CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211939Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA 505 (b)(2)
Application Number(s)	211939
Priority or Standard	Standard
Submit Date(s)	December 7, 2018
Received Date(s)	December 7, 2018
PDUFA Goal Date	October 7, 2019
Division/Office	DBRUP/ODEIII
Review Completion Date	September 24, 2019
Established/Proper Name	Teriparatide
(Proposed) Trade Name	Bonsity
Pharmacologic Class	Human parathyroid hormone analog
Code name	PF708
Applicant	Pfenex
Dosage form	Injection
Applicant proposed Dosing Regimen	20 mcg subcutaneously daily
Applicant Proposed Indication(s)/Population(s)	Treatment of postmenopausal women with osteoporosis at high risk of fracture; increase of bone mass in men with primary or hypogonadal osteoporosis at high risk of fracture; treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	64859006 Osteoporosis (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of postmenopausal women with osteoporosis at high risk of fracture Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk of fracture Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	102447009 Postmenopausal osteoporosis (disorder) 276661002 Primary osteoporosis (disorder) 703264005 Secondary osteoporosis (disorder)
Recommended Dosing Regimen	20 mcg subcutaneously daily

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report

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PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

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1 Executive Summary

1.1. Product Introduction

The applicant, Pfenex, Inc. has submitted this New Drug Application (NDA) for PF708 (teriparatide injection), proposed trade name Bonsity, relying on FDA's findings of safety and effectiveness for Forteo (teriparatide, NDA 021318) for the following indications:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture
- Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture
- Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture

The proposed dose of PF708 is 20 microgram (mcg) administered subcutaneously daily. The PF708 drug product is delivered using a manual, fixed-dose pen injector device. The PF708 drug product pen injector has a prefilled drug cartridge that delivers 20 mcg teriparatide per 80-microliter (mcL) dose by subcutaneous injection once daily for 28 days.

The active pharmaceutical ingredient, teriparatide, is manufactured by recombinant means for both PF708 and Forteo. PF708 is manufactured using a strain of *Pseudomonas fluorescens*, whereas Forteo is manufactured using a strain of *Escherichia coli*. PF708 (teriparatide) is a 34 amino acid analog of human parathyroid hormone (PTH). The amino acid sequence is identical to the N-terminal sequence of the full-length 84-amino acid parathyroid hormone (PTH).

The applicant is seeking marketing approval of PF708 via the 505(b)(2) pathway for the same indications approved for Forteo. The applicant justifies relying on FDA's findings of safety and effectiveness for Forteo by providing evidence of physicochemical comparability, nonclinical comparability with a 28-day nonclinical pharmacodynamic study and a 28-day nonclinical subcutaneous toxicity study, a pharmacokinetic bridging study and a clinical study evaluating the immunogenicity potential of PF708 compared to Forteo.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This application relies on the FDA's findings of safety and effectiveness for Forteo for the proposed indications. The applicant has demonstrated physiochemical comparability between PF708 and Forteo. Additionally, the application is supported by demonstration of comparative bioavailability between PF708 and Forteo in a randomized, double-blind, 2-treatment crossover pharmacokinetic study and similar immunogenicity in a 6-month, randomized, parallel-arm, clinical immunogenicity study. The applicant has also demonstrated nonclinical comparability between PF708 and Forteo. Therefore, the applicant's data adequately demonstrates that

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PF708 is expected to have clinical effectiveness and safety similar to that of Forteo and it is acceptable to rely on FDA's findings of Forteo's safety and effectiveness for approval of PF708 (approved tradename Bonsity) for the proposed indications.

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1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The applicant has adequately demonstrated comparability between PF708 (Bonsity) and Forteo with physiochemical data as well as nonclinical, clinical pharmacology, and clinical data. It is reasonable to expect that Bonsity will have the same risks and benefits as Forteo for the three indications sought. The potential risk of osteosarcoma involves a tumor type that is quite rare. Therefore, postmarketing surveillance will include enhanced pharmacovigilance to better characterize cases of osteosarcoma reported with Bonsity by obtaining additional data, including risk factors, diagnostic imaging, and other relevant clinical patient data.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Osteoporosis is a bone disease characterized by loss of bone mass, leading to an increased risk for fractures. Primary osteoporosis (e.g., postmenopausal osteoporosis and male osteoporosis) is due to typical age-related loss of bone. Secondary osteoporosis (e.g., glucorticoid-induced osteoporosis) results from the presence of other conditions or the use of therapies that predispose to bone loss.	Osteoporosis increases the risk of fracture in postmenopausal women, men with primary or hypogonadal osteoporosis and men and women with glucocorticoid-induced osteoporosis. The risk of fracture increases with age and a history of a prior osteoporosis-related fracture.
Current Treatment Options	• Current treatment options for osteoporosis include medications that inhibit bone loss (bisphosphonates, RANK ligand inhibitors, estrogen agonists/antagonists, and calcitonin) and medications that stimulate bone formation (parathyroid hormone and parathyroid hormone related peptide analogs, and a sclerostin inhibitor) • Bisphosphonates are the most widely prescribed medications for osteoporosis. Rare but serious side effects with bisphosphonates	Multiple therapies are available for the treatment of osteoporosis in postmenopausal women, men with primary or hypogonadal osteoporosis and men and women with glucocorticoid-induced osteoporosis. Rare but serious side effects have decreased the usage of some of the currently available therapies

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(osteonecrosis of the jaw and atypical femoral fractures) have reduced the use of these medications. • Denosumab is a potent antiresorptive therapy that also is associated with osteonecrosis of the jaw and atypical femoral fractures. Denosumab is also associated with an increased risk of fracture after discontinuation. • Teriparatide and abaloparatide are bone anabolic therapies. Their use is limited to two years because of the potential risk of osteosarcoma, which was noted in animal studies. • Romosozumab, another anabolic therapy, has the following safety concerns: major adverse cardiac events, injection site reactions, hypersensitivity reactions, hypocalcemia, osteonecrosis of the jaw and atypical femoral fractures.	and many patients with osteoporosis who would benefit from therapy remain untreated. Additional therapies will expand available treatment options.
Benefit	• The applicant has adequately demonstrated comparability between PF708 (Bonsity) and Forteo with physiochemical data as well as nonclinical, clinical pharmacology, and clinical data. Therefore, the clinical benefit of Bonsity is expected to be the same as that for Forteo.	The clinical benefits of Bonsity are expected to be the same as those for Forteo.
Risk and Risk Management	• The applicant has adequately demonstrated comparability between PF708 (Bonsity) and Forteo with physiochemical data as well as nonclinical, clinical pharmacology, and clinical data. Therefore, the safety profile of Bonsity is expected to be the same as that for Forteo.	The clinical risks of Bonsity are expected to be the same as those for Forteo and product labeling will be the same, outlining the same risks as the Forteo labeling. A medication guide will inform patients about these important risks. Labeling alone is adequate to inform the risks. A Risk Evaluation and Mitigation Strategy for

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		this product is not necessary for the benefit to outweigh the risks. The potential risk of osteosarcoma involves a tumor type that is quite rare. Therefore, postmarketing surveillance will include enhanced pharmacovigilance to better characterize cases of osteosarcoma reported by obtaining additional data including risk factors, diagnostic imaging, and other relevant clinical patient data.

1.4. Patient Experience Data

Table 1 Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application.**			

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2 Therapeutic Context

2.1. Analysis of Condition

Osteoporosis is a skeletal disorder characterized by low bone mass and structural deterioration of bone, which leads to bone fragility and increased fracture risk. Osteoporosis results from imbalances between resorption of bone by osteoclasts and formation of new bone by osteoblasts during bone remodeling. The World Health Organization (WHO) defines osteoporosis by BMD criteria obtained using dual-energy X-ray absorptiometry (DXA). A T-score is generated by measurements of the BMD at the lumbar spine, total hip, and femoral neck. Osteoporosis is defined by T-score ≤ 2.5 standard deviations below the mean BMD of a young, healthy cohort of adults at the same location.

Osteoporosis affects over 10 million Americans and is a major cause of morbidity and mortality. Primary osteoporosis (e.g., postmenopausal osteoporosis and male osteoporosis) is due to typical age-related loss of bone. Secondary osteoporosis results from the presence of other conditions or the use of therapies that predispose to bone loss. Glucocorticoid-induced osteoporosis is the most common form of secondary osteoporosis. Hypogonadal osteoporosis is another form of secondary osteoporosis.

Osteoporotic fractures, most notably hip fractures, are associated with increased morbidity and mortality. Despite the morbidity and mortality associated with osteoporosis, and the availability of multiple treatments to reduce fracture risk, osteoporosis remains underdiagnosed and undertreated.

2.2. Analysis of Current Treatment Options

The table below summarizes the currently approved pharmacologic therapies for postmenopausal osteoporosis, osteoporosis in men and glucocorticoid-induced osteoporosis. These therapies include several classes of antiresorptive therapies, two types of bone-forming (anabolic) agents that act through the PTH receptor, and an anabolic agent that acts through inhibition of sclerostin. Bisphosphonates, the main class of antiresorptive therapy, are currently the standard of care for first-line therapy of osteoporosis. Denosumab, a RANKL antagonist, raloxifene, an estrogen receptor agonist/antagonist, and calcitonin are the other available antiresorptive therapies. Available bone-forming agents include the PTH analog teriparatide, the PTH related peptide (PTHrP) analog abaloparatide, and romosozumab, a sclerostin inhibitor.

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Table 2 Summary of FDA-Approved Pharmacologic Treatment Options for Postmenopausal Osteoporosis, Men with Osteoporosis and Glucocorticoid-induced Osteoporosis

Drug Class	Product Name	Year of Approval	Approved Indications	Dosing/ Administration	Important Safety and Tolerability Issues
Bisphosphonates	Fosamax (alendronate)	1995	PMO, MO, GIOP	70 mg PO weekly (tablet or solution) 10 mg PO daily (tablet)	Hypocalcemia, osteonecrosis of the jaw (ONJ), atypical femoral fractures (AFF), Not recommended or contraindicated in patients with severe renal impairment Upper gastrointestinal adverse events with oral formulations
	Fosamax Plus D (alendronate/ cholecalciferol)	2005	PMO, MO, GIOP	70 mg alendronate/2800 or 5600 IU cholecalciferol, 1 tablet weekly	
	Binosto (alendronate)	2012	PMO, MO	70 mg PO weekly (effervescent tablet for oral solution)	
	Actonel (risedronate)	2000	PMO, MO, GIOP	Tablets: 5 mg PO daily 35 mg PO weekly 150 mg PO monthly	
	Atelvia (risedronate)	2010	PMO	35 mg PO weekly (delayed release tablet)	
	Boniva (ibandronate)	2003	PMO	150 mg PO monthly (tablet)	
	Boniva (ibandronate)	2006	PMO	3 mg IV q3 months	Hypocalcemia, ONJ, AFF,
	Reclast (zoledronic acid)	2007	PMO, MO, GIOP	5 mg IV yearly	Hypocalcemia, renal toxicity, acute phase reactions, ONJ, AFF
Sclerostin inhibitor	Evenity* (romosozumab)	2019	PMO	210 mg SC monthly	Major adverse cardiac events, hypersensitivity, hypocalcemia, ONJ, AFF
RANKL antagonist	Prolia* (denosumab)	2010	PMO, MO, GIOP,	60 mg SC q6 months	Hypersensitivity, hypocalcemia, ONJ, AFF, multiple vertebral fractures following discontinuation, serious infections, dermatologic reactions
Estrogen agonist/antagonist	Evista (raloxifene)	1997	PMO	60 mg PO daily (tablet)	Venous thromboembolism, death due to stroke

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Drug Class	Product Name	Year of Approval	Approved Indications	Dosing/ Administration	Important Safety and Tolerability Issues
PTH analog/ PTHrP analog	Forteo* (teriparatide)	2002	PMO, MO, GIOP	20 mcg SC daily	Osteosarcoma risk (animal data) limiting use duration to 2 years, hypercalcemia
	Tymlos* (abaloparatide)	2017	PMO	80 mcg SC daily	Osteosarcoma risk (animal data) limiting use duration to 2 years, hypercalcemia
Calcitonin-salmon	Miacalcin**	1986	PMO	SC or IM injection, 100 IU every other day	Hypersensitivity, hypocalcemia, malignancy
	Miacalcin**	1995	PMO	Nasal spray, 200 IU daily	
	Fortical**	2005	PMO	Nasal spray, 200 IU daily	

Abbreviations: PMO = postmenopausal osteoporosis; MO = men with osteoporosis; GIOP = glucocorticoid-induced osteoporosis
*approved only for osteoporotic patients at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy
**approved only for osteoporotic patients for whom alternative treatments are not suitable (e.g., patients for whom other therapies are contraindicated or for patients who are intolerant or unwilling to use other therapies). Fracture efficacy for calcitonin-salmon has not been established.

Excluding the calcitonin products (which were approved based on total body calcium and/or BMD data), the pharmacologic therapies listed in the above table were approved for the treatment of postmenopausal osteoporosis based on reduction of morphometric vertebral fractures, consistent with the 1994 FDA guidance on osteoporosis drug development. Such fractures are defined solely by radiographic criteria and may be asymptomatic. However, the presence of morphometric vertebral fractures is a strong predictor of subsequent fractures (vertebral and nonvertebral).

The applicant has developed PF708 drug product (pen injector) as an alternative to Forteo to expand access to an anabolic therapy for high-risk osteoporosis patients.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

PF708 has never been approved or marketed in any country.

3.2. Summary of Presubmission/Submission Regulatory Activity

A PIND meeting was held on March 15, 2016 with the Division of Bone, Reproductive, and Urologic Products (DBRUP) to discuss the development plan for the proposed 505(b)(2)

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application for PF708. At this meeting, the division communicated several scientific concerns that would need to be considered with the PF708 development plan including the need for immunogenicity data. In addition to a comparative bioavailability study, immunogenicity data should be provided in a 6-month clinical study evaluating the immunogenicity of PF708 versus Forteo. The division agreed that a 6-month immunogenicity study would be sufficient if there were no safety concerns or differences noted in comparative bioavailability between PF708 and Forteo. However, if there were concerns related to a lack of comparative bioavailibity or safety or immunogenicity in the conducted studies, then a 12-month clinical study evaluating bone mineral density (BMD) would be needed to determine the comparative clinical effect of PF708 versus Forteo using a noninferiority design.

A pre-NDA meeting with the division was held on July 17, 2018 to discuss the proposed data package, format, and content to support filing and review of the 505(b)(2) NDA. It was agreed that the available physiochemical, nonclinical and pharmacokinetic and clinical data would support the review of the NDA. Key information requested by DBRUP at this meeting included additional data regarding the immunogenicity assay, additional information on the impurity levels measured in the drug substance and product batches, additional product stability data, and additional specifications and testing results for the pen injector.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No inspections of clinical sites participating in Studies PF708-101 and PF708-301 were deemed necessary. Study PF708-101 was conducted at a single site in the US (Covance Clinical Research Unit, Inc.), and there were no concerns regarding study conduct or data integrity. Study PF708-301 was conducted at 27 US sites, and each site only had a few participating subjects. All study data was obtained and processed by a single contract research organization ((b) (4) (b) (4) . There were no notable differences in study results between sites, and no concerns regarding study conduct or data integrity.

4.2. Product Quality

The review team from the Office of Pharmaceutical Quality recommends approval of Bonsity (teriparatide injection). Please see the OPQ reviews for complete details.

Bonsity is drug/device combination product containing teriparatide, a 34 amino acid analog of parathyroid hormone, in a single-patient-use pen device. Each pen contains 28 daily doses of 20 mcg teriparatide.

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Drug Substance: The drug substance, teriparatide, is a recombinant analog consisting of the first (N-terminus) 34 amino acids of human parathyroid hormone (PTH). The drug substance is a clear and colorless aqueous solution manufactured (b) (4). (b) (4) with a recombinant strain of Pseudomonas fluorescens. (b) (4)

The drug substance is an aqueous solution, containing (b) (4) teriparatide (b) (4) manufactured at (b) (4) The peptide sequence is H-SerValSerGluIleGlnLeuMetHisAsnLeuGlyLysHisLeuAsnSerMetGluArgsValGluTrpLeuArgLysLysLeuGlnAspValHisAsnPhe-OH. The molecular weight of PF708 drug substance is 4117.773 Da with a molecular formula of $C_{181}H_{291}N_{55}O_{51}S_2$. The PF708 drug substance complies with the current USP monograph tests for identification, bioidentity, endotoxins and, with the exception of the limit for total oxidation impurities (Met8, Met18, and Met8,18), product-related impurities. While the limit for total oxidation impurities of not more than (NMT) (b) (4)% in PF708 (b) (4) the USP limit of NMT 0.5%, the limits for related impurities in the drug product comply with the USP monograph for teriparatide injection.

Drug Product: Bonsity (teriparatide injection) is a drug/device combination product consisting of a sterile, colorless, clear solution provided in a glass cartridge pre-assembled into a disposable multi-dose pen for single-patient use. The glass cartridge is fitted with a rubber septum and rubber plunger. The cartridge is filled with approximately (b) (4) mL of teriparatide injection which is sufficient to provide 28 injections of 80 microliter. Each milliliter contains 250 mcg teriparatide, 0.41 mg glacial acetic acid, 0.10 mg sodium acetate, 45.4 mg mannitol, 3 mg metacresol, and water for injection. The drug product is a pH 4.0 solution. The excipients are all compendial excipients. The filled cartridge is then assembled into a disposable, multi-dose, single-patient use, manual pen injector.

Drug product (filled cartridge) specification includes tests for visual inspection, pH, particulate matte, sterility, bacterial endotoxins, identification and assay of teriparatide, metacresol content, product-related impurities, aggregates, bioidentity, and container content for injections. The product specification includes essential performance requirements (i.e., break loose force and sustaining glide force). The suitability of the analytical procedures has been adequately demonstrated.

The finished drug-device combination product specification includes tests for identification of teriparatide, visual inspection, functional operation, and essential performance requirements (dose accuracy [80 µL (b) (4) mcL], injection force and dose button pull force).

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A 24-month expiration dating period when stored at long-term storage at 2ºC-8ºC is supported by the available stability data. Patients may store the product at 25ºC for 28 days (in-use storage).

Microbiology: The drug product is sterilized by [redacted] (b) (4). The sterile, aqueous solution of teriparatide includes [redacted] (b) (4). Antimicrobial effectiveness testing (AET) demonstrated the adequacy of the preservative throughout the shelf-life (24 months) and in-use period (28 days) of the product.

The sterilization [redacted] (b) (4) have been adequately documented. Adequate controls have been established. Completed process validation studies demonstrate the overall suitability of the manufacturing process with respect to product sterility.

Facilities: The flowing facilities are involved in the manufacture and testing of the Bonsity drug substance and combination drug device product:

- [redacted] (b) (4) (FEI [redacted] (b) (4)) is the site responsible for PF708 drug substance manufacture and fill; release testing and stability storage chambers and testing; release testing of PF708 drug product cartridge; and stability testing of PF708 drug product (pen injector). Because of an overall high-risk ranking, a prior approval inspection (PAI) was conducted. A form 483 was issued and the firm's responses were reviewed. The inspection was finalized as voluntary action indicated (VAI).
- [redacted] (b) (4) (FEI [redacted] (b) (4)) is the site responsible for PF708 drug product formulation and fill; release testing of PF708 drug product cartridge; and stability testing of PF708 finished drug product (pen injector). The site was recommended for approval based on file review.
- [redacted] (b) (4) (FEI [redacted] (b) (4)) PF708 is the site responsible for finished drug product (pen injector) assembly, packaging, and labeling. The site was recommended for approval based on file review for both drug and device components. The site was recommended for approval based on file review.
- [redacted] (b) (4) (FEI [redacted] (b) (4)) is the site responsible for release and stability testing of PF708 drug substance; release testing of PF708 drug product cartridge; release and stability testing PF708 finished drug product (pen injector). The site was recommended for approval based on file review.
- [redacted] (b) (4) (FEI [redacted] (b) (4)) is responsible for release testing of PF708 drug product cartridge; release and stability testing of PF708 finished drug product (pen injector); and stability storage chambers for PF708 drug substance. The site was recommended for approval based on file review.
- [redacted] (b) (4) (FEI [redacted] (b) (4)) is responsible for release testing of PF708 drug substance. Based on file review of previous inspection history and a cGMP compliant status, this facility was found acceptable.
- [redacted] (b) (4) (FEI [redacted] (b) (4)) is responsible for release and stability testing of

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PF708 drug product cartridge. Because of an overall high-risk ranking, a prior approval inspection (PAI) was conducted. The site was found acceptable.

- (b) (4) (FEI (b) (4)) is the site responsible for the manufacture of pen injector subassemblies (dosing mechanism and cartridge units). The site was recommended for approval based on file review.
- Pfenex, Inc (FEI 3009462856, San Diego, CA) is responsible for release of PF708 drug product cartridge and finished drug product (pen injector). No evaluation was necessary.

Environmental Assessment: The applicant concludes that an environmental assessment for the manufacturing of Bonsity is categorically excluded according to 21 CFR 25.31(b). The applicant estimates that the environmental introductory concentration (EIC) will be below 1 part per billion. The requested categorical exclusion is acceptable.

Labeling: Labeling changes have been conveyed to the applicant and accepted.

Postmarketing Commitments: No OPQ postmarketing commitments are needed for this application.

4.3. Devices and Companion Diagnostic Issues

The device component of Bonsity is a manually operated "pull and push" type, fixed-dose, multiple-dose, single-patient use, disposable pen injector. It is an ISO 11608 system designation C pen injector. The device constituent parts (subassemblies) are manufactured at (b) (4) The drug product cartridges and all subassembly parts are shipped to (b) (4) for PF708 drug product pen injector assembly. CDRH has determined that the device constituent parts of the combination product can be approved.

The PF708 drug product pen injector is designed to administer the doses from an integrated, non-replaceable 3-mL cartridge pre-filled with drug product using commercially available pen needles (e.g., BD 29-31 G ultrafine pen needles). The PF708 pen injector contains (b) (4) full doses. An active stop in the PF708 pen injector prevents the setting of any additional dose after delivery of the (b) (4) dose. The patient is instructed to use a dose daily for 28 days. The entire pen injector is to be disposed 28 days after first use. The dose is preset to 80 microliters.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

NDA 211939 is a 505(b)(2) NDA application relying on the FDA's previous findings of safety for Forteo (NDA 021318 approved 11/26/02). Pfenex also conducted two nonclinical studies: pharmacodynamic study in a rat OVX model (Study No PF-01) and 4-week subcutaneous toxicity

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study in rats (Study No PTLX-0011). Overall, these studies have demonstrated that subcutaneous administration of PF708 resulted in responses that were comparable to Forteo.

- PF708 and Forteo at the subcutaneous dose of 8 µg/kg/day induced similar bone effects in the rat OVX model of human postmenopausal osteoporosis.

- PF708 at the subcutaneous dose of 30 µg/kg/day for 4-weeks resulted in responses that were comparable to Forteo, including non-adverse effects on hematology and clinical chemistry, no gender differences in systemic exposure, no detectable ADA findings, increased bone in the sternum and distal femur and proximal tibia of the femorotibial joint, and increased extramedullary hematopoiesis in the spleen.

- The safety of the excipient components of teriparatide injection was established as the quantities of each excipient were at concentrations less than or equal to the maximum potency outlined in the Agency's Inactive Ingredient Search for Approval Drug Product Database (IID) in approved parenteral products.

- The 4-week repeat-dose bridging rat toxicity study results, including the lack of immunogenicity responses, have provided support regarding the safety of the excipients and qualification of impurities in PF708.

Based on FDA's previous findings of safety for Forteo, published literature for teriparatide, and two nonclinical studies [pharmacodynamic study in a rat OVX model (Study No PF-01) and 4-week subcutaneous toxicity study in rats (Study No PTLX-0011)], there are no nonclinical concerns from a pharmacology/toxicology perspective and approval is recommended.

5.2. Referenced NDAs, BLAs, DMFs

NDA 021318 – Forteo (Eli Lilly), IND 129196 (PF708), DMF (b) (4)

5.3. Pharmacology

Endogenous 84-amino acid parathyroid hormone (PTH) is the primary regulator of calcium and phosphate metabolism in bone and kidney. Physiological actions of PTH include regulation of bone metabolism, renal tubular reabsorption of calcium and phosphate, and intestinal calcium absorption. Teriparatide is a recombinant PTH receptor analog that is comprised of the active N-terminal amino acids of PTH, 1-34. The biological actions of PTH and teriparatide are mediated through binding to specific high-affinity cell-surface receptors. Teriparatide and the 34 N-terminal amino acids of PTH bind to these receptors with the same affinity and have the same physiological actions on bone and kidney. Teriparatide is not expected to accumulate in bone or other tissues.

