1 SCIENTIFIC DISCUSSION

1.1 Introduction

Postmenopausal osteoporosis (PMO) is a common disorder affecting a large number of women above the age of 50 years. It is currently defined as a systemic skeletal disease characterised by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk. Osteoporosis affects an estimated 75 million people in Europe, United States and Japan combined. Osteoporotic fractures represent a major health problem.

The treatment of osteoporosis in postmenopausal women generally involves the use of therapeutic agents that inhibit bone resorption (hormone replacement therapy, bisphosphonates, selective oestrogen receptor modulators and calcitonin). These drugs are effective in reducing bone turnover, as indicated by the changes in markers of both bone formation and resorption[1, 2]. The effect of these drugs on bone density is maximal during the first year, resulting in total gains in bone density of less than 10% over 3 years [3, 4]. However, many postmenopausal women have lost over 30% of their peak bone mass and continue to have fractures after being treated with anti-resorptive drugs. An ideal therapy for osteoporosis would not only inhibit further bone loss, but would also continually stimulate new bone formation. Parathyroid hormone (PTH) increases trabecular bone density by stimulating bone formation [5, 6]. Markers of bone formation and resorption increase during PTH treatment[7], and vertebral bone density increases by about 10% after 2 years[8].

The anabolic activity of PTH and N-terminal fragment analogues of PTH has been investigated for many years. The mechanism by which PTH or N-terminal fragments of PTH increase rather than decrease bone mineral density (BMD) is not fully elucidated; however, it is well established that the duration of exposure is critical [9]. PTH is secreted primarily in response to a fall in plasma calcium levels and is the principal regulator of calcium homeostasis [10, 11]. PTH acts in the kidney to increase renal tubular calcium re-absorption and to increase the synthesis of 1,25-dihydroxyvitamin D, which increases intestinal calcium absorption [10, 12]. PTH acts in bone to increase the number and activity of osteoblasts and osteoclasts and increases bone turnover. With sustained elevations in PTH, osteoclastic activity could exceed that of osteoblasts resulting in a net release of calcium from bone and a decrease in BMD [13, 14]. In contrast, single daily injections of PTH that cause transient stimulation of the PTH-1 receptor, could increase osteoblastic activity preferentially, thereby increasing BMD and bone strength.

About the product

Parathyroid hormone (PTH) is recombinant human parathyroid hormone, a bone anabolic agent that is being developed by NPS Allelix Corp. (a subsidiary of NPS Pharmaceuticals, Inc.) for the treatment of osteoporosis in postmenopausal women. Acronyms used during the development were ALX1-11, Preotact, recombinant (rDNA) parathyroid hormone, parathyroid hormone (r.E.coli), parathyrin, parathormone PTH(1-84), hPTH, hPTH(1-84), rhPTH, rhPTH(1-84), rPTH, rPTH(1-84). PTH is identical to endogenous human PTH. Endogenous PTH is a polypeptide consisting of 84 amino acids, that is synthesized and secreted by the parathyroid glands and is the principal regulator of plasma calcium homeostasis through concerted actions on kidney, intestine, and bone.

The drug substance is produced by recombinant DNA technology in Escherichia coli. In contrast to already authorised PTH products, PTH contains the full PTH sequence of 84 amino acids. Previously authorised PTH products only contain the N-terminal fragment PTH (amino acid 1-34), as the C-terminal fragment (amino acid 35-84) was believed to be
biologically unimportant. It has however been found that the C-terminal has intrinsic biological activity that is mediated by a specific C-terminal PTH receptor [15, 16].

With the present application, the applicant sought a marketing authorization for the “Treatment of osteoporosis in postmenopausal women as diagnosed by clinically acceptable criteria such as low bone mineral density (BMD) or prior fragility fractures”.

The dose proposed by the applicant was 100 µg administered as a daily subcutaneous injection in the thigh or abdomen for a duration of up to 2 years.

### 1.2 Quality aspects

**Introduction**
The drug substance of Preoject is a recombinant human parathyroid hormone (rhPTH) produced in *E. coli* that is identical to the endogenous human PTH. RhPTH is manufactured by fermentation at an 1100 L scale, followed by a 2-step recovery and a 5-step purification process and terminated by filtration and filling.

The intended therapeutic indication of PTH is the treatment of osteoporosis in postmenopausal women at high risk of fractures. PTH has been demonstrated to increase bone size and mineral content, thereby improving bone quality and strength.

PTH is presented as a powder and solvent for solution for injection. The container closure system is comprised of a Type I glass dual-chamber cartridge, a bromobutyl rubber center stopper, an aluminum crimp cap containing a bromobutyl rubber seal and sealing the first chamber, and a bromobutyl rubber end stopper sealing the second chamber. The first chamber contains the lyophilised drug substance (100 µg per dose) and the excipients (citric acid monohydrate, sodium chloride, hydrochloric acid, sodium hydroxide, mannitol); the second chamber contains the solvent for mixing (water for injections and m-cresol). PTH is administered with a reusable CE-marked pen device. Each cartridge contains 14 doses.

**Drug Substance**

**Nomenclature**

*INN Name:* Parathyroid hormone  
*Compendial name:* N/A  
*Chemical name:* Parathormone (human recombinant)  
*USAN/BAN/JAN Name:* Parathyroid hormone (r.E.coli)  
*Laboratory Code:* ALX1-11, PTH  
*CAS Registry Number:* 68893-82-3  
*Other Names:* PTH(1-84), hPTH, hPTH(1-84), rhPTH, rhPTH(1-84), rPTH, rPTH(1-84)

**Description of the drug substance**

RhPTH is produced as a fusion protein. Post-translational processing involves the cleavage of the OmpA leader sequence, leaving the mature protein as a single-chain 84 amino-acids polypeptide (9.4 kDa) whose sequence is identical to that of the full-length native endogenous human PTH. It has no disulfide bonds and no glycosylation sites.

The biological actions of rhPTH are mediated through binding to at least two distinct high-affinity cell-surface receptors specific for the N-terminal and C-terminal regions of the molecule, both of which are required for normal bone metabolism. The N-terminal portion of the molecule is primarily responsible for the bone building effects of parathyroid hormone. The C-terminal portion of the molecule has antiresorptive activity and is necessary for normal regulation of N-terminal fragment activity.
Manufacture

The drug substance is produced by SynCo Bio Partners B.V, Amsterdam, The Netherlands. This manufacturing site was last inspected in September 2003 and authorised in June 2004. The facilities are operated in current GMP (cGMP) compliance, with standard operating procedures in place to describe all procedures and controls.

Development genetics

The expression plasmid pJT42 was constructed using a synthetically produced PTH expression region, the lactose operator for the induction of PTH gene, a tetracycline-resistance gene for selection and an origin of replication. The PTH expression region produces a fusion protein of 105 amino acids, which consists of the PTH protein (84 amino acids) and the signal peptide of \( E. coli \) outer membrane protein A (OmpA, 21 amino acids) permitting the secretion of PTH into the culture medium. This leader sequence is removed from the fusion protein by an \( E. coli \) signal peptidase. The rhPTH gene was codon-optimized to utilise the codons most frequently used in \( E. coli \).

pJT42 was introduced into an \( E. coli \) host cell line PAL1000. After selection with tetracycline, one stable clone was isolated and sub-cloned to obtain the parental cell line from which the master cell bank (MCB) was prepared.

Cell bank system

A two-tiered cell bank system was developed and maintained in accordance to cGMP. The Master Cell Bank (MCB) and the initial Working Cell Bank (WCB) were prepared in 1992 according to the same procedure. An appropriate range of tests was performed for their characterisation, including culture purity, viability, phenotypic characteristics, bacteriophage test, plasmid DNA sequence, plasmid stability, plasmid identity, plasmid copy number. All specifications were met. Cells banks were extensively examined for the presence of adventitious agents.

Upon exhaustion of the initial WCB, a second WCB was prepared in 2004 with a similar procedure. This new WCB was not available for clinical studies and will be used for commercial production of the drug substance. It was tested and released by the same methods and with the same specifications as for the MCB and the original WCB. The two WCBs were shown to be comparable by release testing and additional qualification tests and by characterisation of production cells (extended generations).

Fermentation process

The fermentation process consists of inoculation, cell growth in a production fermentor, induction and secretion into the fermentation broth. The recovery process involves cell separation by centrifugation and filtration followed by an ultrafiltration/diafiltration step. No reprocessing is permitted.

The original fermentation was conducted at the 200 L scale for preclinical studies, early Phase I and Phase II clinical studies and then scaled-up to 1100 L for the other Phase I studies, for Phase III studies and for commercial manufacture.

The operations and controls of the process were adequately described and appropriate validation data were provided. Full details of the cell culture raw materials, their source and control were provided.

Purification process

The purification process consists of 5 chromatographic steps. The product is then filtered through a 0.2 µm filter and filled into sterile stainless steel containers.

The drug substance is shipped under controlled temperature conditions to the manufacturer of the drug product and stored at or below -70°C.
The purification process was adequately described. Details about column dimensions and operating conditions such as volumes, pH, flow rates, temperature and buffer composition (including sanitization and storage) of each step were provided. In-process control batch data from the filtered solution for storage complied with the established parameters.  
4 categories of process-related impurities were identified:  
- Host organism-derived impurities: *E. coli* protein, endotoxin, DNA;  
- Process reagents: tetracycline, EDTA, acetonitrile, silicone (antifoam);  
- Chromatography resin leachates;  
- Filter extractables.  
Levels of these process-related impurities were assessed by routine measurement in production lots of PTH drug substance and/or clearance studies. Analysis of in-process products for a number of host-organism derived impurities and process material-derived impurities, as well as additional clearance studies, demonstrate that the presence of these impurities is well controlled in the process. The results presented by the applicant show consistent removal of process-related impurities.  
A number of product-related impurities have been identified that consist of N- or C-terminally truncated variants or of other variants appearing as a result of chemical modifications, such as oxidation, deamidation. Detection of the truncated peptides was obtained by mass spectrometry (MS) analysis. Identification of the oxidized variants was obtained by cyanogen bromide digestion and comparison to chemically generated reference material. Relevant product-related impurities (PTH(1-80), Met$_{8}[\text{ox}]$ PTH, Met$_{18}[\text{ox}]$ PTH) are routinely measured in PTH drug substance as part of release testing. Results of release testing were presented and demonstrate that the levels of these impurities are all within the specification limits.  
The identification of product-related impurities has been conducted on various rhPTH drug substance lots representative of the commercial scale (1100 L fermentation) and used to produce PTH product for the Phase III clinical trials.  
Of the three specified impurities, both Met$_{18}[\text{ox}]$ PTH and PTH(1-80) are biologically active and can be categorized as PTH-related substances. Several other impurities have also been identified and characterized. These impurities are all present at levels < 0.1% peak area and may not be consistently present in all rhPTH drug substance lots. Therefore, a common specification has been set but an individual limit or separate analysis will not be carried out.  
With regard to adventitious agents safety, tryptone and are the only raw materials of animal origin used in the process; they both belong to the category of milk derivatives from milk collected for human consumption, in accordance with Ph. Eur.  
The manufacturing process and facility are designed to prevent contamination during production. Potential non-viral adventitious agents such as contaminating bacteria, mycoplasma, *Shig* , TSE agents are controlled at several levels. The bacterial cells used to initiate the fermentation process do not contain mammalian viruses and have been shown to be free of bacteriophage. Appropriate environmental controls are exerted during the manufacture in order to prevent the introduction of adventitious viruses.  
No viral validation studies were performed, which is considered acceptable since no human or animal cell lines are used.  
The overall adventitious agents safety is considered satisfactory.

*Manufacturing process development and process validation*  
The drug substance is manufactured using a standard fermentation and purification process. A number of changes were made during development, in one single revision before the start of Phase III clinical studies. They include scale-up of the fermentation process from 200 L to 1100 L, with consequential scale-up of the purification process, implementation of the ultrafiltration/diafiltration step and an additional chromatographic step and finally storage of the purified drug substance as a frozen liquid instead of lyophilised.
It was considered that the changes introduced are not likely to have an impact on the quality attributes of the drug substance. A comparability exercise was performed and was mainly based on process performance data, drug substance release data and a limited number of additional tests. This was considered adequate to support the manufacturing changes introduced and the results obtained were satisfactory.

The objective of the validation studies was to demonstrate that the manufacturing process is suitable for its intended purpose and capable of consistently and reliably producing product that meets all predefined quality attributes. The manufacturing process has been carefully validated. Validation data from 3 consecutive batches were provided and were considered satisfactory.

**Characterisation**

- Physicochemical characterisation:
The amino-acid sequence, determined by N-terminal Edman degradation, is identical to that of the native human parathyroid hormone. MS analysis confirmed the molecular weight of 9.42 kDa, the removal of the OmpaA leader sequence and the absence of any post-translational modification.

Secondary structure was determined by circular dichroism.

RhPTH is a monomeric protein as demonstrated by MS, SDS-PAGE and analytical ultracentrifugation. Covalent or non-covalent aggregates were not detected at a significant level.

RhPTH does not contain cysteine residues, so no intra- or intermolecular disulfide bridge exists.

- Biological characterisation

The biological activity assay is based on the interaction of the hormone with its receptors localized in the plasma membrane of target cells. The significance of the PTH receptor complex in mediating the actions of PTH is supported by studies of resistance to PTH. Therefore, the method chosen was considered relevant in order to mimic a clinical response.

Methods used for the characterisation of the drug substance are considered state-of-the-art. The drug substance has been well characterised and the results provided are considered satisfactory.

**Specifications**

Establishment of specifications were based on 59 released lots of drug substance produced using the commercial process. All batches used for pivotal clinical and stability studies have been included.

The analytical methods included in the control system are used to evaluate the identity, quality, safety, purity, potency of the drug substance and to assure the consistency of physicochemical and biological attributes of rhPTH. The methods were carefully validated. The specifications that have been set are considered sufficiently justified. Based on the data presented in the dossier showing that the purification process is consistently capable to remove DNA at an acceptable low level, it was considered acceptable not to perform a release test for DNA content.

**Stability**

The applicant has performed real-time and accelerated stability studies designed in accordance with ICH guidelines to monitor the time-temperature stability of cGMP lots.

Stability data on 10 full-scale production batches of drug substance were presented. Data include storage at -70°C, -20°C and 4-5°C as follows:

- Five batches manufactured at the 1100 L scale and stored in stainless steel containers. One lot has been analyzed up to 36 months, two lots up to 24 months and 3 lots up to 12 months.
- Five batches manufactured at the 1100 L scale and stored in glass containers have been presented as supportive studies. Data up to 5 years of storage have been presented for 4 lots and up to four years for one lot.

The stability data provided were considered satisfactory and support the proposed storage conditions of the commercial drug substance (30 months at -70 °C in stainless steel containers).

Shipping of drug substance to the manufacturer of the drug product is performed under controlled temperature conditions below -20°C. This is considered acceptable as the stability studies performed at -20°C indicate that the drug substance is stable for several months at this temperature.

**Drug Product**

- **Pharmaceutical Development**

The clinical formulation used in Phase Ia, Ib and II clinical studies was a single-use lyophilised formulation in a glass vial to be reconstituted with water for injections. The drug substance was formulated with a citrate buffer pH 6 and mannitol which is a bulking agent commonly used for lyophilised products.

The proposed commercial multi-dose formulation was introduced prior to Phase III studies. Sodium chloride was added to minimize variability in concentration of sodium chloride coming from drug substance. It also serves as a tonicity modifier. The pH was adjusted with hydrochloric acid and sodium hydroxide aqueous, based on stability data and in an effort to minimise pain upon injection. The change from a single-use to a multi-dose formulation required the presence of a preservative agent; m-cresol was selected. All selected excipients comply with Ph. Eur.

A bioequivalence study was conducted in adult males to compare the single-use formulation used in Phase II studies to the multi-dose formulation used in Phase III studies. Data demonstrated that the two formulations have similar bioavailability.

The commercial container/closure system is a dual-chamber cartridge containing the front chamber (lyophilised drug substance formulated with the excipients) and the rear chamber (solvent for mixing containing water for injections and m-cresol). The cartridge is constructed from Type I glass. Each chamber is closed with bromobutyl rubber stoppers. These standard pharmaceutical materials have been shown to be safe and compatible with the lyophilised powder and the solvent for mixing.

The cartridge is mounted with a self-injection pen (CE-marked) for subcutaneous administration. The multi-dose cartridge and pen have been evaluated for dose accuracy and found to be compliant with the relevant ISO standards.

Each cartridge contains 14 doses of 100 µg of drug substance. The dual-chamber cartridge contains no overage.

- **Manufacture of the product**

The drug product is manufactured by Vetter Pharma-Fertigung GmbH, Ravensburg, Germany. This site was inspected in April 2004 by the German authorities and was found GMP compliant.

The PTH solution is compounded using the drug substance, sterile filtered, aseptically filled into the front chamber of the glass cartridge, and lyophilised. The solvent for mixing is compounded, sterile filtered and aseptically filled into the rear chamber of the cartridge. The cartridge is sealed and inspected. Cartridges are packaged in cartons. Reprocessing is not performed.

Pooling of maximum of two drug substance batches is considered acceptable.
- Preparation of lyophilised powder:
Mannitol, citrate buffer, and sodium chloride are mixed in a stainless steel container. The drug substance is thawed and added to the mixture, the pH is adjusted, and additional citrate buffer is added to achieve the final target weight. Water for injections is added to dilute the compounded PTH solution to the target concentration. The pH is measured and adjusted if necessary. The compounded PTH solution is tested for pH and bioburden. The diluted PTH solution is filtered into a stainless steel pressure vessel through a 0.22 µm filter and then stored at 2°C to 8°C for up to 24 hours prior to filling. The filtered PTH solution is tested for bioburden.

