 µg/day N=15**	**PTH 21 µg/day N=15**	**All PTH Subjects N=44**	**Placebo[a] N=15**
SD, SE	0.866, 0.433	1.000, 0.577	1.414, 1.000	0.968, 0.323	1.225, 0.612
Median	2.50	2.00	2.00	2.50	2.50
Min, Max	2.0, 4.0	1.0, 3.0	1.0, 3.0	1.0, 4.0	1.0, 4.0
n	4	3	2	9	4
Mean	2.75	2.00	2.00	2.33	2.50

Abbreviations: Max = maximum; Min = minimum; n, N = number of subjects; SD = standard deviation; SE = standard error; mg = milligram; TransCon PTH = palopegteriparatide; µg = micrograms
a Consists of pooled dosage placebo groups.
b Six (6) subjects on Natpara, 6 subjects on PTH (1-84) (source: DB Listing 16.2.4.3). Ten of the subjects that received Natpara within 6 months of Screening were likely impacted by the Natpara US withdrawal on May 9, 2019.
c From electronic data capture.

At baseline, subjects randomized to palopegteriparatide treatment were taking higher mean doses of hypoparathyroidism supplements as documented by site staff in the EDC system than those randomized to placebo:

-calcium citrate/carbonate (2020 mg [range 500 to 8000 mg] vs 1490 mg range [800 to 3200]);

-calcitriol (0.759 mg [range 0.50 to 2.00 mg] vs 0.542 mg [range 0.25 to 1.00 mg]);

-alfacalcidol (2.71 µg/day [range 2.0 to 4.0 µg/day] vs 0.83 µg/day [range 0.5 to 1.0 µg/day]);

-cholecalciferol (58 µg/day [range 11 to 123 µg/day] vs 53 µg/day [range 15 to 125 µg/day]), and

-magnesium (584 mg [range 43 to 3340 mg] vs 487 mg [range 143 to 720 mg]).

Numbers analysed

All efficacy analyses were based on the Full Analysis Population.

Outcomes and estimation

The primary efficacy endpoint was the proportion of responders to treatment at Week 4 of the Fixed Dose Blinded Period. The primary efficacy analysis compared the proportion (%) of responders between palopegteriparatide-treated subjects (overall and at each individual dose level) with the pooled placebo-treated subjects. Two sensitivity analyses of the primary analysis were performed.

In addition to the sensitivity analyses supplementing the primary efficacy analysis, the proportion of responders at Week 84 of the OLE was accompanied by 5 sensitivity analyses.

<u>Primary Efficacy Analysis – Week 4 of the Blinded Period:</u>

Overall, 50.0% (95% CI: 34.6, 65.4) of palopegteriparatide subjects and 26.7% (95% CI: 7.8, 55.1) of placebo subjects met criteria for and were considered responders to treatment at Week 4 of the Blinded Period.

Table 10. Primary Efficacy Analysis (Full Analysis Population)

	TransCon PTH				
	PTH 15 µg/day (N=14)	PTH 18 µg/day (N=15)	PTH 21 µg/day (N=15)	All PTH Subjects (N=44)	Placebo[a] (N=15)
Number of Subjects Meeting the Primary Endpoint (Responders)	7	6	9	22	4
Proportion (95% CI)	50.0 (23.0, 77.0)	40.0 (16.3, 67.7)	60.0 (32.3, 83.7)	50.0 (34.6, 65.4)	26.7 (7.8, 55.1)
Hypothesis Test: P-value (Treatment vs Pooled Placebo)[b]	0.2635	0.6999	0.1394	0.1419	
Number of Subjects Meeting Each Component					
Serum calcium within the normal range[c]	12	12	14	38	14
Spot AM FECa within normal range (<=2 %) or a reduction by at least 50% from baseline	10	8	9	27	7
Not taking active vitamin D supplements	14	14	15	43	6
Taking ≤1000 mg/day of calcium	13	13	15	41	8

Abbreviations: CI = confidence interval; FECa = fractional excretion of calcium; mg = milligram; N = number of subjects; TransCon PTH = palopegteriparatide
a Consists of pooled dosage placebo groups.
b Fisher's exact test is used to compare differences in proportions.
c The normal range for albumin-adjusted serum calcium is 8.3 to 10.6 mg/dL (2.07 to 2.64 mmol/L) and the normal range for ionized serum calcium is 1.16 to 1.32 mmol/L.

After 4 weeks of treatment, while there was a higher response rate in subjects receiving palopegteriparatide treatment compared to placebo, the difference was not statistically significant when comparing either the individual palopegteriparatide dose groups or pooled palopegteriparatide subjects to placebo.

Most palopegteriparatide-treated subjects (>85%) had serum calcium in the normal range, were not taking active vitamin D supplements, and were taking ≤1000 mg/day of calcium. Fewer subjects, but varying by dose group (53.3% to 71.4%), had spot FECa within the normal range or a reduction by ≥50% from baseline.

For placebo subjects, nearly all (93.3%) had serum calcium in the normal range, but approximately half or less met responder criteria for having a spot AM FECa within normal range/reduction by ≥50% from baseline (46.7%), not taking active vitamin D (40.0%), or taking ≤1000 mg/day of calcium supplements (53.3%).

Sensitivity Analysis 1:

For Sensitivity Analysis 1, the requirement that spot AM FECa be within the normal range or reduced by ≤50% from baseline, was removed.

The results of Sensitivity Analysis 1 are stated in the table below:

Table 11. Sensitivity Analysis 1 – Primary Endpoint at Week 4 of the Blinded Period (Full Analysis Population)

	TransCon PTH				
	PTH 15 µg/day (N=14)	PTH 18 µg/day (N=15)	PTH 21 µg/day (N=15)	All PTH Subjects (N=44)	Placebo[a] (N=15)
Number of Subjects Meeting the Revised Primary Endpoint					
Responders	11	10	14	35	4
Proportion (95% CI)	78.6 (49.2, 95.3)	66.7 (38.4, 88.2)	93.3 (68.1, 99.8)	79.5 (64.7, 90.2)	26.7 (7.8, 55.1)
Hypothesis Test: P-value (Treatment vs Pooled Placebo)[b]	0.0092	0.0656	0.0005	0.0004	
Number of Subjects Meeting Each Component:					
Serum calcium within the normal range[c]	12	12	14	38	14
Not taking active vitamin D supplements	14	14	15	43	6
Taking ≤1000 mg/day of calcium	13	13	15	41	8

Abbreviations: CI = confidence interval; FECa = fractional excretion of calcium; mg = milligram; TransCon PTH = palopegteriparatide
a Consists of pooled dosage placebo groups.
b Fisher's exact test is used to compare differences in proportions.
c The normal range for albumin-adjusted serum calcium is 8.3 to 10.6 mg/dL (2.07 to 2.64 mmol/L) and the normal range for ionized serum calcium is 1.16 to 1.32 mmol/L.

Sensitivity Analysis 2:

For Sensitivity Analysis 2, the study population was restricted to subset of subjects achieving albumin adjusted serum calcium within the 8.8 to 10 mg/dL range at Week 4. In consequence, notably, the proportion of responders has been calculated only for patients who met the first criterium (e.g. N=6 for Placebo).

Table 12. Sensitivity Analysis 2 – Primary Endpoint at Week 4 of the Blinded Period (Full Analysis Population)

	TransCon PTH				
	PTH 15 µg/day (N=7)	PTH 18 µg/day (N=8)	PTH 21 µg/day (N=11)	All PTH Subjects (N=26)	Placebo[a] (N=6)
Number of Subjects Meeting the Revised Primary Endpoint					
Responders	5	3	7	15	4
Proportion (95% CI)	71.4 (29.0, 96.3)	37.5 (8.5, 75.5)	63.6 (30.8, 89.1)	57.7 (36.9, 76.6)	66.7 (22.3, 95.7)
Hypothesis Test: P-value (Treatment vs Pooled Placebo) [a]	>0.9999	0.5921	>0.9999	>0.9999	
Number of Subjects Meeting Each Component:					
Serum calcium within the range 8.8 to 10.0 mg/dL	7	8	11	26	6
Spot AM FECa within normal range (<=2 %) or a reduction by at least 50% from baseline	5	4	7	16	4
Not taking active vitamin D supplements	7	8	11	26	4
Taking ≤1000 mg/day of calcium	7	7	11	25	6

Abbreviations: CI = confidence interval; FECa = fractional excretion of calcium; mg = milligram; TransCon PTH = palopegteriparatide
a Consists of pooled dosage placebo groups.
b Fisher's exact test is used to compare differences in proportions.

Analysis of the primary endpoint at Week 84 of the OLE

A total of 42 subjects had data available at Week 84 of the OLE for analysis of the primary efficacy endpoint, using 24 h urine calcium instead of spot FECa. Of these, 28 subjects (66.7%; 95% CI: 50.5, 80.4) met criteria for being responders to treatment, see table below:

Table 13. Primary Endpoint at Week 84 of the Open-Label Period (Full Analysis Population)

	All TransCon PTH (N=59)
Number of Subjects Who Have Data on All Criteria at Week 84	42
Number of Subjects Meeting the Endpoint Criteria at Week 84	28
Proportion (95% CI)*	66.7 (50.5, 80.4)
Number of Subjects Meeting Each Component	
Serum calcium within the normal range[a]	32
24-Hour urine calcium within normal range	39
Not taking active vitamin D supplements	42
Taking ≤1000 mg/day of calcium supplements	40

Abbreviations: CI = confidence interval; FECa = fractional excretion of calcium; mg = milligram; sCa = serum calcium
Note: All TransCon PTH are the group of subjects who received palopegteriparatide during the Blinded Period and/or during the Open-label Extension.
*Percentage is based on the number of subjects who have data on all criteria at Week 84.
a The normal range for albumin-adjusted serum calcium is 8.3 to 10.6 mg/dL (2.07 to 2.64 mmol/L). The normal range for 24-h urine calcium is defined as ≤250 mg/day for female, ≤300 mg/day for male.

Analysis of the primary endpoint at Week 110 of the OLE

A total of 51 subjects had data available at Week 110 of the OLE for analysis of the primary efficacy endpoint, using 24 h urine calcium instead of spot FECa. Overall, 27 of 51 subjects (52.9%; 95% CI: 38.5%, 67.1%) met the criteria for the primary composite endpoint and were considered responders to treatment at Week 110, including 19 of 38 subjects in the TransCon PTH/TransCon PTH group (50.0%; 95% CI: 33.4%, 66.6%) and 8 of 13 subjects in the Placebo/TransCon PTH group (61.5%, 95% CI: 31.6%, 86.1%), see table below:

Table 14. TCP-201: Primary Endpoint at Week 110 (Full Analysis Population)

	TransCon PTH/ TransCon PTH (N=44)	Placebo/ TransCon PTH (N=15)	Total TransCon PTH (N=59)
Number of Subjects Who Have Data on All Criteria at Week 110	38	13	51
Number of Subjects Meeting the Endpoint Criteria at Week 110	19	8	27
Proportion (95% CI)[a]	50.0 (33.4, 66.6)	61.5 (31.6, 86.1)	52.9 (38.5, 67.1)
Number of Subjects Meeting Each Component:			
Albumin-adjusted sCa within the normal range	26	10	36
24-Hour urine calcium within normal range	30	10	40
Not taking active vitamin D supplements	38	13	51
Taking ≤ 1000 mg/day of calcium supplements	37	13	50

Source: TCP-201 120-day safety update Table-14.2.1.1
Abbreviations: CI, confidence intervals; sCa, serum calcium; TransCon PTH, palopegteriparatide.
[a] Percentage is based on the number of subjects who have data on all criteria at Week 110. The normal range for albumin-adjusted sCa is 8.3-10.6 mg/dL (2.07-2.64 mmol/L). The normal range for 24-hour urine calcium is defined as ≤ 250 mg/day for female, ≤300 mg/day for male.

Additional Sensitivity Analysis Blinded Period and OLE

The analysis of the primary efficacy endpoint at Week 84 of the OLE (using 24 h urine calcium instead of spot AM FECa) was accompanied by the following 5 sensitivity analyses:

Table 15. Sensitivity Analyses of the Primary Efficacy Endpoint for the Open-Label Extension

	Responder Criteria Sets			
			Standard of Care	
Endpoint	Serum Calcium	Urine Calcium	Calcium (mg/day)	Active Vitamin D
Sensitivity 1	Normal[a]	24 h FECa normal or ≥50% reduction from BL[b]	≤1000	0
Sensitivity 2	Normal[a]	Spot AM FECa normal or ≥50% reduction from BL[c]	≤1000	0
Sensitivity 3	Normal[a]	(unspecified)	≤1000	0
Sensitivity 4	Normal[a]	(unspecified)	≤600	0
Sensitivity 5	Normal[a]	(unspecified)	0	0

Abbreviations: BL= baseline; FECa = fractional excretion of calcium, NS= not significant,
a The normal range for albumin-adjusted serum calcium is 8.3 to 10.6 mg/dL (2.07 to 2.64 mmol/L) and the normal range for ionized serum calcium is 1.16 to 1.32 mmol/L.
b 24 h FECa within normal range (≤2%) or a reduction by at least 50% from baseline
c Spot AM FECa within normal range (≤2%) or a reduction by at least 50% from baseline

The results for this additional sensitivity analysis outlined above ("PTH Subjects" only, Blinded Period and OLE)) are summarised in the table below:

Table 16. Primary and Key Secondary Efficacy Analysis Results for the Blinded Period and Open-Label Extension (Full Analysis Population)

Responder Criteria Sets				Responder Analysis (%, [n/N], [95% CI, P-value])	
		Standard of Care Supplements			
Serum Calcium	Urine Calcium	Calcium (mg/d)	Active Vitamin D	Blinded Period – Week 4 (PTH Subjects Only, N=44)	OLE – Week 84 (N=59)
Normal[a]	Spot AM FECa normal or reduced ≥50% from BL[b]	≤1000	0	Primary Efficacy Analysis 50.0% (22/44) (34.6, 65.4; P=NS[e])	Sensitivity #2 67.9% (36/53) (53.7, 80.1)
Normal[a]	(Not specified)	≤1000	0	Sensitivity #1 79.5% (35/44) (64.7, 90.2; P=0.0004[e])	Sensitivity #3 69.0% (40/58) (55.5, 80.5)
8.8–10.0 mg/dL	Spot AM FECa normal or reduced ≥50% from BL[b]	≤1000	0	Sensitivity #2 57.7% (15/26) (36.9, 76.6; P=NS[e])	(Not performed)
Normal[a]	24 h Normal[c]	≤1000	0	(Not performed)	Primary Endpoint 66.7% (28/42) (50.5, 80.4)
Normal[a]	24 h FECa normal or reduced ≥50% from BL[d]	≤1000	0	(Not performed)	Sensitivity #1 71.4% (30/42) (55.4, 84.3)
Normal[a]	(Not specified)	≤600	0	(Not performed)	Sensitivity #4 67.2% (39/58) (53.7, 79.0)
Normal[a]	(Not specified)	0	0	(Not performed)	Sensitivity #5 51.7% (30/58) (38.2, 65.0)
Normal[a]	Spot AM FECa normal or reduced ≥50% from BL[b]	≤500	0	Key Secondary 45.5% (20/44) (30.4, 61.2; P=NS[e])	Key Secondary Sensitivity #2 64.2% (34/53) (49.8, 76.9)
Normal[a]	24 h Normal[c]	≤500	0	(Not performed)	Key Secondary 61.9% (26/42) (45.6, 76.4)
Normal[a]	24 h FECa normal or reduced ≥50% from BL[d]	≤500	0	(Not performed)	Key Secondary Sensitivity #1 66.7% (28/42) (50.5, 80.4)

Abbreviations: BL= baseline; FECa = fractional excretion of calcium; mg = milligram(s); n = number of subjects meeting criteria; N = number of subjects in treatment group; NS = not significant. Note: Percentages are based on the number of subjects who had available data on all criteria specified. *a The normal range for albumin-adjusted serum calcium is 8.3 to 10.6 mg/dL (2.07 to2.64 mmol/L) and the normal range for ionized serum calcium is 1.16 to 1.32 mmol/L. b Spot AM FECa within normal range (≤2%) or a reduction by at least 50% from baseline c The normal range for 24-h urine calcium was defined as ≤250 mg/day for females, ≤300 mg/day for males. d 24 h FECa within normal range (≤2%) or a reduction by at least 50% from baseline e Fisher's exact test was used to compare differences in proportions.*

A total of 54 subjects had data available at Week 110 of the OLE for analysis of the sensitivity analyses 4 for the primary efficacy endpoint (*ad-hoc analysis)*. Overall, 35 of 54 subjects (64.8%; 95% CI: 50.6%, 77.3%) met the criteria at week 110.

Analysis of the Key Secondary Endpoint at Week 4 of the Blinded Period:

The key secondary efficacy endpoint revised the definition of a treatment responder by lowering the maximum intake of supplemental calcium to ≤500 mg/day, with other responder criteria remaining the same as for the primary efficacy analysis. Analysis of the key secondary endpoint at Week 4 resulted in a responder rate for palopegteriparatide-treated subjects of 45.5% (95% CI: 30.4, 61.2) vs 20.0% (95% CI: 4.3, 48.1) for placebo subjects. The treatment difference was not statistically significant.

Analysis of the Key Secondary Endpoint at Week 84 of the OLE:

The key secondary efficacy endpoint at week 84 also revised the definition of a treatment responder by lowering the maximum intake of supplemental calcium to ≤500 mg/day, with all other responder criteria remaining the same as for the primary efficacy analysis at week 84 (including 24-h urine calcium within the normal range). At Week 84 there were 42 of 59 subjects who had data available on all 4 key secondary endpoint responder criteria. Of these, 26 subjects met responder criteria, giving a response rate of 61.9% for pooled subjects, for the key secondary efficacy endpoint (95% CI: 45.6, 76.4).

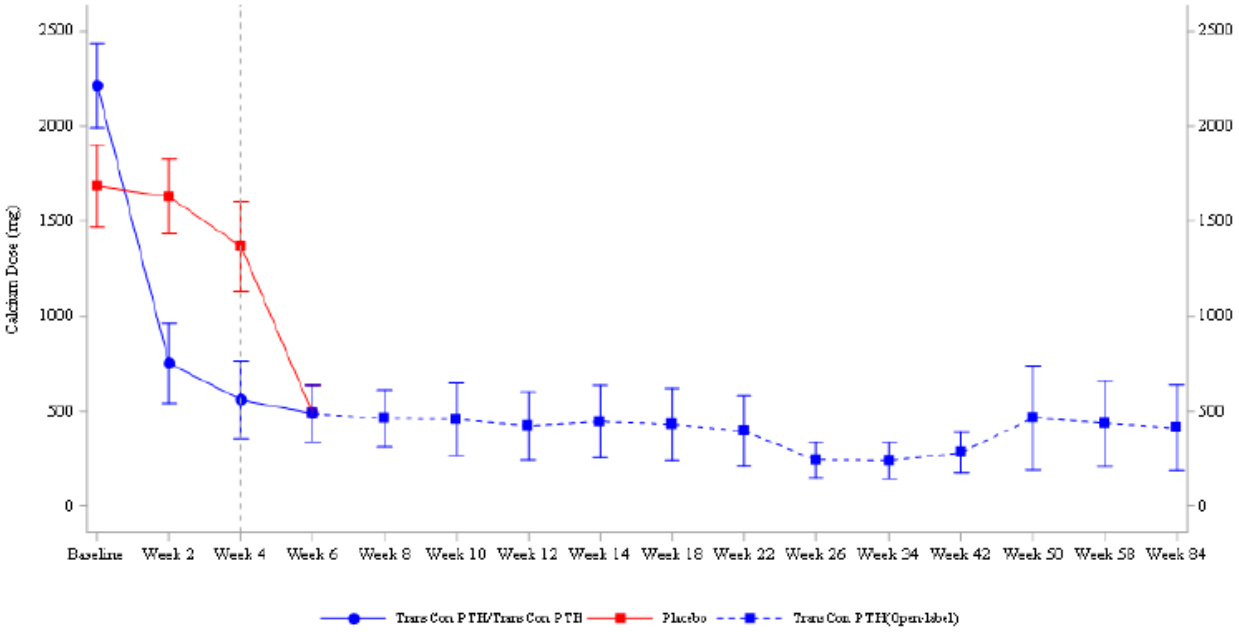
Analysis of the Other Secondary Endpoint:

Calcium dose

At study baseline, subjects assigned to palopegteriparatide treatment (pooled dose groups) were overall taking 24% higher average daily amounts of calcium supplementation, corresponding to mean (observed values) 2214 mg calcium (range 500 to 8000 mg) versus mean 1685 mg (range 800 to 3200 mg) for subjects assigned to placebo.
From baseline, daily use of calcium supplementation decreased for both groups to the end of the Blinded Period at Week 4, to a mean (observed values) of 561 mg calcium (range 0 to 8000 mg) for pooled palopegteriparatide-treated subjects, compared with mean 1368 mg (range 400 to 3000 mg) for placebo-treated subjects.
The treatment difference in calcium supplementation at Week 4, i.e., the difference in LS means (pooled palopegteriparatide – placebo) of -1119 mg calcium (95% CI: -1715, -523) was significant (nominal p=0.0004), in favour of reduced calcium supplement use for palopegteriparatide-treated subjects over 4 weeks of blinded treatment.
By Week 84, daily use of calcium supplementation had decreased for the overall group (N=59 subjects) to a mean (observed values) of 412 mg calcium (range 0 to 12000 mg), corresponding to a mean change from baseline of -1682 mg from a mean baseline value of 2094 mg.

Calcium supplementation use during the trial is illustrated in the figure below:

Figure 13. ***Calcium Dose (Mean ±SE) by Visit (Full Analysis Population)***

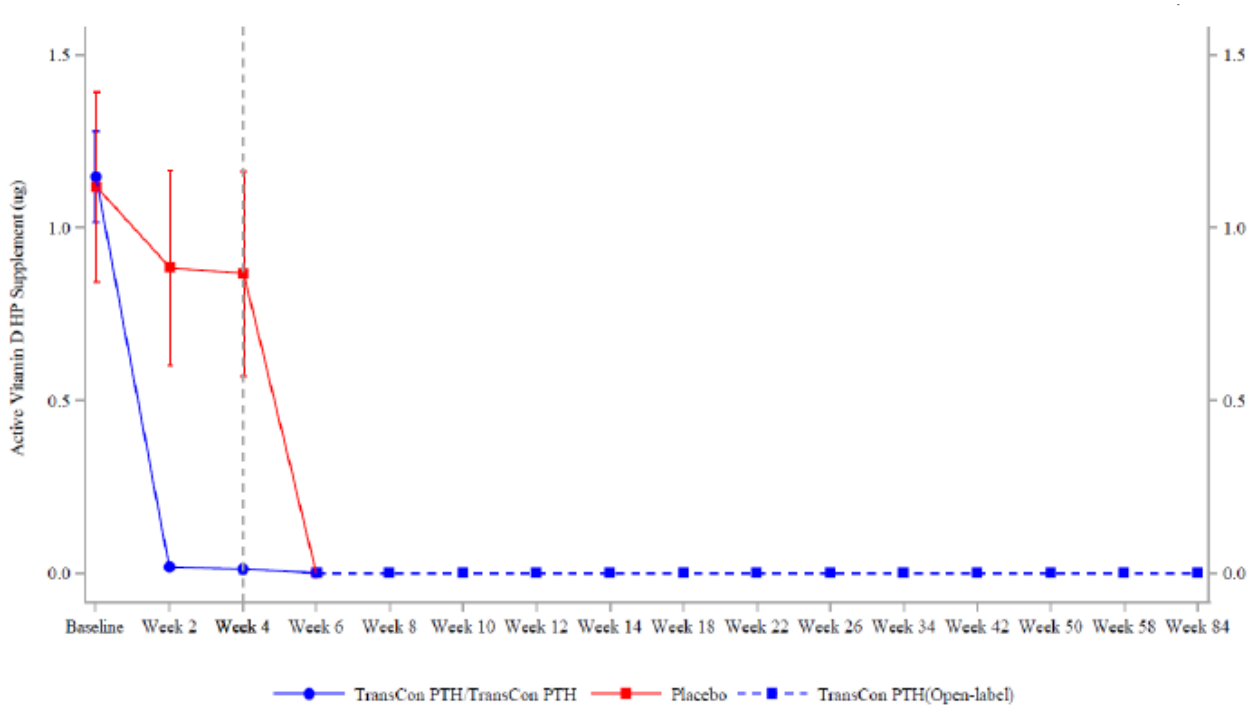


Active Vitamin D Dose

At baseline, subjects assigned to both treatment groups were taking nearly the same mean dose of active vitamin D (observed values): 1.15 µg/day (range 0.50 to 4.00 µg/day) for subjects assigned to palopegteriparatide treatment compared with 1.12 µg/day (range 0.25 to 4.00 µg/day) for subjects assigned to placebo.
From baseline, active vitamin D supplementation decreased to (observed means) 0.02 µg/day (range 0 to 0.5 µg/day) by Week 2 and to 0.01 µg/day (range 0.00 to 0.50 µg/day) at Week 4 for pooled palopegteriparatide-treated subjects.
For placebo-treated subjects, active vitamin D use initially decreased less sharply to a mean of 0.88 µg/day (range 0 to 4.0 µg/day) at Week 2, to 0.87 µg/day (range 0.0 to 4.0 µg/day) at Week 4.
During the OLE, mean active vitamin D supplementation was 0.00 µg/day from Week 6 through Week 84, and all subjects remained off of active vitamin D. By Week 110, 57 of 57 (100%) patients were taking not taking active vitamin D supplements.

Active vitamin D supplementation (µg/day) use during the trial is illustrated in the figure below:

Figure 14. Active Vitamin D Dose (Mean ±SE) by Visit (Full Analysis Population)



Daily Pill Burden

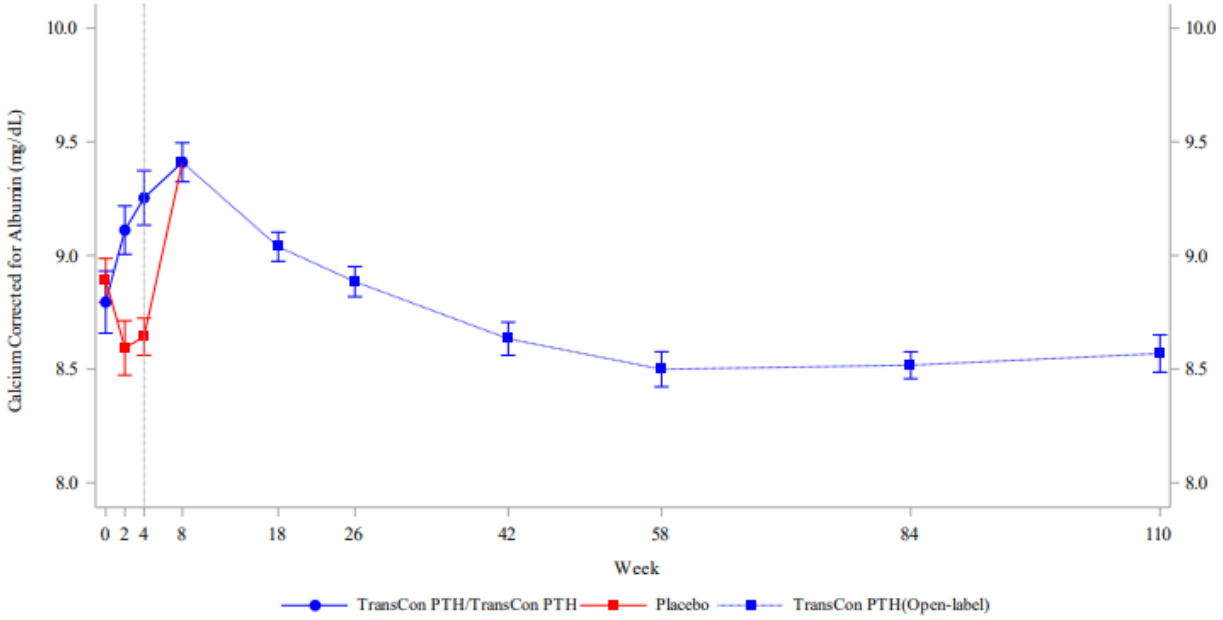
Pill burden was defined as the total daily pill count taken by the subject for SOC supplements, i.e., calcium, active vitamin D, and magnesium supplements. Daily Pill Burden decreased significantly during the treatment.

Serum Calcium

The normal range defined for albumin-adjusted serum calcium during was 8.3 to 10.6 mg/dL.
At baseline, subjects assigned to both treatment groups had nearly the same serum calcium (observed means), 8.80 mg/dL (range 7.80 to 13.50 mg/dL) for palopegteriparatide treatment compared with 8.89 mg/dL (range 7.90 to 9.28 mg/dL) for placebo treatment. As outlined in the CSR, this is regarded to be a reflection of the requirement for optimization of serum calcium within the lower half of the normal range prior to randomization.
From baseline, for palopegteriparatide-treated subjects, serum calcium increased steadily from Weeks 2 through 4 and at Week 4 was 9.25 mg/dL (range 7.40 to 11.08 mg/dL).
In contrast, for placebo-treated subjects, serum calcium decreased from baseline to 8.59 mg/dL (range 7.90 to 9.60 mg/dL) at Week 2 and to 8.64 mg/dL (range 7.80 to 9.12 mg/dL) at Week 4.
The mean treatment difference between palopegteriparatide-treated subjects and placebo at Week 4 was 0.606 mg/dL (95% CI: 0.178, 1.033), (P=0.0063).
Following enrolment into the OLE, mean serum calcium values were within the normal range for every study visit. The Week 84 mean serum calcium was 8.52 mg/dL (range 7.30 to 9.50 mg/dL).

Serum Calcium concentrations (Mean ±SE) during the trial are illustrated in the figure below:

Figure 15. Serum Calcium (Mean ±SE) by Visit (Full Analysis Population)



Palopegteriparatide treatment maintained mean serum calcium within the normal range at all study visits through Week 110.

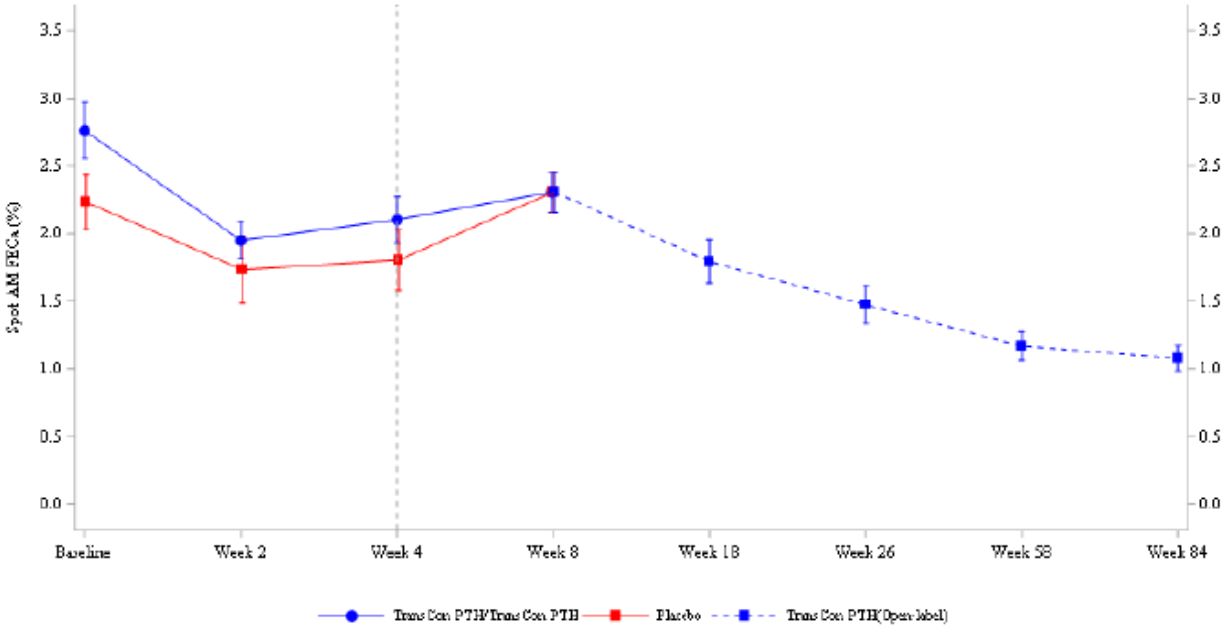
Spot Morning Fractional Excretion of Calcium

The fractional excretion of calcium was defined as:

$$FECa = \frac{[\text{urine calcium} \times \text{serum creatinine}]}{[\text{serum calcium} \times \text{urine creatinine}]}$$

The spot AM FECa normal range is ≤2%. For the purposes of this trial, less than or equal to 2% was considered as normal range which is the generally accepted established cut-off.
The mean spot AM FECa was lower at baseline for subjects assigned to receive placebo at 2.23% (range 0.91 to 3.39%) vs 2.76% (range 0.70 to 6.04%) for palopegteriparatide subjects.
For subjects in both treatment groups, mean spot AM FECa values decreased from baseline to Week 2, then rose slightly to Week 4 but remained below baseline for both groups. There were no statistically significant treatment differences in mean spot AM FECa values between.

Figure 16. Spot Morning Fractional Excretion of Calcium by Visit (Full Analysis Population)



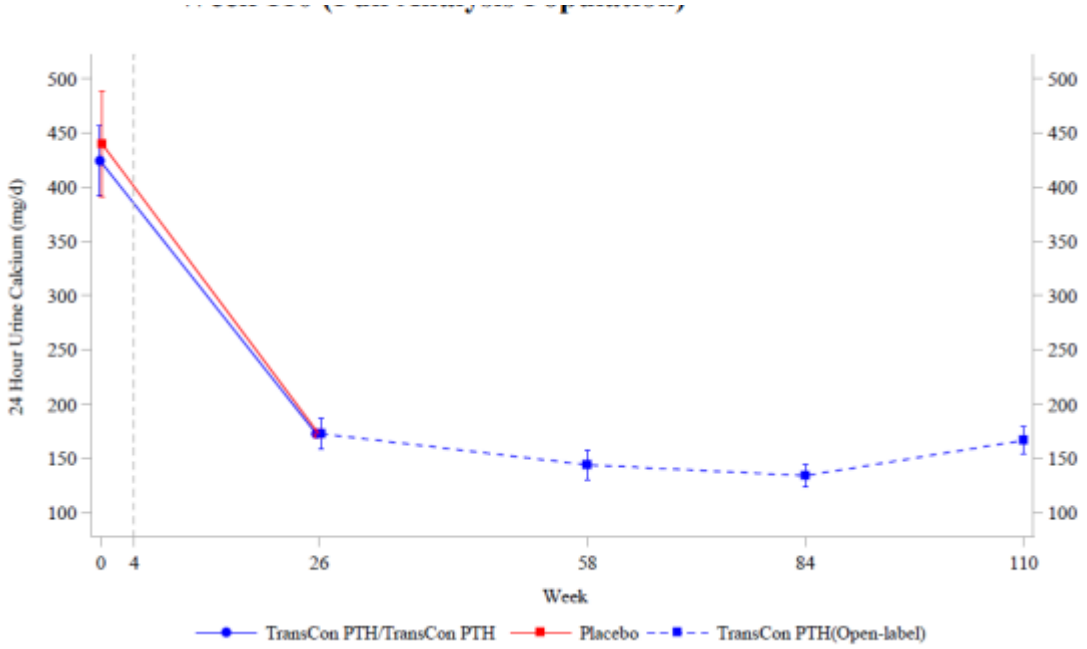
The applicant highlighted that despite higher serum calcium (see above), and thus higher filtered calcium load, there were no significant treatment differences in mean spot AM FECa values between palopegteriparatide-treated subjects and placebo-treated subjects at Week 2 or at Week 4 of the Blinded Period, when comparing either the individual palopegteriparatide dose groups or the combined palopegteriparatide group to placebo-treated subjects.

After Week 8, mean spot AM FECa values steadily decreased for pooled subjects to approximately 1.10% (range 0.15 to 4.46%) at Week 84. The applicant reasoned that although the mechanism of continued decline in FECa from week 8 is not entirely clear, this may be related to sustained renal exposure to active PTH over time, as well as normalization of bone metabolism after initial increase in bone turnover with exposure to PTH.

24-Hour Excretion of Calcium

Mean 24 h urine calcium fell from 428 mg/24 h (high) at baseline to 178, 144, 134 and 166 mg/24 h (normal <250 mg/24 h) at Weeks 26, 58, 84 and 110, respectively, showing normalization by Week 26, see figure

Figure 17. 24-Hour Urine Calcium (Mean +/- SE) by Visit (Full Analysis Population)



The submitted CSR reasons that results from this substudy are consistent with restoration of this key component of homeostasis, as observed urinary calcium excretion remained generally stable and below the upper limit of normal for each 4-h collection.

Results for 24-Hour Urine Calcium at week 110 were available for 54 of 59 patients, and although the change from baseline could be calculated for 45 of 59 patients (Source OLE Table 14.2.3.4.7, now tcp-201-tfls). Maximum observed results for 24-Hour Urine Calcium at week 84 were 379.0 mg/dL and 494 mg/dL at week 84 and 110, respectively.

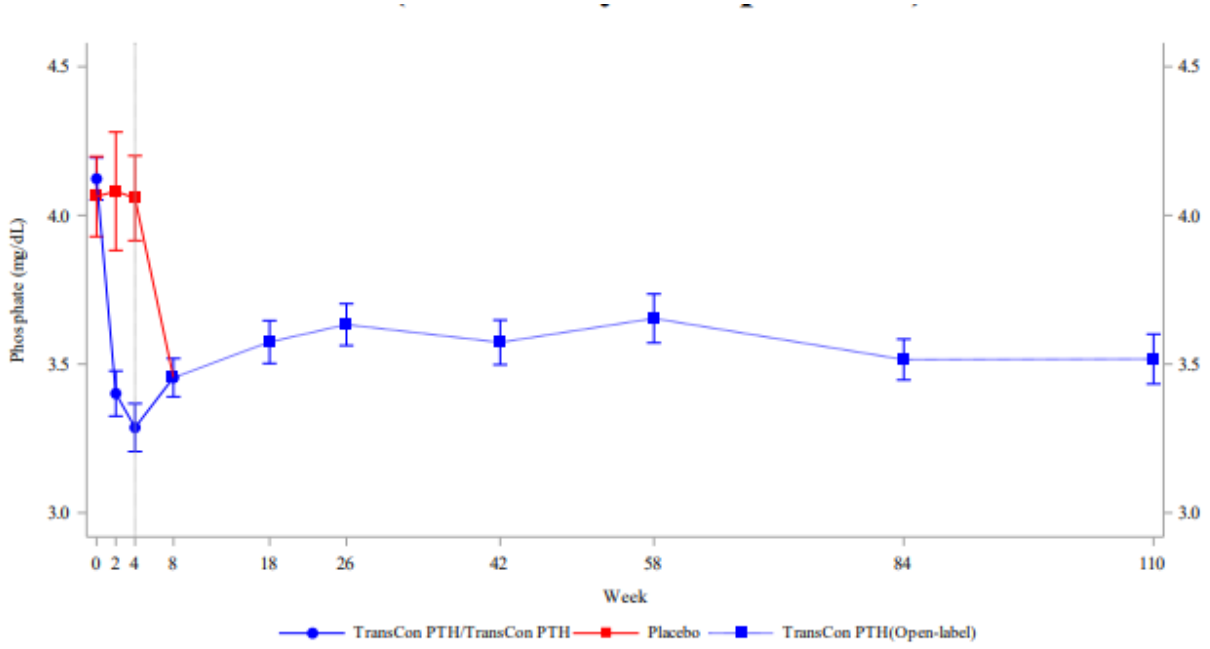
Serum Phosphate

At baseline, subjects assigned to both treatment groups had nearly the same serum phosphate level at (observed means) 4.1 mg/dL (range 3.0 to 4.9 mg/dL) for palopegteriparatide subjects compared with 4.1 mg/dL (range 2.7 to 5.1 mg/dL) for placebo subjects.
Overall, mean serum phosphate started within the central laboratory normal range (2.2 to 5.1 mg/dL). Immediately following initiation of treatment, mean serum phosphate values decreased sharply for palopegteriparatide-treated subjects at Week 2 to 3.4 mg/dL (range 2.3 to 4.6 mg/dL) and remained in the normal range over the entire 84-week follow-up period.
In contrast, mean serum phosphate values for placebo-treated subjects remained unchanged relative to baseline; Week 2 values = 4.1 mg/dL (range 2.8 to 6.0 mg/dL); Week 4 values = 4.1 mg/dL (range 3.0 to 4.7 mg/dL).
All mean treatment differences between the individual palopegteriparatide dose groups and placebo at Week 2 and at Week 4 were significant in favour of palopegteriparatide, including for pooled palopegteriparatide dose group subjects (LS mean differences at Week 4: pooled palopegteriparatide: -0.8 mg/dL (95% CI: -1.1, -0.5), nominal p<0.0001).

During the OLE, serum phosphate values for the overall group remained well below baseline values at Week 8; observed mean: 3.5 mg/dL (range 2.5 to 4.7 mg/dL) and remained stable within a narrow range within the normal range through to Week 84 where the observed mean value for the overall group was 3.5 mg/dL (range 2.3 to 4.8 mg/dL).

Serum phosphate values (Mean ±SE) during the trial is illustrated in the figure below:

Figure 18. Serum Phosphate (Mean ±SE) by Visit (Full Analysis Population)



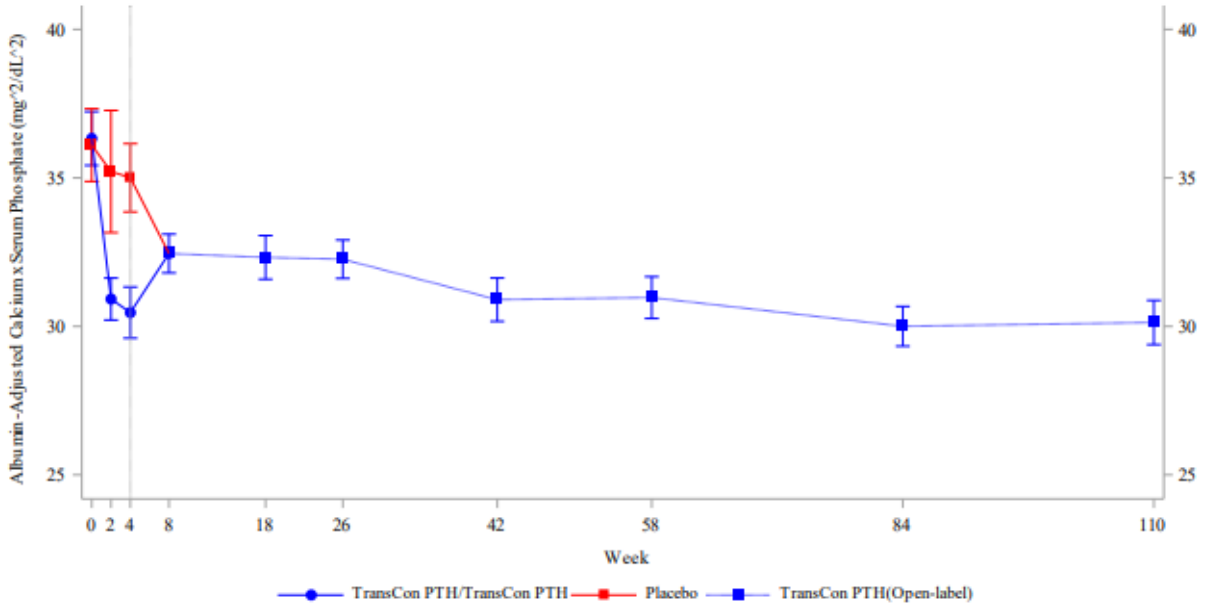
Mean serum phosphate was maintained within the normal range through Week 110.

Serum Calcium-Phosphate Product

Guidelines for treatment of hypoparathyroidism recommend a goal of keeping the serum calcium×serum phosphate product below 55 mg^2/dL^2 (4.4 $mmol^2/L^2$) (Brandi 2016).The mean serum calcium×serum phosphate product was comparable (36 ±0.3 mg^2/dL^2) at baseline and were below 55 mg^2/dL^2 for subjects assigned to both treatment groups.
Following baseline, the serum calcium×phosphate product decreased for both treatment groups but decreased more for palopegteriparatide-treated subjects.
At Week 4, all mean treatment differences were significant, including for pooled palopegteriparatide subjects: pooled palopegteriparatide subjects versus placebo = -4.6 mg^2/dL^2 (95% CI: -7.8, -1.4), nominal p=0.0053.
Mean values continued to decrease slightly thereafter at Week 4 to 30.5 mg^2/dL^2 (range 19.2 to 44.3 mg^2/dL^2) for palopegteriparatide-treated subjects and to 35.0 mg^2/dL^2 (range 25.5 to 41.8 mg^2/dL^2) for placebo-treated subjects and continued to decrease at Week 84 to a mean of 30.0 mg^2/dL^2 (range 17.9 to 44.2 mg^2/dL^2) for the overall group (below the recommended level of 55 mg^2/dL^2).

