## VI.2 Elements for a Public Summary

### VI.2.1 Overview of Disease Epidemiology

Hypoparathyroidism is a rare hormonal condition caused by absent or very low circulating PTH levels in the blood. PTH is necessary to maintain normal calcium and phosphate levels in the blood. Surgical removal of or damage to the parathyroid glands in the neck are the most common causes of hypoparathyroidism in adults. The symptoms of hypoparathyroidism are related to low blood calcium levels and high phosphate levels, and include abnormal sensations, muscle cramps, mental changes, and kidney stones. Historically, hypoparathyroidism has been treated with oral calcium and vitamin D.

### VI.2.2 Summary of Treatment Benefits

Natpar has been studied in one main study involving 124 male and female patients with chronic hypoparathyroidism receiving oral calcium and vitamin D. Natpar was compared with placebo (a dummy treatment). The main measure of effectiveness was the amount of reduction or replacement of oral calcium and vitamin D with Natpar while maintaining calcium levels. About 55 % of patients treated with Natpar achieved this goal versus 2.5 % of patients taking placebo. At week 24, 43% of Natpar patients were independent of active vitamin D treatment and were receiving no more than 500 mg of calcium citrate per day, compared with 6 % of placebo patients. Sixty-nine percent of patients taking Natpar showed a reduction in oral calcium of ≥50% compared to 7.5% of patients taking placebo.

Natpar was also studied in an extension study involving 49 patients who had previously completed participation in other Natpar clinical trials. Patients received Natpar at doses of 25 micrograms, 50 micrograms, 75 micrograms, or 100 micrograms per day for up to approximately 40 months. The results demonstrated continued positive effects of Natpar over 36 months including stable calcium levels, decreased calcium in the urine, decreased serum phosphate, and stable calcium-phosphate product.

### VI.2.3 Unknowns Relating to Treatment Benefits

Missing information includes use in paediatric patients under 18 years of age; use in pregnant or lactating women; long-term effects on bone structure and development in paediatric patients under 18 and young adults with open epiphyses; use in patients older than 65 years of age; use in non-Caucasians; use in patients with severe renal or hepatic disease; and long-term safety and efficacy.

### VI.2.4 Summary of Safety Concerns

**Table 1: Important Identified Risks**

| Risk | What is Known | Preventability |
|---|---|---|

**Table 1: Important Identified Risks**

| Risk | What is Known | Preventability |
|---|---|---|
| High calcium levels (Hypercalcaemia) | High calcium levels (hypercalcaemia) were reported in clinical trials with Natpar. Hypercalcaemia most commonly occurred during the titration period, during which oral calcium and active vitamin D and NATPAR doses were being adjusted. | High calcium levels may be minimised by following the recommended dosing and monitoring information, including reduction of calcium supplements and oral vitamin D during treatment initiation with PTH and based on serum calcium level. |
| Low calcium levels (Hypocalcaemia) | Low calcium levels (hypocalcaemia) are a common symptom of hypoparathyroidism and were seen during clinical trials. The risk of developing low calcium levels occurred most often after NATPAR was stopped. | Low calcium levels may be minimised by following the recommended dosing, and monitoring information. |

PTH=parathyroid hormone

**Table 2: Important Potential Risks**

| Risk | What is Known (Including reason why it is considered a potential risk) |
|---|---|
| Cancer of the bones (osteosarcoma and other bone tumours) | No cases of cancer in the bones have been identified in humans with the use of Natpar.<br>In animal studies, Natpar (rhPTH [1-84]) and a similar drug, For(s)teo (rhPTH [1-34]), were shown to produce bone cancer (osteosarcoma) in rats that were given the drugs for long periods of time.<br>In humans, there have been three reports of bone cancer (osteosarcoma) with the use of For(s)teo over the last 10 to 15 years. |
| Medication errors | Medication errors are unintended mistakes in the prescribing, dispensing and administration of a medicine that could cause harm to a patient.<br>The package leaflet and instructions for use are provided to help lessen the chance of medication errors from occurring. |
| Immunogenicity/neutralisation of rhPTH (1-84) biological activity | It is possible to develop antibodies (produced by the immune system) to Natpar and this may make the medication less effective.<br>There are no tests available to determine if antibodies to Natpar have developed. If you experience any side effects you must tell your doctor immediately. |
| Lack of effect overtime (Tachyphylaxis) | It is possible that the calcium-raising effect of NATPAR may decrease over time in some patients. |

