EU Risk Management Plan for Zandoriah (Teriparatide)

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Term / Abbreviation	Description
ADR	Adverse Drug Reaction
ATC	Anatomic Therapeutic Chemical
AUC	Area Under The Curve
BMD	Bone Mineral Density
BSAP	Bone-Specific Alkaline Phosphatase
CCDS	Company Core Data Sheet
CI	Confidence Interval
CrCl	Creatinine Clearance
CT	Clinical Trial
CTX	C-Telopeptide Crosslink
DNA	Deoxyribonucleic Acid
DP	Drug Product
ECG	Electrocardiogram
FDA	Food And Drug Administration
HCP	Healthcare Professional
HRT	Hormone Replacement Therapy
IBD	International Birth Date
ICH	International Conference on Harmonization
INN	International Non-Proprietary Name
IU	International Unit
MAH	Marketing Authorization Holder

MedDRA	Medical Dictionary For Regulatory Activities
NTX	N-Telopeptide Crosslink
OC	Osteocalcin
OECD	Organization for Economic Co-operation and Development
P1NP	Procollagen 1 Intact N-Terminal Peptide
PBRER	Periodic Benefit-Risk Evaluation Report
PhV	Pharmacovigilance
PT	Preferred Term
PTH	Parathyroid Hormone
REMS	Risk Evaluation and Mitigation Strategy
RMP	Risk Management Plan
RSI	Reference Safety Information
SAE	Serious Adverse Event
SERMs	Selective Estrogen Receptor Modulators
SmPC	Summary Of Product Characteristics
$T_{1/2}$	Half-Life
USA	United States of America
WHO	World Health Organization

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Part I: Product Overview

Table 1. Product Overview

Active substance(s)	Teriparatide
Pharmacotherapeutic group(s) (ATC Code)	Parathyroid Hormone Analog (ATC Code: H05AA02)
Marketing Authorisation Holder	CinnaGen Co.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	P044
Marketing authorisation procedure	Centralized
Brief description of the product including: • Chemical class • Summary of mode of action	• Teriparatide belongs to Parathyroid Hormone analog pharmacologic category. • Endogenous 84–amino–acid parathyroid hormone (PTH) is the primary regulator of calcium and phosphate metabolism in bone and kidney. The biological actions of PTH and Teriparatide are mediated through binding to specific high-affinity cell–surface receptors. The skeletal effects of Teriparatide depend upon the pattern of systemic exposure. Once-daily administration of Teriparatide stimulates new bone formation on trabecular and cortical (periosteal and/or endosteal) bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity. In monkey studies, Teriparatide improved trabecular microarchitecture and increased bone mass and strength by stimulating new

• Important information about its composition (e.g. origin of active substance of biological, relevant adjuvants or residues for vaccines)	bone formation in both cancellous and cortical bone. In humans, the anabolic effects of Teriparatide are manifest as an increase in skeletal mass, an increase in markers of bone formation and resorption, and an increase in bone strength. By contrast, continuous excess of endogenous PTH, as occurs in hyperparathyroidism, may be detrimental to the skeleton because bone resorption may be stimulated more than bone formation. • Teriparatide is recombinant human parathyroid hormone (PTH), and is also called rhPTH (1-34). It has an identical sequence to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone. Teriparatide has a molecular weight of 4117.8 D. • Teriparatide is manufactured using a strain of *Escherichia coli* modified by recombinant DNA technology. • P044 20 mcg/80 mcL, has been produced in 2.4 mL solution for injection in pre-filled pen. Excipients in this product are: Glacial acetic acid, Sodium acetate (anhydrous), Mannitol, Meta-Cresol and Water for injections. Hydrochloric acid (for pH adjustment) and/ or Sodium hydroxide might be used for pH adjustment. One pre-filled pen of 2.4 mL contains 600 micrograms of Teriparatide (corresponding to 250 micrograms per mL). Each dose of 80 microlitres contains 20 micrograms of Teriparatide.

Hyperlink to the Product Information	https://www.ema.europa.eu/en/documents/product-information/forsteo-epar-product-information_en.pdf
Indication(s) in EEA: Current (if applicable)	P044 is administrated for the following indications: Teriparatide is indicated in adults. • Treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture. • In postmenopausal women, a significant reduction in the incidence of vertebral and non-vertebral fractures but not hip fractures has been demonstrated. • Treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture.
Proposed (if applicable)	Not applicable.
Dosage in the EEA Current (if applicable)	20 micrograms administered once daily.
Proposed (if applicable)	Not applicable.
Pharmaceutical form and strengths Current (if applicable)	20 mcg/80 mcL, 2.4 mL solution for injection in pre-filled pen.
Proposed (if applicable**)**	Not applicable
Is the product be subject to additional monitoring in the EU?	Yes

ATC code = Anatomic Therapeutic Chemical code; INN = International Non-Proprietary Name; RMP = Risk Management Plan; CCDS = Company Core Data Sheet; IU = International Units; RMP = Risk Management Plan.

Part II Safety specification

Part II: Module SI- Epidemiology of the indications and target population

Teriparatide is a recombinant parathyroid hormone (PTH) analog and a potent osteoanabolic agent. It consists of the first 34 amino acids of the human PTH's N-terminal sequence. First approved in the United States in November 2002 and in Europe in April 2003, teriparatide is the first approved drug in a new category of osteoporosis therapy called anabolic therapy [12].

Indications for teriparatide include the following:

- Treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture. In postmenopausal women, a significant reduction in the incidence of vertebral and non-vertebral fractures but not hip fractures have been demonstrated.

- Treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture.

Incidence and prevalence:

As the average age of the world's population shifts upward, the incidence and prevalence of osteoporosis and its economic burden on society will increase further. Due to its prevalence worldwide, osteoporosis is considered a serious public health concern. Currently it is estimated that over 200 million people worldwide suffer from this disease. Risk for osteoporosis increases with age as BMD declines. Senile osteoporosis is most common in persons aged 70 years or older. Secondary osteoporosis, however, can occur in persons of any age. Women are at a significantly higher risk for osteoporosis. Half of all postmenopausal women will have an osteoporosis-related fracture during their lifetime. Osteoporosis can occur in persons of all races and ethnicities. In general, however, whites (especially of northern European descent) and Asians are at increased risk. Since the clinical outcome of osteoporosis is bone fracture, attention is now increasingly focused on the identification of patients at high risk of fracture rather than the identification of people with osteoporosis as defined by BMD alone.

Surveys based on data from developed countries show that the number of individuals aged 45 years and older increased from about 155 million in 1960 to 206 million in 1980. This number can be expected to rise to 257 million by the year 2000. This trend is true not only for industrialized countries, but also in the developing countries. The world population of women older than 45 is therefore set to more than double in this time. More than 200 million women worldwide have osteoporosis. Due to its prevalence worldwide, osteoporosis is considered a serious public health concern. Currently it is estimated that over 200 million people worldwide suffer from this disease. Approximately 30% of all postmenopausal women have osteoporosis in the United States and in Europe. At least 40% of these women and 15-30% of men will sustain one or more fragility fractures in their remaining lifetime. Ageing of populations worldwide will be responsible for a major increase in the incidence of osteoporosis in postmenopausal women [1,2].

Demographics of the target population:

Age demographics

Risk for osteoporosis increases with age as BMD declines. Senile osteoporosis is most common in persons aged 70 years or older. Secondary osteoporosis, however, can occur in persons of any age. Although bone loss in women begins slowly, it speeds up around the time of menopause, typically at about or after age 50 years. The frequency of postmenopausal osteoporosis is highest in women aged 50-70 years.

The number of osteoporotic fractures increases with age. Wrist fractures typically occur first, when individuals are aged approximately 50-59 years.

Vertebral fractures occur more often in the seventh decade of life. Jensen et al studied Danish women aged 70 years and found a 21% prevalence of vertebral fractures. Melton et al reported that 27% of women in their study had evidence of vertebral fractures by age 65 years.

Ninety percent of hip fractures occur in persons aged 50 years or older, occurring most often in the eighth decade of life.

The target population for teriparatide primarily includes:

1. Postmenopausal Women: Teriparatide is often prescribed to postmenopausal women with osteoporosis who are at high risk of fractures. This group typically includes women aged 50 and above who have experienced one or more fragility fractures.

2. Men with Osteoporosis: Men, particularly those aged 50 and older, who have been diagnosed with osteoporosis and are at high risk of fractures, are also candidates for teriparatide treatment.

3. Patients with Long-term Glucocorticoid Therapy: Individuals who have osteoporosis due to long-term glucocorticoid therapy are also considered for teriparatide treatment.