Before the front chamber is filled, the center stopper is inserted into the cartridge. The front chamber is filled to a target volume of 1.2 mL. Process tests performed during the filling operation include glide force measurement, stopper position check and fill weight check. Filter integrity is tested before and after filtration. The filled cartridges are transferred to the freeze dryer and a freeze-drying cycle, consisting of freezing, primary drying and secondary drying, is performed. After the freeze-drying cycle, the front chamber is sealed with a crimp cap prior to the rear chamber fill. The lyophilized powder is tested for residual moisture.

- Preparation of solvent for mixing (rear chamber):
M-cresol is added to a vessel containing water for injections and the volume is adjusted with water for injections to the required final weight. The m-cresol solution is tested for bioburden. The m-cresol solution is filtered through a 0.22 µm filter into a stainless steel pressure vessel and stored at 2°C to 8°C for up to 6 days prior to filling. The filtered solvent for mixing is tested for bioburden.

Prior to filling, the solvent for mixing is filtered through a 0.22 µm in-line filter. The cartridges are sealed with rubber stoppers and moved to storage. Process tests performed during the filling of the rear chamber include end stopper position and fill weight check. Filter integrity is tested before and after filtration. The drug product manufacturing process has been validated for four batches with regard to filtration, holding times, filling, lyophilisation cycle, container closure and major equipment. It is considered that relevant validation studies have been performed and the results are considered acceptable.

- Specifications
All methods for release testing of the drug product have been adequately described and are validated. The selected parameters tested on drug product have been adequately justified and are considered acceptable. Sufficient batch analysis results confirm the consistency of the drug product. No new impurities are formed during the manufacture of the drug product and the purity profile of the drug product is comparable to that of the drug substance. The proposed limits are considered acceptable.

- Stability of the Product
The proposed storage conditions are:
- For the drug product: 30 months stored below 25°C;
- For the mixed solution: 28 days stored at 2-8°C with storage of up to 7 days below 25°C.

The stability of the drug product was extensively investigated and included real-time data at 4°C or 5°C, 25°C and 30°C and accelerated data at 40°C for up to 6 months, the drug product being stored in the proposed dual-chamber cartridge. Long-term data on 6 batches manufactured with the commercial process were provided for up to 30 months. The proposed shelf life specification limits for purity by RP-HPLC and by CE-HPLC and impurities by RP-HPLC were wider than the release limits. Stability data for the drug product clearly showed that it is more stable when stored at 2-8°C compared to storage at room temperature.
temperature, especially with regard to impurity levels. However, given that the impurity levels were shown to be safe in toxicological studies, the proposed storage conditions at 25°C was considered acceptable.

For the mixed product, in-use data at 4°C, 25°C and 40°C for up to 30 days were provided. The applicant committed to perform in-use stability studies at the end of the drug product shelf life for 6 batches.

A photostability study evaluated the exposure of lyophilized PTH product in cartridges. These results showed that PTH product is light sensitive. Therefore, the proposed condition “Keep the dual-chamber cartridge in the outer carton in order to protect from light” is adequate.

**Discussion on chemical, pharmaceutical and biological aspects**

In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

Cell banks have been established and adequately characterised. However, with regard to the most recent working cell bank (WCB) that will be used in production, the applicant committed to provide the data of three commercial batches derived from this new WCB, including the results of the tests used for the characterisation of the drug substance.

The drug substance manufacturing process is well defined and adequately controlled with appropriate in-process controls in place, and sufficient in-process specifications are set based on process validation. The manufacturing process has been carefully validated with respect to all relevant parameters and good consistency has been shown, based on the large number of commercial-scale batches produced.

The comparability exercise of materials from the old and new process was mainly based on process performance data, release testing data on the drug substance and drug product and a limited number of additional tests. This comparability study was considered acceptable and the results satisfactory.

The drug substance has been well characterised. Sources of heterogeneity have been assessed in detail using a wide variety of state-of-the-art techniques. The test methods chosen are considered adequate.

The release tests for the drug substance and the specifications that have been set, based on release data from 59 full-scale batches and stability data, are considered appropriate. Specifications for product-related impurities (two oxidised forms and one truncated variant) were recently introduced.

With the responses to the Day 120 List of Questions (D120 LoQ), the applicant provided updated stability data on five lots of drug substance. All parameters are within the specification limits and, therefore, the proposed shelf life of 30 months at -70°C for the drug substance was considered acceptable.

The pharmaceutical development of the drug product has been thoroughly and adequately described. The applicant provided a new preservative efficacy study for m-cresol that complies to Ph. Eur. and whose results are acceptable.

The drug product manufacturing process, together with in-process controls, has been adequately described; critical steps have been defined and controlled. The applicant confirmed that pooling of a maximum of two lots of drug substance is allowed. Process validation has been performed for four batches with regard to filtration, holding times, filling, lyophilisation cycle, container closure system and major equipment and the results obtained are considered satisfactory.

The specification limits for the drug product have been adequately justified and are considered acceptable. Following the D120 LoQ, a test for osmolality (Ph. Eur.) has been added to the specifications of the mixed solution of drug product; the proposed limit is acceptable.

The proposed storage conditions of 30 months below 25°C for the non-mixed product and 28 days at 2-8°C for the mixed solution, with storage of up to 7 days below 25°C, have been
The quality of Preotact has been adequately demonstrated. Except for a number of quality points that the applicant agreed to address by commitments and a post authorisation follow-up measure, the overall quality of Preotact is considered acceptable.

1.3 Non-clinical aspects

Introduction

Apart from a few safety pharmacology studies, all pivotal in vivo safety studies used the subcutaneous (SC) route, included appropriate toxicokinetic monitoring and were GLP-compliant.

Pharmacology

- Primary pharmacodynamics (in vitro/in vivo)

Primary pharmacodynamics have been investigated in vivo in ovariectomized (OVX) rat and monkey, which are well-established models of human postmenopausal osteoporosis [17-21]. Ovariectomy leads to a moderate bone loss due to oestrogen depletion. Two pivotal treatment studies were performed in aged OVX rat (10 months old) and monkey (12-17 years old), respectively. Both studies had a duration of more than the recommended six bone remodelling cycles [22].

OVX rat showed clear signs of osteopenia based on decreased trabecular BMD and histomorphometric parameters whereas bone strength was not affected. By six months, daily SC administration of 15 and 30 µg/kg rhPTH(1-84) dose-dependently increased the BMD to or above the sham vehicle level at all investigated skeletal sites (both trabecular and cortical). Treatment increased trabecular bone volume and thickness. Similarly, dose-dependent increases in cortical bone area and thickness were seen. Femur and lumbar vertebrae-4 bone strength increased dose-dependently with treatment. Altogether, the lowest effective dose in OVX rats was 15 µg/kg/day given subcutaneously.

In the pivotal monkey study, ovariectomy lead to a decrease in bone mass in all analysed bones, although was not statistically significant in all cases. With respect to histomorphometry, no statistically significant signs of osteopenia were seen even after 25 months of oestrogen deficiency. Furthermore, no significant decrease in bone strength was seen. Over a period of 16 months, OVX monkey were administered 5, 10 or 25 µg/kg/day PTH subcutaneously. Treatment caused dose-dependent increases in BMD at primarily trabecular bone sites and 5 µg/kg/day increased BMD to sham-vehicle levels. Trabecular bone volume was increased primarily due to an increase in trabecular number and not thickness, which corresponds to what is seen in the clinic. Treatment-related increases in vertebral bone strength were seen in the compression test. However, dose-dependent decreases in BMD were seen in cortical bone. Furthermore, cortical area, cortical thickness and porosity were increased while the BMC was decreased. These findings question the quality of the cortical bone formed as a response to PTH treatment. Particularly as some femur and radius cortical bone strength parameters were decreased in all dose groups when evaluated in the 3-point bending test, although the decrease was only significant in the high-dose group. The femur neck shear test showed no significant differences between femoral peak-load and stiffness in PTH treated and vehicle animals besides an increase in the work-to-failure parameter.
• Secondary pharmacodynamics

A secondary pharmacodynamics study showed that PTH had a negative inotropic effect on the myocardium in vitro, with an IC50 value of 2.5x10^{-9} M. In women, a SC injection of PTH leads to a C_{max} value of 0.3 ng/ml, corresponding to a maximal plasma concentration of 3.5x10^{-11} M. At this concentration, PTH did not have a significant negative inotropic effect.

• Safety pharmacology

The potential for QT-prolongation was investigated in two in vitro tests PTH tested negative in the hERG-test and in isolated dog Purkinje fibres. The analytical part of these studies did not meet GLP requirements. In non-GLP cardiovascular studies in anaesthetised and conscious rat and anaesthetised dog, PTH had no effects on heart rate and blood pressure at clinically relevant doses. ECG recordings revealed no adverse effects on cardiac conduction in the repeat-dose toxicity study in monkey.

• Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies were not conducted.

Pharmacokinetics (PK)

Two different immunoassays were used to quantify PTH. The antibody used initially was subsequently shown to lack specificity for full-length PTH and at least two biologically important PTH fragments (3-84 and 7-84) were shown to cross-react in the assay. Therefore, a new assay was developed which did not cross-react with these fragments. The latter assay, which employed a mixture of ^{125}I-labelled polyclonal anti-PTH(1-34) and anti-PTH(44-88) antibodies, was validated for the quantification of PTH in rat plasma and monkey serum and used for the intravenous (IV) PK and absolute bioavailability studies as well as the rat carcinogenicity study. Since the PK program was limited in scope and a validated assay was used in all pivotal investigations, this is an acceptable approach.

• Absorption- Bioavailability

PK parameters were determined in the dog and monkey in several single-dose studies and in the course of the repeat-dose toxicity studies. Absolute bioavailability of SC injected PTH was not determined in dog and monkey. In the rat, it was in the order of 50%, with about 95% of the bioavailable dose being absorbed from the skin within 90 min. Plasma levels peaked within 15 min of injection. As is often the case with SC administration, C_{max} values were underproportional to the magnitude of single doses, whereas both C_{max} and AUC values were significantly greater after multiple daily doses than after a single dose. Both values, however, stabilised after 2-3 days of treatment and then remained constant through at least 12 months. Dog had a more blunted and prolonged profile than rat or monkey, and inter-individual variability was substantial. In cynomolgus and rhesus monkey, T_{max} ranged from 20-40 min. Dose-normalised C_{max} and AUC values were in between those of the rat and dog, but remained fairly constant in repeat-dose studies; the dose-normalised AUC values were comparable to those observed in humans. There were no appreciable gender differences in any parameter.

• Distribution

Conventional distribution studies were not conducted and are not required. In the rat, the volume of distribution was 0.05-0.10 l/kg, or slightly larger than the plasma volume. The corresponding value in humans was approximately 0.08 l/kg.

• Metabolism (in vitro/in vivo)

Metabolism studies were not conducted and are not required. Data from the literature shows that PTH is rapidly cleared from plasma, primarily by Kupffer cells in the liver [23]. PTH
binds to a transporter on the surface of these cells that recognises an amino acid sequence within the 28-48 amino acid domain [23]. Hepatic hydrolysis is catalysed by nonspecific peptidases as its primary clearance pathway. Following hydrolysis in the liver, C-terminal fragments are released into the systemic circulation, while N-terminal fragments are degraded in situ and are not released from the Kupffer cells [24-29]. To a lesser extent, PTH is cleared by filtration and reabsorption by the kidney. In the kidney tubules, PTH and its fragments are further hydrolysed to smaller fragments to facilitate reabsorption and natural conservation of amino nitrogen.

- **Excretion**
  Excretion studies were not conducted.

**Toxicology**

- **Single dose toxicity**
  Single-dose toxicity was investigated in mice and rat. The minimum lethal dose was > 10 mg/kg SC in both species.

- **Repeat dose toxicity (with toxicokinetics)**
  Repeat-dose toxicity studies were conducted in SD rat, dog and cynomolgus monkey. In all studies, PTH was administered once daily by SC injection. In preliminary studies over 7-21 days, the maximal tolerated dose (MTD) was 1000 µg/kg/day in rat and 20 µg/kg/day in monkey. In dog, a pyramid and two preliminary 28-day studies were conducted. Overall, these dog studies identified a no observed effect level (NOEL) based on kidney toxicity equivalent to 0.1 µg/kg/day in males and 1.0 µg/kg/day in females, which is below the proposed human dose. The observed renal toxicity was characterised by tubular dilatation, regeneration and mineralization with interstitial fibrosis and correlated with the degree of treatment-induced hypercalcaemia. The sensitivity of the dog to PTH-induced hypercalcaemia and subsequent renal damage precluded the use of this animal as a non-rodent species. Therefore, pivotal studies were conducted in SD rat and cynomolgus monkey. SD rat were also employed in the primary pharmacology studies and shown to exhibit pharmacodynamic effects at the MTD. Rhesus rather than cynomolgus monkey were used for primary pharmacology. Pharmacodynamic effects in the pivotal repeat-dose study in the cynomolgus monkey were limited to a small increase in BMD in the proximal and distal femur and 2nd-4th lumbar vertebrae in mid-dose females.

  In the pivotal rat study, the test compound was administered SC for 26 weeks at 0, 50, 300 or 1000 µg/kg/day. Major findings in the mid- and high-dose group included death, heart and kidney mineralization, abnormal red blood cells parameters, a slight increase in blood urea nitrogen in high-dose males, a dose-dependent increase in urine calcium, a decrease in urine phosphorus, and increases in adrenal, kidney, and liver weights. Histological changes included a dose-dependent osteosclerosis of the femur and sternbrae with secondary bone marrow reduction and extramedullary haematopoeisis, and increased mineralization and tubular regeneration of the kidneys of male and female rat. PTH elicited a weak immune response in rats as measured by anti-PTH antibody titers. However, the frequency of antibody formation was low and had no observed effect on the pharmacological responses. Based on the results of this study, the nonthreshold effects limit (NTEL) in the rat was 50 µg/kg/day.

  In the monkey study, the test compound was administered SC for 26 weeks at 0, 2, 10 or 30 µg/kg/day, with a 4-week recovery period. Decreases in serum phosphorus concentrations were noted during the latter half of the study. Elevations in serum calcium levels were transient and minimal throughout the study. Doses ≥10 µg/kg/day caused slight or mild, focal or multifocal renal tubular mineralization in some animals. Low-titer antibodies specific for PTH were detected in a single female monkey in the high-dose group at week 25. Based on
the results of this study, the NTEL in cynomolgus monkey was 2 µg/kg/day. In summary, the most significant target organ in both species was the kidney.

- Genotoxicity
  PTH was tested for mutagenic potential in two conventional in vitro tests in bacteria and mammalian cells, respectively. PTH tested negative in both tests.

- Carcinogenicity
  Carcinogenicity studies were conducted in Fischer 344 rat and included a modified 2-year bioassay and a mechanistic study of the effect on osteoblast proliferation and bone formation. In the long-term study, rats were treated SC with 0, 10, 50 or 150 µg/kg/day of PTH for 94-104 weeks. Two separate control groups were employed and an additional high-dose group was added to begin dosing at 8 months of age to determine the impact of endochondral bone growth on the incidence of neoplasia. The only statistically significant tumour finding was a dose-related increase in the frequency of bone tumours in mid- and high-dose animals of either sex. In comparison to pooled control group incidences, high-dose males had statistically significant increases in terms of osteoblastoma, osteoma, osteosarcoma, and all bone neoplasms. High-dose females showed a similar pattern, except that the incidence of osteoma did not attain statistical significance. In the mid-dose group, using the same comparator, osteosarcoma and all bone neoplasms were significantly increased in males, and osteoblastoma and all bone neoplasms in females. When started at 8 months of age, there was a notable reduction in bone tumor incidence in males whereas the incidence in females was equivalent in both groups. AUC values were lower in females than in males and exposure measurements taken within the first month were lower than those at 6 and 12 months. Therefore, exposure ratios were calculated separately for each sex from the average 6 and 12-month AUC values at the NTEL based on all bone neoplasms (10 µg/kg/day) and the average AUC in humans receiving 100 µg/day (0.8 ng.hr/mL). The resulting safety margins were 6 and 4 based on male and female rats, respectively. In the mechanistic study, groups of 4 normal 3-month-old Fischer 344 rats were treated SC with either rhPTH(1-84) 10 or 50 µg/kg/day or rhPTH(1-34) 5 or 30 µg/kg/day for 14-18 days to compare their effects on serum osteocalcin levels, osteoblast progenitor proliferation as determined by 5-BrdU labelling, osteoblast density and cancellous bone formation. The study concluded that rhPTH(1-34) was more effective at increasing osteoblast number and bone formation whereas osteoblast progenitor proliferation was stimulated to the same extent by either hormone.

- Reproductive and developmental studies
  Since the proposed indication for PTH is restricted to postmenopausal women, reproductive and developmental toxicity studies are not required. The Applicant nevertheless conducted a conventional Segment I study in which male and female rats were injected SC with 0, 100, 300 or 1000 µg/kg/day of PTH. Treatment-related findings in females included small but significant reductions in the number of corpora lutea, implantation sites and live fetuses in mid- and high-dose animals. In males, they included reduced absolute and relative prostate and cauda epididymis weights and a slight decrease in group mean sperm motility percentages in high-dose animals. There was a slight reduction in body weight gain in high dose males, but this was less than 10% and therefore not indicative of general toxicity. Thus, the NTEL for females was 100 µg/kg/day and the NTEL for males 300 µg/kg/day.