**Table 3: Missing Information**

| Risk | What is Known |
|---|---|
| Use in paediatric patients less than 18 years of age | Clinical studies have not been performed in patients under 18 years of age. The effect and safety of Natpar when given to these patients is not known. Studies are planned to investigate the use of Natpar in paediatric subjects. |

| **Table 3: Missing Information** | |
|---|---|
| **Risk** | **What is Known** |
| Use in pregnant or lactating women | There are no data on the use of Natpar in pregnant women. Animal studies did not show a negative effect on the reproductive system.<br>There are no data on the effect of Natpar on human fertility. Animal studies did not show any effect on fertility.<br>The results of animal studies showed excretion of Natpar in breast milk. It is unknown whether Natpar is excreted in human milk. |
| Long-term effects on bone structure and development in paediatric patients <18 years of age and young adults with open epiphyses | The effect on bone growth and development in paediatric patients and young adults with open epiphyses is unknown. |
| Use in patients older than 65 years of age | Although the number of patients older than 65 years was limited in clinical studies of Natpar, the data did not show an increased frequency of serious adverse events or adverse events in patients in this age group.<br>Additional medical diseases, like heart, liver, or renal diseases, some cancers, high blood pressure, overweight, gout, and diabetes, may be more common in patients over the age of 65, which may increase the risk of developing a higher risk of drug-drug interactions with events related to high calcium levels, such as irregular heart rhythm. Patients taking medication that may influence the calcium levels in the blood, such as lithium, glycosides, bisphosphonates, and thiazide diuretics, should have their calcium level checked by their physician. |
| Use in non-Caucasians | There is a higher incidence of osteosarcoma in patients of African descent. Natpar may further increase this risk in these patients. |
| Use in patients with severe kidney disease | No dose adjustment is necessary for patients with mild or moderate impairment of kidney function. There are no data available in patients with severe kidney dysfunction. |
| Use in patients with severe liver disease | No dose adjustment is necessary for patients with mild or moderate impairment of liver function. There are no data available in patients with severe liver dysfunction. |
| Long-term safety and efficacy | There are no data on the long-term safety and effectiveness of Natpar. |

### VI.2.5 Summary of Risk Minimisation Measures by Safety Concern

All medicines have a SmPC which provides physicians, pharmacists, and other health care professionals with details on how to use the medicine, the risks, and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet. The measures in these documents are known as routine risk minimisation measures.

The SmPC and the Package leaflet for Natpar can be found in the Natpar EPAR page.

## VI.2.6 Planned Post Authorisation Development Plan

**Table 4: List of Studies in Post-authorisation Development Plan**

| Study/Activity (including study number) | Objectives | Safety Concerns/Efficacy Issue Addressed | Status | Planned Date for Submission of (Interim and) Final Results |
|---|---|---|---|---|
| Clinical study SHP634-403: A Randomized, 3-Arm, Single-blind, Placebo-Controlled, Phase 4 Study to Evaluate Metabolic Control, Safety, and Symptoms Among Adult Subjects with Hypoparathyroidism Treated With Recombinant Human Parathyroid Hormone (rhPTH[1-84]) as a Single Daily Injection and <<Alternative Dosing Regimen TBD>><br><br>(Category 2) | **Primary:**<br>To evaluate the effect of rhPTH (1-84) dosed as <<alternative dosing regimen TBD>> on overall metabolic control (as defined by pre-specified treatment targets) compared with active vitamin D and calcium supplements (conventional care) in subjects with hypoparathyroidism.<br>**Secondary:**<br>To evaluate the effect of rhPTH (1-84) dosed once daily on overall metabolic control (as defined by pre specified treatment targets) compared with conventional care.<br>To evaluate the effect of rhPTH (1-84) dosed once daily and as <<alternative dosing regimen TBD>> on cognitive status, hypoparathyroidism-related symptoms, and health-related quality of life compared with conventional care.<br>To evaluate the effect of rhPTH (1-84) dosed once daily and as <<alternative dosing regimen TBD>> on urine calcium excretion compared with conventional care.<br>To evaluate the effect of rhPTH (1-84) dosed once daily and as <<alternative dosing regimen TBD>> on the proportion of subjects achieving normal albumin- | Hypercalcaemia<br>Hypocalcaemia<br>Immunogenicity/neutralisation of rhPTH (1-84) biological activity<br>Tachyphylaxis<br>To confirm the appropriateness of QD dosing regimen of rhPTH(1-84) | Planned | Final report:<br>June 2023 |