4. Patients with Severe Osteoporosis: Teriparatide is often prescribed to patients with severe osteoporosis, characterized by low bone mineral density (BMD) and a history of fractures.

5. Patients with Prior Osteoporosis Treatments: Some patients who have not responded to or cannot tolerate other osteoporosis treatments may be prescribed teriparatide.[13]

Sex demographics

Women are at a significantly higher risk for osteoporosis. Half of all postmenopausal women will have an osteoporosis-related fracture during their lifetime; 25% of these women will develop a vertebral deformity, and 15% will experience a hip fracture. Risk factors for hip fracture are similar in different ethnic groups.

Men have a higher prevalence of secondary osteoporosis, with an estimated 45-60% of cases being a consequence of hypogonadism, alcoholism, or glucocorticoid excess. Only 35-40% of osteoporosis diagnosed in men is considered primary in nature. Overall, osteoporosis has a female-to-male ratio of 4:1.

Fifty percent of all women and 21% of all men older than 50 years' experience one or more osteoporosis-related fractures in their lifetime. Eighty percent of hip fractures occur in women. Women have a two-fold increase in the number of fractures resulting from non-traumatic causes, as compared with men of the same age

Teriparatide, a recombinant parathyroid hormone, is pivotal in osteoporosis treatment, particularly in post-surgical recovery for hip fractures. This study investigates its efficacy in functional

recovery post-hip fracture surgery in elderly patients, a demographic particularly susceptible to osteoporotic fractures.

In this retrospective cohort study, 150 elderly patients with proximal femoral fractures undergoing open reduction and internal fixation were enrolled. They were categorized into two groups: receiving 20 μg of daily teriparatide injections for 18 months and receiving standard antiresorptive medications during a 24-month follow-up. Detailed records of patient demographics, Fracture Risk Assessment Tool scores, and comorbidities were kept. Key outcomes, including bone mineral density (BMD) and functional scores (Barthel Index and Visual Analog Scale for hip pain), were evaluated at 3 and 24 months' post-surgery.

Out of the original cohort, 126 patients (20 men and 106 women with an average age of 85.5 ± 9.3 years) completed the study. The teriparatide group exhibited significant enhancements in both functional scores and BMD when compared to the control group. Notably, functional improvements were less pronounced in male patients compared to female patients. Additionally, the incidence of new fractures was markedly lower in the teriparatide group.

Administering teriparatide daily for 18 months' post-surgery for proximal femoral fractures significantly benefits very elderly patients by improving functionality and bone density, with observed differences in recovery between genders. These results reinforce the efficacy of teriparatide as a potent option for treating osteoporosis-related fractures in the elderly and highlight the importance of considering gender-specific treatment and rehabilitation strategies [14].***Racial demographics***

Osteoporosis can occur in persons of all races and ethnicities. In general, however, whites (especially of northern European descent) and Asians are at increased risk. In particular, non-Hispanic white women and Asian women are at higher risk for osteoporosis. In the most recent government census, 178 million Chinese were over age 60 years in 2009, a number that the United Nations estimates may reach 437 million—one-third of the population—by 2050.

These numbers suggest that approximately 50% of all hip fractures will occur in Asia in the next century. In fact, age-standardized incidence rates of fragility fractures, particularly of the hip and forearm, have been noted to be decreasing in the last decade across many countries, with the notable exception of Asia [3].

The 2020 American Association of Clinical Endocrinologists guidelines for assessing osteoporosis among postmenopausal women stratified postmenopausal women with osteoporosis to "high" and "very-high" fracture risk categories and recommended anabolic agents as initial therapy followed by an antiresorptive agent. Switching the order can blunt the effect of anabolic agents, and failing to follow with an antiresorptive can lead to loss of bone generated by the anabolic agent. It would be helpful to understand the real-world prescribing patterns of anabolic agents. Using the 2010-2015 Medicare 100% osteoporosis database, we assessed patient profiles, teriparatide prescribers, persistence of teriparatide therapy, and antiresorptive agent use after teriparatide discontinuation among elderly women who initiated teriparatide from 2011 to 2013. This study included 14,786 patients. In the year before teriparatide initiation, 30.0% of them had a fracture, 67.6% had a dual energy x-ray absorptiometry scan, 74.4% had a diagnosis of osteoporosis, and 47.9% used antiresorptive agents (non-naïve teriparatide users). Among those who had fractures, 49.4% initiated teriparatide within 3 months postfracture. Teriparatide was prescribed for 37% of users by primary care doctors, 19% by rheumatologists, 13% by endocrinologists, and 7.0% by orthopedists. Median time of teriparatide use was 7.2 months. After teriparatide discontinuation, 40.8% switched to antiresorptive agents (31.9% among naïve teriparatide users, 50.5% among non-naïve users). Among switchers, 42.5% switched within 60 days, 50.5% switched to denosumab, and 31.6% switched to oral bisphosphonates. This study of real-world prescribing data found that about half of teriparatide users switched from an antiresorptive agent, and less than half switched to antiresorptive agents after teriparatide discontinuation. Persistence of teriparatide use was suboptimal. In the management of postmenopausal osteoporosis, increasing the persistence of teriparatide use and improving the appropriate treatment sequence of anabolic and antiresorptive drugs are critical to maximizing gains in bone mass, providing the greatest protection against fractures. © 2021 American Society for Bone and Mineral Research (ASBMR) [15].

Risk factors for the disease:

Since the clinical outcome of osteoporosis is bone fracture, attention is now increasingly focused on the identification of patients at high risk of fracture rather than the identification of people with osteoporosis as defined by BMD alone.

Although osteoporosis is defined in terms of BMD and microarchitectural deterioration of bone tissue, BMD is just one component of fracture risk. Accurate assessment of fracture risk should ideally take into account other proven risk factors that add information to that provided by BMD.

- Osteoporosis has been shown in studies to have a large genetic component. A parental history of fracture (particularly hip fracture) confers an increased risk of fracture that is independent of BMD.
- Studies have provided evidence that weight in infancy is a determinant of bone mass in adulthood
- Physical inactivity and a sedentary lifestyle as well as impaired neuromuscular function (e.g., reduced muscle strength, impaired gait and balance) are risk factors for developing fragility fractures.
- Smoking can lead to lower bone density and higher risk of fracture and this risk increases with age.
- A high intake of alcohol confers a significant risk of future fracture (e.g., over 4 units of alcohol/day can double the risk of hip fracture). The risk of vertebral and hip fractures in men increases greatly with heavy alcohol intake, particularly with long term intake
- Prolonged use of corticosteroids is the most common cause of secondary osteoporosis. It is estimated that 30-50% of patients on long term corticosteroid therapy will experience fractures, with an increase in risk of hip fracture by 2-fold in women and 2.6-fold in men.
- Proton pump inhibiting drugs can reduce the absorption of calcium from the stomach and long term use of these drugs can significantly increase the risk of an osteoporosis-related fracture.
- Low body weight and weight loss is associated with greater bone loss and increased risk of fracture.
- Some young females, particularly those training for elite athletic competition, exercise too much, eat too little, and consequently experience amenorrhea which makes them at risk for low bone mass and fractures.
- After an initial low trauma fracture from a simple fall, both older men and women have an increased equivalent risk of all types of subsequent fractures, especially in the next 5-10 years.

- Middle-aged and older men and women with annual height loss >0.5 cm are at increased risk of hip and any fracture.
- Falls contribute to fractures - 90% of hip fractures result from falls. A third of people over age 65 fall annually, with approximately 10-15% of falls in the elderly resulting in fracture, and almost 60% of those who fell the previous year will fall again.
- Use of anxiolytics, sedatives, neuroleptics and antidepressants has been shown to increase risk of hip fracture

In addition to these classical risk factors, data in the literature provide indirect evidence that several co-morbidities increase osteoporosis severity. These comorbidities include inflammatory bowel and joint diseases with or without glucocorticoid therapy, breast and prostate cancer treated with chemotherapy or hormone therapy, diabetes (chiefly type 1), and celiac disease. Studies suggest an adverse impact of moderate renal failure and depression, although their methodological weaknesses preclude definitive conclusions. The underlying mechanisms are incompletely understood but may involve effects on sex steroids (hormone therapy for cancer), calcium-phosphate metabolism (celiac disease), or bone remodeling and, more specifically, bone resorption with an increased rate of bone loss and impaired trabecular network quality (chronic inflammatory diseases). In practice, these co morbidities should be taken into account when evaluating the fracture risk and making treatment decisions. Patients with one or more of these co-morbidities are candidates for intensified osteoporosis screening, a detailed risk assessment including BMD measurement and imaging studies to detect vertebral fractures, and closely spaced follow-up visits. The treatment should be intensified, if needed, based on the co-morbidity profile and fracture history [4].