- Local tolerance
  Conventional non-clinical local tolerance study was not conducted. An assessment of the local irritation at the injection sites was conducted in both the rat and monkey 26-week studies. In the rat study, at the highest dose, 1000 µg/kg/day, there was an increased incidence and severity of interstitial fibrosis at the injection site. The concentration of PTH at the highest dose was 2 mg/ml (concentration of PTH in the proposed clinical formulation is 1.14
The dosing volume in the rat study was 0.5 ml/kg compared to 0.001 ml/kg for humans. In the 26-week monkey study, the histological observations at some of the injections sites in the control and PTH-treated animals included hemorrhage and/or cellulitis.

- **Other toxicity studies**
  Anti-PTH antibodies were determined in the course of the repeat-dose toxicity studies. In a study of the hemolytic potential of PTH for human whole blood the compatibility of PTH with human serum and plasma were investigated. There was no haemolysis precipitation or coagulation observed when either PTH (1.4 mg/ml) or vehicle were mixed with human whole blood, serum or plasma.

**Ecotoxicity/environmental risk assessment**
No environmental risk assessment was submitted.

**Discussion on the non-clinical aspects**

*Pharmacology*

Two primary pharmacodynamics pivotal studies were conducted, one in rat and one in monkey, in which the effects of PTH on bone mineral density, strength and architecture were studied. Treatment with PTH for 12 months in rat resulted in a dose-related gain in bone mass at trabecular and cortical bone sites, associated with increased bone strength. In monkey, PTH treatment for 39 weeks increased markers of bone turnover. Formation markers were increased to a greater extent than resorption markers. Also, treatment with PTH at 25 µg/kg for 16 months resulted in significant increases in trabecular bone mass and increases in vertebral and femoral neck bone strength.

PTH influenced cardiac tissue contractility *in vitro* but the effects occurred at concentrations exceeding those occurring *in vivo*. Therefore, the negative inotropic effect of PTH *in vitro* was considered not clinically relevant.

The chosen clinical dose was 1.5 µg/kg/day PTH in patients. Based on pharmacokinetics (AUC), the clinical dose corresponds to exposures 1.75, 2.5 and 9.3 times less the exposures obtained in the pivotal monkey study (5, 10 and 25 µg/kg/day). Since 5 µg/kg/day was effective in increasing trabecular bone mass values to sham-vehicle levels but still displayed negative effects on cortical bone, the lower clinical dose was considered reasonable.

PTH tested negative in two *in vitro* QT-prolongation tests. PTH was considered unlikely to be associated with any clinically relevant risk of QT-prolongation.

There is published evidence of a link between PTH exposure and left ventricular hypertrophy with ensuing cardiovascular morbidity and mortality [34, 35]. Concerns over potential cardiovascular effects of PTH appear to be relevant only when PTH concentrations are sufficiently high to produce a catabolic effect on bone, and so the fact that PTH given intermittently to patients produced a pronounced anabolic effect is in itself reassuring.

Furthermore, data from the phase III clinical trials conducted with PTH showed no clinically important effects on cardiovascular function (see clinical safety section), and mean PTH concentrations tended to be slightly lower in treated patients compared to levels in patients in the placebo group. No pharmacodynamic drug interaction studies were conducted with medicinal products that may be concomitantly administered with PTH. Non-clinical findings suggested that PTH-receptor agonists may interact with oestrogen receptor agonists and modifiers and growth hormone, but not with bisphosphonates and 1,25-dihydroxyvitamin. The available non-clinical and clinical literature indicates that concurrent HRT and SERM use does not influence the anabolic response to PTH, whereas concomitant alendronate use clearly blunts or abolishes the increase in markers of bone formation and BMD (see SPC section 4.5).

*Pharmacokinetics*
PK parameters were determined in rat, dog and monkey in several single-dose studies and in the course of the repeat-dose toxicity studies. The serum $C_{\text{max}}$ and $t_{\text{max}}$ values were not significantly different between the neck and tail injection sites, suggesting that the lymphatic system does not play an important role in the uptake of PTH from a subcutaneous injection site. In dog absorption was much slower than in rat and the $t_{\text{max}}$ was considered to be on average 1.5 hour for both sexes. Studies performed with monkey revealed that the absorption was slower than in rat, and $t_{\text{max}}$ values ranged from 35 to 1.5 hour (average 50 minutes) for both sexes.

Conventional distribution studies were not conducted and are not required [36]. The expected consequence of metabolism of biotechnology-derived pharmaceuticals is the degradation to small peptides and individual amino acids. Therefore, the metabolic pathways are generally understood. Biotransformation studies as performed for pharmaceuticals are not required [36]. It is unknown whether PTH is excreted in the milk of lactating animals (see SPC section 5.3). Such knowledge is irrelevant, as long as the use of PTH is restricted to postmenopausal women. However, section 4.6 of the SPC includes a recommendation for not using PTH during breast-feeding. The potential for PK drug interactions was not investigated but is considered remote in view of the metabolic pathways described above and the expected plasma level of the drug product ($C_{\text{max}} < 10^{-10}$ M).

Toxicology
Repeat-dose toxicity studies were conducted in SD rat, dog and cynomolgus monkey. Overall, the dog studies identified a NOEL based on kidney toxicity equivalent to 0.1 $\mu$g/kg/day in males and 1.0 $\mu$g/kg/day in females, which is below the proposed human dose. The observed renal toxicity was characterised by tubular dilatation, regeneration and mineralization with interstitial fibrosis and correlated with the degree of treatment-induced hypercalcaemia. Whereas the safety margin determined in rats was not a cause for concern, the low value determined in monkeys (0.5 based on conservative criteria) indicated a potential for kidney toxicity in humans. It was therefore considered appropriate that section 5.3 of the SPC states that in monkeys receiving daily subcutaneous doses for 6 months, there was an increased occurrence of renal tubular mineralization at exposure levels below clinical exposure levels. The major findings in the pivotal rat study, included death, heart and kidney mineralization, abnormal RBC parameters, a slight increase in BUN in high-dose males, a dose-dependent increase in urine calcium, a decrease in urine phosphorus, and increases in adrenal, kidney, and liver weights. Histological changes included a dose-dependent osteosclerosis of the femur and sternabrae with secondary bone marrow reduction and extramedullary haemopoiesis, and increased mineralization and tubular regeneration of the kidneys of male and female rat. Based on the results of this study, the NTEL in the rat was 50 $\mu$g/kg/day. In the monkey study, doses $\geq 10$ $\mu$g/kg/day caused slight or mild, focal or multifocal renal tubular mineralization in some animals. Based on the results of this study, the NTEL in cynomolgus monkey was 2 $\mu$g/kg/day.

In vitro assays in bacterial and mammalian cells showed that PTH did not produce in vitro mutagenicity. Carcinogenicity studies in rat treated with near lifetime daily injections showed dose dependent exaggerated bone formation and an increased incidence of bone tumours, including osteosarcoma, most probably due to an epigenetic mechanism. Due to the differences in bone physiology in rats and humans, the clinical relevance of these findings was considered minor. No osteosarcomas have been observed in clinical trials (see section 5.3 SPC). However, until further clinical data becomes available, it is recommended in section 4.4 of the SPC that the treatment time does not exceed 24 months. A test for chromosome aberrations was not conducted; however, this is not required for biotechnology-derived drugs as it is not expected that these substances would interact directly with DNA or other chromosomal material [36].
Since the proposed indication for PTH is restricted to postmenopausal women, the absence of reproductive and developmental toxicity studies was considered acceptable. However, section 4.6 of the SPC includes a recommendation for not using PTH hormone during pregnancy.

In the pivotal repeat-dose rat study, there were minimal to moderate hemorrhage, fibrosis and cellulitis at the injection site in both control and high-dose groups, with increased severity at the high dose. A conventional local tolerance study with the final formulation was not conducted, but was not considered necessary, given the negative findings in the repeat-dose toxicities and the available clinical data. (see also SPC section 5.3).

The frequency and intensity of antibody formation was low in rat and minimal in monkey and did not compromise the interpretation of the non-clinical safety studies.

The drug substance and drug product contain three impurities whose proposed release specifications and/or shelf life limits exceed the qualifications thresholds stipulated in ICH Q3A/B, namely Met₈[ox]PTH, Met₁₈[ox]PTH and PTH(1-80). For these impurities, the proposed upper (shelf life) limit is 1, 2 and 2%, respectively. While PTH(1-80) has actually been tested at this level, batches used for non-clinical studies probably contained as little as 1/5 of the proposed limit for Met₈[ox]PTH and Met₁₈[ox]PTH. The Applicant argues that the Met[ox] impurities have been qualified at the proposed limit (or higher) since the safety margins in the long-term repeat-dose studies in rat and monkey were 11 and 19, respectively. Based on conservative criteria, however, the safety margin in monkey was less than 1 and therefore this argument is untenable. Since oxidised methionine (sulfoxide and sulfone) residues are found in many processed foods and have no known toxic effect in humans [30-32], it is nevertheless considered unnecessary to conduct further non-clinical studies to qualify these impurities.

Since PTH is a naturally occurring peptide hormone, the absence of environmental risk assessment was considered acceptable [38]. Any unused product or waste material should be disposed of in accordance with local requirements (see SPC section 6.6).
1.4 Clinical aspects

Introduction

GCP
The clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the standards of Directive 2001/20/EC.

Pharmacokinetics
The pharmacokinetics of PTH has been evaluated in two bioavailability studies in healthy subjects with both intravenous administration of PTH and subcutaneous administration in the abdomen and/or thigh. In addition, for characterisation of the pharmacokinetic and pharmacodynamic properties of PTH, four phase I studies were conducted in healthy postmenopausal women in order to determine safety and pharmacokinetics, and two studies were conducted in non-osteoporotic men and women with either renal or hepatic impairment. One phase II study was conducted in younger, healthy men to determine relative bioequivalence. Three sub-studies of larger population studies in postmenopausal osteoporotic women were conducted in order to determine population pharmacokinetics and acute calcemic response to treatment with PTH.

No PK study with radiolabelled PTH has been carried out. Consequently, the observed PTH levels are the result of the sum of the natural occurring PTH plus the exogenous fraction. PTH concentrations in serum or plasma were assayed with immunoradiometric assay.

- Absorption

Bioavailability

Table 1 - Summary of bioavailability and bioequivalence studies

<table>
<thead>
<tr>
<th>Study Reference No.</th>
<th>Study Objective</th>
<th>Study Design</th>
<th>Patients(^a)</th>
<th>Study Design</th>
<th>Treatments</th>
<th>Mean (SD) Pharmacokinetic Parameter Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>C11-11-013</td>
<td>Absolute BA of subcutaneous dosing</td>
<td>Single dose, 2-way, randomised, crossover, Single-label</td>
<td>M</td>
<td>SC IV</td>
<td>100 µg SC abdomen</td>
<td>332 (110)</td>
</tr>
<tr>
<td>SH-PTH-0001</td>
<td>PK, BE of the Phase II and Phase III formulations</td>
<td>Single dose Open-label, 2-way, Randomised cross-over</td>
<td>M</td>
<td>SC IV (15 min)</td>
<td>100 µg SC abdomen</td>
<td>693 (1185)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase II formulation</td>
<td>100 µg SC in abdomen</td>
<td>605 (233)</td>
<td>0.56 (0.10 – 3.00)</td>
<td>2260 (532)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>New (Phase III) formulation</td>
<td>100 µg SC in abdomen</td>
<td>8162 (1365)</td>
<td>0.26 (0.23 – 0.32)</td>
<td>2301 (329)</td>
</tr>
</tbody>
</table>

\(^a\) Patients included in the studies.
<table>
<thead>
<tr>
<th>Study Reference No.</th>
<th>Study Objective</th>
<th>Study Design</th>
<th>Patients* Gender Age Mean (Range)</th>
<th>Treatments</th>
<th>PTH Dose Route and Site</th>
<th>Mean (SD) Pharmacokinetic Parameter Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL1-11-007</td>
<td>Relative BA comparison of injection site</td>
<td>Single dose, 3-way, randomised, crossover, open-label</td>
<td>18 F 60.5 (47-75)</td>
<td>Abdomen – 1</td>
<td>100 µg SC in abdomen</td>
<td>C&lt;sub&gt;max&lt;/sub&gt;&lt;sup&gt;b&lt;/sup&gt; (pg/mL)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Abdomen – 2</td>
<td>100 µg SC in abdomen</td>
<td>528 (224)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thigh</td>
<td>100 µg SC in thigh</td>
<td>435 (189)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>269 (135)</td>
</tr>
</tbody>
</table>

* Number of patients receiving at least 1 dose of study drug.  
* Baseline corrected values.  
* Range of individual values reported.  
* Baseline corrected AUC<sub>0-24</sub>.  
BE = Bioequivalence; PK = Pharmacokinetics; BA = Bioavailability; ND = Not determined; SC = Subcutaneous; IV = Intravenous.

Study CL1-11-013 was a phase I pharmacokinetic and bioavailability study conducted to determine the pharmacokinetics of a single 100 µg dose of PTH administered as an intravenous infusion or subcutaneous injection in order to evaluate the subcutaneous absolute bioavailability of PTH in healthy postmenopausal women. The study was an open-label, randomised, 2-way crossover with a 1-week washout between treatments. The mean absolute bioavailability of subcutaneously injected PTH was 55% with a range of 36% to 92%. Despite the substantially lower PTH exposure (C<sub>max</sub> and AUC<sub>0-24</sub>), the systemic calcium response was greater following subcutaneous compared with intravenous dosing.

Study CL1-11-007 was a phase I injection site bioavailability study. This study was designed as a randomised, 3-way crossover study with a 7-day washout period between treatments. All patients received 3 subcutaneous injections, 2 in the abdomen and 1 in the thigh. The primary objectives of the study were to compare the pharmacokinetic profiles and bioavailability of PTH following a single 100 µg dose administered subcutaneously in the abdomen or thigh of healthy postmenopausal women, and to assess intra-subject variability.

Subcutaneous injection in the thigh produced lower PTH concentrations initially but more sustained concentrations at later time points compared with subcutaneous injection in the abdomen. The mean C<sub>max</sub> following injection in the thigh was nearly half that observed following injection in the abdomen, while the overall exposure to PTH was similar between the 2 injection sites. The decline from the peak concentration was slower after administration in the thigh, suggesting that a rate of absorption was slower and more prolonged for this injection site. Despite the lower peak PTH concentrations observed after injection in the thigh, the peak systemic calcium response was similar between treatments. However, the longer duration of PTH concentrations following injection in the thigh resulted in a correspondingly longer duration of the calcium response.

A population pharmacokinetic (PPK) model was developed to estimate the PK parameters of PTH and to investigate possible covariate-parameter relationships within the population. The final population model was a one-compartment model with first-order absorption and elimination parameterized in terms of CL/F, V/F, and BL, when ka was fixed at 1.5 hr⁻¹. The typical values for CL/F, V/F, and BL of PTH are 130 L/hr, 269 L, and 18.8 pg/mL. The covariates examined included age, race, weight, height, BMI, serum creatinine, serum total calcium, hepatic enzymes, injection site, smoking history, concomitant therapy, BMD, creatinine clearance, postmenopausal fracture incidence, and years postmenopausal. The pharmacokinetics of PTH, after subcutaneous injection, is highly variable but consistent with the values obtained in other studies. A significant association between creatinine clearance and volume was observed. CL/F is not significantly affected by any of the covariates; however, associations were suggested with the covariates BMD and injection site.
Bioequivalence

Study Astra SH-PTH-0001 was a phase I, single-dose, open-label, randomised, 2-way crossover study with a 28-day washout period between treatments to compare the pharmacokinetics of single 100-µg subcutaneous injection of a phase II and III formulations in the abdomen of 43 healthy male subjects randomised to 1 of 2 treatment sequences. The AUC\textsubscript{0-24} values were 10% higher for the phase III formulation than for the phase II formulation. The 90% CI for the ratio of AUC\textsubscript{0-24} values for the phase III and phase II formulation was 1.08 to 1.15. C\textsubscript{max} values were 17% higher on average for the phase III formulation than for the phase II formulation. The 90% CI for the ratio of C\textsubscript{max} values for the phase III formulation to the phase II formulation was 1.08 to 1.27, which exceeded the upper limit for establishing bioequivalence. The mean half-life (phase II, 2.4 hours; phase III, 2.5 hours) and t\textsubscript{max} values (phase II, 0.47 hours; phase III, 0.56 hours) were also similar for both formulations.

The mean serum calcium profiles following the administration of both formulations were similar.

- Distribution
  Study CL1-11-013, which involved intravenous administration of the medicinal product as a 15-minute infusion, showed that the volume of distribution at steady state following intravenous injection was approximately 5.4l. Inter-subject variability in the volume of distribution of PTH was about 40% (see also SPC section 5.2).

- Elimination
  No specific metabolism studies in humans were performed with PTH. In vivo and in vitro studies available in the literature have demonstrated that the clearance of PTH is primarily a hepatic process with a lesser role played by the kidneys [24, 39-45]. Circulating PTH is taken up in the liver by an efficient transporter on the surface of Kupffer cells [23]. Either during the uptake of PTH into the Kupffer cell or within the cell itself, PTH is cleaved by non-specific proteases into N- and C-terminal fragments [24, 29, 41, 42, 45]. The C-terminal fragments are released back into the systemic circulation, but the N-terminal fragments are retained and undergo further transformation and degradation within the cell [46-48]. The ratio of C-terminal fragments to intact hormone is regulated by systemic calcium concentrations and clearance pathways [49-53]. C-terminal fragments of PTH released to the circulation following hepatic metabolism are cleared exclusively by renal processes [25-27]. Following glomerular filtration and peri-tubular secretion [26], the fragments are further metabolised during tubular reabsorption [29, 54, 55]. Since the C-terminal fragments are primarily cleared by the kidney, these fragments can accumulate in patients with diminished renal function.

