EU RISK MANAGEMENT PLAN (RMP)

for

NATPAR™

(Recombinant human parathyroid hormone [1-84])

RMP Version number: 3.7

Date of final sign off: 09-June-2025

[redacted]

[redacted]

EU Risk Management Plan for NATPAR™ (Recombinant human parathyroid hormone [1-84])

Administrative Information

RMP version to be assessed as part of this application:

RMP Version number: 3.7

Data lock point (DLP) for this RMP: 23-April-2020

Date of final sign off: 09-June-2025

Rationale for submitting an updated RMP: Update to align with the extended date of completion for study SHP634-403.

Summary of significant changes in this RMP:

RMP Module:	Significant Changes:
Part I Product Overview	Updated the Marketing Authorisation Holder (MAH) name as "Takeda Pharmaceuticals International AG, Ireland Branch".
Part II Safety Specification	
• **Module SI Epidemiology of the indication(s) and target population(s)**	Not applicable
• **Module SII Non-clinical part of the safety specification**	Not applicable
• **Module SIII Clinical trial exposure**	Not applicable
• **Module SIV Populations not studied in clinical trials**	Not applicable
• **Module SV Post-authorisation experience**	Not applicable
• **Module SVI Additional EU requirements for the safety specification**	Not applicable
• **Module SVII Identified and potential risks**	Not applicable
• **Module SVIII Summary of the safety concerns**	Not applicable
Part III Pharmacovigilance plan	-Updated the name from 'Shire' to 'Takeda'. -Update of milestone for clinical study SHP634-403.
Part IV Plans for post-authorisation efficacy studies	Not applicable
Part V Risk minimisation measures	Not applicable

[redacted]

RMP Module:	Significant Changes:
Part VI Summary of the risk management plan	Not applicable
Part VII Annexes	Annex 2: Update of milestone for clinical study SHP634-403. Annex 8: Updated to reflect the impacted section changes.

Other RMP versions under evaluation:

Not applicable

Details of the currently approved RMP:

Version number: 3.6

Approved with procedure: EMEA/H/C/003861/II/0042

Date of approval (opinion date): 30-March-2023

QPPV name: Jean-Marie Heim, MD

Please note that e-signature may also be performed by Deputy EU QPPV [redacted], [redacted], or [redacted], on behalf of the EU QPPV (i.e. 'per procurationem').

QPPV signature: [redacted] RMP signatures are kept on file.

[redacted]

Table of Contents

[redacted]

[redacted]

ABBREVIATIONS

Abbreviation	Definition/Description
AESI	Adverse event of special interest
ATC code	Anatomical Therapeutic Chemical classification system
AUC	Area Under the Curve
BMD	Bone Mineral Density
CASR	Calcium-Sensing Receptor
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum Concentration
CNS	Central Nervous System
CrCl	Creatinine Clearance
CSR	Clinical Study Report
DDD	Defined Daily Dose
DLP	Data Lock Point
ECG	Electrocardiogram
eCTD	Electronic Common Technical Document
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
GLPs	Good Laboratory Practices
hERG	Human ether-a-go-go-Related Gene
HLGT	High Level Group Term
HR	Hazard Ratio
HRQOL	Health Related Quality of Life

[redacted]

Abbreviation	Definition/Description
IIT	Investigator-Initiated Trial
INN	International Non-proprietary Names
ISS	Integrated Summary of Safety Data
IV	Intravenous
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MAP	Mean Arterial Pressure
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	No observed adverse effect level
NPS	NPS Pharmaceuticals, Inc.
PARADIGHM™	Hypoparathyroidism Registry Study, PAR-R13-001
PD	Pharmacodynamic
PhV	Pharmacovigilance
PI	Product Information
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PL	Package Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term
PTH	Parathyroid Hormone
PTH (1-34)	Parathyroid Hormone (1-34)
PTH (rDNA)	recombinant human parathyroid hormone (1-84) (NATPAR)
Q	Quarter
QPPV	Qualified Person Responsible for Pharmacovigilance (in the European Union)
QTcF	Fridericia-corrected QT interval

[redacted]

Abbreviation	Definition/Description
RACE	NATPAR study PAR-C10-008
rDNA	Recombinant Deoxyribonucleic Acid
RELAY	NATPAR study PAR-C10-007
REPLACE	NATPAR study CL1-11-040
rhPTH (1-84)	recombinant human parathyroid hormone (1-84) (NATPAR)
RMP	Risk Management Plan
SC	Subcutaneous
SmPC	Summary of Product Characteristics
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
UK	United Kingdom
US/USA	United States of America
WHO	World Health Organisation

[redacted]

PART I: PRODUCT OVERVIEW

Table 1. Product Overview	
Active Substance(s) **(INN or common name)**	Recombinant human parathyroid hormone (1-84) (rhPTH [1-84])
Pharmacotherapeutic group(s) (ATC Code)	H05AA03
Name of Marketing Authorisation Holder	Takeda Pharmaceuticals International AG, Ireland Branch.
Medicinal products to which this RMP refers	NATPAR™
Invented name(s) in the EEA:	NATPAR™
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class** The active pharmaceutical ingredient, rhPTH (1-84), has an identical primary structure to the full-length human 84 amino acid protein. During the years of initial development, rhPTH (1-84) or PTH (rDNA) was also designated in documents as PTH, PTH (1-84), hPTH, hPTH (1-84), rhPTH, rhPTH (1-84), rPTH, and rPTH (1-84). rhPTH (1-84) was originally developed for osteoporosis and, subsequently, for hypoparathyroidism. [redacted]
	Summary of mode of action Endogenous PTH is secreted by the parathyroid glands as a polypeptide of 84 amino acids. PTH exerts its action via cell-surface PTH receptors, present in bone, kidney and nerve tissue. PTH receptors belong to the family of G-coupled protein receptors. PTH has a variety of critical physiological functions that include its central

[redacted]

Table 1. Product Overview	
	role in modulating serum calcium and phosphate levels within tightly regulated levels, regulating renal calcium and phosphate excretion, activating vitamin D, and maintaining normal bone turnover. NATPAR is identical to the 84 amino acid sequence of endogenous human PTH.
	Important information about its composition NATPAR is manufactured using a strain of *Escherichia coli* modified by rDNA technology.
Hyperlink to the Product Information (PI)	EU SmPC
Indication(s) in the EEA	**Current:** NATPAR is indicated as adjunctive treatment of adult patients with chronic hypoparathyroidism who cannot be adequately controlled with standard therapy alone.
	Proposed: Not applicable
Dosage in the EEA	**Current:** <u>General</u> Treatment should be supervised by a physician or other qualified healthcare professional experienced in the management of patients with hypoparathyroidism. The goal of treatment with NATPAR is to achieve calcaemic control and to reduce symptoms (see also section 4.4 of SmPC). The optimisation of parameters of calcium-phosphate metabolism should be in line with current therapeutic guidelines for the treatment of hypoparathyroidism. Prior to initiating and during treatment with NATPAR: • Confirm 25-OH vitamin D stores are sufficient. • Confirm serum magnesium is within the reference range. Please refer to the SmPC Section 4.2 for additional information.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	**Current:** NATPAR (PTH [rDNA]) powder and solvent for solution for injection is supplied as a multiple dose, glass dual-chamber cartridge which is available in 4 nominal dosage strengths (25, 50, 75, or 100 µg). Depending on the dosage strength, each medication cartridge contains 0.40, 0.80, 1.21, or 1.61 mg NATPAR, 4.5 mg sodium chloride, 30 mg mannitol, and 1.26 mg citric acid monohydrate as a sterile lyophilised powder, with 1.13 mL of a sterile 3.2 mg/mL aqueous solution of m-cresol as the reconstitution diluent. Reconstitution results in a nominal solution concentration of 0.35 mg/mL (25 µg/dose), 0.70 mg/mL (50 µg/dose), 1.05 mg/mL (75 µg/dose), or 1.40 mg/mL (100 µg/dose).

[redacted]

Table 1. Product Overview	
	The NATPAR cartridge will be supplied with a reusable pen injector manufactured by Haselmeier GmbH, Germany, for the cartridge holder and the reusable pen and by Duoject Medical Systems Inc. for the mixing device for NATPAR. Using the pen injector, each medication cartridge delivers 14 doses; each dose contains 25, 50, 75, or 100 µg of rhPTH (1-84) depending on the product dosage strength. NATPAR, after reconstitution, contains the following excipients: sodium chloride, mannitol, citric acid monohydrate, sodium hydroxide, m-cresol, and water for injections.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes.
ATC=Anatomical Therapeutic Chemical; EEA=European Economic Area; EU=European Union; PTH=parathyroid hormone; rDNA=recombinant deoxyribonucleic acid; rhPTH (1-84)= recombinant human parathyroid hormone (1-84); RMP=Risk Management Plan; SmPC=Summary of Product Characteristics	

[redacted]

PART II: SAFETY SPECIFICATION

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

Indication

NATPAR is indicated as adjunctive treatment of adult patients with chronic hypoparathyroidism who cannt be adequately controlled with standard therapy alone.

Table 2. Epidemiology for Hypoparathyroidism

Incidence and prevalence	Consistent with the EU (Commission Regulation (EC) No 847/2000B and section B on `Prevalence of the condition' of Guideline ENTR/6283/00), the Sponsor assessed the prevalence of hypoparathyroidism through review of reference databases. The use of these data sources show conclusively in as many Member States as possible that the population prevalence of hypoparathyroidism is well below the orphan medicinal product designation threshold prevalence of no more than 5 in 10,00 people in the EU. To obtain more accurate estimates of the true hypoparathyroidism prevalence, the sponsor utilised the CPRD to determine the point prevalence in the UK. The CPRD is one of the largest data sources with longitudinal primary care electronic medical records in the World. Established in 1987, it contains de-identified medical information on over 11 million patients in the UK (6.9% of total UK population) cumulatively and is widely considered to be representative of the UK population based on age, gender, and ethnicity[redacted]. The sponsor considers this database to be closely representative of the EU population and provides table detailing end-of-year point prevalence for each year from 2010 to 2014 (see Table 2a below); hypoparathyroidism cases were identified through readcodes (C121.00, C121z00, C121100, C121200). The identified prevalent cases were adjusted to reflect 100% of the UK population rather than 6.9% which are presented in the CPRD database. To further assess consistency of the hypoparathyroidism prevalence estimates, the sponsor utilised the Truven Health Analytics MarketScan Research Databases to obtain hypoparathyroidism prevalence estimates in the US. MarketScan is a real world data source which contains anonymised healthcare information on over 170 million patients across the United States cumulatively. Since 1995, healthcare data on US patients have been collected and linked together at the individual patient level to create longitudinal records for the purpose of economic, treatment patterns, and other HEOR and healthcare analysis. The MarketScan database captures the continuum of care in multiple settings, including physician office visits, hospital stays, and pharmacies. For the purpose of this analysis the Commercial Claims and Medicare Supplemental data from MarketScan for the years of 2010-2014 were used. The gender, age, and geographic distribution of the MarketScan population are in general considered to be representative of Americans covered by health insurance. The Table 2a with US data below details the results of this analysis; ICD 9 code of 252.1 was used to identify hypoparathyroidism patients. Based on the CPRD data the prevalence of hypoparathyroidism in the UK varied between 0.9-1.1 per 10,000 UK population (see Table 2a below) during 2010-2014.

Table 2. Epidemiology for Hypoparathyroidism

Table 2a: Prevalence of hypoparathyroidism in the UK from 2010 through 2014, CPRD

Year	Number patients	Total UK population in mid-year (million)*	Prevalence per 10,000
2010	5,710	62.8	0.91
2011	6,043	63.3	0.95
2012	6,377	63.7	1.00
2013	6,754	64.1	1.05
2014	7,246	64.6	1.12

*Data obtained from the Office for National Statistics website, http://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates; accessed February 15, 2016.

These UK prevalence rates compare with the US estimated higher hypoparathyroidism prevalence ranging between 1.5 and 2.4 per 10,000 US population (see Table 2b below).

Table 2b: Prevalence of hypoparathyroidism in the US from 2010 through 2014, MarketScan

Year	Number patients	US patients in MarketScan (million)	Prevalence per 10,000
2010	3,538	24.1	1.47
2011	4,716	26.7	1.77
2012	5,280	26.5	2.00
2013	4,902	21.5	2.28
2014	4,966	20.4	2.44

[redacted] published results from their research indicating that the prevalence of hypoparathyroidism between 1988 and 2012 was 2.4 / 10,000 Danish population. The prevalence results from this study in Denmark are also more closely aligned with a study in the US; 2.3 / 10,000[redacted]. Vadiveloo et al in Scotland and Cianferroti in Italy reported prevalence estimates of 4.7/10,000 and 2.7/10,000 respectively [redacted]

Astor et al, in Norway reported a prevalence of 1.02/10,000 [redacted]. The sponsor is aware that the UK population may not be 100% representative of the EU population. For this reason, a range of the true hypoparathyroidism prevalence using the UK and

[redacted]

Table 2. Epidemiology for Hypoparathyroidism	
	Norway data as the lower and the Scotland study results as the upper limits of the prevalence range (0.9 – 3.2 /10,000) is considered to be representative of the prevalence in the EU countries, which is well below the threshold of rare disease definition in the EU of < 5/10,000 population.
Demographics of the population in the proposed indication	As is the case for most rare diseases, the burden of illness for hypoparathyroidism has not been well described or studied. Considering the need to better understand the burden of illness associated with this condition, NPS Pharmaceuticals, Inc. (NPS) conducted an extensive quantitative study in conjunction with the Hypoparathyroidism Association and the Mayo Clinic [redacted]. This study is the largest conducted in this condition and included 374 patients with hypoparathyroidism. A comprehensive cross-sectional web-based survey was developed in collaboration with key opinion leaders to quantify the consequences of hypoparathyroidism endured by patients. Members of the Hypoparathyroidism Association and other patients who also suffer from hypoparathyroidism were invited to complete the survey. Of the 374 respondents with hypoparathyroidism, 318 (85.0%) were female and 56 (15.0%) were male, 193 (51.6%) were ≤50 years of age and 181 (48.4%) were over age 50 (mean age=49.4 years). The mean duration of disease was 13 years and the cause of the disease for most patients (78.3%) was due to postsurgical complications. Only two subjects did not have any therapeutic intervention for hypoparathyroidism. The majority (66.6%) took a combination of oral calcium and vitamin D.
Main existing treatment options	Current treatment consists of calcium and vitamin D in pharmacological doses sufficient to maintain the serum calcium level without the disabling symptoms of hypocalaemia. Various forms of oral calcium are available, both as calcium carbonate and calcium citrate. In order to improve the absorption of calcium from the gastrointestinal tract, pharmacological supplementation with activated forms of vitamin D, such as calcitriol itself or the analogue, alfacalcidol, is also required. Both active forms of vitamin D overcome the synthetic block in endogenous production of active vitamin D in hypoparathyroidism. Together oral calcium and active vitamin D form the mainstay of current treatment of patients with hypoparathyroidism. Despite the availability of treatment with calcium and active vitamin D, comorbidities (e.g. renal complications) and reduced Health Related Quality of Life (HRQOL) in patients with hypothyroidism are common [redacted].
Natural history of the indicated condition in the untreated population, including mortality and morbidity	Hypoparathyroidism causes hypocalcaemia because PTH secretion is inadequate to mobilise calcium from bone, reabsorb calcium from the distal nephron, and stimulate renal 1α-hydroxylase activity. As a result, insufficient 1,25-dihydroxyvitamin D (1,25$[OH]_2$ vitamin D) is generated for efficient intestinal absorption of calcium [redacted]. It is associated with hypocalcaemia, hyperphosphataemia, hypercalciuria and hypophosphaturia. Hypoparathyroidism can be congenital or acquired. Acquired hypoparathyroidism is most commonly the result of inadvertent removal or irreversible damage to the parathyroid glands, usually to their blood

[redacted]

Table 2. Epidemiology for Hypoparathyroidism	
	supply, during thyroidectomy, parathyroidectomy, or radical neck dissection. Immune-mediated destruction of the parathyroid glands can be either isolated or part of autoimmune polyendocrine syndrome type 1. Hypoparathyroidism may also be caused by accumulation in the parathyroid glands of iron (haemochromatosis or transfusion dependent thalassemia), or copper (Wilson's disease), or (in rare cases) by iodine-131 therapy for thyroid diseases. Additional causes include metastatic infiltration of the parathyroid glands by tumour, genetic disorders, such as DiGeorge syndrome and familial hypoparathyroidism. Magnesium depletion or excess may cause hypocalcaemia by inducing functional hypoparathyroidism. Other disorders that include hypoparathyroidism are the hypoparathyroidism, retardation, and dysmorphism syndrome and disorders due to mitochondrial-gene defects (CASR gene)[redacted]. Hypocalcaemia can present dramatically as tetany, seizures, altered mental status, refractory congestive heart failure, or stridor. The duration, severity, and rate of development of hypocalcaemia determine the clinical presentation. Neuromuscular symptoms are typically the most prominent; these symptoms include muscle cramping, twitching, and spasms; circumoral and acral numbness and paraesthesias; laryngospasm; bronchospasm; and even seizures. Other complications include premature cataracts, pseudotumour cerebri, and calcifications of the basal ganglia. Cardiac function may be affected, manifested by a prolonged QTc on electrocardiographic examination and, in rare cases, depressed systolic function and heart failure [redacted]. Patients with hypoparathyroidism require treatment to control symptoms and minimise acute and long-term complications [redacted] Acute symptoms are linked mainly to the low serum calcium levels and are generally reversible. These are mainly of the neuromuscular system and appear first when the serum calcium levels drop: numbness, paraesthesias, twitching, tetany, cardiac arrhythmias, seizures, and also difficulty in concentrating called "brain fog" are commonly reported. According to a retrospective case-control study in Denmark, mortality of subjects with postsurgical hypoparathyroidism is not increased after a mean follow-up of 8 years although the risk of seizures and renal complications is increased [redacted]. These complications can be due to the difficulty of regulating calcium homeostasis with oral therapy. Seizures would be caused by low serum calcium and excessive calcium intake could cause renal damage. Oral active vitamin D and calcium supplementation raise calcium and phosphate levels without normalisation of calcium and phosphate metabolism. Active vitamin D increases the absorption of both calcium and phosphate from the gastrointestinal tract. Furthermore, increasing serum calcium and phosphate levels (i.e., raising the calcium phosphate product, which would cause calcium phosphate crystals to precipitate in the body) worsens or precipitates ectopic calcification of the kidney and brain in patients treated in this manner. Hypoparathyroidism occurring over a long period of time potentiates the accumulation of these calcifications in the brain and the kidneys, potentially leading to irreversible and severe damages [redacted].

[redacted]

Table 2. Epidemiology for Hypoparathyroidism	
Important comorbidities	NPS conducted a quantitative burden of illness study in hypoparathyroidism patients in conjunction with the Hypoparathyroidism Association and the Mayo Clinic, in which 374 patients with hypoparathyroidism were surveyed [redacted]. Respondents were asked to indicate the presence or absence of 38 symptoms of hypoparathyroidism (presented randomly) occurring over the past year. The symptoms were broken into 3 categories: physical, emotional, and cognitive. Physical complaints experienced by more than 50% of the respondents were: fatigue (82%); muscle pain or cramping (78%); paraesthesia (76%); tetany (70%); joint or bone pain (67%); and pain, heaviness, or weakness in extremities (53%). Emotional symptoms were anxiety, fear, or inner unrest (59%) and feeling sad, down, blue, or depressed (53%). Cognitive symptoms were brain fog or mental lethargy (72%), inability to focus or concentrate (65%), memory loss or forgetfulness (61%), and sleep disturbances (57%). Overall, 69.3% of respondents reported experiencing comorbidities since the time of diagnosis. The comorbidities included: heart arrhythmias (66.4%), kidney stones (35.5%), elevated BMD (22.4%), decreased BMD (20.5%), seizures/convulsions/fits (17.8%), and bone fractures (15.8%) [redacted]. The MAH conducted a retrospective cohort study of diagnosed hypoparathyroidism patients (N=10,104) compared to an age-, gender-, and calendar-year matched control group (N=40,416). This was completed using a large US administrative claims database and identifying patients from 01 Jan 2009 through 31 Dec 2013 (Data on file). The cohort of hypoparathyroidism patients was predominantly female (approximately 75%) with a mean age of 51.6 years. Hypoparathyroidism patients had evidence of more frequently diagnosed conditions that may have been associated with their diagnosis (postsurgical hypothyroidism [27.02%]; malignant neoplasm of thyroid gland [26.89%]). Other commonly occurring diagnoses included unspecified essential hypertension (29.84%); other and unspecified hyperlipidemia (21.82%); and diabetes mellitus (16.58%). Clarke et al [redacted] also compared the prevalent comorbid conditions among 54 hypoparathyroidism cases to 108 controls. The cases were limited to those still residing locally in 2009, and comorbid conditions were identified from 2006 through 2008, using the Rochester (Minnesota) Epidemiology Project data resources. They found that although hypoparathyroidism is relatively rare, patients with this disorder have a substantial burden of comorbidities compared to controls. A few of these comorbidities include neoplasms, endocrine/nutritional/metabolic/immune disorders, congenital anomalies, infectious/parasitic diseases, and diseases of the respiratory system, genitourinary system, and skin/SC tissue. Mitchell et al studied 120 hypoparathyroidism patients who were seen at a Boston tertiary care hospital system between 1988 and 2009 [redacted]. The mean age at the end of the observation period was 52±19 years, the cohort was 73% female, and the mean duration of hypoparathyroidism was 17±16 years; the mean length of follow-up was 7.4±5.1 years. Rates of chronic kidney disease stage 3 or higher were 2- to 17-fold greater than age-appropriate norms. The authors concluded that their analysis showed a high rate of complications in patients with hypoparathyroidism, even though serum calcium levels were within the targeted range 88% of the time. These complications included

[redacted]

Table 2. Epidemiology for Hypoparathyroidism	
	symptomatic episodes of both hypocalcaemia and hypercalcaemia and significant rates of renal calcification and impairment. Underbjerg et al evaluated patients with postsurgical hypoparathyroidism to evaluate their risks of renal complications and cardiovascular disease in relation to their disease and its treatment [redacted]. The prevalence of postsurgical hypoparathyroidism was 22/100,000. The average age at diagnosis was 49 years (range 17 to 87 years), and 88% were women. Sixteen percent of all patients had neck surgery prior to the operation causing hypoparathyroidism. Compared with controls, patients with hypoparathyroidism had an increased risk of renal complications (HR 3.67; 95% CI, 2.41-5.59) and hospitalisation due to seizures (HR 3.82; 95% CI, 2.15-6.79), whereas there was no increased risk of cardiac arrhythmias (HR 1.11; 95% CI, 0.79-1.57) or cardiovascular disease or death (HR 0.89; 95% CI, 0.73-1.09). Mendonca et al studied 16 hypoparathyroidism postmenopausal women and 17 age-, weight-, height-, and body mass index-matched controls from Brazil [redacted]. They conclude that vertebral fragility occurs in hypoparathyroidism despite normal or even high BMD. Underbjerg et al studied 688 patients diagnosed with hypoparathyroidism caused by neck surgery due to non-malignant diseases from 1988 to 2011 [redacted]. Compared with controls, patients did not have an increased risk of cataract (p =0.52), spinal stenosis (p=0.59), or any fracture (p=0.98). Compared with controls, patients had a significantly increased risk of hospitalisation due to infections (HR 1.42, 95% CI 1.20-1.67), and depression/bipolar affective disorders (HR 1.99, 95% CI 1.14-3.46). The risk of malignant diseases did not differ between groups. Underbjerg L, et al. published data linking abnormal calcium-phosphate, a condition of NAC, with higher risk of long-term comorbidities, with renal and cardiovascular risk in particular [redacted]. Siggelkow et al. surveyed 398 patients with chronic hypoparathyroidism and 207 caregivers using the 36-item Short Form version 2 (SF-36 v2.0) and Five-Level EuroQoL 5 Dimensions (EQ-5D-5L) instruments, respectively. Hypoparathyroidism-associated symptoms were assessed by a disease-specific Hypoparathyroidism Symptom Diary and caregiver burden via the Modified Caregiver Strain Index (MCSI). Patients reported moderate-to-severe symptoms of physical fatigue (73%), muscle cramps (55%), heaviness in limbs (55%) and tingling (51%) over a 7-day recall period. Impacts (rated 'somewhat' or 'very much') were reported by 84% of patients for ability to exercise, 78% for sleep, 75% for ability to work and 63% for family relationships. Inverse relationships were observed between patient self-rated overall symptom severity and HRQoL and health status assessment scores—the greater the symptom severity, the lower the SF-36 and EQ-5D-5L scores. It was also reported that caregiver burden increased with patient self-rated symptom severity [redacted].