Calcium×serum phosphate product values (Mean ±SE) during the trial are illustrated in the figure below:

Figure 19. Serum Calcium* Serum Phosphate Product (Mean +/- SE) by Visit (Conventional Unit) Full Analysis Population



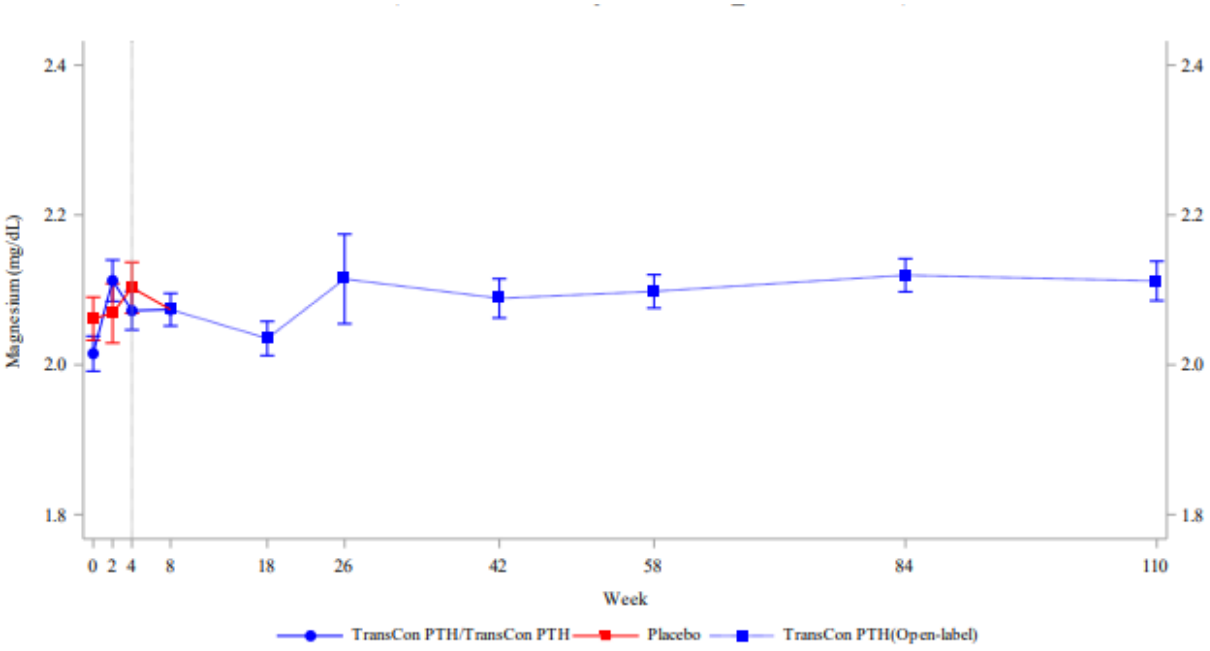
The mean serum calcium×phosphate product was maintained below the cut-off of 55 mg^2/dL^2 (4.4 $mmol^2/L^2$) up to Week 110.

Serum Magnesium

The normal reference range for magnesium used in the trial was 1.6 mg/dL (0.66 mmol/L) to 2.6 mg/dL (1.07 mmol/L).
At baseline, subjects assigned to both treatment groups had nearly the same serum magnesium level at 2.0 mg/dL (range 1.7 to 2.3 mg/dL, observed means) for palopegteriparatide subjects compared with 2.1 mg/dL (range 1.8 to 2.3 mg/dL) for placebo subjects.
Mean serum magnesium levels trended slightly higher from baseline for both treatment groups at Week 2 and at Week 4 (by approximately 0.06 to 0.10 mg/dL).
During the OLE period, mean values for the overall group of subjects fluctuated in a narrow range within the normal reference range between 2.0 mg/dL at Week 18 to 2.1 mg/dL at Week 84.

Serum magnesium values (Mean ±SE) during the trial is illustrated in the figure below:

Figure 20. Serum Magnesium (Mean +/- SE) by Visit (Conventional Unit) Full Analysis Population



Ancillary analyses

Analyses for the demographic, primary, and key secondary efficacy endpoints were not performed due to insufficient data in one or more categories.

2.5.5.2. Main study

PaTHway TRIAL: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Trial, with an Open-Label Extension, Investigating the Safety, Tolerability and Efficacy of TransCon PTH Administered Subcutaneously Daily in Adults with Hypoparathyroidism

Study **TCP-304** is the pivotal phase III study in adult patients with hypoparathyroidism

The applicant provided the interim report for the double-blind, placebo-controlled period (Blinded Period) of Study TCP-304. The Blinded Period analysis was triggered when the last subject reached Visit 10. The Open-label Extension (OLE) period of the study, planned for up to 156 weeks (3 years), is ongoing at the time of this clinical study report (CSR). Available results through week 52 has been provided. The submitted clinical study report includes a brief summary of the OLE data as of 12 Jan 2022, which is the last subject's Visit 10 date.

- **Methods**

TCP-304 was a Phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel group, 26-week trial, with an open-label extension of 3 years of daily palopegteriparatide (TransCon PTH) in male and female adults with chronic hypoparathyroidism of postsurgical, autoimmune, genetic, or idiopathic etiology for at least 26 weeks, treated with calcitriol (an active vitamin D) ≥0.5 µg/day, or alfacalcidol (an active vitamin D) ≥1.0 µg/day and elemental calcium ≥800 mg/day for at least 12 weeks prior to Screening.

Main study

Screening

The duration of the Screening Period (supplement optimization) was up to approximately 4 weeks (plus a recommended period of up to approximately 2 weeks between randomization and Visit 1).

Blinded Main Period

For the Main Study with a duration of 26 weeks, subjects were randomized in a 3:1 ratio into 2 treatment groups:

• Palopegteriparatide 18 µg/day*, co-administered with conventional therapy

• Placebo for palopegteriparatide (excipient solution) 18 µg/day, co-administered with conventional therapy

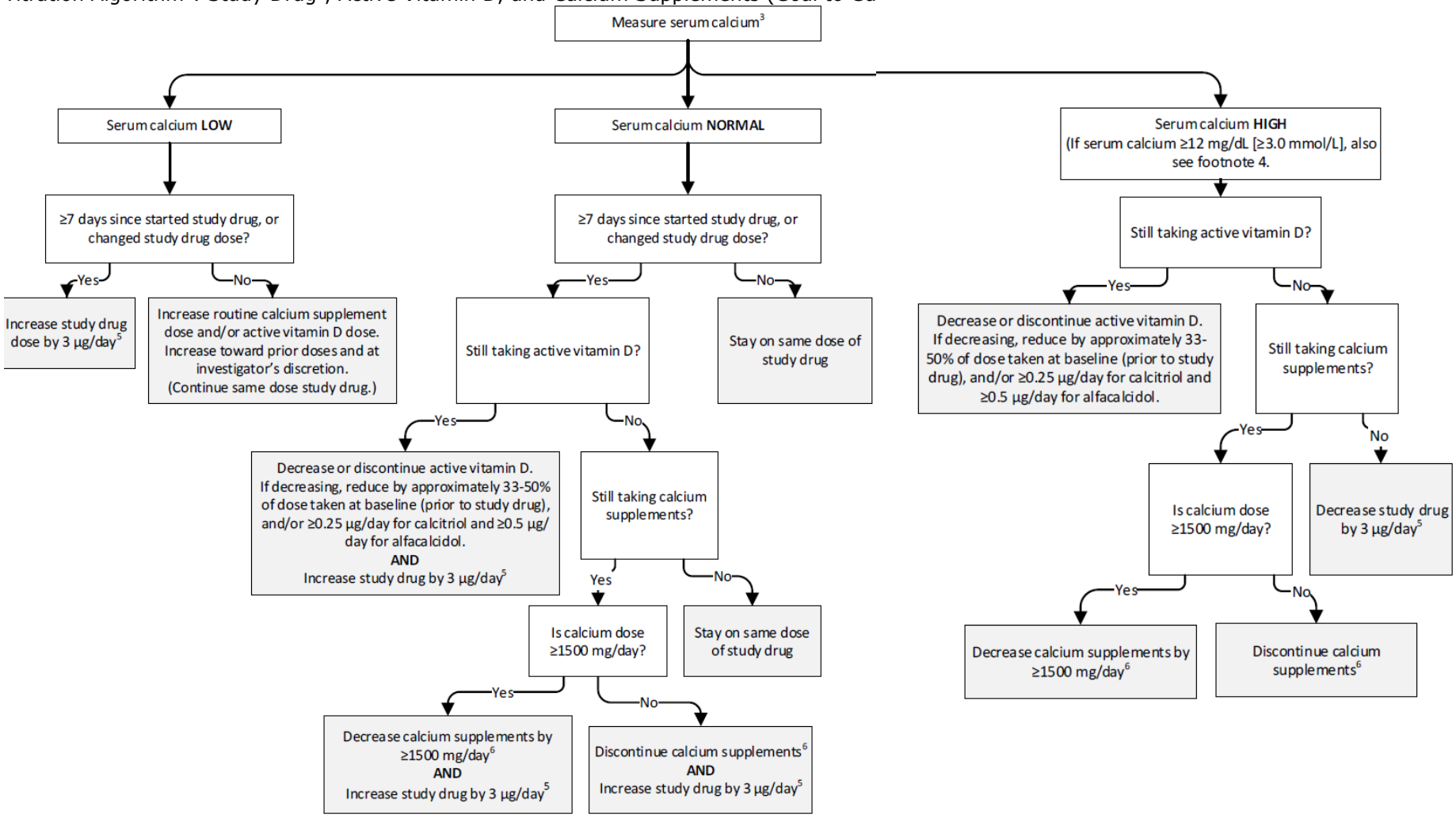
**Dose of palopegteriparatide refers to dose of PTH(1-34) administered*

Randomization was stratified by etiology of hypoparathyroidism (post-surgical versus all other).

All subjects started with study drug 18 µg/day and were individually and progressively titrated to an optimal dose in dose increments of 3 µg/day as shown in the figure below:

Figure 21. TCP-304 TITRATION ALGORITHM

Titration Algorithm[1]: Study Drug[2], Active Vitamin D, and Calcium Supplements (Goal to Gain Independence from Conventional Therapy)



1 At Visit 1 (Week 0, Day 1), start study drug at 18 µg/day and decrease active vitamin D dose by 33-50% (e.g., skip second dose of the day if taking BID, and skip final dose of the day if taking TID).

2 Study drug refers to TransCon PTH or placebo.
3 sCa refers to either albumin-adjusted sCa and/or ionized calcium. For the purposes of this trial, the normal ranges are: albumin-adjusted sCa 8.3-10.6 mg/dL (2.07-2.64 mmol/L); ionized calcium 1.16-1.32 mmol/L.
4 If albumin-adjusted sCa ≥12.0 mg/dL (3.00 mmol/L) or ionized calcium ≥1.50 mmol/L, hold study drug for approximately 2-3 days. Remember to resume study drug therapy afterwards. Also reduce study drug, active vitamin D, or calcium as per algorithm.
5 Check sCa within 7-14 days after any changes in study drug dose; standing calcium, standing vitamin D doses; or sCa outside the normal range. A scheduled visit or LV within 7-14 days meets this requirement. When scheduled study visits occur less frequently (e.g. 13 weeks apart) then an ULV should be pursued.
6 The goal is to demonstrate independence from therapeutic doses of calcium supplements. In case needed to meet recommended dietary intake of calcium, it is permitted to take calcium supplements ≤600 mg/day as a nutritional supplement for the sake of reaching the recommended dietary intake.
Notes: Adjustments of study drug, calcium and/or active vitamin D will be made per the titration algorithm based on the results of the most recent laboratory results whether scheduled or unscheduled. When central and local calcium values are obtained concurrently, local values should be used to guide titration. At all times during the trial, subjects with symptoms of hypocalcemia may take PRN doses of calcium (preferred) and/or active vitamin D, and/or do an ULV visit to measure sCa. Subjects with symptoms of hypercalcemia may hold doses of study drug for 1 day and/or do an ULV to measure sCa. An ULV must be performed within 7 days of a PRN supplement dose or a held dose. If due to symptoms >2 PRN doses of SoC are taken or >2 doses of SoC and/or study drug are held within those 7 days, an ULV is required within 2 days of the third PRN or held dose.

Study drug, calcium and active vitamin D were titrated according to the Titration Algorithm on each occasion serum calcium was measured.

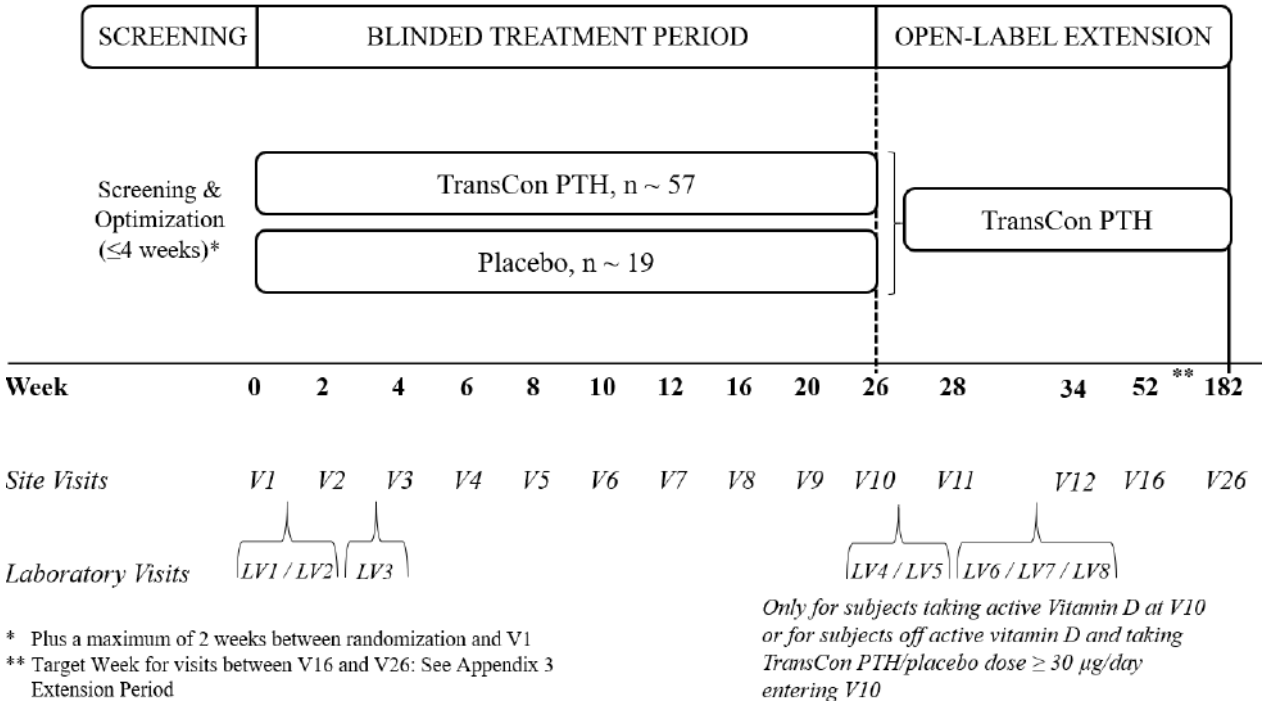
Dose range for the trial was supported by 3 pen presentations delivering discrete doses of 6, 9, and 12 µg/day; 15, 18, and 21 µg/day; and 24, 27 and 30 µg/day, respectively. The palopegteriparatide allowed dose range was 6 to 60 µg/day.

Open Label Extension period

Following successful completion of the Blinded Treatment Period, subjects were allowed to enter the open-label Extension Period when all subjects received palopegteriparatide. The duration of the OLE part is 156 weeks.

A schematic representation of the study design is provided in the figure below:

Figure 22. TCP-304 Main Study Design and OLE



Note: Screening period duration approximately 4 weeks; TransCon PTH = palopegteriparatide, V = Visit; LV = Laboratory visit

- **Study Participants**

As outlined in the Clinical Study Protocol (Version 5 dated 20 December 2021), the trial was to be conducted at up to approximately 40 study sites. All centres needed to be specialized treatment centres in the management of HP. The study centres as listed in the CSR were 21 sites in 7 countries (Canada, Denmark, Germany, Hungary, Italy, Norway, and United States).

According to the Study Protocol, patients must meet the requirements of all in- and exclusion criteria to be eligible for the main study:

Inclusion criteria

1. Males and females, ≥18 years of age

2. Subjects with postsurgical chronic HP, or auto-immune, genetic, or idiopathic HP for at least 26 weeks. Diagnosis of HP is established based on a history of hypocalcemia in the setting of inappropriately low serum PTH levels (Hypocalcemia is defined as a value below the reference range for normal at the performing laboratory. Inappropriately low serum PTH levels are defined as at or

below the median value of the reference range for normal at the performing laboratory while the concomitant serum calcium is low. If specific lab results at the time of original diagnosis are not available, as historical diagnosis affirming these two components is adequate for inclusion)

3. Requirement for doses of SoC (e.g., calcitriol, alfacalcidol, calcium supplements) at or above a minimum threshold:

- For countries other than Japan: requirement for a dose of calcitriol ≥0.5 µg/day, or alfacalcidol ≥1.0 µg/day and (elemental) calcium ≥800 mg/day (e.g., calcium citrate, calcium carbonate etc.) for at least 12 weeks prior to Screening*. In addition, the dose of calcitriol, or alfacalcidol, or calcium should be stable** for at least 5 weeks prior to Screening

- For Japan: requirement for a dose of calcitriol ≥1.0 µg/day, or alfacalcidol ≥2.0 µg/day for at least 12 weeks prior to Screening*. In addition, the dose of calcitriol or alfacalcidol should be stable** for at least 5 weeks prior to Screening. In Japan only (due to local practice and dietary patterns), there is no requirement to exceed a minimum dose of calcium supplements

** Excluding individuals receiving PTH-like drugs within 12 weeks of the screening visit, who need only demonstrate a stable requirement for elemental calcium and active vitamin D above minimum thresholds for 5 weeks prior to the screening visit.*
*** Does not preclude occasional (≤2/week) PRN doses of calcium and/or active vitamin D for symptomatic hypocalcemia*

4. Optimization of supplements prior to randomization to achieve the target serum levels of:

- 25(OH) vitamin D levels of 20-80 ng/mL (49-200 nmol/L) and

- Magnesium level in the normal range, or just below the normal range i.e.: ≥1.3 mg/dL (0.53 mmol/L) and

- Albumin-adjusted or ionized sCa level in the normal range, or *just below the normal range, i.e.:
  - Albumin-adjusted sCa 7.8-10.6 mg/dL (or 1.95-2.64 mmol/L)
  - Ionized sCa 4.40-5.29 mg/dL (or 1.10-1.32 mmol/L)

** Just below the normal range implies the numerical range of 7.8-8.2 mg/dL (or 1.95-2.06 mmol/L) for albumin-adjusted sCa and the numerical range of 4.40-4.636 mg/dL (or 1.10-1.159 mmol/L) for ionized sCa.*

5. The subject demonstrates a 24-hour uCa excretion of ≥125 mg/24 h (on a sample collected within 52 weeks prior to Screening or during the Screening Period)

Note: Although 24-hour urine samples prior to Screening may be done on or off thiazide therapy, thiazide therapy is prohibited during the trial; and the 24-hour urine collection scheduled prior to Visit 1 must be done while off thiazides for at least 4 weeks prior to collection

6. BMI 17- 40 kg/m^2 at Screening

7. If ≤25 years of age, radiological evidence of epiphyseal closure based on X-ray of non-dominant wrist and hand

8. Thyroid-stimulating hormone (TSH) within normal laboratory limits within the 6 weeks prior to Visit 1; if on suppressive therapy for a history of thyroid cancer, TSH level must be ≥0.2 mIU/L

9. If treated with thyroid hormone replacement therapy, the dose must have been stable for at least 5 weeks prior to Screening

10. eGFR ≥30 mL/min/1.73 m2 during Screening

11. Able to perform daily SC self-injections of study drug (or have a designee to perform injections) via a pre-filled injection pen

12. Able and willing to provide written and signed ICF in accordance with GCP

13. For France only: The subject is obligated to be affiliated with, or beneficiary of a social security system or assimilated.

Exclusion criteria

1. Impaired responsiveness to PTH (pseudohypoparathyroidism) which is characterized as PTH-resistance, with elevated PTH levels in the setting of hypocalcemia

2. Any disease that might affect calcium metabolism or calcium-phosphate homeostasis or PTH levels other than HP, such as active hyperthyroidism; Paget disease of bone; severe hypomagnesemia; type 1 diabetes mellitus or poorly controlled type 2 diabetes mellitus (HbA1C >9%, documented HbA1C result drawn within 12 weeks prior to Screening is acceptable); severe and chronic liver, or renal disease; Cushing syndrome; multiple myeloma; active pancreatitis; malnutrition; rickets; recent prolonged immobility; active malignancy (other than low-risk well differentiated thyroid cancer or non-melanoma skin cancer); active hyperparathyroidism; parathyroid carcinoma within 5 years prior to Screening; acromegaly; or multiple endocrine neoplasia types 1 and 2

3. High risk thyroid cancer within 2 years, requiring suppression of TSH <0.2 mIU/L

4. 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)

5. Use of thiazide diuretic within 4 weeks prior to the 24-hour urine collection scheduled to occur within 1 week prior to Visit 1

6. Use of PTH-like drugs (whether commercially available or through participation in an investigational trial), including PTH(1-84), PTH(1-34), or other N-terminal fragments or analogs of PTH or PTH-related protein, within 4 weeks prior to Screening

7. Use of other drugs known to influence calcium and bone metabolism, such as calcitonin, fluoride tablets (>0.5 mg/day), strontium, or cinacalcet hydrochloride, within 12 weeks prior to Screening

8. Use of osteoporosis therapies known to influence calcium and bone metabolism, i.e., bisphosphonate (oral or intravenous [IV]), denosumab, raloxifene, or romosozumab therapies within 2 years prior to Screening

9. Non-hypocalcemic seizure disorder with a history of a seizure within 26 weeks prior to Screening

Note: History of seizures that occur in the setting of hypocalcemia is not exclusionary

10. 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

11. Pregnant or lactating women

Note: Acceptable highly effective contraception (see Appendix 1) is required for sexually active women of childbearing potential during the trial and for 2 weeks after the last dose of study drug, and pregnancy testing will be performed throughout the trial.
Sexually active women of childbearing potential who are unwilling to use acceptable highly effective contraception are excluded from the trial

12. Male who has a female partner who intends to become pregnant or is of childbearing potential and is unwilling to use adequate contraceptive methods during the trial

Note: Male subjects must use a condom, or his female partner of childbearing potential must use an effective form of contraception (as per CTFG definition), from the beginning of screening to the last trial visit

13. Diagnosed drug or alcohol dependence within 3 years prior to Screening

14. 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 AIRE gene mutations with malabsorption

15. 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, 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

16. Cerebrovascular accident within 5 years prior to Screening

17. Within 26 weeks prior to Screening: acute colic due to nephrolithiasis, or acute gout. Subjects with asymptomatic renal stones are permitted

18. Participation in any other interventional trial in which receipt of investigational drug or device occurred within 8 weeks (or within 5.5 times the half-life of the investigational drug) (whichever comes first) prior to Screening

19. Any disease or condition that, in the opinion of the investigator, may require treatment or make the subject unlikely to fully complete the trial, or any condition that presents undue risk from the investigational product or procedures, including treated malignancies that are likely to recur within the approximate 3.5-year duration of the trial

20. Known allergy or sensitivity to PTH or any of the excipients [metacresol, mannitol, succinic acid, NaOH/(HCl)]

21. Likely to be non-compliant with respect to trial conduct

22. Any other reason that in the opinion of the investigator would prevent the subject from completing participation or following the trial schedule

- **Treatments**

Investigational treatment

Palopegteriparatide [a pro-drug consisting of PTH(1-34), an inert mPEG carrier, and a TransCon linker] in a delivery system consisting of a multi-use cartridge integrated into a modified Ypsomed Uno Pen Fix using 31Gx5 mm pen needles. The cartridge contained a liquid formulation of palopegteriparatide 0.3 mg PTH(1-34)/mL with a fill volume sufficient for 14 doses.

Placebo

The reference (i.e. placebo) therapy was a modified Ypsomed Uno Pen Fix, with cartridges containing excipient solution to match palopegteriparatide.

Administration

Palopegteriparatide or placebo control (vehicle only) was to be self-administered (following training by study staff). There was a total of 4 possible injection areas for the s.c. injection: right abdomen, left abdomen, right anterior thigh, and left anterior thigh, and multiple sub-areas within each area. Subjects were instructed to rotate injection sites.

The study drug allowed dose range was 6 to 60 µg/day. All doses >30 µg/day were delivered in the form of two single doses injected one after another at different injection sites using two pens of the same pen presentation, except for the 45 µg/day dose which was delivered as a combination of the mid-dose and high-dose pen presentations.

Required HP Therapies prior to screening

Prior to Screening, subjects must be taking doses of the following SoC HP treatments for at least 12 weeks with a minimum of 5 weeks being stable on these doses (inclusion criteria 3):

• Calcitriol ≥0.5 µg/day or alfacalcidol ≥1.0 µg/day and

• Elemental calcium ≥800 mg/day (e.g., calcium citrate, calcium carbonate, etc.)

Subjects should receive calcium supplementation in the form of calcium citrate in case of concomitant use of proton pump inhibitors or anti-acid therapies.

Subjects may also be on cholecalciferol (vitamin D3) and magnesium supplements as part of their HP treatment or to achieve the recommended daily allowance (RDA), as needed to maintain target ranges of each. The 25 (OH) vitamin D target range is 30-80 ng/mL during treatment phases of the trial. Subjects are to be instructed to take their HP-related supplements at approximately the same time every day throughout the trial. Subjects taking a thiazide diuretic should discontinue at least 4 weeks prior to the baseline Screening 24-hour urine collection scheduled during the week prior to Visit 1.

Screening Period (Supplement Dose Adjustments)

During the Screening Period, adjustments to doses of hypoparathyroidism-related supplements (SOC, magnesium, vitamin D) were made to achieve the following laboratory levels (inclusion criteria 4):

- 25(OH) vitamin D levels of 20-80 ng/mL (49-200 nmol/L) and

- Magnesium level in the normal range, or just below the normal range i.e.: ≥1.3 mg/dL (0.53 mmol/L) and

- Albumin-adjusted or ionized sCa level in the normal range, or *just below the normal range, i.e.:
  - Albumin-adjusted sCa 7.8-10.6 mg/dL (or 1.95-2.64 mmol/L)
  - Ionized sCa 4.40-5.29 mg/dL (or 1.10-1.32 mmol/L)

** Just below the normal range implies the numerical range of 7.8-8.2 mg/dL (or 1.95-2.06 mmol/L) for albumin-adjusted sCa and the numerical range of 4.40-4.636 mg/dL (or 1.10-1.159 mmol/L) for ionized sCa.*

Main Study (Blinded Treatment Period)

Subjects were randomized 3:1 into palopegteriparatide or placebo.

• Palopegteriparatide 18 µg/day, co-administered with conventional therapy

• Placebo for palopegteriparatide, co-administered with conventional therapy

– Mimicking dose of 18 µg/day

All subjects started with study drug 18 µg/day and were individually and progressively titrated to an optimal dose in dose increments of 3 µg/day as per the treatment algorithm outlined in above. As outlined there, at Visit 1 (Week 0, Day 1), the study drug was started and parallel to that the active vitamin D dose was decreased by 33-50% e.g. by skipping the second dose of the day if taking BID or skipping the final dose of the day if taking TID.
As outlined in the titration algorithm, if patients were still taking SOC, SOC was to be downtitrated if patients had serum calcium levels in the normal range and at least 7 days had passed since start of the study drug, or a changed study drug dose.
If serum calcium levels were below the lower limit of normal (below 8.3 mg/dL by definition), SOC would not be further downtitrated (if at least 7 days had passed since start of the study drug, or a changed study drug dose) or it would be increased towards prior doses (if less than 7 days had passed since start of the study drug, or a changed study drug dose).

Open-label Extension Period

At Visit 10 (Week 26), subjects were assigned to open-label treatment as follows:

• If still taking active vitamin D: Palopegteriparatide was started at a dose of 18 µg/day, and subsequently followed the titration algorithm outlined above.

• If NOT taking active vitamin D:

– And taking study drug ≥30 µg/day: Palopegteriparatide was started at a dose of 18 µg/day, and subsequently follow the titration algorithm.

– And taking study drug <30 µg/day: Palopegteriparatide was started at the same dose of study drug taken at the end of the Blinded Treatment Period, except in cases of an out-of-range serum calcium level at Visit 10, when the palopegteriparatide and/or calcium doses were adjusted.

In consequence, at Visit 10 (Week 26), the following categories of subjects started palopegteriparatide 18 µg/day.

• Those still taking active vitamin D (this group could be enriched with subjects initially randomized to placebo)

• Those off active vitamin D and taking study drug ≥30 µg/day

As such, when selecting the appropriate doses of SoC (active vitamin D and calcium supplements) to accompany the palopegteriparatide 18 µg/day, investigators were advised to:

• Consider the doses of active vitamin D and calcium required at trial baseline (before exposure to the study drug)

AND

• Reduce the active vitamin D (taken before exposure to study drug) by 33 to 50% when starting palopegteriparatide 18 µg/day at Visit 10

Start the new conventional therapy regimen:

• On the day of Visit 10 for those subjects who were still taking active vitamin D at the time of Visit 10

• On the day after Visit 10 for those subjects who were off active vitamin D and taking study drug ≥30 µg/day at Visit 10

Pro Re Nata

At all times during the trial, subjects with symptoms of hypocalcemia could take pro re nata ((abbreviated PRN) meaning "rescue medication" or "as needed") doses of calcium (preferred) and/or active vitamin D, and/or do an unscheduled laboratory visit (ULV) to measure serum calcium.

Subjects with symptoms of hypercalcemia could hold doses of study drug for 1 day and/or do an ULV to measure serum calcium. An ULV was performed within 7 days of a PRN supplement dose or a held dose.

If due to symptoms >2 PRN doses of conventional therapy were taken or >2 doses of conventional therapy and/or study drug were held within those 7 days, an ULV was required within 2 days of the third PRN or held dose.

- **Objectives**

Primary Objective

The primary objective of the study was to assess the treatment effect of daily palopegteriparatide on serum calcium levels and therapeutic doses of active vitamin D (i.e., calcitriol or alfacalcidol) and calcium at 26 weeks of treatment.

Secondary Objectives

• To assess the safety and tolerability of daily palopegteriparatide

• To assess the treatment effect of daily palopegteriparatide on hypoparathyroidism patient experience scale (HPES) and Short Form-36 (SF-36) domain scores

• To assess the treatment effect of daily palopegteriparatide on pharmacodynamic (PD) markers (including serum calcium) and active vitamin D and calcium doses

• To assess the treatment effect of daily palopegteriparatide on serum phosphate, calcium×phosphate (albumin-adjusted serum calcium-phosphate product) and serum magnesium

• To assess anti-PTH, anti-TransCon PTH and anti-polyethylene glycol (PEG) antibody responses

• To assess the treatment effect during the Extension Period

• To assess the treatment effect of daily palopegteriparatide on

– BMD and trabecular bone score (TBS) by DXA

– Bone turnover markers (serum P1NP and CTx)

• To assess the effect of treatment on patient-reported health-related QOL and a clinician-reported outcome (ClinRO) assessment

Exploratory Objectives

• To assess the usability of the pre-filled injection pen

• To assess the effect of treatment on Patient-reported Symptoms, Impact and Employment

- **Outcomes/endpoints**

Primary Endpoint

Proportion of subjects with the following at 26 weeks of treatment:

• Albumin-adjusted serum calcium measured within 4 weeks prior to and on Week 26 visit within the normal range (8.3-10.6 mg/dL)*****; and

• Independence from active vitamin D within 4 weeks prior to Week 26 visit (i.e., all daily standing dose of active vitamin D equal to zero AND use of pro re nata (PRN, as needed/rescue) ≤7 days during the 4 weeks); and

• Independence from therapeutic doses of calcium within 4 weeks prior to Week 26 visit (i.e., average daily standing dose of elemental calcium ≤600 mg AND use of PRN doses on ≤7 days during the 4 weeks). This dose of elemental calcium ≤600 mg/day in the form of tablets, powder, liquid suspension, or transdermal patch was considered as "supplemental" to meeting recommended daily intake for general health, as opposed to a "therapeutic" dose to treat hypoparathyroidism; and

• No increase in prescribed study drug within 4 weeks prior to Week 26 visit. ******

** Except for at the Week 26 visit, confirmation that an albumin-adjusted serum calcium is "abnormal" requires 2 consecutive results outside the normal range within 4 weeks prior to the Week 26 visit.*

*** Dose decrease permitted for safety reasons.*

Measurement

The primary efficacy variables included albumin-adjusted serum calcium, use of active vitamin D and therapeutic doses of calcium, and prescribed study drug dose. Serum calcium was based on laboratory data. Use of conventional therapy medications was derived from diary data. The study drug prescription dose, as recorded by the investigator, was derived from eCRF.

Subjects were trained on the diary during Screening and diary date were reviewed at the visit by site staff as part of study drug compliance and conventional therapy/PRN medication doses review. An eDiary solution was used with the subject's own device or with a provision device. A paper diary was used as back-up solution. Subjects were required to complete a daily diary until Visit 13 to capture the following:

• Study drug, starting at Visit 1 (administration date and time, dose, location of injection site)

• Conventional therapy (administration date, name and dose), including PRN medication doses

Note that missed diary entries were considered missed doses.

Subjects were also required to complete a weekly diary starting from Visit 13 to Visit 18 to capture palopegteriparatide administration and any conventional therapy/PRN medication doses.

Secondary Endpoints

Key Secondary Efficacy Endpoints

Key secondary endpoints included the change from baseline at 26 weeks of treatment for the following parameters:

• HPES - Symptom - Physical domain score

• HPES - Symptom - Cognitive domain score

• HPES - Impact – Physical Functioning domain score

• HPES - Impact – Daily Life domain score

• 36-Item Short Form Survey (SF-36) Physical Functioning subscale score

The Hypoparathyroidism Patient Experience Scale (HPES) is a disease-specific PRO that was developed and validated by the Sponsor to assess relevant patient-reported symptom and disease impacts. The HPES - Symptom assesses the key hypoparathyroidism-related physical and cognitive symptoms from the patient perspective. The HPES - Impact assesses the key impacts of these symptoms on patient functioning and well-being (physical functioning, daily life, psychological well-being, social life and relationships).

The 36-Item Short-Form Survey (SF-36) V2 Health Survey (1-week recall) is a multipurpose short-form health survey with 36 questions that yields an eight-scale profile of functional health and general well-being, as well as two psychometrically based physical and mental health summary measures and a preference-based health utility index. The SF-36 is a generic health survey as it can be used across age (18 and older), disease, and treatment group, as opposed to a disease-specific health survey, which focuses on a particular condition or disease.
The SF-36v2 is a well-validated measure which has previously been used in several studies examining burden of illness and impact of treatment experienced by adult patients with HP. However, the content

validity of this measure has not been formally assessed for this population. Therefore, cognitive debriefing interviews were conducted with adults who have hypoparathyroidism in order to assess the content validity of the SF-36v2 Health Survey Acute measure in this population.

Other Secondary Efficacy Endpoints

The following endpoints were evaluated at predefined timepoints during the Blinded Treatment and will be evaluated during the Extension Period:

• Calcium and active vitamin D doses

• Daily "pill burden" of active vitamin D and calcium (as oral tablets, powder, liquid solutions, liquid suspensions, or transdermal patches) assessed

• Serum phosphate

• Albumin-adjusted serum calcium-phosphate product, including proportion of subjects with albumin-adjusted serum calcium-phosphate product ≤55 mg2/dL2, ≤52 mg2/dL2, and ≤44 mg^2/dL^2

• Albumin-adjusted serum calcium

• BMD and TBS by DXA

• Bone turnover markers (serum P1NP and CTx)

• Serum magnesium

• EQ-5D

• CGI-S

• HPES: HPES - Impact domain scores (Psychological Well-being and Social Life and Relationships) and HPES - Symptom and Impact total scores

• SF-36: SF-36 subscale scores (Role Limitations due to Physical Health Problems, Bodily Pain, General Health, Vitality, Social Functioning, Role Limitations due to Emotional Problems, and Mental Health) and SF-36 component summary scores (Physical component score [PCS] and Mental component score [MCS])

Measurement

Efficacy variables included PD markers, which were derived from laboratory data, BMD and trabecular bone scores, which were assessed via DXA, bone turnover markers, which were also derived from laboratory data, HPES, HRQOL instruments and a clinician-reported outcome assessments, pen usability, and patient reported outcomes.

Safety Endpoints

The following safety endpoints were assessed during the Blinded Treatment and Extension Periods:

• Incidence of adverse events (AEs), adverse events of special interest (AESI) and serious adverse events (SAEs)

• Serum chemistry and hematology

• 24-hour urine chemistry (including urine calcium and urine creatinine clearance)

• Clinical events of hypo- or hypercalcemia (emergency/urgent care visits and hospitalizations)

• Injection site tolerability (based on AEs)

• Evaluation of anti-PTH, anti-TransCon PTH and anti-PEG antibody responses

• Vital signs

Exploratory Endpoints

The following exploratory endpoints were assessed at predefined timepoints:

• Device usability questionnaire

• The effect of treatment on Patient-reported Symptoms, Impact and Employment by the following measures:

– Work Limitations Questionnaire (WLQ)

– Patient Global Impression of Severity (PGIS) Symptom and Impact

- **Sample size**

The sample size was determined based on considerations from both statistical power and adequate safety exposure perspectives. Assuming that the response rate was 70% for palopegteriparatide and 15% for placebo for the primary endpoint at 26 weeks, 68 subjects randomized 3:1 to active palopegteriparatide vs. placebo would have approximate statistical powers of 99% at alpha = 0.05, and 95% at alpha = 0.01 (two-sided) to demonstrate statistically significant difference between palopegteriparatide and placebo. The assumption of 70% response rate for palopegteriparatide was considered conservative, since approximately 86% of subjects taking palopegteriparatide with efficacy data (N=56) would meet the primary endpoint proposed for study TCP-304 based on phase 2 study TCP-201 6-month data. Taking into account a dropout rate of approximately 10% dropout, a total sample size of 76 was targeted.

- **Randomisation and Blinding (masking)**

A randomization schedule was developed by an independent party to maintain blinding. Subjects were randomized 3:1 to receive palopegteriparatide or placebo during the Blinded Treatment Period with etiology of hypoparathyroidism (post-surgical versus others) as stratification factor. Randomization was conducted via Interactive Web Randomization System (IWRS). All subject received palopegteriparatide during the open-label Extension Period.

- **Statistical methods**

The statistical analysis plan was finalized and signed prior to database lock.

Efficacy analyses were conducted for ITT population including all subjects in the Randomized Population who received at least one dose of blinded study drug according to the randomized treatment assignment.

As primary analysis, the 2-sided CMH test controlling for etiology of hypoparathyroidism (post-surgical versus other) was conducted to test the following hypothesis for the primary efficacy endpoint with alpha = 0.05:

H0: $OR_{Post} = OR_{Other} = 1$,

where OR_{Post} and OR_{Other} were the odds ratios (i.e., the odds of meeting the primary endpoint in the palopegteriparatide group compared to the odds in the placebo group) within post-surgical and other groups, respectively. The p-value from the CMH test is reported. The common odds ratio between treatment group and primary endpoint controlling for etiology of hypoparathyroidism with 95% CI was also planned to be reported but was finally not generated for ITT population or subgroups, because the placebo group has only 1 responder, which would make the confidence interval very wide.

Subjects with no Week 26 albumin-adjusted serum calcium were considered as non-responders. Subjects with >25% (i.e., >7 days) missing diary data of active vitamin D or calcium during the 4 weeks were considered as non-responders.

ANCOVA models with unequal variance were used to analyze the above key secondary endpoints after potential multiple imputation. Treatment assignment and etiology of hypoparathyroidism were entered as fixed effects and baseline value of the variable of interest was entered as a covariate. A 2-sided 95% confidence interval was calculated for the difference in least square means between the 2 treatment groups. Subjects with missing data for key secondary endpoints had the post-baseline data imputed using a multiple imputation model stratified by treatment group, under the assumption of missing at random (MAR).

The primary and five key secondary endpoints were tested sequentially to control the overall significance level at 0.05. No adjustments were planned for multiple testing/comparisons in the other secondary and exploratory endpoints.

To assess the robustness of the primary analysis, the following sensitivity analyses of the primary endpoint were performed.

In Sensitivity Analysis 1, the primary endpoint was analyzed for the Completer Population. The Completer Population was defined as subjects in the ITT population who completed 26 weeks of blinded study treatment and had data on all components for the primary endpoint.

In Sensitivity Analyses 2,4,5,7 the components of the primary endpoint were alternatively defined.

In Sensitivity Analysis 3, the 2-sided CMH test controlling for gender (female versus male) was conducted to test the primary endpoint.

A post hoc Sensitivity Analysis 6 was conducted based on FDA comment regarding primary endpoint missing data handling received on Feb 18, 2022. The primary endpoint definition was the same as Sensitivity Analysis 5 except that subjects with any missing active vitamin D or calcium data during the 4 weeks prior to the Week 26 visit were considered as non-responders in this analysis.

To assess the robustness of the treatment effect across subgroups, subgroup analyses were conducted for the primary and key secondary efficacy endpoints.

Results

- **Participant flow**

As illustrated in the flow-chart and the table below, a total of 106 subjects were screened and 84 of these met eligibility criteria and were randomized into the study.

Subjects were randomized to either palopegteriparatide (n=63), or placebo (n=21). Two subjects randomized to palopegteriparatide were not treated.

A total of 82 subjects were therefore included in the ITT and the Safety analysis populations. Most subjects completed the 26-week Blinded Period.

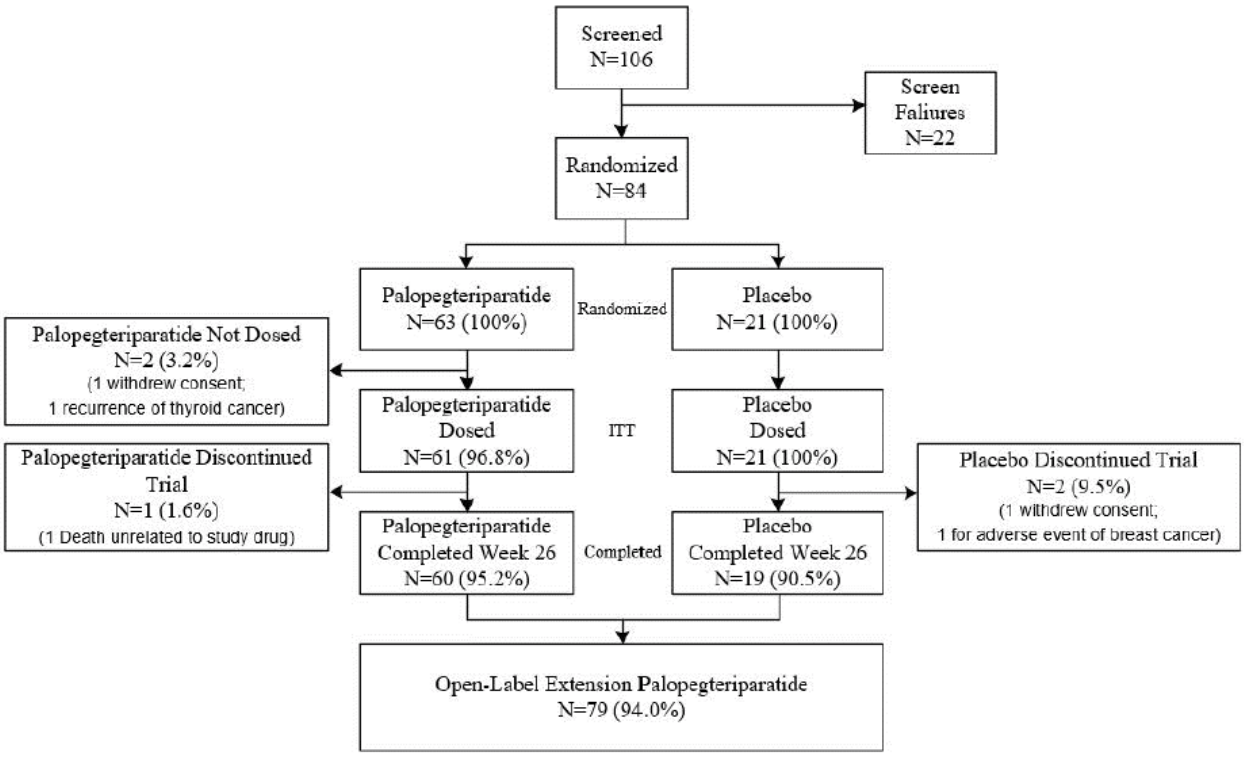
Three subjects, including 1 subject receiving palopegteriparatide and 2 subjects receiving placebo discontinued treatment during the Blinded Period due to an AE. None of these TEAEs were considered related to study drug by the investigator:

• One subject (palopegteriparatide) experienced Grade 4 cardiac arrest on Day 111. The event was fatal. Death led to discontinuation of study drug and withdrawal from the trial. The event was not considered related to study drug by the investigator.