Main Treatment options:

Because Teriparatide is indicated for treatment of patients with osteoporosis at high risk for fracture, patients treated with this drug are often of high clinical concern, especially since this drug has been approved for a total treatment duration limited to 24 months. Accordingly, optimal use of the drug is important to achieve the best possible outcomes. Both the biochemical and histological data suggest ongoing bone formation through 24 months, resulting in increases in bone mass, even in patients with low bone turnover induced by long-term previous anti-resorptive

treatment. Consistent with these observations, bone mass and strength increase and fracture risk decreases during longer treatment with the drug.

There are currently several medications available to treat osteoporosis. These include medications that block the breakdown of bone (anti-resorptive therapies). Examples include bisphosphonates such as alendronate (Fosamax), which is a pill, and zoledronate (Reclast), which is given intravenously. Other types of anti-resorptive agents include raloxifene (Evista) and denosumab (Prolia). enhance the formation of bone (anabolic therapies). Examples include teriparatide (Forteo) and abaloparatide (Tymlos). Treatments can be broadly divided into two categories: anti-resorptive (or anti-catabolic) and anabolic agents. A number of effective medications are approved for the prevention and treatment of osteoporosis. These medications must be tailored to a person's specific needs and used in conjunction with recommended lifestyle changes:

- Bisphosphonates
- Denosumab
- elective Estrogen Receptor Modulators (SERMS)
- Strontium ranelate
- Teriparatide
- Romosozumab
- Hormone replacement therapy (HRT)

Anti-resorptive agents, which include estrogen, selective estrogen receptor modulators and bisphosphonates, reduce bone resorption (and subsequently bone formation), preserving bone mineral density (BMD).

Anabolic agents, which include full-length parathyroid hormone (PTH1-84) and Teriparatide (PTH1-34) stimulate bone formation (and subsequently bone resorption), thereby increasing BMD. Strontium ranelate is another agent that reduces fracture risk. It has weak effects on bone remodeling and probably improves bone strength mainly through effects on bone material properties.

Now, for the first time since 2010, a new class of medication is available to treat osteoporosis. Romosozumab (Evenity) is in a class called sclerostin inhibitors and is considered an anabolic agent. Sclerostin is a protein that helps regulate bone metabolism. Produced by osteocytes (bone cells), it inhibits bone formation (making new bone). Romosozumab binds sclerostin, which keeps

it from blocking the signaling pathway for new bone formation. The result is an increase in new bone. To a lesser degree, it also decreases bone resorption (breakdown of bone). Romosozumab is approved by the FDA to treat osteoporosis in women who have completed menopause and are at high risk for fracture. A history of fracture due to osteoporosis, multiple risk factors for fracture, no success with other therapies, or being unable to tolerate other therapies are reasons to consider romosozumab [16].

Romosozumab, marketed under the brand name Evenity, is a medication used to treat osteoporosis in postmenopausal women who are at high risk of fractures. some key points about romosozumab Romosozumab is a sclerostin inhibitor. Sclerostin is a protein that inhibits bone formation. By blocking sclerostin, romosozumab increases bone formation and, to a lesser extent, decreases bone resorption (breakdown of bone). It is administered as a subcutaneous injectiononce a month. The treatment duration is typically limited to 12 months. Clinical trials have shown that romosozumab significantly reduces the risk of vertebral fractures. In one study, it reduced the risk of new vertebral fractures by 73% compared to placebo. Common side effects include headache, joint pain, and injection site reactions. However, romosozumab carries a Boxed Warning** for an increased risk of heart attack, stroke, and cardiovascular death. It should not be used in patients who have had a heart attack or stroke within the past year. Romosozumab was approved by the FDA in April 2019 and is also approved in Japan and the European Union [16].

In addition to drug therapy, calcium and vitamin D supplements can be prescribed to ensure adequate intake and to ensure maximum effectiveness of the drug therapy.
Doctors and patients should also be aware that attention to lifestyle factors must go hand in hand with any drug treatment prescribed [1].

Mortality and morbidity:

Osteoporosis is a disorder of major societal impact, and osteoporotic fractures are associated with significant disease burden, healthcare cost, morbidity and mortality. Osteoporotic fractures, particularly hip fractures, result in disability related to difficulty with ambulation and the performance of activities of daily living and are thus associated with increased nursing home and rehabilitation hospital admissions. The mortality rates for both men and women who have sustained hip or vertebral fragility fractures are increased as compared with the general population,

especially in the first year post fracture. Hip fractures cause the most morbidity with reported mortality rates up to 20-24% in the first year after a hip fracture, and greater risk of dying may persist for at least 5 years afterwards. Loss of function and independence among survivors is profound, with 40% unable to walk independently, 60% requiring assistance a year later. Because of these losses, 33% are totally dependent or in a nursing home in the year following a hip fracture. About 20-25% of hip fractures occur in men. The overall mortality is about 20% in the first 12 months after hip fracture and is higher in men than women.

Although the overall prevalence of fragility fractures is higher in women, men generally have higher rates of fracture related mortality.

As in women, the mortality rate in men after hip fracture increases with age and is highest in the year after a fracture. Over the first 6 months, the mortality rate in men approximately doubled that in similarly aged women [5].

Teriparatide is a recombinant form of parathyroid hormone (PTH) used to treat osteoporosis by stimulating new bone formation. Concerns about its safety, particularly regarding mortality, have been addressed in several studies. A meta-analysis published in the Journal of Postgraduate Medical Association (JPMA) in 2024 reviewed data from multiple randomized controlled trials involving teriparatide. The analysis found no significant difference in mortality rates between patients treated with teriparatide and those in the control group. This suggests that teriparatide does not increase the risk of death compared to other treatments for osteoporosis. However, it's important to note that individual studies may have different findings, and the overall safety profile of teriparatide should be considered in the context of each patient's medical history and risk factors. [17]

Important co-morbidities:

Osteoporosis is most common in older women. In general, women are at a higher risk than men due to naturally thinner bones and lower bone mass. A personal history of broken bones or fragility fractures in adulthood (past age 45) can indicate an increased risk of osteoporosis. Teriparatide is the only currently available therapeutic agent that increases the formation of new bone tissue and can provide some remediation of the architectural defects in the osteoporotic skeleton. The most

commonly reported adverse reactions in patients treated with Teriparatide are nausea, pain in limb, headache and dizziness.

Teriparatide is generally well-tolerated, but there are some co-morbidities and conditions that may affect its use:

1. Hypomagnesemia: Some patients treated with teriparatide may develop low magnesium levels (hypomagnesemia). This condition can be more common in older adults and those with lower baseline magnesium levels.

2. Chronic Kidney Disease (CKD): Patients with CKD may be at higher risk for adverse effects, as kidney function can affect the metabolism and excretion of the drug.

3. Gastrointestinal Disorders: Conditions that because chronic diarrhea can affect the absorption of magnesium and other nutrients, potentially exacerbating hypomagnesemia.

4. History of Parathyroidectomy: Patients who have had their parathyroid glands removed may have different responses to teriparatide treatment.

5. Diabetes: There is some evidence that diabetes may be associated with an increased risk of hypomagnesemia in patients treated with teriparatide. It's important for patients with these co-morbidities to be closely monitored by their healthcare provider while on teriparatide therapy. Regular blood tests to check magnesium levels and kidney function can help manage these risks [18].

Part II: Module SII - Non-clinical part of the safety specification

This section relies on the findings of Non-clinical safety information for FORSTEO®. CinnaGen Company has demonstrated a clinical trial comparability between P44 and FORSTEO®. Therefore, the data adequately demonstrates that P044 is expected to have clinical effectiveness and safety similar to that of FORSTEO® and it is acceptable to rely on EMA findings of FORSTEO®'s safety and effectiveness for approval of P044 for the proposed indications.

Furthermore, an open label, randomised, two-treatment, two-sequence, two-period, crossover study is conducting to assess the bioequivalence of proposed Teriparatide biosimilar, P044, for

subcutaneous injection after single dose administration of 20 mcg versus FORSTEO® 20mcg in 60 healthy female subjects.

In addition, P044 is produced in the same host cell type as the innovator product and also the same drug product formulation is used. Thus from this perspective, no special considerations are to be raised.