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The skeletal effects of teriparatide depend upon the pattern of systemic exposure. Once-daily administration of teriparatide stimulates new bone formation on trabecular and cortical (periosteal and/or endosteal) bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity. In monkey studies, teriparatide improved trabecular microarchitecture and increased bone mass and strength by stimulating new bone formation in both cancellous and cortical bone. In humans, the anabolic effects of teriparatide manifest as an increase in skeletal mass, an increase in markers of bone formation and resorption, and an increase in bone strength. By contrast, continuous excess of endogenous PTH, as occurs in hyperparathyroidism, may be detrimental to the skeleton because bone resorption may be stimulated more than bone formation.

Study No PF-01

Since PF708 is a PTH analog, it can stimulate *de novo* bone formation to increase bone mass and improve bone microarchitecture. The applicant submitted one pharmacology study (Study No. PF-01) to compare the effects of PF708 with Forteo in the rat OVX model of human postmenopausal osteoporosis.

Female Sprague-Dawley rats were ovariectomized at the age of 6 months (Study Day 0). Treatment with PF708, Forteo, or vehicle was started at 7 weeks after the surgery (at Study Day 49) and continued daily for 6 weeks (up to Study Day 90) (Figure 1). Vehicle consisted of 0.41 mg/mL glacial acetic acid, 0.1 mg/mL sodium acetate ([redacted] (b) (4)), 45.4 mg/mL mannitol, 3 mg/mL meta-cresol, and water for injection. Treatment effects were analyzed by measuring body weight, changes in bone cross-sectional dimensions, BMC and volumetric BMD in tibial metaphysis and diaphysis by pQCT, and changes in serum BTMs (Bone Turnover Markers) during the in-life phase of the study, as well as by measuring relative uterine weight at the end of the in-life phase (at Study Day 91). BTMs included procollagen type I N-terminal propeptide (PINP) as a marker of bone formation, N-terminal mid-fragment of osteocalcin (OC) as a marker of bone turnover, C-terminal crosslinked telopeptides of type I collagen (CTX-I) as a marker of bone resorption, and tartrate-resistant acid phosphatase isoform 5b (TRACP 5b) as a marker of osteoclast number.

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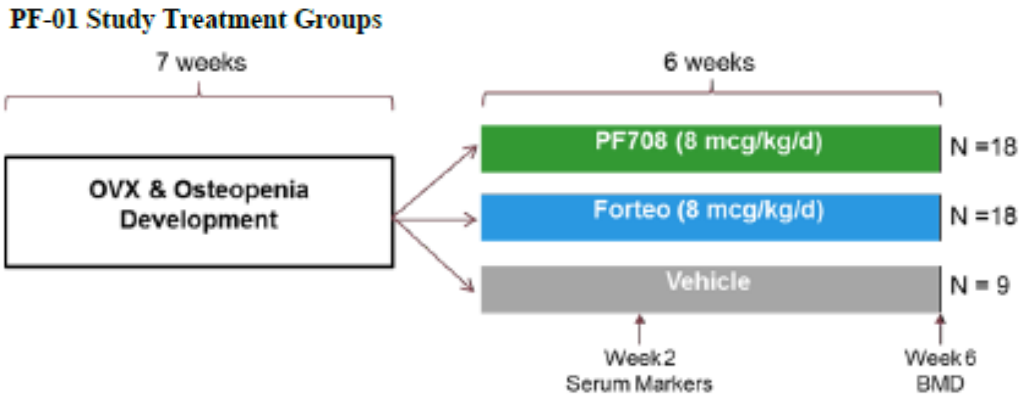
Figure 1 Study No PF-01: Study Design



Differences between the effects of subcutaneously administered PF708 and Forteo were evaluated by comparing OVX rats treated with 8 mcg/kg/day Forteo with OVX rats treated with 8 mcg/kg/day PF708.

- PF708 treatment had the following effects on body weight, bone and serum BTM levels in adult female OVX rats: slightly increased body weight (compared to OVX vehicle controls; comparable to Forteo treatment), increased amount of metaphyseal and trabecular bone, increased amount of diaphyseal and cortical bone, decreased endocortical perimeter, increased serum PINP and OC levels, decreased serum TRACP 5b activity.
- Forteo treatment had the following effects on bone and serum BTM levels in adult female OVX rats: slightly increased body weight (compared to OVX vehicle controls; comparable to PF708 treatment), increased amount of metaphyseal and trabecular bone, increased amount of diaphyseal and cortical bone, improved biomechanical bond properties predicted from diaphyseal cortical bone distribution, increased serum PINP and OC levels, decreased serum TRACP 5b activity.

This comparison demonstrated that there were no significant differences between the effects of PF708 and Forteo treatments on body weight; relative uterine weight; metaphyseal, trabecular, diaphyseal, and cortical bone parameters obtained by pQCT; and serum BTM levels in adult female OVX rats. In particular, treatment effects on metaphyseal trabecular bone were similar between PF708 and Forteo treatments (Figure 2).

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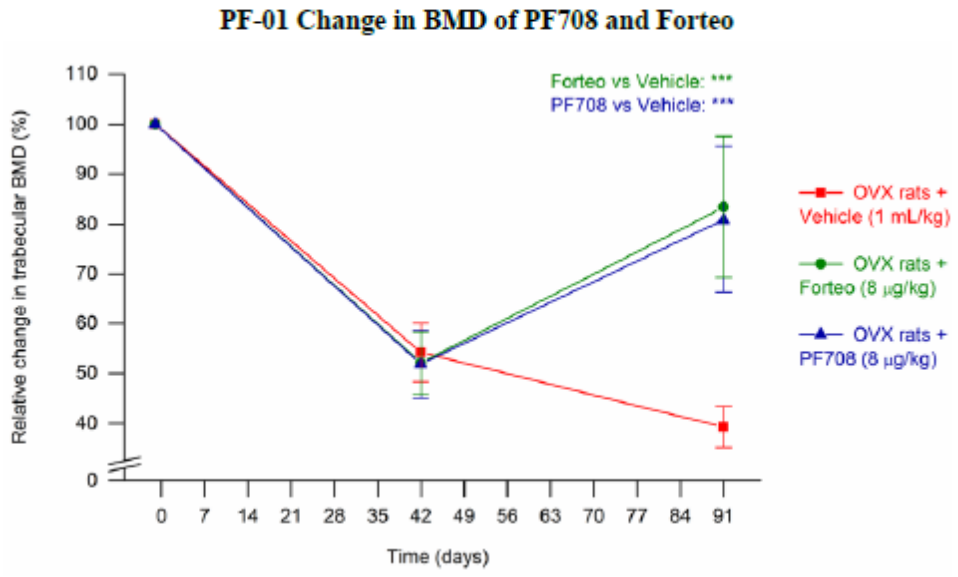
Figure 2 Study No PF-01: Change in Trabecular BMD in Tibial Metaphysis of PF708 and Forteo



5.4. ADME/PK

Table 3: Summary of Pharmacokinetics/Toxicokinetics of PF708

Type of Study	Major Findings
Absorption	
Forteo prescribing information and published literature	Teriparatide is absorbed after subcutaneous injection; the absolute bioavailability is approximately 95% based on pooled data from 20-, 40-, and 80- mcg doses. The rates of absorption and elimination are rapid. The peptide reaches peak serum concentrations about 30 minutes after subcutaneous injection of a 20-mcg dose and declines to non-quantifiable concentrations within 3 hours.
Distribution	
Forteo prescribing information and published literature	Systemic clearance of teriparatide (approximately 62 L/hr in women and 94 L/hr in men) exceeds the rate of normal liver plasma flow, consistent with both hepatic and extra-hepatic clearance. Volume of distribution, following intravenous injection, is approximately 0.12 L/kg. Intersubject variability in systemic clearance and volume of distribution is 25% to 50%. The half-life of teriparatide in serum is 5 minutes when administered by intravenous injection and approximately 1 hour when administered by subcutaneous injection. The longer half-life following subcutaneous administration reflects the time required for absorption from the injection site. Animal studies have shown that severely reduced hepatic blood flow decreases exposure of PTH to the principal cleavage system (Kupffer cells) and consequently clearance of PTH(1-84). It has been reported that following subcutaneous administration of teriparatide acetate, teriparatide is rapidly absorbed and distributed to the liver or kidneys, where it is immediately degraded. It was determined that the kidneys play a particularly important role in the distribution and metabolism of teriparatide.

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Type of Study	Major Findings
Metabolism	
Forteo prescribing information and published literature	No metabolism or excretion studies have been performed with teriparatide. However, the mechanisms of metabolism and elimination of PTH(1-34) and intact PTH have been extensively described in published literature. Peripheral metabolism of PTH is believed to occur by non-specific enzymatic mechanisms in the liver followed by excretion via the kidneys.
Excretion	
Forteo prescribing information and published literature	No excretion studies have been performed with teriparatide. However, teriparatide is eliminated through hepatic and extra-hepatic clearance (approximately 62 L/h in women and 94 L/h in men). It is not known whether teriparatide is excreted in human milk.
TK data from general toxicology studies	
4-week toxicology study in rats Study No PTLG-0011	Individual plasma teriparatide concentrations were highly variable across both treatments and sexes (n=3 male and female rats per time point). Teriparatide concentrations following a single or multiple daily dose of 30 mcg/kg PF708 or Forteo were quantifiable starting at 0.25 hours through 1-hour postdose on Days 1 and 28. Mean overall concentrations were similar between Day 1 and Day 28 for both PF708 and Forteo. No sex differences were observed. On Day 1, TK parameters values for PF708 seemed to be higher than those of Forteo. Due to the high variability, no clear treatment difference can be attributed. On Day 28, TK parameters values for PF708 were comparable to those of Forteo.

Sex	Day	Treatment	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (hr*ng/mL)	AUC_{0-inf} (hr*ng/mL)	$t_{1/2}$ (hr)
Male	1	PF708	14.69	0.25	5.58	5.80	0.19
	1	Forteo	7.47	0.25	2.64	2.71	0.17
	28	PF708	10.75	0.25	5.13	5.67	0.25
	28	Forteo	8.96	0.25	4.83	5.69	0.31
Female	1	PF708	5.82	0.25	2.20	2.26	0.16
	1	Forteo	6.27	0.25	2.59	2.65	0.14
	28	PF708	8.62	0.25	3.60	3.80	0.20
	28	Forteo	9.46	0.25	3.75	3.85	0.16

5.5. Toxicology

5.5.1. General Toxicology

Forteo prescribing information

In single-dose rodent studies using subcutaneous injection of teriparatide, no mortality was seen in rats given doses of 1000 µg/kg (540 times the human dose based on surface area, mcg/m^2) or in mice given 10,000 µg/kg (2700 times the human dose based on surface area, mcg/m^2).

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In a long-term study, skeletally mature ovariectomized female monkeys (N=30 per treatment group) were given either daily subcutaneous teriparatide injections of 5 µg/kg or vehicle. Following the 18-month treatment period, the monkeys were removed from teriparatide treatment and were observed for an additional 3 years. The 5 µg/kg dose resulted in systemic exposures that were approximately 6 times higher than the systemic exposure observed in humans following a subcutaneous dose of 20 µg (based on AUC comparison). Bone tumors were not detected by radiographic or histologic evaluation in any monkey in the study.

Study title: PF708 and Forteo®: A 4-Week Subcutaneous Injection Toxicity Study in Rats (Study No PTLG-0011)

- Daily subcutaneous administration of PF708 or Forteo for 4 weeks was associated with non-adverse effects on hematology and clinical chemistry, no gender differences in systemic exposure, no detectable ADA findings, increased bone in the sternum and distal femur and proximal tibia of the femorotibial joint and increased extramedullary hematopoiesis in the spleen.
- The incidence and severity of these findings were similar between PF708 and Forteo.
- These findings are known pharmacologic effects of parathyroid hormone in bone and spleen. Increased bone results in decreased medullary cavity volume and decreased medullary hematopoiesis. Increased extramedullary hematopoiesis in the spleen is a compensatory response.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	30 µg/kg/day once daily
Route of administration:	Subcutaneous injection
Formulation/Vehicle:	0.9% saline
Species/Strain:	Sprague Dawley CD rats
Number/Sex/Group:	10/sex/group
Age:	11-13 weeks
Satellite groups/ unique design:	TK animals
Deviation from study protocol affecting interpretation of results:	No

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Table 4 Study No PTLG-0011: Summary of Study Findings

Parameters	Major findings
Mortality	All animals survived until the scheduled sacrificed.
Clinical Signs	There were no test-item related effects on clinical observations.
Body Weights	There were no test-item related effects on body weights.
Ophthalmoscopy	There were no test-item related effects on ophthalmology at the end of dosing.
Hematology	There were changes in hematology parameters observed with both PF708 and Forteo. However, there were no toxicologically significant differences between PF708 and Forteo. PF708-related hematology changes included: ▪ decreases in hemoglobin (0.97 × control; females only), hematocrit (0.96 × control; females only), and red blood cells (0.96 × control; females only) ▪ increases in red cell distribution (1.05 to 1.07 × control) and platelets (1.10 × control; males only) ▪ decreases in neutrophils (0.74 × control; males only) Forteo-related hematology changes included: ▪ increases in red cell distribution (1.04 to 1.06 × control) and platelets (1.16 × control; males only) ▪ decreases in neutrophils (0.81 × control; males only)
Coagulation	There were no PF708 or Forteo-related coagulation changes at 30 mcg/kg/day.
Clinical Chemistry	There were changes in clinical chemistry parameters observed with both PF708 and Forteo. However, there were no toxicologically significant differences between PF708 and Forteo. PF708-related clinical chemistry changes included: ▪ increases in albumin (1.06 × control; males only) with corresponding increases in total protein (1.03 × control; males only) ▪ increases in calcium (1.12 × control; males only). Forteo-related clinical chemistry changes included: ▪ increases in albumin (1.06 × control; males only) with corresponding increases in total protein (1.05 × control; males only) increases in calcium (1.05 × control; males only).
Urinalysis	There were no test-item related effects on urinalysis parameters.
Gross Pathology	There were no macroscopic findings related to PF708 or Forteo.
Organ Weights	Slightly increased mean absolute and relative splenic weights were observed in female rats following administration of PF708 compared to controls. These treatment-related changes correlated microscopically with increased extramedullary hematopoiesis.

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Parameters	Major findings
Histopathology Adequate battery: Yes	Treatment-related microscopic findings (PF708 and Forteo) were present in the bone (sternum and femorotibial joint) and spleen in both male and female rats. <u>Bone</u> Slight to moderate increases in trabecular and cortical bone were present in all PF708- and Forteo-treated males and females. Increased bone was observed in the sternum and in the distal femur and proximal tibia of the femorotibial joint, which was characterized by increased thickness of trabeculae and cortex. <u>Spleen</u> Extramedullary hematopoiesis was slightly increased in the spleen of PF708- and Forteo-treated males and females compared to the controls. The incidence and severity of these findings were similar in the PF708 and Forteo treated groups.
Immunogenicity	There were no detectable ADA findings before injection on day 1 and following multiple (Day 28) daily subcutaneous injection of PF708 or Forteo. There were no findings of immunogenicity for either PF708 or Forteo, despite the supraphysiological circulating levels of teriparatide following subcutaneous injection of either PF708 or Forteo.

Overall, subcutaneous administration of 30 mcg/kg/day PF708 drug product (cartridge) for 28 days resulted in responses that were comparable to Forteo, including effects on bone. In addition, results of this study, including the lack of immunogenicity response, support the safety of the excipients and qualification of impurities in PF708. The safety of the components of teriparatide injection (glacial acetic acid, sodium acetate, mannitol, metacresol, and water for injection) is established as the quantities of each excipient is at concentrations less than or equal to the maximum potency outlined in the Agency's IID in approved parenteral (subcutaneous, intramuscular, and intravenous) products.

5.5.2. Genetic Toxicology

<u>Forteo prescribing information</u>
Teriparatide was not genotoxic in any of the following test systems: the Ames test for bacterial mutagenesis; the mouse lymphoma assay for mammalian cell mutation; the chromosomal aberration assay in Chinese hamster ovary cells, with and without metabolic activation; and the in vivo micronucleus test in mice.

5.5.3. Carcinogenicity

<u>Forteo prescribing information</u>
In carcinogenicity studies in Fischer 344 rats, Forteo resulted in marked dose related increase in the incidence of osteosarcoma, osteoblastoma, and osteoma in both male and female rats at 3-

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60X the human systemic exposure at 20 µg based on AUC, and even though the occurrence of these tumors was dependent upon dose and duration of exposure, there was no difference in susceptibility to bone tumor formation between mature and immature rats. Based on bone tumor findings, the boxed warning (risk of osteosarcoma) was included in the Prescribing Information for Forteo®.

- In the first study, male and female rats were given daily subcutaneous teriparatide injections of 5, 30, or 75 µg/kg/day for 24 months from 2 months of age. These doses resulted in systemic exposures that were 3-, 20-, and 60-times higher, respectively, than the systemic exposure observed in humans following a subcutaneous dose of 20 µg (based on AUC comparison). Teriparatide treatment resulted in a marked dose-related increase in the incidence of osteosarcoma, a rare malignant bone tumor, in both male and female rats. Osteosarcomas were observed at all doses and the incidence reached 40% to 50% in the high-dose groups. Teriparatide also caused a dose-related increase in osteoblastoma and osteoma in both sexes. No osteosarcomas, osteoblastomas or osteomas were observed in untreated control rats. The bone tumors in rats occurred in association with a large increase in bone mass and focal osteoblast hyperplasia.
- The second 2-year study was carried out in order to determine the effect of treatment duration and animal age on the development of bone tumors. Female rats were treated for different periods between 2 and 26 months of age with subcutaneous doses of 5 and 30 µg/kg (equivalent to 3- and 20-times the human exposure at the 20-mcg dose, based on AUC comparison). The study showed that the occurrence of osteosarcoma, osteoblastoma, and osteoma was dependent upon dose and duration of exposure. Bone tumors were observed when immature 2-month old rats were treated with 30 mcg/kg/day for 24 months or with 5 or 30 mcg/kg/day for 6 months. Bone tumors were also observed when mature 6-month old rats were treated with 30 mcg/kg/day for 6 or 20 months. Tumors were not detected when mature 6-month old rats were treated with 5 mcg/kg/day for 6 or 20 months. The results did not demonstrate a difference in susceptibility to bone tumor formation, associated with teriparatide treatment, between mature and immature rats.

The relevance of these animal findings to humans is uncertain.

5.5.4. Reproductive and Developmental Toxicology

Forteo prescribing information

- No effects on fertility were observed in male and female rats given subcutaneous teriparatide doses of 30, 100, or 300 µg/kg/day prior to mating and in females continuing through GD 6 (16X to 160X the human dose of 20 µg based on body surface area, µg/m^2).
- In embryo-fetal development studies, pregnant mice received teriparatide at subcutaneous doses 8X to 267X the human dose during organogenesis. Teriparatide caused increased skeletal deviations or variations in fetuses (interrupted rib, extra vertebra or rib), at doses ≥ 60X the human dose based on µg/m^2. However, when

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pregnant rats received teriparatide at subcutaneous doses 16X to 540X the human dose during organogenesis, there were no fetal abnormal findings.

- In a prenatal/postnatal development study, pregnant rats received teriparatide at subcutaneous doses of 30 to 1000 µg/kg/day from organogenesis through lactation. Mild growth retardation in female offspring at doses ≥ 120X the human dose (based on $\mu g/m^2$). Mild growth retardation in male offspring and reduced motor activity in both male and female rat offspring occurred at maternal dose 540X the human dose (based on $\mu g/m^2$). There were also no developmental or reproductive effects in mice or rats at doses 8X or 16X the human dose, respectively.

Published literature

Literature results identified potential new uses for PTH(1-34) in gravid animals and/or neonates in multiple animal models and species.

- Early postnatal mortality has been prevented in 2 murine models including achondroplasia and hypocalcemia.
- Subcutaneous administration of PTH(1-34) in gravid mice or to neonates immediately after birth appeared to rescue the retarded skeletal development and early postnatal lethality, and improved bone quality in achondroplasia and thanatophoric dysplasia mice models.
- Twice daily subcutaneous administration of PTH(1-34) started within 12 hours after birth in a *Pth-/-;Hyp/Y* mice model (homozygous for the Pth null allele and hemizygous hypophosphatemic) resulted in an increase in serum calcium levels and prevented early mortality that has been previously observed in the severely hypocalcemic neonate.
- In ewes, a significant increase in the placental transfer of calcium from the gravid ewe to the fetus was observed following intravenous in utero administration of synthetic PTH related peptide (1-34) in the cannulated fetus, indicating that PTH related peptide (1-34) stimulates placental calcium transfer by potentially acting directly on the plasma increases in 1,25 dihydroxy-vitamin D concentrations.

5.5.5. Other Toxicology Studies

Local Tolerance

Injection site reactions including injection site pain, swelling, erythema, localized bruising, pruritis, and minor bleeding have been reported.

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6 Clinical Pharmacology

6.1. Executive Summary

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 3, has reviewed the clinical pharmacology information submitted for NDA 211939 of BONSITY (teriparatide injection) which is also referred to as PF708 during development. We find the current application acceptable for approval from the clinical pharmacology's standpoint.

The key clinical pharmacology review assessments are summarized below (Table 5).

Table 5. The key clinical pharmacology review issues and assessments

Review issue	Key assessments
PK similarity	Study PF708-101 was a single-dose, randomized, double-blind, 2-way crossover study to compare the PK of teriparatide following a single subcutaneous (SC) injection of PF708 and Forteo in healthy subjects. The 90% confidence intervals (CI) of the PK parameters, maximum observed concentration (C_{max}) and area under the concentration-time curve (AUC) values, were within the specified no-effect boundary of 80% to 125%. This finding demonstrated PK similarity between PF708 and Forteo.
Immunogenicity comparability	Study PF708-301 was an open-label, randomized, parallel group study to compare the effects of PF708 and Forteo on immunogenicity and their PK, pharmacodynamics (PD), and safety in patients with osteoporosis following once daily SC injection for 24 weeks. The incidence of detectable anti-drug antibody (ADA) following administration of PF708 was similar to that of Forteo. Neutralizing activity was detected in one patient in the PF708 treatment group. There were no cases in which ADA had a significant impact on the pharmacological responses of teriparatide. These findings indicated that there was no increased immunogenicity risk for PF708 compared to Forteo.

In conclusion, the observed PK results and immunogenicity findings in this NDA provided evidence that PF708 and Forteo were clinically similar.

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6.2. Summary of Clinical Pharmacology Assessment

PF708 contains the active ingredient teriparatide, a 34-amino acid analog of human parathyroid hormone (PTH 1-34) and has been developed as an alternative to Forteo. The applicant is seeking approval via the 505(b)(2) pathway for the same indications approved for Forteo. The applicant assessed the PK and immunogenicity of PF708 in comparison with Forteo, the listed drug, in two clinical studies, PF708-101 and PF708-301, as clinical pharmacology information in support of this NDA.

6.2.1. Clinical Pharmacokinetics

PK assessment results from Study PF708-101 are summarized in Table 6. The 90% CI for geometric mean ratios (GMRs) of primary PK parameters, C_{max} and AUC values, were within the no-effect boundary of 80% to 125% for PF708 compared to Forteo.

Table 6. PK Parameters of Teriparatide Following a Single Dose of PF708 or Forteo, 20 mcg in Healthy Subjects

	PF708(Test)	n	Forteo (Reference)	n	Statistics
	Mean (CV%)		Mean (CV%)		GMR (90% CI)
AUC_t (pg*hr/mL)	75.88 (47.5)	66	78.67 (43.8)	66	96.53 (90.01 - 103.52)
AUC_{inf} (pg*hr/mL)	85.83 (38.7)	54	87.22 (39.6)	61	98.99 (92.54 - 105.89)
C_{max} (pg/mL)	74.28 (44)	66	78.21 (38.9)	66	95.02 (88.41 - 102.12)

Mean = geometric mean; GMR = geometric mean ratio presented as 100 % x (test/reference)

AUC_t and AUC_{inf}: AUC from time 0 to time of last observed concentration and from time 0 to infinity, respectively.

Source: Clinical Study Report and PK Report of Study PF708-101

6.2.2. Immunogenicity

The incidence of immunogenicity for PF708 and Forteo was compared following once daily dosing for 24 weeks in 179 subjects (88 subjects for PF708 and 91 subjects for Forteo) with osteoporosis. Two subjects in each treatment group showed detectable ADA levels during the study. Antibody titers in the two PF708-treated subjects showing detectable ADA were low and resolved with cessation of therapy during follow-up (refer to Section 14.4.2). Out of the two subjects who had detectable ADA in the PF708 treatment group, one subject showed detectable in vitro neutralizing activity at Week 4 only. No apparent impact of ADA on the pharmacological responses of teriparatide was observed based on the observed changes in serum calcium and phosphorous levels, bone mineral density (BMD), and bone turnover markers (BTMs) in the two subjects with detectable ADA, including the subject who had transient finding of detectable in vitro neutralizing activity, compared to those of other subjects in both treatment groups in the study. These results indicated that there were no increases in

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the immunogenicity risk for PF708 compared to Forteo and transient in vitro neutralizing activity did not result in an apparent loss of pharmacological activity of teriparatide.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics of Teriparatide

Teriparatide is PTH (1-34), the biologically active 34 N-terminal amino acid fragment of the 84-amino acid PTH (1–84). Teriparatide binds to PTH receptors with the same affinity as PTH and has the same physiological actions such as bone-mineral metabolism. The skeletal effects of teriparatide depend upon the pattern of systemic exposure. Once-daily administration of teriparatide stimulates new bone formation on trabecular and cortical (periosteal and/or endosteal) bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity (Forteo, Prescribing information).

