Health Technology Briefing
September 2023

TransCon PTH for treating hypoparathyroidism

Company/Developer	Ascendis Pharma

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 28187	NICE ID: Not available	UKPS ID: 672257

Licensing and Market Availability Plans

In phase III clinical development.

Summary

TransCon PTH is in clinical development for the treatment of hypoparathyroidism (HP). HP can be caused when the parathyroid glands do not produce enough parathyroid hormone (PTH). This causes low blood calcium levels (hypocalcaemia). The parathyroid glands are very small glands situated in the neck just behind the thyroid gland and they control calcium levels in the bloodstream to make sure one does not have too little or too much calcium. HP can happen after neck surgery (thyroidectomy) or because of rare genetic conditions. The main symptoms of HP include fatigue, tingling, pins and needle sensations, and muscle cramps. Treatment of HP has been challenged by the limited number of effective medicinal products and side-effects associated with them.

TransCon PTH is an investigational prodrug (inactive substance converted in the body into an active form) of PTH that is in development as a once-daily hormone replacement therapy. It is designed to provide a sustained release of active PTH to maintain stable PTH levels within the physiological (normal) range for 24 hours daily as well as address both the short-term symptoms and long-term complications of hypoparathyroidism. TransCon PTH is administered subcutaneously (under the skin). If licensed, TransCon PTH will provide a treatment option that addresses the underlying physiologic cause of the disease for patients with HP who currently have few well-tolerated and effective treatment options.

Proposed Indication

Treatment of hypoparathyroidism (HP) in adults.[1]

Technology

Description

TransCon PTH, an inactive prodrug of PTH (1-34) is designed to maintain a steady concentration of parathyroid hormone (PTH) in the bloodstream within the normal range, comparable to the profile obtained during continuous pump delivery, thereby overcoming the fundamental limitations of short-acting PTH molecules. To ensure an infusion-like profile, PTH(1-34) is transiently bound via the TransCon linker to a chemically inert, branched 40 kDa methoxypolyethylene glycol (mPEG) carrier that efficiently shields PTH from binding to the PTH1R and prolongs the peptide's circulation half-life due to reduced renal clearance.[2] Following subcutaneous injection and on exposure to physiologic conditions, autocleavage of the linker occurs, and active PTH is released in a controlled manner.[3]

TransCon PTH is currently in clinical development for the treatment of HP. In the phase III clinical trial, PaTHway (NCT04701203), patients receive TransCon PTH at a starting dose of 18 mcg delivered once daily by subcutaneous injection via a single-patient-use prefilled pen.[1]

Key Innovation

Conventional therapy for HP consisting of active vitamin D and calcium supplements and therapy with adjunct recombinant human PTH (1-84) both aim to alleviate hypocalcaemia but neither therapy optimally controls urinary calcium (uCa) or significantly reduces the incidence of hypercalcemia and hypocalcaemia. Conventional therapy also fails to restore normal physiologic levels of PTH.[4,5] Furthermore, the long term use of conventional therapy can lead to complications that include severe diseases such as chronic kidney diseases, liver and basal ganglia calcifications, cardiovascular complications, and bone damage.[6] TransCon PTH is designed to restore physiologic levels of PTH 24 hours a day as well as address both the short-term symptoms and long-term complications of hypoparathyroidism with the goal of providing PTH replacement therapy that normalizes serum and urinary calcium, as well as serum phosphate levels, and improve quality of life.[6]

Patients with HP currently have few well-tolerated and effective treatment options. If licensed, TransCon PTH will provide a treatment option for patients with HP that addresses the underlying deficiency of endogenous PTH.

Regulatory & Development Status

TransCon PTH does not currently have Marketing Authorisation in the EU/UK for any indication.

TransCon PTH is in phase III clinical development for endocrine system and parathyroid diseases.[1]

TransCon PTH was granted an orphan designation for HP by the EMA and US FDA in February 2022 and June 2018 respectively.[7,8]

Patient Group

Disease Area and Clinical Need

HP is a rare condition where the parathyroid glands, which are in the neck near the thyroid gland, produce too little PTH. This makes blood calcium levels fall (hypocalcaemia) and blood phosphorus levels rise (hyperphosphataemia).[9] PTH is the major circulating regulator of calcium homeostasis. It acts on the bone and kidney cells directly and has a secondary role in calcium homeostasis of the gastrointestinal tract due to its influence on the production of active vitamin D (1,25-dihydroxyvitamin D3). When PTH production is absent or deficient, the expected calcium-conserving effects of PTH on the renal tubule are lost. The phosphaturic effects of PTH are also lost. These two pathophysiological processes are responsible, in part, for the characteristic hypocalcemia and hyperphosphatemia of hypoparathyroidism.[10] Due to the involvement of calcium and phosphate in several key physiologic processes, patients with hypoparathyroidism experience various physical and cognitive symptoms, including fatigue, muscle cramps, pain or cramps particularly in the legs, feet or tummy, twitching facial muscles, and mood changes.[9] Majority of hypoparathyroidism cases are post-surgery for benign and malignant thyroid disorders, hyperparathyroidism, and laryngeal or other head and neck cancers. Nonsurgical causes include rare genetic conditions and syndromes; autoimmune destruction of the glands; destruction or invasion due to tumour, radiation, or infiltration by iron or copper; hypomagnesaemia and magnesium depletion; and idiopathic.[11]