BMD=bone mineral density; CASR=calcium-sensing receptor; CI=confidence interval; CPRD=Clinical Practice Research Datalink; EU=European Union; HR=hazard ratio; hypoPARA=hypoparathyroidism; ICD=International Classification of Diseases; MAH=Marketing Authorisation Holder; PTH=parathyroid hormone; SC=subcutaneous; UK=United Kingdom; US=United States

[redacted]

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

A comprehensive nonclinical evaluation of rhPTH (1-84) has been completed. This is a summary of the important safety risks that have been considered in developing the RMP.

The nonclinical development programme addressing the toxicity of rhPTH (1-84) is comprised of studies on single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, antigenicity, local tolerance, and special studies. All of the toxicology studies performed on rhPTH (1-84) have been conducted in compliance with US Food and Drug Administration (FDA) Good Laboratory Practices (GLPs) and are mutually acceptable in the EU in accordance with Decision C (97)186/Final of the Organisation for Economic Co-operation and Development council except for the 21-day rat study and the antigenicity studies in rats, dogs and monkeys. Formulations of rhPTH (1-84) used in the toxicology studies contained varying concentrations in buffer (5% mannitol in 10 mM citrate buffer, pH 5.5 or 6.0), which were similar to the formulations used in clinical studies and to the to-be-marketed product.

Table 3: Key Safety Findings from Nonclinical Studies

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Key findings identified from acute or repeat-dose toxicity studies **Single and Repeat-dose Toxicity** Repeat-dose toxicity studies have been conducted in 3 species (juvenile and adult rats, dog, cynomolgus monkey). Study durations ranged from 13 weeks in juvenile rats, 1 or 2 weeks to 26 weeks in the adult rats and monkeys and up to 4 weeks in the dog. The pivotal studies were conducted in rats and monkeys. It was determined early in the program that dogs were not an appropriate animal model for assessing the effects of rhPTH (1-84) because they were shown to be overly sensitive to the calcaemic effects of the drug. The NOAEL for the pivotal 6-month chronic toxicity study in rats was 50 µg/kg/day and in monkeys was 30 µg/kg/day which corresponds to an 8.8- and 13.9-fold margin of exposure based on the mean AUC values in the 2 species, respectively, as compared to the mean AUC value in hypoparathyroid subjects receiving 100 µg/day (Studies PH460-ALX-001-93; CTBR 86142). Primary target organs of toxicity following chronic administration of PTH (rDNA) were noted in the kidneys, bones and spleen of juvenile rats and the kidney and bones of adult rats and monkeys. These findings were not unexpected based on the pharmacological activity of PTH and the high doses of rhPTH (1-84) that were evaluated. In addition, in rats mineralised heart lesions secondary to renal changes were observed at the highest dose in the chronic 6 -month study.	The nonclinical findings are consistent with the pharmacology of the drug. Additionally, exposure margins (based on AUC) from the chronic toxicology studies of 8.8- (rat) and 13.9- (monkey) fold compared to the mean AUC in hypoparathyroid patients receiving 100 µg/day of rhPTH (1-84) provide for an adequate level of safety.

[redacted]

Table 3: Key Safety Findings from Nonclinical Studies	
Key Safety Findings (From Nonclinical Studies)	**Relevance to Human Usage**
In rats, bone changes included a dose-dependent osteosclerosis of the femur and sternebrae. This led to a reduction in the marrow cavity with a simultaneous decrease in the bone marrow. Similar changes in bone were not observed in monkeys. This may be due to differences in bone metabolism in rats compared to primates. **Nephrotoxicity** Renal toxicity was observed in rats and dogs, but only minor changes in the kidneys were noted in monkeys. In the chronic rat study, this consisted of a dose-related increased incidence and severity of pelvic and tubular mineralisation; the NOAEL was 50 µg/kg/day (Study PH460-ALX-001-93). The increase in circulating calcium levels induced by rhPTH (1-84) administration increased the amount of calcium filtered by the kidney thereby increasing the tubular load of calcium. When serum calcium levels were high, more calcium was delivered to the distal nephron, the site at which PTH stimulates calcium reabsorption, and overwhelms the capacity of the kidney to protect itself against large calcium fluxes. In dogs, renal toxicity consisted of varying degrees of tubular dilation, regeneration, and mineralisation with interstitial fibrosis; the no observed effect level after 28 days was 0.1 and 1.0 µg/kg/day in males and females, respectively (Study PH436-ALX-004-93). In a 14-day dose range finding study in monkeys' microscopic findings in the kidney included slight or mild tubular mineralisation, mild tubular dilation occasionally associated with intraluminal granulocytes, and tubular regeneration only in animals administered 100 µg/kg/day. The NOAEL for monkeys after 6 months of dosing was 30 µg/kg/day, which was the highest dose administered (Study CTBR 86142). It was concluded that the NOAEL for renal toxicity of rhPTH (1-84) in rats and monkeys gives an approximate safety margin of 8 to 18 times greater than the human exposure at the clinical dose of 100 µg/day.	In contrast to humans and monkeys, calcitonin acts as an anti-calcaemic hormone in rats. Increased calcitonin secretion prevents rhPTH (1-84)-induced increases in serum calcium. Hypoparathyroidism patients treated with oral calcium and active vitamin D are at risk of developing kidney stones or nephrocalcinosis. Hypoparathyroid patients also have high phosphate levels which may precipitate causing calcifications [redacted]. Calcium levels of hypoparathyroid patients given rhPTH (1-84) are monitored and the dose may be adjusted accordingly if hypercalcaemia and/or hypercalciuria develop. The most frequent adverse reactions among the PTH (rDNA)-treated patients were hypercalcaemia, hypocalcaemia, and their associated clinical manifestations including headache, diarrhoea, vomiting, paraesthesia, hypoaesthesia, and hypercalciuria. rhPTH (1-84) decreased mean calciuria in the pivotal trial and extension study, PAR-C10-008. The final safety data over 6 years of exposure to rhPTH (1-84) in 49 patients show that the trend of decreasing urinary calcium excretion continued.

[redacted]

Table 3: Key Safety Findings from Nonclinical Studies	
Key Safety Findings (From Nonclinical Studies)	**Relevance to Human Usage**
Reproductive and Developmental Toxicity rhPTH (1-84) did not affect reproductive performance, early embryonic development or sperm parameters in rats, did not increase malformations or produce developmental toxicity in rats and rabbits, and did not affect pre- and post-natal development in rats (Studies CTBR98356; XGW00013; XGW00015; XGW00020). The NOAEL for reproductive and developmental changes associated with rhPTH (1-84) was considered to be 1000 µg/kg/day in rats and 50 µg/kg/day in rabbits; these were the highest doses tested. In the embryo-foetal development studies, AUC values in rats and rabbits produced margins of exposure 123- and 71.6-times higher, respectively, than the AUC in hypo parathyroid patients administered 100 µg/day of PTH (rDNA). The NOAEL for the 13-week juvenile rat study was 38 µg/kg/day (nominal dose of 50 µg/kg/day) based on the severity of the decreases in hematology parameters and osteoblast hyperplasia noted at ≥ 150 µg/kg/day.	<u>Pregnancy</u> There are no data from the use of rhPTH (1-84) in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see Section 5.3 of SmPC). A risk to the pregnant woman or developing foetus cannot be excluded. A decision must be made whether to initiate or discontinue treatment with rhPTH (1-84) during pregnancy taking into account the known risks of therapy versus the benefit for the woman. <u>Breastfeeding</u> It is unknown whether rhPTH (1-84) is excreted in human milk. Available pharmacology data in animals have shown excretion of rhPTH (1-84) in milk (for details see Section 5.3 of SmPC). A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue rhPTH (1-84) therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman. <u>Fertility</u> There are no data on the effects of rhPTH (1-84) on human fertility. Animal data do not indicate any impairment of fertility.
Genotoxicity The mutagenic potential of rhPTH (1-84) was evaluated in 2 in vitro assays - the bacterial reverse mutation assay (Ames assay) and the AS52/XPRT mammalian cell forward gene mutation assay (Studies PH301-ALX-001-93; PH314-ALX-001-93). These tests revealed that rhPTH (1-84) did not induce mutations in salmonella or Chinese Hamster Ovary cells. It was concluded from these assays that rhPTH (1-84) was not mutagenic.	rhPTH (1-84) is not genotoxic.
Carcinogenicity In a 104-week carcinogenicity study in rats, rhPTH (1-84) was administered at doses of 10, 50 and 150 µg/kg/day (Study CTBR89712). The	Most of the attention related to the safety of PTH administration in human subjects relates to rat toxicity data. Two-year carcinogenicity studies of teriparatide (PTH [1-34]) in Fisher

[redacted]

Table 3: Key Safety Findings from Nonclinical Studies

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
systemic exposure at the no-carcinogenic effect dose of rhPTH (1-84) (10 µg/kg/day) was 3.3 (females) to 4.8-fold (males) greater (based on AUC) than the exposure from Clinical Study C09-002 in hypoparathyroid subjects at the clinical dose of 100 µg/day. The lowest dose at which a rhPTH(1-84)-related increase in osteosarcoma was observed (50 µg/kg/day) occurred at an exposure margin of 19.2 (females) to 26.0 (males). Proliferative changes were noted in bones of rats treated with PTH (rDNA). These findings included mainly osteosarcomas and, with lesser frequency, fibrosarcomas, osteoblastomas, osteomas, and focal osteoblast hyperplasia. This dose-dependent, test article-related effect was observed in both genders at 50 and 150 µg/kg/day and did not occur at 10 µg/kg/day. Osteosarcoma, the most prevalent osseous neoplasm, affected both the appendicular and axial skeleton. In the appendicular skeleton, the most frequent locations were the tibia and femur, with approximately one-third of the osteosarcomas localised in the routine histological sections of the distal femur and proximal tibia. Involvement of the forelimbs was uncommon. In the axial skeleton, osteosarcomas were distributed all along the spine. These findings were not unexpected based on the high doses of rhPTH (1-84) administered and its anticipated effect on bone. However, since bone metabolism in the rat differs from that in primates the relevance of these findings to humans is uncertain. The incidence of osteosarcoma in rats may be a species-specific occurrence.	344 rats and Sprague-Dawley rats indicated that osteosarcoma occurs regularly in a dose- and time-dependent manner [redacted]. Consistent findings were reported in a 2-year PTH (1–84) study, which examined Fisher 344 rats [redacted] The osteoanabolic effect of PTH has also been extensively studied in cynomolgus macaque monkeys. Osteosarcoma has not developed in this non-human primate with exposure range of 1 to 25 µg/kg/d of teriparatide or PTH (1-84) for up to 18 months of treatment and 36 months of observation [redacted]. There are fundamental differences in bone physiology between rats and primates [redacted]. In contrast to humans and non-human primates in which PTH stimulates bone turnover and remodelling and whose epiphyses close in early adulthood, rats respond to PTH primarily by new bone formation and continue to model their skeleton throughout life[redacted]. In human subjects, results from clinical trials with both PTH (1–34) and PTH (1–84) have not reported any skeletal malignancies. The cumulative number of patients in these trials and observational studies amounts to more than 16,000 and up to 3 years of continuous treatment. The post approval experience with teriparatide and PTH (1–84) has given us additional information. The cumulative experience has reached 10 years for teriparatide and 6 years for PTH (1–84). The worldwide experience is well over 1 million subjects for teriparatide and 57,000 patient-years of exposure for PTH (1–84), respectively. Three cases of osteosarcoma in patients treated with teriparatide have been reported [redacted]. Childhood and adolescent osteosarcoma rates are relatively consistent around the world ranging from 3 to 4.5 cases/million population /year. Osteosarcoma represents approximately 55% of child and adolescent malignant bone tumours in the US. As osteosarcoma occurs most commonly during puberty, a time of rapid bone growth and remodelling, it is highly plausible that factors related to growth and development play a role in osteosarcoma

[redacted]

Table 3: Key Safety Findings from Nonclinical Studies	
Key Safety Findings (From Nonclinical Studies)	**Relevance to Human Usage**
	aetiology [redacted].
Safety Pharmacology Safety pharmacology studies conducted with rhPTH (1-84) included in vitro hERG and canine Purkinje fibre assays, a study assessing blood pressure in conscious, normal rats, a study evaluating cardiac and circulatory functions in open-chest, anesthetised dogs, and a CNS functional observational battery in rats. *Cardiovascular*: rhPTH (1-84) did not significantly inhibit hERG currents (Study 040218.OQQ). In isolated canine cardiac Purkinje fibres, PTH (1-84) did not significantly prolong action potential nor induce changes in resting membrane potential, action potential amplitude, or the maximum rate of depolarisation at any of the tested concentrations (Study 040219.OQQ). MAP in rats decreased rapidly following injection of rhPTH (1-84) and reached a nadir at 1 to 2 minutes. MAP then increased and, depending on the dose, had returned to or close to predose levels by 20 minutes. The decrease in MAP was dose-dependent with an estimated median effective dose of 5.92 ± 1.25 nmol/kg and a maximum decrease of 45 ± 2 mmHg (PH04-026). No cardiovascular affects effects were observed following IV administration in dogs. The potential effect of PTH (1-84) on the cardiovascular system was investigated in vitro where PTH (1-84) showed a negative effect on cardiac tissue contractility at high concentrations only. The potential for QT prolongation was investigated in 2 in vitro tests where PTH (1-84) tested negative in the hERG-test and in isolated dog Purkinje fibres. In cardiovascular studies in anaesthetised and conscious rats, PTH (1-84) decreased blood pressure transiently. In anaesthetised dogs, PTH (1-84) had no biological biologically significant effect on blood pressure, heart rate, cardiac output, left ventricular pressure or contractility. ECG recordings revealed no adverse effects on cardiac conduction in the repeat-dose toxicity study in monkeys. *Central Nervous System:* In a CNS safety pharmacology study, rhPTH (1-84) did not adversely affect any of the	No relevant safety issues were identified. There were no adverse effects on pulse and blood pressure. No subjects in company sponsored efficacy and safety studies in hypoparathyroidism had QTcF values below the lower limit of normal (<370 ms) and none had a short QT-related arrhythmia. Hypotension was rarely reported with rhPTH (1-84).

[redacted]

Table 3: Key Safety Findings from Nonclinical Studies

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
functional observational battery parameters in male or female rats at doses up to 300 µg/kg, the highest dose tested (administered as the drug substance or drug product) (Study 1150-004).	
Mechanisms for Drug Interactions No nonclinical studies were performed to assess potential PD drug interactions.	Since PTH is an endogenous peptide in healthy people, the most likely predominant metabolism is hydrolytic degradation and not related to cytochrome P450-dependent oxidative enzyme activity. Therefore, rhPTH (1-84) is unlikely to be involved in any drug-drug interactions related to cytochrome activity. It is not expected to bind to plasma proteins and has a low volume of distribution similar to extracellular fluid volume; therefore, it is not expected to be involved in drug displacement interactions. From the knowledge of the mechanism of action, combined use of rhPTH (1-84) and cardiac glycosides may predispose patients to digitalis toxicity if hypercalcaemia develops. Coadministration of alendronic acid and rhPTH (1-84) may lead to a reduction in the calcium sparing effect, which can interfere with the normalisation of serum calcium. Concomitant use of rhPTH (1-84) with bisphosphonates such as alendronate is not recommended. Based on the data from the clinical programme, no interactions with other medicinal products are anticipated. For any drug that affects serum calcium levels (i.e., lithium, thiazides), patients' serum calcium levels should be monitored.

AUC=area under the curve; CNS=central nervous system; ECG=electrocardiogram; hERG= human ether-a-go-go-related gene; IV=intravenous; MAP=mean arterial pressure; NOAEL=no observed adverse effect level; PD=pharmacodynamic; PTH=parathyroid hormone; PTH (rDNA)=recombinant human parathyroid hormone (Natpar); QTc=corrected QT interval; QTcF=Fridericia-corrected QT interval; SmPC=Summary of Product Characteristics

Because of osteosarcoma findings in a 2-year rat carcinogenicity study with teriparatide, a 1 to 34 PTH fragment, the MAH conducted a 104-week carcinogenicity study with rhPTH (1-84) at drug doses of 10, 50 and 150 µg/kg/day. The doses used in the rhPTH (1-84) study were approximately equimolar to those used in the teriparatide study. At the noncarcinogenic dose, this represents a margin of exposure based on AUC of 3.3 (females) to 4.8 (males) compared to humans receiving the highest rhPTH (1-84) dose of 100 µg/day. In addition, various assays proved that rhPTH (1-84) was not genotoxic. And in the total safety database with rhPTH (1-84) including the studies in osteoporosis and our post-marketing experience, no case of osteosarcoma has been reported to date. Taking into account the differences between the skeletal biology of rats and humans, and that osteosarcoma with rhPTH (1-84) was not detected at low dose levels, an increased risk of osteosarcoma in humans is unlikely; however, the risk cannot be ruled out. A nonclinical 13-week repeated-dose toxicity study with rhPTH (1-84) in juvenile

rats at drug doses of 50, 150 and 300 µg/kg/day, target organ effects were observed at all dose levels and consisted of hyperostosis and physeal hypertrophy in the femur, tibia and/or sternum and increased hematopoiesis in the spleen.

Based on the severity of the decreases in hematology parameters and osteoblast hyperplasia noted at ≥ 150 µg/kg/day, the no-observed-adverse-effect level (NOAEL) was determined to be 38 µg/kg/day (nominal dose of 50 µg/kg/day).

There were no other safety concerns identified in nonclinical studies.

Safety Concerns
Important identified risks (confirmed by clinical data) Hypercalcaemia Hypocalcaemia
Important potential risks (not refuted by clinical data or which are of unknown significance) Osteosarcoma and other bone tumours Immunogenicity/neutralisation of rhPTH (1-84) biological activity Tachyphylaxis
Missing information Long-term effects on bone structure and development in paediatric patients < 18 and young adults with open epiphyses

[redacted]

PART II: MODULE SIII – CLINICAL TRIAL EXPOSURE

The primary human safety database consists of a total of 4,209 unique subjects in 27 primary data source studies (24 completed and 3 ongoing). The clinical development programme includes 15 clinical pharmacology studies, 5 efficacy and safety studies in hypoparathyroidism, and 7 osteoporosis studies.

As of 23 April 2020, 477 patients including subjects with hypoparathyroidism and healthy volunteers received rhPTH (1-84) in the clinical pharmacology studies. Two thousand eight hundred and sixty-four (2,864) subjects received rhPTH (1-84) in clinical efficacy and safety studies in osteoporosis and 176 subjects received rhPTH (1-84) in clinical efficacy and safety studies in hypoparathyroidism.

The exposure and demographic characteristics are shown on the following tables (from Table 4 to Table 6) (data cut-off date: 28 February 2020).