The absolute bioavailability after SC injection of Forteo is approximately 95% (Forteo prescribing information). Volume of distribution following intravenous injection is approximately 0.12 L/kg. The half-life of teriparatide in serum is 5 minutes when administered by intravenous injection. Peripheral metabolism of PTH is believed to occur by non-specific enzymatic mechanisms in the liver followed by excretion via the kidneys (Forteo prescribing information).

In men and postmenopausal women with osteoporosis, when teriparatide 20 mcg is administered once daily, the serum calcium concentration increases transiently, beginning approximately 2 hours after dosing and reaching a maximum concentration between 4 and 6 hours (median increase, 0.4 mg/dL). The serum calcium concentration begins to decline approximately 6 hours after dosing and returns to baseline by 16 to 24 hours after each dose (Forteo, Prescribing information).

The immunogenic potential of Forteo has been reported to be clinically insignificant. In the clinical studies, ADAs were detected in 3% of women (15/541) receiving Forteo and generally first detected after at least 12 months of treatment and diminished after withdrawal of therapy (Forteo, prescribing information). There have been no case reports of endogenous PTH activity being neutralized by ADA following use of Forteo. No literature reports were identified to show any clinical impact of recombinant human teriparatide-induced ADA up to now.

6.3.2. Clinical Pharmacology Questions

What are the design features of the clinical pharmacology and/or clinical studies to support similarity of PF708 to the reference?

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The applicant performed one pivotal comparative PK study and one immunogenicity, PK, PD and safety study as outlined in Section 7.1.

Study PF708-101 was a pivotal bioequivalence study using a single SC dose in healthy subjects (N=70) including female subjects to support PK similarity between PF708 and Forteo. The PK parameters, C_{max}, AUC_t and AUC_{inf}, were used to evaluate the relative bioavailability of PF708 versus Forteo.

Study PF708-301 was a comparative clinical study in female subjects with postmenopausal osteoporosis and male subjects with primary osteoporosis. The primary endpoint was the incidence of ADA after 24 weeks of treatment with PF708 or Forteo (91 subjects per group). The incidence and titers of ADAs for 24 weeks were compared. All positive ADA cases were also assessed for neutralizing activity.

The to-be-marketed (TBM) formulation was used in both clinical studies described above. However, there were modifications (i.e. (b) (4)) on the pen injector device for PF708 after completion of the two studies. These minor changes from the device used in the clinical studies to the TBM device are not expected to impact the performance specifications of the device (refer to OPQ reviews for complete details).

Are the study design and the bioanalytical assay adequate to assess PK similarity?

Yes. The study design of Study PF708-101 is considered adequate to assess PK similarity between PF708 and Forteo based on the following reasons:

- The study design (two-way, crossover, randomized study design with a washout of 3 days) appears reasonable to compare the PK between the two products based on the PK characteristics of teriparatide.
- The number of subjects was determined to achieve adequate power based on the proposed study design and predefined null hypothesis (the ratio of the test mean to the reference mean of the PK parameters is below 80% or above 125%).
- Conducting the study in healthy subjects to compare the PK of teriparatide between the two products is acceptable. More than 40% of subjects enrolled in the study were female. This is reasonable considering that the majority of the target patient population are postmenopausal women with osteoporosis.
- A validated bioanalytical method was used to measure the plasma concentrations of teriparatide.

Does the comparative PK study provide supportive evidence for PK similarity between the proposed drug product and the listed drug?

Yes.

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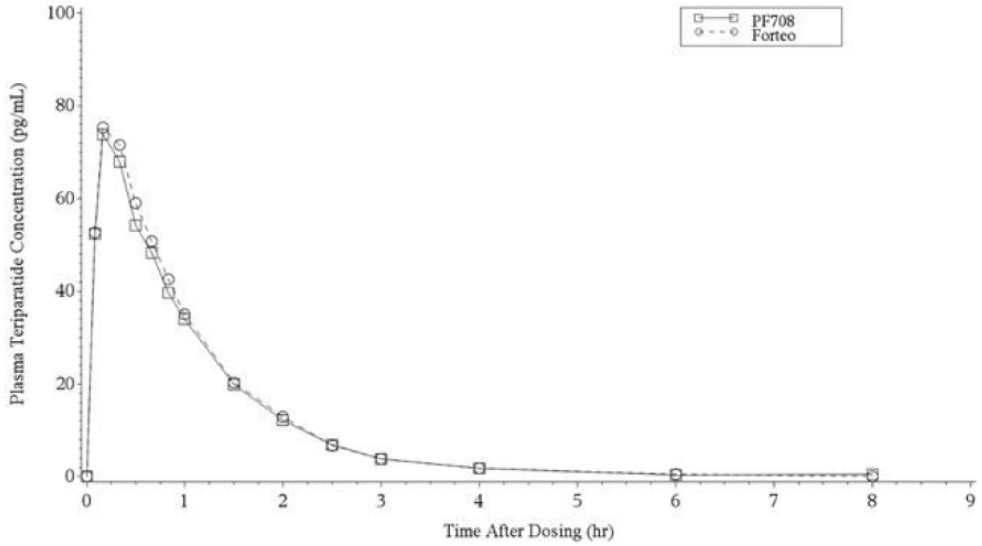
The mean plasma concentration-time profiles of PF708 and Forteo were similar and largely overlapped (Figure 3). C_{max}, AUC_t, AUC_{inf}, and T_{max} of teriparatide were comparable between the two products (Table 7). The 90% CIs of GMRs of C_{max}, AUC_t, and AUC_{inf} for PF708 compared to Forteo were within the no-effect boundary of 80% to 125% (Table 6). These findings demonstrated PK similarity between PF708 and Forteo.

Figure 3. Mean Time-Teriparatide Concentration Profile After SC Single Dose of PF708 or Forteo in 66 Healthy Subjects (Study PF708-101)



(Source: Clinical Study Report of Study PF708-101)

Table 7. Summary of PK Parameters of Teriparatide Following Single Dose of PF708 vs. Forteo (Study PF708-101)

	PF708	n	**Forteo**	n
	Mean ± S.D.		Mean ± S.D.	
T_{max} (hour)*	0.167 (0.0833, 0.500)	66	0.167 (0.0833, 0.833)	66
C_{max} (pg/mL)	80.77 ± 32.78	66	83.83 ± 32.15	66
$AUC_{0\text{-}t}$ (pg*hr/mL)	83.32 ± 34.97	66	85.80 ± 37.33	66
$AUC_{0\text{-}inf}$ (pg*hr/mL)	91.66 ± 33.01	54	93.74 ± 37.24	61
$t_{1/2}$ (hour)	0.89 ± 0.48	54	0.81 ± 0.29	61
CL/F (L/hr)	250.1 ± 100.74	54	246.3 ± 98.107	61

Arithmetic mean ± S.D.; T_{max}* = median (minimum, maximum)
Source: Clinical Study Report and PK Report of Study PF708-101

In this primary PK and statistical analyses, four subjects who had positive pre-dose concentrations, defined as exceeding 5% of their respective C_{max} for that treatment, were

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excluded. Additional analyses including data from these subjects did not show any significant difference compared to the primary analyses (refer to Section 14.4.2).

Is the immunogenicity assay and sampling plan adequate to detect the anti-drug antibodies (ADA) throughout the study?

The applicant developed an ADA assay, which includes screening, confirmatory and cross-reactivity with endogenous PTH (1-84) assays. The ADA assay used a direct ELISA format. All patient samples were tested with the ADA screening assay and the screening positive samples were also tested in the PTH (1-34) confirmatory assay and the PTH (1-84) cross-reactivity assay. All PTH (1-34) confirmed positive samples were tested in a cell based neutralizing antibody assay. Overall, both ADA and neutralizing antibody assay were appropriately validated and appeared adequate for the intended use. Refer to Product Quality Reviewer's Immunogenicity Review.

The sampling schedule for the studies was as follows: before dosing on Day 1, Week 1, Week 4, Week 12, and Week 24. Study subjects who tested positive for ADA upon analysis of the final sample were asked to return for additional testing. Subsequent sampling was scheduled to occur approximately every 4 to 8 weeks until: (1) ADA was no longer detectable, or (2) ADA titer was stable for two consecutive visits and deemed to be clinically insignificant by the applicant. The sampling schedule of immunogenicity assessment in Study PF708-301 appeared appropriate to detect the ADA in the subjects after as well as during the study.

What is the incidence of anti-drug antibodies (ADA)?

In Study PF708-301, two subjects showed detectable ADA levels in each group during 24-week treatment (Table 8). In PF708 group, one subject had detectable levels of ADA at Weeks 1, 4, 12, and 24 and the other subject had detectable levels of ADA at Weeks 12 and 24. Antibody titers in these two subjects were low and resolved with cessation of therapy (refer to Section14.4.2). Similar incidences of ADAs were observed following daily treatment of PF708 or Forteo for 24 weeks (Table 8).

Table 8 The Incidence of Subjects Who Tested Positive for ADA in Study PF708-301

	N*	Baseline	Treatment-induced	Percentage
PF708	87	0	2	2.3%
Forteo	90	0	2	2.2%

*The number of subjects that were measured at Week 1.

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What is the impact of ADA on the PK, PD, efficacy, and safety of teriparatide?

PK assessments of PF708 were performed in Study PF708-101 following a single dose in healthy subjects and in Study PF708-301 following the first dose administration in subjects with osteoporosis. The impact of ADA on the PK of teriparatide is unknown. The PK sampling of the studies was not designed to investigate the impact of ADA on PK of teriparatide. ADA occurred after PK assessment was completed on Day 1 in Study PF708-301. Therefore, based on the study PK and ADA assessment schedule, it was not possible to evaluate the effect of ADA on teriparatide PK.

Based on the changes of serum calcium and phosphorous levels, BMD, and BTM compared to baseline, the pharmacological responses of PF708 in the two ADA-positive subjects, including the subject who had detectable neutralizing antibodies, were not different from those in the non-ADA subjects in both treatment groups (PF708 and Forteo). No significant safety issues related to ADA findings were identified in these subjects (refer to Section 8.2). In addition, there were no findings of cross-reactivity against endogenous PTH (1-84) in any of the ADA-positive samples. These findings indicate that the observed detectable ADA and transient neutralizing activity following administration of PF708 are unlikely to affect the pharmacological activity of teriparatide.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The table below lists the clinical studies that are relevant to the review of the NDA.

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Table 9: Listing of Clinical Studies Relevant to this NDA/BLA

Trial Identity	NCT no.	Study Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of subjects enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
PF708-101	02656810	Double-Masked, Randomized, Two-Treatment Cross-over Study Comparing the Pharmacokinetics of PF708 and Forteo	Single subcutaneous (SC) injections of PF708 20 mcg and Forteo 20 mcg with 3-day washout between doses	Primary: plasma area under the curve and maximum observed concentration of PF708 drug substance and Forteo; Secondary: change in serum calcium concentration after a single subcutaneous dose of PF708 drug product and Forteo	6 days	70	Healthy adults ages 18-55	One center in U.S.
PF708-301	03002428	Randomized, parallel- group, open-label Study Comparing the Effects of PF708 and Forteo	SC injections of PF708 20 mcg once daily for 24 weeks or sc injections of Forteo 20 mcg once daily for 24 weeks	Primary: Incidence of antidrug antibodies (ADAs) after 24 weeks of treatment; Secondary: PK parameters, mean percentage	24 weeks	182	Female patients with postmenopausal osteoporosis and male patients with primary osteoporosis	27 centers in U.S.

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Trial Identity	NCT no.	Study Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of subjects enrolled	Study Population	No. of Centers and Countries
				change from baseline in lumbar-spine BMD after 24 weeks of Treatment, median percentage change from baseline in serum bone turnover markers after 24 weeks of treatment			aged 30 to 85 years,	

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7.2. Review Strategy

The applicant is seeking to rely on FDA's findings of safety and effectiveness for Forteo. Two studies were performed. Study PF708-101, which demonstrated comparative bioavailability of PF708 to Forteo, is reviewed in Section 6 and in detail in the Clinical Pharmacology Appendix section of this review. A brief summary of this study is also provided in Section 8.1. Study PF708-301 is the comparative clinical study required to evaluate immunogenicity. Although bone mineral density (BMD) and bone turnover marker efficacy were secondary endpoints, the design of this trial is not adequate to allow comparison of BMD and bone turnover marker results between PF708 and Forteo. The applicant was aware that a 6-month study was not sufficient to allow comparison of BMD effects between PF708 and Forteo. The applicant was also aware that the Division would require a one-year BMD noninferiority study should comparative bioequivalence not be demonstrated or if different immunogenicity patterns were noted between Forteo and PF708. Therefore, the BMD and bone turnover marker results of study PF708-301 are not considered for efficacy and no efficacy review is needed for this application.

Evaluation of the safety of PF708, discussed in Section 8.2 of this review, is based on the safety results of Studies PF708-101 and PF708-301, as well as the FDA's previous findings of safety of Forteo based on determination of bioequivalence between PF708 and Forteo.

Evaluation of immunogenicity of PF708 is based on the results of Study PF708-301. Immunogenicity results are discussed in detail in the Clinical Pharmacology Appendix section of this review. Clinical safety outcomes related to immunogenicity are discussed in Section 8.2.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Studies

8.1.1. Study PF708-101: A Double-Masked, Randomized, 2-Treatment, Crossover Study Comparing the Pharmacokinetics of PF708 and Forteo Administered by Subcutaneous Injection in Healthy Adult Subjects

Study Synopsis

Study PF708-101 was a double-blind, randomized, 2-treatment, crossover study with sentinel dosing, designed to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), and safety of PF708 and Forteo in healthy adult subjects after a single subcutaneous (SC) dose. This study was conducted at a single center in the United States.

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Seventy healthy subjects aged 20-53 years were enrolled, with female subjects constituting approximately 40% of the study population. Subjects were randomized 1:1 to receive PF708 first and Forteo second, or to receive the drugs in reverse sequence. Each sequence had a single sentinel subject who was dosed 24 hours prior to the rest of the subjects. If no unexpected drug-related side effects occurred during the 24-hour observation period of the sentinel subjects, the remaining subjects were dosed.

Each subject completed two 1-day study periods (Period 1 and Period 2), separated by a 3-day washout period. The dose of PF708 and Forteo was 20 mcg. Both PF708 and Forteo were administered once by SC injection into the lower abdomen (lower right quadrant on day 1 [period 1] and lower left quadrant on day 5 [period 2]). Subjects were admitted to the clinical research unit (CRU) on day 1 and remained in the CRU until day 6 for clinical observations and blood draws for PK, PD, and safety assessments. Safety assessments performed during the study included the following: monitoring of adverse events, vital signs, electrocardiograms, clinical laboratory evaluations and anti-drug antibody assessments.

All 70 subjects completed the study and were included in the safety, PK, and PD assessments. Subject age, sex, race, weight, height, and body mass index (BMI) were similar between sequences.

See Section 6 of this review for the PK and PD results from this study and Section 8.2 for safety results from this study.

8.1.2. Study PF708-301: A Randomized Study Comparing the Effects of PF708 and Forteo in Patients with Osteoporosis

Study Design

Study PF708-301 was a randomized, multi-center, parallel-group, open-label study conducted at 27 centers in the United States designed to compare the effects of 24 weeks of treatment with PF708 and Forteo. Subjects were randomized 1:1 to receive either PF708 or Forteo. Randomization was stratified by sex.

The physical shapes of the PF708 and Forteo delivery devices are different. Therefore, subjects, investigators, and study personnel were not blinded. This open-label design would likely have minimal impact on PK and PD measurements but could impact the reporting of adverse events.

<u>Objectives</u>

The primary objective of this study was to compare the effects of PF708 and Forteo on immunogenicity after 24 weeks of SC daily dosing.

The secondary objective was to compare the PK and PD effects of PF708 and Forteo. The safety

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objective was to compare the adverse event profile of PF708 and Forteo.

Assessments

Assessments were performed according to the schedule of events presented in the table below.

Table 10 Study PF708-301: Schedule of Assessments

	Day –28 to –1	Day 1	Wk 1 (±1d)	Wk 4 (±2d)	Wk 8 (±2d)	Wk 12 (±2d)	Wk 16 (±2d)	Wk 20 (±2d)	Wk 24 (±2d)	Wk 25 (±2d)	Early Term
Informed consent[1]	X										
Inclusion/ Exclusion criteria[2]	X	X									
Medical history[2]	X	X									
Weight, height	X										
Vital signs[3]	X	X	X			X			X		X
Physical examination, complete	X										
Spinal x-ray evaluation[4]	X										
Concomitant medications assessment	X	X	X	X	X	X	X	X	X		X
Physical examination, symptom directed		X	X	X	X	X	X	X	X		X
Safety laboratory analyses[5]	X	X	X			X			X		
Eligibility laboratory analyses[6]	X										
ECG[7]	X	X									
Randomization		X									
Study drug dispensation/ accountability		X		X	X	X	X	X	X		X
Assessment of AEs		X	X	X	X	X	X	X	X		X
Injection site assessment[8]		X									
DXA	X					X			X		
PK sample collection[9]		X									
PD (BTM) sample collection[10]		X				X			X		
Anti-drug antibody sample collection[10]		X	X	X		X			X		X
Safety follow-up[11]										X	
*Source: Table 3-22 of Clinical Study Report (CSR)											

1 Informed consent was obtained before any study-related procedures were performed.

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2 Comprehensive inclusion/exclusion criteria assessment and medical history evaluation was conducted at screening and, if necessary, updated on Day 1 prior to dosing.
3 Subjects were required to rest in a supine position for at least 5 minutes before vital signs (blood pressure, pulse, respirations, and temperature) were obtained. Subjects then stood for 3 minutes, after which potential orthostatic changes in blood pressure and pulse were assessed. On Day 1, vital signs (both supine and orthostatic) were obtained within 0.5 hours pre-dose and postdose at 0.5 hours (±15 minutes) and 1.5 hours (±15 minutes).
4 For female subjects only. Spinal x-ray was not required if historical x-ray was deemed acceptable by the central reader. An x-ray was also not required for females with a DXA score below –2.5.
5 Safety laboratory analyses included chemistries, hematology, and urinalysis.
6 Thyroid stimulating hormone, free thyroxine, intact parathyroid hormone, 25-hydroxyvitamin D, and follicle-stimulating hormone (FSH; for female subjects only).
7 Subjects were required to rest in a supine position for at least 5 minutes prior to the ECG recording. On Day 1, ECG was obtained within 0.5 hours pre-dose and postdose at 0.5 hours (±5 minutes).
8 The injection site assessment was performed postdose on Day 1 at 0.5 hours (±15 minutes) and 1 hour (±15 minutes). Injection site assessments were performed at subsequent visits if clinically indicated.
9 PK samples were collected at the following timepoints: within 30 minutes pre-dose and postdose at 10, 15, 30, 60, 90, 120, 180, and 240 minutes (±3 minutes).
10 Anti-drug antibody and PD samples were collected pre-dose.
11 Subjects had a telephone call safety follow-up 1 week after treatment was completed.

An interim analysis focusing on safety and PK findings was conducted after all PK samples were collected and analyzed. The interim analysis results were reviewed at a scheduled meeting of the study's Safety Review Committee.

Diagnosis and Main Eligibility Criteria

Adult male and female subjects with osteoporosis aged 30 to 85 years were included in the study. Female subjects had to be ≥ 5 years postmenopausal and have a screening DXA BMD with a T-score (standard deviation (SD) compared to the mean peak bone mass) of -1.0 to -2.5 with an osteoporotic fracture, or a T-score of -2.5 or lower. Male subjects had to have a DXA BMD T-score of at least -2.0.

For documentation of osteoporotic vertebral fractures, an historical or screening spinal x-ray was reviewed and confirmed by a central, independent reader. Other osteoporotic fractures were documented by previous x-ray report or other medical records.

Key exclusion criteria included the following:

- Treatment with any of the following osteoporosis therapies:
  - Oral bisphosphonates (once daily or once weekly) within 6 months of screening;
  - Oral bisphosphonates (once monthly) within 12 months of screening;
  - Intravenous (IV) bisphosphonates within 24 months of screening;
  - Injectable or nasal calcitonin within 3 months of screening;
  - Oral, vaginal, transdermal, or injectable estrogen/progestin-based products (e.g., estrogens, progestins, raloxifene) within 3 months of screening. Topical applications were not exclusionary;
  - Subcutaneous denosumab within 6 months of screening;

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  - Any current or prior use of products derived from human PTH or PTH-related peptide (egg, Forteo, Teribone, Natpara, Tymlos), including for investigational purposes;
  - Activated vitamin D analogs (i.e., calcifediol, calcitriol) within 3 months of screening.
- Immobility due to severe or chronically disabling conditions (e.g., stroke, Parkinson's disease, multiple sclerosis).
- History of fractures caused by diseases other than PMO for women or primary osteoporosis for men.
- History of Paget's metabolic bone diseases other than osteoporosis.
- History of malignant disease (solid or hematological)
- Unexplained, clinically significant elevation of serum alkaline phosphatase as determined by the Investigator.
- History of prior external beam or implant radiation therapy involving the skeleton.
- History of nephrolithiasis or urolithiasis within 2 years of screening.
- History of more than 1 attack of gout arthritis within 2 years of screening.
- Active primary hyperparathyroidism.
- Currently used digitalis.
- History of gastrointestinal disorders, such as sprue or inflammatory bowel disease, that could have led to malabsorption syndrome.
- History of receiving major organ or bone marrow transplantation.
- History of systemic corticosteroids therapy, defined as any dose level of IV, intramuscular (IM), or oral therapy, for >10 total cumulative days within 2 years of screening. Intraarticular and epidural corticosteroids were not exclusionary.
- Clinically significant abnormal clinical laboratory test values, as determined by the Investigator.
- Any out-of-normal range values for serum calcium during screening.
- Clinically significant abnormal serum values of TSH, free thyroxine (T4), and intact PTH as determined by the Investigator, or 25-hydroxyvitamin D ≤25 nmol/L during screening.
- An estimated creatinine clearance of ≤30 mL/min according to the Cockcroft-Gault equation.
- Known allergy to any components of the investigational products (either PF708 or Forteo).

The eligibility criteria were adequate to ensure reliable interpretation of study results and adequate to minimize safety risks to participating subjects. Additionally, the enrollment criteria were consistent with the pivotal Forteo studies in women with postmenopausal osteoporosis and men with osteoporosis.

<u>Dose Regimen</u>

The dose of PF708 and Forteo was 20 mcg SC daily for 24 weeks. After an initial training dose,

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subjects administered a single dose subcutaneously in the abdomen or thigh daily. All subjects were to receive 1000 mg of calcium and 400 IU of vitamin D supplementation daily, which was supplied and managed by the study sites from the start of screening through the end of the follow-up period.

Study Endpoints

The primary endpoint was the percentage of subjects with detectable serum ADA to teriparatide after 24 weeks of treatment with PF708 or Forteo. Also called the immunogenicity endpoint.

The secondary endpoints of this study were as follows:

- For ADA-positive subjects, ADA titer, incidence of neutralizing antibodies (NAb), and incidence and titer of ADA that cross-react with endogenous PTH1-84.
- Mean percentage change from baseline in lumbar-spine (L1-L4) BMD after 24 weeks of treatment with PF708 or Forteo.
- Area under the concentration-time curve from time 0 to the time of the last observed/measured non-zero concentration ($AUC_{0\text{-last}}$), area under the concentration-time curve from time 0 extrapolated to infinity ($AUC_{0\text{-inf}}$), maximum observed concentration (C_{max}), apparent first-order terminal elimination half-life ($t_{1/2}$), apparent total plasma clearance after extravascular administration (CL/F), time to reach the maximum observed concentration (T_{max}), and apparent first-order terminal elimination rate constant (Kel) of teriparatide after a single injection of PF708 or Forteo.
- Median percentage change from baseline in serum BTM concentrations of N-terminal propeptide of type 1 procollagen (P1NP) (reflecting bone formation) and crosslinked C-terminal telopeptide of type 1 collagen (CTX) (reflecting bone resorption) after 24 weeks of treatment with PF708 or Forteo.

The safety endpoints of this study were the incidence of adverse events (AEs) and serious adverse events (SAEs) with PF708 and Forteo.

Statistical Analysis Plan

<u>Analysis populations</u>
The primary efficacy endpoint of immunogenicity was analyzed in the Immunogenicity Population, which included all subjects who received at least one dose of study drug, with a nonmissing baseline value and at least one post-dose blood sample analyzed for ADA.

The secondary efficacy endpoints of BMD and BTM were analyzed in the BMD Population, which included all subjects who received at least one dose of study drug, a non-missing baseline value, and at least one post-dose DXA assessment.

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Analysis of Immunogenicity
The frequency of ADA positive subjects at Week 24 is analyzed using Fisher's exact test.