- Dose proportionality and time dependencies
  In studies PBR930811 (single dose) and PBR930812 (multiple doses) PTH was administered adjusted by body weight at doses between 0.02 to 5.0µg/kg to postmenopausal women. The PK relationship between dose and systemic exposure for PTH was both linear and proportional after single and multiple administrations in the whole range of studied doses. A similar dose-response relationship was observed for serum calcium concentrations, serum ionised calcium, AMPc and calcium/creatinine ratio. There was no apparent carry-over from one dosing period to the next.
  The plasma concentration data from the long-term studies (CL1-11-006 and the ACR sub-study of N01-AR-9-2245; PaTH) showed that there was no accumulation and no apparent change in the pharmacokinetics of PTH after 12 to 15 months of daily therapy.
Special populations

Impaired renal & hepatic function
One open label, single dose, multicentre study (CL1-11-0010) was conducted in order to evaluate the effect of renal impairment on bioavailability / pharmacokinetics. The mean maximum concentration (Cmax) and mean baseline-corrected Cmax of PTH following 100µg PTH to patients with mild-to-moderate renal impairment was approximately 22% and 23%, respectively, higher than that observed in subjects with normal renal function. The variability of Cmax was high, with CV% estimates of 77% to 81%, for subjects with mild-to-moderate renal impairment and 63% to 67% for subjects with normal renal function. Exposure to PTH as measured by AUC (0-last) and baseline-corrected AUC (0-last) was approximately 3.9% and 2.5%, respectively, higher than that observed for subjects with normal renal function. The variability of AUC (0-last) was moderate to high, with CV% estimates of 35% to 49% for subjects with mild-to-moderate renal impairment and 54% to 79% for subjects with normal renal function.

One open label, single dose study (CL1-11-0019) was conducted in order to evaluate the effect of hepatic impairment on bioavailability/pharmacokinetics. The mean baseline PTH concentrations (Cbase) were similar between the hepatic function groups. Subjects with normal function had a mean value of 19.5 pg/ml and subjects with moderate impairment had a mean value of 18.3 pg/mL. The mean and individual plasma PTH concentration-time profiles over the 24-hour sampling interval were comparable between the normal subjects and subjects with moderate hepatic impairment. The median time to reach maximum concentration was slightly shorter for subjects with moderate hepatic impairment. Pharmacokinetic parameters were calculated with and without correction for endogenous levels of PTH. The mean Cmax and baseline-corrected Cmax values were 18% to 20% greater in the moderately impaired subjects than in those with normal function. The mean AUC0-last was similar between the groups, while the baseline corrected AUC0-last was 20% greater in the moderately impaired group. Variability was high, with coefficient of variation values ranging from 40% to 91% for these exposure parameters.

Gender: No studies in this application have been performed in men with osteoporosis.

Race: Race was included as a covariate in the population pharmacokinetic analysis of PTH in TOP study patients. Of the 274 patients who had ethnicity data and were included in the analysis, 92% reported their race as Caucasian.

Weight: The influence of weight was not studied as an endpoint in any study. The population PK studies did not find any association between weight and pharmacokinetics.

Elderly: Age was included as a covariate in the population pharmacokinetic analysis of PTH in TOP study patients. Of the 274 patients who had age data and were included in the analysis, the median age was 65 (47 to 88 years). No effect of age on the clearance or volume of distribution of PTH could be established.

Children: Since the intended patient population is postmenopausal women, there is no paediatric development for PTH.

Pharmacokinetic interaction studies
No data on drug-drug interactions has been provided. No studies assessing the influence of food intake on the PK profile of PTH have been carried out.
Pharmacodynamics

- Primary and Secondary pharmacology

Primary pharmacology

The pharmacodynamic response to PTH administration was assessed primarily in terms of changes in serum total calcium concentrations after dosing. In addition, serum phosphate, 1,25-dihydroxyvitamin D, osteocalcin, bone-specific alkaline phosphatase and tartrate resistant acid phosphatase were measured along with urinary calcium, phosphate, cyclic AMP, deoxypyridinoline, and hydroxyproline in selected studies. Changes in BMD and fracture rate were assessed as efficacy in clinical efficacy studies.

In 3 multiple daily dosing (7 days, and 12 and 15 months) studies, the increase in serum total calcium concentration was slower than the increase in PTH. Tmax was 6 to 8 hours for serum calcium compared with 2 hours for plasma PTH. The decline was also slower than the decline for plasma PTH. The differences in the maximum effects on total serum calcium concentrations were relatively minor compared to plasma PTH (50% lower after injection into the thigh). Intravenous dosing resulted in a peak PTH concentration roughly 4-fold greater and overall PTH exposure nearly 2-fold greater than after subcutaneous dosing. In contrast, intravenous dosing resulted in peak serum calcium responses that were roughly 2-fold less and exposure that was also roughly 2-fold less than after subcutaneous dosing. No changes in serum calcium were observed at PTH doses < 0.5 µg/kg, and an apparent plateau in the response was observed at doses > 2 µg/kg.

In study CL1-11-006, there was an initial decrease in mean serum phosphate levels of 0.4 mg/dL after 15 months of dosing; this response was similar following placebo treatment. The nature of the response in relation to systemic concentrations of PTH indicates that other factors including absorption of dietary phosphate or diurnal variation are major contributors to the observed changes in serum phosphate.

In study PBR 930812, a dose-dependent increase in serum 1,25-dihydroxyvitamin D concentrations was observed at 12 hours for 1.5- to 3.0-µg/kg doses of PTH. An increase of 11pg/mL was also observed at 8 hours post-dose. Pre-dose, no significant increases were seen.

Single dose or daily dosing with PTH for 7 days, had no meaningful effect on markers of bone turnover. The effects of long-term dosing with PTH on markers of bone turnover were assessed in Phase II, TOP, OLES, POWER, and PaTH studies.

Increases (twice that of the placebo group) in cyclic AMP/creatinine ratio were detected in the 0- to 12-hour urine samples after single doses of 2.0 to 5.0 µg/kg, however, no clear dose-response relationship was observed.

Dose-dependent increases in urinary phosphate/creatinine ratios were detected in the 0- to 12-hour and 24-hour urine samples for dose levels of 1.5 to 5 µg/kg PTH but then decreased during the remainder of the 7-day treatment period, returning to baseline after 5 to 7 days. The urinary phosphate excretion data indicates a direct relationship between PTH exposure and the magnitude of the acute phosphaturic effect.

Secondary pharmacology

No data on secondary pharmacology, except those collected from phase III studies have been provided.

Discussion on Clinical Pharmacology

Subcutaneous administration of 100 µg of PTH into the abdomen produces a rapid increase in plasma PTH levels and achieves a peak at 1 to 2 hours after dosing. The average half life is of about 1.5 hours. The absolute bioavailability of 100 µg of PTH after subcutaneous
administration in the abdomen is 55% (see SPC section 5.2). The terminal elimination phase depends on the absorption rate rather than the elimination rate. The overall extent of absorption (AUC) from an injection into the thigh was approximately the same as that of the abdomen. However, PTH absorption was slightly slower from the thigh than the abdomen resulting in a plasma PTH profile that has a lower peak level and longer duration. Injection of PTH into the thigh resulted in a similar but later maximum effect on serum total calcium compared with injection into the abdomen. Predominant use of the thigh in patients receiving chronic therapy for 15 months seems to be associated with a greater increase in pre-dosing levels and a higher incidence of patients with values above the upper limit of normal (see also SPC section 5.2). Therefore, it has been considered that the subcutaneous injection should be administered in the abdomen only, and thus this is stated in section 4.2 of the SPC. Patients must be trained to use the proper injection techniques. Instructions are provided in section 6.6 of the SPC.

No studies assessing the influence of food intake on the PK profile of PTH have been carried out. Taking into consideration that the drug is to be administered by SC route, no relevant impact of food intake is expected [56].

In vivo and in vitro studies show that the clearance of PTH is primarily a hepatic process with a lesser role played by the kidneys [24, 25, 39, 41-45]. A greater within-subject variability was observed for C_{max} than for AUC\textsubscript{0-24}. Notably, the inter-individual variability with the weight adjusted dosing schedule at dose levels close to the one finally selected (1.5µg/kg and 100 µg respectively) appears to be lower than that exhibited by the fixed dosing schedule. In individual cases, values on the second dosing occasion were higher than they were on the first occasion, but there was an overall decrease in the mean exposure following the second administration in these patients. Restricting dosing to the abdominal wall will contribute to a reduction in this variability.

No dose adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance 30 to 80 ml/min) or mild to moderate hepatic impairment (total score of 7 to 9 on the Child-Pugh scale). There is no data available in patients with severe renal or hepatic impairment and therefore PTH should not be used in these patients (see section 4.3 of the SPC).

Although no effect of race on the clearance or volume of distribution of PTH could be established, the predominance of Caucasians would have precluded the identification of an effect even if one existed. Even though no trial investigated the effect of ethnicity as primary endpoint, there is no reason to suspect that different ethnic backgrounds influence the pharmacokinetics of PTH [57]. No differences in PTH pharmacokinetics were detected with regard to age (range 47-88 years). Dosage adjustments based on age is not required (see also section 5.2 of SPC).

No data on drug-drug interactions has been provided [56]. Parathyroid hormone is not metabolised by, and does not inhibit, hepatic microsomal drug-metabolising enzymes (e.g. cytochrome P450 isoenzymes). Furthermore, PTH is not protein bound and has a low volume of distribution. Consequently, no interaction with other medicinal products would be anticipated (see SPC section 4.5).

Clinical efficacy

Introduction

The clinical program evaluating the clinical efficacy of PTH in the treatment of osteoporosis in postmenopausal women included one phase II dose ranging study, one pivotal phase III placebo controlled study (TOP), an open-label extension/safety study (OLES) and two phase
III active control studies (PaTH, and POWER). The studies and the supportive publications submitted are detailed in the table below.

Table 2 - Clinical program of parathyroid hormone (PTH)

<table>
<thead>
<tr>
<th>(Study Number)</th>
<th>Title/Comment</th>
<th>Treatment Groups</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo Control</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ALX1-11-821)(^b)</td>
<td>A phase II double-blind, placebo-controlled, parallel-group study to assess the safety and efficacy of 3 doses of PTH (50, 75, and 100 µg) in the treatment of postmenopausal osteoporosis</td>
<td>Placebo</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTH 50 µg</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTH 75 µg</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTH 100 µg</td>
<td>55</td>
</tr>
<tr>
<td><strong>TOP</strong></td>
<td>An 18-month double-blind, placebo-controlled, phase III trial with a 12-month analysis of the effect of PTH on fracture incidence in women with postmenopausal osteoporosis / patients were eligible to continue in OLES</td>
<td>Placebo</td>
<td>1246</td>
</tr>
<tr>
<td>(ALX1-11-93001)</td>
<td></td>
<td>PTH 100 µg</td>
<td>1286</td>
</tr>
<tr>
<td><strong>Active Control</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaTH (N01-AR-9-2245)</td>
<td>PTH and ALN in combination for the treatment of osteoporosis</td>
<td>Year 1: 100 µg PTH + placebo</td>
<td>119</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo + 10 mg ALN</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 µg PTH + 10 mg ALN</td>
<td>59</td>
</tr>
<tr>
<td><strong>POWER</strong></td>
<td>A phase III trial of PTH in women with low bone mass on stable oestrogen replacement therapy</td>
<td>HRT + Placebo</td>
<td>90</td>
</tr>
<tr>
<td>(CL1-11-003)</td>
<td></td>
<td>HRT + PTH 100 µg</td>
<td>90</td>
</tr>
<tr>
<td><strong>Sequential Therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaTH (N01-AR-9-2245)</td>
<td>PTH and ALN in combination for the treatment of osteoporosis</td>
<td>Year 2: 100 µg PTH + Placebo/10 mg ALN</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo + 10 mg ALN/10 mg ALN</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 µg PTH + 10 mg ALN/ 10 mg ALN</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 µg PTH/10 mg ALN</td>
<td>53</td>
</tr>
<tr>
<td><strong>Rittmaster et al., 2000</strong></td>
<td>Enhancement of bone mass in osteoporotic women with PTH followed by ALN</td>
<td>10 mg ALN</td>
<td>66</td>
</tr>
<tr>
<td><strong>Uncontrolled</strong></td>
<td>An 18-month open-label extension study (OLEs) of the safety and efficacy of PTH, in women with postmenopausal osteoporosis who participated in TOP Study / 24 month safety includes patients from TOP and OLE and not just OLE.</td>
<td>placebo/PTH 100 µg</td>
<td>900</td>
</tr>
<tr>
<td>OLES(^a) (CL1-11-002)</td>
<td></td>
<td>PTH 100 µg/ PTH 100 µg</td>
<td>781</td>
</tr>
</tbody>
</table>

\(^a\)Safety population (patients who received at least one dose of study drug). \(^b\)Dose Ranging. ALN = alendronate

- Dose response study

The selection of the dose was based on a 12-month, randomised, double blind, multicentre, parallel-group, placebo-controlled study of PTH 50, 75, and 100 µg in postmenopausal osteoporotic women who received calcium (1000 to 1500 mg/day) and vitamin D\(_3\) (400 IU/day) as dietary supplements.

The main criteria for inclusion were: postmenopausal women with osteoporosis aged 50 to 75 years, lumbar spine BMD at least 2.5 SD below the mean of healthy young women and patients with 2 measurable contiguous vertebral bodies in lumbar region L1-L4. Overall, 217
patients were randomised to receive PTH 50 µg (n=52), PTH 75 µg (n=55), PTH 100 µg (n=55) or placebo (n=55).

The primary analysis was the change from baseline in lumbar spine L1-L4 BMD until month 12 for the ITT population. At 6 months the mean percentage increase from baseline in lumbar spine BMD was statistically significant in all PTH group but not in the placebo group (0.4 % placebo; 1.6 % 50 µg; 3.1 % 75 µg; 4 % 100µg). However, the 12-months study results confirmed the superiority of the 100µg over 75µg in terms of BMD. At that time, the mean percentage increase from baseline in lumbar spine BMD in the ITT population were significantly greater in the 100µg dose group (7.9%) compared with the placebo (0.9%), 50µg (3.1%) and 75µg (4.9%) dose groups.

- Main studies

**TOP study (Treatment of Osteoporosis with Parathyroid Hormone)**

This was an international, multi centre, randomised (1:1), double-blind, placebo-controlled, parallel-group, phase III study to compare the effects of 18 months of treatment with PTH or placebo on the incidence of new and/or worsened thoracic and lumbar vertebral fractures in postmenopausal women with osteoporosis receiving calcium and vitamin D3 supplements.

**METHODS**

**Study Participants**

The main inclusion criteria were: women postmenopausal for at least 1 year, 45 years of age or older. If 45 to 54 years of age: Dual-energy X-ray absorptiometry (DXA) BMD ≥ 3.0 standard deviations (SD) below mean peak bone mass (mPBM) of a young adult female or ≥ 2.5 SD below mPBM with at least 1 prevalent vertebral fracture. If ≥ 55 years of age: DXA BMD≥ 2.5 SD below mPBM or ≥ 2.0 SD below mPBM with at least 1 prevalent vertebral fracture. Enrolment of patients with or without a prevalent vertebral fracture was allowed.

**Treatments**

Patients were randomised to receive either 100µg PTH or placebo administered as a daily subcutaneous injection. In addition, patients received daily oral calcium (700 mg) and vitamin D3 (400 IU) supplements. Increases in serum and urine calcium concentrations following the administration of ALX1-11 were anticipated and protocol-specified management algorithms were put in place to reduce elevated calcium levels.

**Objectives**

The primary objective was to compare the effects of 18 months of treatment with PTH or placebo on the incidence of new and/or worsened thoracic and lumbar vertebral fractures in postmenopausal women with osteoporosis receiving calcium and vitamin D3 supplements.

**Outcomes/endpoints**

The primary efficacy endpoint was the incidence of new and/or worsened vertebral fractures as assessed by spinal radiographs (X-rays). Lateral and A/P radiographs of the thoracic and lumbar spine (T4 to L4) were obtained. The primary assessment of vertebral fractures was made using a semiquantitative 4-point grading scale (0 to 3). Grade 0 (normal), Grade 1 (mild deformity), Grade 2 (moderate deformity), Grade 3 (severe deformity) corresponded to no reduction ≥ 20%, or approximately 20-25%, 25-40% or >40% reduction in anterior and/or middle and/or posterior vertebral height. At each imaging timepoint, X-ray images were displayed for review by a single radiologist who had no knowledge of patient identity or medical history. The radiologist was required to review morphometric point placement for each vertebrae and, if appropriate, move or remove points to provide a more accurate assessment of the anterior, posterior, and midheight of each vertebrae. The fracture
assessment from previous X-rays by previous readers was displayed and allowed the
determination of new or worsened fracture by semiquantitative visual assessment at the
current timepoint. At the end of the study, all X-rays for each patient with a change request
were subjected to a blinded over-read by a single radiologist who adjudicated the request and
authorized or denied the requested change. A prevalent (pre-existing) vertebral fracture at
baseline was identified by semiquantitative visual grading. Semiquantitative visual analysis
was the primary method for identifying prevalent vertebral fractures at baseline. A
morphometric evaluation was used as a secondary definition of prevalent fracture. The
definition of a prevalent vertebral fracture by morphometric analysis was:
- A ≥ 2.5 difference in the ratio of the A/P height or mid-height to posterior height within any
1 vertebra,
- A ≥ 2.5 decrease in the height of any 1 vertebra compared to the height of the vertebrae
above and below unless these comparison vertebrae were assessed as having a deformity. In
the latter case, the vertebral height was compared to the nearest unaffected vertebra.
An incident (new or worsened) vertebral fracture was identified by a change in grade from
baseline using the semiquantitative visual grading scale.