Table 4: Distribution of Subjects by Type of Study

Studies	Placebo/Active Control	rhPTH (1-84)	Total
Clinical pharmacology	49	477	506
Hypoparathyroidism	40	176	201
Total person time (months)	**230.93**	**5,761.14**	**5,992.07**

rhPTH (1-84)=recombinant human parathyroid hormone (NATPAR)
For CL1-11-012, subjects who are only exposed to zinc formulation are enumerated in this table but are excluded from all subsequent tabular displays.
** Subjects who received both NATPAR and placebo across successive studies are counted once in the placebo column, once in the NATPAR column, and once in the total column.
The 58 subjects from Study PAR-C13-004 are not represented in this table.
The 10 subjects from site 1002 are not represented in this table.
Clinical Pharmacology Studies include: PAR-C10-005, CL1-11-007, CL1-11-012, CL1-11-013, CL1-11-017, SH PTH-0001, PBR-930811, PBR-930812, C09-002, Mosekilde Investigator-Initiated Trial (IIT) PK/PD Substudy, CL1-11-009, CL1 11 010 and SHP634-101, SHP634-102 and SHP634-103. For CL1 11-012, the demographic information includes subjects who are exposed to phase 3 formulation. SHP634-101 is being conducted in subjects with hypoparathyroidism.
Efficacy and safety studies in hypoparathyroidism include: CL1-11-040, PAR C10 007 (REPLACE), PAR C10 008 (RACE), PAR C10 009 and SHP634-402.
Data from ongoing study SPH634-401 were not included.
Efficacy and safety studies in osteoporosis include: ALX1-11-93001, ALX1-11-821, CL1-11-008, N01 AR 9 2245, CL1 11-003, CL1-11-002, and CL1-11-016.
This table does not include subjects from site 1002.
*Person time (month) is defined as the total weeks of exposure for all subjects divided by 4 weeks.

[redacted]

Table 5: Distribution of Subjects by Type of Study			
	PTH (rDNA)		
Parameter	**Clinical pharmacology studies (N=477)**	**Efficacy and safety studies in hypoparathyroidism (N=176)**	**Efficacy and safety studies in osteoporosis (N=2864)**
Age at screening (n)			
<45 years	174	62	0
45-64 years	255	98	1475
65-74 years	42	14	1389
≥75 years	6	2	318
Gender (n)			
Female	292	140	2864
Male	168	36	0
Race (n)			
White	338	167	2420
Black or African American	65	2	39
Asian	12	3	27
Native Hawaiian/Pacific Islander	0	2	2
American Indian/Native American	0	0	3
Multiracial or Other	2	2	373
Geographic Region of Enrolment (n)			
North America	-	116	1888
Western Europe	-	27	72
Central and Eastern Europe	-	33	190
Other	-	0	714

N: total number of subjects; n: number of subjects within the specified category; PTH (rDNA)=recombinant human parathyroid hormone (NATPAR)
Note: Clinical Pharmacology Studies include: PAR-C10-005, CL1-11-007, CL1-11-012, CL1-11-013, CL1-11-017,

[redacted]

Table 5: Distribution of Subjects by Type of Study
SH-PTH-0001, PBR-930811, PBR-930812, C09-002, Mosekilde IIT PK/PD Substudy, CL1-11-009, CL1-11-010 and SHP634-101, SHP634-102 and SHP634-103. For CL1-11-012, the demographic information includes subjects who are exposed to phase 3 formulation. SHP634-101 is being conducted in subjects with hypoparathyroidism Note: Efficacy and safety studies in hypoparathyroidism include: CL1-11-040 (REPLACE), PAR C10 007(RELAY), PAR C10 008 (RACE), PAR C10 009 (REPEAT), SHP634-402 and SHP634-404. Data from ongoing study SPH634-401 were not included. Note: Efficacy and safety studies in osteoporosis include: ALX1-11-93001, ALX1-11-821, CL1-11-008, N01-AR-9-2245, CL1-11-003, CL1-11-002, and CL1-11-016.

Table 6: Distribution of Subjects by Type of Study and Duration of Exposure – PTH (rDNA)			
	PTH (rDNA)		
Parameter	**Clinical pharmacology studies (N=477)**	**Efficacy and safety studies in hypoparathyroidism (N=176)**	**Efficacy and safety studies in osteoporosis (N=2864)**
Duration of Exposure (n)			
<1 week	442	-	63
1 to <12 weeks	35	6	249
12 to <24 weeks	0	9	145
24 to <52 weeks	0	65	465
52 - <104 weeks	0	18	1461
104 - <156 weeks	0	34	432
156 - <260 weeks	0	4	49
260 - <364 weeks	0	28	-
364 - <468 weeks	0	12	-
468 - <572 weeks	0	-	-
Cumulative Exposure (n)			
Any exposure	477	176	2864
≥1 week	35	176	2801
≥12 weeks	0	170	2552
≥24 weeks	0	161	2407
≥52 weeks	0	96	1942

[redacted]

Table 6: Distribution of Subjects by Type of Study and Duration of Exposure – PTH (rDNA)			
≥104 weeks	0	78	481
≥156 weeks	0	44	49
≥260 weeks	0	40	-
≥364 weeks	0	12	-
Person years of exposure*	2.88	438.77	-

N: total number of subjects; n: number of subjects within the specified category; PTH (rDNA)=recombinant human parathyroid hormone (NATPAR)

Note: Clinical Pharmacology Studies include: PAR-C10-005, CL1-11-007, CL1-11-012, CL1-11-013, CL1-11-017, SH-PTH-0001, PBR 930811, PBR 930812, C09-002, Mosekilde IIT PK/PD Substudy, CL1-11-009, CL1-11-010, SHP634-101, SHP634-102 and SHP634-103. For Study CL1-11-012, the zinc formulation exposure is excluded from this table.

Note: Efficacy and safety studies in hypoparathyroidism include: CL1-11-040, PAR-C10-007, PAR-C10-008, PAR-C10-009, SHP634-402 and SHP634-404..

This table does not include subjects from site 1002.

Note: Efficacy and safety studies in osteoporosis include: ALX1-11-93001, ALX1-11-821, CL1-11-008, N01-AR-9-2245, CL1-11-003, CL1-11-002, and CL1-11-016.

*Person years of exposure is defined as the total days of exposure for all subjects divided by 365.25 days.

SIII.1. Duration of Exposure

The following tables (from Table 8 to Table 15) describe the exposure to rhPTH (1-84) during clinical trials for hypoparathyroidism (data cut-off date: 28 February 2020):

Table 7: Duration of Exposure - All Clinical Trials (Including Open Extension)		
Hypoparathyroidism (N=176)		
Duration of exposure (at least)	**Persons**	**Person-time (Month)***
Any exposure	176	5723.57
≥1 month	174	5722.36
≥3 months	170	5716.07
≥6 months	161	5669.79
≥12 months	112	5331.18
≥24 months	79	4902.29
≥36 months	51	3991.54
≥48 months	43	3686.79
≥60 months	41	3576.71

[redacted]

Table 7: Duration of Exposure - All Clinical Trials (Including Open Extension)		
Hypoparathyroidism (N=176)		
Duration of exposure (at least)	**Persons**	**Person-time (Month)***
≥72 months	40	3514.11
≥84 months	31	2790.07
≥96 months	2	193.36

Note: Efficacy and safety studies in hypoparathyroidism include: CL1-11-040, PAR-C10-007, PAR-C10-008, PAR-C10-009, SHP634-402, SHP634-404.

Note: For subjects who participated in more than one study, treatment interruptions between studies will be excluded.

Note: This table does not include subjects from site 1002.

Person-time (month) is defined as the total weeks of exposure for all subjects divided by 4 weeks.

SIII.2. Age Group and Gender

Table 8: Exposure by Age Group and Sex				
Hypoparathyroidism (N=176)				
Age Group	**Persons**		**Person-time (month)***	
	Male	**Female**	**Male**	**Female**
<45 years	11	51	191.25	1613.75
45-64 years	18	80	906.46	2692.36
65-74 years	6	8	94.61	151.61
≥75 years	1	1	36.57	36.96
Total	**36**	**140**	**1,228.89**	**4,494.68**

Note: All clinical trials include: CL1-11-040, PAR-C10-007, PAR-C10-008, PAR-C10-009, SHP634-402 and SHP634-404. and CL1-11-040.
Note: Subjects participating in multiple studies, the age at the start of first study is being considered. E.g. USUBJID CL1-11-040-1012-004 who was 44 years in study CL1-11-040 (REPLACE) but had turned 45 in the PAR-C10-008 (RACE) study. from the first participated study will be used. Subject 1007-0003 from study CL1-11-040 had gender transformation before study enrolment.
Note: This table does not include subjects from site 1002.
* Person-time (month) is defined as the total weeks of exposure for all subjects divided by 4 weeks

[redacted]

SIII.3. Dose

Table 9: Exposure by Dose		
Hypoparathyroidism (N=176)		
Dose of exposure	**Persons (N=176)**	**Person-time (month)***
25 µg	34	264.71
50 µg	149	1300.86
75 µg	136	1236.18
100 µg	108	2921.82
Total	**176**	**5,723.57**

Note: All clinical trials include: CL1-11-040, PAR-C10-007, PAR-C10-009, SHP634-402, SHP634-404.
Note: A subject may be counted in more than one dose level, but is counted only once in the 'Total' row.
Note: This table does not include subjects from site 1002.
* Person-time (month) is defined as the total weeks of exposure for all subjects divided by 4 weeks.

SIII.4. Race and Ethnic Origin

Table 10: Exposure by Hispanic or Latino Origin		
Hypoparathyroidism (N=176)		
Ethnic/Racial Origin	**Persons**	**Person-time (month)***
Hispanic or Latino	4	56.96
Not Hispanic or Latino	168	5560.04
Unknown	4	106.57
Total	**176**	**5,723.57**

Note: All clinical trials include: CL1-11-040, PAR-C10-007, PAR-C10-008, PAR-C10-009, SHP634-402 and SHP634-404.
Note: This table does not include subjects from site 1002.
* Person-time (month) is defined as the total weeks of exposure for all subjects divided by 4 weeks.

Table 11: Exposure by Race		
Hypoparathyroidism (N=176)		
Race	**Persons**	**Person-time (month)***
White	167	5543.57
Black	2	16.29
Asian	3	144.89
Native Hawaiian/Pacific Islander	2	9.61

[redacted]

Table 11: Exposure by Race		
American Indian/Native American	0	0
Other	2	9.21
Total	**176**	**5,723.57**

Note: All clinical trials include studies CL1-11-040, PAR-C10-007, PAR-C10-008, PAR-C10-009, SHP634-402 and SHP634-404.
This table does not include subjects from site 1002.
*Person-time (month) is defined as the total weeks of exposure for all subjects divided by 4 weeks.

[redacted]

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

SIV.1. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Table 12. Exclusion Criteria

Exclusion criterion	Reason for exclusion	Included as missing information	Rationale
Hypersensitivity to the active substance(s) or to any of the excipients listed in SmPC, Section 6.1	Safety precaution	No	Included in SmPC as Contraindication
Patients receiving or who have previously received radiation therapy to the skeleton	Potential risk of osteosarcoma based on animal data	No	Included in SmPC as Contraindication
Skeletal malignancies or bone metastasis	Increased risk of hypercalcaemia	No	Included in SmPC as Contraindication
Increased baseline risk for osteosarcoma such as in patients with Paget's disease of the bone or hereditary disorders	Potential risk of osteosarcoma based on animal data	No	Included in SmPC as Contraindication
Unexplained elevations of bone-specific alkaline phosphatase	Increased bone specific alkaline phosphatase is an indicator of bone metastasis or tumour	No	Included in SmPC as Contraindication
Pseudohypopara-thyroidism	PTH levels are high and the patient will not benefit from PTH replacement.	No	Included in SmPC as Contraindication
Any disease that might affect calcium metabolism or calcium-phosphate homeostasis other than hypoparathyroidism, such as active hyperthyroidism, Paget's disease, Type 1 and poorly controlled Type 2 diabetes mellitus (HbA1c >8%), severe and chronic cardiac, Cushing's syndrome, neuromuscular disease such as rheumatoid	These concomitant endocrine diseases could interfere with the regulation of calcium and/or phosphate metabolism and affect the bone remodelling processes which were part of the primary or secondary endpoints of the study. The risk of developing bone tumours has a peak in paediatric patients and young adults with open epiphyses. This is added as a precaution for use in the	No	There is no metabolic or physiologic reason why PTH would not work in these patients. Patients with hypoparathyroidism and some of these concomitant diseases may still benefit from rhPTH (1-84) Natpar is contraindicated in patients who are at increased baseline risk for osteosarcoma such as patients with Paget's

[redacted]

Table 12. Exclusion Criteria

Exclusion criterion	Reason for exclusion	Included as missing information	Rationale
arthritis, myeloma, pancreatitis, malnutrition, rickets, recent prolonged immobility, active malignancy, primary or secondary hyperparathyroidism, a history of parathyroid carcinoma, hypopituitarism, acromegaly, or multiple endocrine neoplasia Types I and II	SmPC. Other diseases with an increased risk of osteosarcoma include Paget's disease of the bone mostly occurring in patients >40 years, prior external beam or implant radiation therapy involving the skeleton		disease of bone or hereditary disorders
Disease processes that may adversely affect gastrointestinal absorption, including but not limited to, short bowel syndrome, bowel or gastric resection, tropical sprue, celiac disease, ulcerative colitis, Crohn's disease or active peptic ulcer disease requiring medical therapy	The possible effect of these diseases may make the absorption of calcium and active vitamin D even more unpredictable and affect the study primary endpoint.	No	rhPTH (1-84) is administered as a SC injection and is not absorbed through the gastrointestinal system. rhPTH (1-84) reduces the need for oral calcium and vitamin D, thereby decreasing the likelihood of unpredictable effects of oral supplementation
Chronic/severe cardiac disease including but not limited to cardiac insufficiency, arrhythmias, bradycardia (resting heart rate <60 beats/minute), or hypotension (systolic and diastolic blood pressures <100 and 60 mmHg, respectively)	There was a potential risk of hypotension following the administration of rhPTH (1-84)	No	rhPTH (1-84) helps control hypoparathyroidism by exerting the same physiological effects as the native hormone and reduces the need for supplements. rhPTH (1-84) would be beneficial to these patients because it maintains calcium levels in the normal range rhPTH (1-84) has a short half-life and prolonged episodes of hypercalcaemia are not expected Per the cardiovascular toxicity report the efficacy and safety studies of hypoparathyroidism support the conclusion

[redacted]

Table 12. Exclusion Criteria

Exclusion criterion	Reason for exclusion	Included as missing information	Rationale
			that rhPTH (1-84) administered to hypoparathyroid subjects has no adverse effects on pulse and blood pressure.
Seizure disorder/epilepsy with a history of a seizure within the previous 6 months prior to screening	Seizure was considered an indicator of severe hypocalcaemia or unstable hypoparathyroidism. These patients were unsuitable for a placebo-controlled, randomised trial in which supplements given to subjects on active drug and placebo may be withdrawn in case of uptitration	No	rhPTH (1-84) helps control hypoparathyroidism by exerting the same physiological effects as the native hormone and reduces the need for supplements
Pregnant or lactating women	At the start of the pivotal trial, the segment II and III data in animal studies were not available. The nonclinical studies showed that rhPTH (1-84) did not adversely affect fertility or early embryonic development in rats, embryo-foetal development in rats and rabbits, or pre/post-natal development in rats at doses up to 1000 µg/kg/day (rats) and 50 µg /kg/day (rabbits). These doses represented the highest dose tested in each study and correspond to margins of exposure of 123 and 72 fold (based on AUC) relative to a clinical dose of 100 µg/day for the rat and rabbit, respectively	Yes	
Presence of open epiphyses	Per the SmPC: rhPTH (1-84) should be used with caution in young adult patients with open epiphyses as these patients may be at increased risk for osteosarcoma	No	rhPTH (1-84) is not indicated for children <18 years of age. In a 3-year randomised trial in 12 children ages 5 to 14 with chronic hypoparathyroidism it was concluded that PTH (1-34) therapy was safe

[redacted]

Table 12. Exclusion Criteria

Exclusion criterion	Reason for exclusion	Included as missing information	Rationale
			and effective in maintaining stable calcium homeostasis. Additionally, PTH (1-34) treatment allowed normal skeletal development because there were no differences in bone mineral accrual, linear growth, or weight gain between the 2 treatment arms over the 3-yr study period [redacted]. Results from clinical trials with both PTH (1-34) and PTH (1-84) have not reported any skeletal malignancies. The cumulative number of patients in these trials and observational studies amounts to more than 16,000 and up to 3 years of continuous treatment. The post approval experience with teriparatide and PTH (1-84) has given us additional information. The cumulative experience has reached 10 years for teriparatide and 6 years for PTH (1-84). The worldwide experience is well over 1 million subjects for teriparatide and 57,000 patient-years of exposure for PTH (1-84), respectively. Three cases of osteosarcoma in patients treated with teriparatide have been reported [redacted]
Clinical history of renal calculi within the past 12 months	During initiation of rhPTH (1-84) treatment, peaks of hypercalciuria were observed while regulating the calcium level	No	Adverse reactions and/or laboratory values of hypocalcaemia, hypercalcaemia, and hypercalciuria were

[redacted]

Table 12. Exclusion Criteria

Exclusion criterion	Reason for exclusion	Included as missing information	Rationale
	and could lead to renal calculi The reason for excluding patients with a history of urolithiasis within the past 12 months was to minimise the risk of early dropout due to relapsing urolithiasis		reported in hypoparathyroidism clinical trials and reflect the known underlying disease characteristics and the mechanism of action of PTH. These reactions were generally mild to moderate in severity and transient, and were managed with adjustments in rhPTH (1-84), calcium and/or active vitamin D dose rhPTH (1-84) decreased mean calciuria from baseline in the pivotal trial and extension study. Long-term effects are not available
History of gout	PTH increases serum levels of uric acid in some patients, possibly increasing the risk of gout attacks	No	Slight increases in serum uric acid levels were reported in clinical trials, but no increase in gout attacks was observed
Serum 25-hydroxyvitamin D levels greater than 1.5-fold the laboratory upper limit of normal prior to randomisation	High levels of Serum 25-hydroxyvitamin D could lead to high levels of serum 1, 25-dihydroxyvitamin D and hypercalcaemia	No	In a PK/PD study (C09-002), it was shown that high serum calcium levels are inhibitory of the 1α hydroxylase that produces the 1, 25-dihydroxyvitamin D. This risk is thus minimal. The SmPC recommends confirming 25-OH vitamin D stores are sufficient prior to initiating treatment and during treatment with rhPTH (1-84)
Subjects dependent on regular parenteral calcium infusions (e.g., calcium gluconate) to maintain calcium homeostasis	This was considered an indicator of severe hypocalcaemia or unstable hypoparathyroidism and these patients were unsuitable for a placebo-controlled, randomised trial where supplements were to	No	rhPTH (1-84) helps control hypoparathyroidism by exerting the same physiological effects as the native hormone and reduces the need for supplements

[redacted]

Table 12. Exclusion Criteria

Exclusion criterion	Reason for exclusion	Included as missing information	Rationale
	be withdrawn in case of up-titration in subjects receiving active study medication and placebo		
Use of prohibited medications such as loop and thiazide diuretics, raloxifene hydrochloride, lithium, estrogens and progestins for replacement therapy, methotrexate, systemic corticosteroids within respective prohibited periods or bisphosphonate preparations	These medications could interfere with the regulation of calcium and/or phosphate metabolism and affect the bone remodelling process, which was part of the primary or secondary endpoints of the study	No	rhPTH (1-84) is a protein that is not metabolised by and does not inhibit hepatic microsomal drug-metabolising enzymes (e.g. cytochrome P450 isoenzymes). rhPTH (1-84) is not protein bound and has a low volume of distribution. Based on the data from the clinical programme, no interactions with other medicinal products are anticipated. For any drug that affects serum calcium levels (e.g., lithium, thiazides), patients' serum calcium levels should be monitored Coadministration of alendronic acid and rhPTH (1-84) lead to a reduction in the calcium sparing effect, which can interfere with the normalisation of serum calcium. Concomitant use of rhPTH (1-84) with bisphosphonates such as alendronate is not recommended
Use of other drugs known to influence calcium and bone metabolism, such as calcitonin, fluoride tablets, or cinacalcet hydrochloride within the prohibited period	These medications could interfere with the regulation of calcium and/or phosphate metabolism and affect the bone remodelling process, which was part of the primary or secondary endpoints of the study	No	This was not a concern in clinical practice as these medications are of little relevance in hypoparathyroidism
History of thyroid cancer less than 5 years prior	This was considered as a potential factor for study	No	This is not a concern in clinical practice in

[redacted]

Table 12. Exclusion Criteria

Exclusion criterion	Reason for exclusion	Included as missing information	Rationale
to enrolment	drop outs due to relapsing thyroid cancer requiring radiation or chemotherapy		patients with diagnosed hypoparathyroidism as it is very unlikely that existing hypoparathyroidism is altered under thyroid cancer treatment regimens

AUC=area under the curve; HbA1c=glycosylated haemoglobin, PD=pharmacodynamic; PhV=pharmacovigilance; PK=pharmacokinetic; PTH= parathyroid hormone; rhPTH (1-84)=recombinant human parathyroid hormone (1-84) (NATPAR); SC=subcutaneous; SmPC=Summary of Product Characteristics

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

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

The number of patients studied with hypoparathyroidism over long-term use is low. Long-term safety and efficacy are considered missing information.

Overall, the published literature evaluating the use of rhPTH (1-84) support the safety conclusions from the rhPTH (1-84) development program, indicating that the product is generally safe and well tolerated, with no evidence of osteosarcoma reported in clinical trials.