Table 2. Key Safety Findings

Key Safety Findings	**Relevance to Human Use**
Toxicity	
Acute or repeat-dose toxicity studies	• Teriparatide is not acutely toxic. No mortality occurred in rats given doses of 1000 mcg/kg (540 times the human dose) or in mice given 10,000 mcg/kg (2700 times the human dose) [6]. • In single-dose rodent studies using subcutaneous injection of teriparatide, no mortality was seen in rats given doses of 1000 mcg/kg (540 times the human dose based on surface area, mcg/m^2) or in mice given 10,000 mcg/kg (2700 times the human dose based on surface area, mcg/m^2). • Repeated dose toxicity studies were conducted in rat up to 6 months using doses up to 300 µg/kg/day and cynomolgus monkeys up to one-year using doses up to 10 µg/kg/day subcutaneously. Two chronic specific toxicity studies have been carried-out in Cynomolgus monkey, one evaluating special renal function (4 months of treatment with 3-months reversibility period) and one evaluating special histopathologic patterns (8 months of treatment or 12 months of treatment with 6-month reversibility period). Histological changes observed

	in renal function study are probably related to an exaggerated pharmacological effect induced by hypercalcaemia. In summary, toxicity studies revealed a similar pattern of findings, which resulted from exaggerated pharmacological effects of high doses of teriparatide. The main target organs were the bone, liver, spleen and kidney. Data suggest that the renal changes observed are secondary to increased calcium mobilisation. Since hypercalcaemia is not observed in patients at the intended clinical dose, the occurrence of kidney lesions seems unlikely. The changes are more evident in rat than in monkey. Absence of antigenic response is reported in the rodent and a weak antigenic potential is reported in the monkey. In a long-term study, skeletally mature ovariectomized female monkeys (N=30 per treatment group) were given either daily subcutaneous teriparatide injections of 5 mcg/kg or vehicle. Following the 18-month treatment period, the monkeys were removed from teriparatide treatment and were observed for an additional 3 years. The 5 mcg/kg dose resulted in systemic exposures that were approximately 6 times higher than the systemic exposure observed in humans following a subcutaneous dose of 20 mcg (based on AUC comparison). Bone tumors were not detected by radiographic or histologic evaluation in any monkey in the study [6]. • The primary effects produced by Teriparatide in repeated-dose studies in rats and monkeys up to 1 year in duration were either directly or indirectly related to the known pharmacologic actions of PTH on bone metabolism and mineral ion regulation. Systemic exposure of rats and

	monkeys to Teriparatide at the NOAELs in the chronic studies were estimated to be 2 to 5 times greater than for humans given a dose of FORTEO Injection 20 mcg/day.
Reproductive/Developmental toxicity	In a long-term study, skeletally mature ovariectomized female monkeys (N=30 per treatment group) were given either daily subcutaneous Teriparatide injections of 5 mcg/kg or vehicle. Following the 18-month treatment period, the monkeys were removed from Teriparatide treatment and were observed for an additional 3 years. The 5 mcg/kg dose resulted in systemic exposures that were approximately 6 times higher than the systemic exposure observed in humans following a subcutaneous dose of 20 mcg (based on AUC comparison). Bone tumors were not detected by radiographic or histologic evaluation in any monkey in the study. In animal reproduction studies, pregnant mice received Teriparatide during organogenesis at subcutaneous doses equivalent to 8 to 267 times the human dose (based on body surface area, mcg/m^2). At subcutaneous doses ≥ 60 times the human dose, the fetuses showed an increased incidence of skeletal deviations or variations (interrupted rib, extra vertebra or rib). When pregnant rats received Teriparatide during organogenesis at subcutaneous doses 16 to 540 times the human dose, the fetuses showed no abnormal findings. In a perinatal/postnatal study in pregnant rats dosed subcutaneously from organogenesis through lactation, mild growth retardation was observed in female offspring at doses ≥120 times the human dose. Mild growth retardation in male offspring and reduced motor activity in both male and female offspring were observed at maternal doses of 540 times the human dose [6].

	Impairment of Fertility: No effects on fertility were observed in male and female rats given subcutaneous Teriparatide doses of 30, 100, or 300 mcg/kg/day prior to mating and in females continuing through gestation Day 6 (16 to 160 times the human dose of 20 mcg based on surface area, mcg/m^2) [6].
Genotoxicity	Teriparatide was not genotoxic in any of the following test systems: the Ames test for bacterial mutagenesis; the mouse lymphoma assay for mammalian cell mutation; the chromosomal aberration assay in Chinese hamster ovary cells, with and without metabolic activation; and the in vivo micronucleus test in mice.
Carcinogenicity	Two carcinogenicity bioassays were conducted in Fischer 344 rats. In the first study, male and female rats were given daily subcutaneous Teriparatide injections of 5, 30, or 75 mcg /kg/day for 24 months from 2 months of age. These doses resulted in systemic exposures that were, respectively, 3, 20, and 60 times higher than the systemic exposure observed in humans following a subcutaneous dose of 20 mcg (based on AUC comparison). Teriparatide treatment resulted in a marked dose-related increase in the incidence of osteosarcoma, a rare malignant bone tumor, in both male and female rats. Osteosarcomas were observed at all doses and the incidence reached 40% to 50% in the high-dose groups. Teriparatide also caused a dose-related increase in osteoblastoma and osteoma in both sexes. No osteosarcomas, osteoblastomas or osteomas were observed in untreated control rats. The bone tumors in rats

	occurred in association with a large increase in bone mass and focal osteoblast hyperplasia. The second 2-year study was carried out in order to determine the effect of treatment duration and animal age on the development of bone tumors. Female rats were treated for different periods between 2 and 26 months of age with subcutaneous doses of 5 and 30 mcg/kg (equivalent to 3 and 20 times the human exposure at the 20-mcg dose, based on AUC comparison). The study showed that the occurrence of osteosarcoma, osteoblastoma and osteoma was dependent upon dose and duration of exposure. Bone tumors were observed when immature 2-month old rats were treated with 30 mcg/kg/day for 24 months or with 5 or 30 mcg/kg/day for 6 months. Bone tumors were also observed when mature 6-month old rats were treated with 30 mcg/kg/day for 6 or 20 months. Tumors were not detected when mature 6-month old rats were treated with 5 mcg/kg/day for 6 or 20 months. The results did not demonstrate a difference in susceptibility to bone tumor formation, associated with Teriparatide treatment, between mature and immature rats. The relevance of these findings to humans is not known. Osteosarcoma has not been observed in Teriparatide clinical studies.
Safety pharmacology	
cardiovascular system, including potential effect on the QT interval	Decreased blood pressure and increased heart rate were observed in conscious rat and dog models reflecting Teriparatide-induced vasodilation. The no observed effect level (NOEL) for cardiovascular changes in the rat was 4.3 μg/kg of Teriparatide. In female dog a decrease of arterial pressure and

	increase of left ventricular inotropic state and heart rate were observed after treatment with 6-µg/kg/day doses. A quantitative assessment of ECG data after repeated-dose (toxicological studies) in monkey did not show any effects on cardiac conduction, re-polarisation (QTc) or production of cardiac arrhythmia.
nervous system	In male adult mice, Teriparatide at doses 100 µg/kg did not produce secondary pharmacology effect related to central nervous system and behavioural functions such as changes in body temperature, ambulatory and non-ambulatory activity levels, central nervous system depression, and convulsive thresholds.
Other toxicity-related information or data	
The tumorigenic effect of PTH in selected animal species	Seems to be specific to skeletal tissue. No increase in nonskeletal tissue has been reported, also when evaluating data coming from clinical trials. In clinical practice, the history of any cancer in the past 5 years represents a contraindication to the use of PTH. The rationale behind this relates to the possible presence of PTH receptors in malignant cells. However, the 5-year limitation is hard to explain in light of the finding showing that dormant cancer cells may persist lifelong in niches [7].
Determination the effect of treatment duration and animal age on the development of bone tumors	Female rats were treated for different periods between 2 and 26 months of age with subcutaneous doses of 5 and 30 mcg/kg (equivalent to 3 and 20 times the human exposure at the 20-mcg dose, based on AUC comparison). The study showed that the occurrence of osteosarcoma, osteoblastoma and osteoma was dependent upon dose and duration of exposure. Bone tumors were observed when immature 2-month old rats were treated

	with 30 mcg/kg/day for 24 months or with 5 or 30 mcg/kg/day for 6 months. Bone tumors were also observed when mature 6-month old rats were treated with 30 mcg/kg/day for 6 or 20 months. Tumors were not detected when mature 6-month old rats were treated with 5 mcg/kg/day for 6 or 20 months. The results did not demonstrate a difference in susceptibility to bone tumor formation, associated with Teriparatide treatment, between mature and immature rats [8]. The relevance of these rat findings to humans is uncertain.
Rat toxicology findings of osteosarcoma	Most of the problems related to the safety of rhPTH 1-34 administration are related to data obtained in rats. Indeed, during a 2-year carcinogenicity study, a 26% incidence of osteosarcoma in 360 Fischer 344 rats was reported. Of note, the doses administrated were 5, 30, or 75 µg/kg/day, beginning at 6 weeks of age for up to 2 years' duration. A 2-year exposure in rats represents most of the life span of these animals; secondly, the doses used are very large (3-fold to 58-fold) compared with the doses used in human patients. Interestingly osteosarcoma did not develop in nonhuman primates (cynomolgus monkeys) with exposure to approximately eight times the human dose [9], mainly because their skeletal biology is similar to that of humans [10]. Without discussing this specific effect of huge administration of PTH in rats and mice in greater detail, it appears that similar problems are not encountered in human beings. Important differences between the rat study and clinical use in adult humans suggest that the increased incidence of bone neoplasia in rats treated for 2 years is likely not predictive of an increased risk of bone cancer in skeletally mature adult humans being

	given PTH(1-34) for a limited period of time in the treatment of osteoporosis.