Sample size
For the primary endpoint of immunogenicity, it was assumed that approximately 1 to 1.5% of subjects would develop a positive ADA finding after 24 weeks of treatment. A sample size of 70 in each treatment group would rule out, with 95% confidence, an absolute incidence rate of greater than approximately 4% if no positive subjects are observed, and greater than approximately 6.5% if one positive subject is observed (based on exact binomial calculation).

Protocol Amendments

The original protocol (Version 1.0), dated September 7, 2016, was revised 4 times. No subjects were enrolled under Versions 1.0 or 1.1. One subject was enrolled under Version 1.2, 58 under Version 1.3, and 123 subjects under Protocol Version 2.0.

Version 1.1, dated September 26, 2016:

- (b) (4), and added the mean percentage change from baseline in lumbar spine (L1-L4) BMD after 24 weeks of treatment as a secondary objective
- Specified that immunogenicity results are the primary endpoint, and that lumbar spine BMD is one of the secondary endpoints

Version 1.2, dated October 18, 2016:

- (b) (4) The parallel-group, open-label study to compare the effects of PF708 and Forteo after 24 weeks of treatment became the primary study design that included PK assessments
- Specified that the first dose of study drug would be administered by the Principal Investigator or a trained and qualified designee in the clinic and subsequent doses would be self-administered by subjects
- Clarified that an interim analysis of safety and PK findings would be conducted after all PK samples were collected and analyzed for review by the SRC

Version 1.3, dated 15 December 2016:

- Additional injection sites (thighs) were added as self-injection sites, as allowed in the Forteo labeling
- An X-ray eligibility criterion was clarified; if no historical x-ray was available, one would be taken at screening to confirm the fracture criterion
- Clarification that any available PK and PD data could be reviewed by the SRC

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Version 2.0, dated June 2, 2017:

- Clarified ADA testing time such that subjects who tested positive for ADA on the final sample were asked to return for additional testing
- Added current or prior use of Tymlos as a reason for study exclusion
- Revised the malignant disease exclusion to allow for the inclusion of subjects whose malignancy (except osteosarcoma) was considered resolved or cured for >5 years

The majority of these amendments were made in response to FDA requests. All of these changes were acceptable to FDA.

8.1.3. Study PF708-301 Results

Compliance with Good Clinical Practices

The study report states that the study was conducted in accordance with International Council for Harmonisation tripartite guideline E6(R1): Good Clinical Practice. The study appears to have been conducted in compliance with the protocol requirements.

Financial Disclosure

A Financial Disclosure form (3454) states that there was no arrangement by which compensation of the investigators could be affected by the study outcomes, and that no investigators had any financial arrangements or interests to disclose as defined in 21 CFR 54.2.

Data Quality and Integrity

Study Monitoring

A medical monitor was responsible for reviewing adherence to the protocol, compliance with Good Clinical Practices, and the completeness, accuracy, and consistency of the data at the study centers. A safety review committee reviewed interim safety analysis results during the study. The applicant used the following Contract Research Organization (CRO) for this study: (b) (4)

Standardization of Laboratory and Radiographic Procedures

The following central laboratory was used to analyze all screening and on-study laboratory samples: (b) (4) Lateral spine X-rays and DXA images were acquired according to specific instructions provided by the central imaging vendor ((b) (4) and all images were analyzed at the central imaging center.

Overall, it appears that adequate measures were in place to ensure data quality and integrity.

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Data and Analysis Quality

The submitted raw and derived datasets were well documented and accessible. This reviewer reproduced the immunogenicity (primary) and lumbar spine bone mineral density (secondary) efficacy results using the derived datasets. The final statistical analysis plan was submitted prior to unblinding and there were no changes to the pre-specified primary analyses as presented in the protocol.

Disposition

A total of 182 were randomized 1:1 to treatment. A total of 181 subjects received treatment (90 PF708 and 91 Forteo). Subject disposition by treatment is summarized in the table below.

Table 11 Study PF708-301: Subject Disposition by Treatment (All Randomized Subjects)

	PF708 n (%)	Forteo n (%)
Randomized	91	91
Treated	90 (99)	91 (100)
Discontinued Study Treatment	9 (10)	10 (11)
Withdrawal by subject	0 (0)	4 (4)
Adverse event	6 (7)	4 (4)
Protocol deviation	0 (0)	1 (1)
Physician decision	1 (1)	0 (0)
Other[a]	2 (2)	1 (1)
Completed Study Treatment	82 (90)	81 (89)

*Source: Table 5-1 of Clinical Study Report (CSR)
[a] One subject in the PF708 group discontinued due to difficult venous access, 1 subject in the PF708 group was terminated early per decision by the Principal Investigator, and 1 subject in the Forteo group was withdrawn due to sponsor decision.

One subject in the PF708 group withdrew prior to dosing, and 82 (90%) subjects in the PF708 group and 81 (89%) subjects in the Forteo group completed study treatment. The most common reasons for discontinuation from study treatment was the occurrence of an adverse event (6 (7%) subjects in the PF708 group and 4 (4%) subjects in the Forteo group.

Overall the study had an acceptable level of completion of study treatment and rates of discontinuation were similar between treatment groups.

Protocol Violations/Deviations

A total of 37 (20%) subjects had at least 1 significant protocol deviation, as outlined in the table below. The most common types of significant protocol deviations in the PF708 and Forteo groups were study procedures and assessments (5 [6%] subjects and 8 [9%] subjects, respectively). Deviations in study procedures and assessments occurred due to missed, late or improperly performed assessments. Two were related to immunogenicity assessments. In one PF708-treated subject, Day 1 and Week 1 ADA samples were lost due to a shipping error. In one

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Forteo-treated subject, the week 24 ADA sample was received at the wrong temperature. The second most common protocol deviations were related to study treatment compliance, occurring in 3 [3%] subjects in the PF708 group and 9 [10%] subjects in the Forteo group.

Demographic Characteristics

Demographic and baseline characteristics were similar between the PF708 and Forteo groups. Overall, subjects were a mean of 67 years of age, and 59% were between the ages of 65 and 85 years. The majority of subjects were female (72%) and white (90%). Mean body mass index was 26 kg/m^2. Overall, demographic characteristics were similar between the PF708 and Forteo treatment groups, with no notable imbalances.

The number and percentage of subjects who met the spinal fracture eligibility criteria were also similar between the PF708 and Forteo groups. Of the 29 female subjects in each group who had their spine x-ray assessed, 16 (25%) of the 65 females in the PF708 group and 17 (26%) of the 66 females in the PF708 group met spine x-ray eligibility criteria.

Exposure and Treatment Compliance

Study drug exposure was similar between the PF708 and Forteo groups. Mean duration of exposure to study drug was 22.6 weeks and 22.5 weeks in the PF708 and Forteo groups, respectively. Mean cumulative doses were 3127 mcg in the PF708 group and 3098 mcg in the Forteo group.

Study drug compliance was similar between the PF708 and Forteo groups. The mean number of study drug doses planned was 158 in both groups, and the mean number of reported missed doses was 1.8 in the PF708 group and 2.7 in the Forteo group.

The rates of treatment compliance were acceptable and overall balanced between treatment groups. As listed in the table above, the mean compliance rate (defined as number of doses received/number of doses planned) was 99% in the PF708 group and 98% in the Forteo group.

Prior and Concomitant Medications

The prior use of active Vitamin D analogues, bisphosphonates, and denosumab was low in both groups.

Concomitant medication use by subjects in the PF708 and Forteo groups was generally similar. Calcium and Vitamin D supplements were required study treatments. Their use was reported as concomitant medications. Vitamin D and analogues were taken by 86 (96%) subjects in the PF708 group and by 88 (97%) subjects in the Forteo group. Calcium was taken by 81 (90%) subjects in the PF708 group and by 84 (92%) subjects in the Forteo group. However, not all subjects received the same type of vitamin D and calcium supplementation, and there were some differences in types received between the treatment groups.

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Glucocorticoids were taken by 17 (19%) subjects in the PF708 group and by 10 (11%) subjects in the Forteo group.

Results

Primary Endpoint: Percent of Subjects with Detectable Antidrug Antibodies (ADA)

Immunogenicity results are presented in detail in Section 6 and the Clinical Pharmacology Appendices. Overall, the incidence of ADAs was low, and the development of ADAs did not appear to have a negative impact on the efficacy of PF708, as measured by the BMD and BTM pharmacodynamic markers.

The clinical review team agrees with the conclusions of the clinical pharmacology team regarding the immunogenicity assessment of PF708, as discussed in Section 6 and the Clinical Pharmacology Appendices.

Other Secondary Endpoints (Efficacy)

As discussed, the 24-week BMD and bone turnover data from Study PF708-301 are not informative to demonstrate comparability between PF708 and Forteo.

8.1.4. Integrated Assessment of Effectiveness

Through a randomized, double-blind, 2-treatment crossover pharmacokinetic study, comparable bioavailibity between PF708 and Forteo has been demonstrated. In addition, a 6-month randomized, parallel-arm, clinical immunogenicity study demonstrated a similar pattern of antibody formation between the two products. Therefore, the applicant's data adequately demonstrates that PF708 is expected to have clinical effectiveness to that of Forteo and it is acceptable to rely on FDA's findings of Forteo's effectiveness for the proposed indications.

8.2. Review of Safety

8.2.1. Safety Review Approach

The review of safety is based on results from Study PF708-101 and PF708-301. Due to differences in subject population (healthy volunteers versus patients with osteoporosis) and design (two-treatment crossover versus parallel group) of the two studies, safety data from the two studies are not integrated.

8.2.2. Review of the Safety Database

Overall Exposure

A total of 160 subjects were exposed to PF708 in the clinical studies of PF708. Of these, 70

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subjects were healthy volunteers (Study PF708-101) and 90 subjects had osteoporosis (Study PF708-301). Additionally, a total of 161 subjects were exposed to Forteo. Of these, 70 subjects were healthy volunteers (study PF708-101) and 91 subjects had osteoporosis (study PF708-301). Overall, study drug exposure and compliance were similar between the PF708 and Forteo groups in both studies of PF708.

In study PF708-101, subjects received a single 20-mcg subcutaneous injection of both PF708 and Forteo, in a crossover fashion. All injections were administered within the clinical research facility; therefore, compliance was 100% for all 70 subjects.

In study PF708-301, mean duration of exposure to study drug was 22.6 weeks and 22.5 weeks in the PF708 and Forteo groups, respectively. Mean cumulative doses were 3127 mcg in the PF708 group and 3098 mcg in the Forteo group, with actual dose intensities of 138 mcg/week in both groups. See Section 8.1.3 for additional information describing exposure and compliance in Study PF708-301.

Adequacy of the safety database

The overall drug exposure in the submitted studies appears to be adequate for safety evaluation of PF708.

Of note, while Study PF708-101 was double-blind, Study PF708-301 was open label, which could have potentially impacted the reporting of adverse events in Study PF708-301.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Submission quality is adequate regarding overall organization, ease of finding information, and proper location of information and data. There were no data quality or integrity issues identified.

Categorization of Adverse Events

The applicant's approach to the definition and categorization of adverse events was appropriate. Adverse event analyses were categorized using Medical Dictionary for Regulatory Activities (MedDRA) version 19.1.

Routine Clinical Tests

The methodology and frequency of routine clinical testing of the two studies (as described in Section 8.1) was adequate to monitor for known and potential safety risks of teriparatide in the study population.

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8.2.4. Safety Results

Deaths

No deaths were reported in Study PF708-101 or Study PF708-301.

Serious Adverse Events

No serious adverse events (SAEs) were reported in Study PF708-101.

In total, 16 SAEs were reported in Study PF708-301 (7 in the PF708 group and 9 in the Forteo group). 14 subjects experienced at least 1 SAE: 6 (7%) subjects in the PF708 drug product pen injector group and 8 (9%) subjects in the Forteo group. Pneumonia and syncope were reported as SAEs by 1 subject in each of the treatment groups; all other SAEs occurred as individual events. SAEs reported during the study are listed in the table below.

Table 12 Study PF708-301: Number (%) of Subjects with Serious Adverse Events (Safety Population)

	PF708 N=90 n (%)	Forteo N=91 n (%)	All N=181 n (%)
Subjects with at least one SAE	6 (7)	8 (9)	14 (8)
Pneumonia	1 (1)	1 (1)	2 (1)
Syncope	1 (1)	1 (1)	2 (1)
Abdominal pain	1 (1)	0	1 (1)
Anaphylactic reaction	1 (1)	0	1 (1)
Asthenia	0	1 (1)	1 (1)
Atrial fibrillation	1 (1)	0	1 (1)
Carotid artery stenosis	0	1 (1)	1 (1)
Chronic obstructive pulmonary disease	0	1 (1)	1 (1)
Myocardial infarction	1 (1)	0	1 (1)
Non-cardiac chest pain	1 (1)	0	1 (1)
Non-small cell lung cancer	0	1 (1)	1 (1)
Pancreatitis	0	1 (1)	1 (1)
Paralysis	0	1 (1)	1 (1)
Squamous cell carcinoma of lung	0	1 (1)	1 (1)
Source: modified from Table 7-5 of CSR			

The only SAE considered by investigators related to treatment was an anaphylactic reaction in the PF708 group. This SAE occurred in a 64-year-old woman on study day 5 (at approximately 20 hours after the subject's 5th dose of PF708). This SAE involved tongue and throat swelling, which lead to difficulties with swallowing and breathing. The subject was treated for anaphylaxis with oxygen, dexamethasone, intramuscular epinephrine and diphenhydramine and instructed to discontinue study drug. However, 3 days later the subject self-administered another injection of PF708. There were no adverse events reported following this injection. Of

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note, the subject was not taking prednisone or any other anti-allergic treatment when she self-rechallenged with the study drug.

Dropouts and/or Discontinuations Due to Adverse Effects

In Study PF708-101, no subjects discontinued study treatment due to a treatment-emergent adverse event (TEAE).

In Study PF708-301, 8 subjects (4%) discontinued study treatment due to TEAEs: 3 (3%) subjects in the PF708 drug product pen injector group and 5 (6%) subjects in the Forteo group. There was no notable difference between the groups in TEAEs that led to treatment discontinuation; all events by preferred term occurred as single events. TEAEs leading to treatment discontinuation are summarized in the table below.

Table 13 Study PF708-301: Number (%) of Subjects with TEAEs leading to Treatment Discontinuation (Safety Population)

Preferred Term	PF708 N=90 n (%)	Forteo N=91 n (%)	All N=181 n (%)
Subjects with at least one TEAE leading to discontinuation	3 (3)	5 (6)	8 (4)
Asthenia	1 (1)	0	1 (1)
Injection site pain	0	1 (1)	1 (1)
Malaise	0	1 (1)	1 (1)
Arthralgia	1 (1)	1 (1)	2 (1)
Myalgia	0	1 (1)	1 (1)
Neck pain	1 (1)	0	1 (1)
Non-small cell lung cancer	0	1 (1)	1 (1)
Squamous cell carcinoma of lung	0	1 (1)	1 (1)
Abnormal electrocardiogram	1 (1)	0	1 (1)
Dyspnea	1 (1)	0	1 (1)
Hyperhidrosis	1 (1)	0	1 (1)
Source: modified from Table 7-6 of CSR			

Adverse Events of Special Interest

Adverse events (AEs) of special interest in the two studies included the following events previously identified as risks of teriparatide and likely related to its mechanism of action: hypercalcemia, hyperuricemia, nephrolithiasis, and orthostatic hypotension.

Serum Calcium
Hypercalcemia is an adverse event reported with parathyroid products, including Forteo.

Study PF708-101

No adverse events of hypercalcemia were reported. There were no abnormal serum calcium values reported during the study. A summary of serum calcium changes from baseline is

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presented in the table below. For serum calcium, the normal reference range was 8.5 to 10.5 mg/dl.

Table 14 Study PF708-101: Summary of Serum Calcium Changes from Baseline

		PF708 N=70		Forteo N=70	
Timepoint	**Statistic**	**Actual value**	**Change from baseline**	**Actual value**	**Change from baseline**
Baseline	**Mean**	9.4	-	9.3	-
	SD	0.31	-	0.29	-
	Median	9.3	-	9.3	-
	Min	8.6	-	8.5	-
	Max	10.0	-	10	-
Day 2/Day 6 (1 day post-dose)	**Mean**	9.3	0	9.3	0
	SD	0.28	0.25	0.31	0.29
	Median	9.4	0	9.3	0
	Min	8.7	-0.6	8.5	-0.7
	Max	9.9	0.5	9.9	0.6
Source: Table 14.3.4.1-1 of Study PF708-101 CSR					

Study PF708-101 also analyzed serum concentrations of ionized calcium (both unadjusted for pH and normalized to pH 7.4) at various timepoints on Day 1 and Day 5 (for 24 hours following administration of study drug). The serum concentration-time profiles of PF708 and Forteo were similar on both Days 1 and 5 for ionized calcium. On Day 1, small increases in serum ionized calcium were initially observed, with the maximum concentrations occurring at approximately 6 hours postdose. Serum ionized calcium levels then declined to below baseline at 12 hours postdose, returning to near baseline by 24 hours postdose. On Day 5, a similar trend was observed. Concentration-time profiles of serum ionized calcium (both unadjusted for pH and normalized to pH 7.4) on Day 1 and Day 5 are presented in the figures below. For ionized calcium, the normal reference range was 1.1-1.35 mmol/L.

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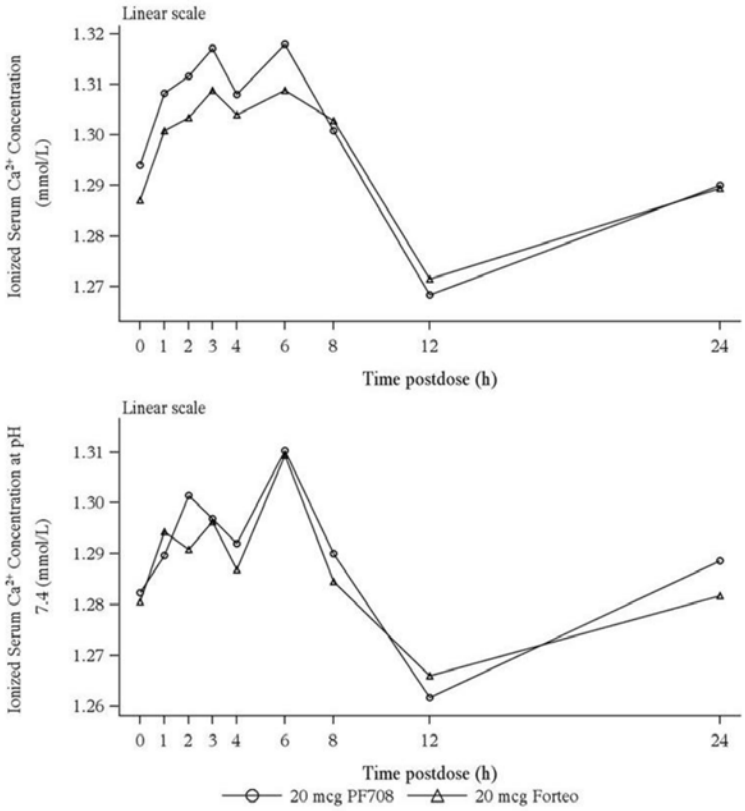
Figure 4 Study PF708-101: Mean Serum Ionized Calcium Concentrations After Treatment with PF708 or Forteo on Day 1



* Source: Figure 11-2 of Study PF708-101 CSR

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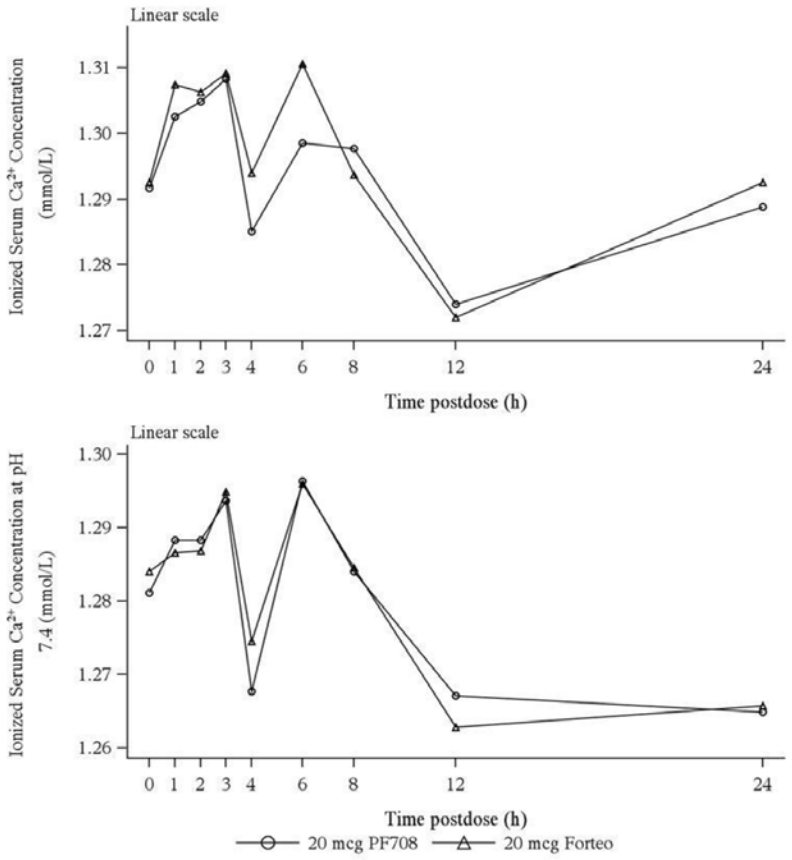
Figure 5 Study PF708-101: Mean Serum Ionized Calcium Concentrations After Treatment with PF708 or Forteo on Day 5



Source: Figure 11-2 of Study PF708-101 CSR

Adequate assessments were performed in the study to characterize the effect of PF708 on serum calcium. The pattern observed for serum concentrations of ionized calcium following PF708 administration is consistent with the pattern observed in the Forteo clinical trials, as described in the Forteo USPI.

Study PF708-301

Adverse events of hypercalcemia were reported in two (2%) subjects receiving PF708and one (1%) subject receiving Forteo. Study PF708-101 assessed calcium levels at multiple timepoints during the 24-hour post-dose period. In study PF708-301, serum calcium levels were assessed on Day 1, Week 1, Week 12 and Week 24. It is unlikely that the study PF708-301 study schedule captured the potential calcium increases for this multi-dose trial.

The number of subjects with any newly notable (i.e., not present at baseline) above normal (>2.62 mmol/L) serum calcium result during the study was 13/90 (14%) in the PF708 group and 17/91 (19%) in the Forteo group.

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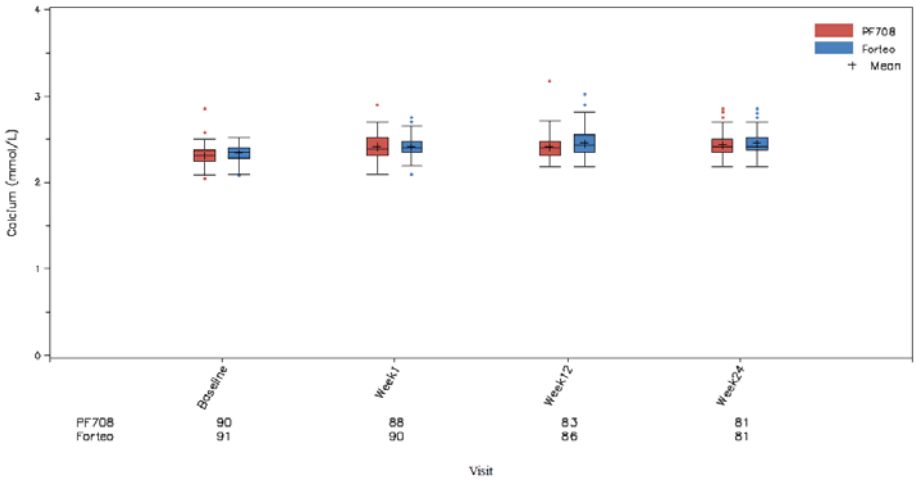
Mean calcium levels increased slightly from baseline for the PF708 and Forteo treatment groups (by 0.096 mmol/L and 0.072 mmol/L, respectively, at week 1, and by 0.118 mmol/L and 0.109 mmol/L, respectively, at week 24). These increases in mean calcium were not considered clinically meaningful and were similar between treatment groups. Absolute values over time are plotted for calcium in the figure below. The normal reference range for calcium was 2.12 – 2.62 mmol/L.

Figure 6: Study PF708-301: Box Plot of Absolute Values for Calcium (Safety Population)



Horizontal line: Median, Box: Q1 - Q3.
Whiskers extend to the most extreme observation within 1.5 times the interquartile range from the nearest quartile, so that all outliers >1.5 times the interquartile range are individually displayed.

Source: Figure 7-1 of CSR

Overall, the results observed for serum calcium were consistent with the expected pattern based on data from the Forteo clinical trials, as described in the Forteo USPI.