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

Table 13. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program.There are no data from the use of rhPTH (1-84) in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. A risk to the pregnant woman or developing foetus cannot be excluded. A decision must be made whether to initiate or discontinue treatment with rhPTH (1-84) during pregnancy taking into account the known risks of therapy versus the benefit for the woman.
Breastfeeding women	Not included in the clinical development programme. It is unknown whether rhPTH (1-84) is excreted in human milk. A minimal amount of rhPTH (1-84) is excreted in the milk of lactating rats. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue rhPTH (1-84) therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Table 13. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Fertility	Not included in the clinical development programme. There are no data on the effects of rhPTH (1-84) on human fertility. rhPTH (1-84) did not adversely affect fertility or early embryonic development in rats, embryo-foetal development in rats and rabbits, or pre/post-natal development in rats.
Patients with relevant comorbidities: • Patients with hepatic impairment	A PK study (CL1-11-009) in non-hypoparathyroidism subjects was conducted in 6 men and 6 women with moderate hepatic impairment (Child-Pugh Classification of 7-9 [Grade B]) as compared with a matched group of 12 subjects with normal hepatic function. Following a single 100 µg SC dose of rhPTH (1-84), the mean C_{max} and baseline-corrected C_{max} values were 18% to 20% greater in the moderately impaired subjects than in those with normal function. There were no apparent differences in the serum total calcium concentration-time profiles between the 2 hepatic function groups. Moreover, there is no reason to expect that N-terminal fragments of rhPTH (1-84) might accumulate in hepatic impairment, even after long duration of exposure to rhPTH (1-84). Further study of this in animal models of liver insufficiency resulting from partial hepatectomy would not provide further insights as such surgery would also remove the Kupffer cells. • No dose adjustment is necessary for patients with mild or moderate hepatic impairment. There are no data available in patients with severe hepatic impairment.
• Patients with renal impairment	• In study CL1-11-010, PK following a single rhPTH (1-84) 100 µg SC dose was evaluated in 16 non-impaired subjects (CrCl >80 mL/min) and 16 subjects with mild-to-moderate renal impairment (CrCl 30 to 80 mL/min). The mean C_{max} of PTH following 100 µg rhPTH (1-84) in subjects with mild-to-moderate renal impairment was approximately 22% higher than that observed in subjects with normal renal function. Exposure to PTH as measured by $AUC_{0\text{-last}}$ and baseline-corrected $AUC_{0\text{-last}}$ was approximately 3.9% and 2.5%, respectively, higher than that observed for subjects with normal renal function. Although this analysis did not extend for 24 hours, inspection of the concentration-time profiles showed that, at 8 hours after the injection of rhPTH (1-84), plasma C-terminal PTH immunoreactivity was decreasing rapidly towards predose levels. Since PTH (1-84) levels return to baseline levels by approximately 12 hours, it is very unlikely that any C-terminal PTH fragments would remain in the circulation at 24 hours after the injection. No chronic accumulation of C-terminal PTH fragments is anticipated. • High levels of C-terminal PTH fragments will not develop in patients with hypoparathyroidism in whom the only source of PTH occurs following the exogenous administration of rhPTH (1-84).

Table 13. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
	• No dose adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance 30 to 80 mL/min). No studies were conducted in patients on renal dialysis. There are no data available in patients with severe renal impairment.
• Patients with other relevant comorbidity	• The most common medical and surgical histories for subjects in the company sponsored efficacy and safety studies in hypoparathyroidism were related to parathyroid and thyroid disease or surgery. The specific terms occurring at an incidence of >20% for the total rhPTH (1-84) group included hypoparathyroidism, thyroidectomy, hypothyroidism, hypertension, and thyroid cancer.
• Patients with a disease severity different from inclusion criteria in clinical trials	• Not applicable
Population with relevant different ethnic origin	In a study of hypoparathyroidism patients, approximately 19% were Black, Hispanic, Asian, or Other/Not recorded [redacted]. A summary of on-treatment TEAEs occurring in at least 5% of subjects in the placebo-controlled studies in osteoporosis and among all rhPTH (1-84)-treated subjects across the efficacy and safety studies in osteoporosis is presented in the Integrated Summary of Safety Data (ISS). In general, there were no clinically relevant differences between the incidences of individual on-treatment adverse event preferred terms between rhPTH (1-84)- or placebo-treated subjects by race. As there were very few subjects whose race was Black or Other in either the rhPTH (1-84) or placebo treatment groups in the efficacy and safety studies in hypoparathyroidism, it is difficult to draw any conclusions regarding differences in the incidence of on-treatment TEAEs by race. A high incidence of osteosarcoma has been observed in 2 African countries, Sudan and Uganda, compared to the relative frequency in populations of European origin. This is consistent with the finding that young and middle-aged individuals of African American descent in the US had higher rates of osteosarcoma than whites. One could also speculate that the increased rates in subjects of African descent are related to differences in vitamin D absorption. This hypothesis in osteosarcoma susceptibility has yet to be tested [redacted]. Distribution of subject by type of study and demographics is presented in Table 5.

[redacted]

Table 13. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Subpopulations carrying relevant genetic polymorphisms	Not applicable.
Children	Not included in the clinical development programme. The safety and efficacy of rhPTH (1-84) in children less than 18 years of age have not been established. Hypoparathyroidism is a rare disease in individuals less than 18 years of age and accounts for only about 3% of all cases [redacted]. A Paediatric Investigation Plan (PIP) was approved by the Paediatric Committee at its June 2014 meeting. As of 23 April 2020, there were no safety data available in paediatric patients.
Elderly	In one prevalence study using a database of insurance claims, approximately 37% of hypoparathyroidism patients were ≥65 [redacted]. rhPTH (1-84) has been given to 1767 subjects 65 years of age and older (including 324 patients 75 years of age and older) with no unusual safety issues identified. Forty-seven (47) subjects were in clinical pharmacology studies, thirteen (13) subjects were being treated for replacement of hypoparathyroidism in efficacy and safety clinical studies, and 1707 were being treated for osteoporosis. The hypoparathyroidism programme clinical studies of rhPTH (1-84) did not include sufficient numbers of subjects aged 65 and over, therefore it is difficult to determine whether response in these patients will differ from that in younger patients. However, no differences in PK were detected with regard to age. In addition, although the number of patients >65 years was limited, safety across all efficacy and safety studies in hypoparathyroidism did not show an increased frequency of TEAEs in patients in this age group. In the efficacy and safety studies in osteoporosis safety population, no increased incidence of TEAE preferred terms by age categories <65 years (n = 1475), ≥65 years (n = 1389), and ≥75 (n = 318) years was observed. Comorbidities such as renal insufficiency, cardiovascular disorders, and cancer may be more common in patients over the age of 65, which may increase the risk of developing events related to hypercalcaemia more prevalent, such as hypercalcemia of malignancy, malignancies with bone metastases, severe renal impairment with potential alterations of blood calcium, hypercalciuria and increased bone calcium release, or atrial rhythm disorders or cardiac insufficiency requiring potentially interacting medication of loop diuretics or cardiac glycosides. To minimise the risk of developing renal and cardiac events related to hypercalcaemia in elderly patients with hypoparathyroidism, the adjustment of the serum calcium level can be fine-tuned together with variable doses of oral calcium and active vitamin D

[redacted]

Table 13. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
	as 4 different dosages of rhPTH (1-84) are offered. Distribution of subject by type of study and demographics is presented in Table 5.
Limited exposure in male patients	Of hypoparathyroidism patients, about 75-80% are women [redacted] No clinically relevant gender differences were observed in REPLACE. The population in the trials represents gender distribution in epidemiological studies and a greater risk in males is not anticipated. Distribution of subject by type of study and demographics is presented in Table 5.

$AUC_{0\text{-last}}$=area under the curve from time zero to the last available time point; C_{max}=maximum concentration; CrCl=creatinine clearance; PIP=paediatric investigation plan; PK=pharmacokinetic(s); PTH=parathyroid hormone; rhPTH (1-84)=recombinant human parathyroid hormone (1-84) (NATPAR); SC=subcutaneous; TEAE=treatment-emergent adverse event; US=United States

[redacted]

PART II: MODULE SV – POST-AUTHORISATION EXPERIENCE

SV.1. Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Methodology

As per Pharmacovigilance Risk Assessment Committee (PRAC) request, for rhPTH (1-84), the MAH should indicate the number of cartridges of each strength sold and calculate patient years of exposure using the World Health Organisation (WHO) defined daily dose (DDD) for parathyroid hormone which is 100 mcg. Hence, the revised method and formula for calculating patient exposure is described below:

Person-years of exposure = total mcg / 100 (WHO DDD)/((average number of doses used per person per day [1 dose]) x 365.25 days per year).

****Patient exposure has been adjusted to account for 14 doses per cartridge***

SV.1.2 Exposure

rhPTH (1-84) was approved in the US on 23 Jan 2015 as an adjunct to calcium and vitamin D to control hypocalcaemia in patients with hypoparathyroidism. It was launched on 01 April 2015.

As of 23 April 2020, the total exposure globally is estimated to be approximately 4,884.50 patient-years.

[redacted]

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

SVI.1. Potential for Misuse for Illegal Purposes

There is no potential for abuse with rhPTH (1-84).

PART II: MODULE SVII – IDENTIFIED AND POTENTIAL RISKS

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

The table below lists the safety concerns as described in the initial approved EU RMP (EU-RMP v 2.5)

Important identified risks	Hypercalcaemia Hypocalcaemia
Important potential risks	Osteosarcoma and other bone tumours Medication errors Immunogenicity/neutralisation of rhPTH (1-84) biological activity Tachyphylaxis
Missing information	Use in patients <18 years of age Use in pregnant or lactating women Long-term effects on bone structure and development in paediatric patients <18 years of age and young adults with open epiphyses Use in patients >65years of age Use in non-Caucasians Long-term safety and efficacy Use in patients with severe renal disease Use in patients with severe hepatic disease

rhPTH (1-84)=recombinant human parathyroid hormone (1-84) (Natpar)

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

There are no risks associated with the use of NATPAR which are not considered important risks for inclusion as safety concerns in the RMP.

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

Table 14. Important Identified Risks

Important identified risk	Risk-benefit impact
Hypercalcaemia	NATPAR increases serum calcium levels. Therefore, transient hypercalcemia may occur in patients treated with NATPAR. However, patients with hypercalcemia are often asymptomatic. If the hypercalcemia progresses to hypercalcaemic crisis, this is a life-threatening emergency. For individual patients, hypercalcaemia may impair quality of life.
Hypocalcaemia	Hypocalcaemia was observed more frequently in the pivotal study with NATPAR than with placebo and is therefore considered an identified risk with treatment. Hypocalcaemia may occur in the event of missed dose, inadequate absorption, rapid reduction in supplemental calcium therapy and discontinuation of NATPAR. Acute hypocalcaemia can result in severe symptoms requiring

[redacted]

Table 14. Important Identified Risks	
Important identified risk	**Risk-benefit impact**
	hospitalisation.

AESI=adverse event of special interest; IV=intravenous; PTH=parathyroid hormone; rhPTH (1-84)=recombinant human parathyroid hormone (NATPAR); TESAE=treatment-emergent serious adverse event

Table 15. Important Potential Risks	
Important potential risk	**Risk-benefit impact**
Osteosarcoma and other bone tumours	In male and female rats, parathyroid hormone caused an increase in the incidence of osteosarcoma. There is no evidence that there is an increased risk in human.
Medication errors	Medication errors are unintended mistakes in the prescribing, dispensing and administration of a medicine that could cause harm to a patient. Medication errors may result in hypercalcemia or hypocalcemia.
Immunogenicity/neutralisation of rhPTH (1-84) biological activity	Administration of NATPAR may trigger the development of antibodies. The role of neutralizing antibodies on efficacy of NATPARA is yet to be determined. The long-term impact of antibodies to rhPTH(1-84) needs further study.
Tachyphylaxis	There have been no reports of tachyphylaxis with rhPTH (1-84) in clinical trials. However, it is hypothesised that the calcium-raising effect of NATPARA may diminish over time in some patients. If tachyphylaxis develops, lack of effect may be observed.

BMD=bone mineral density; PTH=parathyroid hormone; rhPTH (1-84)=recombinant human parathyroid hormone (NATPAR); SC=subcutaneous

Table 16. Missing Information	
Missing information	**Risk-benefit impact**
Use in paediatric patients <18 years of age	Clinical studies have not been performed in patients under 18 years of age. The effect and safety of rhPTH (1-84) when given to these patients is not known. There is no evidence for an increased risk of osteosarcoma in humans. However, the baseline risk of osteosarcoma is the highest in children and young adults and therefore this potential risk needs to be closely monitored in this population. The objective is to investigate long-term effects of rhPTH (1-84) in pediatric patients and young adults.
Use in pregnant or lactating women	Animal reproduction studies have revealed no evidence of impaired fertility or harm to the foetus due to rhPTH (1-84). There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of

[redacted]

Table 16. Missing Information	
Missing information	**Risk-benefit impact**
	human response, this drug should be used during pregnancy only if clearly needed. The results of a lacteal excretion study suggested that there was a small, but measurable transfer of rhPTH (1-84) to the milk of lactating rats. The objective is to further characterise the safety of NATPAR in pregnant or lactating women.
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. The objective is to further characterise long-term effects of Natpar on bone structure and development in paediatric patients <18 years of age and young adults.
Use in patients >65 years of age	Although the number of patients older than 65 years was limited in clinical studies of rhPTH (1-84), the data did not show an increased frequency of adverse events in patients in this age group. The objective is to further investigate effects of rhPTH (1-84) in patients >65 years of age.
Use in non-Caucasian patients	Hypoparathyroidism generally occurs in the middle-aged, Caucasian population. There is a higher incidence of osteosarcoma in patients of African descent. There are no data to support or refute the potential risk of osteosarcoma in this patient population. As in other populations, a risk of osteosarcoma with rhPTH(1-84) treatment cannot be ruled out. The objective is to further characterise the safety of rhPTH (1-84) in non-Caucasian patients.
Use in patients with severe renal disease	There are no data available in patients with severe kidney dysfunction. The objective is to further evaluate the safety profile of rhPTH (1-84) in patients with severe renal disease.
Use in patients with severe hepatic disease	There are no data available in patients with severe liver dysfunction. The objective is to further evaluate the safety profile of rhPTH (1-84) in patients with severe hepatic disease.
Long-term safety and efficacy	There are limited data on the long-term safety and effectiveness of rhPTH (1-84). The MAH is currently investigating long-term safety and efficacy of rhPTH (1-84) in the PAR-R13-001 (PARADIGHM) registry. Results from the completed open label extension PAR-C10-008 study showed that the observed safety profile was consistent with shorter term studies.

MAH=Marketing Authorisation Holder; PIP=Paediatric Investigation Plan; PTH=parathyroid hormone; rhPTH (1-84) = recombinant human parathyroid hormone (NATPAR)

[redacted]

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

Not applicable.

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

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

Table 17. Important Identified Risk: Hypercalcaemia

MedDRA Terms	PT: Hypercalcaemia, Blood calcium increased; Blood calcium abnormal; Calcium intoxication; Calcinosis, Calciphylaxis; Calcium metabolism disorder; Chondrocalcinosis pyrophosphate; Hypercalcaemic nephropathy; Hypercalciuria, calcium phosphate product, calcium phosphate product increased, urine calcium increased
Potential mechanisms	PTH is the principal regulator of plasma calcium homeostasis. In the kidney, PTH (1-84) increases renal tubular reabsorption of calcium (while inversely inhibiting phosphate reabsorption) and increases the synthesis of 1, 25(OH) 2 vitamin D from its precursor 25-hydroxyvitamin D. Although 1, 25(OH) 2 vitamin D has a short *in vivo* half-life (approximately 6 hours), it directly increases intestinal calcium and phosphate absorption. PTH (1-84) increases the efflux of calcium from bone, both from the rapidly exchangeable pool of calcium within bone, and by increasing the number and activity of osteoblasts and osteoclasts, thereby increasing bone turnover. As PTH (1-84) also acts to inhibit the reabsorption of phosphate in the proximal nephron, it prevents an increase in plasma phosphate levels that could result from increased intestinal phosphate absorption and efflux of phosphate from bone. The net result of increasing PTH (1-84) levels is to increase serum calcium.
Evidence source(s) and strength of evidence	Clinical trials, literature
Characterisation of the risk	**Analysis of Hypercalcaemia by Study Period, Safety Population CL1-11-040**

Time Period	rhPTH (1-84) (N=84) n (%)	Placebo (N=40) n (%)
Titration period	12 (14.3%) 95% CI 5.9-27.2	1 (2.5%) 95% CI 0.1-13.2
Stable period	8 (9.5%) 95% CI 4.2-17.9	0 95% CI 0-8.8

N=total number of subjects; n=number of subjects in specified category
Source: 5.3.5.3 ISS, Table 8-18 Summary of Hypocalcaemia, Hypercalcaemia, and Hypercalciuria by Study Period – Study

[redacted]

Table 17. Important Identified Risk: Hypercalcaemia	
	CL1-11-040 – Safety Population In study CL1-11-040, most incidences of hypercalcaemia occurred during the initial 12 weeks of treatment (titration period). During the titration period, concomitantly to the up-titration of study drug, step-wise reductions in oral calcium and active vitamin D supplements took place. Unlike in the pivotal trial, CL1-11-040 (REPLACE), where patients had a limited titration window, a simplified algorithm was used in the open-label, extension study, PAR-C10-008 (RACE). Physicians could increase or decrease the rhPTH (1-84) dose at any time to maintain or normalise serum calcium levels. However, consistent with REPLACE, 4 out of the 7 hypercalcaemia events in RACE occurred during the first 29 days of the study. Study CL1-11-040 allowed for a closer analysis of whether hypercalcaemic events occurred during the titration period, where significant adjustments to oral calcium and active vitamin D supplements were taking place, or during the stable phase with lesser changes. As expected, more AESIs of hypercalcaemia occurred in the titration phase than in the stable phase, as a treatment balance between study drug titration and oral supplement decrease was targeted. In the majority of cases, the events were transient, and in all cases managed by titration of study drug or adjustment of oral supplements. This is further supported by the decrease of events in the stable phase of Study CL1-11-040 as well as the reduced number of hypercalcaemic events reported in extension studies. Of the 84 subjects who received rhPTH (1-84) in study CL1-11-040, 1 experienced a TESAE of hypercalcaemia (1.2%), which led to interruption of study medication. The event resolved. A total of 8 (16.3%) subjects had 12 events of hypercalcemia or blood calcium increased reported during the treatment period. No events of hypercalcemia were reported during the post treatment period. There were 2 deaths in the safety and efficacy studies in patients with hypoparathyroidism. Both occurred during study PAR-C10-008 and were unrelated to study drug. One death was due to severe cardiac failure congestive and one was due to severe cardiac arrest. Symptoms of hypercalcaemia are related to the severity and rate of change of serum calcium levels, with more severe symptoms being associated with acute changes rather than chronic elevation. The physiological effect of rhPTH is to elevate serum calcium levels. Clinical manifestations of chronic hypercalcaemia affect the neuromuscular, gastrointestinal, renal, skeletal, and cardiovascular systems. Neuromuscular effects include impaired concentration, confusion, corneal calcification, fatigue, and muscle weakness. Nausea, abdominal pain, anorexia, constipation, and, rarely, peptic ulcer disease or pancreatitis are among the gastrointestinal manifestations. The most important renal effects are polydipsia and polyuria resulting from nephrogenic diabetes insipidus, and nephrolithiasis resulting from hypercalciuria. Other renal effects include dehydration and nephrocalcinosis. Cardiovascular effects include hypertension, vascular calcification, and a shortened QT

[redacted]

Table 17. Important Identified Risk: Hypercalcaemia	
	interval on the ECG. Cardiac arrhythmias are rare. Bone pain can occur in patients with hyperparathyroidism or malignancy. Osteoporosis of cortical bone, such as the wrist, is mainly associated with primary hyperparathyroidism. Excess PTH also can result in subperiosteal resorption, leading to osteitis fibrosa cystica with bone cysts and brown tumours of the long bones. [redacted]. There is no evidence that short periods of hypercalcaemia during replacement therapy causes long-term hypercalcaemia effects such as described above. During the entire titration period of Study CL1-11-040, 12/84 (14.3%) rhPTH (1-84) subjects and 1/40 (2.5%) placebo subjects experienced an event of hypercalcaemia. Two of the events occurred 2 and 3 days after the initiation of 50 µg of rhPTH (1-84); however, all others occurred well into the titration period ranging between Study Day 25 and Study Day 57, following up-titration to 75 or 100 µg of rhPTH (1-84). Of the 12 rhPTH (1-84) treated subjects, 10 (11.9%) of the subjects had events that were mild, 1 (1.2%) that was moderate, and 1 (1.2%) that was severe and reported as a TESAE with an interruption of study drug. All of these events resolved. A higher incidence of hyper- and hypocalcaemia in the rhPTH (1-84) treated group compared to the placebo group suggests a wider fluctuation in serum calcium over the course of 24 hours after each administration. During the stable period of Study CL1-11-040, 8/84 (9.5%) of rhPTH (1-84)-treated subjects had 8 AESIs of hypercalcaemia compared to no placebo subjects. Hypercalcaemic events were primarily mild or moderate and resolved quickly. No TEAEs of nephrocalcinosis or nephrolithiasis were reported during the on-treatment phase for any subject who had hypercalcaemia. In Study PAR-C10-008, 8/49 (16.3%) rhPTH (1-84)-treated subjects experienced TEAEs of hypercalcaemia and/or blood calcium increased. All of the hypercalcaemia events were mild or moderate and all resolved. Nephrolithiasis was reported in 6 subjects. Treatment with rhPTH (1-84) may cause fluctuations in serum calcium levels, especially during the dose titration phase. It is not known if these potential fluctuations are associated with long-term clinical consequences. The daily fluctuations in serum calcium observed during treatment did not result in serious or severe events of hyper or hypocalcaemia or deterioration of renal function in the long-term RACE or Columbia studies. There were also no cardiovascular effects observed and no effect on blood pressure. Decreases in QTc corresponded to increases in serum calcium and no intervals were less than 370 ms; no arrhythmias were reported. Thus, fluctuations are not expected to cause any long-term side effects.
Risk factors and risk groups	For patients with multiple concomitant diseases, such as compromised renal function, history of urolithiasis, hyper/hypo-thyroidism, as well as malignancies that are associated with hypercalcaemia (squamous cell carcinomas of the lung, head, neck, and oesophagus, renal cell carcinoma, breast carcinoma, haematological malignancies such as multiple myeloma), granulomatous disease, endocrinopathies, it is important to monitor serum calcium levels.