• One subject (placebo) withdrew consent in the setting of an adverse event of Grade 2 bipolar disorder on Day 16. This event was not considered related to study drug by the investigator.

• One subject (placebo) experienced Grade 3 breast cancer on Day 62. This event was not considered related to study drug by the investigator.

Figure 23. Subject Disposition Blinded Period (All Subjects)



Abbreviations: ITT Population: Intent-to-treat Population: defined as all randomized subjects who received at least 1 dose of blinded study drug.
Note: the Randomized Population is the denominator used to support the data presented in the figure

Table 17. Disposition of Patients Blinded Period (All Subjects)

	TransCon PTH (N=63) n (%)	Placebo (N=21) n (%)	Total (N=84) n (%)
Screened Population			106
Screen Failure Population			22
Randomized Population	63 (100.0)	21 (100.0)	84 (100.0)
Randomized but Not Treated	2 (3.2)	0	2 (2.4)
ITT Population	61 (96.8)	21 (100.0)	82 (97.6)
Safety Analysis Population	61 (96.8)	21 (100.0)	82 (97.6)
PK Population	58 (92.1)	0	58 (69.0)
Completed Blinded Period (Visit 10)	60 (95.2)	19 (90.5)	79 (94.0)
Discontinued Treatment During Blinded Period	1 (1.6)	2 (9.5)	3 (3.6)
Adverse Event	1 (1.6)	2 (9.5)	3 (3.6)
Discontinued Trial During Blinded Period	3 (4.8)	2 (9.5)	5 (6.0)
Withdrawal by Subject	1 (1.6)	1 (4.8)	2 (2.4)
Adverse Event	1 (1.6)	1 (4.8)	2 (2.4)
Other	1 (1.6)	0	1 (1.2)

Abbreviations: ITT: intent to treat; PK: pharmacokinetics; TransCon PTH: palopegteriparatide.
Note: Percentages were calculated based on Randomized Population.

A total of 5 subjects, including 3 subjects receiving palopegteriparatide and 2 subjects receiving placebo, discontinued the trial during the Blinded Period. These 5 subjects included the 2 subjects who were randomized to palopegteriparatide but not treated, 2 subjects who experienced TEAEs (the subject who had a cardiac arrest and the subject who developed breast cancer), and a subject who withdrew consent (the subject who experienced bipolar disorder as described above).

79 (96.3%) subjects entered the OLE period. One subject discontinued study treatment and trial due to withdrawal by subject within week 52. Additionally, after the data cutoff date, one subject discontinued the trial due to pregnancy.

- **Recruitment**

The first subject was screened on 15 February 2021 (FPFV). The Blinded Period (26 weeks) analysis was triggered when the last subject reached Visit 10, that was on 12 January 2022 (LPLV main study).

The Open-label Extension (OLE) period of the study, planned for up to 156 weeks (3 years), was ongoing at the time of the clinical study report (CSR). Data were available for 78 subjects (59 subjects receiving palopegteriparatide from study start [TransCon PTH/TransCon PTH] and 19 subjects receiving placebo followed by palopegteriparatide [Placebo/TransCon PTH] from Week 26) at Week 52.
The submitted report includes a brief summary of the OLE data as of 12 Jan 2022 (last subject's Visit 10 date, see above).

- **Conduct of the study**

Compliance with study drug and co-administered conventional therapy

Compliance with study drug and co-administered conventional therapy was assessed via a patient recorded daily diary as described in the protocol. A missed diary entry was considered a missed dose for the purposes of this analysis.

Treatment compliance in the blinded period is outlined in the table below:

Table 18. Treatment Compliance – Blinded Period (Safety Analysis Population)

	TransCon PTH (N=61)	Placebo (N=21)
Compliance (%)		
n	61	21
Mean	96.4	93.6
SD, SE	4.05, 0.52	8.92, 1.95
Median	97.8	97.2
Min, Max	80, 100	59, 100
Compliance (%) – n (%)		
≤80	1 (1.6)	1 (4.8)
>80 to ≤90	4 (6.6)	2 (9.5)
>90	56 (91.8)	18 (85.7)

Abbreviations: Max: maximum; Min: minimum; SD: standard deviation; SE: standard error;
TransCon PTH: palopegteriparatide.
Treatment compliance was calculated as (total number of actual doses/total number of planned doses)*100.

Both groups received study drug for a median duration of 182 days. Subjects received palopegteriparatide at a median average daily dose of 20.87 µg, with a median total dosage of 3795 µg.

Study Protocol Amendments

The original study protocol (V1.0) was approved on 23 Sep 2020. There have been 4 major protocol amendments. Brief summaries of the key changes were listed in the study report.

GCP and Audits

According to the Clinical Study reports, Ascendis Pharma conducts clinical trials according to procedures that incorporate the ethical principles of GCP. To ensure compliance with these procedures and to assess the adequacy of quality control procedures, Ascendis Pharma undertakes a GCP audit program.

The CSR states that audits were performed by auditors that operated independently of the trial monitors. The audits within a clinical program are aimed at trial documentation, investigator sites and clinical trial reports. A total of 13 vendor audits and 5 site audits were conducted for this study. Audit certificates for these audits were provided in Appendix 16.1.8 of the CSR.

Protocol deviations

A total of 25 (30.5%) subjects experienced at least 1 major protocol deviation during the Blinded Period. The most frequently reported major protocol deviations pertained to study drug (12/82; 14.6%) and informed consent (11/82; 13.4%). Major protocol deviations pertaining to study drug (which mostly consisted of study drug adjustment not been aligned with titration algorithm) were reported more frequently in placebo subjects (6/21 [28.6%] versus 6/61 [9.8%] subjects receiving palopegteriparatide).

Subjects exhibited COVID-related (minor) protocol deviations. These deviations generally consisted of incomplete physical examination as the study visit was conducted virtually, or visits outside of study window as they had to be postponed due to COVID.

Table 19. Major Protocol Deviations – Blinded Period (ITT Population)

	TransCon PTH (N=61) n (%)	Placebo (N=21) n (%)	Total (N=82) n (%)
Subjects with at Least One Major Protocol Deviation	17 (27.9)	8 (38.1)	25 (30.5)
Study Drug	6 (9.8)	6 (28.6)	12 (14.6)
Informed Consent (ICF)	7 (11.5)	4 (19.0)	11 (13.4)
Other	3 (4.9)	3 (14.3)	6 (7.3)
Assessment	3 (4.9)	2 (9.5)	5 (6.1)
Visit Window	2 (3.3)	2 (9.5)	4 (4.9)
Co-Medication	1 (1.6)	0	1 (1.2)

Abbreviations: ITT: intent to treat; TransCon PTH: palopegteriparatide.

Note: Percentages were calculated based on the number of subjects in the ITT Population. Subjects may have had more than one protocol deviation but were only counted once within each deviation category.

Data Monitoring Committee

As outlined in the Study Protocol, independent oversight of this trial was to be provided by a DMC. Its duty was to regularly review the progress of the trial and assess the accumulating safety data. After each meeting, it was to advise the Sponsor on the continuing safety of current subjects in the trial and on the continuing validity and scientific merit of the trial. All decisions about the conduct of the trial were to rest solely with the Sponsor. The DMC was to consist of members, all with experience in clinical studies, and who will operate based on the Charter agreed upon. The Charter was to define data content, format, and review frequency.

- **Baseline data**

Demographic characteristics

The main baseline characteristics (FAS) are summarised in the tables below:

Table 20. Demographics and Baseline Characteristics - Blinded Period (ITT Population)

	TransCon PTH (N=61)	Placebo (N=21)	Total (N=82)
Age (years)			
n	61	21	82
Mean	49.0	47.3	48.6
SD, SE	13.13, 1.68	11.43, 2.50	12.67, 1.40
Median	50.0	44.0	48.5
Min, Max	19, 75	34, 78	19, 78
Age Group (years) – n (%)			
<50	28 (45.9)	14 (66.7)	42 (51.2)
≥50	33 (54.1)	7 (33.3)	40 (48.8)
Sex at Birth – n (%)			
Female	46 (75.4)	18 (85.7)	64 (78.0)
Male	15 (24.6)	3 (14.3)	18 (22.0)
Geographic Region – n (%)			
North America	39 (63.9)	12 (57.1)	51 (62.2)
Europe	22 (36.1)	9 (42.9)	31 (37.8)
Height (cm)			
n	61	21	82
Mean	168.22	166.67	167.82
SD, SE	8.353, 1.070	8.831, 1.927	8.450, 0.933
Median	167.50	168.00	167.57
Min, Max	149.0, 185.6	150.0, 183.6	149.0, 185.6
Weight (kg)			
N	61	21	82
Mean	77.18	81.61	78.31
SD, SE	17.335, 2.220	15.631, 3.411	16.932, 1.870
Median	73.48	80.90	77.81
Min, Max	50.8, 130.2	49.0, 109.8	49.0, 130.2
Body Mass Index (kg/m^2)			
n	61	21	82
Mean	27.27	29.47	27.83
SD, SE	5.813, 0.744	5.691, 1.242	5.828, 0.644
Median	25.90	29.40	26.26
Min, Max	17.6, 40.0	17.4, 38.4	17.4, 40.0
Menopausal Status – n (%)			
Premenopausal	27 (58.7)	15 (83.3)	42 (65.6)
Postmenopausal	19 (41.3)	3 (16.7)	22 (34.4)

Abbreviations: ITT: intent to treat; TransCon PTH: palopegteriparatide.
Percentages were calculated based on the number of subjects in the ITT Population.
Percentages for menopausal status were based on the number of female subjects in the ITT Population.

Table 21. Hypoparathyroidism History and Characteristics at Baseline – Blinded Period (ITT Population)

	TransCon PTH (N=61)	Placebo (N=21)	Total (N=82)
Cause of Hypoparathyroidism			
Acquired from neck surgery	52 (85.2)	18 (85.7)	70 (85.4)
Autoimmune disease	1 (1.6)	0	1 (1.2)
Intrinsic genetic defects of the parathyroid glands	3 (4.9)	0	3 (3.7)
Idiopathic disease	4 (6.6)	3 (14.3)	7 (8.5)
Other	1 (1.6)	0	1 (1.2)
Duration of Hypoparathyroidism (years)			
n	61	21	82
Mean	12.0	11.1	11.7
SD, SE	11.36, 1.45	8.52, 1.86	10.66, 1.18
Median	9.0	8.0	8.5
Min, Max	1, 56	1, 33	1, 56

Abbreviations: ITT: intent to treat; TransCon PTH: palopegteriparatide.
If a subject had multiple reasons for prior hospitalization/emergency room/urgent care visits related to hypoparathyroidism, each reason was counted in its category.
Note that information in relation to hypoparathyroidism supplements at baseline was derived from the eDiary.

As outlined in detail in the table below, one subject received PTH therapy within 6 months prior to screening from February 2019 until an unknown day in October 2020.

Very few subjects had experienced hospitalization (n=2) or emergency-room visits (n=2) related to hypoparathyroidism within the preceding 6 months. The majority of the subjects did not have a history of renal insufficiency (92.7%), kidney stones (76.8%), ectopic calcifications (100.0%), vascular calcifications (98.8%), brain calcifications (98.8%), cataract (96.3%), or seizure (98.8%).

Table 22. Hypoparathyroidism History and Characteristics at Baseline – Blinded Period (ITT Population)

	TransCon PTH (N=61)	Placebo (N=21)	Total (N=82)
Prior Treatment with PTH Therapy Within 6 Months Prior to Screening			
Yes	0	1 (4.8)	1 (1.2)
No	61 (100.0)	20 (95.2)	81 (98.8)
Prior Hospitalizations Related to Hypoparathyroidism (6 months)			
Hypocalcemic symptoms	1 (1.6)	0	1 (1.2)
Other	1 (1.6)	0	1 (1.2)
Total	2 (3.3)	0	2 (3.3)
Prior Emergency Room/Urgent Care Visits Related to Hypoparathyroidism (6 months)			
Hypocalcemic symptoms	1 (1.6)	0	1 (1.2)
Hypercalcemic symptoms	1 (1.6)	0	1 (1.2)
Other	1 (1.6)	0	1 (1.2)
Total	2 (3.3)	0	2 (2.4)
Renal Insufficiency History			
Yes	5 (8.2)	1 (4.8)	6 (7.3)
No	56 (91.8)	20 (95.2)	76 (92.7)
Kidney Stones History (nephrolithiasis)			
Yes	15 (24.6)	4 (19.0)	19 (23.2)
No	46 (75.4)	17 (81.0)	63 (76.8)
Ectopic Calcifications History			
Yes	0	0	0
No	61 (100.0)	21 (100.0)	82 (100.0)
Vascular Calcifications History			
Yes	1 (1.6)	0	1 (1.2)
No	60 (98.4)	21 (100.0)	81 (98.8)
Brain Calcification History			
Yes	1 (1.6)	0	1 (1.2)
No	60 (98.4)	21 (100.0)	81 (98.8)
Cataract History			
Yes	3 (4.9)	0	3 (3.7)
No	58 (95.1)	21 (100.0)	79 (96.3)
Seizure History			
Yes	0	1 (4.8)	1 (1.2)
No	61 (100.0)	20 (95.2)	81 (98.8)

Abbreviations: ITT: intent to treat; TransCon PTH: palopegteriparatide.
If a subject had multiple reasons for prior hospitalization/emergency room/urgent care visits related to hypoparathyroidism, each reason was counted in its category.
Note that information in relation to hypoparathyroidism supplements at baseline was derived from the eDiary.

Table 23. Hypoparathyroidism History and Characteristics at Baseline – Blinded Period (ITT Population)

	TransCon PTH (N=61)	Placebo (N=21)	Total (N=82)
Hypoparathyroidism Supplements at Baseline			
Elemental calcium (total daily dose [mg])			
n	61	21	82
Mean	1748.0	2104.8	1839.4
SD, SE	903.88, 115.73	1382.47, 301.68	1049.59, 115.91
Median	1625.0	1800.0	1800.0
Min, Max	600, 5000	800, 7200	600, 7200
Calcitriol (active Vitamin D) (total daily dose [µg])			
n	53	17	70
Mean	0.764	0.691	0.746
SD, SE	0.3447, 0.0473	0.3251, 0.0789	0.3392, 0.0405
Median	0.750	0.500	0.750
Min, Max	0.50, 2.00	0.50, 1.75	0.50, 2.00
Alfacalcidol (active Vitamin D) (total daily dose [µg])			
n	8	4	12
Mean	2.50	2.00	2.33
SD, SE	0.886, 0.313	0.408, 0.204	0.778, 0.225
Median	2.50	2.00	2.25
Min, Max	1.0, 4.0	1.5, 2.5	1.0, 4.0
Cholecalciferol (Vitamin D3) (total daily dose [µg])			
n	34	11	45
Mean	76.971	64.885	74.017
SD, SE	57.5533, 9.8703	36.7776, 11.0889	53.0969, 7.9152
Median	55.000	75.000	60.000
Min, Max	10.71, 250.00	20.73, 137.50	10.71, 250.00
Magnesium (total daily dose [mg])			
n	21	7	28
Mean	547.249	940.000	645.437
SD, SE	475.9280, 103.8560	705.4313, 266.6280	555.3037, 104.9425
Median	400.000	750.000	500.000
Min, Max	2.49, 2250.00	160.00, 2250.00	2.49, 2250.00
24-hour Urine Calcium at Baseline (mg/d)			
n	60	21	81
Mean	391.95	328.95	375.62
SD, SE	175.365, 22.639	140.042, 30.560	168.389, 18.710
Median	381.00	322.00	371.00
Min, Max	102.0, 924.0	64.0, 587.0	64.0, 924.0

Abbreviations: ITT: intent to treat; TransCon PTH: palopegteriparatide.
If a subject had multiple reasons for prior hospitalization/emergency room/urgent care visits related to hypoparathyroidism, each reason was counted in its category.
Note that information in relation to hypoparathyroidism supplements at baseline was derived from the eDiary.

Medical history

Details of the medical history by treatment group for the Blinded Period and for the ITT population were provided in the CSR.

The most frequently reported medical conditions pertained to the surgical and medical procedures SOC (79/82; 96.3%), endocrine disorder SOC (73.2%), neoplasms benign, malignant and unspecified (including cysts and polyps) SOC (57.3%), musculoskeletal and connective tissue disorders SOC (42.7%), and injury, poisoning and procedural complications SOC (40.2%).

On a PT basis, the most frequently reported medical conditions were thyroidectomy (75.6%), hypothyroidism (42.7%), papillary thyroid cancer (26.8%), hypertension (24.4%), post procedural hypothyroidism (23.2%), nephrolithiasis (18/82; 22.0%), and goitre (20.7%).

Prior and Concomitant Medications

Details of prior and concomitant medications and therapies were provided in the CSR. Numerically more patients on placebo took magnesium supplements, the same is true for calcium supplements. Doses of supplemental calcium have been assessed as secondary endpoint.

- **Numbers analysed**

The Intent-To-Treat (ITT) Population was to consist of all subjects who were randomized and received at least one dose of blinded study drug. All efficacy analysis were to be based on ITT and treatment assignment per randomization. The Safety Analysis Population was to consist of all randomized subjects who received at least one dose of study drug. The safety analyses was to be based on the Safety Analysis Population and actual treatment received.
All efficacy analyses were based on the ITT population, which included 82 subjects: 61 subjects receiving palopegteriparatide and 21 subjects receiving placebo.

- **Outcomes and estimation**

Primary Efficacy Analysis – Week 26 of the Blinded Period

Forty-eight of 61 (78.7% [95% CI: 66.3, 88.1]) subjects who received palopegteriparatide, and 1 of 21 (4.8% [95% CI: 0.1, 23.8]) subjects who received placebo met the criteria for the primary composite endpoint and were considered responders to treatment at Week 26 of the Blinded Period. This difference was statistically significant ($p<0.0001$). See details in the table below:

Table 24. Primary Efficacy Analysis - Blinded Period (ITT Population)

	TransCon PTH (N=61)	Placebo (N=21)
Number of Subjects Meeting the Primary Endpoint Criteria at Week 26 (Responders)	48	1
Proportion (95% CI)	78.7 (66.3, 88.1)	4.8 (0.1, 23.8)
Hypothesis Test: P-value (TransCon PTH vs Placebo)[a]	<0.0001	
Number of Subjects Meeting Each Component:		
Albumin-adjusted sCa within the normal range[b]	49	10
Independence from active vitamin D[c]	60	5
Independence from therapeutic doses of calcium[d]	57	1
No increase in prescribed study drug[e]	57	12

Abbreviations: CI: confidence interval; ITT: intent to treat; PRN: pro re nata; sCa: serum calcium; TransCon PTH: palopegteriparatide.
a The Cochran-Mantel-Haenszel test controlling for etiology of hypoparathyroidism (post-surgical vs other) was used to compare the odds of meeting the primary endpoint in TransCon PTH group to the odds in the placebo group.
b The normal range for albumin-adjusted sCa was 8.3 to 10.6 mg/dL (2.07 to 2.64 mmol/L).
c Independence from active vitamin D within 4 weeks prior to Week 26 visit (i.e., all daily standing dose of active vitamin D equal to zero AND use of PRN (as needed/rescue) ≤7 days during the 4 weeks).
d Independence from therapeutic doses of calcium within 4 weeks prior to Week 26 visit (i.e., average daily standing dose of elemental calcium ≤600 mg AND use of PRN doses on ≤7 days during the 4 weeks).
e No increase in prescribed study drug within 4 weeks prior to Week 26 visit.

As outlined in the table above, among subjects receiving palopegteriparatide, all but 1 subject achieved independence from active vitamin D (60/61; 98.4%). One subject who achieved independence from active vitamin D died on Day 111 of cardiac arrest, considered unrelated to study drug, and therefore did not complete the Blinded Period. As a result, this subject was therefore considered not to have met this criterion. All palopegteriparatide-treated subjects who completed the Blinded Period achieved independence from active vitamin D.

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

Forty-nine (80.3%) subjects achieved albumin-adjusted serum calcium within the normal range. Among subjects receiving placebo, approximately half achieved albumin-adjusted serum calcium within the normal range (10/21; 47.6%) or no increased in prescribed study drug (12/21; 57.1%).

Approximately one quarter of placebo subjects achieved independence from active vitamin D (5/21; 23.8%), and 1 achieved independence from therapeutic doses of calcium (1/21; 4.8%).

Primary Efficacy Analysis – Week 52 of the OLE Period

The Week 52 primary endpoint criteria were defined as follows:

- Albumin-adjusted serum calcium measured within the normal range (8.3 to 10.6 mg/dL); and
- Independence from active vitamin D (i.e., all daily standing dose of active vitamin D equal to zero on the day prior to the Week 52 visit); and

- Independence from therapeutic doses of calcium (i.e., average daily standing dose of elemental calcium ≤ 600 mg on the day prior to the Week 52 visit)

Data were available for 78 subjects (59 subjects receiving palopegteriparatide from study start (TransCon PTH/TransCon PTH] and 19 subjects receiving placebo followed by palopegteriparatide [Placebo/TransCon PTH] from Week 26) at Week 52.

Overall, 63 of 78 subjects (80.8%; 95% CI: 70.3%, 88.8%) treated with palopegteriparatide met the criteria for the primary composite endpoint and were considered responders to treatment at Week 52, including 48 of 59 subjects in the TransCon PTH/TransCon PTH group (81.4%; 95% CI: 69.1%, 90.3%) and 15 of 19 subjects in the Placebo/TransCon PTH group (78.9%, 95% CI: 54.4%, 93.9%).

Table 25. Primary Efficacy Analysis - OLE (ITT Population) Week 52 Primary Endpoint

ITT Population

	TransCon PTH /TransCon PTH (N=61)	Placebo /TransCon PTH (N=21)	Total TransCon PTH (N=82)
Number of Subjects Who Have Data on All Criteria at Week 52	59	19	78
Number of Subjects Meeting Week 52 Primary Endpoint Criteria (responders)	48	15	63
Proportion (95% CI)[1]	81.4 (69.1, 90.3)	78.9 (54.4, 93.9)	80.8 (70.3, 88.8)
Number of Subjects Meeting Each Component:			
Albumin-adjusted sCa within the normal range (8.3-10.6 mg/dL)	50	17	67
Independence from active vitamin D	59	19	78
Independence from therapeutic doses of calcium	57	17	74

Abbreviations: CI, confidence intervals; ITT, Intent-to-Treat; sCa, serum calcium; TransCon PTH, palopegteriparatide.

a The percentages were calculated based on ITT subjects who had data on all criteria. Independence from active vitamin D refers to standing dose of active vitamin D equal to zero on the day prior to the Week 52 visit; Independence from therapeutic doses of calcium refers to standing dose of elemental calcium ≤ 600 mg on the day prior to the Week 52 visit.

Summary of Sensitivity Efficacy Analyses:

Restricting the population analysed to the Completer Population (subjects in the ITT population who completed 26 weeks of blinded study treatment and had data on all components for the primary endpoint (Sensitivity Analysis 1); modifying the requirement for average daily standing dose of elemental calcium ≤600 mg to not taking any (Sensitivity Analysis 2); using the 2-sided Cochran-Mantel-Haenszel controlling for gender (Sensitivity Analysis 3); extending the serum calcium range criterion and changing calcium and vitamin D criteria to ≥50% reduction relative to baseline (Sensitivity Analysis 4); most importantly, excluding the use of PRN (Sensitivity Analysis 5) as well as excluding the use of PRN together with defining as non-responders subjects with any missing active vitamin D or calcium data (Sensitivity Analysis 6); and finally repeating the primary analysis extending the serum calcium range to 7.5 to 10.6 mg/dL (Sensitivity Analysis 7) had very little impact on the proportion of responders, which remained well above 70% of palopegteriparatide subjects and significantly greater than in placebo subjects.

Subgroup Analyses of the Primary Endpoint:

The following table presents subgroup analysis of the primary endpoint:

Table 26. Primary Endpoint Subgroup Analysis: Proportion of Responders at Week 26 – Blinded Period (ITT Population)

	TransCon PTH n/N Proportion (95% CI)	Placebo n/N Proportion (95% CI)	p-value[a]
Number of Subjects Meeting the Primary Endpoint Criteria at Week 26			
Overall	48/61 78.7 (66.3, 88.1)	1/21 4.8 (0.1, 23.8)	<0.0001
Age			
<50 Years Old	23/28 82.1 (63.1, 93.9)	1/14 7.1 (0.2, 33.9)	<0.0001
≥50 Years Old	25/33 75.8 (57.7, 88.9)	0/7 0.0 (0.0, 41.0)	0.0003
Gender			
Female	39/46 84.8 (71.1, 93.7)	1/18 5.6 (0.1, 27.3)	<0.0001
Male	9/15 60.0 (32.3, 83.7)	0/3 0.0 (0.0, 70.8)	0.2059
Etiology of hypoparathyroidism			
Post-surgical	42/52 80.8 (67.5, 90.4)	1/18 5.6 (0.1, 27.3)	<0.0001
Other (auto-immune, idiopathic, and genetic)	6/9 66.7 (29.9, 92.5)	0/3 0.0 (0.0, 70.8)	0.1818
Duration of hypoparathyroidism			
<5 Years	13/22 59.1 (36.4, 79.3)	0/2 0.0 (0.0, 84.2)	0.1993
≥5 and <10 Years	10/11 90.9 (58.7, 99.8)	1/10 10.0 (0.3, 44.5)	0.0003
≥10 and <20 Years	17/18 94.4 (72.7, 99.9)	0/6 0.0 (0.0, 45.9)	<0.0001
≥20 Years	8/10 80.0 (44.4, 97.5)	0/3 0.0 (0.0, 70.8)	0.0350
Region			
North America region	31/39 79.5 (63.5, 90.7)	0/12 0.0 (0.0, 26.5)	<0.0001
Other than North America region	17/22 77.3 (54.6, 92.2)	1/9 11.1 (0.3, 48.2)	0.0012
Menopausal status (female subjects)			
Premenopausal Status	24/27 88.9 (70.8, 97.6)	1/15 6.7 (0.2, 31.9)	<0.0001
Postmenopausal Status	15/19 78.9 (54.4, 93.9)	0/3 0.0 (0.0, 70.8)	0.0227

Abbreviations: CI: confidence interval; ITT: intent to treat; TransCon PTH: palopegteriparatide.
a The Fisher's exact test is used to compare the primary endpoint response rates between TransCon PTH group and placebo group.
Subjects with missing data on one or more of the criteria are considered as non-responders.

Secondary Efficacy Endpoints Results:

Analysis of the Key Secondary Endpoint:

Key secondary endpoints included the change from baseline at 26 weeks of treatment for the following parameters:

- HPES - Symptom - Physical domain score
- HPES - Symptom - Cognitive domain score
- HPES - Impact – Physical Functioning domain score
- HPES - Impact – Daily Life domain score
- 36-Item Short Form Survey (SF-36) - Physical Functioning subscale score

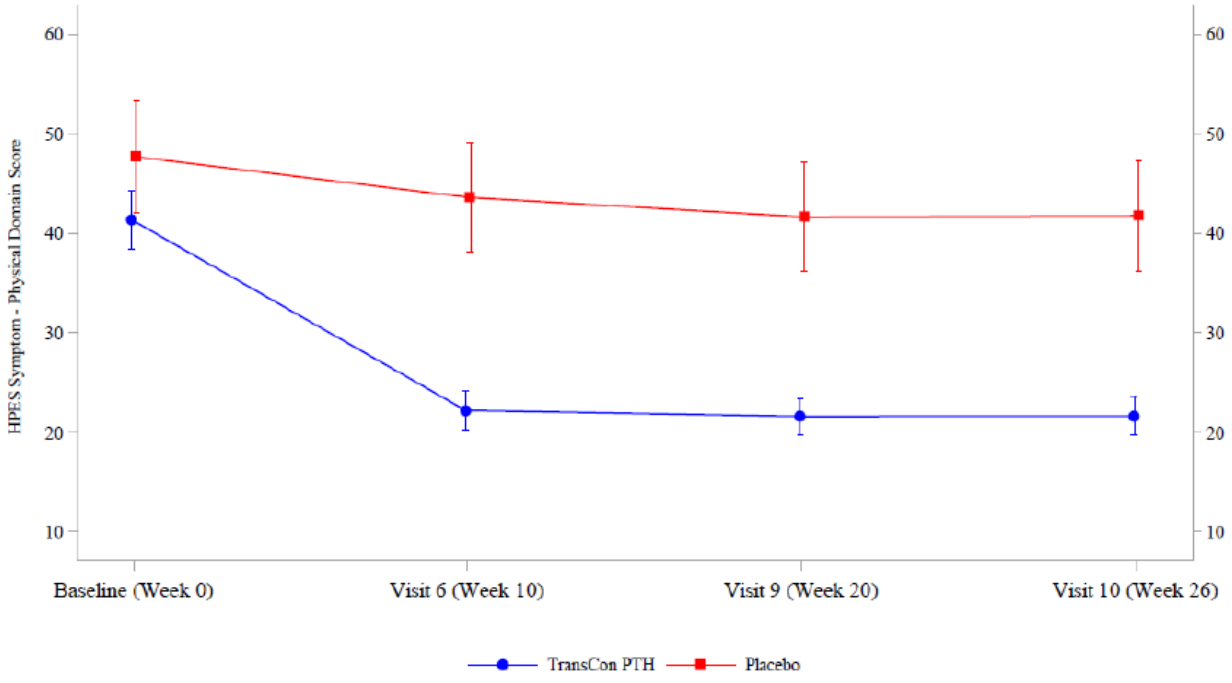
The primary and the five key secondary endpoints were alpha-controlled and tested sequentially in the pre-specified order above to control the overall significance level at 0.05.

Hypoparathyroidism Patient Experience Scale Symptom – Physical Domain Score

As illustrated in the figure below, baseline HPES - Symptom physical domain scores were comparable across treatment groups at baseline. HPES - Symptom physical score improved in palopegteriparatide-treated subjects as early as Week 10, while it remained unchanged in placebo subjects.

By Week 26, the LS mean change from baseline was -21.01 (95% CI: -25.41, -16.60) in palopegteriparatide-treated subjects versus -4.81 (95% CI: -15.22, 5.59) in placebo subjects.

Figure 24. Hypoparathyroidism Patient Experience Scale - Symptom – Physical Domain Score (Mean ±SE) by Visit - Blinded Period (ITT Population)

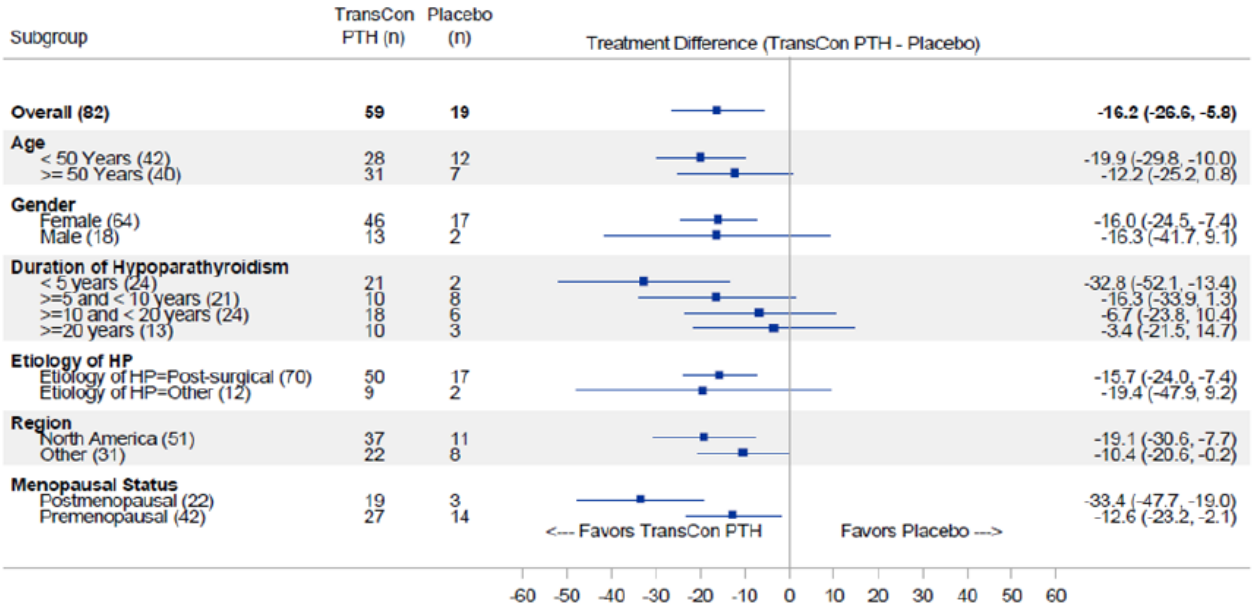


Abbreviations: ITT: intent to treat; SE: standard error; TransCon PTH: palopegteriparatide.

The LS mean difference between treatment groups was -16.20 (95% CI: -26.61, -5.79) in favor of palopegteriparatide according to the ANCOVA model without data imputation (see table in the CSR). This difference was statistically significant (p = 0.0038).
The ANCOVA model that used data imputation (see table in the CSR) generated consistent results, with a LS mean difference of -16.38 (95% CI: -26.53, -6.24; nominal p =0.0016).

A summary of the results of the analysis of the HPES - Symptoms – physical domain score by subgroups is illustrated in the figure below:

Figure 25. Forest Plot of Hypoparathyroidism Patient Experience Scale - Symptom – Physical Domain Score Subgroup Analysis – Blinded Period (ITT Population)



Abbreviations: ITT: intent to treat; TransCon PTH: palopegteriparatide.
n is the number of subjects with both baseline and Week 26 data. The treatment differences were estimated from non-imputed data.

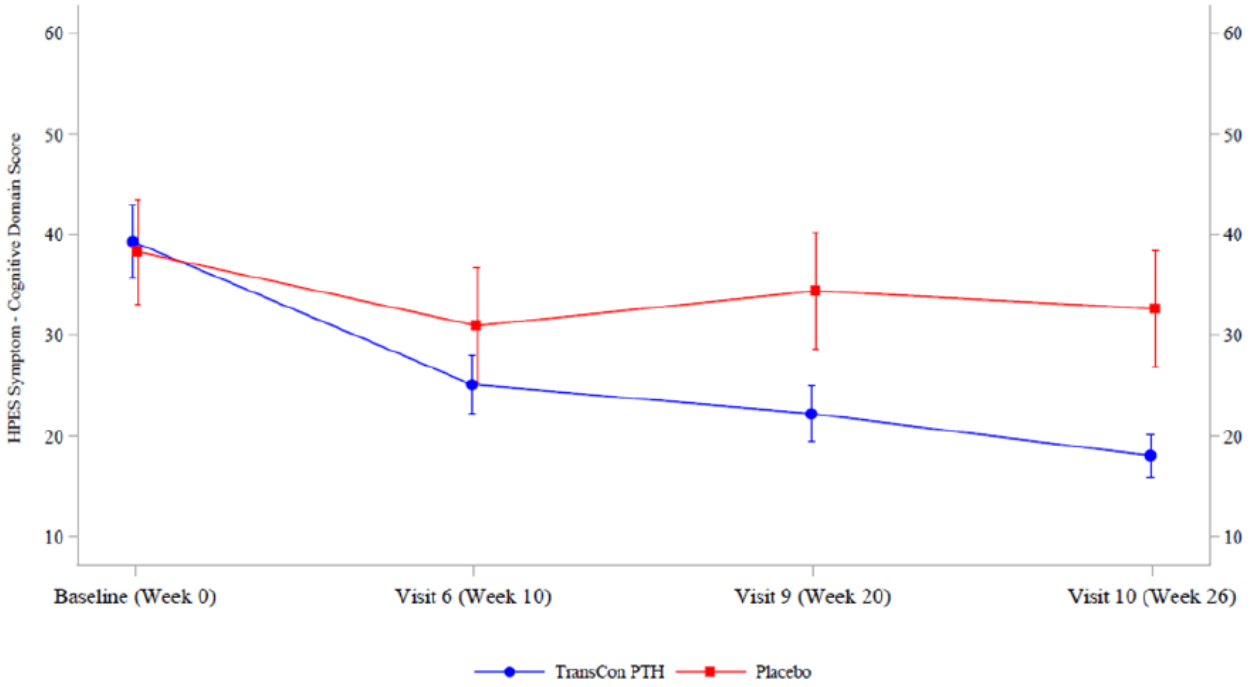
Hypoparathyroidism Patient Experience Scale - Symptom – Cognitive Domain Score

As illustrated in the figure below, baseline HPES - Symptom cognitive domain scores were comparable across treatment groups at baseline. HPES - Symptom cognitive domain score improved in

palopegteriparatide-treated subjects as early as Week 10, while it remained more or less unchanged in placebo subjects.

By week 26, the LS mean change from baseline was -20.49 (95% CI: -25.67, -15.31) in palopegteriparatide-treated subjects versus -6.16 (95% CI: -15.92, 3.60) in placebo subjects.

Figure 26. Hypoparathyroidism Patient Experience Scale - Symptom – Cognitive Domain Score (Mean ±SE) by Visit – Blinded Period (ITT Population)

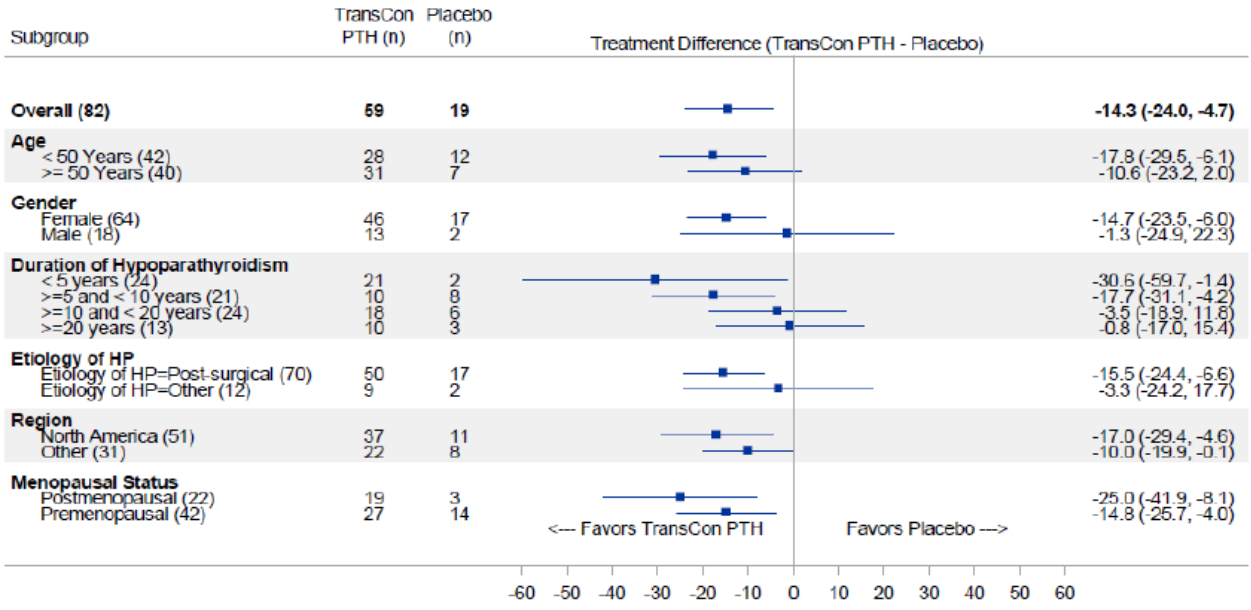


Abbreviations: ITT: intent to treat; SE: standard error; TransCon PTH: palopegteriparatide.

The LS mean difference between treatment groups was -14.33 (95% CI: -24.00, -4.66) in favour of palopegteriparatide according to the ANCOVA model without data imputation (see table in the CSR). This difference was statistically significant (p = 0.0055).
The ANCOVA model that used data imputation (see table in the CSR) generated consistent results, with a LS mean difference of -13.49 (95% CI: -22.51, -4.47; nominal p = 0.0034).

A summary of the results of the analysis of the HPES - Symptoms – cognitive domain score by subgroups is illustrated in the figure below:

Figure 27. Forest Plot of Hypoparathyroidism Patient Experience Scale - Symptom – Cognitive Domain Score Subgroup Analysis – Blinded Period (ITT Population)

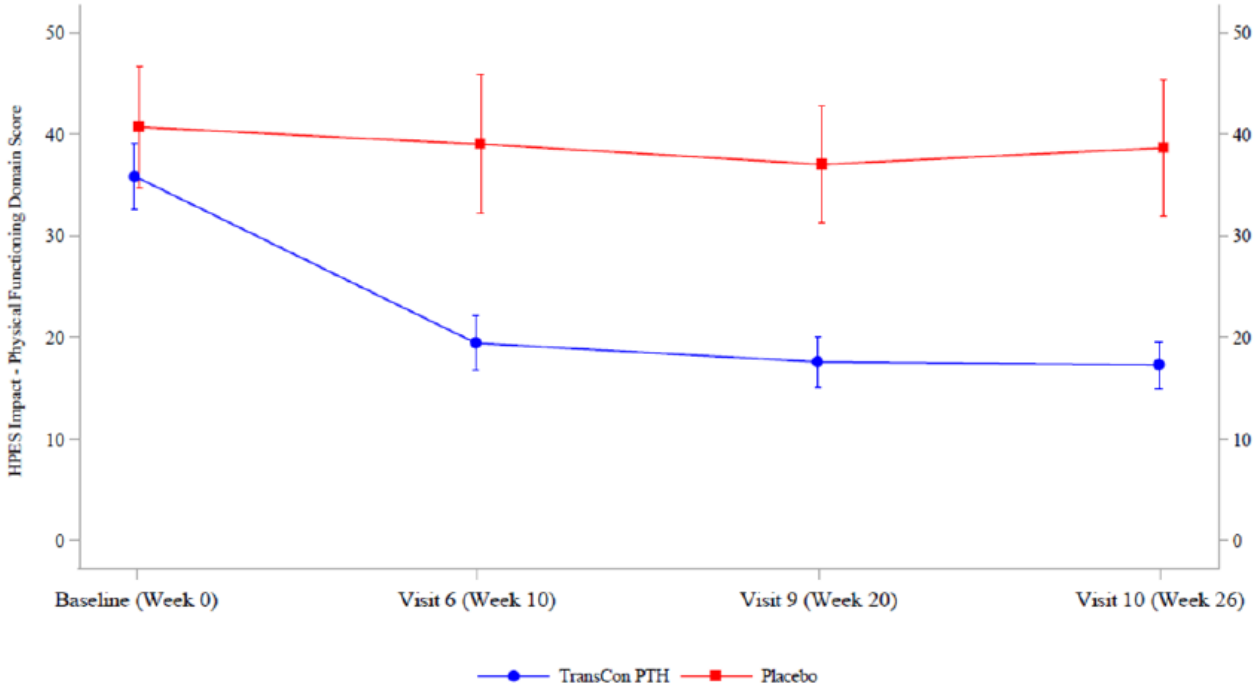


Abbreviations: ITT: intent to treat; TransCon PTH: palopegteriparatide.
n is the number of subjects with both baseline and Week 26 data. The treatment differences were estimated from non-imputed data.

Hypoparathyroidism Patient Experience Scale - Impact – Physical Functioning Domain Score

As illustrated in the figure below, baseline HPES- Impact physical functioning domain scores were comparable across treatment groups at baseline. HPES- Impact physical functioning domain score improved in palopegteriparatide-treated subjects as early as Week 10, while it remained unchanged in placebo subjects. By Week 26, the LS mean change from baseline was -18.29 (95% CI: -23.59, -12.99) in palopegteriparatide-treated subjects versus -1.01 (95% CI: -12.40, 10.38) in placebo subjects.

Figure 28. Hypoparathyroidism Patient Experience Scale - Impact – Physical Functioning Domain Score (Mean ±SE) by Visit – Blinded Period (ITT Population)

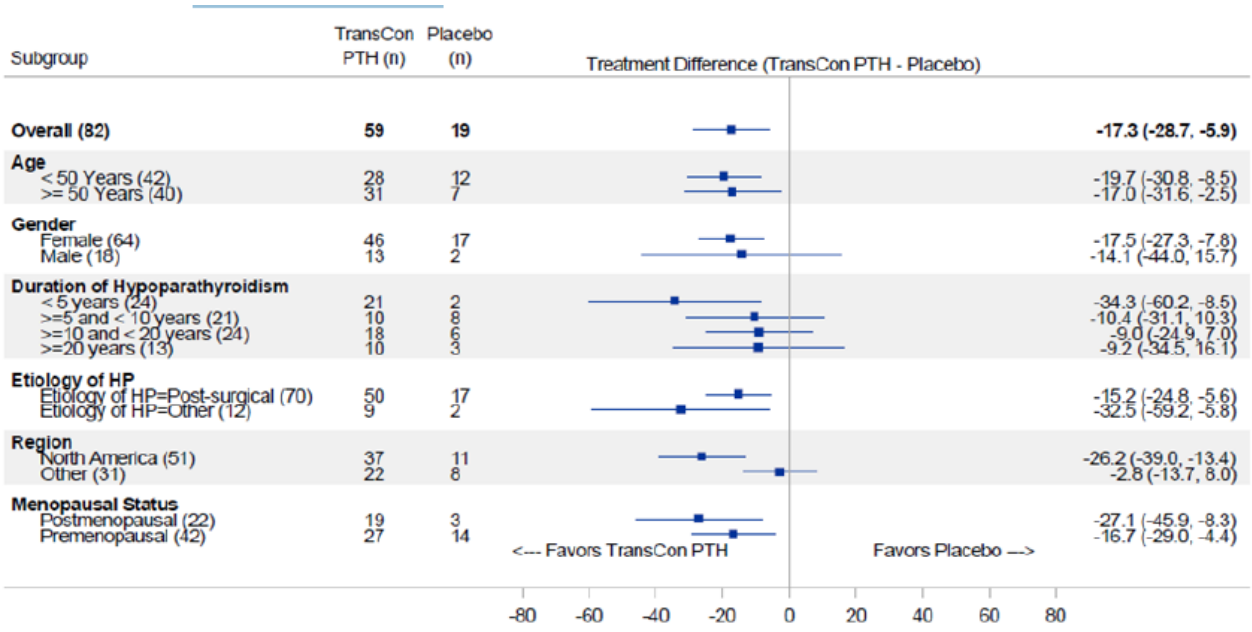


Abbreviations: ITT: intent to treat; SE: standard error; TransCon PTH: palopegteriparatide.