<u>Hyperuricemia</u>
Increases in serum uric acid levels were noted in the Forteo clinical trials. Therefore, serum uric acid levels were followed in the PF708 trials.

Study PF708-101

No adverse events of hyperuricemia were noted in Study PF708-101. Mean uric acid levels in both treatment groups did not change compared to baseline when measured 1-day post-treatment.

Study PF708-301

In Study PF708-301, adverse events of hyperuricemia were reported in one (1%) subject in the PF708 group and no subjects in the Forteo group. Serum uric acid levels were assessed on Day

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1, Week 1, Week 12 and Week 24. This schedule was adequate to characterize the effect of PF708 on serum uric acid.

The number of subjects with any newly notable (i.e., not present at baseline) above normal serum uric acid result during the study was 3/90 (3%) in the PF708 group and 3/91 (3%) in the Forteo group.

Mean uric acid levels increased similarly from baseline for the PF708 and Forteo groups. By week 24, levels increased from baseline by 0.06 mmol/L and 0.05 mmol/L, respectively for the PF708 and Forteo groups. Mean values at week 24 were 0.36 mmol/L and 0.34 mmol/L, respectively. The normal reference range for uric acid was 0.12 – 0.36 mmol/L in women and 0.24 – 0.47 in men.

Overall, the results observed for serum uric acid were consistent with the expected pattern based on data from the Forteo clinical trials, as described in the Forteo USPI.

Urolithiasis
Because of increases in calcium and hypercalciuria due to parathyroid products, there is a potential for urolithiasis. In Study PF708-301, adverse events of urolithiasis were reported in one (1%) subject in the PF708 group and no subjects in the Forteo group.

Orthostatic Hypotension
Orthostatic hypotension was reported in clinical trials of Forteo. In Study PF708-101, there were no adverse events of orthostatic hypotension and orthostatic vital signs were not measured.

In study PF708-301, orthostatic hypotension adverse events were reported in 3 (3%) subjects in the PF708 group and 7 (7%) in the Forteo group. The applicant defined an abnormal supine to standing blood pressure (BP) change as a decrease of 20 mmHg or greater for systolic BP and a decrease of 10 mmHg or greater for diastolic BP. For systolic BP, 9 subjects in each treatment group had abnormal systolic BP changes. For diastolic BP, 39 subjects in the PF708 group and 38 subjects in the Forteo group had abnormal diastolic BP changes.

Treatment Emergent Adverse Events (TEAEs)

In Study PF708-101, 49 (70%) subjects reported a total of 115 TEAEs. The number of TEAEs was similar between the PF708 and Forteo treatment groups, with 45 (64%) subjects having reported a total of 54 TEAEs in the PF708 group and 44 (63%) subjects having reported a total of 61 TEAEs in the Forteo group.

Most TEAEs reported were in the MedDRA system organ class (SOC) of general disorders and administration site conditions (47 [67%] subjects reported a total of 93 such TEAEs). The remainder of the TEAEs were reported in the SOCs of nervous system disorders (11 [16%]

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subjects, 17 TEAEs), gastrointestinal disorders (3 [4%] subjects, 3 TEAEs), cardiac disorders (1 [1%] subject, 1 TEAE), and musculoskeletal and connective tissue disorders (1 [1%] subject, 1 TEAE). Rates of TEAEs by SOC were generally similar between the PF708 and Forteo treatment groups. TEAEs by SOC and preferred term (PT) are listed in the table below.

Table 15 Study PF708-101: Subject Incidence of Treatment-emergent Adverse Events

MedDRA SOC Preferred term	PF708 N=70 n (%)	Forteo N=70 n (%)	All N=70 n (%)
General disorders and administration site conditions	44 (63)	40 (57)	47 (67)
Injection site erythema	44 (63)	40 (57)	47 (67)
Injection site hemorrhage	1 (1)	3 (4)	4 (6)
Injection site pruritus	1 (1)	1 (1)	2 (3)
Catheter site hematoma	0	1 (1)	1 (1)
Catheter site hemorrhage	0	1 (1)	1 (1)
Fatigue	0	1 (1)	1 (1)
Nervous system disorders	5 (7)	8 (11)	11 (16)
Headache	4 (6)	5 (7)	7 (10)
Dizziness	1 (1)	3 (4)	4 (6)
Hypoesthesia	0	1 (1)	1 (1)
Presyncope	0	1 (1)	1 (1)
Gastrointestinal disorders	1 (1)	2 (3)	3 (4)
Nausea	1 (1)	1 (1)	2 (3)
Abdominal pain	0	1 (1)	1 (1)
Cardiac disorders	0	1 (1)	1 (1)
Palpitations	0	1 (1)	1 (1)
Musculoskeletal and connective tissue disorders	0	1 (1)	1 (1)
Myalgia	0	1 (1)	1 (1)
Source: modified from Table 12-2 of Study PF708-101 CSR			

The most frequently reported TEAEs were related to injection site findings. These TEAEs were reported by 44 (63%) subjects in the PF708 group (a total of 46 events) and by 40 (57%) subjects in the Forteo group (a total of 44 events). Most of the injection-site TEAEs were for the PT of injection-site erythema, which was reported by 44 (63%) subjects in the PF708 group (a total of 44 events) and by 40 (57%) subjects in the Forteo group (a total of 40 events). The remainder of injection site findings consisted of injection site hemorrhage (1 [1%] subject and 3 [4%] subjects in the PF708 and Forteo groups, respectively) and injection site pruritus (1 [1%] subject in each treatment group). A single TEAE of catheter site hematoma, catheter site hemorrhage, and fatigue were each reported by 1 (1%) subject in the Forteo group but were not reported in the PF708 group. All injection site TEAEs were considered by the investigator to be related to study treatment.

Of the 115 TEAEs reported, 110 were considered by the investigators to be related to study treatment, largely because so many of the TEAEs were injection site findings.

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Overall, the frequency and nature of TEAEs were similar in the PF708 and Forteo treatment groups in Study PF708-101 and appeared consistent with the known AE profile of Forteo.

In Study PF708-301, 148 (82%) subjects reported a total of 537 TEAEs. The number of TEAEs was similar between the PF708 and Forteo treatment groups, with 75 (83%) subjects having reported a total of 261 TEAEs in the PF708 group and 73 (80%) subjects having reported a total of 276 TEAEs in the Forteo group.

Most TEAEs reported were in the MedDRA system organ class (SOC) of general disorders and administration site conditions (reported in 64 [35%] subjects). The remainder of TEAEs that were reported in >5% of subjects were in the SOCs of infections and infestations (59 [33%] subjects), nervous system disorders (36 [20%] subjects) and gastrointestinal disorders (32 [18%] subjects). Rates of TEAEs by SOC were generally similar between the PF708 and Forteo treatment groups. A summary of TEAEs by SOC and PT is presented in the table below.

Table 16 Study PF708-301: Subject Incidence of Treatment-emergent Adverse Events Reported in > 5% of Subjects in Either Treatment Group

MedDRA SOC Preferred term	PF708 N=90 n (%)	Forteo N=91 n (%)	All N=181 n (%)
General disorders and administration site conditions	32 (36)	32 (35)	64 (35)
Injection site bruising	8 (9)	7 (8)	15 (8)
Injection site erythema	21 (23)	15 (17)	36 (20)
Injection site reaction	3 (3)	5 (6)	8 (4)
Infections and infestations	31 (34)	28 (31)	59 (33)
Nasopharyngitis	7 (8)	9 (10)	16 (9)
Sinusitis	6 (7)	2 (2)	8 (4)
Upper respiratory tract infection	5 (6)	4 (4)	9 (5)
Urinary tract infection	8 (9)	4 (4)	12 (7)
Nervous system disorders	20 (22)	16 (18)	36 (20)
Headache	9 (10)	4 (4)	13 (7)
Gastrointestinal disorders	13 (14)	19 (21)	32 (18)
Diarrhea	0	6 (7)	6 (3)
Nausea	6 (7)	5 (6)	11 (6)
Source: modified from Table 7-4 of Study PF708-301 CSR			

TEAEs considered treatment-related were observed in 48 (53%) subjects in the PF708 drug product pen injector group and 45 (50%) subjects in the Forteo group. The most common TEAE considered treatment-related in both PF708 injector and Forteo groups was injection site erythema (21 subjects [23%] and 15 subjects [17%], respectively).

Overall, the nature and frequency of all TEAEs were similar in the PF708 and Forteo treatment groups, and do not raise concern for any new safety issues with PF708.

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Laboratory Findings

Study PF708-101

In Study PF708-101, the mean chemistry and hematology values were within the normal range at baseline, as required in the individual study inclusion and exclusion criteria. Mean changes from baseline values were generally small. None of the changes were considered clinically significant, and none were reported as a TEAE. Furthermore, changes in laboratory evaluations did not demonstrate any trends overall or between treatment groups. Calcium and uric acid results are discussed above in the events of special interest section.

Study PF708-301

In Study PF708-301, changes in clinical chemistry and hematology values were generally similar for the PF708 and Forteo groups.

A summary of the shifts from baseline to week 24 in select chemistry parameters (those with a shift of 4 or more subjects in either treatment group from normal to either low or high) is presented in the table below. Shifts in chemistry parameters from normal at baseline to low or high at week 24 occurred at similar rates for subjects in the PF708 and Forteo groups, with the exception of creatine phosphokinase and uric acid, which both had more shifts from normal at baseline in the PF708 group compared to the Forteo group. Results for creatine phosphokinase and uric acid are described in further detail below.

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Table 17 Study PF708-301: Summary of Shift from Baseline to Week 24 in Select Chemistry Parameters (Safety Population)

Parameter	Change	PF708 (N = 90) n	Forteo (N = 91) n	Total (N = 181) n
Alkaline phosphatase	Normal to Low	0	0	0
	Normal to High	7	8	15
Calcium	Normal to Low	0	0	0
	Normal to High	7	8	15
Creatine phosphokinase	Normal to Low	0	0	0
	Normal to High	7	2	9
Creatinine	Normal to Low	7	5	12
	Normal to High	2	0	2
Lipase	Normal to Low	1	0	1
	Normal to High	4	4	8
Phosphorus	Normal to Low	0	2	2
	Normal to High	2	2	4
Potassium	Normal to Low	1	3	4
	Normal to High	5	4	9
Sodium	Normal to Low	1	0	1
	Normal to High	1	4	5
Total cholesterol	Normal to Low	1	2	3
	Normal to High	7	5	12
Triglycerides	Normal to Low	0	0	0
	Normal to High	2	5	7
Urea nitrogen	Normal to Low	0	0	0
	Normal to High	9	8	17
Uric acid	Normal to Low	0	1	1
	Normal to High	21	14	35

Source: Table 7-8 of CSR

A summary of the shifts from baseline to week 24 in select hematology parameters (those with a shift of 4 or more subjects in either treatment group from normal to either low or high) is presented in the table below. Shifts in hematology parameters from normal at baseline to either low or high at week 24 occurred at similar rates for subjects in the PF708 and Forteo groups, with the exception of erythrocytes distribution width, which had more shifts from normal at baseline in the Forteo group compared to the PF708 group.

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Table 18 Study PF708-301: Summary of Shift from Baseline to Week 24 in Select Hematology Parameters (Safety Population)

Parameter	Change	PF708 (N = 90) n	Forteo (N = 91) n	Total (N = 181) n
Erythrocytes Distribution Width	Normal to Low	0	0	0
	Normal to High	4	9	13
Leukocytes	Normal to Low	1	0	1
	Normal to High	2	5	7
Mean platelet volume	Normal to Low	0	0	0
	Normal to High	4	7	11
Monocytes/Leukocytes	Normal to Low	0	0	0
	Normal to High	4	1	5
Neutrophils	Normal to Low	0	1	1
	Normal to High	2	6	8
Neutrophils/Leukocytes	Normal to Low	3	1	4
	Normal to High	10	9	19
Platelets	Normal to Low	0	0	0
	Normal to High	4	5	9
Reticulocyte count/Leukocytes	Normal to Low	5	4	9
	Normal to High	0	2	2

Source: Table 7-9 of CSR

Incidence rates of newly notable laboratory (chemistry and hematology) abnormalities for select parameters, including calcium, phosphorus, and uric acid, at any time throughout the study are summarized in the table below. The incidence rates of subjects with notable abnormalities in calcium and in uric acid were similar in the PF708 and Forteo treatment groups. The incidence rates of subjects in both groups with notably low phosphorus were similar, although a higher proportion of subjects in the PF708 group (10 subjects [11%]) had abnormally high phosphorus than in the Forteo group (3 subjects [3%]). Differences between the treatment groups in the incidence rates of notable abnormalities were also observed for lipase, protein, urea nitrogen, erythrocytes distribution width, and reticulocyte count/leukocytes as detailed in the table below.

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Table 19 Study PF708-301: Incidence Rates of Newly Notable Laboratory (Chemistry and Hematology) Abnormalities for Select Parameters (Safety Population)

Parameter (unit)	Notable Criteria	PF708 (N = 90) n (%)	Forteo (N = 91) n (%)	Total (N = 181) n (%)
Calcium (mmol/L)	Low (<2.12)	1 (1)	2 (2)	3 (2)
	High (>2.62)	13 (14)	17 (19)	30 (17)
Lipase (U/L)	Low (<13)	2 (2)	0	2 (1)
	High (>60)	5 (6)	13 (14)	18 (10)
Phosphorus (mmol/L)	Low (<0.81)	2 (2)	5 (6)	7 (4)
	High (>1.45)	10 (11)	3 (3)	13 (7)
Protein (g/L)	Low (<60)	1 (1)	5 (6)	6 (3)
	High (>80)	0	0	0
Urea nitrogen (mmol/L)	Low (<1.78)	0	0	0
	High (>7.14)	23 (26)	11 (12)	34 (19)
Uric acid (mmol/L) , women	Low (<0.119)	0	0	0
	High (>0.357)	23 (26)	22 (24)	45 (25)
Uric acid (mmol/L), men	Low (<0.238)	0	1 (1)	1 (1)
	High (>0.476)	3 (3)	3 (3)	6 (3)
Erythrocytes Distribution Width (%)	Low (<11.5)	0	0	0
	High (>14.5)	11 (12)	18 (20)	29 (16)
Reticulocyte Count/Leukocytes (%)	Low (<0.6)	24 (27)	9 (10)	33 (18)
	High (>2.1)	1 (1)	8 (9)	9 (5)

Source: Table 7-10 of CSR

Notable chemistry laboratory results are further described below. Calcium and uric acid results are discussed above in the events of special interest section.

Mean phosphorus levels did not change notably after baseline at weeks 1 and 12 for either group and were slightly decreased at week 24 (change from baseline of -0.018 mmol/L and -0.047 mmol/L for the PF708 and Forteo groups, respectively). These changes were not considered clinically meaningful. Absolute values over time are plotted for phosphorus in the figure below. The normal reference range for phosphorus was 0.81 -1.45 mmol/L.

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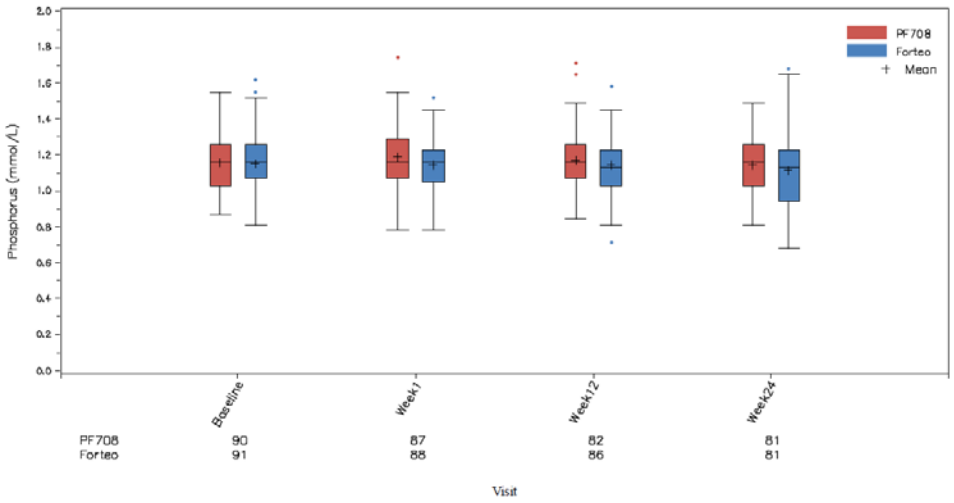
Figure 7 Study PF708-301: Box Plot of Absolute Values for Phosphorus (Safety Population)



Horizontal line: Median, Box: Q1 - Q3.
Whiskers extend to the most extreme observation within 1.5 times the interquartile range from the nearest quartile, so that all outliers >1.5 times the interquartile range are individually displayed.

Source: Figure 7-1 of CSR

Mean alkaline phosphatase levels increased from baseline at weeks 12 and 24 increased similarly for the PF708 and Forteo groups (by 15.0 U/L and 11.5 U/L, respectively, at week 24), likely due to the mechanism of action of teriparatide on bone growth. Mean values at week 24 were 88.4 U/L and 91.2 U/L for the PF708 and Forteo groups, respectively. The normal reference range for alkaline phosphatase was 45- 150 U/L.

Mean creatine phosphokinase levels decreased from baseline for the PF708 and Forteo groups, with greater decreases observed in the Forteo group. By week 24, changes from baseline were -2.0 U/L and -43.1 U/L, respectively, for the PF708 and Forteo groups. Mean values at week 24 were 105.5 U/L and 97.8 U/L, respectively. The normal reference range for was 30-170 U/L.

Mean urea nitrogen levels increased similarly from baseline for the PF708 and Forteo groups. By week 24, increases from baseline were 0.291 mmol/L and 0.502 mmol/L, respectively, for the PF708 and Forteo groups. Mean values at week 24 were 5.879 mmol/L and 6.073 mmol/L, respectively. The normal reference range for was 1.78 - 7.14 mmol/L.

Regarding urinalysis results, there were no concerning patterns of abnormalities or notable imbalances between treatment groups. Calcium oxalate crystals were observed in the urinalysis assessments of 2 PF708-treated subjects (both at week 12) and 2 Forteo-treated subjects (one at week 12 and one at week 1). Of note, urinary calcium excretion was not measured.

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Overall, laboratory findings in Study PF708-301 were consistent with the expected effects of Forteo, and no new safety concerns were identified with PF708.

Vital Signs

In Study PF708-101, there were no clinically significant findings in mean systolic or diastolic blood pressure, pulse rate, respiration rate, or temperature for any subject. No clinically significant changes from baseline in vital signs measurements were reported, and there were no differences between treatment groups.

In Study PF708-301, there were also no clinically-meaningful differences in the change from baseline in vital signs.

Electrocardiograms (ECGs)

In Study PF708-101, no trends in individual ECG parameters were observed. No ECGs were determined by the investigator to be clinically significant. No individual subject had a QT abnormality (QTcF > 450 ms) or an increase from baseline in QTcF > 60 ms during the study.

In Study PF708-301, there were no clinically meaningful changes from baseline to 0.5 hours postdose in ECG parameters in either treatment group. No subjects shifted from a normal ECG interpretation at baseline to a clinically significant abnormal interpretation at 0.5 hours post-dose.

8.2.5. Analysis of Submission-Specific Safety Issues

Immunogenicity

As described in Section 6 and the Clinical Pharmacology Appendices, in study PF708-101, no ADAs were detected 4 days after single-dose administration of PF708 or Forteo, and in study PF708-301, 4 subjects had detectable ADA during the study (2 in each treatment group). None of the positive ADA findings demonstrated cross-reactivity against endogenous PTH_{1-84}.

Overall, there were no apparent safety issues related to ADA findings. No AEs of special interest, SAEs, hypersensitivity reactions or allergic reactions were reported for the 4 subjects who had detectable ADA. Serum calcium and phosphorus levels for subjects with detectable ADA during the study were within normal limits. A summary of TEAEs for the subjects who tested positive for ADAs is presented in the table below.

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Table 20 Study PF708-301: Adverse Events in all ADA-positive Subjects

	PF708 # (b) (6)	PF708 # (b) (6)	Forteo # (b) (6)	PF708 # (b) (6)
Number of adverse events (PTs)	1 (increased prostate specific antigen)	1 (intermittent left knee pain)	5 (upper respiratory tract infection, urinary tract infection, chronic obstructive pulmonary disease, orthostatic hypotension)	0
Source: modified from Table 13-1 of ADA/BTM/PK Report				

The TEAEs reported in these subjects likely have no causal relationship to ADA formation.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable.

8.2.7. Safety Analyses by Demographic Subgroups

Adverse events were not analyzed separately by demographic subgroups given the size of the study populations.

8.2.8. Specific Safety Studies/Clinical Trials

Not applicable.

8.2.9. Additional Safety Explorations

None of the following additional safety explorations were performed for PF708. Many were previously formed for teriparatide, however, in clinical studies of Forteo, as described below.

Human Carcinogenicity or Tumor Development

Osteosarcoma has been seen in nonclinical studies for all parathyroid hormone analogs. The relevance of these findings to humans is unclear (b) (4), (b) (5)

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Human Reproduction and Pregnancy

Teriparatide is not indicated for use in pregnant women. Teriparatide labeling will follow the Pregnancy and Lactation Labeling Rule.

Pediatrics and Assessment of Effects on Growth

Teriparatide has not been studied in children and adolescents. It is recommended that teriparatide not be used in children with open growth plates due to the osteosarcoma risk.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There are no reported incidences of overdose with PF708.

In teriparatide postmarketing spontaneous reports, there have been cases of medication errors in which up to 800 mcg of teriparatide have been administered as a single dose. Transient events reported have included nausea, weakness/lethargy and hypotension. In some cases, no adverse events occurred as a result of the overdose. No fatalities associated with overdose have been reported.

8.2.10. Safety in the Postmarket Setting

There are no postmarketing safety data for PF708. There is extensive postmarketing experience, with Forteo. The following adverse reactions have been identified during post-approval use of Forteo:

- Osteosarcoma: cases of bone tumor and osteosarcoma have been rarely reported in the postmarketing period. The causality to Forteo is unclear and long-term osteosarcoma surveillance studies are ongoing.

- Hypercalcemia: hypercalcemia greater than 13.0 mg/dL has been reported with Forteo use.

8.2.11. Integrated Assessment of Safety

Through a randomized, double-blind, 2-treatment crossover pharmacokinetic study, comparable bioavailibity between PF708 and Forteo has been demonstrated. In addition, a 6-month randomized, parallel-arm, clinical immunogenicity study demonstrated a similar pattern of antibody formation between the two products. In these two trials, the safety profile of PF708 and Forteo appear similar. Therefore, the applicant's data adequately demonstrates that PF708 is expected to have similar clinical safety as that of Forteo and it is acceptable to rely on FDA's findings of Forteo's safety for the proposed indications.

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8.3. Conclusions and Recommendations

The applicant is relying the FDA's findings of safety and effectiveness of Forteo. The applicant has demonstrated physiochemical comparability between PF708 and Forteo. Additionally, a randomized, double-blind, 2-treatment crossover pharmacokinetic study showed comparable bioavailibity between PF708 and Forteo, and a 6-month randomized, parallel-arm, clinical immunogenicity study demonstrated a similar pattern of antibody formation between the two products. Nonclinical comparability has also been demonstrated between PF708 and Forteo. Therefore, the applicant's data adequately demonstrates that PF708 is expected to have clinical effectiveness and safety similar to that of Forteo and it is acceptable to rely on FDA's findings of Forteo's safety and effectiveness for approval of Bonsity for all of the proposed indications.

9 Advisory Committee Meeting and Other External Consultations

No Advisory Committee meeting was held for this NDA as the active ingredient is not a new molecular entity, and no major safety or efficacy concerns were discovered during the review.

10 Pediatrics

The efficacy of teriparatide has not been established in any pediatric population. Teriparatide should not be prescribed in patients at an increased baseline risk of osteosarcoma, which includes pediatric and young adult patients with open epiphyses. Therefore, teriparatide is not indicated for use in pediatric or young adult patients with open epiphyses.

In accordance with 21 CFR 312.23(a)(10)(iii), an initial agreed Pediatric Study Plan was submitted October 23, 2018, outlining a general investigational plan of a full waiver of pediatric assessments because evidence strongly suggests that teriparatide would be unsafe in pediatric patients.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

This 505(b)(2) application relies on FDA findings regarding the safety and efficacy of Forteo. PF708 is expected to have comparable safety and efficacy, therefore labeling should be essentially the same as for Forteo, except for differences in dosing instructions. See separate document for final approved label.

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Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
Highlights of Prescribing Information	Pharmacologic class does not match the Established Pharmacologic Class for teriparatide	Change pharmacologic class to Established Pharmacologic Class for teriparatide
6	No immunogenicity results from Study PF708-301 were included	Added immunogenicity results from Study PF708-301
8	Following Forteo Prescribing Information	Pending listed drug Forteo labeling revisions to occur mid-2019.
12	Following Forteo Prescribing Information	Added the PK profile of teriparatide following administration of BONSITY from Study PF708-101

12 Risk Evaluation and Mitigation Strategies (REMS)

The applicant is relying on FDA's previous findings of safety and efficacy of Forteo. On April 28, 2017, FDA released the REMS requirement for Forteo stating that the Medication Guide and communication plan are no longer necessary to ensure the benefits of the drug outweigh the risks and therefore a REMS is no longer required. The FDA also stated that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208 and will therefore continue to be part of the approved labeling in accordance with 21 CFR 208 and is subject to safety labeling change provisions of section 505(o)(4) of the FDCA.