[redacted]

Table 17. Important Identified Risk: Hypercalcaemia	
	Elderly patients are more likely to be symptomatic from moderate elevations of serum calcium levels. The long-term effects of hypercalciuria are unknown, and the effect of rhPTH (1-84) in patients who may be at greater risk of hypercalciuria remains uncertain. As patients' serum calcium should be monitored and the doses of rhPTH (1-84) adjusted accordingly, the potential of nephrocalcinosis and renal failure is low. Patients at higher risk for hypercalcaemia include elderly patients with renal insufficiency, subjects with a disease predisposing to hypercalcaemia (e.g., active neoplasia, multiple myeloma, granulomatous disease, endocrinopathy), and persons taking concomitant medications that affect serum calcium levels (e.g., thiazide diuretics, lithium,). The contraindications are covered in the SmPC, which highlights risk factors for hypercalcaemia. From the knowledge of the mechanism of action, combined use of rhPTH (1-84) and cardiac glycosides (e.g., digoxin or digitoxin) may predispose patients to digitalis toxicity if hypercalcaemia develops. Coadministration of alendronic acid and rhPTH (1-84) may lead to a reduction in the calcium sparing effect, which can interfere with the normalisation of serum calcium. Concomitant use of rhPTH (1-84) with bisphosphonates including alendronate is not recommended. For any drug that affects serum calcium levels (i.e., lithium, thiazide diuretics), the patient's serum calcium levels should be monitored especially during treatment start or dose adjustment. Thiazide diuretics are sometimes used in hypoparathyroid patients to increase urinary calcium reabsorption at the distal tubule and induce osteoblast differentiation which will contribute to increasing serum calcium levels. In patients with a history of calcium stones, thiazide diuretics are prescribed to reduce recurrent calcium stones, [redacted]. Thus, the concomitant treatment of thiazide diuretics and rhPTH (1-84) is likely to reduce the adverse renal effects (including nephrolithiasis, nephrocalcinosis) but can augment the risk for transient hypercalcaemia. It is therefore recommended to monitor serum calcium when adding or changing the dose of thiazide diuretics in patients treated with rhPTH (1-84).
Preventability	Hypercalcaemia can be minimised by following the recommended dosing and monitoring information in the SmPC.
Impact on the risk-benefit balance of the product	For individual patients, hypercalcaemia may impair quality of life. As increases in serum calcium were transient following rhPTH (1-84) administration it is very unlikely that patients with hypoparathyroidism will develop chronic or acute hypercalcaemia, including consecutive chronic or acute diseases.
Public health impact	None

AESI=adverse event of special interest; CI=confidence interval; ECG=electrocardiogram; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; PTH=parathyroid hormone; QTc=corrected QT interval; rhPTH (1-84)=recombinant human parathyroid hormone (NATPAR); SmPC=Summary of Product Characteristics; TEAE=treatment-emergent adverse event; TESAE=treatment-emergent serious adverse event

[redacted]

Table 18. Important Identified Risk: Hypocalcaemia

MedDRA Terms	PT: Hypocalcaemia, Blood calcium decreased; Blood calcium abnormal; Chvostek's sign; Calcium deficiency; Calcium metabolism disorder; Hypocalcaemic seizure; Hypocalciuria; Tooth demineralisation; Blood calcium abnormal, Urine calcium decreased
Potential mechanisms	In study CL1-11-040 rhPTH (1-84), subjects experienced large reductions or elimination of oral calcium and active vitamin D supplementation in the titration period. After Week 5, rhPTH (1-84) subjects were not allowed to increase their rhPTH (1-84) dose to compensate for their loss in oral calcium and active vitamin D supplementation. Another factor to consider is the decrease in 25-hydroxyvitamin D levels seen in the rhPTH (1-84) subject group. One of the actions of PTH is to convert 25-hydroxyvitamin-D into the active 1, 25(OH) 2D. In the presence of low levels of inactive vitamin D this conversion may have been less productive. Post-treatment hypocalcaemia following the sustained withdrawal of rhPTH (1-84) can be controlled or avoided but must be carefully managed with monitoring of serum calcium and reinstatement of appropriate dosages of calcium and active vitamin D supplements.
Evidence source(s) and strength of evidence	Clinical trials, literature
Characterisation of the risk	Analysis of Hypocalcaemia by Study Period, Safety Population CL1-11-040

Time Period	rhPTH (1-84) (N=84) n (%)	**Placebo (N=40)** **n (%)**
Titration period	9 (10.7%) 95% CI 5.0 -19.4	7 (17.5%) 95% CI 7.3 - 32.8
Stable period	19 (22.6%) 95% CI 14.2 – 33.0	4 (10.0%) 95% CI 2.8 - 23.7
Post Treatment period	27 (32.1%) 95% CI 22.4 - 43.2	4 (10.0%) 95% CI 2.8 - 23.7

N=total number of subjects; n=number of subjects in specified category

Note: The 95% CIs are based on the exact method (Clopper-Pearson intervals)

Source: t_hypocalcemia_by_TP

In the placebo-controlled study, CL1-11-040 in 3 rhPTH (1-84)-treated subjects and 1 placebo subject, the post-treatment hypocalcaemia was considered moderate or severe, and in each of these subjects hypocalcaemia required treatment with IV calcium gluconate. The events occurred between 2 to 8 days in the post-treatment phase for patients previously on the 100 µg dose of rhPTH (1-84). The subjects recovered.

There were no deaths in the safety and efficacy studies in hypoparathyroidism.

[redacted]

Table 18. Important Identified Risk: Hypocalcaemia	
	In the placebo-controlled study CL1-11-040: • For the titration phase, 9/84 (10.7%) rhPTH (1-84) subjects and 7/40 (17.5%) placebo subjects experienced an event of hypocalcaemia. • During the stable phase, 17/79 (21.5%) subjects in the rhPTH (1-84) group experienced hypocalcaemia compared to 5/33 (15.2%) subjects in the placebo group. Events occurring in this phase of the study were generally of short duration and were easily managed by adjustment of oral supplements. • In the post-treatment phase 27/84 (32.1%) rhPTH (1-84)-treated subjects and 4/40 (10.0%) placebo-treated subjects experienced hypocalcaemia. In 3 rhPTH (1-84)-treated subjects and in 1 placebo subject, the post-treatment hypocalcaemia was considered moderate or severe, and in each of these subjects hypocalcaemia required treatment with IV calcium gluconate. A total of 21/49 (40.8%) subjects experienced hypocalcaemia or decreased blood calcium in the open label study PAR-C10-008. None of these events were serious.
Risk factors and risk groups	Patients at risk of developing hypocalcaemia include those with vitamin D deficiency (malabsorption, short bowel), chronic kidney disease, which may result in hyperphosphataemia and rare disorders which may cause hyperphosphataemia such as pseudohypoparathyroidism, isolated hyperparathyroidism, rhabdomyolysis, and tumour lysis. In patients on rhPTH therapy, the highest risk of hypocalcaemia occurs if therapy is abruptly discontinued or interrupted.
Preventability	Hypocalcaemia can be minimised by following the recommended dosing and monitoring information in the SmPC. The SmPC includes precautionary language regarding hypocalcaemia during interruption or withdrawal of therapy. rhPTH (1-84), is contraindicated in patients with pseudohypoparathyroidism and malignancy. Use with precaution in patients with severe renal impairment.
Impact on the risk-benefit balance of the product	For individual patients hypocalcaemia may severely impair quality of life. Please refer to Section SI for more information on comorbid conditions found in hypoparathyroid patients. Hypoparathyroid patients taking PTH have decreased or normalised phosphate and the risk of hypocalcaemia is decreased.
Public health impact	None

CI=confidence interval; IV=intravenous; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; PTH=parathyroid hormone; rhPTH (1-84)=recombinant human parathyroid hormone (NATPAR); SmPC=Summary of Product Characteristics

[redacted]

Table 19. Important Potential Risk: Osteosarcoma and Other Bone Tumours	
MedDRA Terms	HLGT: "skeletal neoplasm malignant and unspecified" under SOC of Neoplasms benign, malignant and unspecified (incl cysts and polyps) In addition, PTs: biopsy bone, biopsy bone abnormal, bone scan, bone scan abnormal, X-ray limb abnormal; extraskeletal osteosarcoma; extraskeletal osteosarcoma recurrent and extraskeletal osteosarcoma metastatic; musculoskeletal pain; sarcoma; sarcoma metastatic; bone pain
Potential mechanisms	Endogenous PTH is secreted by the parathyroid glands as a polypeptide of 84 amino acids. PTH exerts its action via cell-surface PTH receptors, present in bone, kidney and nerve tissue. PTH receptors belong to the family of G-coupled protein receptors. PTH has a variety of critical physiological functions that include its central role in modulating serum calcium and phosphate levels within tightly regulated levels, regulating renal calcium and phosphate excretion, activating vitamin D, and maintaining normal bone turnover. rhPTH (1-84) is produced in *E. coli* using recombinant DNA technology and is identical to the 84 amino acid sequence of endogenous human PTH. In bone, PTH increases the efflux of calcium from bone, both from the rapidly exchangeable pool of calcium within bone, and by increasing the number and activity of osteoblasts and osteoclasts, thereby increasing bone turnover. In hypoparathyroidism patients, PTH is missing. Bone in these patients is abnormally dense with increased BMD. At 24 weeks, there were decreases in BMD in all 3 bone sites (lumbar spine, hip, and radius) in the rhPTH (1-84) group in study CL1-11-040, compared with virtually no change for the placebo group. This may represent the initiation of bone remodeling by a decrease in the anabolic effect and the replacement of PTH by rhPTH (1-84). This is in contrast to what was seen in osteoporosis where exogenous PTH is used to build bone in patients with normal PTH levels.
Evidence source(s) and strength of evidence	Clinical trials, literature
Characterisation of the risk	There have been no reports of osteosarcoma with rhPTH (1-84). In human subjects, results from clinical trials with both PTH (1-34) and PTH (1–84) have not reported any skeletal malignancies. The cumulative number of patients in these trials and observational studies amounts to more than 16,000 and up to 3 years of continuous treatment. The post approval experience with teriparatide and PTH (1–84) has given us additional information. The cumulative experience has reached 10 years for teriparatide and 6 years for PTH (1–84). The worldwide experience is well over 1 million subjects for teriparatide and 57,000 patient-years of exposure for PTH (1-84), respectively. Three cases of osteosarcoma in patients treated with teriparatide have been reported [redacted]. Ongoing retrospective post-marketing safety surveillance studies were initiated in 2003 in the US and in 2004 in 5 Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) to monitor for a

[redacted]

Table 19. Important Potential Risk: Osteosarcoma and Other Bone Tumours	
	possible association between For(s)teo (teriparatide) treatment and osteosarcoma in adults aged 40 and older. Through 30 September 2013, 737 US patients were diagnosed with osteosarcoma from 2003 to 2011; none reported use of For(s) teo prior to the diagnosis of osteosarcoma. As of 30 September 2013, 100 osteosarcoma cases have been abstracted in the Nordic countries; none reported use of For(s)teo prior to the diagnosis of osteosarcoma [redacted]. The Forteo Patient Registry, an ongoing 12-year drug safety surveillance study, was initiated in 2009 to estimate the incidence of osteosarcoma in patients who have been treated with Forteo in the US. Of the 34,872 patients registered, no incident cases of osteosarcoma have been identified as of 30 June 2013 [redacted]. Overall, the published literature evaluating the use of rhPTH (1-84) support the safety conclusions from the rhPTH (1-84) development program, indicating that the product is generally safe and well tolerated, with no evidence of osteosarcoma reported in clinical trials or in over 6 years of post-marketing experience. In the case of rhPTH (1-84), evidence of an association with osteosarcoma exists in one animal species (rat), but this has not been seen in other animal species (e.g., monkey), nor has any association with rhPTH (1-84) and osteosarcoma in humans been reported. This issue appears to be a species-specific finding, with no increase in osteosarcoma reported over the past 6+ (rhPTH [1-84]) or 10+ (rhPTH [1-34]) years of use in humans.
Risk factors and risk groups	Therapeutic radiation is a proven risk factor for osteosarcoma. The incidence of osteosarcoma secondary to Paget's disease is not precisely known, but studies estimate that about 1% of patients with Paget's disease will develop osteosarcoma. In elderly persons, about half of the osteosarcomas reported are estimated to be associated with Paget's disease. Chromosomal aneuploidy is common in osteosarcoma cells which suggests that somatic or germline chromosomal instability could potentially predispose an individual to osteosarcoma [redacted]. Childhood and adolescent osteosarcoma rates are relatively consistent around the world ranging from 3 to 4.5 cases/million population/year. Osteosarcoma represents approximately 55% of child and adolescent malignant bone tumours in the US. As osteosarcoma occurs most commonly during puberty, a time of rapid bone growth and remodelling, it is highly plausible that factors related to growth and development play a role in osteosarcoma aetiology [redacted]. The risk of developing bone tumours has a peak in paediatric patients and young adults with open epiphyses. This is added as a precaution for use in the SmPC. Other diseases with an increased risk of osteosarcoma include Paget's disease of the bone mostly occurring in patients >40 years, prior external beam or implant radiation therapy involving the skeleton. Hereditary disorders predisposing to a higher risk of osteosarcoma such as children with hereditary retinoblastoma or people with

[redacted]

Table 19. Important Potential Risk: Osteosarcoma and Other Bone Tumours	
	trisomia 21 or for bone sarcoma in neurofibromatosis are known. Other bone tumours like Ewing sarcoma also occur most commonly between 15 and 25 years of age. rhPTH (1-84) is contraindicated in patients who are at increased baseline risk for osteosarcoma such as patients with Paget's disease of bone or hereditary disorders. A high incidence of osteosarcoma has been observed in 2 African countries, Sudan and Uganda, compared to the relative frequency in populations of European origin. This is consistent with the finding that young and middle-aged individuals of African American descent in the US had higher rates of osteosarcoma than whites. One could also speculate that the increased rates in subjects of African descent are related to differences in vitamin D absorption. This hypothesis in osteosarcoma susceptibility has yet to be tested [redacted].
Preventability	rhPTH (1-84) is contraindicated in patients: • Who are receiving or who have previously received radiation therapy to the skeleton • With skeletal malignancies or bone metastases • Who are at increased baseline risk for osteosarcoma such as patients with Paget's disease of bone or hereditary disorders • With unexplained elevations of bone-specific alkaline phosphatase The safety and efficacy of rhPTH (1-84) in children <18 years of age have not yet been established. rhPTH (1-84) should be used with caution in young adult patients with open epiphyses as these patients may be at increased risk for osteosarcoma.
Impact on the risk-benefit balance of the product	In male and female rats, parathyroid hormone caused an increase in the incidence of osteosarcoma. There is no evidence that there is an increased risk in humans. The risk-benefit balance of Natpar remains positive.
Public health impact	None

CI=confidence interval; HLGT=high level group term; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; PTH=parathyroid hormone; rhPTH (1-84)=recombinant human parathyroid hormone (NATPAR); SmPC=Summary of Product Characteristics; SOC=system organ class; US=United States

Table 20. Important Potential Risk: Medication Errors	
MedDRA Terms	SMQ: Medication errors
Potential mechanisms	Not applicable
Evidence source(s) and strength of evidence	Post-marketing reports
Characterisation of the risk	No medication errors were reported in clinical trials. In post marketing the majority of report of medication errors involved drug dose omission.

[redacted]

Table 19. Important Potential Risk: Osteosarcoma and Other Bone Tumours	
Risk factors and risk groups	Not applicable
Preventability	There is a potential risk for the misadministration of rhPTH (1-84), due to inappropriate dose preparation or dose administration, leading to suboptimal rhPTH (1-84) PK exposure. Serum calcium and 24-hour urinary calcium should be monitored per the local standard of care once a maintenance dose of rhPTH (1-84) has been established in a patient. If lack of control of serum calcium or hypercalciuria are observed, the physician should confirm that the patient can self-administer Natpar correctly and provide additional education on dose preparation and administration if needed. Medication errors can be prevented by following the instructions for use in the SmPC.
Impact on the risk-benefit balance of the product	Medication errors may result in hypercalcaemia or hypocalcaemia.
Public health impact	None

CI=confidence interval; HLGT=high level group term; MedDRA=Medical Dictionary for Regulatory Activities; rhPTH (1-84)=recombinant human parathyroid hormone (NATPAR); SmPC=Summary of Product Characteristics

Table 21. Important Potential Risk: Immunogenicity/Neutralisation of rhPTH (1-84) Biological Activity	
MedDRA Terms	PT: Neutralizing antibodies positive; Antibody test positive, antibody test abnormal, drug specific antibody present, inhibiting antibodies, inhibiting antibodies positive, neutralizing antibodies, non-neutralising antibodies positive.
Potential mechanisms	Consistent with the potentially immunogenic properties of medicinal products containing peptides, administration of rhPTH (1-84) may trigger the development of antibodies.
Evidence source(s) and strength of evidence	Clinical trials
Characterisation of the risk	The formation of antibodies to PTH was assessed in the efficacy and safety studies in hypoparathyroidism as well as the efficacy and safety studies in osteoporosis. Since the active pharmaceutical ingredient of rhPTH (1-84) is manufactured using a strain of Escherichia coli, there is potential for formation of antibodies to E. coli protein as well. There were no differences in antibody formation against PTH between surgical and non-surgical indications for treatment. There was no evidence of immune-mediated systemic hypersensitivity events related to rhPTH (1-84) in any subjects who had PTH specific antibodies, neutralising antibodies, or antibodies to E. coli protein, or in subjects without these antibodies in either the hypoparathyroidism studies or in the thousands of subjects in the osteoporosis studies. There is no evidence that the level of visible proteinaceous, product-related particles in the drug product increased antibody formation based on the low rates of antibody formation reported in both the osteoporosis and hypoparathyroidism studies. Antibody formation in long-term treatment with rhPTH (1-84) did not have an effect on the safety or efficacy of this PTH replacement in subjects with hypoparathyroidism. This conclusion

[redacted]

Table 21. Important Potential Risk: Immunogenicity/Neutralisation of rhPTH (1-84) Biological Activity	
	is supported by the similarly small numbers of subjects that developed antibodies to PTH in osteoporosis studies. In the placebo-controlled study in adults with hypoparathyroidism, the incidence of anti-PTH antibodies was 8.8% (3/34) and 5.9% (1/17) in subjects who received SC administration of 50 to 100 µg of rhPTH (1-84) or placebo once daily for 24 weeks, respectively. Across all clinical studies in patients with hypoparathyroidism following treatment with rhPTH (1-84) for up to 4 years, the immunogenicity incidence rate was 17/87 (19.5%) and did not appear to increase over time. These 17 patients had low titre anti-PTH antibodies and, of these, 3 subsequently became antibody negative. The apparent transient nature of antibodies to PTH is likely due to the low titre. Three of these patients had antibodies with neutralising activity; these patients maintained a clinical response with no evidence of immune-related adverse reactions. In the open label study PAR-C10-008 (RACE), one subject (2.0% of 49 enrolled subjects) was positive for neutralizing anti-PTH antibodies. This subject was a responder at Week 52 and end of trial. Anti-PTH antibodies appear to have no impact on efficacy and safety although the longer-term impact is unknown.
Risk factors and risk groups	None
Preventability	This potential risk cannot be prevented.
Impact on the risk-benefit balance of the product	If neutralising antibodies develop, a lack of effect may be observed.
Public health impact	None

CI=confidence interval; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; rhPTH (1-84)=recombinant human parathyroid hormone (NATPAR); SC=subcutaneous; SmPC=Summary of Product Characteristics

Table 22. Important Potential Risk: Tachyphylaxis	
MedDRA Terms	PTs: Tachyphylaxis, Therapeutic response decreased, Therapeutic response unexpected, Therapeutic response changed, Drug ineffective, Therapeutic product ineffective, Drug tolerance, Drug tolerance increased, Loss of therapeutic response
Potential mechanisms	Unknown
Evidence source(s) and strength of evidence	None
Characterisation of the risk	There have been no reports of tachyphylaxis with rhPTH (1-84) in clinical trials.