The LS mean difference between treatment groups was -17.3 (95% CI: -28.66, -5.89) in favor of palopegteriparatide according to the ANCOVA model without data imputation (see table in the CSR). This difference was statistically significant (p = 0.0046). The ANCOVA model that used data imputation (see table in the CSR) generated similar results, with a LS mean difference of -16.6 (95% CI: -27.50, -5.76; nominal p =0.0027).

A summary of the results of the analysis of the HPES - Impact – physical functioning domain score by subgroups is illustrated in the figure below:

Figure 29. Forest Plot of Hypoparathyroidism Patient Experience Scale - Impact – Physical Functioning Domain Score Subgroup Analysis – Blinded Period (ITT Population)



Abbreviations: ITT: intent to treat; TransCon PTH: palopegteriparatide.
n is the number of subjects with both baseline and Week 26 data. The treatment differences were estimated from non-imputed data.

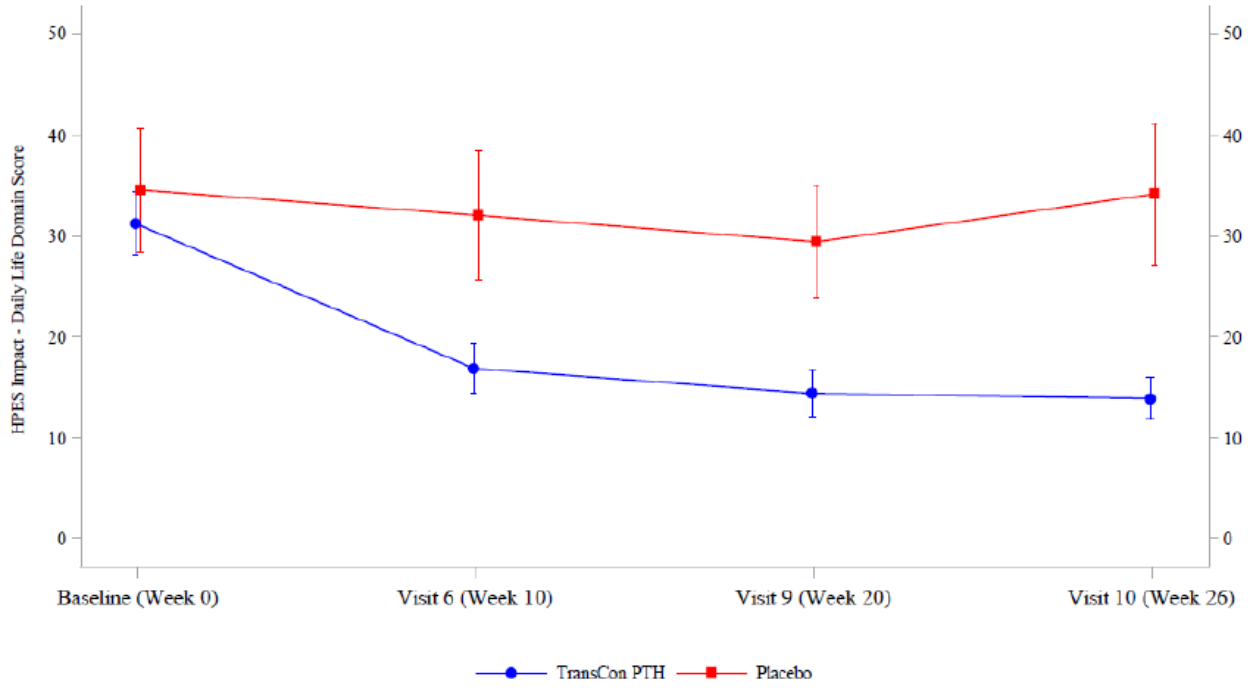
Hypoparathyroidism Patient Experience Scale - Impact – Daily Life Domain Score

As illustrated in the figure below, baseline HPES - Impact daily life domain scores were comparable across treatment groups at baseline. HPES - Impact daily life domain score improved in

palopegteriparatide-treated subjects as early as Week 10, while it remained unchanged in placebo subjects.

By Week 26, the LS mean change from baseline was -17.65 (95% CI: -22.39, -12.91) in palopegteriparatide-treated subjects versus -0.36 (95% CI: -12.19, 11.46) in placebo subjects.

Figure 30. Hypoparathyroidism Patient Experience Scale - Impact – Daily Life Domain Score (Mean ±SE) by Visit – Blinded Period (ITT Population)

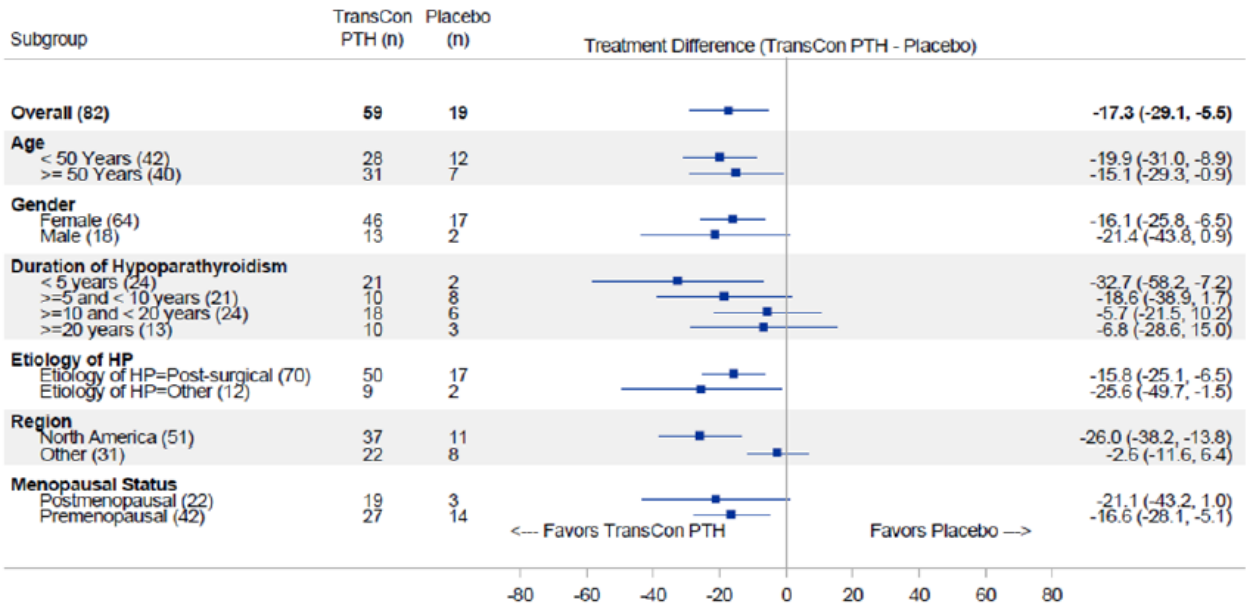


Abbreviations: ITT: intent to treat; SE: standard error; TransCon PTH: palopegteriparatide.

The LS mean difference between treatment groups was -17.29 (95% CI: -29.08, -5.49) in favor of palopegteriparatide according to the ANCOVA model without data imputation (see table in the CSR). This difference was statistically significant (p = 0.0061). The ANCOVA model that used data imputation (see table in the CSR) generated similar results, with a LS mean difference of -16.80 (95% CI: -27.92, -5.67; nominal p =0.0031).

A summary of the results of the analysis of the HPES - Impact – daily life domain score by subgroups is illustrated in the figure below:

Figure 31. Forest Plot of Hypoparathyroidism Patient Experience Scale - Impact – Daily Life Domain Score Subgroup Analysis – Blinded Period (ITT Population)



Abbreviations: ITT: intent to treat; TransCon PTH: palopegteriparatide.
n is the number of subjects with both baseline and Week 26 data. The treatment differences were estimated from non-imputed data.

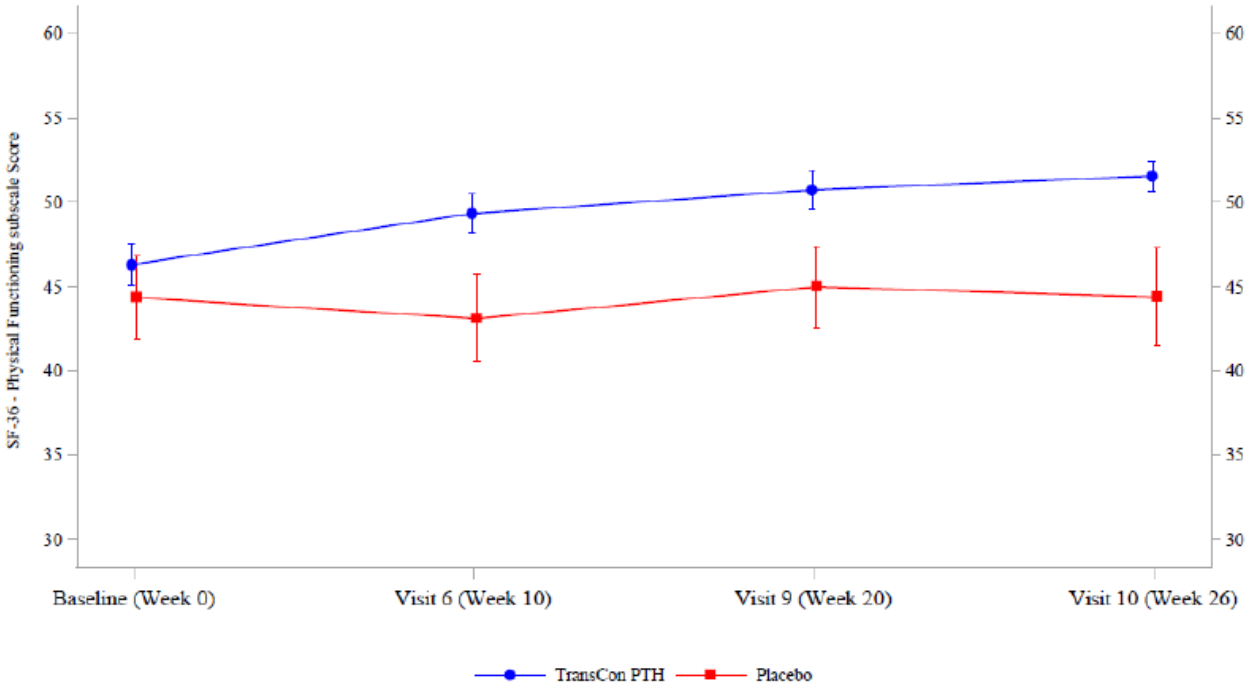
36-item Short Form Survey (SF-36) – Physical Functioning Subscale Score

As illustrated in the figure below, baseline SF-36 physical functioning subscale scores were comparable across treatment groups at baseline. SF-36 physical functioning subscale score improved in

palopegteriparatide-treated subjects as early as Week 10, while it remained unchanged in placebo subjects.

By Week 26, the LS mean change relative to baseline was 5.29 (95% CI: 3.47, 7.10) in palopegteriparatide-treated subjects and 0.12 (95% CI: -4.64, 4.89) in placebo subjects.

Figure 32. 36-item Short Form Survey (SF-36) – Physical Functioning Subscale Score (Mean ±SE) by Visit – Blinded Period (ITT Population)

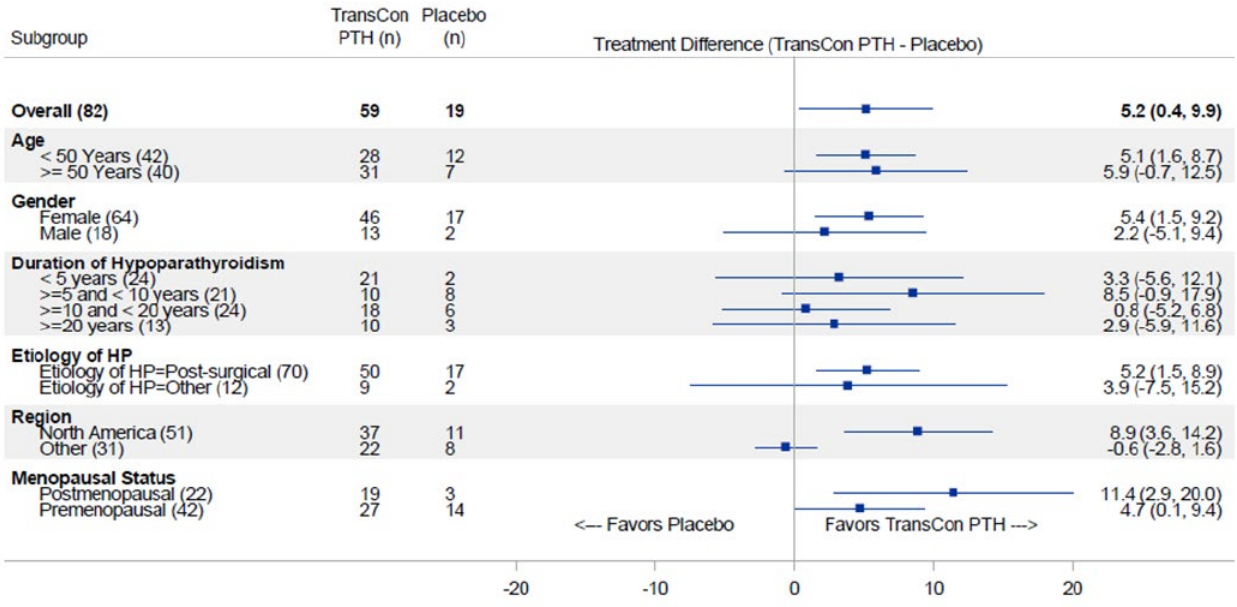


Abbreviations: ITT: intent to treat; SE: standard error; TransCon PTH: palopegteriparatide.

The LS Mean difference between treatment groups was 5.16 (95% CI: 0.41, 9.92) in favour of palopegteriparatide (see table in the CSR). This difference was statistically significant (p = 0.0347). The ANCOVA model that used data imputation generated similar results (see table in the CSR), with a LS Mean difference of 4.779 (95% CI: 0.184, 9.375; nominal p = 0.0415).

A summary of the results of the analysis of the 36-item Short Form Survey (SF-36) – Physical Functioning

Figure 33. Forest Plot of 36-item Short Form Survey (SF-36) – Physical Functioning Subscale Score Subgroup Analysis – Blinded Period (ITT Population)



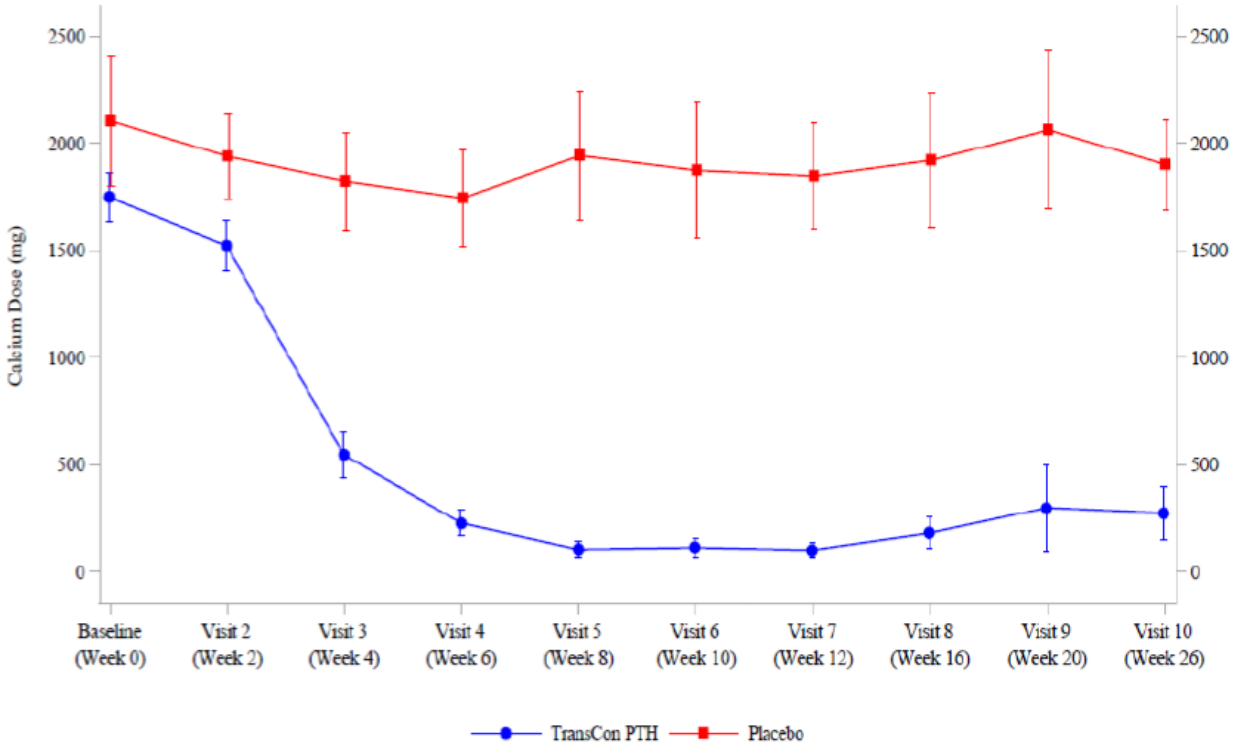
Abbreviations: ITT: intent to treat; TransCon PTH: palopegteriparatide.
n is the number of subjects with both baseline and Week 26 data. The treatment differences were estimated from non-imputed data.

Analysis of the Other Secondary Endpoint:

Calcium dose

Mean (± SE) calcium dose during the study (from baseline through Week 26) by treatment group is illustrated in the figure below:

Figure 34. Calcium Dose (Mean ± SE) by Visit – Blinded Period (ITT Population)



Abbreviations: ITT: intent to treat; SE: standard error; TransCon PTH: palopegteriparatide.

Change in Calcium (mg) Dose at Week 26 by treatment group is illustrated in the table below:

Table 27. Disposition of Patients (Blinded Period and Open-Label Extension (All Subjects)

Visit Statistics	TransCon PTH (N=61)	Placebo (N=21)
Baseline		
n	61	21
Mean	1748.03	2104.76
SD, SE	903.880, 115.730	1382.471, 301.680
Median	1625.00	1800.00
Min, Max	600.0, 5000.0	800.0, 7200.0
Observed Value at Week 26		
n	60	19
Mean	274.17	1847.39
SD, SE	1371.756, 177.093	1325.823, 304.165
Median	0.00	1750.00
Min, Max	0.0, 10500.0	0.0, 6000.0
Change From Baseline (ANCOVA)		
n	60	19
LS Mean (SE)	-1176.93 (218.227)	324.37 (359.490)
95% CI for LS Mean	(-1612.70, -741.16)	(-415.47, 1064.21)
Difference in LS Means (SE)	-1501.30 (359.401)	
95% CI for Difference in LS Means	(-2237.90, -764.69)	
P-value (PTH vs Placebo)	0.0003	

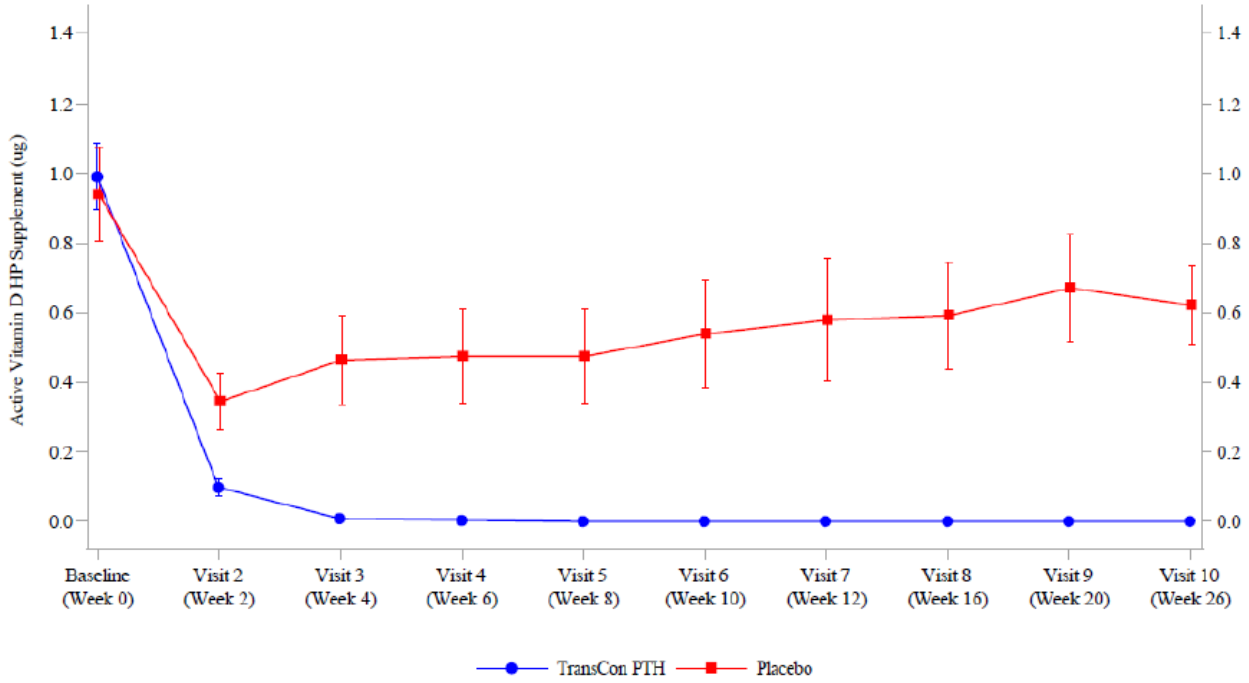
Abbreviations: ANCOVA: analysis of covariance; CI: confidence interval; ITT: intent to treat; LS: least square; Max: maximum; Min: minimum; SD: standard deviation; SE: standard error; TransCon PTH: palopegteriparatide.
At each post-baseline visit, only data from subjects with both baseline and the corresponding visit values available were used to compute the statistical summaries. The ANCOVA model with unequal variance included the change from baseline as the response variable, treatment and etiology of hypoparathyroidism as fixed effects and baseline value of the parameter as a covariate.

At week 52, 74 (94.8%) of subjects were independent from therapeutic doses of calcium.

Active Vitamin D Dose

Mean (± SE) active vitamin D dose during the study (from baseline through Week 26) by treatment group is illustrated in the figure below:

Figure 35. Active Vitamin D Dose (Mean ± SE) by Visit – Blinded Period (ITT Population)



Abbreviations: ITT: intent to treat; SE: standard error; TransCon PTH: palopegteriparatide.

Baseline active vitamin D was a numerical aggregate of 2 different supplements regardless of their potency (i.e., calcitriol and alfacalcidol doses were counted equally).

Change in Active Vitamin D (µg) Dose at Week 26 by treatment group is illustrated in the table below:

Table 28. Change in Active Vitamin D (µg) Dose at Week 26 – Blinded Period (ITT Population)

Visit Statistics	TransCon PTH (N=61)	Placebo (N=21)
Baseline		
n	61	21
Mean	0.992	0.940
SD, SE	0.7373, 0.0944	0.6220, 0.1357
Median	0.750	0.750
Min, Max	0.50, 4.00	0.50, 2.50
Observed Value at Week 26		
n	60	19
Mean	0.000	0.618
SD, SE	0.0000, 0.0000	0.7330, 0.1682
Median	0.000	0.500
Min, Max	0.00, 0.00	0.00, 2.50
Change From Baseline (ANCOVA)		
n	60	19
LS Mean (SE)	-0.993 (0.0599)	-0.373 (0.0915)
95% CI for LS Mean	(-1.112, -0.873)	(-0.555, -0.190)
Difference in LS Means (SE)	-0.620 (0.0917)	
95% CI for Difference in LS Means	(-0.803, -0.437)	
P-value (PTH vs Placebo)	<0.0001	

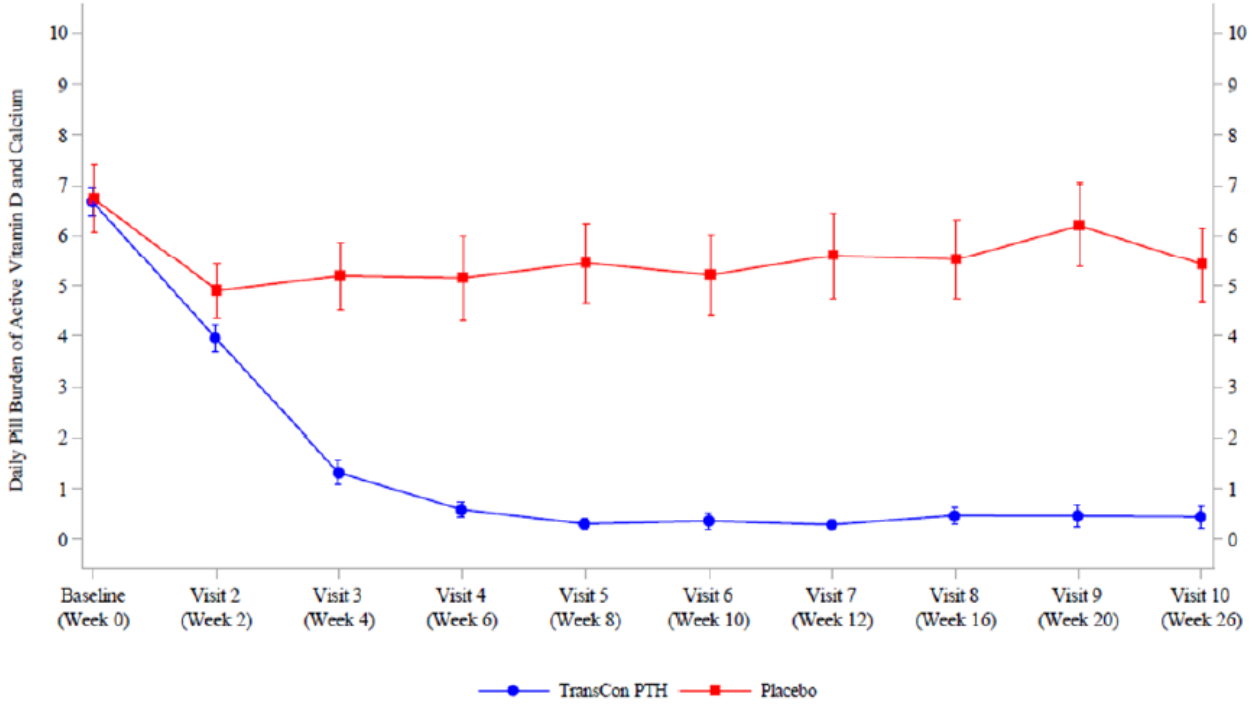
Abbreviations: ANCOVA: analysis of covariance; CI: confidence interval; ITT: intent to treat; LS: least square; Max: maximum; Min: minimum; SD: standard deviation; SE: standard error; TransCon PTH: palopegteriparatide.
At each post-baseline visit, only data from subjects with both baseline and the corresponding visit values available were used to compute the statistical summaries. The ANCOVA model with unequal variance included the change from baseline as the response variable, treatment and etiology of hypoparathyroidism as fixed effects and baseline value of the parameter as a covariate.

At week 52, 78 (100%) of subjects were independent from active vitamin D.

Daily Pill Burden

Pill burden was defined as the total daily amount of active vitamin D and calcium (as oral tablets, powder, liquid solutions, liquid suspensions, or transdermal patches) taken by the subject. The mean total daily pill burden by treatment group is illustrated in the figure below:

Figure 36. (Conventional Therapy) (Mean ± SE) by Visit – Blinded Period (ITT Population)



Abbreviations: ITT: intent to treat; SE: standard error; TransCon PTH: palopegteriparatide.

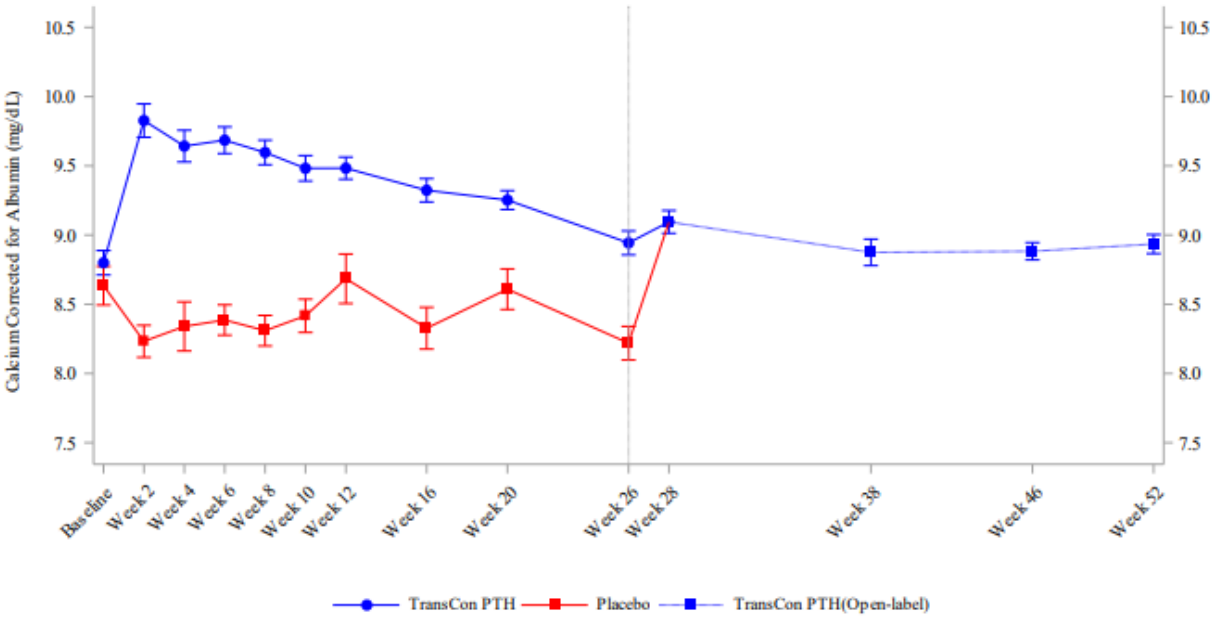
The daily pill burden at baseline was comparable across treatment groups, with a median of 6.0 in both treatment groups, ranging from 2.0 to 12.0 in palopegteriparatide-treated subjects and from 2.0 to 14.0 in placebo subjects.
The daily pill burden decreased sharply in palopegteriparatide-treated subjects from baseline onward. By Week 26, the daily pill burden had decreased by (LS mean change from baseline) -5.61 (95% CI: -6.18, -5.04).
In placebo subjects, the daily bill burden initially decreased significantly (LS mean change from baseline at Week 2 of -1.98 [95% CI: -2.97, -0.99]), but had returned to within baseline level by Week 8 (LS mean change from baseline of -1.35 [95% CI: -2.97, 0.27]).

Serum Calcium (Albumin adjusted)

The normal range defined for albumin-adjusted serum calcium during the blinded period was 8.3 to 10.6 mg/dL (2.07 to 2.64 mmol/L).

Mean (± SE) serum calcium levels at each visit are illustrated in the figure below:

Figure 37. Serum Calcium (Mean ± SE) by Visit – Blinded and OLE Period (ITT Population)



Abbreviations: ITT: intent to treat; SE: standard error; TransCon PTH: palopegteriparatide.

Change in Serum Calcium (mg/dL) at Week 26 by treatment group is illustrated in the table below:

Table 29. Change in Serum Calcium (mg/dL) at Week 26 – Blinded Period (ITT Population)

Visit Statistics	TransCon PTH (N=61)	Placebo (N=21)
Baseline		
n	61	21
Mean	8.800	8.634
SD, SE	0.6888, 0.0882	0.6392, 0.1395
Median	8.760	8.480
Min, Max	7.00, 10.90	7.70, 10.40
Observed Value at Week 26		
n	60	21
Mean	8.943	8.219
SD, SE	0.6701, 0.0865	0.5288, 0.1213
Median	8.980	8.400
Min, Max	6.80, 10.40	7.16, 8.80
Change From Baseline (ANCOVA)		
n	60	19
LS Mean (SE)	0.306 (0.1128)	-0.387 (0.1436)
95% CI for LS Mean	(0.081, 0.531)	(-0.681, -0.094)
Difference in LS Means (SE)	0.693 (0.1459)	
95% CI for Difference in LS Means	(0.398, 0.988)	
P-value (PTH vs Placebo)	<0.0001	

Abbreviations: ANCOVA: analysis of covariance; CI: confidence interval; ITT: intent to treat; LS: least square; Max: maximum; Min: minimum; SD: standard deviation; SE: standard error; TransCon PTH: palopegteriparatide.
At each post-baseline visit, only data from subjects with both baseline and the corresponding visit values available were used to compute the statistical summaries. The ANCOVA model with unequal variance included the change from baseline as the response variable, treatment and etiology of hypoparathyroidism as fixed effects and baseline value of the parameter as a covariate.

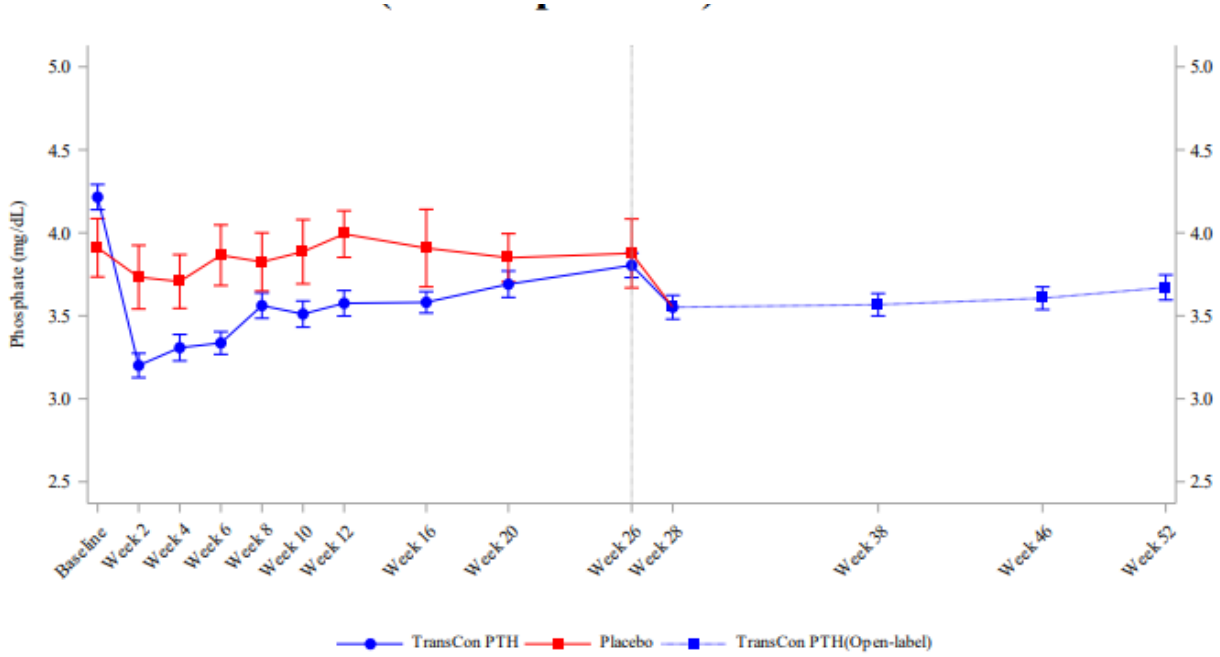
As discussed in the CSR, while remaining within normal range, fluctuations (increases) in serum calcium were initially observed in palopegteriparatide-treated subjects. Fluctuations (decreases) were also observed in placebo subjects, falling below normal range at Week 2 (mean observed value: 8.23 mg/dL) and at Week 26 (mean observed value: 8.22 mg/dL). These changes were explained to be reflective of (or be artefacts of) the trial's titration algorithm.

Mean serum calcium was within the normal range at week 52.

Serum Phosphate

Mean (± SE) serum phosphate levels at each visit are illustrated in the figure below:

Figure 38. Serum Phosphate (Mean ± SE) by Visit – Blinded Period and OLE (ITT Population)



Abbreviations: ITT: intent to treat; SE: standard error; TransCon PTH: palopegteriparatide.

Serum phosphate at baseline was in the normal range and comparable across treatment groups, with a median of 4.21 mg/dL (range: 2.60 to 6.60) in palopegteriparatide-treated subjects and 3.75 mg/dL (range: 2.79 to 5.40) in placebo subjects.

Serum phosphate initially decreased in palopegteriparatide-treated subjects. The change relative to baseline however lessened over time (LS mean change from baseline of -0.963 mg/dL (95% CI: -1.134, -0.792 at Week 2 [Table 14.2.3.5.2], and -0.351 mg/dL (95% CI: -0.521, -0.181) at Week 26 (see table below). These changes were generally small. In placebo subjects, serum phosphate remained more or less unchanged, with LS mean changes from baseline of -0.268 mg/dL (95% CI: -0.620, 0.083) at Week 2 and -0.125 mg/dl (95% CI: -0.469, 0.218) at Week 26.

Small differences were observed between treatment groups at some time points but not at Week 26 (LS mean difference between treatment groups: -0.226 mg/dL [95% CI: -0.568, 0.116; nominal p = 0.1861]).

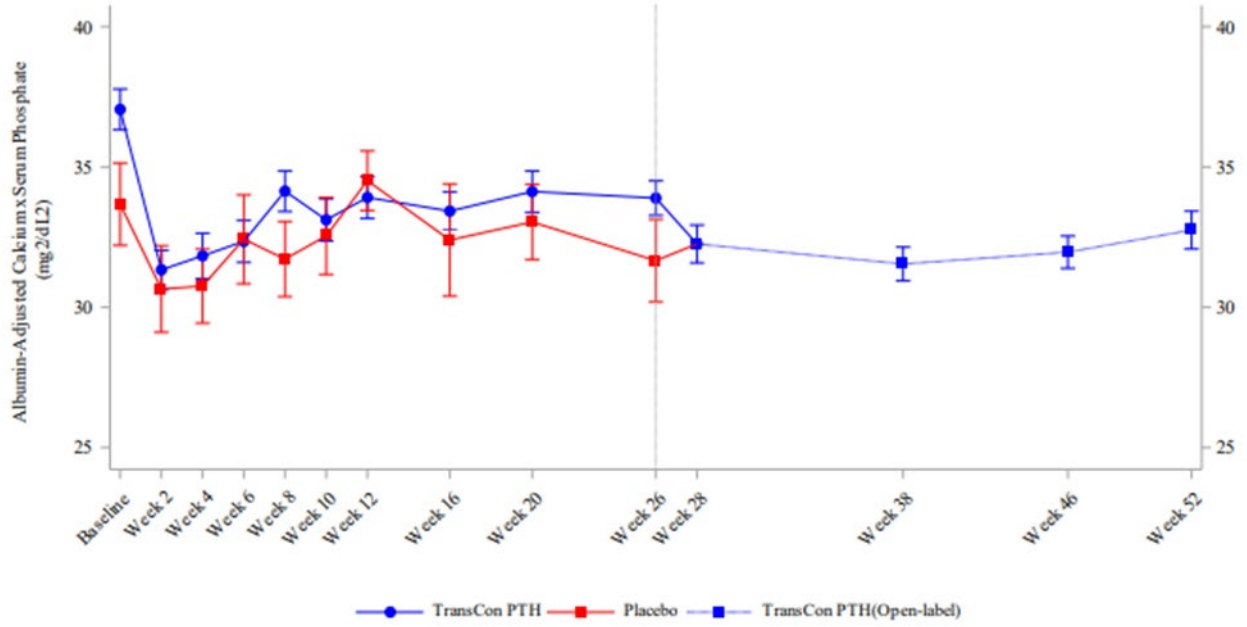
Mean serum phosphate was within the normal range at week 52.

(Albumin-adjusted) Serum Calcium-Phosphate Product

Guidelines for treatment of hypoparathyroidism recommend a goal of keeping the serum calcium×serum phosphate product below 55 mg^2/dL^2 (4.4 mg^2/dL^2) (Brandi 2016).

Mean (± SE) (± SE) serum calcium-phosphate product at each visit is illustrated in the figure below:

Figure 39. (Mean ± SE) by Visit – Blinded Period and OLE (ITT Population)



Abbreviations: ITT: intent to treat; SE: standard error; TransCon PTH: palopegteriparatide.
/

Serum calcium-phosphate product at baseline was within normal range and comparable across treatment groups, with a median of 37.47 mg^2/dL^2 (range: 25.50 to 62.00) in palopegteriparatide-treated subjects and 33.13 mg^2/dL^2 (range: 24.19 to 45.10) in placebo subjects.

The serum calcium-phosphate product initially decreased in both treatment groups. Changes relative to baseline however lessened over time, with a LS mean change from baseline of -4.80 mg^2/dL^2 (95% CI: -6.40, -3.20) at Week 2 and -1.84 mg^2/dL^2 (95% CI: -3.36, -0.31) at Week 26 in palopegteriparatide-treated subjects, and -3.74 mg^2/dL^2 (95% CI: -6.66, -0.82) at Week 2 and -2.77 (95% CI: -5.40, -0.14) at Week 26 in placebo subjects.

No significant treatment difference was observed.

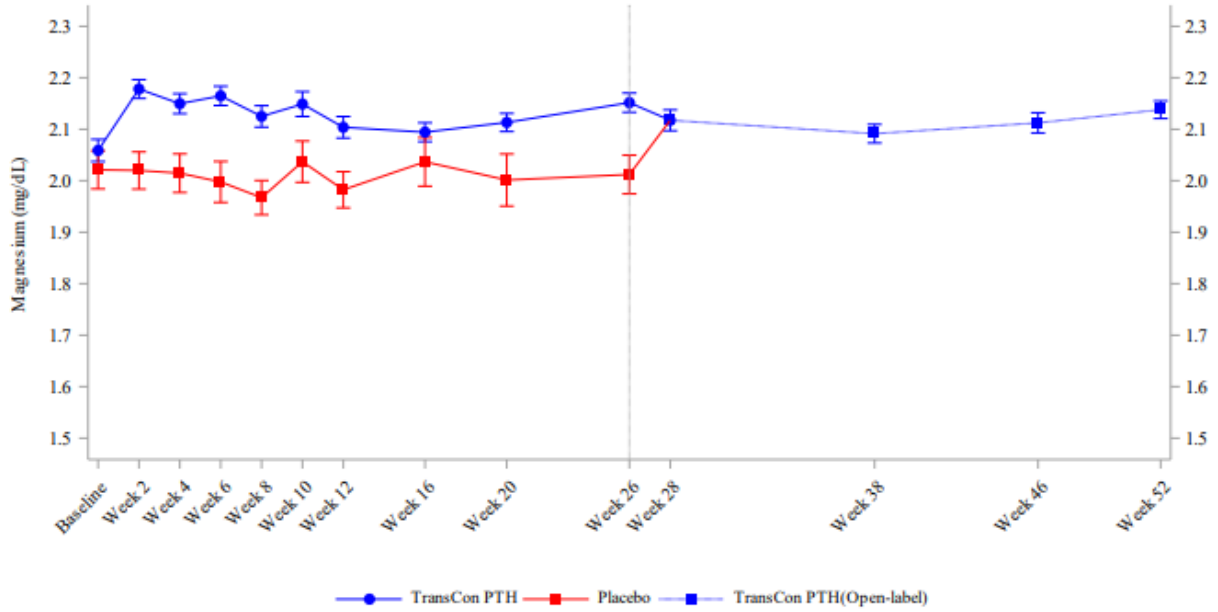
Serum calcium-phosphate product remained within the normal range at week 52 of the OLE period.

Serum Magnesium

The normal reference range for magnesium used in the trial was 1.6 mg/dL (0.62 mmol/L) to 2.4 mg/dL (0.99 mmol/L).

Mean (± SE) serum magnesium levels at each visit are illustrated in the figure below:

Figure 40. Serum Magnesium (Mean ± SE) by Visit – Blinded Period and OLE (ITT Population)



Abbreviations: ITT: intent to treat; SE: standard error; TransCon PTH: palopegteriparatide.