Consistent with the non-REMS requirement for Forteo, the applicant did not include a REMS in this 505(b)(2) application but did including a Medication Guide as part of the approved teriparatide labeling.

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13 Postmarketing Requirements and Commitment

No postmarketing required studies are recommended or required.

Because the potential risk of osteosarcoma involves a tumor type that is quite rare, postmarketing surveillance will include enhanced pharmacovigilance to collect as much relevant data as possible on any osteosarcoma case reported.

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14 Appendices

14.1. References

Balasubramanian A, Zhang J, Chen L, et al. High risk of second fracture within 1, 2, 5 years after prior fracture among women 65 years or older. Abstract presented at The American Society for Bone and Mineral Research Annual Meeting; October 16–18, 2016; Atlanta, Ga. Abstract FR0233.

Forteo United States Prescribing Information

Khosla, S. Surrogates for fracture endpoints in clinical trials. J Bone Miner Res. 2003;18(6):1146-1149.

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14.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): PF708-101 and PF708-301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 30		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

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14.3. Nonclinical Pharmacology/Toxicology

The qualification of the impurity safety profile was supported by the 4-week bridging toxicity study in Sprague Dawley rats that compared the toxicity, toxicokinetics (TK), and immunogenicity of the to-be-marketed PF708 drug product formulation with Forteo. Male and female Sprague Dawley rats were administered bolus subcutaneous injections of 30 µg/kg/day PF708 (drug product cartridge Lot 1614-003). The PF708 drug product cartridge used in the bridging toxicity rat study was approximately 22 months post manufacture.

The impurity levels were not provided on the PF708 drug product cartridge (Lot 1614-003) Certificate of Analysis. However, the PF708 drug product analytical bridging study data did include the impurity levels for this lot at the 24-month stability interval. Both PF708 drug product cartridge (Lot 1614-003) and its corresponding PF708 drug product pen injector (Lot 1614-003A002) were included in the analytical study.

Product-related impurities were quantified using the Teriparatide Injection USP monograph RP-HPLC method. Observed impurities at levels (b) (4)% or greater in PF708 drug product using RP-HPLC were identified, monitored, and quantified:

- truncated rhPTH(1-30)
- teriparatide succinimide (30)
- oxidized methionine residues (specified in the USP monograph for Teriparatide) at amino acid positions 8 (Met+O[8]) and 18 (Met+O[18]) and doubly oxidized rhPTH(1-34) at the same methionine amino acid positions Met+O(8,18)
- largest other related impurity
- total impurities

<u>Drug substance</u>
The PF708 drug substance met the teriparatide USP monograph acceptance criteria for largest other related impurity (not more than [NMT] 0.5%) and for total impurities (NMT 2.5%).

- The drug substance acceptance criteria for rhPTH (1-30) and teriparatide succinimide (30) was NMT (b) (4) .
- The drug substance acceptance criteria for total methionyl sulfoxides of teriparatide (consisting of *Met+O(8)*, *Met+O(18)*, and *Met+O(8,18)*) was NMT (b) (4)%, which was (b) (4) than the acceptance criteria of NMT 0.5% stated in the teriparatide USP monograph. Nonetheless, the PF708 drug product did meet the teriparatide injection USP monograph acceptance criteria for product-related substances and impurities.
- These impurities were also common to Forteo, therefore, were justified.

<u>Safety margin (drug substance impurities)</u>:
To support qualification of these impurities, Pfenex conducted a nonclinical toxicology bridging study with the intended to-be-marketed clinical formulation and Forteo.

- The 30 µg/kg/day rat dose results in a total methionyl sulfoxides of teriparatide impurity dose of (b) (4) µg/m^2/day, which is 10X higher than the maximum clinical impurity dose

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that would be administered at the (b) (4)% drug substance specification level for total methionyl sulfoxides of teriparatide in a 20 µg teriparatide dose.

- The 30 µg/kg/day rat dose results in a rhPTH (1-30) and teriparatide succinimide (30) impurity dose of (b) (4) µg/m^2/day, which is 51X higher than the maximum clinical impurity dose that would be administered at the (b) (4)% drug substance specification level for both rhPTH (1-30) and teriparatide succinimide (30) in a 20-µg teriparatide dose.

<u>Drug product</u>
The PF708 drug product met the teriparatide injection USP monograph acceptance criteria for largest other related impurity (not more than [NMT] (b) (4)) and for total impurities (NMT 7.0%). These acceptance criteria were established using lot analysis and stability data with a proposed 24-month shelf life.

- The drug product acceptance criteria for rhPTH (1-30) and teriparatide succinimide (30) was NMT 1.2%.
- The drug product acceptance criteria for the methionyl sulfoxides of teriparatide (consisting of *Met+O(8)*, *Met+O(18)*, and *Met+O(8,18)*) were NMT (b) (4)%, NMT (b) (4)%, and NMT (b) (4)%, respectively.
    - No further qualification of these drug product impurities is required as all specification levels are equal or less than the FDA Q3B qualification threshold of 1% for a drug product with a < 10 mg maximum clinical dose.

<u>Safety margin (drug product impurities)</u>:

- The 30 µg/kg/day rat dose results in three of methionyl sulfoxides of teriparatide impurities: *Met+O(8)*, *Met+O(18)*, and *Met+O(8,18)*, which is approx. 9.6X, 7.2X, and 5.1X, respectively, higher than the maximum clinical impurity dose that would be administered at the (b) (4)%, respectively, drug product specification level for total methionyl sulfoxides of teriparatide in a 20 µg teriparatide dose.
- The 30 µg/kg/day rat dose results in a rhPTH (1-30) and teriparatide succinimide (30) impurity dose of 1.26 µg/m^2/day, which is 8.5X higher than the maximum clinical impurity dose that would be administered at the 1.2% drug product specification level for both rhPTH (1-30) and teriparatide succinimide (30) in a 20-µg teriparatide dose.

Unspecified product-related impurities were controlled under the largest other related impurity limit (NMT (b) (4)%) established using lot analysis and stability data, and total impurities (NMT 7.0%) were set according to the USP teriparatide injection monograph.

There were no elemental impurities of concern at the 20-µg clinical dose. The drug product formulation is in direct contact with the primary container closure. The pen injector device does not contact the drug solution except for the attached needle during the injection. Extractable study (for primary container closure) showed that all elements were below the analytical threshold. Leachable study (for expired drug product cartridges) showed all results were below the specification listed in USP <232>. Biocompatibility testing for the PF708 pen

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injector (delivery device) showed that all test samples passed the required acceptance criteria per ISO 10993 for ≥ 30 days skin contact materials.

Aggregate

In Section 3.2.P.5.6, the justification and acceptance criterion for aggregate (HMM; impurities with molecular mass greater than that of teriparatide) was provided. The proposed limit for aggregate was (b) (4)%. A dimer of teriparatide was identified as major aggregated species. The observed level for 7 lots of PF708 Drug Product Cartridge, with age ranging from 8 to 36 months, was < LOQ (LOQ = (b) (4)%). The sum of all detectable aggregates was up to (b) (4)%.
CMC reviewer's note: RLD DP specification does not include testing for aggregate.

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14.4. OCP Appendices

14.4.1. Summary of Bioanalytical Method Validation and Performance

The Office of Clinical Pharmacology review team has assessed the adequacy and acceptability of the bioanalytical methods used to measure the plasma concentrations of teriparatide in the clinical studies, PF708-101 and PF708-301. The concentrations of teriparatide in human plasma were determined using an enzyme-linked immunosorbent assay (ELISA) kit (High Sensitivity human PTH [1-34] ELISA kit, Immunotopics). This ELISA method used two antibodies that optimally recognized PTH (1-34) and have been determined to show the cross-reactivity of PTH (1-84) to be less than 3% on a molar basis (Immunotopics, Package Insert)

The applicant conducted a validation study for the bioanalytical method. The validation and performance results of the bioanalytical method are summarized in Table 21.

Table 21 Summary of performance of the bioanalytical method used to measure teriparatide in human plasma

Summary of performance of the bioanalytical method used to measure teriparatide in human plasma

Bioanalytical validation method summary	The bioanalytical method validation study for the determination of teriparatide [PTH (1-34)] in human plasma (EDTA) included an assessment of accuracy, precision, selectivity, sensitivity, matrix effect, co-administered compound evaluation, hemolyzed sample integrity, lipemic sample evaluation, stability (long-term, freeze-thaw, short-term, long-term stability for stock solutions, and short-term stability for stock solutions), stability of analyte during sample collection and handling, response function, and dilution integrity. Fourteen validation batches were performed using 5 quality control (QC) samples (6, 18, 70, 120, and 150 pg/mL) including lower limit of quantitation (LLOQ) and upper limit of quantitation (ULOQ) of teriparatide.
Method description	An ELISA kit (Immunotopics, San Clemente, CA.) for determination of PTH (1-34) in human plasma
Materials used for calibration curve and QCs (lot & concentration)	PTH (1-34) (Forteo) reference standard in human plasma (EDTA), free of significant interfering substances (Lilly/ (b) (4) C329597C / C467022H and 250 mcg/mL)
Validated assay range	6 (LLOQ) – 150 (ULOQ) pg/mL in human plasma
Material used for QCs (lot & concentration) and concentrations	PTH (1-34) (FORTEO) (Lilly/ (b) (4) C329597C/C467022H and 250 mcg/mL) PF708 (Pfenex; 1542-200 and 250 mcg/mL) 6 (LLOQ), 18 (Low), 70 (Medium), 120 (High), and 150 (ULOQ) pg/mL

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Regression model & weighting	4 PL, $1/Y^2$		
Validation parameters	**Method validation summary**		**Acceptability**
Calibration curve performance during accuracy & precision	No of standard calibrators from LLOQ to ULOQ	8	Acceptable
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-1.5 to 3.2%	Acceptable
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 3.6%	Acceptable
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs	4.7 to 8.0%	Acceptable
	Inter-batch %CV	≤ 8.1%	Acceptable
	Percent total error (TE)	≤ 12.9%	Acceptable
Selectivity	No quantitation greater than the LLOQ of PTH (1-34) was observed from endogenous components in any of the 10 human plasma (EDTA) lots screened.		Acceptable
Matrix effect	No significant matrix effect was observed in 7 of the 10 human plasma (EDTA) lots that were fortified with PTH (1-34) at the concentration of the LLOQ (6 pg/mL) or in 9 of the 10 human plasma (EDTA) lots that were fortified with PTH (1-34) at the concentration of the high QC (120 pg/mL) sample.		Acceptable
Interference & specificity	No significant interference for PTH (1-34) was observed in 4 of the 5 hemolyzed human plasma (EDTA) lots (fortified with 2% whole blood) that were fortified at the concentration of the low QC (18.0 pg/mL) or in any of the 5 hemolyzed human plasma (EDTA) lots (fortified with 2% whole blood) that were fortified at 2 times the concentration of the high QC (240 pg/mL) sample.		Acceptable
Hemolysis effect	No significant interference for PTH (1-34) was observed in 4 of the 5 hemolyzed human plasma (EDTA) lots (fortified with 2% whole blood) that were fortified at the concentration of the low QC (18.0 pg/mL) or in any of the 5 hemolyzed human plasma (EDTA) lots (fortified with 2% whole blood) that were fortified at 2 times the concentration of the high QC (240 pg/mL) sample.		Acceptable
Lipemic effect	No significant interference for PTH (1-34) was observed in 2 of the 5 lipemic human plasma (EDTA) lots that were fortified at the concentration of the low QC (18.0 pg/mL) or in any of the 5 human plasma (EDTA) lots that were fortified at the concentration of the high QC (120 pg/mL) sample. Results of lipemic sample evaluation demonstrate		Acceptable

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	that the analyte cannot be accurately measured in highly lipemic samples.	
Dilution linearity & hook effect	Samples having a concentration above the upper limit of the calibration standard range were diluted with blank human plasma (EDTA) to establish the dilution factors that can be applied to dilute such samples into quantifiable range. Results show that samples diluted up to 50-fold can be quantified.	Acceptable
Bench-top/process stability	Short-term stability: 25 hours in polypropylene tubes at ambient temperature under white light	Acceptable
Freeze-Thaw stability	6 freeze (-20°C)-thaw (ambient temperature) cycles in polypropylene tubes under white light	Acceptable
Long-term storage	Long-Term Stability: 398 days in polypropylene tubes at -20°C	Acceptable
Method performance in Study PF708-101		
Assay passing rate	• 84 out of 110 runs met the batch acceptance criteria	Acceptable
Standard curve performance	• Cumulative bias range: -1.8 to 3.8 % • Cumulative precision: ≤ 6.8% CV	Acceptable
QC performance including samples with dilution factors	• Cumulative bias range: -19.2 to 5.0 % • Cumulative precision: ≤ 9.6% CV	Acceptable
Method reproducibility	157 study samples were selected for incurred sample reanalysis (ISR) and 97.5% of the ISR samples met the pre-specified criteria. Therefore, the method is considered reproducible.	Acceptable
Study sample analysis/ stability	Study samples were analyzed without exceeding long-term (398 days in polypropylene tubes at -20°C), short-term, or freeze-thaw stability [6 freeze (-20°C)-thaw cycles in polypropylene tubes under white light].	
Method performance in Study PF708-301		
Assay passing rate	• 81 out of 81 runs met the batch acceptance criteria	Acceptable
Standard curve performance	• Cumulative bias range: -1.3 to 4.3 % • Cumulative precision: ≤ 5.8% CV	Acceptable
QC performance including samples with dilution factors	• Cumulative bias range: -7.5 to 0.0 % • Cumulative precision: ≤ 7.4% CV	Acceptable
Method reproducibility	139 study samples were reassayed for ISR analysis and 95% of the ISR samples met the pre-specified criteria. The method is considered reproducible.	Acceptable
Study sample analysis/ stability	The maximum time from sample collection to the end of sample analysis did not exceed 270 days (Long-term stability was established up to 398 days in polypropylene tubes at -20°C).	

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The method was also cross-validated using Forteo and PF708 drug products in human plasma (Table 22).

Appears this way on original

Reference ID: 4500429

Table 22 Summary of cross-validation results using Forteo and PF708 drug product in human plasma

Cross-validation method summary	Human plasma (EDTA) containing PF708 drug product and Forteo were analyzed using the established ELISA method for the determination of PTH(1-34). The method cross-validation was conducted with respect to accuracy, precision, sensitivity, matrix effect, stability, stability of analyte during sample collection and handling, and response function. Eight precision and accuracy cross-validation batches were performed using 5 QC samples (6, 18, 70, 120, and 150 pg/mL) including LLOQ and ULOQ of Forteo and PF708.		
Analyte materials	Forteo and PF708; Forteo reference was used to prepare calibration standards.		
Material used for QCs & concentration	PTH 1-34 (Forteo) (Lilly/ (b) (4) C467022H and 250 mcg/mL) and PF708 (Pfenex; 1542-200 and 250 mcg/mL)		
Validation parameters	**Cross-validation performance**		**Acceptability**
Calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	-4.7 to 5.4%	Acceptable
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 4.9%	Acceptable
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs · Forteo · PF708	 3.3 to 7.2% 8.3 to 15.0%	Acceptable
	Inter-batch %CV · Forteo · PF708	 ≤ 7.7% ≤ 8.4%	Acceptable
	Percent total error (TE) · Forteo · PF708	 ≤ 12.2% ≤ 21.3%	Acceptable
Deviation	On Batch 2, the % bias for the PF708 LLOQ QC was outside of the applicant's defined acceptance criteria (≤ 25.0%) at 25.2% which is a deviation from the cross-validation protocol. Since the Forteo LLOQ QCs were within acceptance criteria and Forteo QCs were used to determine batch acceptance, Batch 2 statistics was included as an accepted PA batch. The overall inter-day statistics are acceptable for this sample and there were 6 sets of data at that concentration that are acceptable for the study.		

Reference ID: 4500429

The method validation results are acceptable to support the two PK studies. The cross-validation study for the determination of Forteo and PF708 also generally met the requirements as specified in the cross-validation protocol except that the % bias for the PF708 LLOQ QC was outside of acceptance criteria at 25.2% but this deviation is unlikely to affect the data reliability.

The review team requested inspections of the analytical and clinical sites to Division of New Drug Bioequivalence Evaluation (DNDBE), Office of Study Integrity and Surveillance (OSIS). DNDBE declined to conduct an on-site inspection and determined that an inspection was not warranted because the clinical site had been permanently closed and the analytical site had been recently inspected. The final classification from the most recent inspection of the both sites (Covance Clinical Research Unit, Inc. in November, 2015 under BLA125509 by The Office of Regulatory Affairs (ORA) and (b) (4)) indicated no action indicated.

The Office of Clinical Pharmacology review team concludes that the bioanalytical method was acceptable to measure plasma concentrations of teriparatide in the completed clinical studies.

14.4.2. Individual Clinical Pharmacology Summary

Study identifier: PF708-101

Title: A double-masked, randomized, two-treatment cross-over study comparing the pharmacokinetics of PF708 and Forteo administered by subcutaneous injection in healthy adult subjects

Objectives:
- Primary: To evaluate the PK of PF708 and Forteo in healthy adult subjects after a single dose.
- Secondary: To evaluate the PD and safety profile of PF708 and Forteo.

Study Design:
- A double-masked, randomized, two-treatment cross-over study with a 3-day washout period
- The trial was double-masked with the applicant, subjects, and site personnel, but the persons for drug dispensing and administration was not masked to treatment assignment.
- 70 healthy subjects: enrolled and completed
- Single dose SC injection of PF708 and Forteo 20 mcg in the lower quadrants of the abdomen
- PK samples: pre-dose and at 5, 10, 20, 30, 40, and 50 minutes and 1, 1.5, 2, 2.5, 3, 4, 6, and 8 hours
- Bioanalytical assay: the concentrations of teriparatide in human plasma were determined using ELISA (refer to Section 6.4.1.).

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- PD (serum calcium concentrations) samples: pre-dose and at 1, 2, 3, 4, 6, 8, 12, and 24 hours
- Safety: adverse events (AEs), vital signs, 12-lead ECG, clinical laboratory evaluations, medical history, physical examination, and ADA assessment (on Day 1 and Day 5).

Results:

- PK results from the primary analyses: refer to Section 6.3.2. (Figure 1 and Table 6).
- Subjects with preconcentration of teriparatide
  - Four subjects (b) (6)) were excluded from the primary statistical analyses of PK parameters because they had positive pre-dose concentrations which was defined to exceed 5% of their respective C_{max} for that treatment. The applicant stated that this criterion was based on the recommendation the Agency's guidance (The guidance for industry: Bioavailability and bioequivalence studies submitted in NDAs or INDs – General considerations; draft – March 2014).
- The applicant performed additional analyses including the data from the four subjects as requested by the Agency. The statistical results from the analyses were not significantly different from those presented in the primary analyses (Table 23).

Table 23 PK parameters and statistical results of teriparatide from additional analyses without excluding subjects who had positive pre-dose concentrations

PK parameters and statistical results of teriparatide from additional analyses without excluding subjects who had positive pre-dose concentrations

	PF708	Forteo		Statistics
	Mean (n)	Mean (n)		GMR (90% CI)
AUC_t (pg*hr/mL)	77.28 (70)	79.77 (70)		96.89 (90.65 - 103.55)
AUC_{inf} (pg*hr/mL)	87.67 (56)	88.56 (62)		99.00 (92.59 - 105.86)
C_{max} (pg/mL)	74.93 (70)	77.98 (70)		96.08 (89.64 - 102.99)

Mean = geometric mean, geometric mean ratio = 100 x (test/reference)
Source: Clinical Information Amendment responding to the information Request from the Agency

- Ionized Ca^{2+} concentrations: modest increases in the measured calcium concentrations following administration of PF708 or Forteo were initially observed. Maximum concentrations were measured at approximately 6 hours post-dose and levels then decreased to below baseline levels at 12 hours post-dose, returning to near baseline by 24 hours post-dose. The serum concentration-time profiles of PF708 and Forteo were similar.
- Safety: 49 (70.0%) subjects reported a total of 115 TEAEs. The number of TEAEs was similar between the PF708 and Forteo treatment groups. The most frequently reported TEAEs were related to injection site findings. All TEAEs were deemed to be Grade 1 (mild) with the exception of 1 TEAE (headache) that was judged to be Grade 2 (moderate).
- All ADA assessments showed negative.

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Study conclusions:
The applicant concluded as follows:
Evaluation of PK parameters showed that PF708 was bioequivalent to Forteo. PF708 and Forteo had similar effects on the serum concentrations of ionized Ca^{2+} after treatment. There were no clinically significant safety findings.

The reviewer summarizes the study and concludes as follows:

- The study was a pivotal comparative PK study to determine whether there were significant differences in the PK of teriparatide between PF708 and Forteo. The study design (e.g. the sample size, PK sampling points, and statistical analyses) appears reasonable to assess the relative bioavailability of teriparatide between the two products. The study enrolled 27 females (38.6%) out of 70 subjects.
- The mean PK profiles of teriparatide following single dose administration of PF708 and Forteo were similar, overlaying with each other (Figure 1.). The PK parameters were similar after each treatment (Table 6.). The 90% CIs of GMRs of the major PK parameters, C_{max}, AUC_t, and AUC_{inf}, for each product pairwise comparison demonstrated PK similarity between PF708 and Forteo.
- Four subjects who had positive predose concentrations that exceeded 5% of their respective C_{max} were excluded from all the statistics of the PK data. This approach is based on the recommendation from the Agency's guidance for bioavailability and bioequivalence studies that the Agency provided. Results of additional statistical analyses including these subjects were not different from those in the analyses excluding those subjects. Therefore, the conclusion of PK similarity between PF708 and Forteo is not impacted by inclusion or exclusion of these four subjects.
- The reviewer conducted independent PK and statistical analyses using datasets including and excluding the 4 subjects who had positive pre-dose concentrations. The reviewer's analysis results were consistent with those of the applicant.
- The observed time-profiles of serum calcium concentrations over 24 hours following single dose administration were similar between PF708 and Forteo and also appeared consistent with the reported data of Forteo (Forteo, Prescribing information).
- This study demonstrated PK similarity between PF708 and Forteo.

<u>Study identifier: PF708-301</u>

Title: A randomized study comparing the effects of PF708 and Forteo in patients with osteoporosis

Objectives:
Primary: To compare the effects of PF708 and Forteo on immunogenicity after 24 weeks of SC daily dosing in patients with osteoporosis.
Secondary: To compare the PK, PD and safety profile of PF708 and Forteo

Reference ID: 4500429

Study Design:

- A randomized, multi-center, parallel-group, open-label study conducted in the U.S.
- 91 subjects per each group (randomization was stratified according to sex): completion - 82 subjects for PF708 and 81 subjects for Forteo
- Sample size: for the immunogenicity assessment, a sample size of 70 in each treatment group would rule out, with 95% confidence, an absolute incidence rate of greater than approximately 4% if no positive subjects were observed and greater than approximately 6.5% if 1 positive subject was observed.
- Drug administration: each subject received 24 weeks of PF708 or Forteo by daily SC self-injection in the abdomen or thigh (except for the first dose, which was administered in the abdomen by the Principal Investigator or a trained and qualified designee at the clinic).
- Immunogenicity assessments
  - Blood samples were collected before dosing on Day 1 and at Weeks 1, 4, 12, and 24. Subjects who tested detectable ADA at the final scheduled visit were returned for additional testing. All positive ADA findings were assessed for neutralizing activity and cross-reactivity against endogenous PTH (1-84).
  - Assay for immunogenicity assessments: refer to Product Quality Reviewer's Immunogenicity Review.
- PK assessments (after the first dosing on Day 1)
  - Sampling: before dosing, and 10, 15, 30, 60, 90, 120, 180, and 240 minutes after dosing
  - Bioanalytical assay: refer to Section 6.4.1.
- PD assessments
  - BMD measurement: lumbar-spine (L1-L4), femoral neck and total hip BMD were measured by dual x-ray absorptiometry (DXA) at screening, Week 12, and Week 24.
  - Bone turnover marker (BTM): blood samples for measurements of P1NP and CTX were collected on Day 1, Week 12, and Week 24
- Safety: AEs, vital signs, 12-lead ECG, clinical laboratory evaluations including serum calcium and phosphorus levels, medical history, physical examination, and ADA assessment.

Results: This summary focuses on the study results of immunogenicity and PK assessments.

- Subject disposition in the study are presented in the table below.