Hypoparathyroidism is an area of major unmet medical need with an estimated 200,000 patients in the United States, Europe, and Japan.[6] A Danish study suggested that 27 in every 100,000 people have HP. It seems to be more prevalent in women than men and rates of surgical HP are increasing as the number of thyroid cancer cases rises.[12] In England 2021-22, there were 174 finished consultant episodes (FCE) and 147 admissions for HP, unspecified (ICD-10 code E20.9) which resulted in 245 FCE bed days and 92 day cases.[13]

Recommended Treatment Options

There are no National Institute for Health and Care Excellence (NICE) recommended treatments for hypoparathyroidism. Treatment for hypoparathyroidism aims to relieve symptoms and bring the levels of calcium and other minerals in the blood back to normal. This involves taking supplements (i.e. vitamin D and calcium), usually for life, to restore calcium and phosphorus levels.[9]

Clinical Trial Information

Trial	**PaTHway**, NCT04701203; 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 **Phase III:** Active, not recruiting **Locations:** 4 EU countries, USA, Canada, and Norway **Primary completion date (actual):** January 2022
Trial Design	Randomised, parallel assignment, quadruple blinded
Population	N=84 (actual); subjects with postsurgical chronic HP or auto-immune, genetic, or idiopathic HP for at least 26 weeks aged 18 years and older
Intervention(s)	TransCon PTH at a starting dose of 18 mcg delivered once daily by subcutaneous injection, individually and progressively titrated to an optimal

	dose over a 10 week period, followed by an individualized dosing period up to 16 weeks.
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome: Efficacy - The proportion of subjects with albumin-adjusted serum calcium (sCa) within the normal range, 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 [Time frame: 26 weeks] See trial record for full list of all outcomes
Results (efficacy)	At week 26, 79% (48/61) of participants treated with TransCon PTH versus 5% (1/21) with placebo met the composite primary efficacy endpoint ($p < 0.0001$). TransCon PTH treatment demonstrated a significant improvement in all key secondary endpoint HPES domain scores (all $p < 0.01$) and the SF-36 Physical Functioning subscale score ($p = 0.0347$) compared with placebo. Additionally, 93% (57/61) of participants treated with TransCon PTH achieved independence from conventional therapy. Treatment with TransCon PTH enabled rapid and sustained reduction of elemental calcium and complete discontinuation of active vitamin D within 8 weeks. TransCon PTH treatment normalized mean 24-hour urine calcium (uCa).[14]
Results (safety)	Overall, 82% (50/61) treated with TransCon PTH and 100% (21/21) with placebo experienced adverse events; most were mild (46%) or moderate (46%). No study drug-related withdrawals occurred.[14]

Trial	**PaTH Forward, NCT04009291;** 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 **Phase II:** Active, not recruiting **Locations:** 3 EU countries, USA, Canada, and Norway **Primary completion date (actual):** March 2020
Trial Design	Randomised, parallel assignment, double-blind
Population	N=59 (actual); Subjects with postsurgical chronic HP or auto-immune, genetic, or idiopathic HP for at least 26 weeks aged 18 years and older
Intervention(s)	TransCon PTH administered once daily by subcutaneous injection at either 15mcg, 18mcg, or 21mcg
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome: The proportion of subjects with albumin-adjusted sCa 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 [Time frame: 4 weeks].

	See trial record for full list of outcomes
Results (efficacy)	At week 4, 82% of patients receiving TransCon PTH achieved independence from standard of care (SoC, defined as active vitamin D = 0 µg/day and calcium [Ca] ≤ 500 mg/day, compared to 15% in the placebo group. At week 26, 91% of participants treated with TransCon PTH achieved independence from SoC. Mean 24-hour uCa decreased from a baseline mean of 415 mg/24h to 178 mg/24h by week 26 (n = 44) while normal sCa was maintained, and serum phosphate and serum calcium-phosphate product fell within the normal range. By week 26, mean scores on the generic 36-Item Short Form Health Survey domains increased from below normal at baseline to within the normal range. The Hypoparathyroidism Patient Experience Scale symptom and impact scores improved through 26 weeks.[15]
Results (safety)	TransCon PTH was well tolerated with no treatment-related serious or severe adverse events.[15]

Estimated Cost

The cost of TransCon PTH is not yet known.

Relevant Guidance

NICE Guidance

No relevant guidance identified.

NHS England (Policy/Commissioning) Guidance

NHS England. 2013/14 NHS Standard Contract for Specialised Endocrinology services (adult). A03/S/a.

Other Guidance

- American Thyroid Association (HTA). HTA Statement on Postoperative Hypoparathyroidism: Diagnosis, Prevention, and Management in Adults. 2018.[16]
- Brandi ML, et al. Management of Hypoparathyroidism: Summary Statement and Guidelines. 2016.[10]
- European Society of Endocrinology (ESO). ESO Treatment of chronic hypoparathyroidism in adults. 2015.[17]

Additional Information

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