Serum magnesium at baseline was comparable across treatment groups, with a median of 2.09 mg/dL (range: 1.70 to 2.50) in palopegteriparatide-treated subjects and 2.00 mg/dL (range: 1.70 to 2.31) in placebo subjects.

Serum magnesium increased slightly in palopegteriparatide-treated subjects, with a LS mean change from baseline of 0.157 mg/dL (95% CI: 0.117, 0.197) at Week 2 and 0.111 mg/dL (95% CI: 0.066, 0.157) at Week 26.

In placebo subjects, serum magnesium levels remained more or less unchanged.

A small, but significant treatment difference was observed at most timepoints, with a LS mean treatment difference of 0.128 mg/dL (95% CI: 0.053, 0.203; nominal p = 0.0016) at Week 26.

Mean serum magnesium levels remained within the normal range at week 52 of the OLE period.

Skeletal Health

Bone Mineral Density

A summary of BMD by DXA across numerous regions (lumbar spine/L1, lumbar spine/L2, lumbar spine/L3, lumbar spine/L4, lumbar spine adjusted total, hip/femoral neck, hip/total, hip/trochanter, forearm/radius 1/3 distal, and forearm/radius ultra-distal) at baseline and at Week 26 and change from baseline at Week 26 including ANCOVA analysis results has been provided in the CSR. Observed BMD values in g/cm^2 were transformed to T-scores and corrected Z-scores.

See table stating the results for palopegteriparatide below (palopegteriparatide left, placebo right table):

Table 30. Mineral Density by Dual-Energy X-Ray Absorptiometry– Blinded Period (ITT Population)

Palopegteriparatide:

Location/Region Parameter (Mean)	Baseline[a]	Week 26 (Observed Value)	Change from Baseline to Week 26[b]	% Change from Baseline to Week 26
Lumbar Spine/Adjusted Total (Corrected Values)				
n	59	55	55	55
BMD (g/cm^2)	1.198	1.109	-0.097	-8.027
T-score	0.895	0.082	-0.854	-
Z-score	1.483	0.715	-0.829	-
Hip/Total (Corrected Values)				
n	60	56	56	56
BMD (g/cm^2)	1.042	0.977	-0.069	-6.638
T-score	0.413	-0.081	-0.538	-
Z-score	0.931	0.457	-0.520	-
Hip/Femoral Neck (Corrected Values)				
n	60	56	56	56
BMD (g/cm^2)	0.938	0.881	-0.066	-7.040
T-score	-0.014	-0.455	-0.501	-
Z-score	0.787	0.369	-0.479	-
Forearm/Radius 1/3 Distal (Corrected Values)				
n	60	56	56	56
BMD (g/cm^2)	0.763	0.765	-0.001	-0.071
T-score	-0.356	-0.343	-0.010	-
Z-score	0.305	0.304	0.018	-
Forearm/Radius Ultra-Distal (Corrected Values)				
n	60	56	56	56
BMD (g/cm^2)	0.446	0.442	-0.007	-1.603
T-score	-0.436	-0.491	-0.124	-
Z-score	0.092	0.035	-0.101	-

Placebo:

Location/Region Parameter (Mean)	Baseline[a]	Week 26 (Observed Value)	Change from Baseline to Week 26[b]	% Change from Baseline to Week 26
Lumbar Spine/Adjusted Total (Corrected Values)				
n	20	17	17	17
BMD (g/cm^2)	1.292	1.256	0.001	0.080
T-score	1.491	1.238	0.011	-
Z-score	1.997	1.831	0.040	-
Hip/Total (Corrected Values)				
n	20	17	17	17
BMD (g/cm^2)	1.086	1.063	0.000	0.061
T-score	0.754	0.622	0.003	-
Z-score	1.202	1.132	0.023	-
Hip/Femoral Neck (Corrected Values)				
n	20	17	17	17
BMD (g/cm^2)	1.004	0.979	0.012	1.360
T-score	0.322	0.220	0.095	-
Z-score	1.046	1.016	0.119	-
Forearm/Radius 1/3 Distal (Corrected Values)				
n	21	18	18	18
BMD (g/cm^2)	0.800	0.791	-0.003	-0.343
T-score	-0.006	-0.002	-0.034	-
Z-score	0.467	0.543	-0.009	-
Forearm/Radius Ultra-Distal (Corrected Values)				
n	21	18	18	18
BMD (g/cm^2)	0.465	0.456	0.001	0.300
T-score	0.002	-0.113	0.010	-
Z-score	0.366	0.310	0.032	-

Abbreviation: BMD = bone mineral density
a Statistical summaries are computed from all subjects with data at baseline.
b At post-baseline visit, only data from subjects with both baseline and the corresponding visit values available were used to compute the statistical summaries.

BMD Z-scores at baseline were high (as expected with PTH insufficiency) reflecting abnormal bone density above norms for age and sex (Bioclinica 2021). With palopegteriparatide treatment, Z-scores decreased toward age- and sex-matched norms (i.e., Z-score of 0.0). The largest incremental change of Z-score was achieved by Week 26. Observed values at Week 26 were still above age- and sex-matched reference ranges but trended towards normalization.

Trabecular Bone Score

A summary of Trabecular Bone Scores (TBS) by DXA at baseline and at Week 26 and change from baseline at Week 26 including ANCOVA are provided in the table below:

Table 31. Change in Trabecular Bone Score by Dual-Energy X-Ray Absorptiometry at Week 26 – Blinded Period (ITT Population)

Visit Statistics	TransCon PTH (N=61)	Placebo (N=21)
Lumbar Spine/Adjusted Total		
Baseline		
n	59	20
Mean	1.394	1.396
SD, SE	0.1326, 0.0173	0.1331, 0.0298
Median	1.414	1.408
Min, Max	0.97, 1.69	1.13, 1.58
Observed Value		
n	55	17
Mean	1.356	1.362
SD, SE	0.1351, 0.0182	0.1438, 0.0349
Median	1.368	1.366
Min, Max	1.08, 1.59	1.18, 1.60
Change from Baseline (ANCOVA)		
n	55	17
LS Mean (SE)	-0.048 (0.0112)	-0.032 (0.0170)
95% CI for LS Mean	(-0.071, -0.026)	(-0.066, 0.002)
Difference in LS Means (SE)	-0.016 (0.0168)	
95% CI for Difference in LS Means	(-0.050, 0.017)	
P-value (PTH vs Placebo)	0.3304	

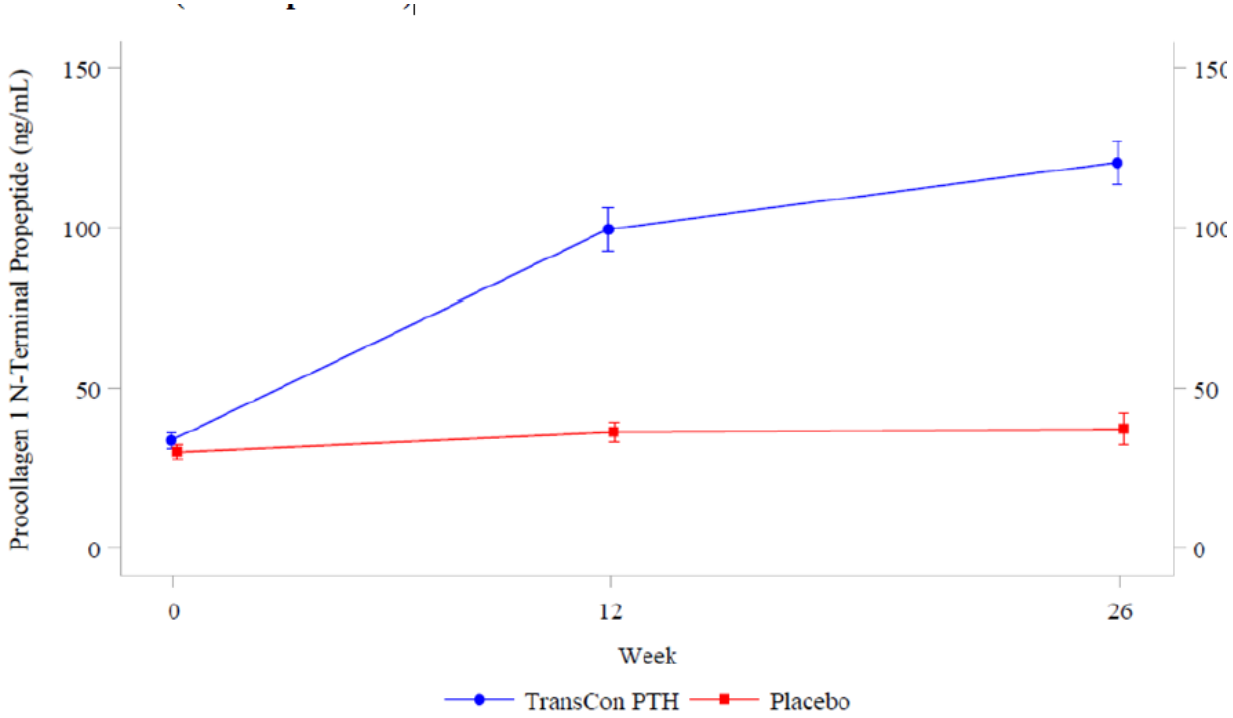
Abbreviations: ANCOVA: analysis of covariance; CI: confidence interval; ITT: intent to treat; LS: least square; Max: maximum; Min: minimum; SD: standard deviation; SE: standard error; TBS = trabecular bone score; TransCon PTH: palopegteriparatide.
At post-baseline visit, only data from subjects with both baseline and the corresponding visit values available were used to compute the statistical summaries. The ANCOVA model with unequal variance included the change from baseline as the response variable, treatment and etiology of hypoparathyroidism as fixed effects and baseline value of the parameter as a covariate.

There was a slight decrease in TBS in both treatment groups for adjusted total of lumbar spine.

The decrease was however slightly more pronounced in palopegteriparatide-treated subjects, with a LS mean change from baseline of -0.048 (95% CI: -0.071, -0.026) in palopegteriparatide-treated subjects compared with placebo subjects -0.032 (95% CI: -0.066, 0.002) at Week 26. No significant treatment difference was observed (LS mean treatment difference: -0.016 [95% CI: -0.050, 0.017], nominal p = 0.3304).

Bone Turnover Marker Procollagen Type 1 N-Terminal Propeptide (P1NP)

Figure 41. Procollagen 1 N-Terminal Propeptide (Mean ± SE) by Visit – Blinded Period (ITT Population)



Abbreviations: ITT: intent to treat; SE: standard error; TransCon PTH: palopegteriparatide.
Procollagen 1 N-Terminal Propeptide normal ranges (ng/mL): premenopausal women (age ≥18 years) = 15 to 59; postmenopausal women (age ≥18 years) = 16 to 74; men (age ≥18 years) = 14 to 86 (LabCorp Drug development 2021.

P1NP levels at baseline were comparable across treatment groups, with a median of 29 ng/mL (range: 8 to 132) in palopegteriparatide-treated subjects and 29 ng/mL (range: 13 to 57) in placebo subjects.

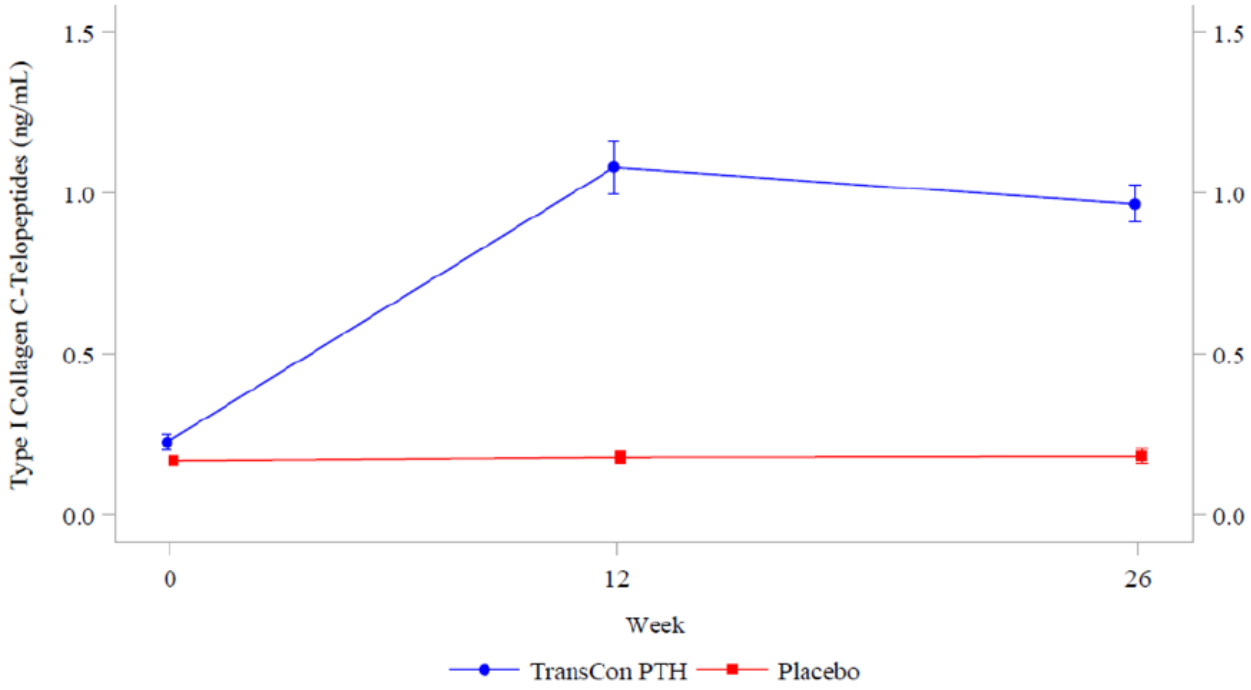
P1NP increased in palopegteriparatide-treated subjects over the first 12 weeks of the Blinded Period, with a LS mean change from baseline of 63 ng/mL (95% CI: 52, 74). A slight increase was then observed from Week 12 to Week 26, with a LS mean change from baseline of 81 ng/mL (95% CI: 70, 93) at Week 26.

No change in P1NP was observed in placebo subjects.

A significant difference was observed in favor of palopegteriparatide at Week 12 (LS means difference of 60 ng/mL [95% CI: 49, 71], nominal p<0.0001) and Week 26 (LS means difference of 78 ng/mL [95% CI: 66, 89], nominal p<0.0001).

Bone Turnover Marker C-Terminal Telopeptide of Type I Collagen

Figure 42. Type I Collagen C-telopeptide (Mean ± SE) by Visit – Blinded Period (ITT Population)



Abbreviations: ITT: intent to treat; SE: standard error; TransCon PTH: palopegteriparatide.
Note: 1 ng/mL = 1000 ng/L.
Type I Collagen C-Telopeptide normal ranges (ng/L): premenopausal women (age ≥18 years) = 30 to 570; postmenopausal women (age ≥18 years) = 100 to 1010; men (age: 18 to 30 years) = 160 to 870; men (age: 31 to 50 years) = 90 to 630; men (age: 51 to 71 years) = 40 to 840; men (age ≥71 years) = no reference range (LabCorp Drug Development 2021.

CTx levels at baseline were comparable across treatment groups, with a median of 180 ng/L (range: 60 to 1420) in palopegteriparatide-treated subjects and 169 ng/L (range: 70 to 280) in placebo subjects.

CTx increased in palopegteriparatide-treated subjects over the first 12 weeks of the Blinded Period, with a LS mean change from baseline of 830 ng/L (95% CI: 689, 970) at Week 12. CTx levels then remained stable or even decreased slightly, with a LS mean change from baseline 765 ng/L (95% CI: 662, 868) at Week 26.

No change in CTx was observed in placebo subjects.

A treatment difference was observed in favor of palopegteriparatide at Week 12 (LS means difference of 827 ng/L [95% CI: 685, 968], nominal p<0.0001) and Week 26 (LS means difference of 712 ng/L [95% CI: 607, 818], nominal p<0.0001).

EQ-5D

EQ-5D Domain Score

At baseline, more placebo subjects had moderate to severe mobility problems compared with palopegteriparatide-treated subjects at baseline (moderate problems: 28.6% versus 11.5%; severe problems: 9.5% versus 1.6%).

Most subjects in both treatment groups had no problem with self-care (86.9% palopegteriparatide-treated subjects and 81.0% placebo subjects).

The proportion of subjects experiencing no problem, slight problems, moderate problems, or severe problems with usual activities were not substantially different across treatment groups (42.6%, 32.8%, 19.7%, and 4.9% palopegteriparatide-treated subjects, respectively, and 47.6%, 23.8%, 23.8%, and 4.8% placebo subjects, respectively).

More placebo subjects experienced severe problems with pain/discomfort than palopegteriparatide-treated subjects (19.0% versus 4.9%), although 1 (1.6%) palopegteriparatide-treated subject experienced extreme problems with pain/discomfort. It should be noted that relatively few (18.0% and 14.3%, respectively) subjects experienced no problem with pain/discomfort.

More placebo subjects experienced moderate problems with anxiety/depression than palopegteriparatide-treated subjects (38.1% versus 23.0%).

By Week 26 in the palopegteriparatide group, the proportion of subjects experiencing no problem with mobility had increased from 57% to 77%, no problem with usual activities from 43% to 62%, no problem with pain/discomfort from 18% to 31%, and no problem or only slight problems with anxiety/depression from 39% to 48% (no problem) and 31% to 43% (slight problems).

By Week 26 in the placebo group, fewer subjects experienced moderate problems with mobility (14% instead of 29%), moderate problems with usual activities (10% instead of 24%), or moderate problems with anxiety/depression (4% instead of 38%), but the proportion of subjects experiencing no problem in any of these domains did not increase, and in some instance the proportion of subjects experiencing severe problems increased (anxiety/depression: 19% instead of 5%).

EQ-5D Visual Analogue Score

Median EQ-5D VAS at baseline was 70 (range: 19 to 97) in palopegteriparatide-treated subjects and 65 (range: 8 to 100) in placebo subjects. EQ-5D VAS increased over time in palopegteriparatide-treated subjects, with a LS mean change from baseline of 8 (95% CI: 3, 14) at Week 26, while it remained more or less unchanged in placebo subjects (LS mean change from baseline was 0 (95% CI: -9, 9). LS mean difference between treatment groups was 8 (95% CI: -1, 17; nominal p = 0.0706).

Clinical Global Impression of Severity

A summary of clinical impression of severity (CGIS) as evaluated by the treating physicians and including overall hypoparathyroidism symptoms, hypoparathyroidism physical symptoms, and hypoparathyroidism cognitive symptoms at baseline and Week 26 and change from baseline at each visit as well as overall change is provided in the table below:

Table 32. Change in Clinical Global Impression of Severity at Week 26 – Blinded Period (ITT Population)

Visit Statistics	TransCon PTH (N=61)	Placebo (N=21)
Overall Hypoparathyroidism Symptoms		
Baseline		
n	61	20
Mean	47.9	45.0
SD, SE	16.44, 2.11	15.73, 3.52
Observed Value		
n	47	14
Mean	24.7	45.7
SD, SE	16.79, 2.45	21.38, 5.71
Change from Baseline (ANCOVA)		
n	47	14
LS Mean (SE)	-22.2 (3.75)	-0.3 (6.86)
95% CI for LS Mean	(-29.7, -14.6)	(-14.5, 13.8)
Hypoparathyroidism Physical Symptoms		
Baseline		
n	61	20
Mean	47.2	44.0
SD, SE	16.75, 2.14	15.36, 3.43
Observed Value		
n	47	14
Mean	25.5	47.1
SD, SE	18.51, 2.70	23.01, 6.15
Change from Baseline (ANCOVA)		
n	47	14
LS Mean (SE)	-19.7 (4.12)	3.1 (7.38)
95% CI for LS Mean	(-28.0, -11.4)	(-12.0, 18.3)
Hypoparathyroidism Cognitive Symptoms		
Baseline		
n	61	20
Mean	40.3	40.0
SD, SE	20.16, 2.58	15.89, 3.55
Observed Value		
n	47	14
Mean	24.3	41.4
SD, SE	19.53, 2.85	22.82, 6.10
Change from Baseline (ANCOVA)		
n	47	14
LS Mean (SE)	-12.8 (4.15)	5.9 (7.53)
95% CI for LS Mean	(-21.2, -4.5)	(-9.7, 21.4)

Abbreviations: ANCOVA: analysis of covariance; CI: confidence interval; ITT: intent to treat; LS: least square; Max: maximum; Min: minimum; SD: standard deviation; SE: standard error; TransCon PTH: palopegteriparatide.
At each post-baseline visit, only data from subjects with both baseline and the corresponding visit values available were used to compute the statistical summaries. The ANCOVA model with unequal variance included the change from baseline as the response variable, treatment and etiology of hypoparathyroidism as fixed effects and baseline value of the parameter as a covariate.

HPES - Impact Domain scores (Psychological Well-being and Social Life and Relationships), and HPES Symptom and Impact Total Scores

HPES-Symptom Total Score

Baseline HPES - Symptom total scores were comparable across treatment groups at baseline.

An improvement in the HPES - Symptoms - total score was observed as early as Week 10 in palopegteriparatide-treated subjects (TCP-304 CSR, Figure 24, not shown).

At Week 26, subjects in both treatment groups experienced a reduction in mean HPES - Symptom total score. This reduction was however more pronounced in palopegteriparatide-treated subjects, with a LS mean change from baseline of -20.6 (95% CI: -25.1, -16.3) versus -5.3 (95% CI: -14.7, 4.1) in placebo subjects.

The LS mean difference between treatment groups was -15.4 (95% CI: -24.7, -6.0; nominal p = 0.0025) in favour of palopegteriparatide according to the ANCOVA model with no data imputation.

The ANCOVA model with data imputation generated similar results (LS mean difference between treatment group of -14.8 [95% CI: -23.8, -5.8; nominal p = 0.0013]).

HPES-Impact Domains and Total Score

Psychological Well-being Domain

Baseline HPES - Impact – psychological well-being scores were comparable across treatment groups at baseline.

An improvement in the HPES - Impact – psychological well-being score was observed as early as Week 10 in palopegteriparatide-treated subjects, while it remained unchanged in placebo subjects (TCP-304 CSR, Figure 25, not shown).

By Week 26, subjects in both treatment groups experienced a reduction in mean HPES impact – psychological well-being score. This reduction was however more pronounced in palopegteriparatide-treated subjects, with a LS mean change from baseline of -15.4 (95% CI: -20.1, -10.7) versus 0.19 (95% CI: -11.0 11.4) in placebo subjects.

The LS mean difference between treatment groups was -15.6 (95% CI: -26.7, -4.4; nominal p = 0.0085) in favour of palopegteriparatide according to the ANCOVA model without data imputation.

The ANCOVA model with data imputation generated similar results (LS mean difference between treatment group of -15.2 [95% CI: -25.7, -4.7; nominal p = 0.0047]).

Social Life and Relationships Domain

Baseline HPES - Impact – social life and relationships scores were comparable across treatment groups at baseline.

An improvement in the HPES - Impact – social life and relationships score was observed as early as Week 10 in palopegteriparatide-treated subjects, while it remained more or less unchanged in placebo subjects (TCP-304 CSR, Figure 26, not shown).

By Week 26, subjects in both treatment groups experienced a reduction in mean HPES - Impact – social life and relationships score. This reduction was however more pronounced in palopegteriparatide-treated subjects, with a LS mean change from baseline of -14.8 (95% CI: -19.7, -9.9) versus -1.57 (95% CI: -13.6 10.5) in placebo subjects.

The LS mean difference between treatment groups was -13.2 (95% CI: -25.2, -1.2; nominal p = 0.0328) in favour of palopegteriparatide according to the ANCOVA model without data imputation.

The ANCOVA model with data imputation generated similar results (LS mean difference between treatment group of -12.7 [95% CI: -24.0, -1.4; nominal p = 0.0276]).

Impact Total Score

Baseline HPES - Impact – total score was comparable across treatment groups at baseline.

An improvement in the HPES - Impact – total score was observed as early as Week 10 in palopegteriparatide-treated subjects, while it remained unchanged in placebo subjects (TCP-304 CSR, Figure 27, not shown).

By Week 26, subjects in both treatment groups experienced a reduction in mean HPES - impact – total score. This reduction was however more pronounced in palopegteriparatide-treated subjects, with a LS mean change from baseline of -16.6 (95% CI: -20.8, -12.9) versus -0.7 (95% CI: -11.5, 10.1) in placebo subjects.

The LS mean difference between treatment groups was -15.9 (95% CI: -26.7, -5.2; nominal p = 0.0058) in favour of palopegteriparatide according to the ANCOVA model without data imputation.

The ANCOVA model with data imputation generated similar results (LS mean difference between treatment group of -15.3 [95% CI: -25.4, -5.2], nominal p = 0.0029]).

SF-36 Subscale Scores

A summary of SF-36 subscale scores (Role Limitations due to Physical Health Problems, Bodily Pain, General Health, Vitality, Social Functioning, Role Limitations due to Emotional Problems, and Mental Health) and SF-36 component summary scores (Physical component score [PCS] and Mental component score [MCS]) at baseline, Visit 6 (Week 10), Visit 9 (Week 20) and Visit 10 (Week 26) and change from baseline at these timepoints together with analysis were provided in the TCP-304 CSR (data not shown).

Compared with placebo subjects, significant improvements were observed in palopegteriparatide-treated subjects in physical component summary score, role physical score, general health score, vitality score, and social functioning score. These changes were observed as early as Week 10.

Results obtained using the ANCOVA model with or without data imputation were comparable.

- **Ancillary analyses**

Not applicable

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Table 33. Summary of Efficacy for trial TCP-304

Title: PaTHway TRIAL: A Phase 3, Multicenter, Randomized, Double-blind, Placebo controlled, Parallel Group Trial, with an Open-Label Extension, Investigating the Safety, Tolerability and Efficacy of TransCon PTH Administered Subcutaneously Daily in Adults with Hypoparathyroidism	
Study identifier	TCP-304 - PaTHway EUDRACT no: 2020-003380-26 NCT no: NCT04701203 See Trial TCP-304 report body (M5.3.5.1)

Design	The trial is a phase 3, multicenter, randomised, double-blind, placebo-controlled trial with an open-label extension. The double-blind period of this trial randomised 84 subjects across 21 sites in 7 countries (Canada, Denmark, Germany, Hungary, Italy, Norway, and United States). The trial consisted of: • Screening Period (supplement optimization): Up to approximately 4 weeks (plus a maximum of 2 weeks between randomization and Visit 1) • Blinded Treatment Period (study drug titrated to optimal dose based on algorithm and co-administration with conventional therapy): 26 weeks • Open-Label Extension Period (open-label palopegteriparatide treatment): 156 weeks Subjects were randomised in a 3:1 ratio into 2 treatment groups: • Palopegteriparatide starting dose of 18* µg/day, co-administered with conventional therapy • Placebo for palopegteriparatide (excipient solution) 18 µg/day, co-administered with conventional therapy * The dose of palopegteriparatide refers to dose of PTH(1-34) administered	
	Duration of main phase:	26 weeks
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	156 weeks
Hypothesis	Primary Objective • To assess the treatment effect of daily palopegteriparatide on serum calcium levels, and therapeutic doses of active vitamin D (i.e., calcitriol or alfacalcidol) and calcium at 26 weeks of treatment. Secondary Objectives • To assess the treatment effect of daily palopegteriparatide on hypoparathyroidism patient experience scale (HPES) and Short Form-36 (SF-36) domain scores • To assess the treatment effect of daily palopegteriparatide on pharmacodynamic markers (including serum calcium) and active vitamin D and calcium doses • To assess the treatment effect of daily palopegteriparatide on serum phosphate • To assess the treatment effect of daily palopegteriparatide on BMD by DXA • To assess the treatment effect of daily palopegteriparatide on bone turnover markers (serum P1NP and CTx)	
Treatments groups	Palopegteriparatide	Palopegteriparatide starting dose of 18 µg/day, co-administered with conventional therapy. 63 subjects were randomised; 61 received at least 1 dose of treatment.
	Placebo	Placebo for palopegteriparatide (excipient solution) starting dose of 18 µg/day, co-administered with conventional therapy. 21 subjects were randomised and received at least 1 dose of treatment.

Endpoints and definitions	Primary endpoint:	Quadruple Endpoint	At 26 weeks of treatment, the proportion of subjects with: • Albumin-adjusted serum calcium measured within 4 weeks prior to and on the Week 26 visit are within the normal range (2.07 to 2.64 mmol/L); and • Independence from active vitamin D and • Independence from therapeutic doses of calcium (i.e., taking calcium supplements ≤600 mg/day), and • No increase in prescribed study drug within 4 weeks prior to Week 26 visit. The Cochran-Mantel-Haenszel test controlling for aetiology of hypoparathyroidism (post-surgical vs other) was used to compare the odds of meeting the primary endpoint in palopegteriparatide group to the odds in the placebo group
	Key secondary endpoints:	Change from baseline at 26 weeks in HPES-Symptom -Physical domain score	An ANCOVA model with unequal variance was used to compare each of the key secondary endpoints between palopegteriparatide and Placebo groups. In the ANOVA model, the key secondary endpoint was entered as response
		Change from baseline at 26 weeks in HPES-Symptom - Cognitive domain	
		Change from baseline at 26 weeks in HPES-Impact - Physical Functioning domain	
		Change from baseline at 26 weeks in HPES-Impact - Daily Life domain score	
		Change from baseline at 26 weeks in 36-Item Short Form Survey (SF-36) Physical Functioning subscale score	
	Additional endpoints:	Calcium Dose	Change from baseline in each of the endpoint by visit over 26 weeks was analysed using ANCOVA model with unequal variance including treatment assignment and aetiology of hypoparathyroidism as fixed factors and baseline value of the response variable as a covariate.
		Active vitamin D Dose	
		Daily Pill Burden of Active Vitamin D and Calcium supplement	
		Serum phosphate	
		Albumin-adjusted serum calcium	
		BMD by DXA	

		Bone turnover markers (serum P1NP and CTx)	
		24-hour urine calcium excretion	Change from baseline in 24-hour urine calcium by visit over 26 weeks was analysed using ANCOVA model with unequal variance including treatment assignment and aetiology of hypoparathyroidism as fixed factors and baseline 24-hour urine calcium as a covariate. The percentage of subjects with normal 24-hour uCa excretion (or >=50% reduction from baseline) at Week 26 was summarised.
Database lock	12 Jan 2022		

Efficacy Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	The primary analysis of the quadruple endpoint at Week 26 was based on the ITT population. The ITT population included all randomised subjects who had received at least 1 dose of active treatment.		
Results		Palopegteriparatide (N=61)	Placebo (N=21)
Quadruple endpoint	Number of Subjects meeting the Primary Endpoint Criteria at Week 26 (Responders)	48	1
	Proportions (95% CI)	78.7 (66.3, 88.1)	4.8 (0.1, 23.8)
	P-value (Palopegteriparatide vs Placebo)	<0.0001	
Components of primary endpoint	Number of Subjects (%) Meeting Each Component:		
	Albumin-adjusted serum calcium measured within 4 weeks prior to and on the Week 26 visit are within the normal range (2.07 to 2.64 mmol/L)[a]	49 (80.3%)	10 (47.6%)
	Independence from active vitamin D[b]	60 (98.4%)	5 (23.8%)
	Independence from therapeutic doses of calcium (i.e., taking calcium supplements ≤600 mg/day)[c]	57 (93.4%)	1 (4.8%)
	No increase in prescribed study drug within 4 weeks prior to Week 26 visit.[d]	57 (93.4%)	12 (57.1%)
Notes	[a] Except for at the Week 26 visit, confirmation that an albumin-adjusted sCa is "abnormal" requires 2 consecutive results outside the normal range within 4 weeks prior to the Week 26 visit. [b] Independence from active vitamin D is defined as a daily standing dose equal to zero on all days AND use of any PRN vitamin D ≤7 days within 4 weeks prior to the Week 26 visit. [c] Independence from therapeutic calcium is defined as average daily standing dose ≤600 mg AND use of PRN doses on ≤7 days within 4 weeks prior to the Week 26 visit. [d] Dose decrease permitted for safety reasons.		

Analysis description	**Key Secondary Analyses**	
Analysis population and time point description	The analysis of key secondary endpoints (change from baseline to Week 26 in specific HPES and SF36 scores) was based on ITT population.	
	Change from baseline to Week 26 in LS Mean (SE)	P-value

	Palopegteriparatide (n/N=59/61)	Placebo (n/N=19/21)	Treatment Difference	
HPES-Symptom – Physical domain score	-21.01 (2.20)	-4.81 (5.02)	-16.20 (5.02)	0.0038
HPES-Symptom - Cognitive domain score	-20.49 (2.59)	-6.16 (4.71)	-14.33 (4.67)	0.0055
HPES-Impact - Physical Functioning domain score	-18.29 (2.65)	-1.01 (5.49)	-17.28 (5.50)	0.0046
HPES-Impact - Daily Life domain score	-17.65 (2.37)	-0.36 (5.68)	-17.29 (5.68)	0.0061
36-Item Short Form Survey (SF-36) Physical Functioning subscale score	5.29 (0.91)	0.12 (2.29)	5.16 (2.29)	0.0347
Notes	A decrease in HPES scores denotes an improvement in health-related quality of life. An increase in SF-36 score denotes an improvement in health-related quality of life.			

Analysis description	**Additional Analyses**				
	Visit	Mean (SD)		LS Mean CFB Treatment Difference (Palopegteriparatide – Placebo) (SE)	P-Value
		Palopegteriparatide N=61	Placebo N=21		
Calcium Dose (mg/day)	Baseline	1748 (904)	2105 (1382)		
	Week 26	274 (1372)	1847 (1326)	1501 (359)	0.0003
Active vitamin D Dose (mcg/day)	Baseline	0.992 (0.7373)	0.940 (0.6220)		
	Week 26	0	0.618 (0.7330)	-0.620 (0.0917)	<0.0001
Daily Pill Burden of Active Vitamin D and Calcium supplement (#/day)	Baseline	6.69 (2.203)	6.74 (2.990)		
	Week 26	0.45 (1.661)	5.42 (3.220)	-5.08 (0.735)	<0.0001
Serum phosphate (mmol/L)	Baseline	1.361 (0.1918)	1.263 (0.2600)		
	Week 26	1.229 (0.1846)	1.252 (0.2919)	-0.073 (0.0536)	0.1861
Albumin-adjusted serum calcium (mmol/L)	Baseline	2.200 (0.1722)	2.159 (0.1598)		
	Week 26	2.236 (0.1675)	2.055 (0.1322)	0.173 (0.0365)	<0.0001
BMD by DXA (Corrected Z-scores)	Baseline	Lumbar Spine: 1.5 (1.54) Total Hip: 0.9 (1.28) Femoral Neck: 0.8 (1.25) Dis 1/3 Radius: 0.3 (1.01)	2.0 (1.29) 1.2 (0.73) 1.0 (0.82) 0.5 (0.93)		

	Week 26	Lumbar Spine: 0.7 (1.49) Total Hip: 0.5 (1.28) Femoral Neck: 0.4 (1.31) Dis 1/3 Radius: 0.3 (1.05)	1.8 (1.02) 1.1 (0.71) 1.0 (0.77) 0.5 (0.92)	-0.9 (0.09) -0.5 (0.05) -0.6 (0.07) 0.0 (0.08)	<0.0001 <0.0001 <0.0001 0.7993
Serum P1NP (ng/mL)	Baseline	33.788 (19.4846)	30.185 (10.3563)		
	Week 12	99.518 (52.0555)	36.331 (13.0313)		
	Week 26	120.450 (52.5390)	37.322 (21.4166)	77.748 (5.8940)	<0.0001
Serum CTx (ng/L)	Baseline	227.5 (193.99)	168.6 (60.77)		
	Week 12	1079.1 (610.96)	178.9 (81.95)		
	Week 26	966.3 (445.07)	182.1 (98.13)	712 (52.8)	<0.0001
24-hour urine calcium excretion (mg/day)	Baseline	391.95 (175.365)	328.95 (140.042)		
	Week 26	219.79 (122.663)	292.47 (125.484)	-89.81 (31.738)	0.0085
24-hour urine calcium excretion (%)		Number (Proportion) of Subjects, n(%), with normal 24-hour urine calcium (≤250 mg/day)		P-Value	
		Palopegteriparatide	Placebo		
	Week 26	37 (60.7)	6 (28.6)	0.0213	

Table 34. Summary of efficacy for trials TCP-201

Title: 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	
Study identifier	TCP-201 PaTH Forward, EUDRACT no: 2018-004815-33 NCT no: NCT04009291 See Trial TCP-201 report body (M5.3.5.1)
Design	The study is a phase 2, multicenter, randomised, double-blind, placebo-controlled, parallel group trial with an open-label extension. The double-blind period of this trial randomised 59 subjects across 12 sites in 6 countries (Canada, Denmark, Germany, Italy, Norway, and the United States). The trial consisted of: • Screening period (optimization): Up to approximately 4 weeks • Blinded Treatment period (fixed study drug co-administered with conventional therapy): 4 weeks • Open-Label Extension period (i.e., open-label palopegteriparatide treatment): up to 210 weeks, study drug titrated to optimal dose based on algorithm and co-administration with conventional therapy Subjects were randomised into 4 fixed dose treatment groups (1:1:1:1) for the initial 4 week Blinded Treatment Period: • Palopegteriparatide* 15 µg/day • Palopegteriparatide 18 µg/day • Palopegteriparatide 21 µg/day • Placebo to match palopegteriparatide [1:1:1] (excipient solution)

	Duration of main phase: Duration of run-in phase: Duration of extension phase:	4 weeks Not applicable Up to 210 weeks	
Hypothesis	Primary Objective at end of the 4-week Blinded period • To assess the effectiveness of daily palopegteriparatide on serum and urine calcium levels (FECa) and active vitamin D and calcium doses at 4 weeks of treatment Secondary Objectives To assess the treatment effect of daily palopegteriparatide in the Open-Label Extension (OLE) period • To assess the effectiveness of daily palopegteriparatide on serum and urine calcium levels • To assess the effectiveness of daily palopegteriparatide on active vitamin D and calcium doses • To assess the treatment effect of daily palopegteriparatide on daily pill burden (active vitamin D and calcium) • To assess the treatment effect of daily palopegteriparatide on serum phosphate Exploratory Objectives • To assess the treatment effect of daily palopegteriparatide on BMD by DXA • To assess the treatment effect of daily palopegteriparatide on bone turnover markers (serum P1NP and CTx) • To assess the treatment effect of daily palopegteriparatide on patient reported outcomes		
Treatments groups	Blinded Period (Weeks 0-4)		
	Palopegteriparatide	15, 18, or 21 µg/day once-daily injection, co-administered with the subject's stable dose of magnesium and vitamin D (cholecalciferol) and doses of active vitamin D and calcium. 4 weeks, 44 randomised subjects	
	Placebo	Placebo once-daily injection equivalent to palopegteriparatide (excipient solution), co-administered with the subject's stable dose of magnesium and vitamin D cholecalciferol) and doses of active vitamin D and calcium. To maintain blinding, the placebo group will be sub-randomised into 3 groups (1:1:1) to mimic doses of 15, 18, and 21 µg/day. 4 weeks, 15 randomised subjects	
	Open Label Extension (Weeks 4-214)		
	Palopegteriparatide	At Week 4, subjects were enrolled into the OLE: • If on active vitamin D: Started palopegteriparatide 15 µg/day and conventional therapy titrated as per the Blinded Period • If not on active vitamin D: Maintained same dose of palopegteriparatide as during the Blinded Period. Palopegteriparatide dose and conventional therapy is titrated to the optimal dose based on algorithm Week 84 (data cut-off date), 59 subjects enrolled	
Endpoints and definitions	Primary endpoint at Week 4	Quadruple Endpoint	At 4 weeks of treatment, the proportion of subjects with: • Serum calcium (albumin-adjusted) within the normal range (2.07 to 2.64 mmol/L) • Spot AM FECa within the normal range or a reduction by ≥50% from baseline • Not taking active vitamin D supplements, and • Taking ≤1000 mg/day of calcium supplements Fisher's exact test is used to compare differences in proportions.

	Secondary Endpoints at Week 84	Calcium Dose	Summary statistics (number of subjects, mean, SD/SE, median, minimum, and maximum values) of the observed values and change from baseline were provided for each of the endpoints at each scheduled timepoints up to Week 58.
		Active vitamin D Dose	
		Daily Pill Burden of Active Vitamin D and Calcium	
		Serum phosphate	
		Albumin-adjusted serum calcium	
		24-hour urine calcium excretion	
	Exploratory Endpoints	Triple Composite Endpoint at Week 84	At 84 weeks of treatment, the proportion of subjects with: • Serum calcium within the normal range (2.07 to 2.64 mmol/L) • Not taking active vitamin D supplements • Taking ≤600 mg/day of calcium supplements The proportion of subjects meeting the composite endpoint was presented.
		BMD by DXA	Summary statistics (number of subjects, mean, SD/SE, median, minimum, and maximum values) of the observed values and change from baseline were provided for each of the endpoints at each scheduled timepoints up to Week 58.
		Bone turnover markers (serum P1NP and CTx)	
		HPS-Total HPES-Symptom Score	
		HPI-Total HPES-Impact Score	
Database lock	24 Sep 2021		

Efficacy Results and Analyses

Analysis description	**Primary Analysis**
Analysis population and time point description	The primary analysis of the quadruple endpoint at Week 4 was based on the Full Analysis Population (FAS). The FAS population included all randomised subjects who had received at least 1 dose of study drug.

Quadruple Endpoint

Treatment group	Palopegteriparatide				Placebo (N=15)
	15 µg/day (N=14)	18 µg/day (N=15)	21 µg/day (N=15)	All PTH Subjects (N=44)	
Number of Subjects Meeting the Primary Endpoint (Responders)	7	6	9	22	4
Proportion (95% CI)	50.0 (23.0, 77.0)	40.0 (16.3, 67.7)	60.0 (32.3, 83.7)	50.0 (34.6, 65.4)	26.7 (7.8, 55.1)
Hypothesis Test: P-value (Treatment vs Pooled Placebo)	0.2635	0.6999	0.1394	0.1419	

Components of primary endpoint	Number of Subjects Meeting Each Component:					
	Serum calcium within the normal range (2.07 to 2.64 mmol/L)	12	12	14	38	14
	Spot AM FECa within normal range (<=2 %) or a reduction by at least 50% from baseline	10	8	9	27	7
	Not taking active vitamin D supplements	14	14	15	43	6
	Taking ≤1000 mg/day of calcium	13	13	15	41	8

Analysis description	**Secondary Analyses**		
	Visit	All Palopegteriparatide Subjects Mean (SD)	Mean Change from Baseline (SD)
Calcium Dose (mg/day)	Baseline	2079.2 (1355.12)	
	Week 84	412.1 (1714.24)	-1682.3 (1724.01)
Active vitamin D Dose (mcg/day)	Baseline	1.140 (0.9148)	
	Week 84	0 (0)	-1.116 (0.9047)
Daily Pill Burden of Active Vitamin D and Calcium supplement (#/day)	Baseline	8.55 (3.580)	
	Week 84	1.44 (4.598)	-7.11 (4.294)
Serum phosphate (mmol/L)	Baseline	1.327 (0.1557)	
	Week 84	1.135 (0.1686)	-0.191 (0.2073)
Albumin-adjusted serum calcium (mmol/L)	Baseline	2.205 (0.2006)	
	Week 84	2.129 (0.1125)	-0.074 (0.2159)
24-hour urine calcium excretion (mg/day)	Baseline	427.97 (190.692)	
	Week 84	134.29 (63.292)	-298.28 (181.933)

Analysis description	**Additional Analyses**	
Triple Composite Endpoint at Week 84		All Palopegteriparatide Subjects
	Number of Subjects Who Have Data (All Criteria)	58
	Number of Subjects Meeting the Endpoint Criteria	39
	Proportion (95% CI)	67% (53.7%, 79.0%)

	Number of Subjects (%) Meeting Each Component:		
	Components of Triple Composite Endpoint	Serum calcium within the normal range (2.07 to 2.64 mmol/L)	41 (71)
		Not taking active vitamin D supplements	58 (100)
		Taking ≤600 mg/day of calcium supplements	54 (93)
Analysis description	**Additional Analyses**		
		All Palopegteriparatide Subjects Mean (SD)	Mean Change (SD)
BMD by DXA (Corrected Z-scores)	Baseline	Lumbar Spine: 1.65 (1.6789) Total Hip: 0.96 (1.1541) Femoral Neck Hip: 0.98 (1.1355) Distal 1/3 Radius: 0.35 (1.2901)	
	Week 26	 Lumbar Spine: 0.99 (1.6110) Total Hip: 0.58 (1.1321) Femoral Neck Hip: 0.54 (1.1394) Distal 1/3 Radius: 0.33 (1.0110)	Mean Change from Baseline: -0.618 (0.4606) -0.435 (0.3746) -0.480 (0.3565) -0.066 (0.6949)
	Week 58	 Lumbar Spine: 0.94 (1.5370) Total Hip: 0.51 (1.0315) Femoral Neck Hip: 0.45 (1.0356) Distal 1/3 Radius: 0.30 (0.9927)	Mean Change from Week 26: -0.045 (0.3881) -0.100 (0.2390) -0.115 (0.3012) -0.030 (0.3299)
Analysis description	**Additional Analyses**		
		All Palopegteriparatide Subjects Mean (SD)	Mean Change from Baseline (SD)
Serum P1NP (ng/mL)	Baseline	35.417 (20.6392)	
	Week 12	76.759 (42.1787)	44.786(36.8352)
	Week 26	88.354 (43.5794)	52.722 (37.9697)
	Week 58	69.995 (28.3230)	34.093 (25.7443)
Serum CTx (ng/L)	Baseline	202.759 (112.6988)	
	Week 12	804.174 (517.2140)	607.000 (446.2001)
	Week 26	762.982 (412.2369)	560.073 (350.0420)
	Week 58	532.982 (319.4560)	329.825 (261.9032)
HPES-Symptom – Physical domain score	Baseline	38.768 (22.2564)	
	Week 58	17.336 (12.0113)	-21.801 (18.8276)
HPES-Symptom - Cognitive domain score	Baseline	37.6 (30.16)	
	Week 58	18.3 (19.82)	-19.1 (27.82)

HPES-Impact - Physical Functioning domain score	Baseline	34.831 (26.7486)	
	Week 58	9.821 (13.0720)	-24.643 (24.3993)
HPES-Impact - Daily Life domain score	Baseline	31.432 (26.3964)	
	Week 58	7.518 (10.9772)	-24.004 (24.8282)
36-Item Short Form Survey (SF-36) Physical Functioning subscale score	Baseline	46.089 (9.7204)	
	Week 58	51.395 (6.4179)	5.268 (7.1543)

2.5.5.3. Clinical studies in special populations

There were no efficacy studies in special populations.