[redacted]

Table 22. Important Potential Risk: Tachyphylaxis	
Risk factors and risk groups	Unknown
Preventability	Per SmPC: The response of serum calcium concentration to administration of rhPTH (1-84) should be monitored at intervals to detect this and the diagnosis of tachyphylaxis considered. If serum concentration of 25-OH vitamin D is low then appropriate supplementation may restore serum calcium response to rhPTH (1-84).
Impact on the risk-benefit balance of the product	Lack of effect may be observed
Public health impact	None

MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; rhPTH (1-84)=recombinant human parathyroid hormone (NATPAR); SmPC=Summary of Product Characteristics

SVII.3.2 Presentation of the Missing Information

Table 23. Missing Information: Use in paediatric patients <18 years of age	
Evidence source	Not applicable.
Population in need of further characterisation	Paediatric patients <18 years of age

PIP=Paediatric Investigation Plan

Table 24. Missing Information: Use in pregnant or lactating women	
Evidence source	Not applicable.
Population in need of further characterisation	Pregnant or lactating women

rhPTH (1-84)=recombinant human parathyroid hormone (NATPAR)

Table 25. Missing Information: Long-term effects on bone structure and development in paediatric patients <18 years of age and young adults with open epiphyses	
Evidence source	Not applicable
Population in need of further characterisation	Paediatric patients <18 years of age and young adults with open epiphyses

PhV=pharmacovigilance; rhPTH (1-84)=recombinant human parathyroid hormone (NATPAR)

Table 26. Missing Information: Use in patients >65 years of age	
Evidence source	Not applicable
Population in need of further	Elderly patients >65 years of age

[redacted]

Table 23. Missing Information: Use in paediatric patients <18 years of age	
characterisation	

PhV=pharmacovigilance; rhPTH (1-84)=recombinant human parathyroid hormone (NATPAR)

Table 27. Missing Information: Use in non-Caucasian patients	
Evidence source	Not applicable
Population in need of further characterisation	Non-Caucasian patients

Table 28. Missing Information: Use in patients with severe renal disease	
Evidence source	Not applicable
Population in need of further characterisation	Patients with severe renal disease

PhV=pharmacovigilance; rhPTH (1-84)=recombinant human parathyroid hormone (NATPAR)

Table 29. Missing Information: Use in patients with severe hepatic disease	
Evidence source	Not applicable
Population in need of further characterisation	Patients with severe hepatic disease

Table 30. Missing Information: Long-term safety and efficacy	
Evidence source	Not applicable
Population in need of further characterisation	Long-term safety and efficacy in patients treated with rhPTH (1-84)

rhPTH (1-84)=recombinant human parathyroid hormone (NATPAR)

[redacted]

PART II: MODULE SVIII – SUMMARY OF THE SAFETY CONCERNS

Table 31. Summary of Safety Concerns

Important identified risks	Hypercalcaemia Hypocalcaemia
Important potential risks	Osteosarcoma and other bone tumours Medication errors Immunogenicity/neutralisation of rhPTH (1-84) biological activity Tachyphylaxis
Missing information	Use in patients <18 years of age Use in pregnant or lactating women Long-term effects on bone structure and development in paediatric patients <18 years of age and young adults with open epiphyses Use in patients >65 years of age Use in non-Caucasians Long-term safety and efficacy Use in patients with severe renal disease Use in patients with severe hepatic disease

rhPTH (1-84)=recombinant human parathyroid hormone (1-84) (NATPAR)

[redacted]

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

III.1. Routine Pharmacovigilance Activities

The post-authorisation safety profile of rhPTH (1-84) will be evaluated through the routine PhV system of Takeda Pharmaceuticals. Routine PhV includes the following:

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

PhV activities are fully described in the Pharmacovigilance Master File.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

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

Specific adverse reaction follow-up questionnaires for safety concerns:

Not applicable.

Other forms of routine pharmacovigilance activities for safety concerns:

Not applicable.

III.2 Additional Pharmacovigilance Activities

Table 32. SHP634-403

A Randomised, 3-Arm, Single-blind, Placebo-Controlled, Phase 4 Study to Evaluate Metabolic Control, Safety, and Symptoms Among Adult Subjects with Inadequately Controlled Hypoparathyroidism Treated With Recombinant Human Parathyroid Hormone (rhPTH[1-84]) as a Single Daily Injection and <<Alternative Dosing Regimen TBD>>

Rationale and study objectives	Primary: 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 (standard therapy) in subjects with inadequately controlled hypoparathyroidism. Safety concerns addressed: • Hypercalcaemia • Hypocalcaemia • Immunogenicity/neutralisation of rhPTH (1-84) biological activity • Tachyphylaxis
Study design	Randomised, 3-arm, single-blind, placebo-controlled
Study population	Adult Subjects with Inadequately Controlled Hypoparathyroidism Treated With Recombinant Human Parathyroid Hormone (rhPTH[1-84]) as a Single Daily Injection and <<Alternative Dosing Regimen TBD.

[redacted]

Table 32. SHP634-403 **A Randomised, 3-Arm, Single-blind, Placebo-Controlled, Phase 4 Study to Evaluate Metabolic Control, Safety, and Symptoms Among Adult Subjects with Inadequately Controlled Hypoparathyroidism Treated With Recombinant Human Parathyroid Hormone (rhPTH[1-84]) as a Single Daily Injection and <<Alternative Dosing Regimen TBD>>**	
Milestones	Protocol submission (Full draft): Q1/2017 (Completed: 20-July-2017) Final Protocol submission: Q2/2019 Final study report: December-2026

Table 33. PAR-R13-001 **PARADIGHM (Physicians Advancing Disease Knowledge in Hypoparathyroidism): Registry for Patients with Chronic Hypoparathyroidism**	
Rationale and study objectives	To characterise 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, clinical outcomes, and comorbidity. To characterise 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. Safety concerns addressed • Hypercalcaemia • Hypocalcaemia • Medication errors • Tachyphylaxis • Use in pregnant or lactating women • Use in patients > 65 years of age • Use in non-Caucasians • Long-term safety and efficacy
Study design	This is a global, prospective, observational disease and drug registry designed to collect data on patients with chronic hypoparathyroidism.
Study population	Adult and pediatric patients diagnosed with chronic hypoparathyroidism
Milestones	Protocol was approved in 2013 Start of data collection (historical): Q3/2013 Protocol amendment 3 submission: 30 August 2017 (Completed) Start of recruitment (first patient, first visit): 2017 (post-EMA

[redacted]

Table 33. PAR-R13-001 **PARADIGHM (Physicians Advancing Disease Knowledge in Hypoparathyroidism): Registry for Patients with Chronic Hypoparathyroidism**	
	approval) Delivery of interim analysis: PSUR aligned Estimated last patient, last visit: 2034 (17 years after date of first patient) Final study report: 2035

EMA=European Medicines Agency; EU= European Union; PSUR=Periodic Safety Update Report

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 34. Ongoing 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				
PARADIGHM (Physicians Advancing Disease Knowledge in Hypoparathyroidism): A Registry for Patients with Chronic Hypoparathyroidism (Study PAR-R13-001) *Ongoing*	To characterise 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, clinical outcomes, and comorbidity. To characterise 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 • Hypocalcaemia • Medication errors • Tachyphylaxis • Use in pregnant or lactating women • Use in patients >65 years of age • Use in non-Caucasians • Long-term safety and efficacy	Protocol approval Start of data collection (historical):	2013 Q3/2013 (Completed)
			Protocol amendment 5 submission	10-August-2020
			Start of recruitment (first patient, first visit):	2017 (Post-EMA approval, Completed)
			Delivery of interim analysis:	PSUR aligned
			Estimated last patient, last visit:	2034 (Targeted: 17 years after date of first patient)
			Delivery of final analysis:	2035 (Targeted)

[redacted]

Table 34. Ongoing and Planned Additional Pharmacovigilance Activities

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
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				
A Randomised, 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>> (Study SHP634-403) *Planned*	**Primary:** To evaluate the effect of rhPTH(1-84) dosed as <<alternative dosing regimen TBD>> on overall metabolic control (as defined by binary response satisfying all of the following criteria at Week 26: subject free of active vitamin D supplement and on 500 mg of calcium per day or less; and albumin-corrected serum calcium 2.0-2.55 mmol/L [8.0-10.2 mg/dL]; and serum phosphate within the normal range of 0.81-1.45 mmol/L [2.5-4.5 mg/dL]) compared with active vitamin D and calcium supplements (standard therapy) in subjects with inadequately controlled hypoparathyroidism. **Secondary:** To evaluate the effect of rhPTH(1-84) dosed once	• Hypercalcaemia • Hypocalcaemia • Immunogenicity/neutralisation of rhPTH (1-84) biological activity • Tachyphylaxis	Protocol submission (Full draft) Protocol submission (Final) Final study report	Q1/2017 (Completed: 20 July 2017) Q2/2019 (Targeted) December-2026 (Targeted)

Table 34. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	daily on overall metabolic control (as defined by binary response satisfying all of the following criteria at Week 26: subject free of active vitamin D supplement and on 500 mg of calcium per day or less; and albumin-corrected serum calcium 2.0-2.55 mmol/L [8.0-10.2 mg/dL]; and serum phosphate within the normal range of 0.81-1.45 mmol/L [2.5-4.5 mg/dL]) compared with standard therapy. To evaluate the effect of rhPTH(1-84) dosed once daily and as <<alternative dosing regimen TBD>> on urine calcium excretion compared with standard therapy. 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-corrected			

Table 34. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	serum calcium according to the central laboratory normal range compared with standard therapy. 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 standard therapy. 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: To evaluate pre- and post-rhPTH(1-84) dosing serum albumin-corrected calcium levels in the once daily rhPTH(1-84) arm and in the <<alternative dosing regimen TBD>> compared with standard therapy.			

[redacted]

Table 34. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	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 standard therapy. To evaluate the effect of rhPTH(1-84) dosed once daily and as <<alternative dosing regimen TBD>> on change from baseline in bone mineral density compared with standard therapy. 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 standard therapy. To assess safety and tolerability of rhPTH(1-84) dosed once daily and as <<alternative dosing regimen TBD>>			

[redacted]

Table 34. Ongoing and Planned Additional Pharmacovigilance Activities

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
	compared with standard therapy.			
Category 3 – Required additional pharmacovigilance activities				
N/A	N/A	N/A	N/A	N/A

EMA=European Medicines Agency; EU=European Union; N/A=not applicable; PSUR=Periodic Safety Update Report; rhPTH (1-84)=recombinant human parathyroid hormone (NATPAR); TBD=to be determined

[redacted]

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Table 35. Planned and Ongoing Post-Authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due date
Efficacy studies which are conditions of the marketing authorisation				
PARADIGHM (Physicians Advancing Disease Knowledge in Hypoparathyroidism): A Registry for Patients with Chronic Hypoparathyroidism (Study PAR-R13-001) *Ongoing*	To characterise 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, clinical outcomes, and comorbidity. To characterise 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 • Hypocalcaemia • Medication errors • Tachyphylaxis • Use in pregnant or lactating women • Use in patients >65 years of age • Use in non-Caucasians • Long-term safety and efficacy	Protocol approval Start of data collection (historical): Protocol amendment 5 submission – 10 August 2020 Start of recruitment (FPFV): Delivery of interim analysis: Estimated last patient, last visit: Final study report:	2013 (Completed) Q3/2013 10-August-2020 2017 (Post-EMA approval, Completed) PSUR aligned 2034 (Targerted:17 years after date of first patient) 2035 (Targeted)

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due date
Efficacy studies which are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
A Randomised, 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>> (Study SHP634-403) *Planned*	**Primary:** To evaluate the effect of rhPTH(1-84) dosed as <<alternative dosing regimen TBD>> on overall metabolic control (as defined by binary response satisfying all of the following criteria at Week 26: subject free of active vitamin D supplement and on 500 mg of calcium per day or less; and albumin-corrected serum calcium 2.0-2.55 mmol/L [8.0- 10.2 mg/dL]; and serum phosphate within the normal range of 0.81-1.45 mmol/L [2.5-4.5 mg/dL]) compared with active vitamin D and calcium supplements (standard therapy) in subjects with inadequately controlled hypoparathyroidism. **Secondary:** To evaluate the effect of rhPTH(1-84) dosed once daily on overall metabolic control (as defined by binary response satisfying all of the following criteria at Week 26: subject free of active	• Hypercalcaemia • Hypocalcaemia • Immunogenicity/neutralisation of rhPTH (1-84) biological activity • Tachyphylaxis	Protocol submission (Full draft) Protocol submission (Final) Final study report	Q1/2017 (Completed: 20 July 2017) Q2/2019 (Targeted) December-2026 (Targeted)

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due date
	vitamin D supplement and on 500 mg of calcium per day or less; and albumin-corrected serum calcium 2.0-2.55 mmol/L [8.0-10.2 mg/dL]; and serum phosphate within the normal range of 0.81-1.45 mmol/L [2.5-4.5 mg/dL]) compared with standard therapy. To evaluate the effect of rhPTH(1-84) dosed once daily and as <<alternative dosing regimen TBD>> on urine calcium excretion compared with standard therapy. 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-corrected serum calcium according to the central laboratory normal range compared with standard therapy. 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			

[redacted]

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due date
	supplements compared with standard therapy. 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: To evaluate pre- and post-rhPTH(1-84) dosing serum albumin-corrected calcium levels in the once daily rhPTH(1-84) arm and in the <<alternative dosing regimen TBD>> compared with standard therapy. 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 standard therapy. To evaluate the effect of rhPTH(1-84) dosed once daily and as <<alternative dosing regimen TBD>> on change from baseline in bone mineral density compared with standard therapy. To evaluate the effect of rhPTH(1-84) dosed once daily and as <<alternative			

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due date
	dosing regimen TBD>> on cognitive status, hypoparathyroidism-related symptoms, and health-related quality of life compared with standard therapy. To assess safety and tolerability of rhPTH(1-84) dosed once daily and as <<alternative dosing regimen TBD>> compared with standard therapy.			

EMA=European Medicines Agency; EU=European Union; N/A=not applicable; PSUR=Periodic Safety Update Report; rhPTH (1-84)=recombinant human parathyroid hormone (NATPAR); TBD=to be determined

[redacted]

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

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table 36. Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Hypercalcaemia	**Routine risk communication:** SmPC sections 4.2, 4.4, 4.8, 4.9 Corresponding PL sections **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Dosing schedule (including initiation and titration) provided in Section 4.2. Special warnings and precaution in 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 with cardiac glycosides and drugs that affect serum calcium are discussed in Section 4.2. Hypercalcaemia is listed in Section 4.8. Overdose discussed in Section 4.9. **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine
Hypocalcaemia	**Routine risk communication:** SmPC sections 4.2, 4.4, 4.8 Corresponding PL sections **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Dosing schedule (including initiation and titration) provided in Section 4.2. Special warnings and precaution in Section 4.4 regarding withdrawal of PTH (rDNA). Drug interactions with cardiac glycosides and drugs that affect serum calcium are discussed in Section 4.2. Hypocalcaemia is listed in Section 4.8 **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine
Osteosarcoma and other	**Routine risk communication:**

[redacted]

Table 36. Description of Routine Risk Minimisation Measures by Safety Concern	
Safety concern	**Routine risk minimisation activities**
bone tumours	SmPC sections 4.3 and 4.4 Corresponding PL sections **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Natpar is contraindicated in patients who are receiving or who have previously received radiation therapy to the skeleton; with skeletal malignancies or bone metastases; who are at increased baseline risk for osteosarcoma such as patients with Paget's disease of bone or hereditary disorders; with unexplained elevations of bone specific alkaline phosphatase. Special warnings and precautions in Section 4.4: Natpar should be used with caution in young adult patients with open epiphyses as these patients may be at increased risk for osteosarcoma. **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine
Medication errors	**Routine risk communication:** SmPC sections 4.1, 4.2, 4.9 Corresponding PL sections **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Therapeutic indication in Section 4.1. Posology and method of administration described in Section 4.2. Overdose discussed in Section 4.9: Updated IFU. **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine
Immunogenicity/ Neutralisation of rhPTH (1-84) biological activity	**Routine risk communication:** SmPC section 4.8 Corresponding PL sections **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Anti-PTH antibody positive is listed as an ADR in Section 4.8. **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine
Tachyphylaxis	**Routine risk communication:**

[redacted]

Table 36. Description of Routine Risk Minimisation Measures by Safety Concern	
Safety concern	**Routine risk minimisation activities**
	SmPC section 4.4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Special warnings and precaution in Section 4.4 to monitor the response to serum calcium concentration to Natpar at intervals to detect tachyphylaxis. **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine
Use in patients <18 years of age	**Routine risk communication:** SmPC sections 4.1 and 4.2 Corresponding PL sections **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Therapeutic indication in Section 4.1 Use in paediatric population discussed in Section 4.2 **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine
Use in pregnant or lactating women	**Routine risk communication:** SmPC section 4.6 Corresponding PL sections **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:** Prescription only medicine
Long-term effects on bone structure and development in paediatric patients <18 years of age and young adults with open epiphyses	**Routine risk communication:** SmPC sections 4.1 and 4.2 Corresponding PL sections **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Therapeutic indication in Section 4.1: Use in paediatric population discussed in Section 4.2 **Other routine risk minimisation measures beyond the Product Information:**

[redacted]

Table 36. Description of Routine Risk Minimisation Measures by Safety Concern	
Safety concern	**Routine risk minimisation activities**
	Prescription only medicine
Use in patients >65 years of age	**Routine risk communication:** SmPC sections 4.4 and 5.2 Corresponding PL sections **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Warnings and precautions for use in subjects aged 65 and over discussed in Section 4.4. **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine
Use in non-Caucasians	**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:** Prescription only medicine
Long-term safety and efficacy	**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:** Prescription only medicine
Use in patients with severe renal disease	**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 use in patients with severe renal disease discussed in Section 4.4 PK properties regarding renal impairment discussed in Section 5.2.

[redacted]

Table 36. Description of Routine Risk Minimisation Measures by Safety Concern	
Safety concern	**Routine risk minimisation activities**
	Other routine risk minimisation measures beyond the Product Information: Prescription only medicine
Use in patients with severe hepatic disease	**Routine risk communication:** SmPC sections 4.2, 4.4, 5.2 Corresponding PL sections **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Description of requirements in cases of hepatic impairment provided in Section 4.2 Warnings and precautions for use in patients with severe hepatic disease discussed in Section 4.4. PK properties regarding hepatic impairment discussed in Section 5.2. **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine

ADR=adverse drug reaction; AUC=area under the curve; CrCl=creatinine clearance; C_{max}=maximum concentration; ECG=electrocardiogram; IFU= instructions for use; PK=pharmacokinetic; PTH=parathyroid hormone; PTH (rDNA)=recombinant human parathyroid hormone (Natpar); rhPTH (1-84)=recombinant human parathyroid hormone (1-84) (Natpar); SC=subcutaneous; SmPC=Summary of Product Characteristics

V.2 Additional Risk Minimisation Measures

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

V.2.1 Removal of Additional Risk Minimisation Activities

Not applicable.

V.3 Summary of Pharmacovigilance Activities and Risk Minimisation Measures

Table 37. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern		
Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Hypercalcaemia	**Routine risk minimisation measures:** SmPC sections 4.2, 4.4, 4.8, and 4.9 Corresponding PL sections **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Registry Protocol PAR-R13-001 (PARADIGHM)

[redacted]

Table 37. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		Clinical study SHP634-403
Hypocalcaemia	**Routine risk minimisation measures:** SmPC sections 4.2, 4.4, 4.8 Corresponding PL sections **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**None **Additional pharmacovigilance activities:** Registry Protocol PAR-R13-001 (PARADIGHM) Clinical study SHP634-403
Osteosarcoma and other bone tumours	**Routine risk minimisation measures:** SmPC sections 4.3 and 4.4 Corresponding PL sections **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**None **Additional pharmacovigilance activities:** None
Medication errors	**Routine risk minimisation measures:** SmPC sections 4.1, 4.2, 4.9 Corresponding PL sections Updated IFU **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**None **Additional pharmacovigilance activities:** Registry Protocol PAR-R13-001 (PARADIGHM)
Immunogenicity/ Neutralisation of rhPTH (1-84) biological activity	**Routine risk minimisation measures:** SmPC section 4.8 Corresponding PL sections **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**None **Additional pharmacovigilance activities:** Clinical study SHP634-403
Tachyphylaxis	**Routine risk minimisation measures:** SmPC section 4.4 Corresponding PL sections **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**None **Additional pharmacovigilance activities:** Registry Protocol PAR-R13-001 (PARADIGHM)

[redacted]

Table 37. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		Clinical study SHP634-403
Use in patients <18 years of age	**Routine risk minimisation measures:** SmPC sections 4.1 and 4.2 Corresponding PL sections **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**None **Additional pharmacovigilance activities:** None
Use in pregnant or lactating women	**Routine risk minimisation measures:** SmPC section 4.6 Corresponding PL section **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**None **Additional pharmacovigilance activities:** Registry Protocol PAR-R13-001 (PARADIGHM)
Long-term effects on bone structure and development in paediatric patients <18 years of age and young adults with open epiphyses	**Routine risk minimisation measures:** SmPC sections 4.1 and 4.2 Corresponding PL sections **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**None **Additional pharmacovigilance activities:** None
Use in patients >65 years of age	**Routine risk minimisation measures:** SmPC sections 4.4 and 5.2 Corresponding PL sections **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**None **Additional pharmacovigilance activities:** Registry Protocol PAR-R13-001 (PARADIGHM)
Use in non-Caucasians	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**None **Additional pharmacovigilance activities:** Registry Protocol PAR-R13-001 (PARADIGHM)
Long-term safety	**Routine risk minimisation**	**Routine pharmacovigilance activities beyond adverse**

[redacted]

Table 37. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
and efficacy	**measures:** None **Additional risk minimisation measures:** None	**reactions reporting and signal detection:**None **Additional pharmacovigilance activities:** Registry Protocol PAR-R13-001 (PARADIGHM)
Use in patients with severe renal disease	**Routine risk minimisation measures:** SmPC sections 4.2, 4.4, 5.2 Corresponding PL sections **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**None **Additional pharmacovigilance activities:** None
Use in patients with severe hepatic disease	**Routine risk minimisation measures:** SmPC sections 4.2, 4.4, 5.2 Corresponding PL sections **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

SmPC=Summary of Product Characteristics

[redacted]

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for NATPAR (Recombinant human parathyroid hormone (1-84) (rhPTH [1-84]))

This is a summary of the risk management plan (RMP) for NATPAR. The RMP details important risks of NATPAR, how these risks can be minimised, and how more information will be obtained about NATPAR's risks and uncertainties (missing information).