Secondary efficacy variables were incidences of vertebral fractures at Month 12; hip and
wrist; and other clinical fracture; changes in height; changes in BMD, BMC, and BMA of the
lumbar spine, total hip, regional hip (greater trochanter, intertrochanter, Ward’s triangle,
 femoral neck), whole body, and forearm assessed by DXA; changes in cortical and trabecular
bone compartments assessed by QCT/pQCT at lumbar spine, hip, forearm, distal femur, and
central tibia (QCT substudy) and by bone histomorphometry at the iliac crest. Changes in
bone turnover markers; change in quality of life; and change in pharmacoeconomic status and
treatment satisfaction were also examined (data not shown).

Sample size
Enrolment of 2600 patients (1300 patients per treatment group) was determined to provide a
power of at least 90% to detect a difference between the treatment groups based on the
following assumptions: The 18-month fracture in the study population is 4.6-5% for patients
treated with placebo, up to 20% of the patients could drop out of the study early without a
fracture so that the effective fracture rate would be 3.68% for the placebo group (assumes
equal drop out rates for the 2 treatment groups), up to 20% of the patients receiving PTH
could have a reduction in dose; patients treated with PTH will show a 60% reduction in
fracture rate relative to patients treated with placebo provided they continue on a dose of
100µg per day, patients with the reduced dosage will only show a 30% reduction in fracture
relative to the patient treated with placebo.

Randomisation and blinding
This was a double-blind study.

Statistical methods
The vertebral fracture rate for the placebo group was estimate to be 4.6% to 5% over 18
months. The assumptions used to obtain this estimate were:
- The vertebral fracture rate among women with a previous vertebral fracture and BMD < -1.7
at baseline was 15.5% over 3 years (7.75% over 18 months) in the vertebral fracture arm of the
fracture intervention trial. Adjusting for the baseline requirements of BMD < -2.0 and
vertebral fracture definition in the current study, an annual vertebral fracture rate of about
6.5% to 7% (10% over 18 months) was estimated for women with a previous vertebral
fracture.
- The vertebral fracture rate among women with BMD < -2.5 and no previous vertebral
fracture is estimated to be about 25% that of the rate among women with a previous vertebral
fracture or, in this study about 2.5% over 18 months (25% of 10%).
- 33% of women will have had a vertebral fracture at baseline and 67% will not have had a vertebral fracture. This yielded an estimated overall vertebral fracture rate of 4.9% over 18 months.

The ITT population consisted of all patients randomised and who received ≥1 dose of double-blind study medication (i.e., the treated population). Patients who discontinued from the study without a new or worsened vertebral fracture were included in the group who had no new or worsened fractures. For time to new and/or worsened fractures, the time was censored at the time of the last X-ray. Sensitivity analyses were performed to assess the effect of censoring. For the analysis of DXA variables, height, and bone turnover markers, all patients with post baseline data for a variable were included in a last-visit analysis, with their last post-baseline observation included. The per-protocol population was the secondary analysis population analyzed for efficacy. The per protocol population consisted of all patients randomised and who received ≥1 dose of double-blind study medication, and had no significant protocol violation. The Pearson’s Chi-square test was used to compare the proportions of patients who experienced a vertebral fracture in each treatment group.

RESULTS

Participants disposition

There were 10,749 subjects screened for this study and 2,679 subjects were randomised to receive either 100 µg PTH (1,286 patients) or placebo (1,246 patients) administered as a daily subcutaneous injection in the thigh or in 1 of 4 quadrants of the abdomen. Among the patients receiving PTH, 825 completed the study (461 discontinued) and 877 patients receiving the placebo, 877 completed the study (369 discontinued). The reasons for discontinuation are provided in the table below:

<table>
<thead>
<tr>
<th>Reasons for discontinuation: [n (%)]</th>
<th>Placebo (N=1246)</th>
<th>PTH 100 µg (N=1286)</th>
<th>Total (N=2532)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident lumbar vertebral fracture(^a)</td>
<td>19 (1.5)</td>
<td>12 (0.9)</td>
<td>31 (1.2)</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>3 (0.2)</td>
<td>2 (0.2)</td>
<td>5 (0.2)</td>
</tr>
<tr>
<td>Bone loss</td>
<td>64 (5.1)</td>
<td>24 (1.9)</td>
<td>88 (3.5)</td>
</tr>
<tr>
<td>- Vertebral</td>
<td>38 (3.0)</td>
<td>8 (0.6)</td>
<td>46 (1.8)</td>
</tr>
<tr>
<td>- Hip</td>
<td>26 (2.1)</td>
<td>17 (1.3)</td>
<td>43 (1.7)</td>
</tr>
<tr>
<td>Hypercalcemia(^b)</td>
<td>1 (0.1)</td>
<td>3 (0.2)</td>
<td>4 (0.2)</td>
</tr>
<tr>
<td>Hypercalciuria(^b)</td>
<td>15 (1.2)</td>
<td>24 (1.9)</td>
<td>39 (1.5)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>22 (1.8)</td>
<td>17 (1.3)</td>
<td>39 (1.5)</td>
</tr>
<tr>
<td>Other adverse event(^c)</td>
<td>91 (7.3)</td>
<td>212 (16.5)</td>
<td>303 (12.0)</td>
</tr>
<tr>
<td>Investigator decision</td>
<td>13 (1.0)</td>
<td>15 (1.2)</td>
<td>28 (1.1)</td>
</tr>
<tr>
<td>Withdrew consent</td>
<td>120 (9.6)</td>
<td>179 (13.9)</td>
<td>299 (11.8)</td>
</tr>
<tr>
<td>Noncompliance</td>
<td>23 (1.8)</td>
<td>20 (1.6)</td>
<td>43 (1.7)</td>
</tr>
<tr>
<td>Inclusion/exclusion criteria</td>
<td>19 (1.5)</td>
<td>18 (1.5)</td>
<td>37 (1.5)</td>
</tr>
</tbody>
</table>

\(^a\) patients were discontinued if they had an incident fracture; \(^b\) Patients were discontinued if they exhausted the clinical management steps of the hypercalcemia and/or hypercalciuria algorithm, and still had an elevated serum and/or 24-hour urinary calcium level or urinary calcium-to-creatinine ratio; \(^c\) Includes four patients (3 placebo, 1 PTH) with an incident lumbar vertebral fracture whose reason for discontinuation was reported as an AE.

Patients with a major protocol deviation were excluded from the per-protocol population. A total of 662 patients had at least one major protocol deviation. There were more patients in the PTH group with major protocol deviations compared with the placebo group. The most common major protocol deviation for both treatment groups was “less than 75% dosing compliance over the course of the study.”
Conduct of the study
There were 9 amendments to the clinical study protocol. Over 90% of the patients in each treatment group were randomized after implementation of Amendment 5, which changed the inclusion criteria to allow the enrolment of women with mild to moderate osteoporosis and with no prevalent vertebral fractures. Following randomization, the study was conducted according to the most recent, IRB-approved amendment for each patient.
As a result of the findings of osteosarcoma in a rat carcinogenicity study with teriparatide the study duration was reduced from 36 months to 18 months and an open-label extension study for up to a maximum of 24 months (TOP plus OLES studies).

Baseline data
Patients from the ITT population were mostly Caucasian (placebo, 84.9%; PTH, 84.7%), between 55 and 74 years of age (placebo, 77.8%; PTH, 83.1%), baseline mean±SD weight, height and BMI were similar between treatments groups. Most of the patients randomised were postmenopausal for ≥ 5 years (94.1%), with no prevalent vertebral fractures (placebo, 81.1%; PTH, 81.6%). Baseline medical conditions and history data and concomitant medications were similar between treatment groups. The mean duration of bisphosphonate treatment in the placebo group was longer. There were no differences between the treatment groups in mean lumbar spine (-2.96 in the placebo group vs. -3.02 in the PTH group), total hip, and femoral neck T-score (see table 4). Approximately 19% of patients in each treatment group had at least 1 prevalent vertebral fracture and 75% of patients with vertebral fractures at baseline had only 1 fracture. At baseline there was no difference between treatment groups in the frequency of prevalent vertebral fractures (see table 5).

Table 4 - Bone mineral density at baseline – TOP study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>PTH</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-score b</td>
<td>1143</td>
<td>-2.96±0.774</td>
<td>1183</td>
</tr>
<tr>
<td>Hologic BMD (g/cm²)</td>
<td>718</td>
<td>0.717±0.0853</td>
<td>754</td>
</tr>
<tr>
<td>Lunar BMD (g/cm²)</td>
<td>528</td>
<td>0.835±0.10140</td>
<td>532</td>
</tr>
<tr>
<td>Total hip</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-score c</td>
<td>1246</td>
<td>-1.89±0.785</td>
<td>1285</td>
</tr>
<tr>
<td>Hologic BMD (g/cm²)</td>
<td>718</td>
<td>0.7139±0.09432</td>
<td>753</td>
</tr>
<tr>
<td>Lunar BMD (g/cm²)</td>
<td>528</td>
<td>0.771±0.09639</td>
<td>532</td>
</tr>
<tr>
<td>Femoral neck</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-score c</td>
<td>1246</td>
<td>-2.21±0.717</td>
<td>1285</td>
</tr>
<tr>
<td>Hologic BMD (g/cm²)</td>
<td>718</td>
<td>0.5940±0.07823</td>
<td>753</td>
</tr>
<tr>
<td>Lunar BMD (g/cm²)</td>
<td>528</td>
<td>0.7293±0.08598</td>
<td>532</td>
</tr>
</tbody>
</table>

* p-values for the treatment comparison of continuous variables was based on t- tests.
* Calculation of lumbar spine T-score required 4 evaluable lumbar vertebrae.
* one patient in the PTH treatment group had no baseline data at total hip and femoral neck.

Table 5 - Prevalent vertebral fractures at baseline - TOP study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>PTH</th>
<th>Total</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any prevalent fracture</td>
<td>235 (18.9)</td>
<td>236 (18.4)</td>
<td>471 (18.6)</td>
<td>0.734</td>
</tr>
<tr>
<td>Number of vertebrae fractured (total)</td>
<td></td>
<td></td>
<td></td>
<td>0.070</td>
</tr>
<tr>
<td>None</td>
<td>1008 (81.1)</td>
<td>1048 (81.6)</td>
<td>2056 (81.4)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>184 (14.8)</td>
<td>165 (12.9)</td>
<td>349 (13.8)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>27 (2.2)</td>
<td>48 (3.7)</td>
<td>75 (3.0)</td>
<td></td>
</tr>
<tr>
<td>&gt;2</td>
<td>24 (1.9)</td>
<td>23 (1.8)</td>
<td>47 (1.9)</td>
<td></td>
</tr>
</tbody>
</table>
**Vertebral fracture by severity**

<table>
<thead>
<tr>
<th>Severity</th>
<th>Placebo</th>
<th>PTH</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (score=1)</td>
<td>169 (13.3)</td>
<td>160 (12.1)</td>
<td>329 (12.7)</td>
</tr>
<tr>
<td>Moderate (score=2)</td>
<td>75 (5.9)</td>
<td>92 (7.0)</td>
<td>167 (6.4)</td>
</tr>
<tr>
<td>Severe (score=3)</td>
<td>21 (1.6)</td>
<td>22 (1.7)</td>
<td>43 (1.7)</td>
</tr>
</tbody>
</table>

- The p-value for the treatment comparison of categorical variables was based on Pearson Chi-square test.
- If a subject had more than 1 fracture, each severity was counted once.
- Missing baseline evaluable X-ray, no fracture on subsequent X-ray.

**Numbers analysed**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>PTH</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised</td>
<td>1314(100.0)</td>
<td>1365(100.0)</td>
<td>2679(100.0)</td>
</tr>
<tr>
<td>Intent-to-treat (ITT) populationa</td>
<td>1246 (94.8)</td>
<td>1286 (94.2)</td>
<td>2532 (94.5)</td>
</tr>
<tr>
<td>Per-protocol populationb</td>
<td>992 (75.5)</td>
<td>878 (64.3)</td>
<td>1870 (69.8)</td>
</tr>
</tbody>
</table>

- Includes all patients who were randomised and dosed.
- Includes ITT patients who had no major protocol deviations.
Outcomes and estimation

Primary endpoint

At Month 18 (primary time point) significantly fewer patients in the PTH treatment group had a new and/or worsened vertebral fracture compared with placebo: 18 patients in the PTH arm vs. 42 patients in the placebo arm [estimated relative risk ratio: 0.42 (95% CI: 0.24, 0.72), p=0.001]. There was approximately 60% reduction in the risk of a new vertebral fracture in the PTH arm with the placebo arm. One patient (PTH arm) had a worsened vertebral fracture at Month 18.

At Month 12, 40 patients had a new vertebral fracture (23 patients in the placebo arm vs. 17 patients in the PTH arm). The difference between the two groups was not significant (p = 0.290). No patients had a worsened vertebral fracture.

The results obtained in the per-protocol population at Month 18 showed similar results with a 62% reduction in the relative risk of a new and/or worsened vertebral fracture [relative risk ratio: 0.38 (95% CI: 0.19, 0.74)] in the PTH arm compared with the placebo arm. There was a 66% reduction in the risk of a new vertebral fracture in the per-protocol PTH arm compared with placebo at Month 18 (3.33% in the placebo arm vs. 1.14% in the PTH arm, p=0.002), see table 6.

Table 6: Incidence of new and/or worsened vertebral fractures – ITT population

<table>
<thead>
<tr>
<th>Visit</th>
<th>Placebo (N=1246)</th>
<th>PTH (N=1286)</th>
<th>PTH vs placebo</th>
<th>Relative risk ratio (95% CI)</th>
<th>p-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>23 (1.85)</td>
<td>17 (1.32)</td>
<td>0.72 (0.38, 1.33)</td>
<td>0.290</td>
<td></td>
</tr>
<tr>
<td>New</td>
<td>23 (1.85)</td>
<td>17 (1.32)</td>
<td>0.72 (0.38, 1.33)</td>
<td>0.290</td>
<td></td>
</tr>
<tr>
<td>Worsened</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Month 18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>42 (3.37)</td>
<td>18 (1.40)</td>
<td>0.42 (0.24, 0.72)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>New</td>
<td>42 (3.37)</td>
<td>17 (1.32)</td>
<td>0.39 (0.22, 0.69)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Worsened</td>
<td>0</td>
<td>1 (0.08)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

a p-values for the treatment group comparisons were derived using the Pearson Chi-square test.

Table 7: New vertebral fractures, by number of vertebrae fractured and fracture severity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (N=1246)</th>
<th>PTH (N=1286)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any new vertebral fracture</td>
<td>42 (3.37)</td>
<td>17 (1.32)</td>
</tr>
<tr>
<td>Number of vertebrae fractured (total)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>34 (2.73)</td>
<td>16 (1.24)</td>
</tr>
<tr>
<td>2</td>
<td>5 (0.40)</td>
<td>0</td>
</tr>
<tr>
<td>≥3</td>
<td>3 (0.24)</td>
<td>1 (0.08)</td>
</tr>
<tr>
<td>Fracture severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild (grade 1)</td>
<td>18 (1.44)</td>
<td>9 (0.70)</td>
</tr>
<tr>
<td>Moderate (grade 2)</td>
<td>23 (1.85)</td>
<td>8 (0.62)</td>
</tr>
<tr>
<td>Severe (grade 3)</td>
<td>1 (0.08)</td>
<td>0</td>
</tr>
</tbody>
</table>

At Month 18, most patients with a new vertebral fracture had only 1 new fracture. Eight patients in the placebo treatment group compared with 1 patient in the PTH treatment group had multiple vertebral fractures at Month 18. There were more patients with moderate and severe fractures in the placebo group than in the PTH treatment group.
The incidence of nonvertebral clinical fractures in TOP study at Month 12 and 18 for the ITT population is shown in the table below.

Table 8 - Incidence of nonvertebral clinical fractures - TOP study (ITT population)

<table>
<thead>
<tr>
<th>Visit</th>
<th>Placebo (N = 1246)</th>
<th>ALX1-11 (N = 1286)</th>
<th>PTH vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (%) of subjects</td>
<td>Number (%) of subjects</td>
<td>Relative RR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Any nonvertebral</td>
<td>Hip</td>
<td>Wrist</td>
</tr>
<tr>
<td>Month 12</td>
<td>41 (3.29)</td>
<td>54 (4.20)</td>
<td>1.28 (0.86, 1.90)</td>
</tr>
<tr>
<td></td>
<td>3 (0.24)</td>
<td>1 (0.08)</td>
<td>0.32 (0.03, 3.10)</td>
</tr>
<tr>
<td></td>
<td>7 (0.56)</td>
<td>9 (0.70)</td>
<td>1.25 (0.47, 3.33)</td>
</tr>
<tr>
<td></td>
<td>31 (2.49)</td>
<td>44 (3.42)</td>
<td>1.38 (0.87, 2.16)</td>
</tr>
<tr>
<td>Month 18</td>
<td>73 (5.86)</td>
<td>71 (5.52)</td>
<td>0.94 (0.69, 1.29)</td>
</tr>
<tr>
<td></td>
<td>3 (0.24)</td>
<td>3 (0.23)</td>
<td>0.97 (0.20, 4.79)</td>
</tr>
<tr>
<td></td>
<td>10 (0.80)</td>
<td>13 (1.01)</td>
<td>1.26 (0.55, 2.86)</td>
</tr>
<tr>
<td></td>
<td>61 (4.90)</td>
<td>56 (4.35)</td>
<td>0.89 (0.62, 1.27)</td>
</tr>
</tbody>
</table>
|<sup>a</sup> P-values for the treatment group comparisons were derived using the Pearson Chi-square test.  
<sup>b</sup> Other clinical fractures includes fractures other than hip, thoracic or lumbar vertebrae, or wrist.