Part II: Module SIII - Clinical trial exposure

This section relies on the findings of safety and effectiveness for FORSTEO® for the proposed indications. CinnaGen Company has demonstrated a clinical trial comparability between P044 and FORSTEO®. Therefore, the data adequately demonstrates that P044 is expected to have clinical effectiveness and safety similar to that of FORSTEO® and it is acceptable to rely on findings of FORSTEO®'s safety and effectiveness for approval of P044 for the proposed indications.
Additionally, an open label, randomised, two-treatment, two-sequence, two-period, crossover study conducted to assess the bioequivalence of proposed Teriparatide biosimilar, P044, for subcutaneous injection after single dose administration of 20 mcg versus FORSTEO® 20mcg in 60 healthy female subjects.

Clinical studies of FORSTEO®:

FORSTEO has been studied in three main studies. The first study involved 1637 women with osteoporosis who had been through the menopause (average age: 69.5 years), in which FORSTEO was compared with placebo (a dummy treatment) for an average of 19 months. The main measure of effectiveness was the number of new vertebral fractures at the end of the study, although the study also looked at non-vertebral fractures. The patients were treated for up to 23 months. The second study looked at the use of FORSTEO in 437 men with osteoporosis, comparing its effect on the density of bones in the spine with that of placebo. The third study compared the effects of FORSTEO and alendronate (another medicine used to treat osteoporosis) on spine bone density over three years. The study included 428 women and men who had osteoporosis and had been taking glucocorticoids for at least three months. An additional study looked at the effects of FORSTEO on bone density over two years in 234 women who had been through the menopause.

The safety and efficacy of FORSTEO® [Teriparatide (rDNA origin) injection] once-daily for up to 24 months (median: 19 months), were examined in a double-blind, placebo-controlled clinical study of 1637 postmenopausal women (mean age: 69.5 years) with severe osteoporosis (mean Tscore: -2.6). Among these women, 541 received FORSTEO® 20 mcg. All women received 1000 mg of calcium per day and at least 400 IU of vitamin D per day. Ninety percent of the women in the study had 1 or more radiographically diagnosed vertebral fractures at baseline. The primary

efficacy endpoint was the occurrence of new radiographically diagnosed vertebral fractures defined as changes in the height of previously undeformed vertebrae.

Table 3. Summary of Patient Demographics for FORSTEO® Clinical Trials in Postmenopausal Women with Osteoporosis.

Trial design Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Double-blind, placebo-controlled	Placebo, FORSTEO® 20 mcg, or teriparatide 40 mcg, subcutaneous injection, once daily. Up to 24 months (median: 19 months)	69.5 years (42 to 86 years)	Women

Effect on fracture incidence

New vertebral fractures - FORSTEO®, when taken with calcium and vitamin D and compared with calcium and vitamin D alone, significantly reduced the risk of 1 or more new vertebral fractures from 14.3% of women in the placebo group to 5.0% in the FORSTEO® group ($p<0.001$). The absolute reduction in risk was 9.3% and the relative reduction was 65%. Eleven women would need to be treated with FORSTEO® for a median of 19 months to prevent one or more new vertebral fractures. FORSTEO® was effective in reducing the risk for vertebral fractures regardless of age, baseline rate of bone turnover, or baseline bone mineral density (BMD).

Table 4. Effect of FORSTEO® on Vertebral Fracture Incidence in Postmenopausal Women with Osteoporosis.

	Placebo (N=448) (%)	FORSTEO® (N=444) (%)	Absolute Risk Reduction (%)	95% CI (%)	P-Value
New fracture (≥ 1)	14.3	5.0	9.3	(5.3, 13.4)	<0.001
Multiple fractures (≥ 2)	4.9	1.1	3.8	(1.3, 6.2)	0.001
Moderate or severe fracture (≥ 1)	9.4	0.9	8.5	(5.4, 11.5)	<0.001

Effect on height loss - Both treatment groups lost height during the trial. The mean decreases were 3.61 and 2.81 mm in the placebo and FORSTEO® groups, respectively. For the 86 postmenopausal women who experienced vertebral fractures, those treated with FORSTEO® had significantly less height loss when compared to placebo ($p = 0.001$).

Post- treatment fracture efficacy - Following treatment with FORSTEO®, 1262 postmenopausal women from the pivotal trial enrolled in a post-treatment follow-up study. After 18 months, approximately 50% of the women in each former treatment group had begun an approved

osteoporosis therapy (not including FORSTEO®) at the discretion of their physician. All women were offered 1000 mg of calcium per day and at least 400 IU of vitamin D per day. During a median of 18 months following discontinuation of FORSTEO® treatment, there was a significant 40% reduction in relative risk for new vertebral fractures in women previously treated with FORSTEO®, compared to placebo. (The relative risk reduction was similar for women with and without osteoporosis treatment, 41% and 37%, respectively). During the same observation period, there was a 42% risk reduction for nonvertebral fragility fractures in women previously treated with FORSTEO®, compared with placebo.

Treatment to Increase Bone Mass in Men with Primary or Hypogonadal Osteoporosis Study demographics and trial design

The safety and efficacy of FORSTEO® once-daily for up to 14 months (median: 10 months) were examined in a double-blind, placebo-controlled clinical study of 437 men (mean age: 58.7 years) with either primary (idiopathic) or hypogonadal osteoporosis (FORSTEO® 20 mcg, n=151). All men received 1000 mg of calcium per day and at least 400 IU of vitamin D per day. The primary efficacy endpoint was change in lumbar spine bone mineral density (BMD).

Table 5. Summary of Patient Demographics for Clinical Trials in Men with Primary or Hypogonadal Osteoporosis.

Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Double-blind, placebo-controlled	Placebo, FORSTEO® 20 mcg, or teriparatide 40 mcg, subcutaneous injection, once daily. Up to 14 months (median: 10 months)	Primary (idiopathic) or hypogonadal osteoporosis (437)	58.7 years (28 to 85 years)	men

Treatment of Men and Women with Glucocorticoid-Induced Osteoporosis Study demographics and trial design

Glucocorticoid-induced osteoporosis affects both men and women. Loss of BMD occurs early after the initiation of glucocorticoid therapy and may continue during sustained glucocorticoid therapy. The safety and efficacy of once-daily FORSTEO® were examined in a multicenter, randomized, double-blind, double-dummy, active comparator-controlled study of 83 men and 345 women taking systemic glucocorticoid medications (prednisone equivalent ≥5 mg/day for ≥3 consecutive months prior to screening) and had a BMD T-score of ≤-2 at the total hip, femoral neck, or lumbar spine, or had ≥1 fragility fracture and a BMD T-score of ≤-1 at the total hip,

femoral neck, or lumbar spine. Patients received either FORSTEO® 20 mcg/day plus oral placebo (N=214) or alendronate 10 mg/day plus injectable placebo (N=214). Patients received supplemental calcium 1000 mg/day and vitamin D 800 IU/day. The mean age of patients with glucocorticoid-induced osteoporosis was 57 years (range 22-89). The baseline median glucocorticoid dose (prednisone equivalent) was 7.5 mg and the median duration of glucocorticoid use was 1.3 years. The mean (SD) baseline lumbar spine BMD was 0.85 ± 0.13 g/cm2 and T-score was -2.5 ± 1. A total of 27% of patients had prevalent vertebral fracture(s) and 43% had prior non-vertebral fracture(s). The patients had chronic diseases that required sustained glucocorticoid therapy including 73% with rheumatologic or other joint and musculoskeletal disorders, and 14% with respiratory disorders. There was no significant difference in these baseline characteristics between the FORSTEO® and alendronate groups.