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Table 24 Subject disposition

Subject disposition		
	PF708	**Forteo**
Number of treated subjects	90	91
Demographics		
Male: Female	25:65	25:66
Mean age (range)	66.1 (41-83)	67.2 (50-85)
Completed study treatment	82	81
Discontinued study treatment	9	10
Analysis population		
Safety	90	91
Immunogenicity	88	91
BMD population	84	86
PK population	89	91
Immunogenicity, BMD and PK populations include all subjects in the Safety Population, with a non-missing baseline value and at least one post-dose sample analyzed for each assessment. Source: Clinical Study Report of Study PF708-301		

- Immunogenicity
  - Analysis results for the percentage of subjects with detectable serum ADA are presented in the table below.

Table 25 Percentage of Subjects with Detectable Serum Anti-Drug Antibody to Teriparatide by Week - (Immunogenicity Population)

	PF708 **n/N (%)** **95% CI**	**Forteo** **n/N (%)** **95% CI**	**p-value[1]**
Week 1	1/87 (1.2) (0.03, 6.2)	0/90 (0) (0.0, 4.0)	
Week 4	1/86 (1.2) (0.03, 6.3)	0/89 (0) (0.0, 4.0)	
Week 12	2/82 (2.4) (0.3, 8.5)	2/86 (2.3) (0.28, 8.2)	
Week 24	2/81 (2.5) (0.3, 8.6)	0/81 (0) (0.0, 4.4)	0.50

Source: Table 6-1, page 80 of clinical study report and submission 0015 dated May 2, 2019.
n/N = number of detectable ADA subjects / total number of subjects
Subjec (b) (6) (PF708) and (b) (6) (Forteo) had missing or not reportable value at week 1 and were excluded for the ADA incidence calculation.
[1] p-value based on Fisher's exact test.

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The percentage of ADA-positive subjects at Week 24 was not different between PF708 and Forteo. For PF708, one subject ([redacted] (b) (6) had detectable levels of ADA at Weeks 1, 4, 12, and 24. An additional PF708 subject ([redacted] (b) (6) had detectable levels of ADA at Weeks 12 and 24. Overall, these two subjects accounted for approximately 2.3% of the 87 PF708 subjects that were measured at Week 1. For Forteo, two subjects ([redacted] (b) (6) and [redacted] (b) (6) had detectable levels at Week 12 only. Overall, these two subjects account for approximately 2.2% of the 90 Forteo subjects that were measured at Week 1. The two subjects with detectable ADA in the PF708 group were low in titer (<1 or 1.1) and resolved with cessation of therapy during follow-up (Table 26).

Table 26 ADA titer in individual subjects showing detectable ADA

	PF708		Forteo	
Time (weeks)	[redacted] (b) (6)	[redacted] (b) (6)	[redacted] (b) (6)	[redacted] (b) (6)
0	Undetectable	Undetectable	Undetectable	Undetectable
1	<1	Undetectable	Undetectable	Undetectable
4	<1*	Undetectable	Undetectable	Undetectable
12	<1	<1	7.4	2.7
24	<1	1.1	Undetectable	Undetectable
Follow-up	Undetectable	Undetectable	Not applicable	Not applicable

*In vitro neutralizing was detected.
Sources: Clinical Study Report and Immunogenicity, Pharmacokinetics, and Pharmacodynamics Report of Study PF708-301

- One subject in PF708 group had detectable in vitro neutralizing activity Week 4 only (subject [redacted] (b) (6)
- Serum calcium and phosphorous levels for the two PF708 subjects with detectable ADA were within normal limits during the study. Pharmacological responses, changes in BMD and BTM, during the study in the two subjects including the subject showing positive neutralizing activity appeared to be not different from those and their variabilities observed in the total study subject population (Table 27). There were no apparent safety issues identified in the two subjects (refer to Section 8.2.5).

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Table 27 Percent change from baseline in Bone Mineral Density (BMD) and Bone Turnover Markers of P1NP and CTX in two PF708 subjects with detectable ADA

	Percent Change from Baseline		
	(b) (6) Male, 55, White	(b) (6) Female, 67, White	**Median (min, max) in PF708 subject population**
Percent change from baseline in L1-L4 total spine BMD	Week 12: -4.8 Week 24: -1.6	Week 12: -4.4 Week 24: -5.0	Male Week 12: 1.6 (-8.1, 10.9) Week 24: 4.5 (-1.6, 13.7) Female Week 12: 2.1 (-4.4, 13.6) Week 24: 4.2 (-5.0, 13.2)
Percent change from baseline in total hip BMD	Week 12: 3.6 Week 24: 5.1	Week 12: 2.3 Week 24: 4.1	Male Week 12: 0.4 (-5.8, 7.3) Week 24: -0.4 (-7.8, 6.0) Female Week 12: 0.7 (-7.0, 5.1) Week 24: 0.9 (-4.8, 6.1)
Percent change from baseline in total femoral neck BMD	Week 12: 3.5 Week 24: 8.8	Week 12: 5.3 Week 24: 4.5	Male Week 12: 2.9 (-8.0, 14.3) Week 24: 1.4 (-7.4, 8.9) Female Week 12: 0.9 (-6.9, 10.1) Week 24: 1.2 (-8.3, 10.2)
Percent change from baseline in serum P1NP concentrations	Week 12: 52.3 Week 24: 79.8	Week 12: 7.3 Week 24: -2.9	Week 12: 90.3 (-40.1, 802.8) Week 24: 100.9 (-34.0, 1720)
Percent change from baseline in serum CTX concentrations	Week 12: 55.7 Week 24: 142.2	Week 12: -9.9 Week 24: -51.6	Week 12: 61.3 (-47.1, 593.1) Week 24: 85.8 (-52.0, 895.6)

Sources: Clinical Study Report (Individual Efficacy Response Data), Table 14.2.2.1 on page 219, Table 14.2.2.2 on page 220, Table 14.2.3.1 on pages 221 to 222, and Table 14.2.3.2 on pages 223 to 224. Immunogenicity, Pharmacokinetics, and Pharmacodynamics Report of Study PF708-301, Table 11-4 on page 23 (P1NP and CTX).

- All positive ADA findings were also assessed for cross-reactivity against endogenous PTH (1-84). No significant findings were observed (refer to Product Quality Reviewer's Immunogenicity Review).

· PK data

- Fourteen subjects one or more missing samples during PK blood collection. One subject in the safety population (subject (b) (6) had unevaluable samples due to a shipping error which resulted in loss of the PK data.

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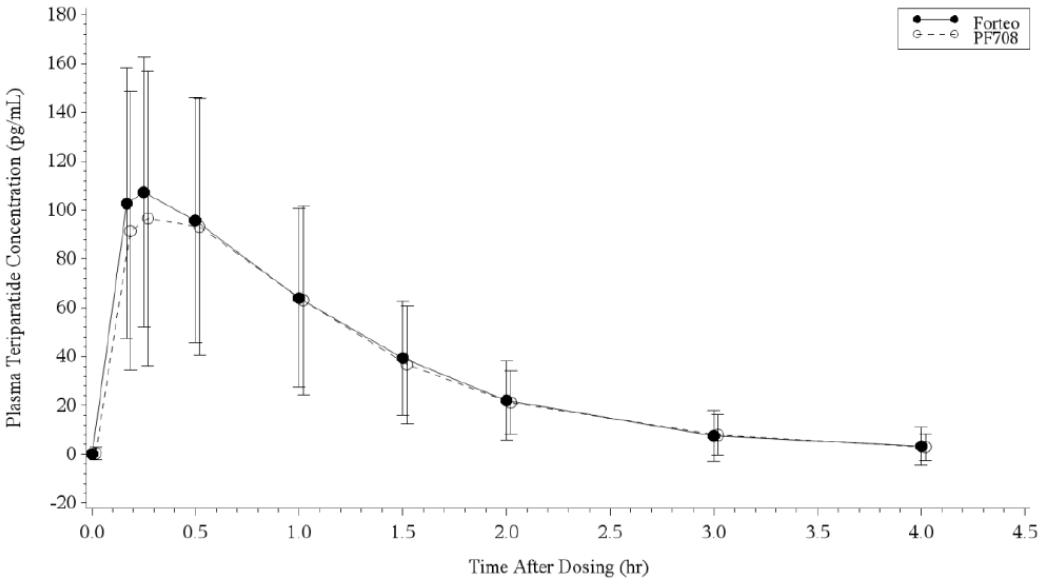
Figure 8 Mean teriparatide concentration-time profile after SC injection of a single dose of PF708 (n=83) or Forteo (n=84) in male or female subjects with osteoporosis



(Source: Immunogenicity, Pharmacokinetics, and Pharmacodynamics Report of Study PF708-301)

Table 28 Summary of PK parameters of teriparatide following single dose of PF708 vs Forteo

Summary of PK parameters of teripartide folowing single dose of PF708 vs Forteo				
	PF708	n	**Forteo**	n
	Mean ± S.D.		Mean ± S.D.	
T_{max} (hour)	0.25 (0.12, 1.08)	83	0.25 (0.12, 1.00)	84
C_{max} (pg/mL)	109.5 ± 62.8	83	123.4 ± 57.2	84
AUC_t (pg*hr/mL)	134.8 ± 79.7	83	139.8 ± 69.5	84
AUC_{inf} (pg*hr/mL)	149.8 ± 68.1	72	157.5 ± 70.2	76
$t_{1/2}$ (hour)	0.79 ± 0.35	72	0.70 ± 0.30	76
CL/F (L/hr)	173.2 ± 112.26	72	160.5 ± 91.940	76
Arithmetic mean ± S.D.; T_{max} = median (minimum, maximum) (Source: Immunogenicity, Pharmacokinetics, and Pharmacodynamics Report of Study PF708-301)				

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Table 29 PK parameters and statistical results of teriparatide excluding subjects who had detectable pre-dose concentrations

PK parameters and statistical results of teripartide excluding subjects who had detectable pre-dose concentrations				
	PF708	**Forteo**		**Statistics**
	Mean (n)	Mean (n)		GMR (90% CI)
AUC_t (pg*hr/mL)	111.4 (83)	122.0 (84)		91.33 (78.03 - 106.90)
AUC_{inf} (pg*hr/mL)	133.6 (72)	141.5 (76)		94.39 (82.40 – 108.12)
C_{max} (pg/mL)	92.45 (83)	111.8 (84)		82.67 (72.02 – 94.88)
Mean = geometric mean, geometric mean ratio = 100 x (test/reference) Source: Clinical Study Report and Immunogenicity, Pharmacokinetics, and Pharmacodynamics Report of Study PF708-301				

· Subjects with pre-dose concentration of teriparatide and insufficient number of quantifiable samples
- Six subjects [redacted] (b) (6)) were excluded from all primary statistical analyses of PK parameters because of positive pre-dose concentrations (exceeding 5% of their respective C_{max}). Seven subjects ([redacted] (b) (6) were also excluded from all primary statistical analyses of PK parameters due to insufficient number of quantifiable samples.
- The applicant performed additional analyses including the data of 6 subjects with the pre-dose concentrations as requested by the Agency. The statistical results from the analyses were not significantly different from those presented in the primary analyses (Table 30).

Table 30 PK parameters and statistical results of teriparatide

PK parameters and statistical results of teripartide from additional analyses without excluding subjects who had detectable pre-dose concentrations.				
	PF708	**Forteo**		**Statistics**
	Mean (n)	Mean (n)		GMR (90% CI)
AUC_t (pg*hr/mL)	112.4 (85)	124.0 (88)		90.62 (77.40 – 106.10)
AUC_{inf} (pg*hr/mL)	134.6 (74)	143.8 (78)		93.59 (81.86 – 107.00)
C_{max} (pg/mL)	93.05 (85)	112.8 (88)		82.51 (72.02 – 94.53)
Mean = geometric mean, geometric mean ratio = 100 x (test/reference) Source: Clinical Information Amendment responding to the information Request from the Agency				

· PD and safety: refer to Section 8.1. and 8.2.

Study conclusions

The applicant concluded as follows:
For the immunogenicity endpoints, two PF708-treated subjects (2.3%) and two Forteo-treated subjects (2.2%) had detectable ADA during the study. One PF708 subject had neutralizing

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activity detected at Week 4, but no apparent impact on pharmacological activity as assessed by BMD or BTM.

Total exposure (by AUC) was similar between PF708 and Forteo, and the $AUC_{0\text{-}inf}$ comparison resulted in a 90% CI within the 80% to 125% interval. PF708 C_{max} was approximately 17% lower than that of Forteo, and the comparison resulted in a 90% CI that was outside the 80% to 125% interval.

The reviewer summarizes the study and concludes as follows:
There were no significant differences in the percentage of subjects with detectable ADA between PF708 and Forteo groups. The ADA titers in two subjects ((b) (6) and (b) (6) in PF708 group were low (<1 or 1.1) and became undetectable after cessation of treatment.

No noticeable differences were identified in serum calcium and phosphorous levels in the two ADA positive subjects treated with PF708 compared to other subjects who were treated with PF708 during the study. Compared to other subjects treated with PF708, the changes in lumbar spine BMD in these two subjects and the change in CTX in subject (b) (6) were relatively low; however, the response to teriparatide in both subjects based on the percent change from baseline in hip and femoral neck BMD was relatively greater compared to that (the observed median and range values) in the subject population. These observations suggest that the PD changes in the two subjects are likely to be within the interindividual variabilities of those observed in the total subject population and does not indicate a negative impact of ADAs on the effect of teriparatide.

- One subject ((b) (6) with ADA positive in PF708 group showed neutralizing activity at Week 4 only, but this did not impact the pharmacological activity of teriparatide as assessed by the changes in BMD or BTM.
- The observed findings in the two PF708 subjects indicated that detectable ADAs are unlikely to cause an apparent impact on the pharmacological activity of teriparatide.
- The PK assessment in this study was performed in all enrolled subjects following the 1st dosing on Day 1. Therefore, the PK sampling of the study was not designed to investigate the impact of ADA on PK of teriparatide in this study.
- The PK evaluation in this study was not designed to assess the PK similarity between the two products, considering that the study had a parallel design in subjects with osteoporosis and multiple clinical sites.
- The concentrations of teriparatide in the early phase (i.e. within 30 min) following injection appeared to be slightly lower in PF708 group than in Forteo group. C_{max} and AUC values, tended to be lower in PF708 group compared to those in Forteo group. The comparison of AUC_{inf} values resulted in a 90% CI within the 80% - 125% interval, but the comparison of AUC_t and C_{max} resulted in a 90% CI that was outside the defined range. C_{max} in PF708 group was approximately 17% lower than that in Forteo group.

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- Thirteen subjects who had positive pre-dose concentrations (6 subjects) or insufficient number of quantifiable samples (7 subjects). The statistical results of the PK dataset including the excluded 6 subjects appeared consistent from those in the analyses excluding those subjects.
- Fourteen subjects had one or more missing PK samples, but one or two samples were missed in those subjects aside from Subject (b) (6) whose all PK samples were missed and who was not included in the PK data. Considering the total number of subjects and the number of the missing time point for individual subjects, the missing PK time points are unlikely to significantly affect the currently observed PK results from the study.
- PK and statistical analyses of the dataset including and excluding 13 subjects were independently performed by the Reviewer. The results were consistent with those provided by the applicant.
- Review of the PD and safety data captured in the current study are deferred to the medical reviewer (Refer to Section 8.1. and 8.2.).

References

- Forteo® prescribing information
- Immunotopics (Immunotopics, Inc.) package insert (June, 2019; http://www.quidel.com)
- NDA 021318 Forteo Clinical Pharmacology and Biopharmaceutics review
- The Guidance for Industry: Bioavailability and bioequivalence studies submitted in NDAs or INDs – General considerations; draft – March 2014

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

THERESA E KEHOE
10/02/2019 11:44:39 AM

CHRISTINE P NGUYEN
10/02/2019 01:57:40 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Silver Spring, MD 20993

My Pharmacology/Toxicology review is complete and has been added to the multidisciplinary review and evaluation document. My review is based on the information currently in the administrative record. If I must review information that is subsequently added to the administrative record, I will update my part of the multidisciplinary review and evaluation document accordingly.

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	211939
Priority or Standard	Standard
Submit Date(s)	12/07/2018
Received Date(s)	12/07/2018
PDUFA Goal Date	10/07/2019
Division/Office	DBRUP/ODEIII
Review Completion Date	04/15/2019
Established Name	PF708 (teriparatide [rDNA origin] injection)
(Proposed) Trade Name	Bonsity
Pharmacologic Class	Parathyroid hormone analog
Code name	PF708
Applicant	Pfenex, Inc.
Formulation(s)	PF708 is supplied as a sterile, colorless, clear, isotonic solution in a glass cartridge, which is pre-assembled into a disposable delivery device (pen) for subcutaneous (SC) injection. Each cartridge delivers the recommended dose of 20 mcg per day for up to 28 days. Each mL of PF708 contains 250 mcg of teriparatide, 0.41 mg of glacial acetic acid, 0.1 mg of sodium acetate (b) (4), 45.4 mg of mannitol, 3 mg of metacresol, and water for Injection.
Dosing Regimen	Subcutaneous injection of 20 µg of teriparatide per 80 µL dose each day for up to 28 days.
Applicant Proposed Indication(s)/Population(s)	▪ Treatment of postmenopausal women with osteoporosis at high risk for fracture ▪ Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture ▪ Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture

Recommendation on Regulatory Action	Pharmacology/Toxicology recommends approval.
Recommended Indication(s)/Population(s) (if applicable)	▪ Treatment of postmenopausal women with osteoporosis at high risk for fracture ▪ Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture ▪ Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture

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1 Product Information

Pfenex Inc submits NDA 211939 (formerly IND 129196) for PF708 (teriparatide [rDNA origin] injection) to treat 1) postmenopausal women with osteoporosis at high risk for fracture, 2) men with primary or hypogonadal osteoporosis at high risk of fracture (increasing of bone mass), and 3) men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture.

PF708 is a 34-amino acid recombinant analog of human parathyroid hormone (rhPTH[1-34]). PF708 will be supplied as a sterile solution in a glass cartridge, which is pre-assembled into a disposable delivery device (pen injector) for subcutaneous injection of 20 μg of teriparatide per 80 μL dose each day for up to 28 days. The sponsor submits PF708 under 505(b)(2) regulatory pathway, using Forteo® (Eli Lilly) as the Listed Drug (LD). Forteo® was approved under NDA 021318. Pfenex uses *P. fluorescens* in the production of PF708, with an amino acid sequence identical to that of Forteo®, whereas Forteo®'s teriparatide (rDNA) is manufactured using *Escherichia coli*. Despite different host DNAs between PF708 and Forteo, PF708 is designed to have the same mechanism of action (improving bone formation), route of administration (SC injection), dosage form (20 μg per day up to 28 days), strength, formulation, and delivery device functionality as Forteo. The use of the product for more than 2 years during a patient's lifetime is not recommended.

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Table 1 Drug Formulation

Composition of Teriparatide Injection

Component	Grade	Function	Quantity per mL (mg)	Quantity per mL (% w/w)	Quantity per Cartridge (mg)[a]	Dose at Maximum Approved Dosage (mg)[b]	Maximum Potency in Approved Parenteral Products[c,d]
Teriparatide	—	Active	0.25	—	(b) (4)	0.020	—
Glacial acetic acid[e]	USP-NF	(b) (4)	0.41	0.041		0.033	(b) (4)
Sodium acetate	USP-NF		0.10	0.010		0.008	
Mannitol	USP-NF		45.4	4.54		3.632	
Metacresol	USP-NF		3	0.3		0.240	
Water for injection	USP-NF		*qs*	—		—	—

im = intramuscular; iv = intravenous; *qs* = quantum sufficit; sc = subcutaneous; USP-NF = United States Pharmacopeia National Formulary; — = not applicable.

[a] = Based on a deliverable volume of (b) (4) mL.

[b] = The recommended adult dose is 20 mcg (0.020 mg) teriparatide, sc injection once a day. The use of the product for more than 2 years during a patient's lifetime is not recommended.

[c] = The sc route of administration is most relevant; however, other parenteral routes (im and iv) support safety.

[d] = FDA Inactive Ingredient Database search for approved drug products; maximum potency in approved products (mg and/or %). It should be noted that database lists the highest amount of the excipient per unit dose in each dosage form in which it is used. Therefore, the amounts shown for maximum potency do not reflect the maximum daily intake of the excipient unless the maximum daily dose of the product that is the basis for the listing is only a single unit.

[e] = (b) (4)

2 Nonclinical Pharmacology/Toxicology Overview (Unireview Sec. 5)

2.1. Executive Summary

Since NDA 211939 is a 505(b)(2) NDA application, Pfenex relied on the FDA's previous findings of safety for Forteo® (NDA 021318 approved 11/26/02). Pfenex also submitted published literature for teriparatide and conducted two nonclinical studies: pharmacodynamic study in a rat OVX model (Study No PF-01) and 4-week subcutaneous toxicity study in rats (Study No PTLX-0011). Overall, these studies have demonstrated that subcutaneous administration of PF708 resulted in responses that were comparable to Forteo.

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- PF708 and Forteo at the subcutaneous dose of 8 µg/kg/day induced similar bone effects in the rat OVX model of human postmenopausal osteoporosis.

- PF708 at the subcutaneous dose of 30 µg/kg/day for 4-weeks resulted in responses that were comparable to Forteo, including non-adverse effects on hematology and clinical chemistry, no gender differences in systemic exposure, no detectable ADA findings, increased bone in the sternum and distal femur and proximal tibia of the femorotibial joint, and increased extramedullary hematopoiesis in the spleen.

- The safety of the excipient components of teriparatide injection was established as the quantities of each excipient were at concentrations less than or equal to the maximum potency outlined in the Agency's Inactive Ingredient Search for Approval Drug Product Database (IID) in approved parenteral products.

- The 4-week repeat-dose bridging rat toxicity study results, including the lack of immunogenicity responses, have provided support regarding the safety of the excipients and qualification of impurities in PF708.

All in all, based on FDA's previous findings of safety for Forteo®, published literature for teriparatide, and two nonclinical studies [pharmacodynamic study in a rat OVX model (Study No PF-01) and 4-week subcutaneous toxicity study in rats (Study No PTLX-0011)], there are no nonclinical concerns from a pharmacology/toxicology perspective and approval is recommended.

2.2. Referenced NDAs, BLAs, DMFs

NDA 021318 – Forteo® (Eli Lilly), IND 129196 (PF708), DMF (b) (4)

2.3. Pharmacology

Endogenous 84-amino acid parathyroid hormone (PTH) is the primary regulator of calcium and phosphate metabolism in bone and kidney. Physiological actions of PTH include regulation of bone metabolism, renal tubular reabsorption of calcium and phosphate, and intestinal calcium absorption. Teriparatide is a recombinant PTH receptor analog that is comprised of the active N-terminal amino acids of PTH, 1-34. The biological actions of PTH and teriparatide are mediated through binding to specific high-affinity cell-surface receptors. Teriparatide and the 34 N-terminal amino acids of PTH bind to these receptors with the same affinity and have the same physiological actions on bone and kidney. Teriparatide is not expected to accumulate in bone or other tissues.

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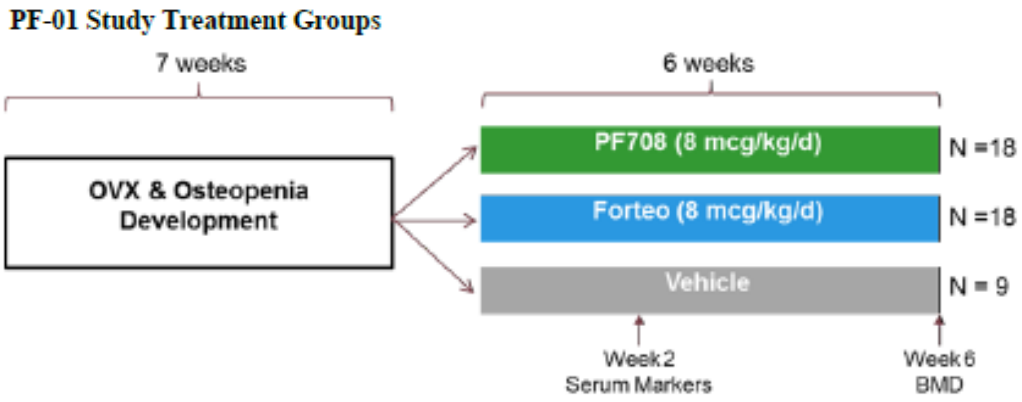
The skeletal effects of teriparatide depend upon the pattern of systemic exposure. Once-daily administration of teriparatide stimulates new bone formation on trabecular and cortical (periosteal and/or endosteal) bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity. In monkey studies, teriparatide improved trabecular microarchitecture and increased bone mass and strength by stimulating new bone formation in both cancellous and cortical bone. In humans, the anabolic effects of teriparatide manifest as an increase in skeletal mass, an increase in markers of bone formation and resorption, and an increase in bone strength. By contrast, continuous excess of endogenous PTH, as occurs in hyperparathyroidism, may be detrimental to the skeleton because bone resorption may be stimulated more than bone formation.

Study No PF-01

Since PF708 is a PTH analog, it can stimulate *de novo* bone formation to increase bone mass and improve bone microarchitecture. The sponsor submitted one pharmacology study (Study No. PF-01) to compare the effects of PF708 with Forteo in the rat OVX model of human postmenopausal osteoporosis.