The apparent target population was patients with baseline T-scores ranging from -1.0 to ≤-5.0. The incidence of new vertebral fractures at Month 18 has been assessed by baseline subgroup. Results are presented in the tables below.

Table 9 – Incidence of new vertebral fractures at Month 18 by baseline subgroup - TOP study (ITT Population)

<table>
<thead>
<tr>
<th>Subgroup category at baseline</th>
<th>Placebo</th>
<th>PTH</th>
<th>PTH vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N (%)</td>
<td>Number (%) of subjects</td>
</tr>
<tr>
<td>Lumbar spine T-score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1.0 to ≥-2.5</td>
<td>255</td>
<td>7 (2.75)</td>
<td>245 (9.60)</td>
</tr>
<tr>
<td>-2.5 to ≥-3.0</td>
<td>959</td>
<td>34 (3.55)</td>
<td>1013 (10.0)</td>
</tr>
</tbody>
</table>

<sup>+</sup> Relative risk calculated

Table 10 - Incidence of new vertebral fractures at Month 18 by subgroups with Baseline T-Score ≥-2.5 or <-2.5 in the TOP study (ITT Population)

<table>
<thead>
<tr>
<th>Subgroup category</th>
<th>Placebo</th>
<th>PTH</th>
<th>PTH vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine T-score</td>
<td>N</td>
<td>N (%)</td>
<td>N</td>
</tr>
<tr>
<td>-1.0 to ≥-2.5</td>
<td>255</td>
<td>7 (2.75)</td>
<td>245</td>
</tr>
<tr>
<td>&lt;-2.5</td>
<td>959</td>
<td>34 (3.55)</td>
<td>1013</td>
</tr>
</tbody>
</table>

Secondary endpoints
Clinical fractures included all nonvertebral fractures reported by the patients. Vertebral fractures were not uniformly reported as adverse events because of frequent absence of clinical signs or symptoms. Results are provided in table 11. Similar results were obtained from the per-protocol population.

### Table 11 - Incidence of Nonvertebral Clinical Fractures (ITT population)

<table>
<thead>
<tr>
<th>Visit</th>
<th>Number (%) of patients</th>
<th>PTH vs placebo relative risk ratio (95% CI)</th>
<th>p-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any nonvertebral</td>
<td>41 (3.29)</td>
<td>54 (4.20)</td>
<td>1.28 (0.86, 1.90)</td>
</tr>
<tr>
<td>Hip</td>
<td>3 (0.24)</td>
<td>1 (0.08)</td>
<td>0.32 (0.03, 3.10)</td>
</tr>
<tr>
<td>Wrist</td>
<td>7 (0.56)</td>
<td>9 (0.70)</td>
<td>1.25 (0.47, 3.33)</td>
</tr>
<tr>
<td>Other&lt;sup&gt;a&lt;/sup&gt;</td>
<td>31 (2.49)</td>
<td>44 (3.42)</td>
<td>1.38 (0.87, 2.16)</td>
</tr>
<tr>
<td>Month 18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any nonvertebral</td>
<td>73 (5.86)</td>
<td>71 (5.52)</td>
<td>0.94 (0.69, 1.29)</td>
</tr>
<tr>
<td>Hip</td>
<td>3 (0.24)</td>
<td>3 (0.23)</td>
<td>0.97 (0.20, 4.79)</td>
</tr>
<tr>
<td>Wrist</td>
<td>10 (0.80)</td>
<td>13 (1.01)</td>
<td>1.26 (0.55, 2.86)</td>
</tr>
<tr>
<td>Other&lt;sup&gt;b&lt;/sup&gt;</td>
<td>61 (4.90)</td>
<td>56 (4.35)</td>
<td>0.89 (0.62, 1.25)</td>
</tr>
</tbody>
</table>

<sup>a</sup> p-values for the treatment group comparisons were derived using the Pearson Chi-square test.

<sup>b</sup> Other clinical fractures includes fractures other than hip, thoracic or lumbar vertebrae, or wrist.

Areal BMD, BMC, and BMA as Assessed by DXA

Lumbar spine and hip DXA scans were obtained for all patients. The first 300 patients randomised at centers that had the capacity to perform whole body and/or forearm (distal one-third of the radius) DXA scans also had these imaging studies conducted. Only Lunar and Hologic densitometers were used. Patients had all post-baseline DXA scans on the same instrument throughout the study. Scans were sent to the central imaging organisation for review and calculation of BMD, BMC, and BMA.

In the PTH treatment group, there was an increase from baseline in lumbar spine BMD at Month 6, which continued throughout the study. Lumbar spine BMD for placebo remained at or below baseline throughout the study. There was a significantly greater percentage (p<0.001) of patients in the PTH group with increases from baseline in lumbar spine BMD of 10% or greater compared with the placebo group. There was also a significantly greater percentage (p=0.026) of patients in the placebo group with a decrease from baseline in lumbar spine BMD of 10% or greater compared with the PTH group. Quantitatively and qualitatively similar changes in BMD, BMC and BMA were observed for total hip, femoral trochanter, femoral intertrochanter and femoral neck.

In the PTH treatment group, there was an initial decrease from baseline in total hip BMD at 6 months followed by an increase at Months 12 and 18. Total hip BMD for the placebo group remained relatively constant for the first 6 months but then decreased gradually throughout the rest of the study period.

Ancillary analyses

**Quantitative Computed Tomography substudy**

This substudy was conducted at a single investigational center. It was a longitudinal study using quantitative computed tomography (QCT) and peripheral QCT (pQCT) to quantify changes in areal and volumetric cortical and trabecular bone volume, BMC, BMD, and structure at several skeletal sites in subjects treated with PTH or placebo. Skeletal sites were either predominantly trabecular (lumbar spine, L3), mixed cortical and trabecular (hip), or predominantly cortical (distal radius and mid-shaft tibia) in composition. These endpoints were used to determine the relationships between areal and volumetric cortical and trabecular
BMC and BMD, and between bone mass and geometry (i.e., spatial distribution of bone) at each skeletal site.
A total of 122 patients were randomized and dosed [62 in the placebo arm, 60 in the PTH arm]; 46 patients in the placebo arm and 36 in the PTH arm completed the study.

The primary efficacy endpoint was the percent change from baseline to Month 18 in lumbar vertebra L3 volumetric trabecular BMD (vTbBMD) measured by QCT. In the PTH treatment group, vTbBMD increased from baseline at Month 3 and this increase continued to 54.2% at Month 12, after which vTbBMD declined to 38.3% above baseline at Month 18. In the placebo group, vTbBMD increased from baseline by 19% at Month 3 and then declined, returning to baseline levels by Month 18. The change from baseline in vTbBMD was significantly greater in the PTH treatment group than the placebo at Months 12 and 18.

**OLES study**
This was an open-label extension study (OLES) of the safety and efficacy of PTH conducted in patients who participated in the TOP study.

**METHODS**

**Inclusion criteria**
Women who had completed or had prematurely discontinued from TOP study (for study participants, see TOP Study).

**Treatments**
All patients were to receive PTH given as 100 µg daily by subcutaneous injection. Patients whose study drug schedule had been reduced as a result of an algorithm for managing hypercalcemia or hypercalciuria were to self-administer PTH on the same schedule as they were following at the end of TOP. Patients also received oral calcium (700 mg) and vitamin D3 (400 IU) supplements unless they had discontinued calcium supplements in TOP. Patients did not resume calcium supplementation in OLES if they had discontinued calcium as the result of the application of a hypercalcemia or hypercalciuria management algorithm. Calcium supplements were to be resumed when PTH was discontinued at the completion of 24 months of treatment.

**Objectives**
The primary objective was to evaluate the safety of continued dosing with PTH, up to a maximum of 24 months, in postmenopausal osteoporotic women.

The secondary objectives were to evaluate the effects of PTH on changes in BMD, BMC and BMA at several skeletal sites, the incidence of vertebral and non-vertebral clinical fractures and changes in height, biochemical markers of bone turnover, and bone histomorphometric variables. Other measurements included quality of life, treatment satisfaction, assessments of dietary calcium intake, and immunological responses to PTH or E. coli proteins. The duration of the effect on BMD after discontinuation of PTH treatment was also evaluated.

**Outcomes/endpoints**
Primary efficacy endpoint was the percent change from baseline in lumbar (L1-L4) vertebral BMD (for secondary efficacy endpoints, see TOP study).

**Statistical methods**
Primary and secondary efficacy endpoints were analysed based on the ITT population. The ITT population included all patients who received at least 1 dose of PTH. Data from patients who consented to participate in the study but did not receive open-label PTH were included in...
the listings but were not included in any analyses. The per-protocol population included all patients who received at least 1 dose of PTH in this OLES and had no major protocol deviations.

Descriptive statistics were used to summarize absolute value, change, and percent change from the TOP baseline for both treatment groups [i.e. placebo/PTH and PTH/PTH], change and percent change from the OLES baseline for the placebo/PTH treatment group, and change and percent change from the follow-up baseline (OLES Month 6) for the PTH/PTH treatment group. For sample size, see TOP Study.

RESULTS

Study participants
A total of 1695 patients consented to participate in this study. Fourteen of them, but did not receive study drug. The remaining 1681 patients received open-label PTH. Treatment with PTH was discontinued when a patients reached a maximum total exposure of 24 months in TOP and OLES combined. Approximately 62% of the PTH/PTH treatment group completed 24 months of treatment, and 29% of the placebo/PTH group completed 18 months of treatment.

Baseline data
Among patients who received a bisphosphonate treatment prior to entering TOP study, the median duration of bisphosphonate treatment was similar in the placebo/PTH treatment group and the PTH/PTH treatment group. For lumbar spine, the OLES baseline mean T-scores for the placebo/PTH treatment group were significantly lower compared with the PTH/PTH treatment group (-3.02 vs -2.67), and Hologic and Lunar mean BMD values where significantly lower in the placebo/PTH treatment group compared with the PTH/PTH treatment group (0.710g/cm² vs 0.758g/cm² and 0.828g/cm² vs 0.859g/cm² respectively). There were no differences between the treatment groups in total hip and femoral neck T-score and Lunar BMD. Approximately 17% of patients in each treatment group had at least 1 prevalent vertebral fracture at the TOP baseline. Most fractures were mild in severity with a comparable distribution of mild, moderate, and severe fractures in both treatment groups.

Numbers analysed

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo / ALX1-11</th>
<th>ALX1-11/ ALX1-11</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consented</td>
<td>905 (100.0)</td>
<td>790 (100.0)</td>
<td>1695 (100.0)</td>
</tr>
<tr>
<td>ITT populationa</td>
<td>900 (99.4)</td>
<td>781 (98.9)</td>
<td>1681 (99.2)</td>
</tr>
<tr>
<td>Per-protocol populationb</td>
<td>735 (81.2)</td>
<td>585 (74.1)</td>
<td>1320 (77.9)</td>
</tr>
</tbody>
</table>

a Includes all subject who consented and were dosed. The ITT population is also the safety population for the study.

<table>
<thead>
<tr>
<th>OLES Visit</th>
<th>Placebo/ PTH</th>
<th>PTH/ PTH</th>
</tr>
</thead>
</table>

Outcomes and estimation
Data were presented for the combined 24 months treatment in both TOP and OLES studies (see table 12 and Figure 1). Changes from baseline for the placebo/PTH treatment group were observed on the baseline values of OLES study and for the PTH/PTH treatment group, changes were observed from the baseline values of the TOP study.

Table 12 - Lumbar spine BMD, BMC, and BMA mean percent change from baseline during treatment with PTH in TOP/OLES - ITT population
<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>mean ± SD</th>
<th>N</th>
<th>mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMD (g/cm²)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Months</td>
<td>664</td>
<td>3.90 ± 4.297</td>
<td>709</td>
<td>6.80 ± 7.653</td>
</tr>
<tr>
<td>12 Months</td>
<td>718</td>
<td>5.68 ± 5.542</td>
<td>679</td>
<td>4.62 ± 7.440</td>
</tr>
<tr>
<td>18 Months</td>
<td>330</td>
<td>6.85 ± 6.059</td>
<td>306</td>
<td>3.88 ± 8.066</td>
</tr>
<tr>
<td><strong>BMC (g)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Months</td>
<td>664</td>
<td>4.95 ± 6.685</td>
<td>709</td>
<td>8.26 ± 9.881</td>
</tr>
<tr>
<td>12 Months</td>
<td>718</td>
<td>7.03 ± 8.064</td>
<td>679</td>
<td>5.49 ± 9.372</td>
</tr>
<tr>
<td>18 Months</td>
<td>330</td>
<td>8.18 ± 8.820</td>
<td>306</td>
<td>4.70 ± 9.589</td>
</tr>
<tr>
<td><strong>BMA (cm²)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Months</td>
<td>664</td>
<td>0.97 ± 3.998</td>
<td>709</td>
<td>1.28 ± 3.895</td>
</tr>
<tr>
<td>12 Months</td>
<td>718</td>
<td>1.21 ± 4.148</td>
<td>679</td>
<td>0.76 ± 3.895</td>
</tr>
<tr>
<td>18 Months</td>
<td>330</td>
<td>1.17 ± 4.588</td>
<td>306</td>
<td>0.74 ± 3.588</td>
</tr>
</tbody>
</table>

Medicinal product no longer authorised
Figure 1 – Percent change in lumbar spine BMD

Percent change from baseline to 6, 12, and 18 months of PTH treatment in BMD values related to the hip were qualitatively similar to those observed for the lumbar spine.

**Forearm BMD, BMC, and BMA**
Forearm and whole body DXA scans were performed on the first 300 patients enrolled in the TOP study. DXA scans of the forearm were obtained only for patients who received PTH during the TOP study and for whom this imaging was done. A total loss in the forearm of 6.1% was observed from baseline in the PTH/PTH group from Month 12 through Month 18.

**Incidence of New and/or Worsened Vertebral Fractures**
From the OLES baseline to Month 18, there were 6 new fractures and 1 worsened fracture in the placebo/PTH group and 2 new fractures and 4 worsened fractures in the PTH/PTH group.

**Incidence of Clinical Fractures**
More patients in the placebo/PTH group (29 patients) than in the PTH/PTH group (19 patients) had non-vertebral clinical fractures.

- **Clinical studies in special populations**
  Clinical studies in special populations were not conducted.

- **Analysis performed across trials (pooled analyses and meta-analysis)**
  Across trials Analyses were not conducted.

- **Supportive studies**

**Study N01-AR-9-2245 (PaTH)**
This was a randomised, placebo-controlled, 2 year, multicentre, double-blind trial to assess the efficacy of PTH and alendronate (ALN) as monotherapy and in combination for the treatment of postmenopausal osteoporosis in women between 55 and 85 years of age, with a bone mineral density scan (DXA) indicating T-scores below -2.5, either at the spine or the femoral neck or total hip, and with at least one additional risk factor for fracture. A total of 238 postmenopausal women, were randomly assigned to one of the following treatment groups: PTH 100 μg, ALN 10 mg, or the combination of both, and followed for 12 months. In
the second year of the study women in the original PTH group were randomly assigned to receive either ALN or matching placebo, and women in the other two groups received ALN. At baseline 165 (69%) women had a T-score below –2.5, and 112 (47%) reported at least one fracture after menopause.

The objectives were to test the hypothesis that the combination of 1 year of PTH with ALN followed by 1 year of ALN alone, will increase bone mass after 2 years more than of ALN alone; to test the hypothesis that the combination of 1 year of PTH with concurrent ALN will increase bone mass more than 1 year of PTH alone; to assess if ALN begun concurrently with PTH is more effective in increasing bone mass than if ALN is initiated after 1 year of PTH; to examine how the combination of ALN and PTH influences biochemical markers of bone turnover.

The primary endpoint was the mean percentage change from baseline in lumbar spine BMD measured by DXA at Month 24. Secondary endpoints included mean percentage change from baseline in BMD at Month 12, bone quality as measured by QCT, height, and biochemical markers of bone turnover.

The results for the primary endpoint showed that PTH/ALN treatment for 2 years significantly increased lumbar spine areal BMD by 12%, compared with PTH+ALN/ALN (8% and 11%) and ALN/ALN (8% and 6%). There was a high discontinuation rate in the PTH + placebo year 1 group (15%). In terms of mean change in hip BMD, there was a 4.5% increase from baseline with one year of ALN compared to a 0.1% decrease after one year of placebo.

At 12 Months, the increases in lumbar spine BMD above baseline were similar in the PTH and combination-therapy groups and were smaller in the ALN group (6.3%, 6.1% and 4.6%, respectively). Increases in BMD at the total hip were 1.9, 0.3, and 2.8% for the 3 groups, respectively.

**Rittmaster study**
This study was a bibliographic study. Upon completion of the phase II (study ALX1-11-821) study, a portion of the osteoporotic women who were treated for one year with PTH 50, 75, or 100µg or placebo, entered a 1-year open-label extension study of daily ALN 10mg administration. The primary objective was to determine whether ALN would preserve or enhance lumbar spinal, femoral neck, and whole body BMD in patients previously treated with PTH. Seventy-five patients were enrolled, and 66 completed the 1-year extension period. There were statistically significant differences for lumbar spinal BMD mean percentage change from baseline in favour of PTH 75µg and 100µg /ALN compared with placebo/ALN.