Table 6. Summary of Patient Demographics for Clinical Trial in Men and Women with Glucocorticoid-Induced Osteoporosis

Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Double-blind, active comparator controlled	Placebo (oral and injection), FORSTEO® 20 mcg/day by subcutaneous injection, once daily, Alendronate 10 mg/day, oral Duration 36 months: Primary phase - 18 months; continuation phase - 18 months	Glucocortico idinduced osteoporosis (428)	57 years (range 22- 89)	Men and Women

2-Year Continuous Treatment of Osteoporosis in Postmenopausal Women with FORSTEO®

The 24-month study, was a multinational, multicenter, outpatient, prospective, open-label, Phase 3/4 trial in postmenopausal women with severe osteoporosis and ≥1 clinical fragility fracture (76% had received antiresorptive drugs). This study had 2 substudies in which all patients received FORSTEO® 20 mcg/day during the first 12 months.

Table 7. Summary of Patient Demographics for Clinical Trial of 24 month Continuous Treatment with FORSTEO®

Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Multicenter, prospective, open-label phase 3/4 trial, 2 substudies. Substudy 1: randomized with 3 treatment arms. Substudy 2: all patients receiving FORSTEO® for 24 months	FORSTEO® 20 mcg/day for 24 months in substudy 1 treatment arm 1 and substudy 2, and for 12 months in substudy 1 treatment arms 2 and 3. raloxifene HCL 60 mg/day for the second 12 months in substudy 1 treatment arm 2. All patients supplemented with 500 mg/day elemental calcium and 400 to 800 IU/day vitamin D;	Substudy 1: 632 Substudy 2: 234 (Total:866)	69.9 years (range 55-92.1)	Postmenopausal women

Clinical studies of P044

P044 pre-filled pen was first marketed in Iran in February 2017.

The strength of P044 is 20 µg/80 µL and there are no other doses available. This medicinal product is only administered subcutaneously (SC).

A randomized double-blind parallel non-inferiority phase 3 clinical trial have been conducted in 2012 in order to compare the efficacy and safety of CinnoPar® (CinnaGen, Iran) with the reference drug (FORSTEO®, Elli Lilly, USA) in the treatment of postmenopausal osteoporotic women, which was the CinnaGen-sponsored interventional study (IRCT registration number: IRCT138810121414N5). 104 eligible patients were enrolled in the study, receiving 20 µg Teriparatide daily for six months. All of them were women aged between 42 and 81 years of age. 52 patients were assigned to each group A (getting FORSTEO®) and 52 patients were assigned to group B (getting CinnoPar®). 94 patients completed the trial (45 in group A and 49 in group B).

Table 8. Estimated cumulative exposure from clinical trials

Treatment	Number of subjects
Medicinal product (CinnoPar®)	49
Comparator (FORSTEO®)	45
Placebo	0

Table 9. Duration of Exposure

Indication: Improvement of bone mineral densitometry (BMD) among Osteoporotic patients.		
Duration of Exposure (at least)	**Persons**	**Person time (patient months)**
1m	3	3
6m	49	294
Total person time	297	

Table 10. Age group and gender

Indication: Improvement of bone mineral densitometry (BMD) among Osteoporotic patients.		
Product: CinnoPar®		
Age group	**Persons**	
	M	**F**
40-49	0	2
50-59	0	26
60-69	0	19
70-79	0	2

Table 11. Applied dose of Teriparatide

Indication: Improvement of bone mineral densitometry (BMD) among Osteoporotic patients.		
Dose of exposure	**Persons**	**Person time (patient-months)**
20 mcg/daily	52	297

In addition, there is one phase I clinical trial with P044. This study is an open label, randomised, two-treatment, two-sequence, two-period, crossover study that assess the bioequivalence of proposed Teriparatide biosimilar, P044, for subcutaneous injection after single dose administration of 20 mcg versus FORSTEO® 20mcg in 60 healthy female subjects (EudraCT number: 2019-004477-82). This purpose of this study is to compare the pharmacokinetics, pharmacodynamics, relative bioavailability, tolerability and safety after a single dose administration of both Test and Reference formulations of Teriparatide in 60 healthy female volunteers under fasting conditions.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Phase 3 clinical trial for CinnoPar® was conducted in 2012. In this clinical trial, 104 patients with postmenopausal osteoporosis were randomized into two groups. 52 patients were assigned to FORSTEO®, and 52 patients were assigned to CinnoPar® but finaly 94 patients were analyzed. Exclusion criteria for this study were:

1. The lack of patient`s informed consent or prediction for missed to follow up
2. The history of taking antiabsorptive drug such as bisphosphonate, estrogen, raloxifen, calcitonin
3. Long time glucocorticoid consumption
4. The existence of disease or treatment which interact with bone metabolism or treatment process
5. Malignancy within five recent years
6. Autoimmune disease
7. Chemotherapy
8. Radiotherapy
9. Epilepsy under treatment
10. Serum Ca > 10 mg/dl
11. PTH taking HX
12. Strontium
13. Recurrent urinary tract stone
14. End stage liver disease
15. End stage kidney disease
16. Malabsorption
17. Hyperparathyroidism
18. Hypoparathyroidism
19. Hyperthyroidism
20. Gout
21. Serum uric acid > 7.5 mg/dl

In addition, there is EU conducted phase I clinical trial with P044. This study is an open label, randomised, two-treatment, two-sequence, two-period, crossover study that assess the bioequivalence of proposed Teriparatide biosimilar, P044, for subcutaneous injection after single dose administration of 20 mcg versus FORSTEO® 20mcg in 60 healthy female subjects. A potential subject who meets any of the following criteria will be excluded from participation in this study:

1. Postmenopausal women (Postmenopausal status is defined as age above 45 years and 12 consecutive months without menstrual period)
2. Subjects with clinically significant abnormalities in the ECG at screening.
3. Subjects with abnormal supine blood pressure (BP) at screening, including:
   - Presence of hypotension, defined as systolic blood pressure below 85 mmHg and diastolic pressure below 50 mmHg at screening.
   - Presence of hypertension, defined as systolic blood pressure above 140 mmHg and diastolic pressure above 90 mmHg at screening.
   - Heart rate > 100 beats per minute or < 40 beats per minute, measured at screening.
4. History of orthostatic hypotension.
5. Clinically significant abnormal biochemistry or haematology values as judged by the Investigator, including detected unexplained elevation of alkaline phosphatase.
6. Evidence for thyroid disease at screening, based on clinical and safety laboratory findings, including thyroid-stimulating hormone (TSH).
7. Relevant history or presence of disease of any major system organ class (e.g. cardiovascular, pulmonary, renal, hepatic, gastrointestinal, reproductive, endocrinological, neurological, psychiatric or orthopedic disease) as judged by the Investigator.
8. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the subject in case of participation in the study. The Investigator should make this determination in consideration of the subject's medical history and/or clinical or laboratory evidence of any of the following:
   - History or presence of liver disease or liver injury as indicated by abnormal liver function tests such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-

glutamyl transferase (GGT), alkaline phosphatase (ALP), or total serum bilirubin elevated more than ≥ 1.5 fold upper limit of normal. Any single parameter elevated ≥ 1.5 fold upper limit of normal should be re-checked once prior to enrolment/randomization.

- Moderate or severe chronic kidney disease with an estimated glomerular filtration rate (eGFR), calculated by using the modification of diet in renal disease (MDRD) equation, < 60 mL/min/1,73m^2.

9. History or presence of hypercalcaemia.
10. Active or recent urolithiasis.
11. History or presence of metabolic bone diseases (including hyperparathyroidism and Paget's disease of the bone).
12. History of skeletal malignancies or bone metastases.
13. History of prior external beam or implant radiation therapy involving the skeleton.
14. History or presence of immunodeficiency diseases including a positive human immunodeficiency virus (HIV) test result, positive hepatitis B antigen or hepatitis C test result.
15. Hypersensitivity to the active substances or to any of the excipients of the investigational medicinal products.
16. Administration of any investigational drug less than 30 days of screening visit and during the study period or intention to enrol in any active study involving the use of investigational devices or drugs; Depending on the nature of the previous investigational drug, a longer washout may be needed.
17. Previous treatment, including for investigational purposes, with any products (e.g., FORSTEO®, Natpara) derived from human parathyroid hormone (PTH).
18. Subject unable to abstain from regular use of any medication (including prescription drugs, over-the-counter drugs, dietary supplements, and herbal remedies like St. John's Wort) from 2 weeks before the Screening Visit and anticipated use during the course of the trial, excluding oral contraceptives in women of childbearing potential, sporadic use of paracetamol and topical medications or nasal sprays without systemic effect.
19. History of any drug or alcohol abuse in the past 2 years;

Alcohol abuse is defined as use of > 14 units per week for females (one unit of alcohol is equal to 240 mL beer (5 %) or 100 mL wine (12 %) or spirits (42.5 g of 40 % volume spirit).