NATPAR's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how NATPAR should be used.

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

Important new concerns or changes to the current ones will be included in updates of NATPAR's RMP.

I. The medicine and what it is used for

NATPAR's is indicated as adjunctive treatment of adult patients with chronic hypoparathyroidism who cannot be adequately controlled with standard therapy alone (see SmPC for the full indication).

NATPAR contains rhPTH (1-84) as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of NATPAR's benefits can be found in NATPAR's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage link to the EPAR summary landing pagehttp://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003861/human_med_002093.jsp&mid=WC0b01ac058001d124

II. Risks associated with the medicine and activities to minimise or further characterise the risks

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

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

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

Together, these measures constitute routine risk minimisation measures.

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

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

II.A List of important risks and missing information

Important risks of NATPAR are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of NATPAR. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs

[redacted]

further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 38. List of Important Risks and Missing Information	
Important identified risks	Hypercalcaemia Hypocalcaemia
Important potential risks	Osteosarcoma and other bone tumours Medication errors Immunogenicity/neutralisation of rhPTH (1-84) biological activity Tachyphylaxis
Missing information	Use in patients <18 years of age Use in pregnant or lactating women Long-term effects on bone structure and development in paediatric patients <18 years of age and young adults with open epiphyses Use in patients >65years of age Use in non-Caucasians Long-term safety and efficacy Use in patients with severe renal disease Use in patients with severe hepatic disease
rhPTH (1-84)=recombinant human parathyroid hormone (NATPAR)	

II.B Summary of important risks

Table 39. Important Identified Risk: Hypercalcaemia	
Evidence for linking the risk to the medicine	Clinical trials, literature
Risk factors and risk groups	For patients with multiple concomitant diseases, such as compromised renal function, history of urolithiasis, hyper/ hypo-thyroidism, as well as malignancies that are associated with hypercalcaemia (squamous cell carcinomas of the lung, head, neck, and oesophagus, renal cell carcinoma, breast carcinoma, haematological malignancies such as multiple myeloma), granulomatous disease, endocrinopathies, it is important to monitor serum calcium levels. Elderly patients are more likely to be symptomatic from moderate elevations of serum calcium levels. The long-term effects of hypercalciuria are unknown, and the effect of rhPTH (1-84) in patients who may be at greater risk of hypercalciuria remains uncertain. As patients' serum calcium should be monitored and the doses of rhPTH (1-84) adjusted accordingly, the potential of nephrocalcinosis and renal failure is low. Patients at higher risk for hypercalcaemia include elderly patients with renal insufficiency, subjects with a disease predisposing to hypercalcaemia (e.g., active neoplasia, multiple myeloma, granulomatous disease, endocrinopathy), and persons taking

[redacted]

Table 39. Important Identified Risk: Hypercalcaemia	
	concomitant medications that affect serum calcium levels (e.g., thiazide diuretics, lithium,). The contraindications are covered in the SmPC, which highlights risk factors for hypercalcaemia. From the knowledge of the mechanism of action, combined use of rhPTH (1-84) and cardiac glycosides (e.g., digoxin or digitoxin) may predispose patients to digitalis toxicity if hypercalcaemia develops. Coadministration of alendronic acid and rhPTH (1-84) may lead to a reduction in the calcium sparing effect, which can interfere with the normalisation of serum calcium. Concomitant use of rhPTH (1-84) with bisphosphonates including alendronate is not recommended. For any drug that affects serum calcium levels (i.e., lithium, thiazide diuretics), the patient's serum calcium levels should be monitored especially during treatment start or dose adjustment. Thiazide diuretics are sometimes used in hypoparathyroid patients to increase urinary calcium reabsorption at the distal tubule and induce osteoblast differentiation which will contribute to increasing serum calcium levels. In patients with a history of calcium stones, thiazide diuretics are prescribed to reduce recurrent calcium stones. Thus, the concomitant treatment of thiazide diuretics and rhPTH (1-84) is likely to reduce the adverse renal effects (including nephrolithiasis, nephrocalcinosis) but can augment the risk for transient hypercalcaemia. It is therefore recommended to monitor serum calcium when adding or changing the dose of thiazide diuretics in patients treated with rhPTH (1-84).
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.2, 4.4, 4.8, 4.9 **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Registry Protocol PAR-R13-001 (PARADIGHM) Clinical study SHP634-403 See section II.C of this summary for an overview of the post-authorisation development plan.

rhPTH (1-84)=recombinant human parathyroid hormone (NATPAR); SmPC=Summary of Product Characteristics

Table 40. Important Identified Risk: Hypocalcaemia	
Evidence for linking the risk to the medicine	Clinical trials, literature
Risk factors and risk groups	Patients at risk of developing hypocalcaemia include those with vitamin D deficiency (malabsorption, short bowel), chronic kidney disease, which may result in hyperphosphataemia and rare disorders which may cause hyperphosphataemia such as pseudohypoparathyroidism, isolated hyperparathyroidism, rhabdomyolysis, and tumour lysis.

[redacted]

Table 40. Important Identified Risk: Hypocalcaemia	
	In patients on rhPTH (1-84) therapy, the highest risk of hypocalcaemia occurs if therapy is abruptly discontinued or interrupted.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.2, 4.4, 4.8 **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Registry Protocol PAR-R13-001 (PARADIGHM) Clinical study SHP634-403 See section II.C of this summary for an overview of the post-authorisation development plan.

rhPTH (1-84)=recombinant human parathyroid hormone (NATPAR); SmPC=Summary of Product Characteristics

Table 41. Important Potential Risk: Osteosarcoma and Other Bone Tumours	
Evidence for linking the risk to the medicine	Clinical trials, literature
Risk factors and risk groups	Therapeutic radiation is a proven risk factor for osteosarcoma. The incidence of osteosarcoma secondary to Paget's disease is not precisely known, but studies estimate that about 1% of patients with Paget's disease will develop osteosarcoma. In elderly persons, about half of the osteosarcomas reported are estimated to be associated with Paget's disease. Chromosomal aneuploidy is common in osteosarcoma cells which suggests that somatic or germline chromosomal instability could potentially predispose an individual to osteosarcoma. Childhood and adolescent osteosarcoma rates are relatively consistent around the world ranging from 3 to 4.5 cases/million population/year. Osteosarcoma represents approximately 55% of child and adolescent malignant bone tumours in the US. As osteosarcoma occurs most commonly during puberty, a time of rapid bone growth and remodelling, it is highly plausible that factors related to growth and development play a role in osteosarcoma aetiology. The risk of developing bone tumours has a peak in paediatric patients and young adults with open epiphyses. This is added as a precaution for use in the SmPC. Other diseases with an increased risk of osteosarcoma include Paget's disease of the bone mostly occurring in patients >40 years, prior external beam or implant radiation therapy involving the skeleton. Hereditary disorders predisposing to a higher risk of osteosarcoma such as children with hereditary retinoblastoma or people with trisomia 21 or for bone sarcoma in neurofibromatosis are known. Other bone tumours like Ewing sarcoma also occur most commonly between 15 and 25 years of age. rhPTH (1-84) is contraindicated in patients who are at increased baseline risk for osteosarcoma such as

[redacted]

Table 41. Important Potential Risk: Osteosarcoma and Other Bone Tumours	
	patients with Paget's disease of bone or hereditary disorders. A high incidence of osteosarcoma has been observed in 2 African countries, Sudan and Uganda, compared to the relative frequency in populations of European origin. This is consistent with the finding that young and middle-aged individuals of African American descent in the US had higher rates of osteosarcoma than whites. One could also speculate that the increased rates in subjects of African descent are related to differences in vitamin D absorption. This hypothesis in osteosarcoma susceptibility has yet to be tested.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.3 and 4.4 **Additional risk minimisation measures:** None

rhPTH (1-84)=recombinant human parathyroid hormone (NATPAR); SmPC=Summary of Product Characteristics; US=United States

Table 42. Important Potential Risk: Medication Errors	
Evidence for linking the risk to the medicine	Post-marketing reports
Risk factors and risk groups	Not applicable
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.1, 4.2, 4.9 **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Registry Protocol PAR-R13-001 (PARADIGHM) See section II.C of this summary for an overview of the post-authorisation development plan.

SmPC=Summary of Product Characteristics

Table 43. Important Potential Risk: Immunogenicity/Neutralisation of rhPTH (1-84) Biological Activity	
Evidence for linking the risk to the medicine	Clinical trials
Risk factors and risk groups	None
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.8 **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Clinical study SHP634-403

[redacted]

Table 43. Important Potential Risk: Immunogenicity/Neutralisation of rhPTH (1-84) Biological Activity	
	See section II.C of this summary for an overview of the post-authorisation development plan.

SmPC=Summary of Product Characteristics

Table 44. Important Potential Risk: Tachyphylaxis	
Evidence for linking the risk to the medicine	None
Risk factors and risk groups	Unknown
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.4 **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Registry Protocol PAR-R13-001 (PARADIGHM) Clinical study SHP634-403 See section II.C of this summary for an overview of the post-authorisation development plan.

SmPC=Summary of Product Characteristics

Table 45. Missing Information: Use in paediatric patients <18 years of age	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.1 and 4.2 **Additional risk minimisation measures:** None

SmPC=Summary of Product Characteristics

Table 46. Missing Information: Use in Pregnant or Lactating Women	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.6 **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Registry Protocol PAR-R13-001 (PARADIGHM) See section II.C of this summary for an overview of the post-authorisation development plan.

SmPC=Summary of Product Characteristics

Table 47. Missing Information: Long-term Effects on Bone Structure and Development in Paediatric Patients <18 Years of Age and Young Adults with Open Epiphyses	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.1, 4.2 **Additional risk minimisation measures:** None

SmPC=Summary of Product Characteristics

[redacted]

Table 43. Important Potential Risk: Immunogenicity/Neutralisation of rhPTH (1-84) Biological Activity	
Table 48. Missing Information: Use in Patients >65 Years of Age	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.4 and 5.2 **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Registry Protocol PAR-R13-001 (PARADIGHM) See section II.C of this summary for an overview of the post-authorisation development plan.

SmPC=Summary of Product Characteristics

Table 49. Missing Information: Use in Non-Caucasian Patients	
Risk minimisation measures	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Registry Protocol PAR-R13-001 (PARADIGHM) See section II.C of this summary for an overview of the post-authorisation development plan.

SmPC=Summary of Product Characteristics

Table 50. Missing Information: Long-term Safety and Efficacy	
Risk minimisation measures	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Registry Protocol PAR-R13-001 (PARADIGHM) See section II.C of this summary for an overview of the post-authorisation development plan.

SmPC=Summary of Product Characteristics

Table 51. Missing Information: Use in Patients with Severe Renal Disease	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.2, 4.4, 5.2 **Additional risk minimisation measures:** None

SmPC=Summary of Product Characteristics

Table 52. Missing Information: Use in Patients with Severe Hepatic Disease

[redacted]

Table 50. Missing Information: Long-term Safety and Efficacy	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.2, 4.4, 5.2 **Additional risk minimisation measures:** None

SmPC=Summary of Product Characteristics

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

Table 53. Studies Which are Conditions of the Marketing Authorisation

Study name	Purpose of the study
PAR-R13-001 PARADIGHM	To characterise 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, clinical outcomes, and comorbidity. To characterise 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. The following safety concerns are addressed: • Hypercalcaemia • Hypocalcaemia • Medication errors • Tachyphylaxis • Use in pregnant or lactating women • Use in patients > 65 years of age • Use in non-Caucasians Long-term safety and efficacy
SHP634-403	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 (standard therapy) in subjects with inadequately controlled hypoparathyroidism. The following safety concerns are addressed: Hypercalcaemia Hypocalcaemia Immunogenicity/neutralisation of rhPTH (1-84) biological activity Tachyphylaxis

rhPTH (1-84)=recombinant human parathyroid hormone (NATPAR)

[redacted]

II.C.2 Other studies in the post-authorisation development plan

There are no studies required for NATPAR.

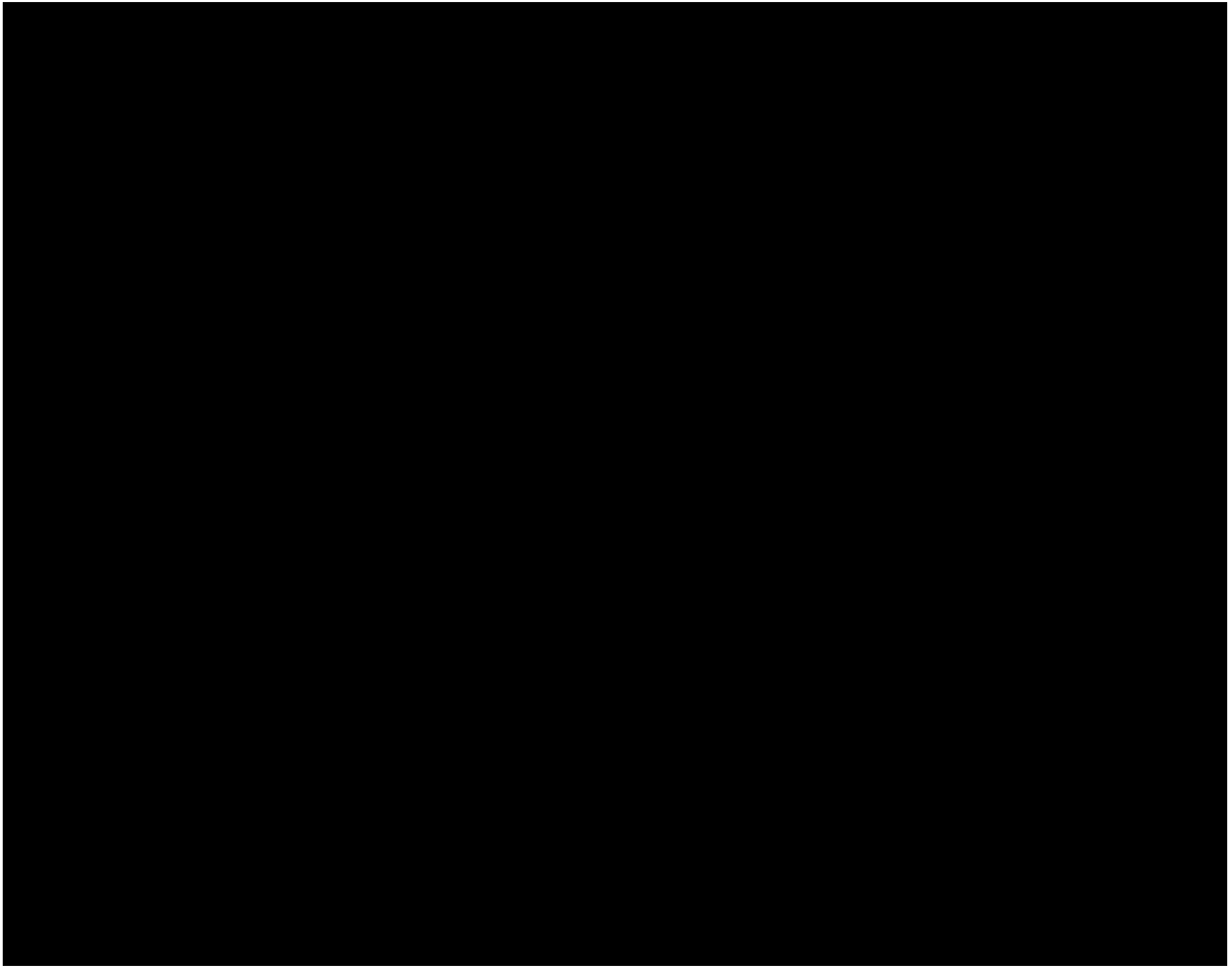
PART VII ANNEXES

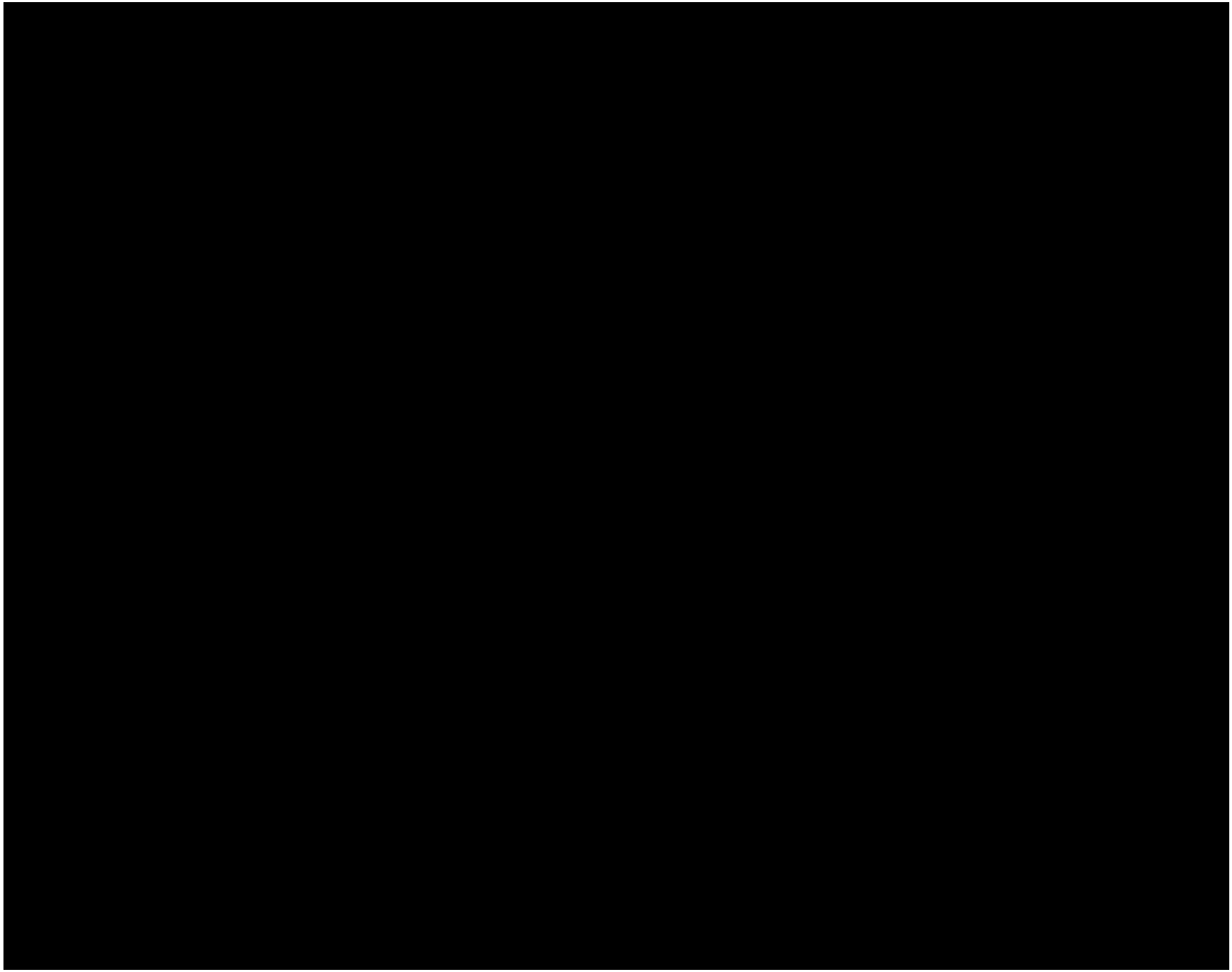
ANNEX	
[redacted]	
4	Specific adverse drug reaction follow-up forms
[redacted]	
6	Details of proposed additional risk minimisation activities (if applicable)
[redacted]	

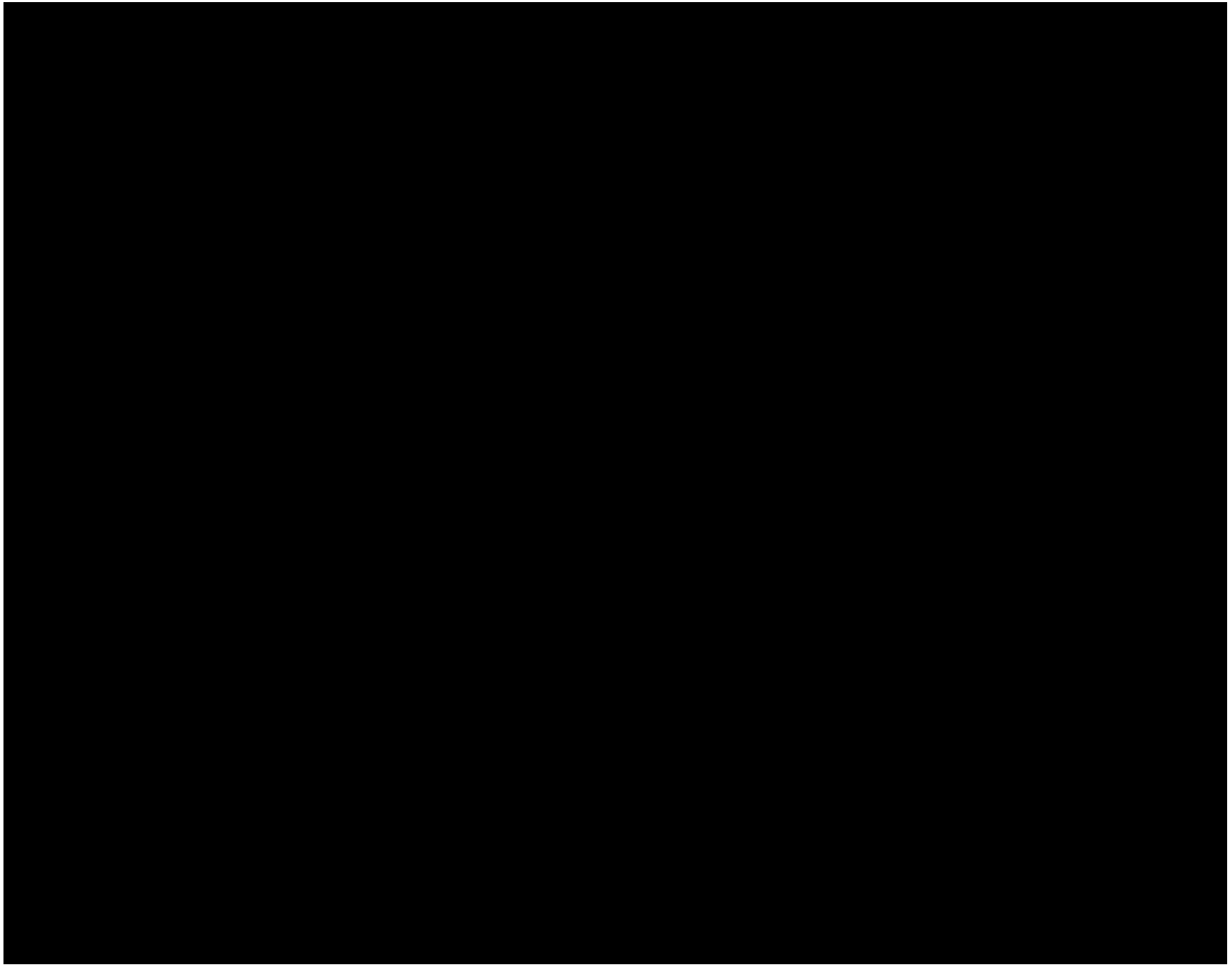
[redacted]