Table 35. Numbers of Elderly Subjects Enrolled in the Palopegteriparatide Clinical Trials Included in the MAA Submission (Safety Populations)

	Age 65-74 (n older subjects / total N)	Age 75-84 (n older subjects / total N)	Age 85+ (n older subjects / total N)
Controlled Trials			
Phase 2 and 3			
TCP-304, TCP-201 combined (TransCon PTH Period)	12/139	3/139	0/139
TCP-304 (TransCon PTH Period)	8/80	2/80	0/80
TransCon PTH (Blinded)	7/61	1/61	0/61
Placebo (Blinded)[b]	1/21	1/21	0/21
TCP-201	4/59	1/59	0/59
TransCon PTH/ TransCon PTH	3/44	1/44	0/44
Placebo/ TransCon PTH	1/15	0/15	0/15
Phase 1			
CT-103 (Phase 1)[a]	0/132	0/132	0/132
TCP-105 (Phase 1)[a]	0/48	0/48	0/48
Non-controlled Trials (Phase 1 only)			
TCP-104[a]	13/38	1/38	0/38

Note: Numbers include placebo and palopegteriparatide-treated subjects treated in each study.

[a] No subjects over 60 years of age were enrolled in CT-103 per the eligibility criteria. In TCP-105, subjects of up to age 65 were eligible, but no subjects 65 years of age were enrolled. TCP-104 enrolled subjects up to 75 years old, inclusive, including 1 subject who was 75.6 years of age.

[b] In TCP-304, 2 subjects in the placebo arm discontinued prior to the start of the TransCon PTH period and are therefore not included in the TransCon PTH period (N =19).

2.5.6. Discussion on clinical efficacy

Clinical efficacy of palopegteriparatide treatment in adult patients with hypoparathyroidism (HP) was evaluated in one **Phase 2 dose-finding study** (**study TCP-201**) and the **pivotal Phase 3 study (study TCP-304)**.
Both studies allowed subjects who completed the main study period to participate in an Open Label Extension (OLE) phase.

Design and conduct of clinical studies

Dose finding

Study TCP-201 was a dose finding study in adult patients with hypoparathyroidism:

PaTH Forward was a Phase 2, Multicenter, Randomized, Double-Blind, 4-week Placebo-Controlled, Parallel Group Trial Investigating the Safety, Tolerability and Efficacy of TransCon PTH Administered Subcutaneously Daily in Adults with Hypoparathyroidism. The Open-label Extension (OLE) period of study TCP-201 is planned for up to 210 weeks (4 years), is ongoing and the submitted clinical study report includes OLE data through Week 110.

Study population

Main inclusion and exclusion criteria were generally comparable between the studies and are discussed for TCP-301 below. Detailed information for TCP-201 are stated in the method section above.

Treatments

The randomized and placebo controlled 4-week main study compared three dose levels of palopegteriparatide administered once daily (15 µg PTH(1-34)/day, 18 µg PTH(1-34)/day, 21 µg PTH(1-34)/day) to placebo. Subjects were to remain on the same dose of study drug throughout the Blinded Treatment period. Active vitamin D and/or calcium doses were adjusted according to serum calcium levels.
In the OLE phase, at every clinic visit (every 2 weeks) up to and including Visit 8 (week 14), the palopegteriparatide dose was to be increased by 3 µg/day if the serum calcium level was <LLN or the subject was experiencing persistent hypocalcemic symptoms. If a subject not taking SOC experienced persistent hypercalcaemic symptoms in the setting of an elevated serum calcium value, the palopegteriparatide dose was decreased by 3 µg/day.
Starting at Visit 9 (week 18), palopegteriparatide, active vitamin D, and calcium doses were expected to remain stable but dose adjustments were allowed as needed based on serum calcium and other indicators. Rescue doses of active vitamin D and/or calcium were permitted throughout the OLE.

Outcomes/endpoints

The primary endpoint was a composite endpoint consisting of 4 components: 1. Albumin-adjusted serum calcium in the normal range, 2. spot AM FECa within the normal range or a reduction by ≥50% from baseline[1], 3. patient independent on standing doses of active vitamin D, 4. doses of elemental calcium to ≤1000 mg/day. The primary endpoint is regarded meaningful and adequate to investigate the efficacy of palopegteriparatide. For the purposes of this trial, the normal range for are albumin-adjusted sCa was defined to be 8.3-10.6 mg/dL (2.07-2.64 mmol/L). This range is in line with e.g. the normal range stated for subjects 18-59 years of age by the Mayo Clinics Laboratories (8.6-10.0 mg/dL). The chosen normal range is acceptable.
With regard to calcium supplements, to put 1000 mg/day into perspective, as an example, the DGE (The German Nutrition Society) recommends Calcium supplements up to a dose of 1000 mg for

[1] 24-h urine calcium excretion was used for analysis of this endpoint in the OLE.

healthy adults. European recommendations seem comparable (e.g. Scientific Opinion on Dietary Reference Values for calcium; EFSA).
The primary endpoint is similar to the primary endpoint used in the pivotal phase 3 study and acceptable.

Secondary endpoints aiming at further explore changes in SOC doses, laboratory values, e.g. for albumin-adjusted serum calcium and serum phosphate, are regarded to be of clinical relevance.

Statistics

For the Phase II dose finding study, statistical tests were conducted but were obviously intended to be exploratory, as no strategy for type 1 error control was defined. Descriptive analyses are acceptable for a dose-finding study.

Analysis Population

Efficacy analyses were based on the Full Analysis Population (subjects who received at least one dose of study drug, analysed as randomized) by study period. The definition of the analysis populations is acceptable.

Main study

The pivotal TCP-304 Phase III study was a multicentre, randomized, double-blind, placebo-controlled, parallel group, 26-week trial, with an open-label extension of 3 years of daily palopegteriparatide (TransCon PTH) in male and female adults with chronic hypoparathyroidism of postsurgical, autoimmune, genetic, or idiopathic etiology for at least 26 weeks, treated with calcitriol (an active vitamin D) ≥0.5 µg/day, or alfacalcidol (an active vitamin D) ≥1.0 µg/day and elemental calcium ≥800 mg/day for at least 12 weeks prior to Screening.
The provided justification of the study design is generally acceptable, especially with regard to the double-blind set-up and the use of placebo. A double-blind, placebo-controlled design is a necessary condition, especially if in addition to rather objective parameters like laboratory findings PROs shall be adequately assessed (key secondary endpoints).

Subjects who received palopegteriparatide or placebo in the main study were able to continue with palopegteriparatide treatment in an open-label extension study. This is endorsed as in this way long term data on efficacy and safety can be generated. Available results for study TCP-304 OLE through week 52 have been submitted. Data were available for 78 subjects (59 subjects receiving palopegteriparatide from study start (TransCon PTH/TransCon PTH] and 19 subjects receiving placebo followed by palopegteriparatide [Placebo/TransCon PTH] from Week 26) at Week 52. As outlined by the Applicant in the safety section of the CSR, at the data cut-off date for the CSR interim report (12 January 2022, last subject visit 10) 79 subjects entered the OLE period. Most subjects had only been in the OLE period for <4 weeks (38/82; 46.3%) or for 4 to <8 weeks (24/82; 29.3%) by the time of the data cut-off date (12 Jan 2022). Sixteen (19.5%) subjects had been in the OLE period for 8 to <12 weeks, and only 1 subject had been in the OLE period for 12 weeks or more.

Study population

Males and females ≥18 years of age were included, which is acceptable as indication is only sought in adult patients.
Study subjects had to have either postsurgical chronic HP, or auto-immune, genetic, or idiopathic HP for at least 26 weeks. Twenty-six weeks is regarded acceptable for postsurgical HP. Brandi et al. state that "chronic hypoparathyroidism can be diagnosed in patients after anterior neck surgery 6 months postoperatively". The study population reflects the general population with hypoparathyroidism. During the procedure, the initially applied indication was to be revised to include patients with chronic

hypoparathyroidism in line with the population studied and to avoid potentially unnecessary long-term treatment with palopegteriparatide in patients with transient hypoparathyroidism. The final indication is as follows: "*Yorvipath is a parathyroid hormone (PTH) replacement therapy indicated for the treatment of adults with chronic hypoparathyroidism*".

Subjects with impaired responsiveness to PTH (pseudohypoparathyroidism), which is characterized as PTH-resistance with elevated PTH levels in the setting of hypocalcemia, were to be excluded. This is reasonable, as additional PTH (here PTH(1-34)) would not be regarded to be possibly effective in these subjects, and has been adequately reflected in the SmPC (Section 4.3, contraindications).
Diagnosis of HP was to be established based on a history of hypocalcemia in the setting of inappropriately low serum PTH levels (hypocalcemia was defined as a value below the reference range for normal at the performing laboratory and inappropriately low serum PTH levels were defined as at or below the median value of the reference range for normal at the performing laboratory). The inclusion criterion is generally acceptable, although it could have been more specific (Brandi et al. state:" The diagnosis should be established by the concurrent measurement of albumin-corrected or ionized serum calcium below the lower limits of the normal range and low or undetectable levels of PTH, as determined by either a second- or third-generation immunoassay on at least two occasions separated by at least 2 weeks."). However, there are no concerns that patients without true hypoparathyroidism have been recruited.

For the pivotal phase III study, if specific lab results at the time of original diagnosis were not available, also historical diagnosis affirming these two components was considered adequate for inclusion into the clinical trial, which is considered acceptable.

There were requirements for doses of SoC (e.g., calcitriol, alfacalcidol, calcium supplements) at or above a minimum threshold.

Calcium supplementation and treatment with active vitamin D are regarded standard for patients with HP. In their Management Guidelines for HP, Brandi et al. quote publications that state that "[….] the range of active vitamin D to manage hypoparathyroidism is enormous, but generally it is between 0.25 and 2 µg daily" and "the amount of calcium supplementation required varies enormously, with amounts as high as 9 g/d in some". One of the study objectives showed that subjects were able to achieve independence from standing doses of calcitriol and alfacalcidol, and to progressively reduce calcium supplements to ≤600 mg/day. Therefore, the requirement of pre-treatment with a certain amount of active vitamin D and calcium supplements is justifiable. Patients had to be stabilised prior to treatment initiation with palopegteriparatide.
As consequence of inclusion criteria "optimization of supplements prior to randomization", only patients that were able to achieve target serum levels of 25(OH) vitamin D, magnesium and albumin-adjusted or ionized serum calcium were to be randomised and have been subsequently investigated. However, no subjects failed initial or final screening due to this Inclusion Criterion. The applicant justified the starting dose recommendations in the SmPC for a "real-world" hypoparathyroid patient population which is not previously optimised for supplements. It was generally stated that 18 mcg/day proved to be a safe and effective starting dose followed by adjustment per the titration algorithm, allowing subjects to be titrated up or down in dose while minimizing the risk of hypocalcemia and hypercalcemia events. Section 4.2 of the SmPC includes more detailed information regarding expected serum 25(OH) vitamin D and serum calcium levels "Before initiating Yorvipath".

Patients should have eGFR >30 mL/min/1.73m^2 during screening.

To exclude disturbing effects on clinical study endpoints, any disease that might affect calcium metabolism or calcium-phosphate homeostasis or PTH levels other than HP (exclusion criterion 2) and the use of concomitant treatment like e.g. PTH-like drugs, loop diuretics, phosphate binders and osteoporosis therapies was excluded (exclusion criteria 4-8), which is reasonable.

Treatments

The selected starting dose of 18 µg/day is based on the results of the phase II dose finding study and regarded to be overall acceptable. Notably, all patients were to be individually titrated based on their corrected sCa concentrations.
Subjects were randomized in a 3:1 ratio into the two treatment group of palopegteriparatide 18 µg/day or placebo for palopegteriparatide (excipient solution), both co-administered with conventional therapy. A 3 to 1 randomisation is acceptable as this increases the number of patients in the Verum group, which is regarded preferable in light of the increase in the safety data set available for evaluation.
The treatment algorithm is adjusting palopegteriparatide, placebo, active vitamin D and calcium based on serum calcium concentrations, the goal is to keep albumin adjusted sCa in the pre-defined normal range ("albumin-adjusted sCa 8.3-10.6 mg/dL (2.07-2.64 mmol/L); ionized calcium 1.16-1.32 mmol/L."). The treatment algorithm aims to first reduce active vitamin D to zero, afterwards calcium supplements will be reduced. In principle, if measured serum calcium was found to be "normal", steps for reduction of active vitamin D or calcium go along with increase of palopegteriparatide (+ 3 µg). The titration algorithm aimed to gain independence from conventional therapy while assuring that serum calcium will be monitored and maintained in the normal range by up- or down titration of study drug, active vitamin D or calcium supplements. This approach is generally acceptable, however, the placebo arm may not represent treatment with "optimised SoC".
Implementing the same titration algorithm (sCa) in both treatment arms was necessary to keep the study blind and patients were not put at increased risk since, in clinical practice, sCa levels down to 7.8 mg/dL are acceptable (Brandi 2016).
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 proposed dosing in the SmPC does overall adequately reflect the dosing algorithm used in the pivotal clinical study and the need for pre-dose optimisation in the screening period.

At all times during the trial, subjects with symptoms of hypocalcemia could take pro re nata (PRN, meaning rescue/"as needed") doses of calcium (preferred) and/or active vitamin D, and/or do an unscheduled laboratory visit (ULV) to measure serum calcium. As requested, the SmPC and PIL were amended to give further information on monitoring and treatment of hypocalcaemia.

Outcomes/endpoints

The primary efficacy endpoint was to assess the effectiveness of palopegteriparatide on calcium levels, and active vitamin D and calcium levels on week 26. At 26 weeks of treatment, the proportion of subjects who met the following 4 criteria were considered responders:

- albumin-adjusted serum calcium within the normal range (albumin-adjusted serum calcium 8.3-10.6 mg/dL-2.07-2.64 mmol/L, and

- independence from active vitamin D, and

- independence from therapeutic doses of calcium (i.e., ≤600 mg/day), and

- no increase in prescribed study drug within 4 weeks prior week 26 visit.

As discussed for TCP-201 above, the chosen normal range for albumin-adjusted sCa is acceptable. With regard to calcium supplements, it is agreed that doses up to 600 mg/day can be regarded to be supplemental, see discussion for phase II study above.

Sensitivity analysis, e.g. strengthening the success criteria for intake of concomitant (standing doses and PRN) active vitamin D and calcium, have been provided.

Key secondary endpoints assessed the treatment effect of daily palopegteriparatide on hypoparathyroidism patient experience scale (HPES) and Short Form-36 (SF-36) domain scores at W26. Both HPES and SF-36 are validated scales. Although it can be agreed that Verum and Placebo were probably indistinguishable in appearance, the Applicant addressed how functional unbinding could have influenced the results of PROs, as these are the endpoints regarded to be most vulnerable to a potential bias. A component of functional unblinding likely occurred and some degree of bias cannot be excluded. However, HPES and SF-36 were key secondary endpoints and included in the hierarchical testing strategy. Results were statistically significant in favour of palopegteriparatide and there is supportive testimony of palopegteriparatide-treated patients of feeling better at the study exit interview. However, based on the comparison to a potentially suboptimal SOC treatment in the Placebo arm as outlined above, the CHMP decided that results on PROs are not to be mentioned in section 5.1 of the SmPC.

Secondary endpoints assessing changes e.g. SOC doses, laboratory values for albumin-adjusted serum calcium, C×P (albumin-adjusted serum calcium-phosphate product) and serum phosphate are regarded to be of clinical relevance. Increased serum calcium-phosphate product (CaP) can result in acute kidney injury due to tubular and interstitial calcium phosphate deposits. CaP of > 55 mg2/dL2 is also associated with systemic calcification. No patient exceeded this threshold.

Statistics

The applicant defined an estimand but its specification was not in line with the requirements from ICH E9(R1), which became effective before protocol version 1. However, the inappropriate estimand specification does not have a relevant influence on the B/R assessment in this case, such that the estimand is not further described and discussed here.

The primary response endpoint was a composite endpoint requiring a patient to be a responder for all components to be an overall responder. An effect on the endpoint does not imply an effect on all components but only allows to conclude that there is an effect on at least one of the components (in contrast to the evaluation of the components as co-primary endpoints, which is usually the more conservative approach). Therefore, assessment of the single components is of key importance for the interpretation of the results for the primary endpoint.

Excluding non-treated patients from the primary analysis is acceptable for a blinded study.

The randomization stratification factors were appropriately taken into account by a correspondingly stratified analysis.

The treatment effect was intended to be expressed as odds ratio. However, the interpretation of the odds ratio and its clinical relevance is not straightforward. Finally, the odds ratio was not provided because there was only 1 responder in the placebo group, which would make the confidence interval very wide. This is agreed. As an alternative effect measure, the applicant provided on request the risk difference with the 95% CI consistent with the CMH method.

The hierarchical testing provides family-wise type 1 error control for the endpoints in the hierarchy.

For the primary endpoint, missing data was handled by non-response imputation. It depends on the targeted estimand and the difference in the proportion of patients with missing data between the treatments whether this can be considered a conservative approach. However, considering the small number of patients who discontinued study and the large treatment effect, handling of missing data for these patients is not of critical importance for the conclusions from the study. Subjects with no Week 26 albumin-adjusted serum calcium, and subjects with>25% (i.e., >7 days) missing diary data of

active vitamin D or calcium during the 4 weeks were considered as non-responders (only 3 patients who discontinued the study early fulfilled these criteria).

For the secondary endpoints, missing data was replaced under a missing at random (MAR) assumption, which can usually be considered to be aligned to the hypothetical effect if all patients had completed treatment. This hypothetical effect is usually not of primary relevance for regulatory decision making, however, considering the small number of patients who discontinued treatment, method for replacing missing data for these patients is not relevant for the conclusions and no additional analyses are requested.

Analysis Population

The Intent-To-Treat (ITT) Population was to consist of all subjects who were randomized and received at least one dose of blinded study drug. All efficacy analysis were to be based on ITT and treatment assignment per randomization. The Safety Analysis Population was to consist of all randomized subjects who received at least one dose of study drug. The safety analyses were to be based on the Safety Analysis Population and actual treatment received.

Efficacy data and additional analyses

Dose finding

Participant flow

All treated subjects competed the main study (4 weeks blinded period), which is endorsed. One subject dropped out in the OLE period due to non-compliance with contraception requirements ("wish for pregnancy"), which is acceptable.

Baseline characteristics

Most patients were female (>80.0%), ≥30 and <65 years old (>78%) and with post-surgical chronic hypoparathyroidism (> 70%). Patients with >65 years included is limited. Baseline characteristics were overall equally distributed between different cohorts and treatments.

Primary efficacy analysis

The primary efficacy endpoint was the proportion of responders to treatment at Week 4 of the Fixed Dose Blinded Period. A higher percentage of patients were considered responders in the palopegteriparatide group, compared to placebo: 50.0% (95% CI: 34.6, 65.4) and 26.7% (95%CI: 7.8, 55.1), respectively. The results were, however, not statistically significant.
No clear dose-effect relation could be observed. At the end of the blinded period, the majority of placebo-treated subjects had calcium levels in the normal range (93.3%), in contrast to 86% of palopegteriparatide-treated subjects. In contrast, most patients in the palopegteriparatide group were not receiving active vitamin D (97.7%) or ≤ 1000 mg of calcium (95.3%), versus 40% and 53.3% in the placebo group, respectively.
No clear trend regarding response rates was seen for the different PTH doses administered: even though the 21 µg showed numerically the highest rate responders, fewer subjects treated with 18 µg/day met all responder criteria than subjects treated with 15 µg/day. The starting dose of 18 µg/d for the phase III study was justified by the fact that it led to less hypercalcemia compared to 21 µg/d without meaningful hypocalcemia.

More than 85% of the palopegteriparatide-treated subjects had serum calcium in the normal range, were not taking active vitamin D supplements, and were taking ≤1000 mg/day of calcium. The responder criterion for spot FECa within the normal range (≤ 2%) or a reduction by ≥50% from

baseline was, however, only met by 53.3% to 71.4% of the subjects treated with palopegteriparatide. The applicant highlighted that subjects were restricted to a fixed dose of the investigational drug that was neither titrated nor optimized during the 4 weeks blinded period. It is agreed that this needs to be taken into account when interpreting the results.

Sensitivity analysis

In sensitivity analysis I, the requirement that spot AM FECa be within the normal range or reduced by ≤50% from baseline, was removed. Reducing the requirements to meet the response criteria regarding urinary calcium leads to higher percentage of responders in subjects treated with PTH (79.5% (64.7%, 90.2%)). Taking into account the results of the primary analysis, this is to be expected.

Results from sensitivity analysis 2 are difficult to interpret, as the proportion of responders has been calculated only for patients who met the first criterium (serum calcium within the range 8.8 to 10.0 mg/dL). Results from this analysis seem contradictory, as responders were higher in the placebo group than in all PTH subjects.
If the proportion of responders were calculated for all patients included in the study, results show that 35%, 20% and 46% of patients responded in the palopegteriparatide 15 mcg/day, 18 mcg/day and 21 mcg/day, respectively, and 26% of patients responded in the placebo group.

Fifty-one (51) subjects had data available at Week 110 of the OLE for analysis of the primary efficacy endpoint, using 24 h urine calcium instead of spot FECa. Overall, 27 of 51 subjects (52.9%; 95% CI: 38.5%, 67.1%) met the criteria for the primary composite endpoint and were considered responders to treatment at Week 110. Fourty-two (42) subjects had data available at W84 of the OLE for analysis of the primary efficacy endpoint, using 24 h urine calcium instead of spot FECa. The analysis of the primary efficacy endpoint at W84 showed that the responder rate (95% CI) for all palopegteriparatide treated patients for whom data on all criteria for the assessment of the primary endpoint have been available (42/59) was 66.7% (50.5, 80.4). As 24 h urine calcium instead of spot FECa was used and the dose was individually titrated, this responder rate cannot directly be compared to the responder rate in the primary analysis after 4 weeks of the blinded period. Furthermore, due to limited available data (from 42 out of 59 patients), the evaluation of long-term available results is challenging.

Analysis of the Key Secondary Endpoints

The key secondary efficacy endpoint revised the definition of a treatment responder by lowering the maximum intake of supplemental calcium to ≤500 mg/day, with other responder criteria remaining the same as for the for the primary efficacy analysis at week 84 (including 24-h urine calcium within the normal range). Lowering the maximum intake of supplemental calcium to ≤500 mg/day, with other responder criteria remaining the same as for the efficacy analysis of the primary endpoint at week 84, did not significantly change the outcome compared to the primary analysis (61.9% vs 66.7%). This result indicated that there was a potential of treatment with palopegteriparatide to lower supplemental calcium to ≤500 mg/day.

Analysis of the Secondary Endpoints

Supplemental calcium doses decreased in palopegteriparatide-treated subjects from baseline onward (mean pooled population 2214 mg) and reached a lower pooled mean levels of 561 mg at week 4 and 412 mg at week 84 of the OLE period. At week 4, the mean treatment difference between palopegteriparatide-treated subjects and placebo subjects was -1119 mg per day (95% CI: -1715, -523; nominal p = 0.0004). By Week 110, 53 of 57 patients (93%) were taking calcium doses ≤ 600 mg/ day.

Supplemental active vitamin D doses decreased in palopegteriparatide-treated subjects from baseline onward and reached a lower pooled mean levels of 0.011 µg (range 0.00-0.50 µg) at the end of the blinded period in week 4 and 0 (zero) mg (range 0.00-0.00 µg) at week 84 of the OLE period. At week 4, the mean treatment difference between palopegteriparatide-treated subjects and placebo subjects was -0.864 µg per day (95% CI: -1.176, -0.552); P<0.0001).

Daily Pill Burden decreased significantly during the treatment from a mean of 8-9 at baseline to a mean of 1-2 through week 58.

Serum calcium initially increased in palopegteriparatide-treated subjects, but then slowly decreased and fluctuated around starting values. Serum calcium was 8.80 mg/dL (range 7.80 to 13.50 mg/dL) at baseline and at week 4, sCA was 9.25 mg/dL (range 7.40 to 11.08 mg/dL).
In placebo subjects, serum calcium levels decreased slightly, from baseline to 8.59 mg/dL (range 7.90 to 9.60 mg/dL) at Week 2 and to 8.64 mg/dL (range 7.80 to 9.12 mg/dL) at Week 4.

Albumin adjusted serum calcium over a 24 h profile have been investigated in a PK/PD substudy in patients. Daily administration of palopegteriparatide led to consistent serum calcium concentrations to just below or within the normal range at all time points over 24 h, see PD section above.

Calcium is one of the essential ions necessary for normal functioning of the organism. The serum calcium concentration under physiological conditions is kept within narrow range.
Data from a PK/PD subpopulation of the dose-finding study suggest that serum calcium levels can be maintained stable in the (low-)normal range throughout the day (24 h) without significant peak-trough fluctuation.

Mean spot AM FECa was above the defined normal cut-off of ≤2% at baseline in both treatment groups placebo (2.23% (range 0.91 to 3.39%) vs. 2.76% (range 0.70 to 6.04%) for palopegteriparatide and placebo treated subject, respectively.

Mean 24 h urine calcium fell from 428 mg/24 h (high) at baseline to 178, 149, and 134 mg/24 h (normal <250 mg/24 h) at Weeks 26, 58, and 84, respectively, showing normalization by Week 26. The cut-off for the normal range for 24-Hour Excretion of Calcium was defined as <250 mg/24 h in the CSR, which is acceptable (e.g. in line with Mayo Clinic Laboratories). Results for 24-Hour Urine Calcium at week 84 were available for 42 of 59 patients, and the change from baseline could be calculated for 35 of 59 patients (Source OLE Table 14.2.3.4.7). Maximum observed result for 24-Hour Urine Calcium at week 84 was 289.0 mg/dL. Results provided are therefore regarded limited and should be assessed in conjunction with requested study results of OLE-304.

Following initiation of treatment, mean serum phosphate values decreased sharply for palopegteriparatide-treated subjects at Week 2 to 3.4 mg/dL (range 2.3 to 4.6 mg/dL) and remained in the normal range over the entire 84-week follow-up period. In contrast, mean serum phosphate values for placebo-treated subjects remained unchanged relative to baseline; Week 2 values = 4.1 mg/dL (range 2.8 to 6.0 mg/dL); Week 4 values = 4.1 mg/dL (range 3.0 to 4.7 mg/dL).

The serum calcium × phosphate product decreased for both treatment groups but decreased more for palopegteriparatide-treated subjects. In the OLE, mean serum calcium×serum phosphate product for the overall group remained stable below the cut-off of 55 mg^2/dL^2 through to Week 84. No maximal values above the cut-off were measured.

Following initiation of treatment, mean serum magnesium levels trended slightly higher from baseline for both treatment groups at Week 2 and at Week 4 (by approximately 0.06 to 0.10 mg/dL). In the

OLE, serum magnesium values for the overall group remained stable within a narrow range within the normal range through to Week 84.

Overall, this phase II study provides supportive evidence for efficacy of palopegteriparatide in patients with HP. All serum and urine parameters were influenced in a way that is expected from a PTH replacement therapy while (high dose) supplements with active vitamin D and calcium, being part of current SoC, could be reduced or even discontinued.

Main study

Participant flow

A total of 106 subjects were screened and 84 met eligibility criteria. Sixty of 61 treated (63 randomised) subjects in the Verum and 19 of the 21 patients in the Placebo group completed the main study (26 weeks blinded period), indicating a high completion rate. The ITT population for the primary analysis consist of 82 of 84 subjects randomised (97.6%): 61 subjects receiving palopegteriparatide and 21 subjects receiving placebo. With regards to the reasons for screening failures in TCP-304, a total of 106 subjects were screened, and 84 of these met eligibility criteria and were randomized into the study. No subjects failed initial or final screening due to Inclusion Criterion Number 4, i.e. optimization of supplements prior to randomization to achieve target levels of 25(OH) vitamin D, magnesium, and albumin-adjusted or ionized serum calcium).

Seventy-nine (79) (96.3%) subjects entered the OLE period. One subject discontinued study treatment and trial due to withdrawal by subject within week 52.

Baseline characteristics

Most patients were female (78.0%), with a mean age around 50 years old and with post-surgical chronic hypoparathyroidism (> 85 %). It is unknown the percentage of patients > 65 and >75 years old. Regarding menopausal status, there were more premenopausal women in the placebo group (58.7% and 83.3% for palopegteriparatide and placebo groups, respectively), and more postmenopausal women in the palopegteriparatide group (41.3% and 16.7% for palopegteriparatide and placebo groups, respectively). Overall, baseline characteristics were similar between groups.

Primary efficacy analysis

The results of the primary efficacy analysis showed that the criteria for the composite endpoint were met by significantly more subjects who received palopegteriparatide than subjects who received placebo: 48/61 (78.7% [95% CI: 66.3, 88.1] vs. 1/21 (4.8% [95% CI: 0.1, 23.8]), respectively. This difference is statistically compelling and clearly clinically relevant.

A significant proportion of patients treated with palopegteriparatide was able to reach albumin-adjusted sCa within the normal range of 8.3 to 10.6 mg/dL without an increase in the prescribed study drug in the 4 weeks prior to the assessment at week 26. As per definition of the composite endpoint, this was achieved while at the same time patients were also I.) independent from active vitamin D within 4 weeks prior to Week 26 visit (i.e., all daily standing dose of active vitamin D equal to zero AND use of PRN (as needed/rescue) ≤7 days during the 4 weeks)) and II.) independent from therapeutic doses of calcium within 4 weeks prior to Week 26 visit (i.e., average daily standing dose of elemental calcium ≤600 mg AND use of PRN doses on ≤7 days during the 4 weeks).

Among subjects receiving palopegteriparatide, all but 1 subject achieved independence from active vitamin D (60/61; 98.4%). Fifty-seven (93.4%) subjects achieved independence from therapeutic doses of calcium. Fifty-seven (93.4%) subjects had no increase in prescribed study drug within 4 weeks prior to Week 26 visit. Forty-nine (80.3%) subjects achieved albumin-adjusted serum calcium within the normal range.

Among subjects receiving placebo, approximately half achieved albumin-adjusted serum calcium within the normal range (10/21; 47.6%) or no increase in prescribed study drug (12/21; 57.1%). Approximately one quarter of placebo subjects achieved independence from active vitamin D (5/21; 23.8%), and 1 achieved independence from therapeutic doses of calcium (1/21; 4.8%).

The Week 52 primary endpoint criteria were defined as albumin-adjusted serum calcium measured within the normal range (8.3 to 10.6 mg/dL), independence from active vitamin D and Independence from therapeutic doses of calcium (i.e., average daily standing dose of elemental calcium ≤ 600 mg on the day prior to the Week 52 visit). Overall, 63 of 78 subjects (80.8%; 95% CI: 70.3%, 88.8%) treated with palopegteriparatide met the criteria for the primary composite endpoint and were considered responders to treatment at Week 52.

Sensitivity analysis

Seven sensitivity analysis have been provided, 5 prespecified and 2 post-hoc. They consisted of restricting the population analysed to the Completer Population (i.e. subjects in the ITT population who completed 26 weeks of blinded study treatment and had data on all components for the primary endpoint (Sensitivity Analysis 1); modifying the requirement for average daily standing dose of elemental calcium ≤600 mg to not taking any (Sensitivity Analysis 2); using the 2-sided Cochran-Mantel-Haenszel controlling for gender (Sensitivity Analysis 3); extending the serum calcium range criterion and changing calcium and vitamin D criteria to ≥50% reduction relative to baseline (Sensitivity Analysis 4); most importantly, excluding the use of PRN (Sensitivity Analysis 5) as well as excluding the use of PRN together with defining as non-responders subjects with any missing active vitamin D or calcium data (Sensitivity Analysis 6); and finally repeating the primary analysis extending the serum calcium range to 7.5 to 10.6 mg/dL (Sensitivity Analysis 7).

The results of the sensitivity analysis all supported the results of the primary analysis. The primary endpoint was also consistently favourable for palopegteriparatide across subgroups. The results can therefore be considered robust.

Key secondary endpoints

Key secondary endpoints included the change from baseline at 26 weeks of treatment for the following parameters: HPES - Symptom - Physical domain score, HPES - Symptom - Cognitive domain score, HPES - Impact – Physical Functioning domain score, HPES - Impact – Daily Life domain score and 36-Item Short Form Survey (SF-36) - Physical Functioning subscale score. The primary and the five key secondary endpoints were alpha-controlled and tested sequentially in the pre-specified order above to control the overall significance level at 0.05. Significant Improvements in all key secondary endpoints have been shown. It seems as if no minimum clinically important difference (MCID) was predefined. With regards to the clinical significance of the measured improvements, the applicant presented a deviation of the MCID using an anchor-based method with PGIS serving as anchor, and distribution-based methods, which is considered acceptable.

Other secondary endpoints

Supplemental calcium doses decreased in palopegteriparatide-treated subjects from baseline onward (mean 1748 mg) and reached a lower mean level of 274 mg after week 6. Notably, not all patients in the palopegteriparatide took very low daily calcium doses, one outlier subject has a transient maximum calcium dose at week 26 in palopegteriparatide patients of 10500 mg in the setting of an unrelated SAE. At week 52, 74 (94.8%) of subjects were independent from therapeutic doses of calcium.

Active Vitamin D doses decreased in palopegteriparatide-treated subjects from baseline onward and reached very low/close to zero levels after week 4. Starting from Visit 5 in week 8 on, none of the subjects took Active Vitamin D. At week 52, 78 (100%) of subjects were independent from active vitamin D.

The daily pill burden at baseline was comparable across treatment groups, with a median of 6.0 in both treatment groups, ranging from 2.0 to 12.0 in palopegteriparatide-treated subjects and from 2.0 to 14.0 in placebo subjects. For palopegteriparatide-treated subjects, daily Pill Burden decreased significantly during the treatment (LS mean change from baseline) -5.61 (95% CI: -6.18, -5.04), whereas daily pill-burden stayed more or less the same (decreased very little) for the placebo group (LS mean change from baseline of -1.35 [95% CI: -2.97, 0.27]).

Median and mean serum calcium levels at baseline were within normal range and comparable across treatment groups. Serum calcium initially increased in palopegteriparatide-treated subjects (visit 2), but then slowly decreased to nearly starting values. LS mean change from baseline (SE) at week 26 was 0.306 (0.1128) mg/dL. In placebo subjects, serum calcium levels decreased slightly, falling slightly below normal range at Week 2 (mean observed value: 8.23 mg/dL) and at Week 26 (mean observed value: 8.22 mg/dL). At week 26, comparable to baseline, the measured range of values (minimal and maximal values) contained some values out of the normal range (8.3 to 10.6 mg/dL): the range was 6.80 - 10.40 mg/dL for palopegteriparatide treated patients and 7.16 - 8.80 mg/dL for placebo treated patients.

While fluctuations (decreases) were initially observed between study visits, median and mean serum phosphate levels were within normal range at baseline in both treatment groups and remained within normal range throughout the 26 weeks of blinded treatment.

Median and mean serum calcium-phosphate product at baseline was below 55 mg^2/dL^2 in both treatment groups and stayed below that recommended cut-off (Brandi et al. 2016).

Mean serum calcium, phosphate levels and serum calcium x serum phosphate product remained within the normal range at week 52 of the OLE period.

These effects on laboratory parameters discussed above (seen in both clinical studies) could be expected due to mechanism of action of palopegteriparatide. However, the clinical relevance is difficult to interpret, as patients had serum phosphate levels within normal range at baseline. Also, mean serum calcium x serum phosphate product was below the upper limit during all treatment period.

According to hypoparathyroidism treatment guidelines, phosphate binders are recommended for patients with serum phosphate > 6.5 mg/dL. As treatment with phosphate binders were not allowed, no data in patients with high phosphate levels is available, and as a consequence no data of serum calcium x serum phosphate product is available in these patients. Nonetheless, as per palopegteriparatide mechanism of action, a drop in phosphate serum levels is expected following treatment initiation and, considering that phosphate binders can be used in clinical practice due to the fact that no relevant clinically interactions exist, only a transient high level of serum calcium x phosphate product could be anticipated, and the clinical impact is agreed to be low.

Mean and median serum magnesium levels were within normal range at baseline in both treatment groups and remained within normal range throughout the 26 weeks of blinded treatment and through week 52 of the OLE period.

Regarding secondary endpoints on skeletal health, overall, bone turnover markers P1NP as well as CTx were generally in the low-normal range at baseline (as expected with PTH insufficiency), and peaked at

Weeks 12 (CTx) and 26 (P1NP) upon exposure to palopegteriparatide. This pattern was discussed to be consistent with an initial increase in bone remodelling followed by normal physiologic mobilization of calcium from the skeleton (i.e. restoration of more normal bone physiology with PTH replacement). For DXA, mean Z-scores showed a decrease at Week 26 in areas measuring primarily trabecular bone, trending towards age- and sex-appropriate normal ranges by Week 26.
The data support the expected increase in bone remodelling with palopegteriparatide towards a normalisation of BMD as best reflected by BMD z-scores.

Below the section on skeletal manifestations of the Management of Hypoparathyroidism: Summary Statement and Guidelines by Brandi et al. is summarised:
"*Bone mineral density (BMD), as determined by dual energy x-ray absorptiometry, is typically above average at all measurement sites in patients with HP. Imaging […] demonstrates that both cortical and trabecular compartments of bone are affected (e.g., increased cortical volumetric BMD and trabecular bone volume fraction and decreased cortical porosity). Lower bone turnover is a characteristic of this disease, as best seen by dynamic histomorphometry of the bone biopsy. Reduced bone remodelling is associated with positive bone balance, which helps to account for the above-average features of skeletal density and microstructure. The abnormally low bone remodelling in hypoparathyroidism and dense bone suggests that hypoparathyroid bone is hypermature and, therefore, potentially more subject to fracture than euparathyroid bone. Fracture data, however, are sparse, in part because this is a rare disease. Large cohorts to ascertain fracture incidence are virtually impossible to assess. A small cohort showed an increase in morphometric vertebral fractures in postmenopausal women with hypoparathyroidism; however, larger registry studies in Denmark did not show a difference in overall fracture rate between hypoparathyroid patients and controls*."

The effects on bone turnover markers P1NP as well as CTx as well as BMD measured with DXA are acknowledged and it is agreed that they indicate a restoration of a closer to normal bone physiology, what could be expected for a PTH substitution therapy. However, it is unclear whether this will have an effect on fracture risk.

During the blinded period, median BMD decreased through the initial 26 weeks, but not below the normal ranges. Results initially provided has been updated with available long-term data. Results from TCP-304 (through Weeks 26 and 52) and TCP-201 (through Weeks 26, 58, and 110) study has been analysed separately. Results provided describe an initial decrease of BMD through week 26, with no further or little changes through week 52/ week 110. Mean T-score BMD available values for each OLE period remained within the normal range. Overall, results presented do not raise safety concerns regarding BMD loss in any subgroup analysed, although a deleterious effect on BMD cannot be discarded in some patients. As a consequence, a warning regarding monitoring in patients with osteoporosis was included in section 4.4 of the SmPC.

Results for the EQ-5D Domain score and Visual Analogue score were not visually compared between treatment groups what would have helped to easily understand the treatment differences (not further pursued). Improvements were more often seen in the palopegteriparatide group, which is acknowledged. However, since the results are not alpha-controlled and since comparison to a potentially suboptimal SOC treatment in the Placebo arm was made as outlined above, the CHMP decided that results on PROs should not be included in section 5.1 of the SmPC.

In the pivotal clinical study, the primary endpoint is focused on maintaining serum calcium within the target plasma level range (8.3-10.6 mg/dL), while down titrating active vitamin D (to zero) and calcium supplementation (to supplemental doses ≤600 mg/day). No data are available on possible effects of palopegteriparatide on the main target organ, i.e. the kidney.

The primary endpoint and the duration of the study does not allow to demonstrate direct clinical benefit versus standard treatment in terms of the avoidance of long-term consequences such as

nephrocalcinosis/lithiasis and renal impairment. Positive effects could possibly be expected based on the reductions observed in 24 h urinary calcium. Effects on rates and/or degree of long-term consequences seen with conventional treatment like nephrocalcinosis/lithiasis and renal impairment are currently not known and will need to be further investigated. Clinical events of "*hypo- or hypercalcemia (emergency/urgent care visits and hospitalizations) and progression of vascular calcifications, nephrocalcinosis, and nephrolithiasis*" were safety variables in CS TCP-201. Concerning how effects of palopegteriparatide treatment on long term outcomes like risk for vascular calcifications, nephrolithiasis, nephrocalcinosis, and chronic kidney disease will be further investigated and reported for regulatory assessment, the applicant confirmed that renal imaging is not part of the examinations in the open-label extension (OLE) periods of TCP 201 and TCP 304 and underlined that there are also currently no plans to implement renal imaging in these ongoing studies. With regard to CT scans of the renal tract, radiation exposure associated with abdominal computed tomography scans at 6-to-12-month intervals is considered unacceptable. However, the CHMP considers the use of renal ultrasounds could be an alternative to the renal CT scan. In line with Bollerslev et al., renal ultrasound could indeed help to detect calcification or stones at an early stage in asymptomatic individuals. Showing a potential benefit regarding the development/worsening of nephrolithiasis and nephrocalcinosis which may be expected from the replacement of the deficient parathyroid hormone and would be relevant information for patients and potentially also for HTAs. This is, however, not necessary in the context of the indication applied for. In addition, baseline values for the study population are not available for comparison. Based on these arguments, it is acceptable that the OLE studies will not include renal US in addition to the monitoring of parameters like the estimated glomerular filtration rate and urine calcium for longitudinal assessment of renal function and risk of calcification. As stated by the Applicant, investigators would be expected to follow clinical guidelines including performance of renal imaging when judged to be clinically required for the investigator to make a diagnosis. Bollerslev et al. state that renal imaging is recommended "at diagnosis; as clinically indicated; every 5 years".

2.5.7. Conclusions on the clinical efficacy

The results of the primary efficacy analysis of the main study showed that the criteria for the composite endpoint were met by significantly more subjects who received palopegteriparatide than subjects who received placebo: 48/61 (78.7% [95% CI: 66.3, 88.1] vs. 1/21 (4.8% [95% CI: 0.1, 23.8]), respectively.
The primary endpoint was consistently favourable for palopegteriparatide across the primary and all sensitivity analysis. The primary endpoint was also consistently favourable for palopegteriparatide across subgroups and supported by various secondary endpoints. The results can therefore be considered robust. Data from the dose-finding study further support efficacy of palopegteriparatide. Also, results from phase 2/phase 3 OLE periods reflect the responder rate is maintained over time, and the majority of patients met independence of therapeutic doses of calcium supplements and active vitamin D.

Secondary efficacy PD endpoints were also consistent with palopegteriparatide mechanism of action, and available results of phase 2/phase 3 OLE show that mean serum calcium, phosphate levels and serum calcium x serum phosphate product remained within the normal range.

Overall, all these results support the use of palopegteriparatide as a replacement therapy in patients with chronic hypoparathyroidism.

In conclusion, a clinically relevant efficacy has been demonstrated in adults with HP for palopegteriparatide with a starting dose of 18 µg/d and then individually and progressively titrated to an optimal dose in dose increments of 3 µg/day as per the treatment algorithm outlined in the CSP.

Statistically significant differences were described in favour of palopegteriparatide for PROs. However, based on the comparison to a potentially suboptimal SOC treatment in the Placebo arm, results on PROs are not included in section 5.1 of the SmPC.

Palopegteriparatide was shown to increase bone turnover resulting in mean BMD initial decreases through the initial 26 weeks, but not below the normal ranges, with no further or little changes through week 52/week 110.