20. Blood donation (greater than or equal to 500 mL) within 3 months prior to Day 1 of Treatment Period 1 or intention to donate blood in the 3 months after completing the study;
21. Female subjects who are pregnant or have a positive pregnancy test result, currently breast-feeding, or planning to become pregnant during the course of the study.
22. Subjects without suitable veins for multiple venepunctures/cannulation as assessed at screening;
23. Any other condition or circumstance that, in the judgment of the Investigator, might increase the risk to the subject or decrease the chance of obtaining satisfactory data to achieve the objectives of the study.
24. Intellectual incapacity or inability to comprehend, precluding adequate understanding or co-operation.
25. Previous completion or withdrawal from this study.
26. Sponsor, the Contract Research Organization (CRO) or Investigator's site personnel directly affiliated with this study.

Effect of exclusion criteria in the clinical trial development plan

Table 12. Exclusion criteria, which will remain as contraindications

Criteria	Implications for target population
Hypersensitivity to the active substance or to any of the excipients in drug formulation	The known adverse reaction profile of P044 includes allergic reactions or hypersensitivity to the active substance or to any of the excipients. Reactions have included angioedema and anaphylaxis. If allergic-anaphylactic reactions occur, the administration of CinnoPar® has to be discontinued immediately (e.g. discontinue injection) and an appropriate treatment has to be initiated.
Pregnancy and breast-feeding	Adverse events were observed in animal studies at doses more than 60 times the human dose; the effect on human fetal development has not been studied. Teriparatide is not indicated for use in pregnant or premenopausal women. There are no adequate and well-controlled studies of Teriparatide in pregnant women. Teriparatide is contraindicated for use during breast-feeding. It is not known whether Teriparatide is excreted in human milk.
Pre-existing hypercalcaemia	In normocalcaemic patients, slight and transient elevations of serum calcium concentrations have been observed following Teriparatide injection. Serum calcium concentrations reach a maximum between 4 and 6 hours and return to baseline by 16 to 24 hours after each dose of Teriparatide.

Severe renal impairment	Teriparatide must not be used in patients with severe renal impairment. In patients with moderate renal impairment, Teriparatide should be used with caution. No special caution is required for patients with mild renal impairment. Since very limited data on Teriparatide use in patients with renal impairment exists, more studies with large sample size should be conducted to evaluate the safety and efficacy of Teriparatide in these patients. In 5 patients with severe renal impairment (CrCl<30 mL/min), the AUC and T1/2 of teriparatide were increased by 73% and 77%, respectively. Maximum serum concentration of teriparatide was not increased.
Metabolic bone diseases	Patients with metabolic bone diseases other than osteoporosis should not be treated with Teriparatide because of the potential to exacerbate this condition.
Unexplained elevations of alkaline phosphatase	if you have unexplained high levels of alkaline phosphatase in your blood, which means you might have Paget's disease of bone (disease with abnormal bone changes).
Prior external beam or implant radiation therapy to the skeleton	Teriparatide should not be prescribed for patients at increased baseline risk for osteosarcoma include prior external beam or implant radiation therapy involving the skeleton.
Patients with skeletal malignancies or bone metastases should be excluded from treatment with Teriparatide.	Patients with bone metastases or a history of skeletal malignancies should not be treated with Teriparatide.

Table 13. Exclusion criteria which are NOT proposed to remain as contraindications

Criteria	Reason for being an exclusion criterion	Justification for not being a contraindication
Advanced hepatic impairment	Since no studies have been performed in patients with hepatic impairment, it is not recommended to use Teriparatide in patient with advance hepatic impairment.	Teriparatide is not hepatotoxic. It is metabolized by non-specific enzymatic pathways in the liver and in hepatic impairment, drug elimination may be reduced but it is not specific and significant.
History of recurrent urolithiasis	Teriparatide should be used with caution in patients with active or recent urolithiasis because of the potential to exacerbate this condition.	In clinical trials, the frequency of urolithiasis was similar in patients treated with Teriparatide and placebo. However, Teriparatide has not been studied in patients with active urolithiasis.
Hypercalciuria with the calcium/creatinine ratio equal to 1 or more	Teriparatide should be used with caution in patients with pre-existing Hypercalciuria or active urolithiasis because of the potential to exacerbate this condition.	Teriparatide may cause small increases in urinary calcium excretion, but the incidence of hypercalciuria did not differ from that in the placebo-treated patients in clinical trials.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The safety of teriparatide has been evaluated in 24 clinical trials that enrolled over 2800 women and men. Four long-term, Phase 3 clinical trials included one large placebo-controlled, double-blind multicentre trial with 1637 postmenopausal women, one placebo-controlled, double-blind multicentre trial with 437 men, and two active-controlled trials including 393 postmenopausal women. A total of 1943 of the patients studied received teriparatide, including 815 patients at 20

mcg/day and 1107 patients at 40 mcg/day. In the long-term clinical trials, 1137 patients were exposed to teriparatide for greater than 1 year (500 at 20 mcg/day and 637 at 40 mcg/day). The maximum exposure duration to teriparatide was 2 years. Adverse events associated with FORSTEO® [teriparatide (rDNA origin) injection] usually were mild and generally did not require discontinuation of therapy.

The safety of teriparatide has also been evaluated in a Phase 3 randomized, double blind, doubledummy, active controlled clinical trial that enrolled 428 men and women with glucocorticoidinduced osteoporosis. Patients received either FORSTEO® 20 mcg/day plus oral placebo (n=214) or alendronate 10 mg/day plus injectable placebo (n=214) for up to 3 years.

An additional Phase 3, randomized, multinational, multicenter, open-label study that enrolled 868 patients evaluated safety and efficacy of up to 24 months continuous treatment with 20 mcg/day of FORSTEO®.

Table 14 lists adverse events occurring in the Phase 3, placebo-controlled clinical trials in postmenopausal women and in men at a frequency ≥ 2.0% in the FORTEO® groups and in more FORTEO®-treated patients than in placebo-treated patients. Adverse events are shown without attribution of causality.

Table 14. Adverse Events in Placebo-Controlled Clinical Trials for FORSTEO® (Irrespective of Causality)

Body System	% Patients	
	FORTEO	Placebo
	(N=691)	(N=691)
BODY AS A WHOLE		
Pain	21.3	20.5
Headache	7.5	7.4
Asthenia	8.7	6.8
Neck Pain	3	2.7
CARDIOVASCULAR		
Hypertension	7.1	6.8
Angina Pectoris	2.5	1.6
Syncope	2.6	1.4
DIGESTIVE SYSTEM		
Nausea	8.5	6.7
Constipation	5.4	4.5
Diarrhea	5.1	4.6

Dyspepsia	5.2	4.1
Vomiting	3	2.3
Gastrointestinal Disorder	2.3	2
Tooth Disorder	2	1.3
METABOLIC		
Hyperuricemia	2.8	0.7
MUSCULOSKELETAL		
Arthralgia	10.1	8.4
Leg Cramps	2.6	1.3
NERVOUS SYSTEM		
Dizziness	8	5.4
Depression	4.1	2.7
Insomnia	4.3	3.6
Vertigo	3.8	2.7
RESPIRATORY SYSTEM		
Rhinitis	9.6	8.8
Cough Increased	6.4	5.5
Pharyngitis	5.5	4.8
Dyspnea	3.6	2.6
Pneumonia	3.9	3.3
SKIN AND APPENDAGES		
Rash	4.9	4.5
Sweating	2.2	1.7

[a] Treatment emergent adverse events that occurred at a frequency ≥2% in patients treated with FORTEO® at 20 mcg/day irrespective of causality assessment by Clinical Study Investigators.

Therefore, there are a wealth of knowledge on teriparatide and this section relies on the findings of adverse reactions for FORSTEO®. CinnaGen Company has demonstrated a clinical trial comparability between P044 and FORSTEO®. The data adequately demonstrates that P044 is expected to have clinical effectiveness and safety similar to that of FORSTEO®. In this study 104

eligible patients were enrolled in the study, receiving 20 µg Teriparatide daily for six months. All of them were women aged between 42 and 81 years of age. 52 patients were assigned to each group A (getting FORSTEO®) and 52 patients were assigned to group B (getting P044).