**Power Study**
This was a phase III, randomized, double-blind, placebo-controlled, parallel-group, multicountry, multicentre study, investigating the effect of PTH in women with low bone mass on stable oestrogen replacement therapy. This study was originally designed to evaluate the effect of combination therapy with HRT and PTH compared to HRT monotherapy after 12 and 24 months of treatment. Despite the fact that almost all patients discontinued the study treatment due to the published data on the risk of long-term HRT, a decision was made to terminate the study after all patients had received at least 18 months of study drug treatment. The primary objective of the study was to evaluate the effect of HRT + PTH on vertebral BMD in women with low bone mass receiving supplemental calcium and vitamin D3 for 24 months, and the duration of the effect on bone mineral density (BMD) after discontinuation of PTH. 180 patients were randomized (90 HRT, 90 HRT + PTH). The primary endpoint was percentage change from baseline to Month 12 in lumbar spine BMD. The result of the study
regarding the principal variable shows that the mean percentage changes from baseline to 12 month post-baseline for lumbar spine BMD was significantly greater in the PTH group compared with the placebo group (7.1% vs. 1.1%, p<0.001). This study confirmed the known effect of PTH on BMD and bone turnover parameters.

Discussion on clinical efficacy

The results of a 12-months dose response study confirmed the superiority of the 100 µg over 75 µg dose in terms of change from baseline in lumbar spine L1-L4 BMD. These results supported the selection of the dose of 100 µg to be further developed in phase III trials. The dose of 100 micrograms, once-daily has been recommended in section 4.2 (posology and method of administration) of the SPC for the use of PTH.

The TOP study was the only trial in the clinical development program, which evaluated fractures as the primary endpoint. This primary endpoint did not, however, comply with the current CHMP guideline recommendations [22] (primary variable should be based on the occurrence of new axial or peripheral fractures and not worsening of previous fractures). The reason given by the applicant to combine endpoints was based on its intention to register the medicinal product in both the EU and the US. In the other clinical studies, BMD change from baseline was the primary efficacy endpoint. These approaches were endorsed by the CHMP.

The TOP study was the only trial in the clinical development program, which evaluated fractures as the primary endpoint. This primary endpoint did not, however, comply with the current CHMP guideline recommendations [22] (primary variable should be based on the occurrence of new axial or peripheral fractures and not worsening of previous fractures). The reason given by the applicant to combine endpoints was based on its intention to register the medicinal product in both the EU and the US. In the other clinical studies, BMD change from baseline was the primary efficacy endpoint. These approaches were endorsed by the CHMP. The TOP study was initially planned to have a follow-up of 36 months, as required in the current CHMP guidelines [22]. However, as a result of the findings of osteosarcoma in a rat carcinogenicity study with teriparatide, the study duration was reduced to 18 months treatment period and an open-label extension study (OLES) for up to a maximum of 24 months (see non-clinical discussion).

Of the 2532 randomised ITT patients, a total of 55 patients experienced at least one new vertebral fracture, [42 (3.37%) in the placebo arm vs. 17 (1.32%) in the PTH arm]. Patients in the PTH treatment group had a 61% relative risk reduction of a new vertebral fracture at month 18 compared to the patients in the placebo group. To prevent one or more new vertebral fractures, 48 women had to be treated for a median of 18 months for the total population. For patients with pre-existing fractures, NNT was 21 patients. There was no significant difference between the treatment groups in the incidence of any non-vertebral clinical fracture; 5.52% for PTH vs. 5.86% for placebo (see section 5.1 of the SPC). Furthermore the provided analyses of the incidence of new vertebral fracture at Month 18 showed that the inclusion of worsened fractures did not influence the efficacy data since only 1 worsened fracture was reported in the 2532 subjects treated.

Although the risk reduction was higher among women without prevalent fractures (68%) than for those with prevalent fractures (53%), the most relevant absolute reduction was observed among those patients with previous fractures. In addition, the most relevant fracture reduction was observed among patients with a lumbar spine T-score of ≤ -3 (see section 5.1).

Relatively few patients less than 5 years postmenopausal and 45-54 years of age were enrolled in the phase III study (2-3%). The results for these patients were not different from the results in the study as a whole. However, this lack of data could affect the representativity of the population included in the study and the extrapolation of the results to the target population. This issue was highlighted in section 5.1 of the SPC.

No consistent trend for the reduction in the risk of fractures was observed in patients having received previous treatment with either bisphosphonates or estrogens despite the relevant number of patients in this sub-group.

The efficacy, in terms of reduction of fractures and BMD was lower among patients using the thigh as injection site compared with patients using the abdomen as injection site. Thus, only administration in the abdomen has been recommended in section 4.2 of the SPC.

No difference between the treatment groups in the incidence of any non-vertebral clinical fracture was observed at 18 months. Although no formal comparisons can be made, the effect
of PTH observed on lumbar spine BMD appeared lower than the effect of other drugs having a similar mechanism of action. However, this difference did not result in a different protection pattern against osteoporotic vertebral fractures. No differences were seen in mean percent change from baseline in BMA at any post-baseline time point.

In the OLES study the evaluation of the primary endpoint, showed a total increase of 6.8% in lumbar vertebral BMD from baseline at all time points in the PTH/PTH group. As the OLES study was an open-label extension of the TOP study, no valid efficacy conclusions could be derived from this analysis and it was considered as supportive only.

The results of the PaTH study were included in section 5.1 of the SPC. Based on the results of this study, section 4.2 of the SPC states that following treatment with PTH patients can be treated with a bisphosphonate to further increase BMD.

Clinical safety

The safety of PTH was evaluated in 13 clinical studies (8 clinical pharmacology and 5 Phase II and III trials). Another study conducted by the investigators evaluated the study drug with a bisphosphonate after PTH in the Phase II study (Rittmaster et al., 2000).

- **Patient exposure**

A total of 3321 patients were randomized in 4 double-blind and 1 open-label study. 3167 patients received PTH. The studies were designed to evaluate exposure to PTH from 12 months (phase II) up to 24 months (long-term safety in TOP and OLES combined). The duration of treatment with 100 µg PTH ranged from a median of 363 days (approximately 12 months) in the phase II study to a median of 540 days (approximately 18 months) in the placebo-controlled phase III study (TOP). The majority of patients in the 100-µg PTH group across all studies received the PTH for at least 12 months. The duration of placebo administration in the placebo-controlled studies was similar to that of PTH. The duration of PTH treatment in the long term 24 month safety population excluded the number of days of treatment interruption between TOP and OLES.

From 65% to 78% of patients who received 100 µg PTH completed the studies, compared with 71% to 84% of patients who received placebo.

Only women were evaluated in the phase II and phase III studies, and the majority of patients across all studies were Caucasian and ranged in age from 45 to 85 years. The mean age of the patients was 65 to 65 years in all studies, except the active-control studies (PaTH and POWER) in which the mean age was 58 to 70 years.

- **Adverse events (AE)**

Systemic adverse events (headache, nausea, arthralgia, back pain, nasopharyngitis, pain in extremities, influenza, and dizziness), laboratory abnormalities reported as adverse events (hypercalciuria and hypercalcaemia), and injection site adverse events were reported. About 71% of patients receiving PTH reported at least one drug reaction.

**Systemic adverse events**

Compared with placebo, headache was reported with a higher incidence in patients receiving PTH in the pooled placebo-controlled studies (23% vs. 29%, respectively). There was a dose-response relationship for nausea, with the incidence increasing with increasing dose (7% of patients in the placebo group vs. 22% of patients in the 100 µg PTH group). Compared with placebo, nausea was reported with a higher incidence in patients receiving PTH in the pooled
placebo-controlled studies (9% of patients vs. 23%, respectively). Nausea was considered related to the treatment in 13.5% of the patients receiving PTH. The incidence of nausea was twice as high when PTH was administered in combination with HRT compared with PTH monotherapy; the incidence was similar in patients receiving PTH monotherapy compared with PTH combined with ALN.

In the pooled placebo-controlled studies, back pain was reported with a higher incidence in patients receiving placebo compared with patients receiving PTH (20% of patients vs. 19%, respectively). The incidence of back pain was higher when HRT was administered alone or in combination with PTH, compared with PTH monotherapy or in combination with ALN (18% and 21% of patients vs. 12% and 14%, respectively).

Pain in extremity was reported with a higher incidence in patients receiving PTH or ALN monotherapy compared with patients receiving HRT, PTH+ALN, or PTH+HRT (18% and 19% vs. 11%, 9% and 9%, respectively).

There was a dose-response relationship for dizziness, with the incidence increasing with increasing dose (7% of patents in the placebo group vs. 16% of patients in the 100 µg PTH group). Compared with placebo, dizziness was reported with a higher incidence in patients receiving 100 µg PTH in the pooled placebo-controlled studies (8% of patients vs. 12%, respectively). The incidence of dizziness was approximately twice as high in patients receiving PTH monotherapy or in combination with either ALN (10%) or HRT compared with patients receiving ALN monotherapy or HRT alone (11%, 10% and 10% vs. 5% and 6%, respectively).

**Laboratory abnormalities reported as adverse events**

Compared with placebo, hypercalciuria was reported in twice the proportion of patients receiving 100 µg PTH in the pooled placebo-controlled studies (21% of patients vs. 44%, respectively).

There was a dose-response for hypercalcaemia with the incidence increasing with increasing dose (placebo, 0%; 50 µg PTH, 2%; 75 µg PTH, 4%; 100 µg PTH, 4%). Compared with placebo (4 %), hypercalcaemia was reported with a higher incidence in patients receiving 100 µg PTH (27%) in the pooled placebo-controlled studies (4% vs. 27%, respectively). Hypercalcaemia and hypercalciuria was considered related to the treatment in 25.3% and 39.3%, respectively, of the patients receiving PTH. PTH increased serum uric acid concentrations. For all patients who received PTH 100 µg blood uric acid increase was reported for 8 patients (0.6 %) and hyperuricemia was reported for 5 patients (0.4 %).

**Injection site adverse events**

Injection site haemorrhage was the most frequently reported injection site AE. The investigators considered the majority of the injection site-related AEs as mild in severity and related to study drug.

**Antibodies to PTH and E. Coli**

The immunological potential was assessed during the clinical studies by measuring antibodies to *E. coli* contaminating protein (ECP) as well as antibodies to PTH. In the TOP and POWER studies, serum samples were collected at screening and at Months 12 and 18 for the determination of antibodies. Serum samples in the phase II study were collected at baseline and at Month 12. In the TOP study a total of 36 patients (3.1%) were positive for PTH antibodies in the PTH treatment group and 2 patients (0.2 %) in the placebo group. Eleven (1.0%) patients treated with placebo had ECP antibodies, compared with 5 (0.4%) patients treated with PTH. In the POWER study one patient in the PTH treatment group developed non specific antibodies against PTH at the Month 12 visit and all post-dose samples were negative for ECP antibodies.
An overview of the adverse drug reactions (incidence at least 0.5% higher on the PTH group compared to placebo). The following categories are used to rank the undesirable effects by frequency of occurrence: very common (> 1/10); common (> 1/100 and <1/10); uncommon (> 1/1000 and <1/100); rare (> 1/10,000 and <1/1000); and very rare (<1/10,000), including isolated reports (N = 1314).

Table 13 – Summary of adverse drug reactions observed in clinical trials:

<table>
<thead>
<tr>
<th>Category</th>
<th>Very common (≥ 1/10)</th>
<th>Common (&gt; 1/100 and ≤1/10)</th>
<th>Uncommon (&gt; 1/1000 and ≤1/100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>25.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood calcium increased</td>
<td></td>
<td>3.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Blood alkaline phosphatase increased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood uric acid increased</td>
<td>0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>9.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>3.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parosmia</td>
<td>0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>13.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercalcuria</td>
<td>39.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine calcium/creatinine ratio increased</td>
<td>2.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine calcium increased</td>
<td>2.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>2.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site irritation</td>
<td>0.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A summary of the adverse events (including adverse drug reactions) observed in the clinical trials is provided in the following table:

Table 14 – Summary of AE observed in clinical trials:
Serious adverse event/ deaths/ other significant events

Serious adverse events
No serious adverse events were reported for patients in the clinical pharmacology studies. Serious adverse events were reported for a total of 10 patients (5 patients in the placebo group; 2 in the 50 µg PTH group; 1 in the 75 µg PTH group and 1 in the 100 µg PTH group) in the phase II study.

In the pooled placebo and PTH studies 182 patients (7.3% of patients in the placebo group; 3.9% in the 50 µg PTH group; 1.8% in the 75 µg PTH group and 6.3% in the 100 µg PTH group) reported at least one serious adverse event. A higher proportion of cardiac disorders were reported as serious AEs in the placebo group (1.5%) than in the 100 µg PTH (0.8%) group. Angina pectoris and atrial fibrillation were the most common cardiac disorders reported as serious adverse events in the placebo treatment group. No cardiac disorder was reported as a serious adverse event in more than 2 patients in the 100 µg PTH treatment group. Two patients receiving placebo were reported to have pancreatitis and 1 patient receiving PTH was reported to have acute pancreatitis.

Deaths
Fourteen patients participating to the clinical studies had adverse events leading to death. Twelve of these patients had adverse events leading to death after study drug was discontinued. Except for 1 patient in OLES, none of the adverse events leading to death occurred on study drug. None of the deaths were reported as associated with study drug.
patient died or had an adverse event leading to death in the clinical pharmacology studies, the phase II study or the POWER study. Three deaths were reported during TOP study.

- Laboratory findings

**Hematology results**
Across all studies, over 85% of patients in all treatment groups who had normal values for RBC parameters at baseline also had normal values at endpoint. However, in the phase II, TOP and OLES studies, almost twice as many patients in the 100 µg PTH treatment group compared with the placebo group had a shift in RBC from normal at baseline to low at endpoint. Over 95% of patients in all treatment groups who had normal WBC and platelet count values at baseline also had normal values at endpoint.

**Clinical chemistry results**
Overall, the proportion of patients with shifts from normal at baseline to high in creatinine was similar in the placebo and 100 µg PTH groups. Over 80% of the patients in both treatment groups in OLES and 93% in PaTH and Power, who had normal creatinine and urea values at baseline also had normal values at endpoint. Across all studies, over 93% of patients in all treatment groups who had normal values at baseline for ALT, AST, total bilirubin, GGT, and lactate dehydrogenase also had normal values at endpoint. A higher proportion of patients in the 100 µg PTH treatment group had a shift in alkaline phosphatase from normal at baseline to high at endpoint than those in the placebo group.

A higher proportion of patients in the PTH treatment groups had a shift in serum calcium from normal at baseline to high at endpoint than patients in the placebo group. However, over 82% of patients in all treatment groups who had a normal serum calcium level at baseline also had a normal level at endpoint. Calcium values of potential clinical importance were reported in approximately 5% of subject patients in the 100 µg PTH group in TOP study, 3% of patients who received placebo/100 µg PTH and less than 1% of patients who received 100 µg PTH/100 µg PTH in OLES, and 2% of patients who received placebo/100 µg PTH and 4% of patients who received HRT/100 µg PTH, 4% in PaTH and POWER.

No patient was reported to have hypocalcaemia after PTH was discontinued. There was no laboratory evidence of parathyroid gland suppression after stopping PTH. In the PaTH study, while mean serum calcium and phosphate values increased between baseline and endpoint for the PTH groups in Year 1 and decreased for the ALN alone group, these increases were reversed when patients were switched to ALN or placebo in Year 2. The values at the end of Year 2 were slightly below the original baseline values in these 3 treatment groups. In the group that remained on ALN throughout the study, there was no further decrease in serum calcium from the end of Year 1 to the end of Year 2. Fewer patients had shifts in calcium from normal at baseline to high in Year 2 compared to Year 1. Shifts in phosphate were similar between Year 1 and Year 2.

**ECG results**
Across all studies, over 80% of patients who had normal ECG results at baseline had normal results at endpoint. Most patients in both treatment groups had a QTc value increase of less than 30 msec from baseline to endpoint.

- Safety in special populations
Age and race
There were no notable differences between the age groups in the occurrence of the more frequently reported adverse events. The number of patients in the respective groups was too small to reach a conclusion regarding the distribution of the more frequently reported adverse events by race category.

Overdose
Acute accidental overdosage of PTH can result in transient hypercalcaemia and hypercalciuria. In the PTH clinical program, accidental overdose was reported for 16 patients. Hypercalcaemia and/or hypercalciuria were reported for the majority of patients who had an accidental overdose of PTH. Study drug was temporarily interrupted in these patients, and the adverse event resolved.

- Safety related to drug-drug interactions and other interactions

The use of concomitant medications was similar in the treatment groups. Compared to the pooled placebo-controlled studies, the most frequently taken concomitant medications were similar except for HMG-CoA reductase inhibitors, thyroid hormones, and coxibs. PTH has been administered to a large number of patients who had received a broad spectrum of concomitant medications that would be expected due to the population studied and the underlying medical problems. No potential for drug interactions was identified.

- Discontinuation due to adverse events

A total of 3167 patients were randomised to the TOP, phase II, POWER and PaTH studies. Of these, 2712 patients (70.5%) completed the studies. The most frequent reason for discontinuation was withdrawal of consent; the next most frequent reason was the occurrence of adverse events. Higher percentages of patients discontinued in the TOP (32.8%) and POWER (32.8%) studies compared with the phase II (14.3%) and PaTH (5.5%) studies. The most common adverse events leading to discontinuation in the PTH treatment group during the pivotal TOP study were nausea (8.8%), headache (1.4%), vomiting (1.1%), and dizziness (0.8%). The most common adverse events leading to discontinuation in the placebo treatment group were bone density decreased (2.2%), and vertebral fracture (0.9). In the pooled placebo and dose comparison PTH studies, gastrointestinal disorders (placebo, 1%; 100 µg PTH, 5%), and nervous system disorders (placebo, 1%; 100 µg PTH, 3%), lead to premature termination occurring in more than 2% of patients in either treatment group.