2.5.8. Clinical safety

The palopegteriparatide safety profile is derived from 5 clinical trials (one Phase 3 trial and one Phase 2 trial in adult subjects with hypoparathyroidism, and three Phase 1 trials in healthy subjects). The main evidence of safety for the registration of palopegteriparatide for parathyroid replacement therapy comes from TCP-304 and TCP-201.

- The pivotal trial is the Phase 3 Trial TCP-304 (PaTHway), an ongoing, multicenter, randomized, double-blind, placebo-controlled, parallel group trial investigating the safety, tolerability and efficacy of palopegteriparatide administered subcutaneously (SC) daily in adult subjects with hypoparathyroidism. The trial includes a 26-week Blinded Treatment Period and an OLE period of 156 weeks. A total of 84 subjects were randomized, and 82 subjects dosed (61 to palopegteriparatide, 21 to placebo) in the trial. A total of 79 subjects (60 palopegteriparatide-treated subjects and 19 placebo subjects) completed the Blinded Treatment Period and transitioned into the OLE. Data are available up to the data cutoff date of 20 July 2022, the date that the last subject completed Week 52 (OLE period).
- Additional data on patient safety is derived from Phase 2 Trial TCP-201 (PaTH Forward), an ongoing, multicenter, randomized, double-blind, placebo-controlled, parallel group trial, investigating the safety, tolerability, and efficacy of palopegteriparatide administered SC daily in adult subjects with hypoparathyroidism. The trial includes a 4-week Blinded Treatment Period and an OLE period of 210 weeks. A total of 59 subjects have been randomized and dosed (44 to palopegteriparatide, 15 to placebo). All 59 subjects successfully completed the Blinded Treatment Period and transitioned into the OLE. Data are available up to the data cutoff date of 01 June 2022, the date that the last subject completed Week 110 of the OLE;
- Data from Phase 1 healthy subjects in trials CT-103, TCP-104, and TCP-105 who received palopegteriparatide

Safety data are summarized in 2 safety pools.

- Safety Pool I: healthy subjects who received palopegteriparatide in CT-103, TCP-104, and TCP-105 (N=186 total).
- Safety Pool II: subjects with hypoparathyroidism in TCP-304 and TCP-201 (N=141 total)

According to the Applicant, if subjects took both palopegteriparatide and placebo during the Blinded Treatment Period (Safety Pool II), the data for these subjects were analyzed according to the treatment that was dosed the majority of time.

2.5.8.1. Patient exposure

Safety Pool I

A total of 136 healthy subjects were treated with palopegteriparatide in the SAD portion of CT-103 or single-dose trials TCP-104 and TCP-105, and 50 healthy subjects were treated with palopegteriparatide

in the MAD portion of CT-103. Most subjects completed their respective trials. No subjects in Safety Pool I discontinued the trial prematurely due to an adverse event. One subject in the Single Dose Group of Safety Pool I (0.7%, 1/136) discontinued due to subject request. Four subjects (8.0%, 4/50) receiving multiple doses of palopegteriparatide in CT-103 discontinued the trial.

Safety Pool II

Overall, in studies TCP-304 and TCP-201 and their OLE periods, a combined total of 139 subjects were exposed at least 1 daily SC dose of palopegteriparatide at a starting dose of at least 15 µg/day.

In TCP-304, 79/80 subjects in the All TransCon PTH group received ≥26 weeks of palopegteriparatide, 59/80 received ≥ 52 weeks. In TCP-201, almost all subjects (58/59) in the All TransCon PTH group in the Safety Analysis Population received ≥84 weeks of treatment, and 57/59 received ≥ 110 weeks.

In TCP-304 study, the mean duration of exposure in the TransCon PTH/TransCon PTH group was 398.5 days, ranging from 109 to 465 days. The mean total number of actual doses administered was 387.4 doses (range: 104 to 462 doses). The mean average actual daily dose of palopegteriparatide (total actual palopegteriparatide dose divided by the duration of palopegteriparatide exposure) was 21.5 µg (range: 9.73 to 36.47 µg), and the mean total actual dosage was 8552.7 µg (range: 2583 to 13641 µg) (Table 2). The mean duration of exposure in the Placebo/TransCon PTH was 216.7 days, ranging from 190 to 260 days. The mean total number of actual doses administered was 207.8 doses (range: 157 to 255 doses). The mean average actual daily dose of palopegteriparatide was 22.7 µg (range: 13.4 to 33.4 µg), and the mean total actual dosage was 4934.1 µg (range: 2634 to 6879 µg).

In TCP-201 study, for all subjects treated with palopegteriparatide (All TransCon PTH group), the mean average actual daily dose during the TransCon PTH Period was 21.1 µg (range: 9.57 to 41.04 µg). The mean average daily dose increased from 22.9 µg (range: 9 to 54 µg, 58/59 subjects) at Week 84 to 25.2 µg (range: 9 to 60 µg, 57/59 subjects) at Week 110. The mean number of actual palopegteriparatide doses for all subjects was 856.5 doses (range: 18 to 961 doses).

In the Safety Analysis Population, most palopegteriparatide-treated subjects (99.0%, 104/105) and placebo-treated subjects (94.4%, 34/36) in Safety Pool II completed the Blinded Periods of their respective trials and continued to receive palopegteriparatide in the OLE periods. One palopegteriparatide-treated subject and 2 placebo-treated subjects (all in TCP-304) discontinued treatment due to adverse events during the Blinded Period. In TCP-304, one subject discontinued study treatment and trial during OLE period due to withdrawal by subject. Additionally, after the data cutoff date, one subject discontinued the trial due to pregnancy (OLE period).

Additionally, one subject in TCP-201 (originally in the placebo group) discontinued treatment and the trial after Visit 4 in the OLE period due to a protocol violation of non-compliance with contraception requirements. Another subject in TCP-201 discontinued study treatment during OLE period due to withdrawal by subject.

The median total number of actual doses administered was 238.0 (range: 1 to 711 doses). The median actual daily dose was 19.9 µg, and the median total actual dosage was 5166.0 µg.

2.5.8.2. Adverse events

An overall summary of AEs in the Phase 2 Study TCP-201 and in the pivotal Study TCP-304 is presented in Table 36.

Table 36. Overview of Treatment Emergent Adverse Events (Blinded Treatment Periods and TransCon PTH Periods) – TCP-304, TCP-201, and Safety Pool II (Safety Analysis Population)

	TCP-304[a] (Up to Week 52)			TCP-201 (Up to Week 110)
Palopegteriparatide-Treated Subjects with:	**TransCon PTH/ TransCon PTH (N=61) n (%)**	**Placebo/ TransCon PTH (N=19) n (%)**	**All TransCon PTH[a] (N = 80) n (%)**	**All TransCon PTH[a] (N=59) n (%)**
TEAEs	56 (91.8)	16 (84.2)	72 (90.0)	56 (94.9)
Serious TEAEs (TESAEs)	5 (8.2)	3 (15.8)	8 (10.0)	6 (10.2)
Severity				
Grade 4	1 (1.6)	0	1 (1.3)	0
Grade 3	3 (4.9)	4 (21.1)	7 (8.8)	4 (6.8)
Grade 2	26 (42.6)	1 (5.3)	27 (33.8)	17 (28.8)
Grade 1	26 (42.6)	11 (57.9)	37 (46.3)	35 (59.3)
Related TEAE	33 (54.1)	9 (47.4)	42 (52.5)	25 (42.4)
Serious related TEAE	1 (1.6)	1 (5.3)	2 (2.5)	0
TEAE related to hyper- or hypocalcemia leading to ER/Urgent Care visit and/or hospitalization	4 (6.6)	2 (10.5)	6 (7.5)	0
TEAE leading to discontinuation of palopegteriparatide	1 (1.6)[b]	0	1 (1.3)[b]	0
TEAE leading to discontinuation of trial	1 (1.6)[b]	0	1 (1.3)[b]	0
TEAE leading to death	1 (1.6)[b]	0	1 (1.3)[b]	0

Sources: TCP-304 120-Day Safety Table 14.3.1.1; TCP-201 120-Day Safety Table 14.3.1.1
Abbreviations: ER = emergency room; TEAE = treatment-emergent adverse event; TransCon PTH = palopegteriparatide.
Note: A TEAE is considered a TransCon PTH Period TEAE if it occurred after the first dose of palopegteriparatide. Only subjects from the Safety Analysis population who had at least 1 dose of palopegteriparatide (i.e., were in the TransCon PTH group) are included in the table. Percentages were calculated based on the number of subjects in the Safety Analysis Population.
In the severity categories, subjects are displayed for the highest severity only. AE severity was assessed by WHO toxicity grading scale.
Note: **Original SCS data cutoff dates**: TCP-304: 12 January 2022 (Week 26); TCP-201: 24 September 2021 (Week 84). **120-day safety update data cutoff dates**: TCP-304: 20 July 2022 (Week 52), TCP-201: 01 June 2022 (Week 110).
[a] The All TransCon PTH column for TCP-304 and TCP-201 is the sum of TransCon PTH/TransCon PTH and Placebo/TransCon PTH columns for each trial. For TCP-201, the TransCon PTH/TransCon PTH and Placebo/TransCon PTH columns are shown in the cited source tables.
[b] Subject [redacted] who suffered a fatal cardiac arrest (unrelated to palopegteriparatide). The death led to discontinuation of study drug and withdrawal from the trial, as described in the original SCS.

Additionally, the summary of adverse events in the Safety Pool I (healthy subjects who received palopegteriparatide in CT-103, TCP-104, and TCP-105) is presented in Table 37

Table 37. Safety Pool I: Overview of Treatment Emergent Adverse Events (Safety Analysis Population)

Subjects with:	**Single Dose (N=136) n (%)**	**Multiple Dose (N=50) n (%)**	**Total (N=186) n (%)**
Treatment-Emergent Adverse Events (TEAEs)	32 (23.5)	33 (66.0)	65 (34.9)
Related TEAE	19 (14.0)	16 (32.0)	35 (18.8)
Treatment-Emergent Serious Adverse Events (TESAEs)	1 (0.7)	1 (2.0)	2 (1.1)
Related TESAE	0	0	0
TEAE Leading to Discontinuation of Study Drug	0	3 (6.0)	3 (1.6)
TEAE Leading to Discontinuation of Trial	0	0	0
TEAE Leading to Death	0	0	0

Source: ISS Table 14.1.3.1.1
Abbreviations: TEAE = treatment-emergent adverse event; TransCon PTH = palopegteriparatide.
Note: Percentages are calculated based on the number of subjects in the Safety Analysis Population.

The incidence of overall exposure-adjusted TEAEs was lower for palopegteriparatide-treated subjects compared to placebo subjects (0.86 events/person-years vs 1.10 events/person-years). Accordingly, the incidence of exposure-adjusted TEAEs was notably lower for palopegteriparatide-treated subjects compared to placebo subjects for a majority of the most common SOCs and PTs.

Treatment related adverse events

Safety Pool II

• During the Blinded Period, a total of 37.1% (39/105) of palopegteriparatide-treated subjects and 25.0% (9/36) of placebo-treated subjects experienced at least 1 treatment-related TEAE.

The most common TEAE (>10%) experienced by palopegteriparatide-treated subjects was the injection site reaction (18.1% of palopegteriparatide-treated subjects vs 0 placebo subjects). Only 1 treatment-related Grade 3 and TESAE (hypercalcemia, in a palopegteriparatide-treated subject in TCP-304) was reported.

• During the TransCon PTH Period, a total of 48.2% (67/139) of palopegteriparatide-treated subjects experienced treatment-related TEAEs. The most common were injection site reaction (15.8%), headache (9.4%), hypercalcaemia (10.8%), nausea (7.2%), hypocalcaemia (5.0%) and paraesthesia (3.6%).

Table 38. Most Common Treatment-Related Treatment-Emergent Adverse Events (>5% in Any TransCon PTH Group in TCP-304, TCP-201, or Safety Pool II) (Safety Analysis Population)

	TCP-304[a] (Up to Week 52)			TCP-201[a] (Up to Week 110)
Subjects with:	**TransCon PTH/ TransCon PTH (N=61) n (%)**	**Placebo/ TransCon PTH (N=19) n (%)**	**All TransCon PTH (N =80) n (%)**	**All TransCon PTH (N=59) n (%)**
Subjects with at least 1 Treatment-Related TEAE	33 (54.1)	9 (47.4)	42 (52.5)	25 (42.4)
Injection site reaction	20 (32.8)	1 (5.3)	21 (26.3)	1 (1.7)
Headache	6 (9.8)	0	6 (7.5)	7 (11.9)
Hypercalcaemia	7 (11.5)	4 (21.1)	11 (13.8)	4 (6.8)
Nausea	6 (9.8)	1 (5.3)	7 (8.8)	3 (5.1)
Hypocalcaemia	3 (4.9)	1 (5.3)	4 (5.0)	3 (5.1)
Paraesthesia	0	1 (5.3)	1 (1.3)	4 (6.8)

Source: TCP-304 120-Day Safety Table 14.3.1.3, Table 14.3.1.14; TCP-201 120-Day Safety Table 14.3.1.4, Table 14.3.1.12
Abbreviations: TEAE = treatment-emergent adverse event; TransCon PTH = palopegteriparatide.
Note: MedDRA version 24.0 for TCP-201 and 24.1 for TCP-304.
TransCon PTH Period TEAE is defined as TEAE occurring after the first dose of palopegteriparatide. Percentages are calculated based on the number of subjects in the Safety Analysis Population. Subjects from the Safety Analysis Population who had at least 1 dose of TransCon PTH were included in this table.
Note: TEAEs within the table are sorted by decreasing frequency of preferred terms within the TCP-304 All TransCon PTH group.
Note: **Original SCS data cutoff dates**: TCP-304: 12 January 2022 (Week 26); TCP-201: 24 September 2021 (Week 84). **120-day safety update data cutoff dates**: TCP-304: 20 July 2022 (Week 52) , TCP-201: 01 June 2022 (Week 110).
[a] The All TransCon PTH column for TCP-304 and TCP-201 is the sum of TransCon PTH/TransCon PTH and Placebo/TransCon PTH columns for each trial. For TCP-201, the TransCon PTH/TransCon PTH and Placebo/TransCon PTH columns are shown in the cited source tables.

Table 39. Summary of Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Blinded Period Safety Analysis Population (TCP-304)

Table 14.3.1.3 Summary of Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Blinded Period Safety Analysis Population

System Organ Class Preferred Term	TransCon PTH (N=61) n (%)	Placebo (N=21) n (%)	Total (N=82) n (%)
Subjects with at Least One Related Treatment-Emergent Adverse Event	30 (49.2)	8 (38.1)	38 (46.3)
General disorders and administration site conditions	25 (41.0)	2 (9.5)	27 (32.9)
Injection site reaction	19 (31.1)	0	19 (23.2)
Injection site bruising	2 (3.3)	1 (4.8)	3 (3.7)
Fatigue	1 (1.6)	1 (4.8)	2 (2.4)
Injection site erythema	2 (3.3)	0	2 (2.4)
Asthenia	1 (1.6)	0	1 (1.2)
Injection site rash	1 (1.6)	0	1 (1.2)
Thirst	1 (1.6)	0	1 (1.2)
Gastrointestinal disorders	9 (14.8)	2 (9.5)	11 (13.4)
Nausea	5 (8.2)	2 (9.5)	7 (8.5)
Diarrhoea	3 (4.9)	0	3 (3.7)
Abdominal discomfort	2 (3.3)	0	2 (2.4)
Constipation	2 (3.3)	0	2 (2.4)
Vomiting	2 (3.3)	0	2 (2.4)
Dry mouth	1 (1.6)	0	1 (1.2)
Metabolism and nutrition disorders	6 (9.8)	3 (14.3)	9 (11.0)
Hypercalcaemia	6 (9.8)	0	6 (7.3)
Hypocalcaemia	1 (1.6)	3 (14.3)	4 (4.9)
Nervous system disorders	7 (11.5)	1 (4.8)	8 (9.8)
Headache	6 (9.8)	1 (4.8)	7 (8.5)
Dizziness	1 (1.6)	0	1 (1.2)
Dizziness postural	1 (1.6)	0	1 (1.2)
Dyspraxia	1 (1.6)	0	1 (1.2)
Skin and subcutaneous tissue disorders	4 (6.6)	0	4 (4.9)

TransCon PTH dose is expressed as µg of PTH(1-34). MedDRA version 24.1. Percentages are calculated based on the number of subjects in the Safety Analysis Population. TEAEs occurring prior to the first dose of open-label treatment are included.

System Organ Class Preferred Term	TransCon PTH (N=61) n (%)	Placebo (N=21) n (%)	Total (N=82) n (%)
Photosensitivity reaction	2 (3.3)	0	2 (2.4)
Rash	1 (1.6)	0	1 (1.2)
Solar lentigo	1 (1.6)	0	1 (1.2)
Injury, poisoning and procedural complications	1 (1.6)	1 (4.8)	2 (2.4)
Incorrect dose administered	0	1 (4.8)	1 (1.2)
Sunburn	1 (1.6)	0	1 (1.2)
Musculoskeletal and connective tissue disorders	1 (1.6)	1 (4.8)	2 (2.4)
Muscle spasms	0	1 (4.8)	1 (1.2)
Myalgia	1 (1.6)	0	1 (1.2)
Cardiac disorders	1 (1.6)	0	1 (1.2)
Palpitations	1 (1.6)	0	1 (1.2)

Table 40. Treatment-Emergent Adverse Events Assessed as Related to Treatment by Preferred Term – Blinded Period (Safety Population, TCP-201)

Preferred Term	TransCon PTH				Placebo[a] N=15 n (%)
	PTH 15 µg/day N=14 n (%)	PTH 18 µg/day N=15 n (%)	PTH 21 µg/day N=15 n (%)	All PTH Subjects N=44 n (%)	
Subjects with at Least One Related Treatment-Emergent Adverse Event	2 (14.3)	3 (20.0)	4 (26.7)	9 (20.5)	1 (6.7)
Headache	2 (14.3)	0	1 (6.7)	3 (6.8)	0
Hypercalcaemia	0	1 (6.7)	2 (13.3)	3 (6.8)	0
Dizziness	0	2 (13.3)	0	2 (4.5)	0
Nausea	1 (7.1)	0	1 (6.7)	2 (4.5)	0
Injection site erythema	0	0	1 (6.7)	1 (2.3)	0
Thirst	0	0	1 (6.7)	1 (2.3)	0
Hypocalcaemia	0	0	0	0	1 (6.7)

Source: DB Table 14.3.1.13
Abbreviation: TransCon PTH = palopegteriparatide
Note: MedDRA version 24.0. Percentages were calculated based on the number of subjects in the Safety Population. A TEAE was considered a PTH TEAE if it occurred after the first dose of TransCon PTH.
[a] Consists of pooled dosage placebo groups.

Table 41. Safety Pool I -Related Treatment-Emergent Adverse Events Reported in >2% of Subjects in the Single or Multiple Dose Group (Safety Analysis Population)

Preferred Term	Single Dose (N=136) n (%)	Multiple Dose (N=50) n (%)	Total (N=186) n (%)
Subjects with at least 1 related TEAE	19 (14.0)	16 (32.0)	35 (18.8)
Headache	5 (3.7)	4 (8.0)	9 (4.8)
Fatigue	4 (2.9)	1 (2.0)	5 (2.7)
Dizziness	2 (1.5)	2 (4.0)	4 (2.2)
Dizziness postural	2 (1.5)	2 (4.0)	4 (2.2)
Palpitations	0	4 (8.0)	4 (2.2)
Nausea	1 (0.7)	2 (4.0)	3 (1.6)
Hypercalcaemia	1 (0.7)	2 (4.0)	3 (1.6)
Presyncope	0	2 (4.0)	2 (1.1)

Source: ISS Table 14.1.3.1.3
Abbreviations: TEAE = treatment-emergent adverse events
Note: MedDRA version 20.0 for CT-103 and version 22.1 for TCP-104 and TCP-105. Percentages are calculated based on the number of subjects in the Safety Analysis Population.

Adverse events of special interest (AESI)

The current section focuses on assessments of adverse events of special interest (AESI) mainly based on data of the Phase 3 study and, in some aspects, on the data from the Phase 2 study and on the data from the Phase 1 studies.

Adverse events of special interest (AESIs) for palopegteriparatide currently comprise the following:

- Persistent severe hypocalcemia (<7.0 mg/dL) for >7 days
- Persistent severe hypercalcemia (>12.0 mg/dL) for >7 days
- Vasodilatory signs and symptoms, which may have included orthostatic dizziness, lightheadedness, weakness, blurring of vision, pre-syncope, syncope, headache, orthostatic hypotension, orthostatic tachycardia/palpitations

For TCP-304, AESIs were collected starting with original protocol. For TCP-201, AESIs were collected starting with Amendment 3 during the OLE; additionally, TCP-201 Amendment 3 was finalized on 10 March 2021, close to the study cutoff date of 24 September 2021 for this trial.

Therefore, the results for the 2 trials are summarized separately. AESIs were not evaluated for Phase 1 trials.

During blinded period for TCP-304, no AESIs were reported for placebo subjects. During all the study (blinded and OLE periods), a total of 10/80 (12.5%) palopegteriparatide-treated subjects experienced AESIs, none of which were serious. All events were vasodilatory signs and symptoms: dizziness postural (2/80 subjects, 2.5%) and postural orthostatic tachycardia syndrome 5/80 (6.3%) subjects each, and blood pressure orthostatic decreased, headache, palpitations, and syncope in 1 (1.3%) subject each. No AESIs of persistent severe hyper- or hypocalcemia were reported.

Most data in TCP-201 as of the cutoff date were collected under the earlier (pre-Amendment 3) versions of the protocol. As of the safety update, 1 new subject treated with palopegteriparatide in TCP-201 reported 1 AESI: Grade 1 orthostatic hypotension, which was considered unrelated to palopegteriparatide.

Other significant adverse events

Hypercalcaemia / Hypocalcaemia

Hyper- and Hypocalcaemia were mainly assessed with regard to Safety Pool II.

During the Blinded Treatment Period, 14.3% (15/105) of palopegteriparatide-treated subjects and 27.8% (10/36) placebo subjects experienced at least 1 TEAE within the Metabolism and nutrition disorders SOC. This difference was due to the incidence of hypo- and hypercalcemia.

Hypocalcemia was less frequent in palopegteriparatide-treated subjects compared to placebo (5.7% vs 27.8%), whereas hypercalcemia was slightly more frequent (8.6% vs 0%). Treatment-related events were reported in 8.6% and 11.1% of subjects, respectively. Treatment-related hypocalcemia was reported in 1 (1.0%) and 4 (11.1%) of subjects, respectively; all palopegteriparatide-treated subjects with hypercalcemia reported at least 1 treatment-related event.

During the TransCon PTH Period, among the 139 subjects who received palopegteriparatide in Safety Pool II, 18.0% had at least 1 TEAE within the Metabolism and nutrition SOC. The most common TEAEs in the TransCon PTH Period (≥5% overall) were hypocalcemia (8.6%, 12/139) and hypercalcemia (7.2%, 10/139), as expected with hypoparathyroidism. Treatment-related TEAEs were experienced in 10.1% of subjects; only hypercalcemia (7.2%, 10/139) and hypocalcemia (3.6%, 5/139) were

treatment-related. One subject each experienced severe (Grade 3) TEAEs of hypercalcemia, hypocalcemia, and hypokalemia. Hypercalcemia, hypocalcemia (Grade 2), hypokalemia, and dehydration were serious in 1 subject each and only hypocalcemia was considered a treatment-related TESAE.

The incidence of hypercalcemia leading to ER/Urgent care visit and/or hospitalization only occurred in the palopegteriparatide-treated group during the Blinded Treatment Period. Most events of hyper- or hypocalcemia were Grade 1 or Grade 2; only 1 event (hypercalcemia) was Grade 3 and a TESAE.

Local tolerability and TEAEs Related to Injections

Results regarding local tolerability in Safety Pool II were similar between palopegteriparatide-treated and placebo subjects in both groups. Overall, ≥75% subjects in all groups reported no redness, itching, swelling, or pain at the time of injection or 15 minutes later; in TCP-201, pain results were similar between doses (15, 18, and 21 µg/day).

In TCP-304 TEAEs related to injections were more common in palopegteriparatide-treated subjects compared to placebo (36.1% [22/61] vs 4.8% [1/21]). However, most events of injection site reaction were Grade 1. No pain was reported. Different injection sites did not seem to have played an important role in the appearance of ISR.

No TEAEs related to injections were reported in TCP-201, probably mostly due to difference in definition of collection of TEAEs compared to TCP-304 and therefore different reporting.

2.5.8.3. Serious adverse event/deaths/other significant events

Serious adverse events

In the phase 2 study (TCP-201), the incidence of SAEs was low and no SAE was considered related to study treatment respectively led to permanent discontinuation from study treatment.

In the phase 3 study (TCP-304), the incidence of SAEs was low and only one of the SAEs was considered related to study treatment, in which Palopegteriparatide was temporarily interrupted.

In Safety Pool I, two subjects experienced TESAEs, both were considered unrelated.

Death

The TESAE of cardiac arrest, in the palopegteriparatide-treated subject (Safety Pool II/TCP-304) was fatal. A brief narrative was provided. No TEAEs leading to death were reported in Safety Pool I or in any placebo group of Phase 1 studies.

2.5.8.4. Laboratory findings

The current section focuses on assessments of Laboratory findings mainly based on data of the Phase 3 (TCP-304) study and, only in some aspects, supportively on the data from the phase 2 (TCP-201) study and on the data from the phase 1 studies.

In general, no treatment-emergent (or, for MAD portion of CT-103, dose-dependent) patterns or changes from baseline in safety laboratory parameters were observed in Safety Pool I (other than increased serum calcium in CT-103 [Trial CT-103 CSR, Section 12.4]). No trends were observed between or among treatment groups.

Haematology

In TCP-304 and TCP-201, no clinically meaningful differences or patterns in serum haematology parameter results were found between palopegteriparatide and placebo subjects.

In Safety Pool II overall, haematology parameter results were generally stable and remained within the normal range. No clinically meaningful differences in results were found between the palopegteriparatide and placebo subjects. Six subjects (4.3%, 6/139), all treated with palopegteriparatide, reported TEAEs associated with abnormal haematology results: iron deficiency anaemia in 3 subjects, and anaemia, lymphadenopathy, and thrombocytopenia in 1 subject each. No events were Grade 3 or above, treatment-related, or serious.

Serum chemistry

No clinically meaningful differences or patterns in serum chemistry parameter results were found between palopegteriparatide and placebo subjects for ALT, AST, bilirubin, bicarbonate, chloride, cholesterol, creatinine, creatine kinase, direct bilirubin, GGT, globulin, glucose, indirect bilirubin, potassium, protein, sodium, urate, or urea nitrogen.

Serum Calcium Excursions

TCP-304

Both analyses showed that excursions to high calcium levels were mostly observed in palopegteriparatide-treated subjects, and that while excursions to low calcium levels were observed in both treatment groups, they were observed more frequently in placebo subjects than in palopegteriparatide-treated subjects. Excursions to high calcium levels were observed only during the first 3 months of the Blinded Period, likely due to the titration algorithm. Excursions to low calcium levels (<8.3 mg/dL) were observed throughout the entire Blinded Period, but more particularly during the first 3 months (TCP-304 CSR, Section 12.5.2.2.1). The incidence and rate were notably reduced when extending the lower limit of serum calcium to 7.5 mg/dL (instead of 8.3 mg/dL).

Abnormal serum calcium values were not considered adverse events unless associated with a sign or symptom. Consequently, the incidence of TEAEs of hyper- or hypocalcemia was lower than the incidence of abnormal serum calcium values in both treatment groups (TEAEs of hypercalcemia: 6/61 [9.8%] palopegteriparatide-treated subjects and no placebo subjects during the first 3 months of the study versus 20/61 [32.8%] and 1/21 [4.8%] high serum calcium values, respectively; TEAEs of hypocalcemia: 2/61 [3.3%] palopegteriparatide-treated subjects and 7/21 [33.3%] placebo subjects versus 8/61 [13.1%] and 16/21 [76.6%] placebo subjects with low serum calcium values during the first 3 months of the study; 4/61 [6.6%] palopegteriparatide- treated subjects and 3/21 [14.3%] placebo subjects versus 13/60 [21.7%] and 9/19 [47.4%] placebo subjects with low serum calcium values during the last 3 months of the study).

TCP-201

Ad hoc analyses of incidence and rate though Week 84 indicated that in palopegteriparatide-treated subjects, the incidence and rate of excursions to low calcium levels initially decreased though Week 4 to Week 12 and subsequently rose, remaining high (approximately 30%) at Week 58 to Week 84. For placebo subjects, the excursions did not change appreciably through the Blinded Period.

Excursions to high serum calcium were zero in placebo subjects, and infrequent in palopegteriparatide subjects; both incidence and rate peaked at Day 1 to Week 4 (at 9.1% and 3.8%, respectively), before declining to zero by ≥Week 12 to Week 26.

For both trials, the proportion of subjects independent from conventional therapy treated with palopegteriparatide increased sharply from baseline by the first 4 weeks of treatment, and to most

subjects in the study by the cutoff date of each respective trial (58/61 for TCP-304 at Week 26 and 54/59 for TCP-201 at Week 84).

Subjects off conventional therapy with serum calcium excursions above the normal range were observed only through Week 10 (i.e., first 3 months of the Blinded Period) for TCP-304, and only through Week 8 for TCP-201.

Other Laboratory findings and vital signs

For Safety Pool II, 25(OH)D3 slightly decreased in palopegteriparatide-treated patients, compared to placebo. Baseline (observed value) were mean (SD) 43.737 (11.6294) ng/mL for palopegteriparatide and 43.453 (12.1467) ng/mL for placebo. At week 26 25(OH)D3 observed value were mean (SD) 37.728 (11.5424) ng/mL for palopegteriparatide and 42.247 (17.4292) ng/mL for placebo.

In Safety Pool II 24-hour urine calcium decreased relative to baseline in both treatment groups at Week 26, but the decrease was more pronounced in palopegteriparatide-treated subjects compared to placebo.

For Safety Pool II overall, alkaline phosphatase values increased in palopegteriparatide-treated subjects relative to placebo and baseline from Week 4 through Week 26. During the overall TransCon PTH period in TCP-201, alkaline phosphatase levels were declining towards baseline by Week 84.

Procollagen Type 1 Amino-terminal Propeptide (P1NP) and C-terminal telopeptide of Type I collagen (CTx) trended downwards after Week 26 through Week 58 but remained above the baseline values.

There were no noteworthy findings on ECG parameters.

2.5.8.5. Safety in special populations

In both studies (TCP-304, TCP-201), in general the treatment groups were well balanced with regard to demographic characteristics and baseline disease characteristics. In summary, a majority of subjects in study TCP-304 and TCP-201 were female and white. In study TCP-304, more subjects in the placebo group were <50 years (66.7% versus 45.9%). In the studies of Safety Pool I, subjects were younger than in the phase 3 and phase 2 study.

Age

Compared with subjects <50 years of age, more (an absolute difference of at least 10%) subjects ≥50 years of age experienced at least 1 TEAE considered related to study treatment in the Blinded Period (41.8% [28/67] vs 27.0% [20/74]) particularly in palopegteriparatide- treated subjects (49.0% [25/51] vs 25.9% [14/54]). A similar pattern was observed during the TransCon PTH Period (44.8% [30/67] in subjects ≥50 years of age vs 33.3% [24/72] subjects <50 years of age). Similarly, more (an absolute difference of at least 2%) palopegteriparatide- treated subjects ≥50 years of age experienced at least 1 TESAEs (Section 2.1.1.5) compared with palopegteriparatide-treated subjects <50 years of age, both during the Blinded Period (7.8% [4/51] vs 1.9% [1/54]) and the TransCon PTH Period (9.0% [6/67] vs 5.6% [4/72]). Given the small number of subjects experiencing TESAEs overall (8 during the Blinded Period and 10 during the TransCon PTH Period), this difference should be viewed with caution. No other notable differences could be discerned between age groups due to the small number of subjects with TEAEs leading to hyper-or hypocalcemia leading to ER/urgent care visit, TEAEs leading to discontinuation of study drug or discontinuation from the trial.

Gender, Race and Region

The proportion of male and female subjects experiencing events within each category were largely comparable both during the Blinded Period and during the TransCon PTH Period. The majority of the

subjects in Safety Pool II were females. More male subjects experienced at least 1 TESAE. More female subjects experienced headache and injection site reactions, while more male subjects experienced fatigue and TEAE related to hyper- or hypocalcemia leading to ER/Urgent Care visit and/or hospitalization (7.1% vs. 1.8%).

The majority of the subjects in Safety Pool II (92.2%, 130/141) were white; only 7 subjects were Asian and 4 were classified as "Other".

The proportion of subjects from North America and from Other Regions experiencing events within each category were largely comparable both during the Blinded Period and during the TransCon PTH Period.

Renal Function

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 impairment (n=8). Overall, 4 of 38 (10.5%) subjects experienced a total of 5 TEAEs; all TEAEs were reported by subjects in the mild or moderate renal impairment group (n=2 each). All TEAEs were mild, 4 TEAEs reported by 3 subjects (7.9%) were considered related to palopegteriparatide by the investigator.

As stated by the applicant, studies TCP-201 and TCP-304 included individual patients with an estimated glomerular filtration rate ≥30 mL/min/1.73 m².

2.5.8.6. Immunological events and mPEG exposure

Immunogenicity

In summary, the assays used to detect and to characterise the ADAs against palopegteriparatide are deemed suitable for their intended purpose and the performance of all the assays was considered consistent and acceptable.

In HV anti-PTH and anti-PEG antibodies were assessed. Anti-PEG IgG and IgM have previously been shown to account for efficacy loss due to accelerated blood clearance of drugs (ABC phenomenon) and may induce hypersensitivity reactions (Gozoma GT et al. Adv Drug Deliv Rev, 2020).

In summary, no anti-PTH antibodies were detected in HV. In approximately 40 % of HV (CT-103, SAD and MAD cohorts) pre-existing anti-PEG antibodies (low titer) were observed. Transient boost of pre-existing low titer anti-PEG antibody was detected in 24 % (5/21) of HV. Impact was observed for PK and serum calcium at Day 14. However, the antibody response was not followed after Day 14, and therefore, it is not possible to determine if the response was transient.

In subjects with hypoparathyroidism anti-PTH antibodies, as well as anti-mPEG and anti-TransCon PTH antibodies were assessed. No Anti-PTH antibodies (non-neutralizing) were detected at baseline. One subject (0.7%) had a detectable anti-PTH antibody response at Week 84 (in study TCP-201). Treatment-emergent response of anti-PEG and anti-TransCon PTH antibodies was detected in 5% (7/139) of subjects exposed to palopegteriparatide.

In approximately 20% of the adults with hypoparathyroidism (TCP-201 und TCP-304), pre-existing anti-PEG antibodies (low titer) were observed. A transient boost of pre-existing low titter anti-PEG antibody for up to 6 months was detected in 2.2% (3/139) of palopegteriparatide-treated patients.

In summary, the transient boost of pre-existing anti-PEG antibodies resulted in temporarily increased clearance of Total PTH, mPEG and decreased PTH concentrations and impact on serum calcium. However, therapeutic effectiveness was maintained by appropriate dose adjustment of palopegteriparatide following the trial titration algorithm.

There was no indication that ISRs were related to immunogenicity against palopegteriparatide or pre-existing anti PEG antibodies.

Of note, the apparent age-related prevalence of pre-existing anti-PEG antibodies is in line with the reports from literature (Chen 2016, Lubich 2016 and Yang 2016). Pre-existing anti-PEG antibodies are not considered to impact the exposure of Free PTH or serum calcium.

mPEG exposure

Palopegteriparatide contains a branched 40 kDa (2x20) methoxypolyethylene glycol (mPEG) carrier. However, regarding the PK analyses the administered mPEG concentrations respectively the associated mPEG exposure were quite low and no unexpected short-term renal, hepatic, immune or neurologic adverse events potentially attributed to mPEG exposure were reported.

2.5.8.7. Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction trials have been conducted with palopegteriparatide because neither PTH nor mPEG are cytochrome P450 (CYP) substrates, and the probability of drug-drug interactions is therefore considered low.

Interactions with drugs acting on calcium and/or phosphate homeostasis such as bisphosphonates, denosumab, romosozumab, thiazide and loop diuretics, systemic corticosteroids, and lithium are well known from marketed PTH analogues (Forsteo SmPC, Forteo USPI, Natpar SmPC, Natpara USPI). Corresponding interactions are possible for the PD effects elicited by PTH released from palopegteriparatide.

Thiazide diuretics are often used for management of chronic hypoparathyroidism patients. The use of thiazide diuretics was not allowed during clinical trials, which is endorsed, as could interfere in the study results. A higher rate of hypercalcaemia was described in palopegteriparatide-treated patients during dose titration. Due to a potential PD drug-drug interaction between palopegteriparatide and thiazide diuretics, and the potential enhanced risk of hypercalcaemia, this drug interaction was included in the product information.

Hypercalcemia has been observed with administration of palopegteriparatide and increases the risk of digoxin toxicity. Concomitant administration of palopegteriparatide with oral bisphosphonates may reduce calcium sparing and subsequently interfere with the normalization of serum calcium. This was not evaluated as part in the clinical trials as digoxin was a prohibited concomitant medication.

Specific clinical trials evaluating abuse potential have not been conducted. Three cases related to overdose/medication errors with palopegteriparatide were recorded in the palopegteriparatide clinical program, all 3 events were Grade 1 and none were TESAEs. The effects of overdose that might be expected include a delayed hypercalcemic effect and risk of orthostatic hypotension.

2.5.8.8. Discontinuation due to adverse events

In TCP-304, and overall for Safety Pool II, TEAEs leading to discontinuation of study treatment occurred in 1 subject treated with palopegteriparatide (cardiac arrest), and 2 placebo subjects (invasive breast carcinoma and bipolar disorder).

The TEAEs of cardiac arrest and invasive breast carcinoma led to discontinuation of trial; the subject with the TEAE of bipolar disorder discontinued the trial due to withdrawing consent (not due to the TEAE). None of the TEAEs leading to discontinuation were considered related to study treatment. All events occurred during the Blinded Period.

No TEAEs leading to discontinuation of study treatment or trial occurred in TCP-201.

No subjects in the Single Dose Group of Safety Pool I experienced TEAEs leading to treatment discontinuation. Three of 50 (6.0%) subjects in the Multiple Dose group of Safety Pool I experienced TEAEs leading to treatment discontinuation: palpitations (n=1), hypercalcemia (n=1), and dizziness postural (n=1). No subject in Safety Pool I experienced TEAEs leading to discontinuation of trial.

2.5.8.9. Post marketing experience

Palopegteriparatide is currently not approved for marketing in any country.

2.5.9. Discussion on clinical safety

The main evidence of safety for the registration of palopegteriparatide for parathyroid replacement therapy comes from TCP-304 (pivotal Phase 3 Trial) and TCP-201 (Phase 2 Trial). TCP-304 included a 26-week Blinded Treatment Period (completed) and an ongoing OLE period of 156 weeks (data cutoff date of 20 July 2022). TCP-201 included a Blinded Treatment Period of 4 weeks (completed), and an ongoing OLE period of up to 210 weeks (data cutoff date of 01 June 2022). Additional safety data from the three Phase 1 trials CT-103, TCP-104, and TCP-105 are also included.

Safety data are summarized in 2 safety pools, Safety Pool I which includes healthy subjects that received palopegteriparatide, and Safety Pool II, including patients with hypoparathyroidism. The contribution of safety information from healthy subjects is considered rather limited, due to differences on calcium and phosphate metabolism, and results from Safety Pool I are not discussed.

A total of 141 of patients were included in the Safety Pool II; during the blinded period (4 weeks for TCP-201 and 26 weeks for TCP-304), a total of 105 patients received palopegteriparatide and 50, placebo. In phase 3 trial, 2 patients in placebo group discontinued before entering OLE period. As a consequence, a total of 139 patients were treated with palopegteriparatide.

Exposure

A total of 139 subjects with hypoparathyroidism were exposed to at least 1 daily SC dose of palopegteriparatide. In TCP-304, 79/80 subjects in the All TransCon PTH group received ≥26 weeks of palopegteriparatide, 59/80 received ≥ 52 weeks. In TCP-201, almost all subjects (58/59) in the All TransCon PTH group in the Safety Analysis Population received ≥84 weeks of treatment, and 57/59 received ≥ 110 weeks.

For Safety Pool II, during the blinded period, 105 patients were exposed to palopegteriparatide and 36 to placebo (of these, 21 during 26 weeks, and 15 during 4 weeks).

Most palopegteriparatide-treated subjects and placebo-treated subjects completed blinded periods (99% 104/105, and 94.4% 34/36, respectively). Two placebo-treated and one palopegteriparatide-treated subjects discontinued treatment due to AE (non-related to study drug by the investigator), all in study TCP-304.

The number of patients treated with palopegteriparatide in the above-mentioned studies is limited (N=139). In general, the assessment of the different safety aspects is sufficient on the short term, given the product's orphan designation, although the number of placebo-treated patients during the blinded period is limited, and makes challenging the evaluation of safety of palopegteriparatide. In order to provide an integrated vision of the safety profile of palopegteriparatide, a comparative assessment of treatment-emergent AEs and treatment-related AEs with the safety profile known for teriparatide and rPTH (Natpar®) was requested. A deep comparison of calcium serum excursions was

provided and some differences regarding the SOCs psychiatric disorders and investigations were detected. While there appears to be an increased frequency between the treatment arm and placebo arm (insomnia 3.8% vs 2.8%, and anxiety 2.9% vs 0%, respectively), the numbers are too low to make a meaningful medical assessment, the reported cases were considered not related and no additional safety concerns were identified from those reviews.

In the course of the procedure, the applicant provided more recent safety data (120-Day Safety Update). In summary, the short-term safety profile remained the same. With regard to the long-term safety profile, the still ongoing OLE periods (TCP-201 and TCP-304) may provide further insights in the safety profile of palopegteriparatide and are suitable for further characterisation of hypercalcaemia and long-term safety. The OLE periods will be implemented as category 3 pharmacovigilance activities in the pharmacovigilance plan. The up-to-date information is reflected in the product information.

In addition, 186 healthy subjects were treated with palopegteriparatide (136 SAD, 50 MAD, different dose levels) within studies CT-103, TCP-104 and TCP 105.

Patients and baseline characteristics

In both studies (TCP-304, TCP-201), in general the treatment groups were well balanced with regard to demographic characteristics and baseline disease characteristics. In summary, a majority of subjects in study TCP-304 and TCP-201 were female and white.

However, in study TCP-304 more subjects in the placebo group were <50 years (66.7% versus 45.9%). The applicant provided age stratified numbers of TEAEs. No major differences were observed between age subgroups either for TransCon PTH or placebo. Overall numbers, particularly for placebo subjects ≥50 years of age, were small. A greater proportion of subjects ≥50 years of age experienced treatment-related TEAEs than subjects <50 years of age (54.5% vs 42.9%, respectively). It is unlikely that the age imbalance between the two arms favorably influenced the safety data for palopegteriparatide.

Adverse events

During the blinded period, 64.8% of palopegteriparatide-treated subjects and 75% of placebo-treated subjects notified an adverse event, of these, 4.8% and 8.3% were serious. Most AE were grade 1 and grade 2 of severity. 49.2% of subjects in palopegteriparatide-treated group and 39.1% of subjects in placebo-treated group had a related-treatment AE, which reflects the complexity of safety assessment, due to many AEs are related to hyper/hypocalcaemia and disease-related symptoms. Most common (>5%) TRTEAE were injection site reaction, headache, hypercalcaemia, nausea, hypocalcaemia and paraesthesia.

In summary, the proportion of subjects who experienced a TEAE, Grade 1-3 TEAE, or TESAE seems to be lower for palopegteriparatide-treated subjects compared to placebo subjects. This difference can be explained mainly by the increased occurrence of hypocalcaemia in the placebo group. The proportion of subjects who experienced a treatment related TEAE was higher for palopegteriparatide-treated subjects.

In addition, the incidence of exposure-adjusted TEAEs (overall and related) was provided. No additional safety signals were identified from those reviews.

In Safety Pool II during the Blinded Period, a total of 37.1% (39/105) of palopegteriparatide-treated subjects and 25.0% (9/36) of placebo-treated subjects experienced at least 1 treatment-related TEAE. The most common treatment-related TEAEs in palopegteriparatide-treated subjects within Safety Pool II were injection site reaction and headache. The most common treatment-related TEAEs in the Single Dose Group of Safety Pool I were headache and fatigue. The most common treatment-related TEAEs reported in the Multiple Dose Group were headache and palpitations.

AESIs were mainly reported and assessed in the phase 3 study. However, in summary, no AESIs of persistent severe hyper- or hypocalcemia were reported, whereas (in TCP-304) 10/80 (12.5%) palopegteriparatide treated subjects experienced vasodilatory signs and symptoms. In summary, the observed events were transient and nonserious. During the Blinded Treatment Period, 14.3% (15/105) of palopegteriparatide-treated subjects and 27.8% (10/36) placebo subjects experienced at least 1 TEAE within the Metabolism and nutrition disorders SOC. This difference was due to the incidence of hypo- and hypercalcemia. Hypocalcemia was less frequent in palopegteriparatide-treated subjects compared to placebo (5.7% vs 27.8%), whereas hypercalcemia was more frequent (8.6% vs 0%), esp. shortly after initiating palopegteriparatide. Therefore, close monitoring of patients is necessary.