| **Table 4: List of Studies in Post-authorisation Development Plan** | | | | |
|---|---|---|---|---|
| **Study/Activity (including study number)** | **Objectives** | **Safety Concerns/Efficacy Issue Addressed** | **Status** | **Planned Date for Submission of (Interim and) Final Results** |
| | corrected serum calcium (2.20-2.55 mmol/L [8.8 10.2 mg/dL]) compared with conventional care.<br>To evaluate the effect of rhPTH (1-84) dosed once daily and as <<alternative dosing regimen TBD>> on the proportion of subjects achieving complete independence from active vitamin D and calcium supplements compared with conventional care.<br>To evaluate the effect of rhPTH(1-84) dosed once daily and as <<alternative dosing regimen TBD>> on the proportion of subjects achieving the following:<br>Free of active vitamin D supplement and on 500 mg of calcium per day or less<br>Albumin-corrected serum calcium 2.0-2.55 mmol/L (8.0-10.2 mg/dL)<br>Serum phosphate normal 0.81-1.45 mmol/L (2.5-4.5 mg/dL)<br>24 hour urine calcium excretion <7.5 mmol (300 mg)/24 hours in men and <6.25 mmol (250 mg)/24 hours in women compared with conventional therapy.<br>To evaluate pre- and post-rhPTH (1-84) dosing serum albumin-corrected calcium levels in the once daily rhPTH (1-84) arm.<br>To evaluate the effect of rhPTH (1-84) dosed once daily and as <<alternative dosing regimen TBD>> on change from baseline in bone turnover markers compared with conventional care.<br>To evaluate the effect of | | | |

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|---|---|---|---|---|
| **Study/Activity (including study number)** | **Objectives** | **Safety Concerns/Efficacy Issue Addressed** | **Status** | **Planned Date for Submission of (Interim and) Final Results** |
| | rhPTH (1-84) dosed once daily and as <<alternative dosing regimen TBD>> on change from baseline in bone mineral density compared with conventional care. | | | |
| PAR-R13-001, (PARADIGHM ) Registry for Patients with Chronic Hypo-parathyroidism,<br>(Category 1) | To characterize and describe the clinical course of chronic hypoparathyroidism under conditions of routine clinical practice. This includes, but is not limited to, treatments, symptoms, health-related quality of life (HRQoL), clinical outcomes, and comorbidity.<br>To characterize and describe the long-term efficacy and safety profile of rhPTH (1-84) treatment in patients with chronic hypoparathyroidism under conditions of routine clinical practice. This includes long-term effects of rhPTH (1-84) on renal, eye, bone, cardiovascular, and other outcomes relevant for patients with hypoparathyroidism. | Hypercalcaemia<br>Hypocalcaemia<br>Medication errors<br>Tachyphylaxis<br>Use in pregnant or lactating women<br>Use in patients > 65 years of age<br>Use in non-Caucasians<br>Long-term safety and efficacy | Planned | Interim analyses with PBRERs<br>Final report: 2035 |
| Clinical study PAR-C10-008 (RACE): A Long-term Open-label Study Investigating the Safety and Tolerability of NPSP558, a Recombinant Human Parathyroid Hormone (rhPTH [1-84]), for the Treatment of Adults with Hypoparathyroidism – A Clinical Extension | **Primary objective:**<br>The objective of this study is to demonstrate the long-term safety and tolerability of SC NPSP558 as hormone replacement therapy for the treatment of adult subjects with hypoparathyroidism.<br>**Secondary objectives:**<br>To evaluate the impact of different preparations of calcium and calcitriol on the response to NPSP558 | Hypercalcaemia<br>Hypocalcaemia<br>Immunogenicity/neutralization of rhPTH (1-84) biological activity<br>Long-term safety and efficacy | Ongoing | Final study report: May 2017 |

| **Table 4: List of Studies in Post-authorisation Development Plan** | | | | |
|---|---|---|---|---|
| **Study/Activity (including study number)** | **Objectives** | **Safety Concerns/Efficacy Issue Addressed** | **Status** | **Planned Date for Submission of (Interim and) Final Results** |
| Study (RACE)<br>(Category 3) | replacement therapy.<br>To demonstrate that dosing with NPSP558 across a dose range of 25 to 100 µg SC can be implemented in a safe and effective manner and can be maintained throughout long-term treatment.<br>To evaluate the impact of calcium-sparing diuretics on serum and urinary calcium. | | | |

PIP=paediatric investigation plan; Q=quarter; rhPTH (1-84) =recombinant human parathyroid hormone (1-84) (Natpar); SC=subcutaneous

VI.2.6.1 Studies which are a Condition of the Marketing Authorisation.

Registry study PAR-R13-001, (PARADIGHM) is a condition of the marketing authorisation.