Only 2 cardiac disorders were reported as adverse events that led to premature termination in more than one patient, myocardial infarction was for 2 patients (placebo) and palpitations were reported for 3 patients (100 µg PTH).

Vascular disorders were reported as adverse events that led to premature termination in 0.2% and 1.0% of patients in the placebo and 100 µg PTH treatment groups, respectively. Only 2 such events were reported in more than one patient, hot flush which was reported in 4 patients (placebo, 1; 100 µg PTH, 3) and hypertension which was reported in 8 patients (100 µg PTH).

Benign neoplasms, malignant and unspecified disorders were reported as adverse events leading to premature termination in less than 0.5% of patients in the placebo and 100 µg PTH groups. For this body system, only 2 adverse events leading to premature termination were reported in more than 1 patient, breast cancer (placebo, 3; 100 µg PTH, 1) and colon cancer (placebo, 1; 100 µg PTH, 2).

- Post marketing experience
PTH has not been approved for marketing in any country at the time of the assessment of this application.

- Discussion on clinical safety

According to the Note for Guidance on Postmenopausal Osteoporosis in Women[22], a duration of randomised treatment of at least 3 years is recommended in order to provide fracture and bone safety data. However, the pivotal randomised study TOP was designed before this guidance document was made public. Safety data were analysed according to subgroups, based on age, race, and region. There were no relevant interactions in the incidence of adverse events, changes in laboratory values, or vital signs based on the subgroup analyses.

PTH was overall well tolerated during the clinical trials. The most frequent treatment related adverse events in the phase II/III program, in which the incidence in the PTH treatment group was significantly greater than the incidence in the placebo group, were hypercalciuria (44% vs. 21%), headache (29% vs. 23%), hypercalcemia (27% vs. 4%), nausea (26% vs. 7%) and dizziness (12% vs. 8%). Artralgia and back pain were reported with a similar incidence in both groups (22% and 20% respectively).

Given the physiological profile of PTH, effects on calcium metabolic parameters in plasma were expected. Hypercalcaemia and/or hypercalciuria reflected the known pharmacodynamic actions of PTH in the gastrointestinal tract, the kidney and the bone. Hypercalcaemia was transient and was reported most frequently in the first 3 months of treatment. It was managed during the clinical programme by monitoring laboratory values and the use of a pre-specified management algorithm (see sections 4.3, 4.4, 4.8 and 5.1 of the SPC).

In response to the risk of hypercalcaemia, section 4.4 of the SPC states patients initiated on PTH therapy should be monitored at months 1, 3 and 6 for elevated levels of serum and/or urinary calcium. Monitoring beyond 6 months is not recommended for patients whose total serum calcium is within the normal limits at 6 months. In patients with pre-existing hypercalcaemia and/or hypercalciuria, PTH treatment was found to be more likely to exacerbate the underlying hypercalcaemia and/or hypercalciuria, and therefore PTH is contra-indicated in these patients (see also section 4.3 of SPC).

ECG surveillance was carried out in patients involved in the phase II and III studies. As expected due to its effects on calcium homeostasis, no effect of the drug on QT prolongation has been observed. In the TOP study, the number of patients who had a change in QTc value of greater than or equal to 30 msec to less than 60 msec and greater than 60 were higher in the placebo/100 µg PTH group than in the 100 µg PTH/100 µg PTH group. Considering the mechanism of action of PTH, its combined use with cardiac glucosides may predispose patients to digitalis toxicity if hypercalcaemia develops. This warning is therefore included in sections 4.4 and 4.5 of the SPC.

Renal calculi were more frequent in the PTH group than in the placebo group. Eleven patients, 8 of them on PTH, were diagnosed with nephrolithiasis, of whom 3 (1 of them receiving PTH) discontinued the study medication for this reason. PTH has not been studied in patients with active urolithiasis. Caution is therefore recommended in patients with active or previous urolithiasis (see section 4.4 of SPC). PTH increases serum uric acid concentrations. Blood uric acid increase and hyperuricaemia were reported in patients who received PTH 100 µg (0.6% and 0.4%, respectively). This difference was statistically significant as compared to placebo. Although gout, arthralgia and nephrolithiasis were reported as adverse drug reactions, the relationship to elevations in uric acid due to PTH administration has not been fully established, as stated in section 4.8 of the SPC.

There were no changes in the renal or liver function tests between groups. However, there was a dose-dependent increase in the serum alkaline phosphatase, which might be attributable to bone-specific alkaline phosphatase. No clinically relevant changes in serum phosphate were observed. PTH is contraindicated in patients with unexplained elevations in bone-
specific alkaline phosphatase, as well as those with severe hepatic or renal impairment (see also section 4.3 of SPC).

A small but significant decrease was observed in the red blood parameters in the PTH group, no other haematology abnormalities were identified (see also section 4.8 of the SPC).

The proportion of patients who had injection site related adverse events was similar in the PTH and placebo groups. In general, the proportion of patients who had injection site related adverse events was similar in the PTH and placebo groups. The investigators considered the majority of the injection site-related adverse events as mild in severity and related to study drug. Patients, however, must be trained to use the proper injection techniques, as stated in section 4.2 of the SPC.

In the TOP study, a total of 198 patients (8.3% in the placebo group, 7.3% in the PTH group) experienced 1 or more SAE. In the pooled placebo and PTH studies 182 patients (6.6%) were reported as having experienced at least one SAE. The most common SAE in the PTH group were hypercalcemia (0.4%) and events related to anaemia (0.4%).

Despite the fact that on the long term basis treatment discontinuations with PTH was not different from placebo, in almost 35% of the PTH treated patients, a dose reduction of PTH was necessary and in almost 60% the supplement of calcium had to be discontinued. Advice to alter the dose of calcium, vitamin D supplements and PTH or to stop supplementation or PTH therapy altogether been included in section 4.4 of the SPC.

The immunological potential was assessed during the clinical studies by measuring antibodies to *E. coli* contaminating protein (ECP) as well as antibodies to PTH. Data on antibodies to PTH were not clearly presented. Although the analysis plan specified that positive samples would be analysed for neutralizing antibody activity, this analysis was not performed. Section 4.8 of the SPC mentions that in women with a positive titre, there was no evidence of hypersensitivity reactions, allergic reactions, effects on BMD response, or on effects on serum calcium.

A substudy of TOP was conducted in order to evaluate the effects of PTH treatment on bone using histomorphometry. A total of 40 bone biopsies were performed but only 28 were evaluable, including 10 biopsies from patients having received PTH. Within this small group, there was no evidence for excessive osteoid accumulation, mineralization defects, marrow fibrosis, or the appearance of abnormal cells and the new bone formed after PTH treatment had normal lamellar structure and normal mineralization. The applicant was proposed to conduct investigations of bone histomorphometry and histopathology post-authorisation, and to include this commitment in the risk management plan.

PTH is contraindicated in patients with a know hypersensitivity to PTH or to any of the excipients in the product. It is also contraindicated in patients who have previously received radiation to the skeleton, patients with disturbances in the phosphocalcic metabolism, patients with metabolic bone diseases other than primary osteoporosis, including hyperparathyroidism and Paget’s disease (see also section 4.3 of SPC).

The safety of PTH in patients under 18 years has not been studied. PTH should not be used in paediatric patients or young adults, as stated in section 4.2 of the SPC. No data are available for the use of PTH in pregnancy and lactation. As stated in section 4.6 of the SPC, PTH should therefore not be used during pregnancy or breast-feeding. No studies on the effects on the ability to drive and use machines have been performed.

No specific antidote to PTH exists and any overdose should be managed with supportive therapy, as detailed in section 4.9 of the SPC.
As some episodes of dizziness have been described in patients treated with PTH, section 4.7 of the SPC recommends patients should refrain from driving or using machines until symptoms have subsided.

1.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system
The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements. The statements provided are adequate to meet the requirement of article 1b of Directive 2001/83/EC.

Risk Management Plan
The Applicant submitted a risk management plan. The risk management plan did not include a risk minimisation plan. The post-marketing safety surveillance will rely on standard pharmacovigilance activities based on passive surveillance and additionally, specific surveillance activities are planned post-marketing for addressing potential safety risks and missing information:

Table 15 - Summary of the risk management plan

<table>
<thead>
<tr>
<th>Safety issue</th>
<th>Proposed pharmacovigilance activities</th>
<th>Proposed risk minimisation activities</th>
</tr>
</thead>
</table>
| Wrist and non-axial fractures       | - Investigation into the incidence of wrist and other non axial fractures using hospital diagnostic registries. Report on feasibility and protocol to be submitted in Q2 2006.  
- Monitoring of wrist and other non-axial fractures in ongoing clinical trials. Review of results to be provided with RMP updates.  
- Monitoring of wrist and other non-axial fractures in proposed clinical trial FP-001-IM. Review of results to be provided with RMP updates.  
- Routine pharmacovigilance.        | - Contraindication included in section 4.3 of the SPC for patients with metabolic bone diseases other than primary osteoporosis.  
- Pre-clinical and clinical safety data on bone disorders included in sections 5.3 and 4.8, respectively, of the SPC. |
| Bone Histomorphometry              | Include evaluation of bone histomorphometry and histopathology in the clinical trial – FP-001-IM         |                                                                                                         |
| Hypercalcaemia/hypercalciuria      | - Expedited reporting of all reports of suspected serious hypercalcaemia and hypercalciuria events from EU and Non-EU countries  
- Review of all serious cases on a 6 monthly basis  
- Routine pharmacovigilance using specific questionnaire | - Contraindication included in section 4.3 of the SPC for patients with pre-existing hypercalcaemia.  
- Special warnings and precautions for use in section 4.4 of the SPC.  
- Information included in section 4.5 of the SPC on combined use of PTH and cardiac glucosides which may predispose patients to digitalis |
The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

1.6 Overall conclusions, benefit/risk assessment and recommendation

Quality
In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The fermentation and purification of the drug substance, have been adequately described, controlled and validated. The drug substance has been well characterised with regard to its physicochemical and biological characteristics, using state-of-the-art methods, and appropriate specifications have been set. The manufacturing process of the drug product has been satisfactorily described and validated. The quality of the drug product is controlled by adequate test methods and specifications. The general safety and the safety concerning other adventitious agents including TSE have been sufficiently assured. Except for a number of quality points that the applicant agreed to address post authorisation, the overall quality of Preotact was considered acceptable.

Non-clinical pharmacology and toxicology
The medicinal product PTH contains recombinant human parathyroid hormone which is identical to full-length native 84-amino acid polypeptide. Physiological actions of PTH include stimulation of bone formation by direct effects on bone forming cells (ostoblasts), indirectly increasing the intestinal resorption of calcium and increasing reabsorption of calcium and excretion of phosphate by the kidney.
Two primary pharmacodynamics pivotal studies were conducted, one in rats and one in monkeys, in which the effect of PTH on bone mineral density, strength and architecture was studied. Treatment with PTH for 12 months in rats resulted in a dose-related gain in bone mass at trabecular and cortical bone sites, associated with increased bone strength. In monkeys, PTH treatment for 39 weeks increased markers of bone turnover. Formation markers were increased to a greater extent than resorption markers. Also, treatment with PTH at 25 µg/kg for 16 months resulted in significant increases in trabecular bone mass and increases in vertebral and femoral neck bone strength.
Preclinical data reveal no special hazard for humans based on conventional studies of safety, pharmacology, mutagenicity, toxicity to fertility and general reproduction, and local tolerance. In monkeys receiving daily subcutaneous doses for 6 months, there was an increased occurrence of renal tubular mineralization at exposure levels below clinical exposure levels. Rats treated with near life-time daily injections had dose dependant exaggerated bone formation and an increased incidence of bone tumours, including osteosarcoma, most probably due to an epigenetic mechanism. Due to the differences in bone physiology in rats and humans, the clinical relevance of these findings was considered minor.

Efficacy
The clinical efficacy of PTH in the treatment of osteoporosis in postmenopausal women was supported by one pivotal phase III placebo controlled study (TOP), an open-label extension/safety study (OLES) and two phase III active control studies (PaTH, and POWER). In the pivotal study, less patients (17, 1.32%) in the PTH treatment group experienced at least one new vertebral fracture than in the placebo group (42, 3.37%). Patients in the PTH
treatment group had a 61% relative risk reduction of a new vertebral fracture at month 18 compared to the patients in the placebo group. At Month 12 the difference between groups was not significant. The most relevant fracture reduction was observed among patients at high risk of fractures such as patients with previous fractures and/or in patients with a lumbar spine T-score of ≤ -3.

In terms of effect on bone mineral density (BMD), the data obtained in the pivotal study showed a significant increase in BMD (6.5%) in the lumbar spine after 18 months of treatment with 100 µg of PTH compared with placebo (-0.3%), p<0.001. Increases in hip BMD (total hip, femoral neck, femoral trochanter) were observed at study endpoint (p<0.001).

The efficacy, in terms of reduction of fractures and BMD was lower among patients using the thigh as injection site compared with patients being injected the PTH in the abdomen. Thus, only administration in the abdomen has been recommended in section 4.2 of the SPC.

Continued treatment for up to 24 months in the open-label extension of this study (OLES) showed a continued increase in BMD. The increase from baseline in lumbar spine and femoral neck BMD was 6.8 % and 2.2%, respectively in patients treated with PTH. As the OLES study was an open-label extension of the TOP study, the results obtained in this study were considered as supportive only.

Safety

The safety analysis has been carried out on a total of 3321 patients randomised in the 4 double-blind and 1 open-label study. Including clinical pharmacology studies, 3167 patients received the study drug. Overall, PTH was well tolerated during the clinical trials. The most frequent treatment related adverse events in the phase II/III program, for which the incidence in the PTH treatment group was greater than the incidence in the placebo group, were hypercalciuria (44% vs. 21%), headache (29% vs. 23%), hypercalcaemia (27% vs. 4%), nausea (22% vs. 7%) and dizziness (12% vs. 8%). Arthralgia and back pain were reported with a similar incidence in both groups, 22% and 20% respectively, as was the proportion of patients who had injection site related adverse events.

In the pooled placebo and PTH studies 182 patients (6.6%) were reported as having experienced at least one serious adverse event. The most common SAE in the PTH group were hypercalcaemia and events related to anaemia. Considering the mechanism of action of PTH, hypercalcaemia is an expected adverse effect. In responses to the risk of hypercalcaemia, adequate recommendation to monitor patients initiated on PTH therapy has been included in the SPC.

The adverse drug reactions reported in clinical trials have been included in the SPC. Having considered the safety concerns described in the risk management plan, the CHMP considered that the proposed surveillance activities described in section 3.5 of this report, adequately address the safety issues raised.

Benefit/risk assessment

The efficacy of PTH has been documented in postmenopausal women with low BMD, with or without prevalent vertebral fractures. Patients receiving PTH had a 61% relative risk reduction of a new vertebral fracture at month 18 compared to patients in the placebo group. A reduction in the incidence of hip fracture has not been demonstrated. Increases in the lumbar spine and hip bone mineral density (BMD) were observed in patients receiving PTH. Although the effect on BMD may be regarded as lower than expected, the risk reduction in vertebral fractures was considered similar to other medicinal products with a similar mechanism of action.

Although the relative risk reduction was consistent in patients with and without prevalent fractures, the absolute risk reduction was much higher in patients with vertebral fractures at entry. The anti-fracture effect was observed among patients with a lumbar spine T-score of ≤ -
3, but not in patients with higher BMD scoring. In addition, patients with less than 5 years from menopause and younger than 55 years were underrepresented in the dossier. Thus, to reflect the actual study population in the indication, the applicant revised the claimed indication, after discussion at the CHMP, limiting it to patients at high-risk. Also, the efficacy profile being numerically different depending on the site of administration, the mode of administration has been limited to subcutaneous injection in the abdomen.

A randomised study (PaTH) showed that sequential treatment with PTH for one year followed by ALN for a further year was associated with a therapeutic benefit in terms of increase in BMD, and suggested that additional therapeutic intervention should be considered following discontinuation of PTH. Although these results were obtained with ALN, the conclusion was extrapolated to other bisphosphonates, considering the well characterised anti-resorptive action of all bisphosphonates.

In terms of safety, PTH was overall well tolerated during clinical trials. More patients treated with 100 \(\mu\)g PTH reported hypercalciuria, hypercalcemia, and nausea as compared to other treatment groups. These adverse events were considered related to the treatment. The CHMP, having considered the safety data and the risk management plan submitted, was of the opinion that a number of pharmacovigilance activities, in addition to the routine pharmacovigilance activities, were needed to further investigate cases of hypercalciuria and hypercalcemia, bone histomorphometry, and cases of wrist and other non-axial fractures.

**Recommendation**

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Preotact in the treatment of osteoporosis in postmenopausal women at high risk of fractures was favourable and therefore recommended the granting of the marketing authorisation.
References


22. CPMP Guideline on the evaluation of new medicinal products in the treatment of primary osteoporosis. 2005, EMEA.


33. ICH S7A: Note for Guidance on safety pharmacology studies for human pharmaceuticals. 2000, EMEA.


36. ICH Topic S6: Note for guidance on pre-clinical safety evaluation of biotechnology-derived pharmaceuticals. 1997, EMEA.
37. ICH Topic Q3 A: Note for guidance on impurities testing: impurities in new drug substances. 1995, EMEA.
38. CHMP Guideline on the environmental risk assessment of medicinal products for human use. 2005, EMEA.
56. CPMP Note for guidance on the investigation of drug interactions. 1997, EMEA.
57. ICH Topic E5: Note for Guidance on Ethnic factors in the acceptability of foreign data. 1998, EMEA.
58. ICH Topic E6: Note for guidance on good clinical practice. 1996, EMEA.
59. The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions. 1994, EMEA.
Medicinal product no longer authorised