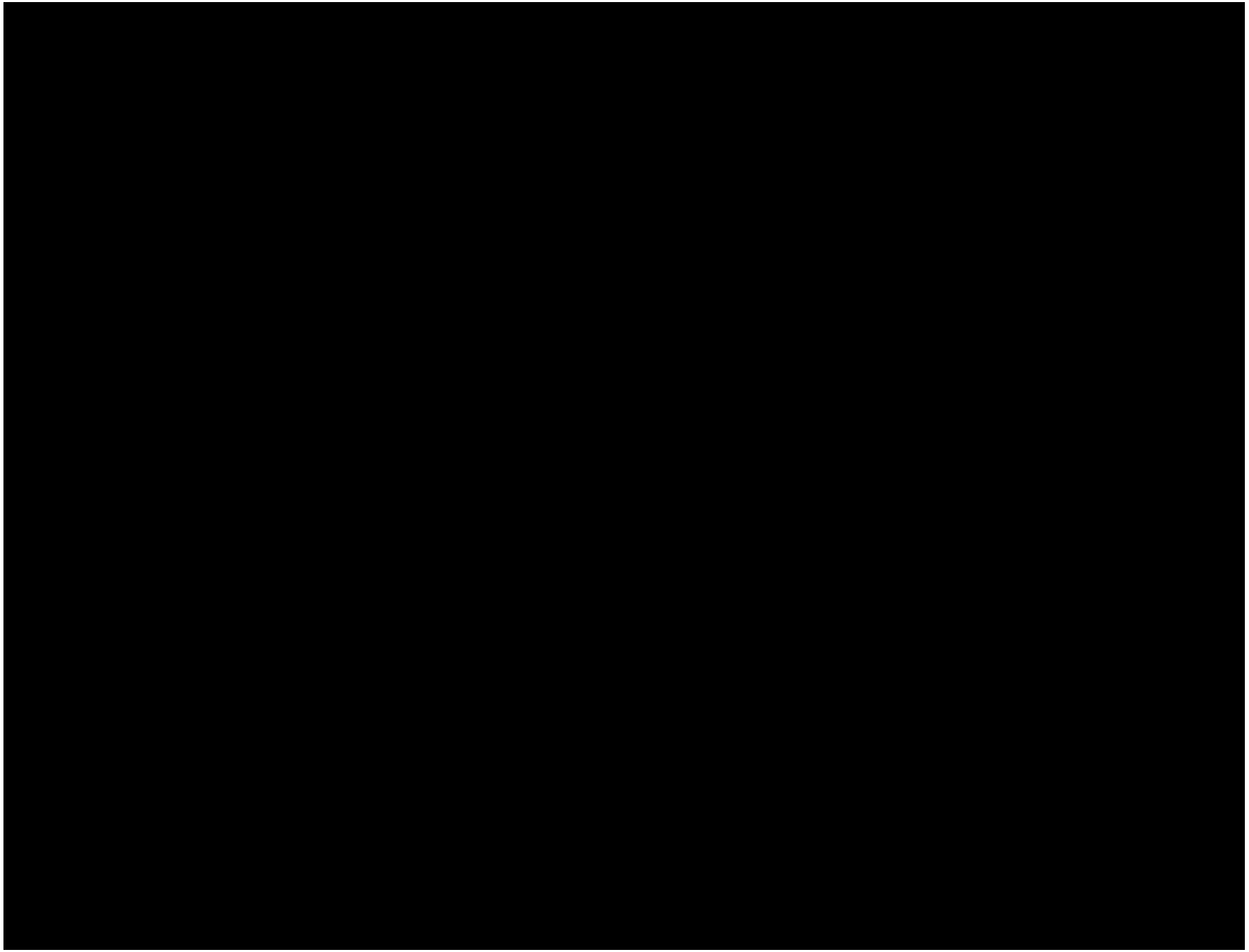
[redacted]

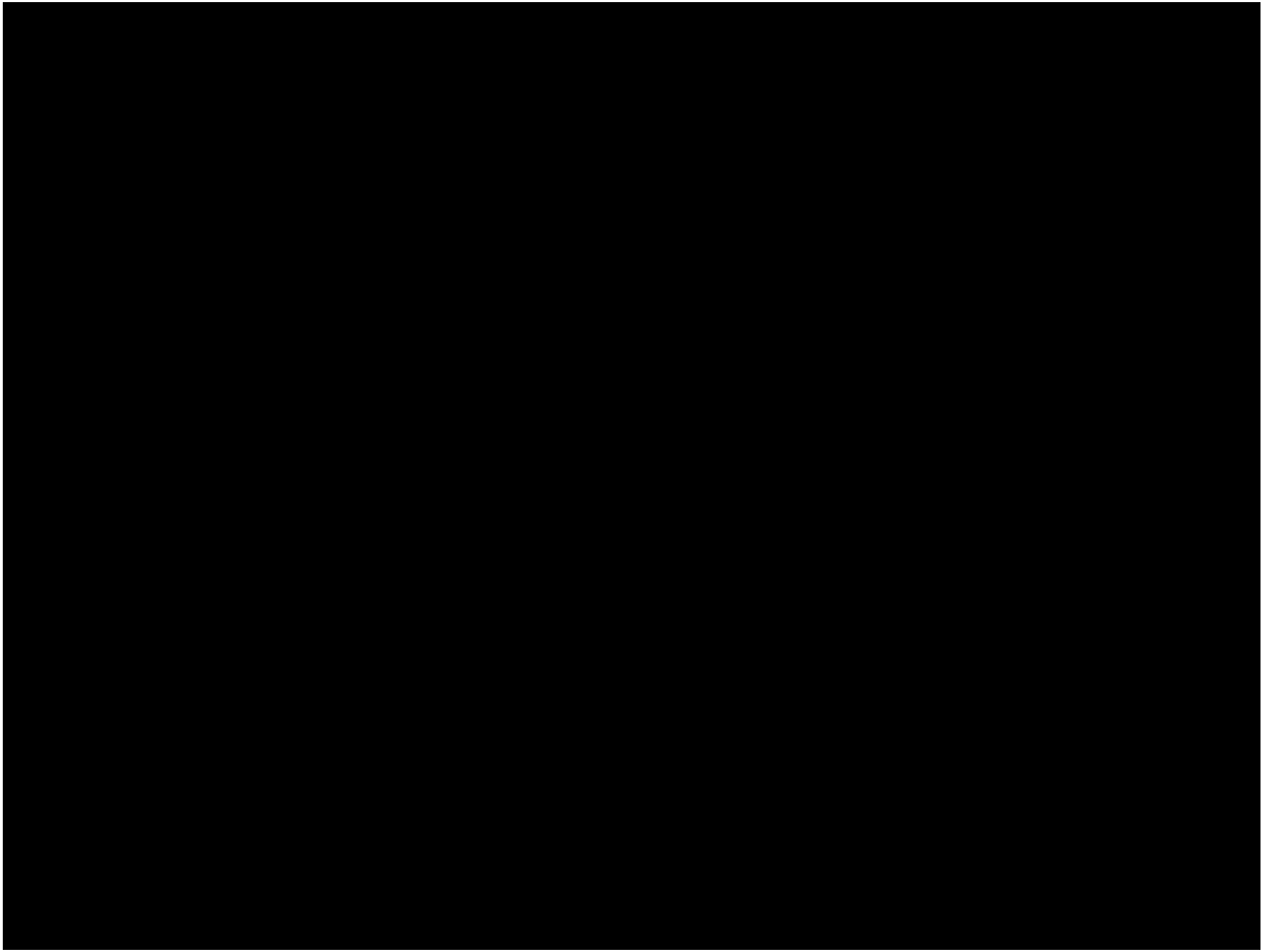
[redacted]

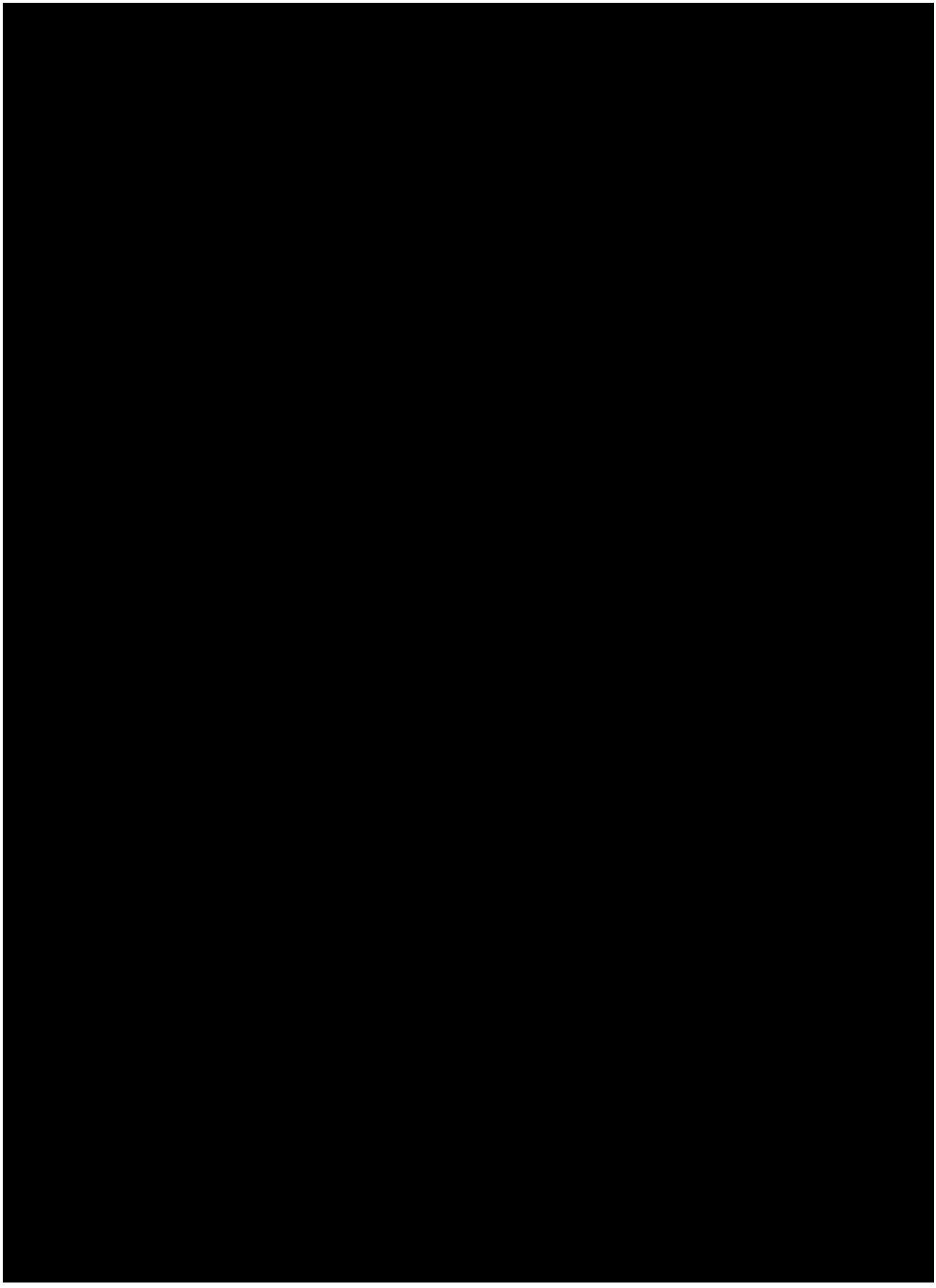








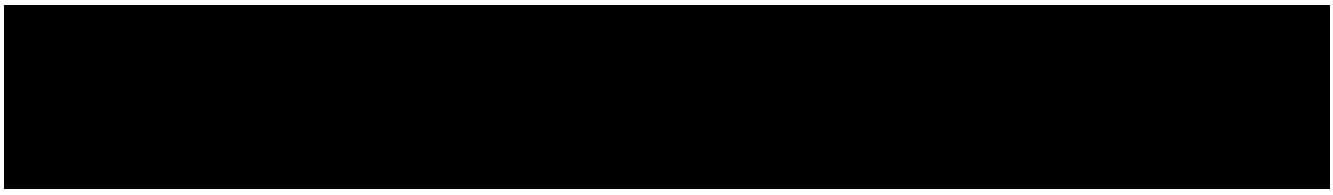




Annex 4 - Specific adverse drug reaction follow-up forms

There are no specific adverse drug reaction follow-up forms for Natpar.

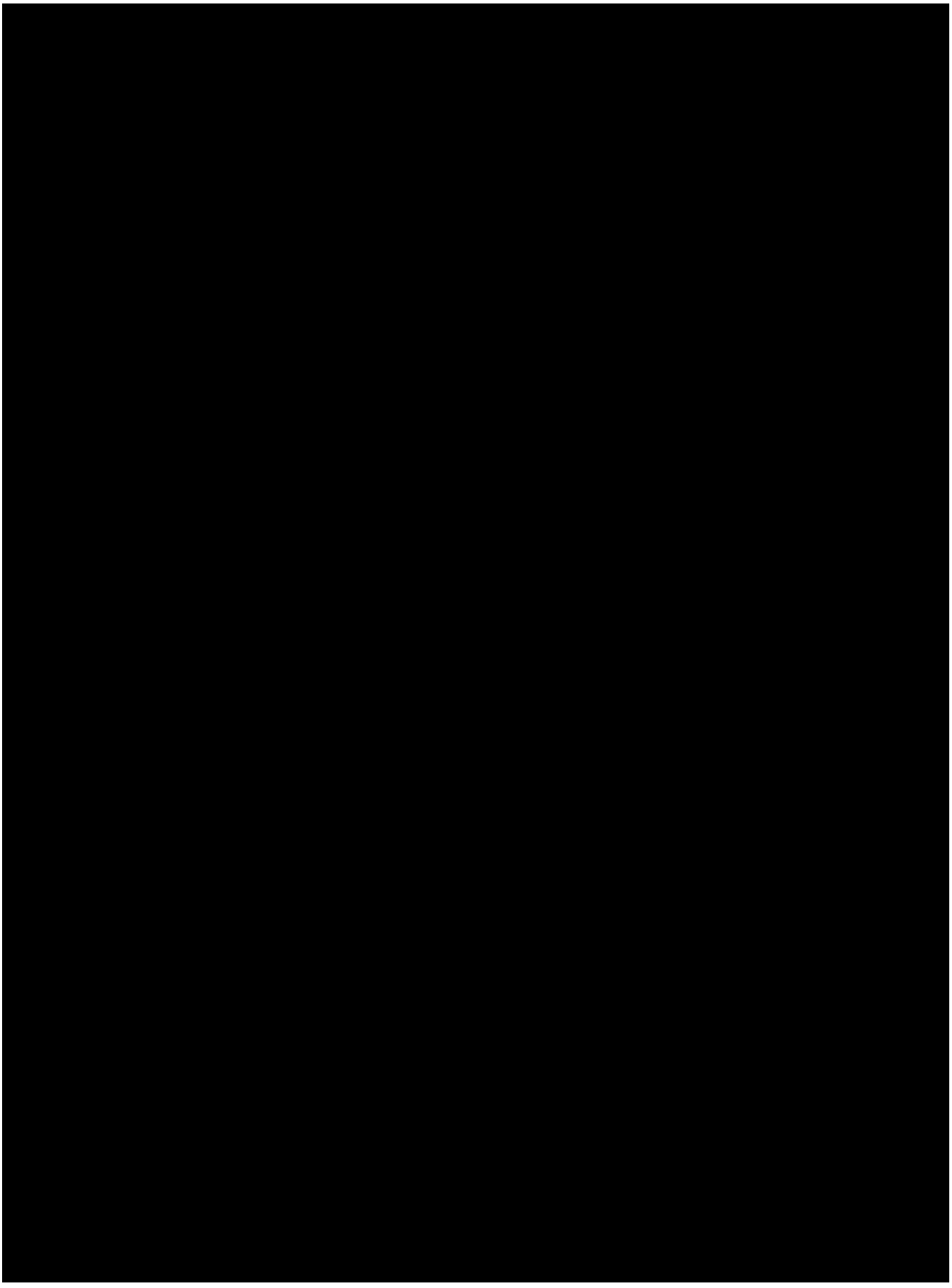
[redacted]



Annex 6 - Details of proposed additional risk minimisation activities

Not applicable

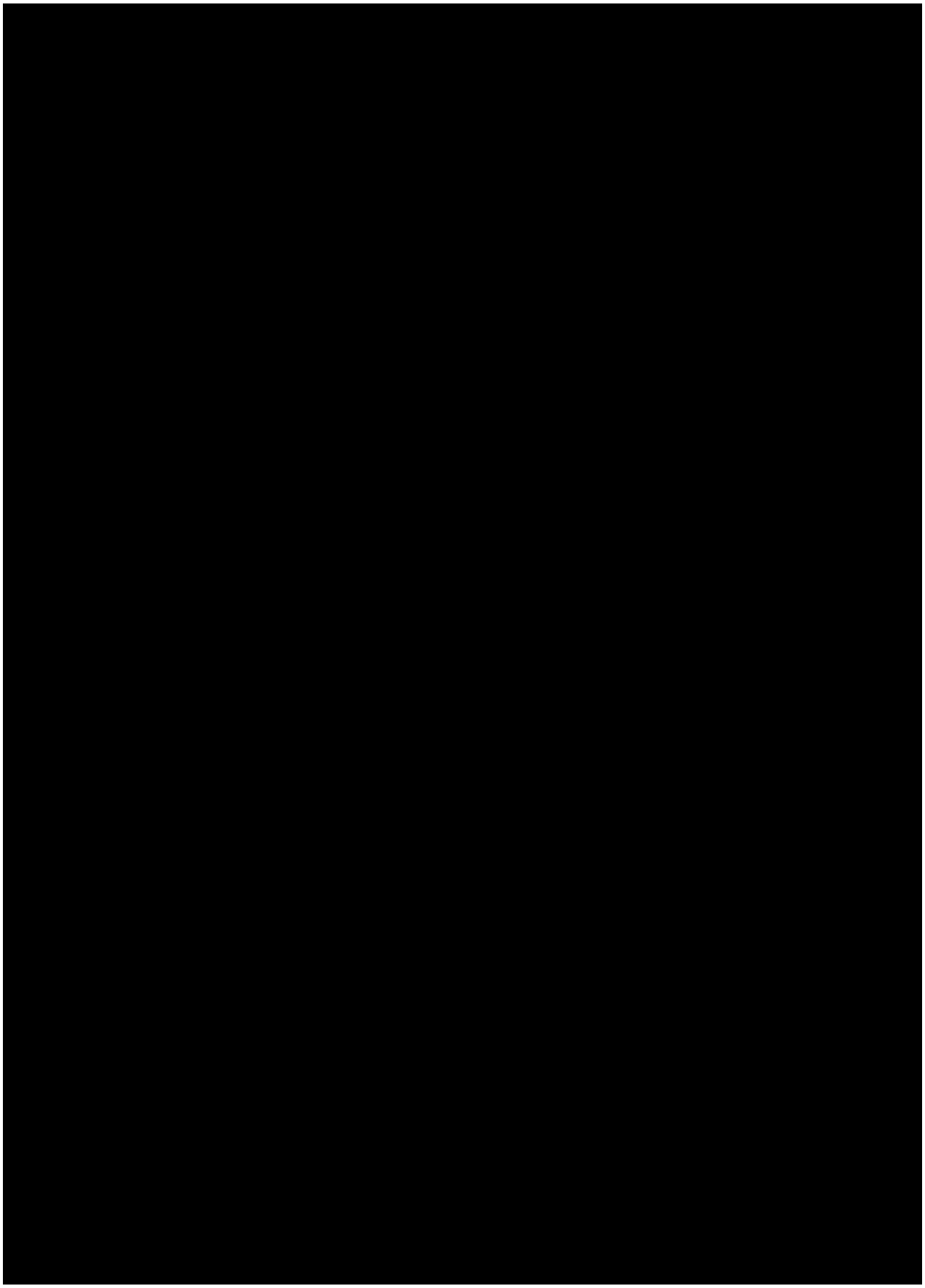
[redacted]



[redacted]

[redacted]

[redacted]



[redacted]

[redacted]