Also during the TransCon PTH period, the incidence of hypercalcemia was higher in the palopegteriparatide-treated subjects than in the placebo-treated subjects, both based on lab results and on TEAEs. To mitigate this potential risk of hypercalcaemia, an updated titration scheme that has been accordingly modified from the titration algorithm used in the TCP- 304 trial is included in SmPC.

4 subjects in the palopegteriparatide-group and 2 subjects in placebo group experienced hypo or hypercalcemia leading to ER/Urgent care visit and/or hospitalization. Only 3/6 of the AES of all treated patients were related to treatment. Most events were grade 1 or grade 2, and only one was grade 3 (hypercalcaemia).

Hypercalcaemia is an important identified risk that needs to be followed up post-marketing. No TEAE of nephrocalcinosis was reported, but 3 subjects were reported with nephrolithiasis during the TransCon PTH Period. No concerns of hypercalcaemia were identified from review of available long-term data of the 3 subjects with TEAEs of nephrolithiasis. Additionally, based on the 120 Day Safety Update, no further patients reported nephrolithiasis during the extended TransCon PTH period.

Results regarding local tolerability in Safety Pool II were similar between palopegteriparatide-treated and placebo subjects. Overall, ≥75% subjects reported no redness, itching, swelling, or pain at the time of injection or 15 minutes later; in TCP-201, pain results were similar between doses (15, 18, and 21 µg/day). As the applicant stated, in TCP-304 TEAEs related to injections were more common in palopegteriparatide-treated subjects compared to placebo (36.1% [22/61] vs 4.8% [1/21]). However, most events of injection site reaction were Grade 1. No pain was reported. Different injection sites did not seem to have played an important role in the appearance of ISR. No TEAEs related to injections were reported in TCP-201, probably mostly due to difference in definition of collection of TEAEs compared to TCP-304 and therefore different reporting. Injection site reactions have been included as transient adverse drug reaction in section 4.8 of the SmPC, especially mentioning aspects like nature of reaction and severity.

In the phase 2 study (TCP-201), the incidence of SAEs was low and no SAE was considered related to study treatment respectively led to permanent discontinuation from study treatment. In the phase 3 study (TCP-304), the incidence of SAEs (severe hypercalcaemia) was low and only one of the SAEs was considered related to study treatment, in which Palopegteriparatide was temporarily interrupted. In Safety Pool I, two subjects experienced TESAEs, both were considered unrelated. One palopegteriparatide-treated subject experienced a Grade 4 (fatal) serious TEAE (TESAE) of cardiac arrest which was considered unrelated to study treatment.

In summary, *treatment-related adverse events in general*, *adverse events of special interest and other significant adverse events (Hyper- and Hypocalcaemia and local tolerability)* were assessed properly and included in the SmPC.

Laboratory findings

Haematology test results were generally stable, remained within the normal range and were comparable between the treatment groups.

Excursions to high calcium levels were mostly observed in palopegteriparatide-treated subjects, and that while excursions to low calcium levels were observed in both treatment groups, they were observed more frequently in placebo subjects than in palopegteriparatide-treated subjects. Excursions to high calcium levels were observed only during the first 3 months of the Blinded Period. These excursions are expected, particularly during titration period.

In Safety Pool II, during the blinded period, 25(OH)D3 slightly decreased in palopegteriparatide-treated patients compared to placebo. Baseline (observed value) were mean (SD) 43.737 (11.6294) ng/mL for palopegteriparatide and 43.453 (12.1467) ng/mL for placebo. At week 26, 25(OH)D3 observed mean (SD) values were 37.728 (11.5424) ng/mL for palopegteriparatide and 42.247 (17.4292) ng/mL for placebo [Source ISS Table 14.2.3.4.2]. The decrease in serum Vitamin D levels is unsurprising considering that active Vitamin D had to be discontinued upon initiation of palopegteriparatide and the majority of patients did not restart active Vitamin D thereafter. PTH itself actually increases active Vitamin D levels by triggering the hydroxylation of 25OH Vitamin D to its active form, 1,25(OH) Vitamin D, in the kidney. As the need for monitoring of Vitamin D levels is already included in the SmPC (section 4.2), no further action is required.

Otherwise no clinically meaningful differences or patterns in serum chemistry were observed in the combined Safety Pool II data between palopegteriparatide and placebo subjects, and the mean values remained within normal range at all timepoints. In Safety Pool II 24-hour urine calcium decreased relative to baseline in both treatment groups at Week 26, but the decrease was more pronounced in palopegteriparatide-treated subjects compared to placebo.

For Safety Pool II overall, alkaline phosphatase values increased in palopegteriparatide-treated subjects relative to placebo and baseline from Week 4 through Week 26. During the overall TransCon PTH period in TCP-201, alkaline phosphatase levels were declining towards baseline by Week 84.

Of note, bone mineral density is further discussed in the efficacy section of this report.

Palopegteriparatide as a replacement therapy provides physiological PTH levels and normalizes bone turnover and has not been shown to lead to a net anabolic effect. The TransCon Linker did not flag concerns about genotoxicity and carcinogenicity in in silico analyses. Therefore, the lack of carcinogenicity studies is considered acceptable and no carcinogenic risk is anticipated for patients. However, long-term data are missing.

Special population

More subjects ≥50 years of age experienced at least 1 TEAE considered related to study treatment in the Blinded Period and during the TransCon PTH Period. More palopegteriparatide- treated subjects ≥50 years of age experienced at least 1 TESAE and experienced hypercalcemia during both the Blinded Period and the TransCon PTH Period. However, in summary, no new safety concerns were identified in subjects ≥65 years of age based on the TEAE profile, although the statements are to be taken with caution due to the small numbers.

The proportion of male and female subjects experiencing events within each category were largely comparable both during the Blinded Period and during the TransCon PTH Period. The majority of the subjects in Safety Pool II were females. More male subjects experienced at least 1 TESAE. More female subjects experienced headache and injection site reactions, while more male subjects experienced fatigue and TEAE related to hyper- or hypocalcemia leading to ER/Urgent Care visit and/or hospitalization (7.1% vs. 1.8%). However, in summary, the described differences do not seem to have a clinical relevance.

With regards to race, there were not enough non-Caucasian subjects to make comment on any difference in safety. However, the applicant provided ideas to generate post-marketing data regarding

non-Caucasian subjects (two Phase 3 trials in Japan and China, routine pharmacovigilance activities from availability across all ethnicities/races). In addition, preliminary safety profiles in these 2 studies are consistent with the overall safety profile of palopegteriparatide and the ethnobridging trial found no difference in exposure.

The applicant stated that no additional safety signals were detected in the trial TCP-104 (trial to investigate the effect of varying degrees of renal function on the pharmacokinetics of TransCon PTH). With regard to study TCP-104, this is supported. Of note, it was not possible to determine if there was any effect of severe RI on the free PTH (1-34) released from palopegteriparatide.

In study TCP-201 and TCP-304, patients with chronic kidney disease with an estimated glomerular filtration rate ≥30 mL/min/1.73 m² were included and assessed. The applicant provided safety data in subjects with medical history of chronic kidney disease/renal failure or BSA-adjusted eGFR of <45.0 mL/min/1.73 m2 at baseline.

The eGFR for most subjects (13/15) either improved or remained stable. Most subjects (14/15) had no renal or renal-associated TEAEs during the study. 24-hour urine calcium normalized or improved for 12 of 15 of these subjects.

A total of 3 palopegteriparatide-treated subjects experienced TEAEs of nephrolithiasis, 1 experienced ureterolithiasis and 1 palopegteriparatide-treated subject experienced renal colic. Of these, 1 subject had a history of CKD and nephrolithiasis and 2 additional subjects had a history of nephrolithiasis. The eGFR for 4 of 5 palopegteriparatide-treated subjects reporting TEAEs during the study either improved or was slightly above baseline at the last available timepoint. Only 1 palopegteriparatide-treated subject experienced a notable postbaseline decrease in eGFR.

In a number of subjects, a drop in eGFR in patients with renal impairment during early weeks of treatment was described. The decrease was transient and the extent seemed neither to be correlated to the severity of renal impairment at baseline nor to baseline eGFR, to study drug starting dose, to the presence of a history of renal disease or with renal or potentially renal-associated TEAEs. Fluctuations in serum calcium were managed through the titration regimen. However, the drop in eGFR was generally observed against a background of elevated serum calcium. As indicated in the SmPC, more frequent monitoring of calcium levels in patients with eGFR < 45 mL/min.

Of note, numbers are too small to assess the safety of the product in patients with severe renal impairment (only 1 patient with eGFR of <30.0 mL/min/1.73 m2 at baseline). Therefore, the SmPC states that palopegteriparatide should be used with caution in such patients.

Immunological events

In summary, the proportion of patients testing positive for binding antibodies at any time during treatment was low. Results provided do not show any positive relation of appearance of antibodies against PTH or PEG with injection site reactions, systemic hypersensitivity or any immunogenicity-related event. However, a transient boost of pre-existing anti-PEG antibodies, which resulted in temporarily increased clearance of total PTH, mPEG and decreased PTH concentrations thereby reducing serum calcium, was detected in 2.2% of the palopegteriparatide-treated patients. Careful monitoring of the calcium levels and appropriate dose adjustment of the palopegteriparatide dose following the trial titration algorithm maintained therapeutic effectiveness. Long-term data is limited (particular from the OLE periods of the phase 3 study) and further data will be provided post-marketing.

mPEG exposure

Regarding the PK analyses, the administered mPEG concentrations and, respectively, the associated mPEG exposure was quite low and no unexpected short-term renal, hepatic, immune or neurologic

adverse events potentially attributed to mPEG exposure were reported. However by now, the characterization of effects of long-term exposure to mPEG is limited, further data will be provided post-marketing.

Drug-drug interactions and Overdose

No formal drug-drug interaction trials have been conducted with palopegteriparatide. Information about concomitant use of cardiac glycosides is provided in section 4.4 of the SmPC.

Due to a potential PD drug-drug interaction between palopegteriparatide and including but not limited to bisphosphonates, denosumab, romosozumab, thiazide and loop diuretics, systemic corticosteroids, and lithium, and the potential enhanced risk of hypercalcaemia, it is recommended to prescribers to monitor serum calcium levels in section 4.5 of the SmPC.

Three cases related to overdose/medication errors with palopegteriparatide were recorded in the palopegteriparatide clinical program, all 3 events were Grade 1 and none were TESAEs. The effects of overdose that might be expected include a delayed hypercalcemic effect and risk of orthostatic hypotension.

2.5.10. Conclusions on the clinical safety

The safety profile of PTH replacement therapy with palopegteriparatide evaluated in the clinical study setting is considered acceptable. The only serious ADR reported was hypercalcaemia, which occurred mainly at treatment initiation with palopegteriparatide. Close monitoring of serum calcium levels is therefore necessary, especially when initiating or up titrating palopegteriparatide. Of note, safety results of palopegteriparatide in healthy subjects do not contribute to a huge extent to safety evaluation, due to differences in calcium and phosphate metabolism in the presence of normal secretion of endogenous PTH.

The still ongoing OLEs (TCP-201 and TCP-304) are expected to provide further insights in the safety profile of palopegteriparatide with regard to effects on bone, frequency of hypercalcaemia and potential sequelae, renal function, immunogenic effects, and potential adverse drug reactions related to chronic mPEG exposure . The OLE periods will be implemented as category 3 pharmacovigilance activities in the pharmacovigilance plan.

2.6. Risk Management Plan

2.6.1. Safety concerns

Table 42. Summary of safety concerns

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)

2.6.2. Pharmacovigilance plan

Table 43. On-going and planned 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)	Hypercalcaemia Long-term safety (including long-term effects on bone health and adverse drug reactions potentially related to mPEG exposure)	Interim analysis Final report	See footnote Projected March 2025

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	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			
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 Final report	See footnote Projected March 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.).

2.6.3. Risk minimisation measures

Table 44. Description of routine risk minimisation measures 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.*
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.*

2.6.4. Conclusion

The CHMP considers that the risk management plan version 0.4 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Yorvipath (palopegteriparatide) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-risk balance

3.1. Therapeutic context

3.1.1. Disease or condition

Hypoparathyroidism (HP) is a rare endocrine disease of parathyroid hormone (PTH) insufficiency resulting in abnormal calcium and phosphate homeostasis, neuromuscular symptoms, and impaired quality of life (QoL).

Causes of HP in adults are neck surgery done to treat conditions of the thyroid gland, or to treat throat or neck cancer, autoimmune disease, hereditary hypoparathyroidism or extensive cancer radiation treatment of the face or neck.

The symptoms, manifestations, and complications of HP affect multiple organ systems. Neuromuscular irritability is often the most prominent feature affecting day-to-day life, with symptoms ranging from paraesthesias and muscle cramps to life-threatening laryngospasm, bronchospasm, seizures, and arrhythmias. Patients with HP are more likely to report pain, fatigue, "brain fog," anxiety, and depression. Additional complications include propensity for infections, heart failure, renal failure, ectopic calcifications (e.g., of the basal ganglia, and lenses), and abnormal skeletal dynamics (Shoback 2008). Insufficient production of PTH leads to reduced bone turnover with a consequent accumulation of unremodeled bone reflected in increased bone mass and density. Hydroxylation of 25OH Vitamin D to its active form, 1,25(OH) Vitamin D, in the kidney, intestinal absorption of calcium and phosphate are both impaired in the setting of insufficient PTH (Brandi 2016, Clarke 2016, Shoback 2016, Mannstadt 2013). Low PTH levels impair renal reabsorption of calcium while decreasing phosphate excretion. The chronic hypercalciuria in patients with hypoparathyroidism is associated with a greater than 4-fold increase in risk of kidney stones and renal insufficiency (Mannstadt 2017). Among patients with postsurgical chronic hypoparathyroidism, the risk of death over approximately a 4-year follow-up is 2-fold higher compared to patients without chronic hypoparathyroidism (Almquist 2018).

3.1.2. Available therapies and unmet medical need

Current treatment consists of administration of calcium supplements, active vitamin D (oral calcitriol or its analogue alfacalcidol), and, in case of hypomagnesaemia, magnesium supplements. The goal is to normalise calcium and phosphate levels and to prevent neuromuscular sequelae. While conventional therapy can be successful for the 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. Chronic conventional therapy likewise fails to restore normal rates of bone turnover; and has failed to alleviate the burdens of diminished QoL (Mitchell 2012, Bilezikian 2016). Although conventional therapy can improve hypocalcaemia, it does not reduce the elevated serum phosphate characteristic of hypoparathyroidism. Consequent increases in the serum calcium×serum phosphate product predispose patients to ectopic calcifications in the renal parenchyma, eye, central nervous system (CNS) (particularly the basal ganglia) and vasculature (Abate 2017).

More recently, Natpar (PTH) has been approved as adjunctive treatment of adult patients with chronic hypoparathyroidism who cannot be adequately controlled with standard therapy alone. As discussed in the EPAR for Natpar, in hypoparathyroidism patients that are well-controlled with their standard

therapy the effects shown for Natpar were considered insufficient to counterbalance the lack of a significant decrease in urine calcium levels compared to standard treatment, the lack of an effect on QoL, the absence of a demonstration of long-term effects on clinical hard endpoints and the observed increase in hyper- and hypocalcaemia, and the remaining uncertainty of the long-term safety, and therefore the indication was restricted to a second line therapy.

Teriparatide has been administered off-label for the management of chronic hypoparathyroidism. However, similar to Natpar, once-daily administration is not sufficient to keep serum calcium levels stable throughout the day.

Palopegteriparatide, the product applied for, has been developed as a PTH replacement therapy that obviates the need for current SoC, i.e. therapeutic doses of calcium and activated vitamin D.

The target indication applied for by the Applicant is "*Yorvipath is a parathyroid hormone (PTH) replacement therapy indicated for the treatment of adults with chronic hypoparathyroidism*".

3.1.3. Main clinical studies

The pivotal trial is the Phase 3 Trial TCP-304 (PaTHway), an ongoing, multicenter, randomized, double-blind, placebo-controlled, parallel group trial investigating the safety, tolerability and efficacy of palopegteriparatide administered subcutaneously (SC) daily in adult subjects with hypoparathyroidism. The trial includes a 26-week Blinded Treatment Period and an OLE period of 156 weeks. Data are available for the blinded period and through week 52 of the OLE period. A total of 84 subjects have been randomized, and 82 subjects dosed (61 to palopegteriparatide, 21 to placebo) in the trial. A total of 79 subjects entered the OLE, and 77 remain in the trial. The primary composite endpoint consisted of the proportion of subjects at week 26 with: I.) Albumin-adjusted serum calcium measured within 4 weeks prior to and on the Week 26 visit are within the normal range (8.3-10.6 mg/dL)[2]; II.) independence from active vitamin D[3] and III.) independence from therapeutic doses of calcium (i.e., taking calcium supplements ≤600 mg/day)[4] and IV.) no increase in prescribed study drug within 4 weeks prior to Week 26 visit[5]. Key secondary endpoints were the validated PRO scales HPES-Symptom, Physical domain score HPES-Symptom, Cognitive domain score HPES-Impact, Physical Functioning domain score HPES-Impact and Daily Life domain score 36-Item Short Form Survey (SF-36) Physical Functioning subscale score.

Additional data is derived from Phase 2 Trial TCP-201 (PaTH Forward), an ongoing, multicenter, randomized, double-blind, placebo-controlled, parallel group trial, investigating the safety, tolerability, and efficacy of palopegteriparatide administered SC daily in adult subjects with hypoparathyroidism. The trial includes a Blinded Treatment Period of 4 weeks, and an OLE period of up to 210 weeks. A total of 59 subjects have been randomized (44 to palopegteriparatide, 15 to placebo); all 59 subjects successfully completed the blinded phase and transitioned into the OLE. Data are available up to data cutoff date of 01 June 2022, after the date of the last subject's Week 110 visit; for subjects enrolled earlier, data after Week 84 are available as of the cut-off date. A total of 57 subjects remain in the trial. The primary endpoints consisted of the proportion of subjects at week 4 that met the following 4 criteria: I.) albumin-adjusted or ionized serum calcium within the normal range and II.) spot morning

[2] Except for at the Week 26 visit, confirmation that an albumin-adjusted serum calcium is "abnormal" required 2 consecutive results outside the normal range within 4 weeks prior to the Week 26 visit.
[3] Independence from active vitamin D is defined as a daily standing dose equal to zero on all days AND use of any PRN vitamin D ≤7 days within 4 weeks prior to the Week 26 visit.
[4] This dose of calcium ≤600 mg/day in the form of tablets, powder, liquid suspension, or transdermal patch is considered as "supplemental" to meeting recommended daily intake for general health, as opposed to a "therapeutic" dose to treat hypoparathyroidism. Independence from therapeutic calcium is defined as average daily standing dose ≤600 mg AND use of PRN doses on ≤7 days within 4 weeks prior to the Week 26 visit.
[5] Dose decrease allowed for safety reasons.

FECa within normal range (≤2%) or a reduction by at least 50% from baseline and III.) not taking active vitamin D supplements and IV.) taking ≤1000 mg/day of calcium supplements.

3.2. Favourable effects

The results of the primary efficacy analysis showed that the criteria for the composite endpoint were met by significantly more subjects who received palopegteriparatide than subjects who received placebo: 48/61 (78.7% [95% CI: 66.3, 88.1] vs. 1/21 (4.8% [95% CI: 0.1, 23.8]), respectively.

A significant proportion of patients treated with palopegteriparatide was able to reach albumin-adjusted sCa within the normal range of 8.3 to 10.6 mg/dL without an increase in the prescribed study drug in the 4 weeks prior to the assessment at week 26. As per definition of the composite endpoint, this was achieved while, at the same time, patients were I.) independent from active vitamin D within 4 weeks prior to Week 26 visit (i.e., all daily standing dose of active vitamin D equal to zero AND use of PRN (as needed/rescue) ≤7 days during the 4 weeks)) and II.) independent from therapeutic doses of calcium within 4 weeks prior to Week 26 visit (i.e., average daily standing dose of elemental calcium ≤600 mg AND use of PRN doses on ≤7 days during the 4 weeks).

Among subjects receiving palopegteriparatide, all but 1 subject achieved independence from active vitamin D (60/61; 98.4%). Fifty-seven (93.4%) subjects achieved independence from therapeutic doses of calcium. Fifty-seven (93.4%) subjects had no increase in prescribed study drug within 4 weeks prior to Week 26 visit. Forty-nine (80.3%) subjects achieved albumin-adjusted serum calcium within the normal range.
Among subjects receiving placebo, approximately half achieved albumin-adjusted serum calcium within the normal range (10/21; 47.6%) or no increase in prescribed study drug (12/21; 57.1%). Approximately one quarter of placebo subjects achieved independence from active vitamin D (5/21; 23.8%), and 1 achieved independence from therapeutic doses of calcium (1/21; 4.8%).

Statistically significant improvements in all key secondary endpoints, i.e. HPES– Symptom– Physical domain score, HPES– Symptom– Cognitive domain score, HPES– Impact – Physical Functioning domain score, HPES– Impact – Daily Life domain score and 36-Item Short Form Survey (SF-36)–- Physical Functioning subscale score, have been shown. The results remained more or less unchanged in the placebo group.

Supplemental calcium doses, active Vitamin D doses and daily Pill Burden decreased in palopegteriparatide-treated subjects from baseline onward. Supplemental calcium doses and daily Pill Burden remained more or less unchanged in the placebo group. By Week 26, the active vitamin D dose had also decreased in the placebo group, but less significantly (LS mean change from baseline -0.99 µg (95% CI: -1.11, -0.87) in palopegteriparatide-treated subjects and -0.37 µg (95% CI: -0.56-0.19) in placebo subjects).

Serum calcium initially increased in palopegteriparatide-treated subjects (visit 2), but then slowly decreased to nearly starting values. LS mean change from baseline (SE) at week 26 was 0.3 (0.11) mg/dL. In placebo subjects, LS mean change from baseline (SE) at week 26 was 0.39 (0.14) mg/dL.

Data from a PK/PD subpopulation of the dose-finding study suggest that serum calcium levels can be maintained stable in the (low-)normal range throughout the day (24 h) without significant peak-trough fluctuation.

While fluctuations (decreases) were initially observed between study visits, median and mean serum phosphate levels were within normal range at baseline in both treatment groups and remained within normal range throughout the 26 weeks of blinded treatment.

Median and mean serum calcium-phosphate product at baseline was below 55 mg^2/dL^2 in both treatment group and stayed below that recommended cut-off (Brandi et al. 2016).

Mean and median serum magnesium levels were within normal range at baseline in both treatment groups and remained within normal range throughout the 26 weeks of blinded treatment.

Bone turnover markers P1NP, as well as CTx, were generally in the low-normal range at baseline (as expected with PTH insufficiency), peaked at Weeks 12 (CTx) and 26 (P1NP) upon exposure to palopegteriparatide. Bone turnover markers remained unchanged in the placebo group. For DXA, mean Z-scores showed a decrease at Week 26 in areas measuring primarily trabecular bone, trending towards age- and sex-appropriate normal ranges by Week 26. No significant changes in corrected Z-Scores were seen in the placebo group, results fluctuated around zero.

In the EQ-5D Domain score and Visual Analogue score, improvements were more often seen in the palopegteriparatide group.

3.3. Uncertainties and limitations about favourable effects

The main objective of the pivotal study was to reach independence of active vitamin D and oral calcium supplementation while achieving normal serum calcium. It should be noted that this goal was virtually not possible to reach for patients in the placebo group due to the titration algorithm stipulating that all patients (including patients on placebo) had to downtitrate their SoC treatment until they reached the lower limit of normal for sCA. SoC could only be uptitrated again when sCA levels fell below normal. Therefore, SoC treatment was not optimal in placebo patients and, consequently, all comparative data from the study are potentially against placebo + not fully optimized SoC. Consequences of this are further discussed below.

In order to be eligible for study enrolment, patients had to be optimized on their SoC treatment reaching stable serum calcium levels in the normal range. The SmPC defines the upper and lower range for albumin-adjusted serum calcium that should be reached (in line with the pivotal study) before initiating palopegteriparatide at a starting dose of 18 mcg per day. Dose adjustments guided by serum calcium measurements should enable achievement of an optimal individualized maintenance dose for most patients.

Results from primary efficacy endpoint from phase 2 study did not show a clear dose-effect relationship, however, the primary efficacy variable included measurements of calcium urinary excretion that can be affected by other factors (i.e, diet). The dose selection is justified, based on efficacy and safety results, and considering that the dose is titrated based on serum calcium level.

In the pivotal clinical study, the primary endpoint is focused on maintaining serum calcium within the target plasma level range (8.3-10.6 mg/dL), while down titrating active vitamin D (to zero) and calcium supplementation (to supplemental doses ≤600 mg/day). The primary endpoint and the duration of the study does not allow to demonstrate clinical benefit versus standard treatment in terms of the avoidance of long-term consequences such as nephrocalcinosis/lithiasis and renal impairment. Positive effects could possibly be expected based on the reductions observed in 24 h urinary calcium. Showing a potential benefit regarding the development/worsening of nephrolithiasis and nephrocalcinosis, which may be expected from the replacement of the deficient parathyroid hormone, would be relevant information for patients and potentially also for HTAs and should be considered by the applicant to investigate post-marketing. This is however not necessary for approval of the indication applied for.

Although the main study was double-blind and it can be agreed that the products were likely indistinguishable, a component of functional unblinding likely occurred due to the clear effects of

palopegteriparatide and the exact magnitude of the bias will remain unknown. It is, however, agreed that this does not render the results of study TCP-304 invalid. Especially, as the effect size of the primary endpoint was very large.

For the PROs assessed as key secondary outcomes, it seems as if no minimum clinically important difference (MCID) was predefined. With regards to the clinical significance of the measured improvements, the applicant presented a derivation of the MCID. This is considered appropriate, however, comparison to a potentially suboptimal SOC treatment in the Placebo arm could have introduced bias leading to an overestimation of the effect size and therefore results on PROs were not to be mentioned in section 5.1 of the SmPC. For the same reason, no comparative data on hypocalcaemia is included in section 5.1 of the SmPC either.

The effects on bone turnover markers P1NP as well as CTx as well as BMD measured with DXA are acknowledged and it is agreed that they indicate a restoration of a closer to normal bone physiology, what could be expected for a PTH substitution therapy. However, it is unclear whether this will have an effect on fracture risk.

Long-term available data from phase 2 and phase 3 OLE period (week 52 and 110 of treatment, respectively) suggest that efficacy is maintained over time. Furthermore, other pharmacodynamic results provided (albumin-adjusted serum calcium, phosphate, and 24-hour urinalysis) support the primary efficacy findings, further substantiating maintenance of effect over time.

3.4. Unfavourable effects

The proportion of subjects who experienced a treatment related TEAE was higher for palopegteriparatide-treated subjects than for those receiving placebo.

The most common *treatment-related TEAEs* in palopegteriparatide-treated subjects with hypoparathyroidism in TCP-304 and TCP-201 (Safety Pool II, N=141 total, blinded period) in Safety Pool II were in the following categories: injection site reaction (18.1% of palopegteriparatide-treated subjects vs 0 placebo subjects), headache (8.6% of palopegteriparatide-treated subjects vs 2.8% placebo subjects), hypercalcemia (8.6% of palopegteriparatide-treated subjects vs 0 placebo subjects) and nausea (6.7% of palopegteriparatide-treated subjects vs 5,6% placebo subjects). The most common treatment-related TEAEs in HV treated in studies CT-103, TCP-104, and TCP-105 (Safety Pool I, N=186 total) were headache (4.8%) and fatigue (2.7%).

No *adverse events of special interest* (AESI) of persistent (> 7 days) severe hypercalcemia (defined as >12mg/dl) and hypocalcaemia (defined <7.0 mg/dL) were reported, whereas 8/61 (13.1%) palopegteriparatide-treated subjects experienced vasodilatory signs and symptoms.

Other significant adverse events like hypocalcaemia were less frequent in palopegteriparatide-treated subjects during the Blinded Treatment Period of Safety Pool II compared to placebo (5.7% vs 27.8%), whereas hypercalcaemia was more frequent (8.6% vs 0%). Also during the TransCon PTH period, the incidence of hypercalcemia was higher in the palopegteriparatide-treated subjects than in the placebo-treated subjects, both based on lab results and on TEAEs. The incidence of hypercalcemia leading to ER/Urgent care visit and/or hospitalization 2.9% in the palopegteriparatide-treated group vs. 0 in the placebo group during the Blinded Treatment Period.

Results regarding *local tolerability* in Safety Pool II were similar between palopegteriparatide-treated and placebo subjects in both groups. In TCP-304 *TEAEs related to injections* were more common in palopegteriparatide-treated subjects compared to placebo (36.1% [22/61] vs 4.8% [1/21]). However, most events of injection site reaction were Grade 1. No pain was reported. No TEAEs related to

injections were reported in TCP-201, probably mostly due to difference in definition of collection of TEAEs compared to TCP-304 and therefore different reporting.

In the phase 2 study (TCP-201), the incidence of serious adverse events (SAEs) was low and no SAE was considered related to study treatment respectively led to permanent discontinuation from study treatment. In the phase 3 study (TCP-304), the incidence of SAEs was low and only one of the SAEs (hypercalcaemia) was considered related to study treatment, in which Palopegteriparatide was temporarily interrupted. One palopegteriparatide-treated subject experienced a Grade 4 (fatal) serious TEAE (TESAE) of cardiac arrest which was considered unrelated to study treatment.

Excursions to increased calcium levels were only observed in palopegteriparatide-treated subjects, while excursions to low calcium levels were observed in both treatment groups, however more frequently in placebo subjects than in palopegteriparatide-treated subjects. Excursions to high calcium levels were observed only during the first 3 months of the Blinded Period. These excursions occurred particularly during the titration period. Data suggest that patients with eGFR of < 45 mL/min may be more susceptible for hypercalcaemic reactions and transient eGFR decrease.

For Safety Pool II overall, *alkaline phosphatase values* increased in palopegteriparatide-treated subjects relative to placebo and baseline from Week 4 through Week 26. During the overall TransCon PTH period in TCP-201, alkaline phosphatase levels were declining towards baseline by Week 84.

Procollagen Type 1 Amino-terminal Propeptide (P1NP) and *C-terminal telopeptide of Type I collagen* (CTx) trended downwards after Week 26 through Week 58 but remained above the baseline values.

For Safety Pool II, 25(OH)D3 slightly decreased in palopegteriparatide-treated patients, compared to placebo.

More *subjects ≥50 years* of age experienced at least 1 TEAE considered related to study treatment in the Blinded Period and during the TransCon PTH Period. The proportion of male and female subjects experiencing events within each category were largely comparable both during the Blinded Period and during the TransCon PTH Period.

The proportion of patients testing positive for *binding antibodies* at any time during treatment was low. However, a transient boost of pre-existing anti-PEG antibodies, which resulted in temporarily increased clearance of Total PTH, mPEG and decreased PTH concentrations, thereby reducing serum calcium levels, was detected in *2,2 % of the palopegteriparatide-treated patients.*

3.5. Uncertainties and limitations about unfavourable effects

The number of patients treated with palopegteriparatide in the above-mentioned studies is limited (N=139), which is acceptable for a rare condition. However, for a product with intended chronic use, data on long-term effects can be considered rather limited, as there are only 57 patients who have received at least 110 weeks of treatment. The still ongoing OLEs (TCP-201 and TCP-304) are expected to provide further insights in the safety profile of palopegteriparatide with regard to effects on bone, frequency of hypercalcaemia and potential sequelae, renal function, immunogenic effects, and potential adverse drug reactions related to chronic mPEG exposure.

With regard to the data provided so far, numbers of treated subjects regarding *subgroups* respectively *special populations* (e.g. age, gender, geographical regions, renal impairment) are small.

In the pivotal study, only patients with eGFR ≥30 mL/min/1.73m² were included. In the dedicated renal impairment (RI) study (TCP-104) subjects with severe RI had a higher apparent exposure (Cmax and AUC0 tlast) to Free PTH(1-34) than subjects with normal renal function. However, due to bioanalytical constraints it was not possible to determine if there was any effect of severe RI on the

Free PTH(1-34) released from palopegteriparatide. No additional safety signals were detected in trial TCP-104. In addition, palopegteriparatide will be monitored based on serum calcium levels.

The characterization of potential effects of long-term exposure to mPEG is missing.

3.6. Effects Table

Table 45. Effects Table for Yorvipath (Palopegteriparatide) indicated for "TRADENAME, a prodrug providing sustained release of parathyroid hormone (PTH(1-34)), is a PTH replacement therapy indicated for the treatment of hypoparathyroidism in adults." (data cut-off: 12 January 2022).

Effect	Short Description	Unit	Palopegteriparatide	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects (main study 304)						
Composite endpoint	Primary efficacy endpoint, treatment effect of daily palopegteriparatide on serum calcium levels and therapeutic doses of active vitamin D (i.e., calcitriol or alfacalcidol) and calcium at 26 weeks of treatment	%	78.7% (95% CI: 66.3, 88.1)	4.8% (95% CI: 0.1, 23.8)	p <0.0001 no clinical hard endpoints (soft tissue calcifications, end-organ damage) largely female & white population	TCP-304
sCA	Change in Serum Calcium at W26	mg/dL	0.31 (95%CI: 0.08,0.53)	-0.38 (95%CI: -0.68, -0.09)	p <0.0001	TCP-304
Phosphate	Change in Serum Phosphate at W26	mg/dL	-0.125 (95% CI: -0.47, 0.22)	-0.351 (95% CI: -0.52, -0.18)	n.s.	TCP-304
Calcium×Phosphate	Change in Albumin-adjusted serum calcium-phosphate product at W26	mg^2/dL^2	-1.84 (95% CI: -3.36, -0.31)	-2.77 (95% CI: -5.40, -0.14)	n.s.	TCP-304
Magnesium	Change in Serum Magnesium at W26	mg/dL	0.111 (95% CI: 0.07, 0.16)	-0.017 (95% CI: -0.09, 0.06)	p = 0.0016	TCP-304

Effect	Short Description	Unit	Palopegteriparatide	Placebo	Uncertainties/ Strength of evidence	References
Hypoparathyroidism patient experience scale (HPES) - Physical - Cognitive - Physical Functioning - Daily Life	LS mean Change from Baseline[6] at W26	- (score)	-21.01 (95% CI: -25.41, -16.60) -20.49 (95% CI: -25.67, -15.31) -18.29 (95% CI: -23.59, -12.99) -17.65 (95% CI: -22.39, -12.91)	-4.81 (95% CI: -15.22, 5.59) -6.16 (95% CI: -15.92, 3.60) -1.01 (95% CI: -12.40, 10.38) -0.36 (95% CI: -12.19, 11.46)	statistically significant improvements	TCP-304
Short Form-36 (SF-36) Daily Life	LS mean Change from Baseline[7] at W26	- (score)	5.29 (95% CI: 3.47, 7.10)	0.12 (95% CI: -4.64, 4.89)	statistically significant improvements	TCP-304
BMD	Change in Bone Mineral Density at W26	g/cm^2	decrease in 3 of 5 measured areas	stable	relevance, long-term fracture prevalence lacking	TCP-304
Bone Turnover Markers	Change from baseline in P1NP and CTx at W26	ng/mL	increased	stable	p <0.0001 results indicate a restoration of a closer to normal bone physiology	TCP-304
Unfavourable Effects						
Hypercalcemia	Number of subjects with TEAE (related)	%	8,6	0	Safety data base of 104 subjects with hypoparathyroidism (60 with exposure ≥26 weeks of palopegteriparatide, 44 ≥84 weeks)	(Blinded Period – Safety Pool II)

[6] decrease in HPES scores denotes an improvement in HRQoL
[7] increase in SF-36 score denotes an improvement in HRQoL

Effect	Short Description	Unit	Palopegteriparatide	Placebo	Uncertainties/ Strength of evidence	References
Vasodilatory signs and symptoms	Number of subjects with TEAE (related)	%	13,1%	0	Vasodilatory signs and symptoms, all non-serious: dizziness postural and postural orthostatic tachycardia syndrome in 2/61 (3.3%) subjects each, and blood pressure orthostatic decreased, headache, orthostatic hypotension, palpitations, and syncope in 1 (1.6%) subject each. Most data in TCP-201 were collected under the earlier versions of the protocol. No AESIs were reported as of the data cutoff for TCP-201 as the definition of AESIs.	TCP-304
TEAEs related to injections	Number of subjects with TEAE (related)	%	36,1%	4,8%	Safety data base of 61 subjects with hypoparathyroidism. No TEAEs related to injections were reported in TCP-201, probably mostly due to difference in definition of collection of TEAEs compared to TCP-304 and therefore different reporting.	TCP-304
Long term safety	Missing data				There are only 58 patients with hypoparathyroidism with at least 1 year exposure.	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Favourable effects

The results of the primary efficacy analysis of the main study TCP-304 demonstrate a statistically compelling and clearly clinically relevant effect of palopegteriparatide in patients with HP. The primary composite endpoint, which is considered clinically meaningful, was consistently favourable for palopegteriparatide 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 for the dose-finding study TCP-201. The efficacy results can therefore be considered robust.

Patients were able to reach albumin-adjusted sCa within the normal range of 8.3 to 10.6 mg/dL and, at the same time, reduce or discontinue their therapeutic doses of calcium and Vit D intake. Patients were also able to substantially reduce their pill burden, chronic intake of medications is one of the factors

discussed to have a negative impact on QoL[8]. Effects on QoL have been measured as key secondary endpoints using validated scales and were statistically significant in favour for palopegteriparatide. However, the comparison to a potentially suboptimal SOC treatment in the Placebo arm could have introduced bias.

Calcium is one of the essential ions necessary for normal functioning of the organism. The serum calcium concentration under physiological conditions is kept within a narrow range. Data from a PK/PD subpopulation of the dose-finding study suggest that palopegteriparatide can maintain serum calcium levels stable in the (low-)normal range throughout the day (24 h) without significant peak-trough fluctuation. This is an important goal in the treatment of patients with hypoparathyroidism.

Results provided show that the majority of patients receiving palopegteriparatide became independent of therapeutic doses of calcium supplements and active vitamin D, which is considered a benefit since keeping the balance between avoiding hypocalcaemia on the one hand and hypercalciuria and its sequelae on the other hand is frequently difficult with conventional treatment. Possible important favourable effects on rates and/or degree of long-term consequences seen with conventional treatment like nephrocalcinosis/nephrolithiasis and renal impairment are currently not shown and are recommended to be further investigated post-marketing. Positive effects could possibly be expected based on the fact that palopegteriparatide will substitute the missing hormone in patients with hypoparathyroidism and the reductions seen, e.g. in 24 h urinary calcium, although no definitive conclusions based on urinary calcium as a surrogate endpoint for renal outcomes can be made. Nonetheless, long-term results provided confirm that reductions in 24 urinary calcium were maintained over time.

Effects on bone turnover markers P1NP as well as CTx as well as BMD measured with DXA indicate a restoration of a closer to normal bone physiology. However, it is unclear whether this will have an effect on fracture risk. Results show that mean BMD decreased through the initial 26 weeks, but not below the normal ranges, with no further or little changes though week 52/ week 110.

Unfavourable effects

The number of patients treated with palopegteriparatide in the above-mentioned studies is limited (N=139), which is acceptable for an orphan disease. The safety profile appears rather benign with hypercalcaemia being the only serious ADR reported in clinical trials. Close monitoring of serum calcium levels, especially after initiation and uptitration of palopegteriparatide, is therefore important and this is adequately addressed in the SmPC.

Up to now, 57 patients have received at least 110 weeks of treatment. These limited safety data do not raise additional safety concerns. Further *long-term data*, particularly regarding effects on bone, frequency of hypercalcaemia and potential sequelae, renal function, immunogenic effects, and potential adverse drug reactions related to chronic mPEG exposure will be provided from the ongoing studies. Long-term safety including long-term effects on bone health and adverse drug reactions potentially related to mPEG exposure are labelled as missing information in the RMP and will be addressed via routine pharmacovigilance.

Treatment-related adverse events and *adverse events of special interest* as well as *other significant adverse events* were assessed properly. In summary, the reported events were Grade 1 and 2 and they appear to be well manageable.

With regard to the data provided so far, numbers of treated subjects regarding *subgroups* respectively within *special populations* (e.g. age, gender, geographical regions, renal impairment) are small.

[8] M. Büttner, Quality of life in patients with hypoparathyroidism receiving standard treatment: a systemic review; Endocrine 2017

The *laboratory parameters* were mainly stable and in the normal range.

The proportion of patients tested positive for *binding antibodies* at any time during treatment was low. Results provided do not show an association of appearance of antibodies against PTH or PEG with injection site reactions, systemic hypersensitivity or any immunogenicity-related event. However, a transient boost of pre-existing anti-PEG antibodies, which resulted in temporarily increased clearance of Total PTH, mPEG and decreased PTH concentrations, thereby reducing serum calcium, was detected in 2,2 % of the palopegteriparatide-treated subjects. The potential impact of anti-PTH or anti-PEG antibodies will be further assessed in the ongoing studies TCP-201 and TCP-304.

Regarding the PK analyses the administered *mPEG concentrations* and, respectively, the associated mPEG exposure were quite low and no unexpected short-term renal, hepatic, immune or neurologic adverse events potentially attributed to mPEG exposure were reported.

3.7.2. Balance of benefits and risks

Since efficacy of palopegteriparatide in patients with HP at the proposed starting dose of 18 µg/d has been demonstrated in adult patients with HP and adverse effects appear to be well manageable, the overall benefit/risk of palopegteriparatide as replacement therapy in patients with chronic hypoparathyroidism is positive.

3.7.3. Additional considerations on the benefit-risk balance

Feedback from patient organisation

Of note, within this submission, the CHMP invited EURORDIS to share patients experience and concerns about their conditions respectively treatments. To receive a sustained feedback, interviews with three patients living with hypoparathyroidism from two EU/EEA Member States, and with various severity forms were conducted. Their responses are summarised as follows:

Medical history of the interviewed patients

All three patients experienced hypoparathyroidism following thyroid gland surgery. Some received Calcium and Magnesium supplement right after surgery, others assumed the symptoms they had were a consequence of the thyroidectomy itself, as they were not aware of the risk of hypoparathyroidism.

Symptoms, burdens and limitations in QoL

Most frequent symptoms include:

- Cramp-like spasms of the hands and fingers that can be prolonged and painful,
- Muscle pain or spasms of the muscles of the face or arms,
- Tingling or burning sensations, or a pins and needles feeling, in the lips, tongue, fingers and toes,
- Seizures,
- Kidney stones,
- Arrhythmias
- Fainting,
- Cataract
- Tartar deposit on teeth,
- Difficulties to concentrate/brain fog.

All three patients had to stop working, either immediately at the onset of symptoms, or when symptoms evolved to a point that was no longer compatible with going to work or even sitting at home to work remotely. The social impact is severe as well. Due to the symptoms, patients often can no longer go out with the friends. In addition, sexual life is severely affected, as cramps or spams are almost systematic.

Calcaemia and calciuria need to be monitored frequently. In addition, a diet is needed (rich in calcium (dairy products, green leafy vegetables, broccoli and foods with added calcium, such as some orange juices and breakfast cereals), low in phosphorus (avoiding carbonated soft drinks, which contain phosphorus in the form of phosphoric acid, and limiting processed foods, meats, hard cheeses, nuts, whole grains, no wine). Low salt in case of lithiasis.

Treatments used

Main treatment consists in Calcitriol (e.g. OneAlfa or Rocaltrol), Calcium (e.g. Calcidrol) and Vitamin D (e.g. Un-Alfa). Some patients reported increased risk of lithiasis due to calciuria they attributed to their medication. In addition, anxiolytics are commonly prescribed. In case of a crisis Calcium Sandoz® 500 mg (as effervescent tablets) is given.

Furthermore, some patients are taking Natpar s/c. Natpar can also be injected via a pump (for patients with PTH levels of 0 pc/mL). However, Natpar will be withdrawn at the end of 2024.

Forsteo (teriparatide) provides fast improvement. However, dose adjustments are often needed, and calcium levels need to be monitored constantly. Of note, teriparatide is not formally approved for the treatment of HP.

Expectations with a new treatment

A new treatment should

- Stabilise the disease, with more stable calcium levels and resulting from this with a reduced need for frequent blood and urine monitoring.
- Reduce the variability in the onset of symptoms/crises as well as the incidence of symptoms/crises.
- Enable patients go back to work or socialise with their friends again
- Lead to an improved physical activity

Of note, a daily SC treatment would be acceptable, a weekly infusion as well.

3.8. Conclusions

The overall benefit/risk balance of Yorvipath is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Yorvipath is not similar to Natpar within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Yorvipath is favourable in the following indication(s):

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

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the review of data on the quality, non-clinical and clinical properties of the active substance, the CHMP considers that palopegteriparatide in comparison to the known teriparatide (Forsteo) and rhPTH(1-84)/parathyroid hormone (Natpar) previously authorised as medicinal products in the European Union is to be qualified as a new active substance as it differs significantly in properties with regard to safety and/or efficacy from the previously authorised substances.