Table 15. Ability to detect adverse reactions

Ability to detect adverse reactions	Limitation of trial programmes	Discussion of implications for target population
Rare ADRs	52 patients were exposed to CinnoPar® over the whole clinical trial program. Common, uncommon, rare and very rare ADRs could not have been detected.	ADRS with a frequency greater than 1 in 100 could be detected if there were no background incidence.
Due to prolonged exposure	49 patients were exposed to CinnoPar® for 6 months. No serious ADR was detected. CinnoPar® has an acceptable safety profile.	Serious ADRs are not common with CinnoPar® in 6 months of follow-up. The patients receiving CinnoPar® should be monitored for longer periods.
Due to cumulative effects	Specific organ toxicity has not been detected for CinnoPar®.	Serious ADRs are not common with CinnoPar® after 6 months of follow-up. The patients receiving CinnoPar® should be monitored for longer periods.
Which have a long latency	During 6 months follow-up serious adverse effects were not common in patients receiving CinnoPar®.	Follow-up of patients was not more than 6 months. So, the adverse drug reactions which have a long latency are not detected. However, such ADRs have not been detected for CinnoPar® during 4 years of post-marketing experience.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programs

This section discusses populations that are under-represented in the clinical trial programme and their relevance to the safety evaluation, especially regarding their potential to constitute contraindications or warnings (or not). It should be noted that many exclusion criteria were defined to avoid confounding of the efficacy or safety evaluations.

Type of special population	Exposure

Pregnant women	There are no available data on teriparatide use in pregnant women to evaluate for drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, teriparatide increased skeletal deviations and variations in mouse offspring at subcutaneous doses equivalent to more than 60 times the recommended 20 mcg human daily dose (based on body surface area, mcg/m2), and produced mild growth retardation and reduced motor activity in rat offspring at subcutaneous doses equivalent to more than 120 times the human dose.
Breastfeeding women	It is not known whether teriparatide is excreted in human milk, affects human milk production, or has effects on the breastfed infant. Because of the potential for osteosarcoma shown with teriparatide in animal studies, teriparatide is contraindicated in breastfeeding patients.
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	• No studies have been performed in patients with hepatic impairment. Non-specific proteolytic enzymes in the liver (possibly Kupffer cells) cleave PTH(1-34) and PTH(1-84) into fragments that are cleared from the circulation mainly by the kidney. • In 5 patients with severe renal impairment (CrCl<30 mL/min), the AUC and T1/2 of teriparatide were increased by 73% and 77%, respectively. Maximum serum concentration of teriparatide was not increased. No studies have been performed in patients undergoing dialysis for chronic renal failure. Teriparatide is contraindicated in patients with severe renal impairment and caution should be exercised in patients with moderate renal impairment. • Spinal diseases are becoming more prevalent among the elderly, diabetics, and other immunocompromised patients. A growing number of these patients are also developing pyogenic spondylitis. There are no available data on teriparatide use in immunocompromised patients.

	• There are no available data on teriparatide use in patients with a disease severity different from inclusion criteria in clinical trials.
Population with relevant different ethnic origin	Because teriparatide meets most of the criteria for being less likely to be sensitive to intrinsic and extrinsic ethnic factors, similar efficacy and safety are expected in other populations [11].
Subpopulations carrying relevant genetic polymorphisms	Genetic factors mainly impact bone mineral density (BMD). No studies have been performed in subpopulations carrying relevant genetic polymorphisms.
Other	• Urolithiasis: Teriparatide has not been studied in patients with active urolithiasis. Teriparatide should be used with caution in patients with active or recent urolithiasis because of the potential to exacerbate this condition. • Bone Metastases and Skeletal Malignancies: Patients with skeletal malignancies or bone metastases should be excluded from treatment with Teriparatide. • Metabolic Bone Diseases: Metabolic bone diseases (including hyperparathyroidism and Paget's disease of the bone) other than primary osteoporosis or glucocorticoid-induced osteoporosis • Hypercalcemia and Hypercalcemic Disorders: Teriparatide has not been studied in patients with pre-existing hypercalcemia. These patients should not be treated with Teriparatide because of the possibility of exacerbating hypercalcemia. Patients known to have an underlying hypercalcemic disorder, such as primary hyperparathyroidism, should not be treated with Teriparatide.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

CinnoPar® is produced in 2.4 mL pen containing 600 mcg of Teriparatide (20 mcg/80 mcL). Each pen provides 28 subcutaneous injections (80 microliters (0.08 mL) or 20 mcg per injection). By considering that each patient uses 1 pen of CinnoPar® per month, it can be estimated how many patients have been exposed to CinnoPar® in one year.

SV.1.2 Exposure

In Iran, CinnoPar® is approved to treat osteoporosis as in following indications:
Teriparatide is indicated in adults.

- Treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture. In postmenopausal women, a significant reduction in the incidence of vertebral and non-vertebral fractures but not hip fractures has been demonstrated.
- Treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture.

The recommended dose for CinnoPar® is 20 mcg which is administrated subcutaneously once a day for maximum 2 years in the patient life time.
CinnoPar® is only available as 2.4 mL pen containing 600 mcg of Teriparatide (20 mcg/80 mcL) for subcutaneous injection.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes:

There have been no spontaneous reports of drug abuse received for CinnoPar®. At present, no potential for misuse or illegal use has been identified.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

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

Nervous system disorders: Dizziness, headache.

Musculoskeletal and connective tissue disorders: Pain in limb, Muscle cramps.

Ear and labyrinth disorders: Vertigo

Skin and subcutaneous tissue disorders: Sweating increased

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

Immune System Disorder: Anaphylaxis

Metabolism and nutrition disorders: hyperuricaemia

Cardiac disorders: Tachycardia

Respiratory, thoracic and mediastinal disorders: Emphysema

Gastrointestinal disorders: Haemorrhoids

Musculoskeletal and connective tissue disorders: Myalgia, arthralgia, back cramp/pain

Renal and urinary disorders: Renal failure/impairment

General disorders and administration site conditions: Injection site erythema, injection site reaction, Possible allergic events soon after injection: acute dyspnoea, oro/facial oedema, generalised urticaria, chest pain, oedema (mainly peripheral)

Investigations: Weight increased, cardiac murmur, alkaline phosphatase increase

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

Blood and lymphatic system disorders: Anaemia

Metabolism and nutrition disorders: Hypercholesterolaemia

Psychiatric disorders: Depression

Nervous system disorders: sciatica, syncope

Cardiac disorders: Palpitations

Respiratory, thoracic and mediastinal disorders: Dyspnoea

Gastrointestinal disorders: Nausea, vomiting, hiatus hernia, gastro-oesophageal reflux disease.

Renal and urinary disorders: Urinary incontinence, polyuria, micturition urgency, nephrolithiasis.

General disorders and administration site conditions: Fatigue, chest pain, asthenia, mild and transient injection site events, including pain, swelling, erythema, localised bruising, pruritus and minor bleeding at injection site

Known risks that do not impact the risk-benefit profile:

None.

Other reasons for considering the risks not important:

None.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Details of important identified and potential risks from clinical development, post-authorisation experience and literature for teriparatide are presented below:

Important identified risks:

None.

Important Potential Risks:

None.

Missing information:

None.

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

Not applicable.

Part II: Module SVIII - Summary of the safety concerns

The safety concerns associated with the use of CinnoPar® in the intended indications are summarized in the following Table:

Table 16. Summary of safety concerns

Important Identified risks	None
Important Potential risks	None
Missing information	None

Part III: Pharmacovigilance Plan

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.

III.1.1. Specific adverse reaction follow-up questionnaires for safety concerns

None.

III.1.2. Other forms of routine pharmacovigilance activities for safety concerns

None.

III.2 Additional pharmacovigilance activities

Not applicable.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorization efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

V.1. Routine Risk Minimisation Measures

Not applicable.

V.2. Additional Risk Minimisation Measures

Not applicable.

V.3 Summary table of risk minimisation measures

Not applicable.

Part VI: Summary of the risk management plan

Summary of risk management plan for Zandoriah (Teriparatide)

VI.I The medicine and what it is used for

Zandoriah is recombinant human parathyroid hormone (PTH), and is also called rhPTH (1-34). It has an identical sequence to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone. Teriparatide (recombinant human parathyroid hormone) is a potent anabolic agent used in the treatment of osteoporosis. Zandoriah (teriparatide) has a molecular weight of 4117.8 Daltons.

Zandoriah is administrated for the following indications:
Teriparatide is indicated in adults.

- Treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture. In postmenopausal women, a significant reduction in the incidence of vertebral and non-vertebral fractures but not hip fractures has been demonstrated.
- Treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture.

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

Measures to minimize the risks identified for medicinal products can be:
Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and summary of product characteristics addressed to patients and healthcare professionals;
Important advice on the medicine's packaging;
The authorized 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 minimize its risks.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed, including Periodic Safety Update Report assessment, so that immediate action can be taken as necessary.

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

VI.II.A List of important risks and missing information

Important risks are risks of Zandoriah 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 Zandoriah. Potential risks are concerns for which an association with the use of this medicine is possible based available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important Identified risks	None.
Important Potential risks	None.
Missing information	None.

VI.II.B Summary of important risks

Not applicable.

VI.II.C. Post-authorisation development plan

VI.II.C.1. Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Zandoriah.

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

There are no studies required for Zandoriah.

Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.