Female Sprague-Dawley rats were ovariectomized at the age of 6 months (Study Day 0). Treatment with PF708, Forteo, or vehicle was started at 7 weeks after the surgery (at Study Day 49) and continued daily for 6 weeks (up to Study Day 90) (Figure 1). Vehicle consisted of 0.41 mg/mL glacial acetic acid, 0.1 mg/mL sodium acetate [redacted] (b) (4)), 45.4 mg/mL mannitol, 3 mg/mL meta-cresol, and water for injection. Treatment effects were analyzed by measuring body weight, changes in bone cross-sectional dimensions, BMC and volumetric BMD in tibial metaphysis and diaphysis by pQCT, and changes in serum BTMs (Bone Turnover Markers) during the in-life phase of the study, as well as by measuring relative uterine weight at the end of the in-life phase (at Study Day 91). BTMs included procollagen type I N-terminal propeptide (PINP) as a marker of bone formation, N-terminal mid-fragment of osteocalcin (OC) as a marker of bone turnover, C-terminal crosslinked telopeptides of type I collagen (CTX-I) as a marker of bone resorption, and tartrate-resistant acid phosphatase isoform 5b (TRACP 5b) as a marker of osteoclast number.

Figure 1 Study No PF-01: Study Design



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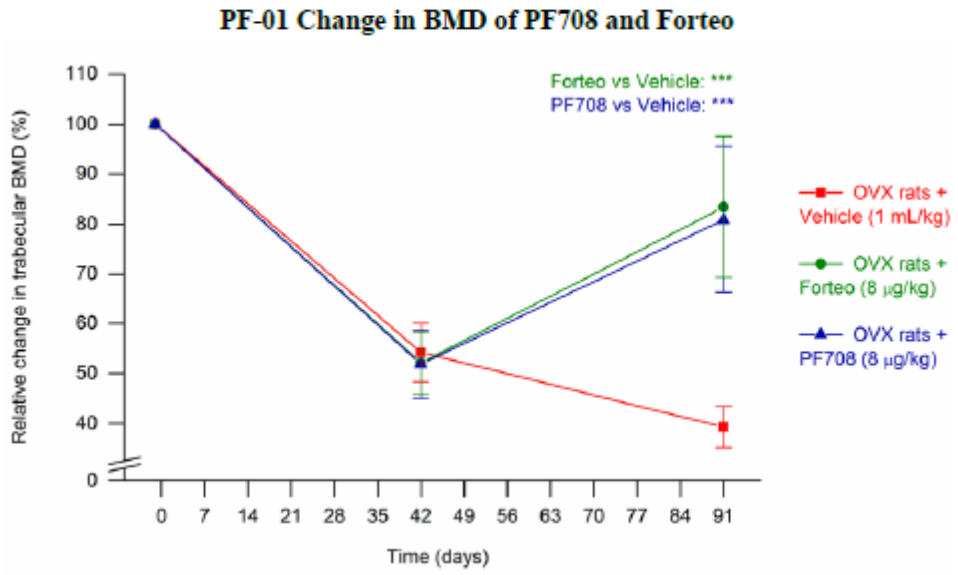
Differences between the effects of subcutaneously administered PF708 and Forteo were evaluated by comparing OVX rats treated with 8 mcg/kg/day Forteo with OVX rats treated with 8 mcg/kg/day PF708.

- The PF708 treatment had the following effects on body weight, bone and serum BTM levels in adult female OVX rats: slightly increased body weight (compared to OVX vehicle controls; comparable to Forteo treatment), increased amount of metaphyseal and trabecular bone, increased amount of diaphyseal and cortical bone, decreased endocortical perimeter, increased serum PINP and OC levels, decreased serum TRACP 5b activity.
- The Forteo treatment had the following effects on bone and serum BTM levels in adult female OVX rats: slightly increased body weight (compared to OVX vehicle controls; comparable to PF708 treatment), increased amount of metaphyseal and trabecular bone, increased amount of diaphyseal and cortical bone, improved biomechanical bond properties predicted from diaphyseal cortical bone distribution, increased serum PINP and OC levels, decreased serum TRACP 5b activity.

This comparison demonstrated that there were no significant differences between the effects of PF708 and Forteo treatments on body weight; relative uterine weight; metaphyseal, trabecular, diaphyseal, and cortical bone parameters obtained by pQCT; and serum BTM levels in adult female OVX rats. In particular, treatment effects on metaphyseal trabecular bone were similar between PF708 and Forteo treatments (Figure 2).

Figure 2 Study No PF-01: Change in Trabecular BMD in Tibial Metaphysis of PF708 and Forteo



2.4. ADME/PK

The ADME/PK profile of PF708 is the same as teriparatide, and is described below from both the approved Forteo prescribing information and publically available information.

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Absorption
Teriparatide is absorbed after subcutaneous injection; the absolute bioavailability is approximately 95% based on pooled data from 20-, 40-, and 80- mcg doses. The rates of absorption and elimination are rapid. The peptide reaches peak serum concentrations about 30 minutes after subcutaneous injection of a 20-mcg dose and declines to non-quantifiable concentrations within 3 hours.

Distribution
Systemic clearance of teriparatide (approximately 62 L/hr in women and 94 L/hr in men) exceeds the rate of normal liver plasma flow, consistent with both hepatic and extra-hepatic clearance. Volume of distribution, following intravenous injection, is approximately 0.12 L/kg. Intersubject variability in systemic clearance and volume of distribution is 25% to 50%. The half-life of teriparatide in serum is 5 minutes when administered by intravenous injection and approximately 1 hour when administered by subcutaneous injection. The longer half-life following subcutaneous administration reflects the time required for absorption from the injection site.

Animal studies have shown that severely reduced hepatic blood flow decreases exposure of PTH to the principal cleavage system (Kupffer cells) and consequently clearance of PTH(1-84).

It has been reported that following subcutaneous administration of teriparatide acetate, teriparatide is rapidly absorbed and distributed to the liver or kidneys, where it is immediately degraded. It was determined that the kidneys play a particularly important role in the distribution and metabolism of teriparatide.

Metabolism
No metabolism or excretion studies have been performed with teriparatide. However, the mechanisms of metabolism and elimination of PTH(1-34) and intact PTH have been extensively described in published literature. Peripheral metabolism of PTH is believed to occur by non-specific enzymatic mechanisms in the liver followed by excretion via the kidneys.

Excretion
No excretion studies have been performed with teriparatide. However, teriparatide is eliminated through hepatic and extra-hepatic clearance (approximately 62 L/h in women and 94 L/h in men). It is not known whether teriparatide is excreted in human milk.

TK data from 4-week toxicology rat study
Only one dose of PF708 was administered in this study.

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Table 2 Summary of Pharmacokinetics/Toxicokinetics of PF708

Type of Study	Major Findings
TK data from general toxicology studies *4-week toxicology study in rats* *Study No PTLG-0011*	Individual plasma teriparatide concentrations were highly variable across both treatments and sexes (n=3 male and female rats per time point). Teriparatide concentrations following a single or multiple daily dose of 30 µg/kg PF708 or Forteo were quantifiable starting at 0.25 hours through 1 hour postdose on Days 1 and 28. Mean overall concentrations were similar between Day 1 and Day 28 for both PF708 and Forteo. No sex differences were observed. On Day 1, TK parameters values for PF708 seemed to be higher than those of Forteo. Due to the high variability, no clear treatment difference can be attributed. On Day 28, TK parameters values for PF708 were comparable to those of Forteo.

Sex	Day	Treatment	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (hr*ng/mL)	AUC_{0-inf} (hr*ng/mL)	$t_{1/2}$ (hr)
Male	1	PF708	14.69	0.25	5.58	5.80	0.19
	1	Forteo	7.47	0.25	2.64	2.71	0.17
	28	PF708	10.75	0.25	5.13	5.67	0.25
	28	Forteo	8.96	0.25	4.83	5.69	0.31
Female	1	PF708	5.82	0.25	2.20	2.26	0.16
	1	Forteo	6.27	0.25	2.59	2.65	0.14
	28	PF708	8.62	0.25	3.60	3.80	0.20
	28	Forteo	9.46	0.25	3.75	3.85	0.16

2.5. Toxicology

2.5.1. General Toxicology

Forteo prescribing information

In single-dose rodent studies using subcutaneous injection of teriparatide, no mortality was seen in rats given doses of 1000 µg/kg (540 times the human dose based on surface area, mcg/m^2) or in mice given 10,000 µg/kg (2700 times the human dose based on surface area, mcg/m^2).

In a long-term study, skeletally mature ovariectomized female monkeys (N=30 per treatment group) were given either daily subcutaneous teriparatide injections of 5 µg/kg or vehicle. Following the 18-month treatment period, the monkeys were removed from teriparatide treatment and were observed for an additional 3 years. The 5 µg/kg dose resulted in systemic exposures that were approximately 6 times higher than the systemic exposure observed in humans following a subcutaneous dose of 20 µg (based on AUC comparison). Bone tumors were not detected by radiographic or histologic evaluation in any monkey in the study.

Study No PTLG-0011

Reference ID: 4593182

Study title/ number: PF708 and Forteo®: A 4-Week Subcutaneous Injection Toxicity Study in Rats

Key Study Findings

- Daily subcutaneous administration of PF708 or Forteo for 4 weeks was associated with non-adverse effects on hematology and clinical chemistry, no gender differences in systemic exposure, no detectable ADA findings, increased bone in the sternum and distal femur and proximal tibia of the femorotibial joint and increased extramedullary hematopoiesis in the spleen.
- The incidence and severity of these findings were similar between PF708 and Forteo.
- These findings are known pharmacologic effects of parathyroid hormone in bone and spleen. Increased bone results in decreased medullary cavity volume and decreased medullary hematopoiesis. Increased extramedullary hematopoiesis in the spleen is a compensatory response.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	30 µg/kg/day once daily
Route of administration:	Subcutaneous injection
Formulation/Vehicle:	0.9% saline
Species/Strain:	Sprague Dawley CD rats
Number/Sex/Group:	10/sex/group
Age:	11-13 weeks
Satellite groups/ unique design:	TK animals
Deviation from study protocol affecting interpretation of results:	No

Observations and Results:
Table 3 Study No PTLG-0011: Summary of Study Findings

Parameters	Major findings
Mortality	All animals survived until the scheduled sacrificed.
Clinical Signs	There were no test-item related effects on clinical observations.
Body Weights	There were no test-item related effects on body weights.
Ophthalmoscopy	There were no test-item related effects on ophthalmology at the end of dosing.
Hematology	There were changes in hematology parameters observed with both PF708 and Forteo. However, there were no toxicologically significant differences between PF708 and Forteo. PF708-related hematology changes included: ▪ decreases in hemoglobin (0.97 × control; females only), hematocrit (0.96 × control; females only), and red blood cells (0.96 × control; females only)

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	▪ increases in red cell distribution (1.05 to 1.07 × control) and platelets (1.10 × control; males only) ▪ decreases in neutrophils (0.74 × control; males only) Forteo-related hematology changes included: ▪ increases in red cell distribution (1.04 to 1.06 × control) and platelets (1.16 × control; males only) ▪ decreases in neutrophils (0.81 × control; males only)
Coagulation	There were no PF708 or Forteo-related coagulation changes at 30 µg/kg/day.
Clinical Chemistry	There were changes in clinical chemistry parameters observed with both PF708 and Forteo. However, there were no toxicologically significant differences between PF708 and Forteo. PF708-related clinical chemistry changes included: ▪ increases in albumin (1.06 × control; males only) with corresponding increases in total protein (1.03 × control; males only) ▪ increases in calcium (1.12 × control; males only). Forteo-related clinical chemistry changes included: ▪ increases in albumin (1.06 × control; males only) with corresponding increases in total protein (1.05 × control; males only) ▪ increases in calcium (1.05 × control; males only).
Urinalysis	There were no test-item related effects on urinalysis parameters.
Gross Pathology	There were no macroscopic findings related to PF708 or Forteo.
Organ Weights	Slightly increased mean absolute and relative splenic weights were observed in female rats following administration of PF708 compared to controls. These treatment-related changes correlated microscopically with increased extramedullary hematopoiesis.
Histopathology Adequate battery: Yes	Treatment-related microscopic findings (PF708 and Forteo) were present in the bone (sternum and femorotibial joint) and spleen in both male and female rats. Bone Slight to moderate increases in trabecular and cortical bone were present in all PF708- and Forteo-treated males and females. Increased bone was observed in the sternum and in the distal femur and proximal tibia of the femorotibial joint, which was characterized by increased thickness of trabeculae and cortex. Spleen Extramedullary hematopoiesis was slightly increased in the spleen of PF708- and Forteo-treated males and females compared to the controls. The incidence and severity of these findings were similar in the PF708 and Forteo treated groups.
Other evaluation(s): Immunogenicity	There were no detectable ADA findings before injection on day 1 and following multiple (Day 28) daily subcutaneous injection of PF708 or Forteo. There were no findings of immunogenicity for either PF708 or Forteo, despite the supraphysiological circulating levels of teriparatide following subcutaneous injection of either PF708 or Forteo.

Overall, subcutaneous administration of 30 mcg/kg/day PF708 drug product (cartridge) for 28 days resulted in responses that were comparable to Forteo, including effects on bone. In addition, results of this study, including the lack of immunogenicity response, support the safety of the excipients and qualification of impurities in PF708. The safety of the components

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of teriparatide injection (glacial acetic acid, sodium acetate, mannitol, metacresol, and water for injection) is established as the quantities of each excipient is at concentrations less than or equal to the maximum potency outlined in the Agency's IID in approved parenteral (subcutaneous, intramuscular, and intravenous) products.

2.5.2. Genetic Toxicology

Forteo prescribing information

Teriparatide was not genotoxic in any of the following test systems: the Ames test for bacterial mutagenesis; the mouse lymphoma assay for mammalian cell mutation; the chromosomal aberration assay in Chinese hamster ovary cells, with and without metabolic activation; and the in vivo micronucleus test in mice.

2.5.3. Carcinogenicity

Forteo prescribing information

In carcinogenicity studies in Fischer 344 rats, Forteo resulted in marked dose related increase in the incidence of osteosarcoma, osteoblastoma, and osteoma in both male and female rats at 3-60X the human systemic exposure at 20 µg based on AUC, and even though the occurrence of these tumors was dependent upon dose and duration of exposure, there was no difference in susceptibility to bone tumor formation between mature and immature rats. Based on bone tumor findings, the boxed warning (risk of osteosarcoma) was included in the Prescribing Information for Forteo®.

- In the first study, male and female rats were given daily subcutaneous teriparatide injections of 5, 30, or 75 µg/kg/day for 24 months from 2 months of age. These doses resulted in systemic exposures that were 3-, 20-, and 60-times higher, respectively, than the systemic exposure observed in humans following a subcutaneous dose of 20 µg (based on AUC comparison). Teriparatide treatment resulted in a marked dose-related increase in the incidence of osteosarcoma, a rare malignant bone tumor, in both male and female rats. Osteosarcomas were observed at all doses and the incidence reached 40% to 50% in the high-dose groups. Teriparatide also caused a dose-related increase in osteoblastoma and osteoma in both sexes. No osteosarcomas, osteoblastomas or osteomas were observed in untreated control rats. The bone tumors in rats occurred in association with a large increase in bone mass and focal osteoblast hyperplasia.
- The second 2-year study was carried out in order to determine the effect of treatment duration and animal age on the development of bone tumors. Female rats were treated for different periods between 2 and 26 months of age with subcutaneous doses of 5 and 30 µg/kg (equivalent to 3- and 20-times the human exposure at the 20-mcg dose, based on AUC comparison). The study showed that the occurrence of osteosarcoma, osteoblastoma, and osteoma was dependent upon dose and duration of exposure. Bone tumors were observed when immature 2-month old rats were treated with 30 mcg/kg/day for 24 months or with 5 or 30 mcg/kg/day for 6 months. Bone tumors were

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also observed when mature 6-month old rats were treated with 30 mcg/kg/day for 6 or 20 months. Tumors were not detected when mature 6-month old rats were treated with 5 mcg/kg/day for 6 or 20 months. The results did not demonstrate a difference in susceptibility to bone tumor formation, associated with teriparatide treatment, between mature and immature rats.

The relevance of these animal findings to humans is uncertain.

2.5.4. Reproductive and Developmental Toxicology

Forteo prescribing information

- No effects on fertility were observed in male and female rats given subcutaneous teriparatide doses of 30, 100, or 300 µg/kg/day prior to mating and in females continuing through GD 6 (16X to 160X the human dose of 20 µg based on body surface area, µg/m^2).
- In embryo-fetal development studies, pregnant mice received teriparatide at subcutaneous doses 8X to 267X the human dose during organogenesis. Teriparatide caused increased skeletal deviations or variations in fetuses (interrupted rib, extra vertebra or rib), at doses ≥ 60X the human dose based on µg/m^2. However, when pregnant rats received teriparatide at subcutaneous doses 16X to 540X the human dose during organogenesis, there were no fetal abnormal findings.
- In a prenatal/postnatal development study, pregnant rats received teriparatide at subcutaneous doses of 30 to 1000 µg/kg/day from organogenesis through lactation. Mild growth retardation in female offspring at doses ≥ 120X the human dose (based on µg/m^2). Mild growth retardation in male offspring and reduced motor activity in both male and female rat offspring occurred at maternal dose 540X the human dose (based on µg/m^2). There were also no developmental or reproductive effects in mice or rats at doses 8X or 16X the human dose, respectively.

Published literature

Literature results identified potential new uses for PTH(1-34) in gravid animals and/or neonates in multiple animal models and species.

- Early postnatal mortality has been prevented in 2 murine models including achondroplasia and hypocalcemia.
- Subcutaneous administration of PTH(1-34) in gravid mice or to neonates immediately after birth appeared to rescue the retarded skeletal development and early postnatal lethality, and improved bone quality in achondroplasia and thanatophoric dysplasia mice models.
- Twice daily subcutaneous administration of PTH(1-34) started within 12 hours after birth in a *Pth*$^{-/-}$;*Hyp*/*Y* mice model (homozygous for the Pth null allele and hemizygous hypophosphatemic) resulted in an increase in serum calcium levels and prevented early mortality that has been previously observed in the severely hypocalcemic neonate.
- In ewes, a significant increase in the placental transfer of calcium from the gravid ewe to

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the fetus was observed following intravenous in utero administration of synthetic PTH related peptide (1-34) in the cannulated fetus, indicating that PTH related peptide (1-34) stimulates placental calcium transfer by potentially acting directly on the plasma increases in 1,25 dihydroxy-vitamin D concentrations.

2.5.5. Other Toxicology Studies

Local Tolerance

Injection site reactions including injection site pain, swelling, erythema, localized bruising, pruritis, and minor bleeding have been reported.

3 Labeling Recommendations (Unireview Sec. 14)

3.1. Prescription Drug Labeling (Nonclinical)

PENDING

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	Proposed Labeling	Approved Labeling
Highlights of Prescribing Information	BONSITY is (b) (4) parathyroid hormone analog (b) (4) PTH(1-34)] indicated for:...	BONSITY is a parathyroid hormone analog indicated for:...
Section 8.1 Pregnancy	Following Forteo prescribing information	Pending listed drug Forteo labeling revision to occur mid-2019. May remove the Forteo box warning.
Section 8.3 Females and males of Reproductive Potential		
Section 13 Nonclinical Toxicology		

4 Appendix

4.1. Impurities

The qualification of the impurity safety profile was supported by the 4-week bridging toxicity study in Sprague Dawley rats that compared the toxicity, toxicokinetics (TK), and immunogenicity of the to-be-marketed PF708 drug product formulation with Forteo. Male and female Sprague Dawley rats were administered bolus subcutaneous injections of 30 µg/kg/day PF708 (drug product cartridge Lot 1614-003). The PF708 drug product cartridge used in the bridging toxicity rat study was approximately 22 months post manufacture.

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The impurity levels were not provided on the PF708 drug product cartridge (Lot 1614-003) Certificate of Analysis. However, the PF708 drug product analytical bridging study data did include the impurity levels for this lot at the 24-month stability interval. Both PF708 drug product cartridge (Lot 1614-003) and its corresponding PF708 drug product pen injector (Lot 1614-003A002) were included in the analytical study.

Product-related impurities were quantified using the Teriparatide Injection USP monograph RP-HPLC method. Observed impurities at level (b) (4)% or greater in PF708 drug product using RP-HPLC were identified, monitored, and quantified:

- truncated rhPTH(1-30)
- teriparatide succinimide (30)
- oxidized methionine residues (specified in the USP monograph for Teriparatide) at amino acid positions 8 (Met+O[8]) and 18 (Met+O[18]) and doubly oxidized rhPTH(1-34) at the same methionine amino acid positions Met+O(8,18)
- largest other related impurity
- total impurities

<u>Drug substance</u>

The PF708 drug substance met the teriparatide USP monograph acceptance criteria for largest other related impurity (not more than [NMT] 0.5%) and for total impurities (NMT 2.5%).

- The drug substance acceptance criteria for rhPTH (1-30) and teriparatide succinimide (30) was NMT (b) (4)%.
- The drug substance acceptance criteria for total methionyl sulfoxides of teriparatide (consisting of *Met+O(8)*, *Met+O(18)*, and *Met+O(8,18)*) was NMT (b) (4)%, which was (b) (4) than the acceptance criteria of NMT 0.5% stated in the teriparatid USP monograph. Nonetheless, the PF708 drug product did meet the teriparatide injection USP monograph acceptance criteria for product-related substances and impurities.
- These impurities were also common to Forteo, therefore, were justified.

Table 4 Impurities: Drug Substance

Structures and Source of Specified Drug Substance Impurities

Name and Structure	Source
Total of methionyl sulfoxides of teriparatide[a]	
Met+O(8) teriparatide	Degradation product
Met+O(18) teriparatide	Degradation product
Met+O(8,18) teriparatide	Degradation product
rhPTH (1-30)[b]	Degradation product
Teriparatide succinimide (30)[b]	Degradation product

rhPTH = recombinant analog of human parathyroid hormone; USP = United States Pharmacopeia.
[a] = Specified in the teriparatide USP monograph.
[b] = Specified in the teriparatide injection USP monograph.
NOTE: The structure of the impurities is provided in *Table 3.2.P.5.5-6*.

<u>Safety margin (drug substance impurities)</u>:

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To support qualification of these impurities, Pfenex conducted a nonclinical toxicology bridging study with the intended to-be-marketed clinical formulation and Forteo.

- The 30 µg/kg/day rat dose results in a total methionyl sulfoxides of teriparatide impurity dose of (b) (4) µg/m^2/day, which is 10X higher than the maximum clinical impurity dose that would be administered at the (b) (4)% drug substance specification level for total methionyl sulfoxides of teriparatide in a 20 µg teriparatide dose.
- The 30 µg/kg/day rat dose results in a rhPTH (1-30) and teriparatide succinimide (30) impurity dose of (b) (4) µg/m^2/day, which is 51X higher than the maximum clinical impurity dose that would be administered at the (b) (4)% drug substance specification level for both rhPTH (1-30) and teriparatide succinimide (30) in a 20-µg teriparatide dose.

Table 5 Impurities: Drug Substance (Safety Margin)

Impurities	Acceptance Criteria NMT %	Impurity Dose at Max. Clinical Dose = 20 µg/day	Impurity Observed in Pen Injector Lot 1614-003A002 (Corresponding Cartridge Lot 1614-003)	Impurity Dose at 30 µg/kg/day in Rats	Safety Margin
Total of methionyl sulfoxides of teriparatide: *Met+O(8)*, *Met+O(18)*, and *Met+O(8,18)*	(b) (4)%	(b) (4) µg/kg/day (b) (4) µg/m^2/day In a 60 kg human	(b) (4)%	(b) (4) µg/kg/day (b) (4) µg/m^2/day	10X
rhPTH (1-30) <u>or</u> teriparatide succinimide (30)	(b) (4)%	(b) (4) µg/kg/day (b) (4) µg/m^2/day In a 60 kg human	(b) (4)%	(b) (4) µg/kg/day (b) (4) µg/m^2/day	51X

<u>Drug product</u>

The PF708 drug product met the teriparatide injection USP monograph acceptance criteria for largest other related impurity (not more than [NMT] (b) (4)%) and for total impurities (NMT 7.0%). These acceptance criteria were established using lot analysis and stability data with a proposed 24-month shelf life.

- The drug product acceptance criteria for rhPTH (1-30) and teriparatide succinimide (30) was NMT 1.2%.
- The drug product acceptance criteria for the methionyl sulfoxides of teriparatide (consisting of *Met+O(8)*, *Met+O(18)*, and *Met+O(8,18)*) were NMT (b) (4)%, NMT (b) (4)%, and NMT (b) (4)%, respectively.
    - No further qualification of these drug product impurities are required as all specification levels are equal or less than the FDA Q3B qualification threshold of 1% for a drug product with a < 10 mg maximum clinical dose.

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Table 6 Impurities: Drug Product

Structures and Source of Specified Drug Product Impurities

Name and Structure	Source
rhPTH (1-30)[a]	Degradation product
Teriparatide succinimide (30)[a]	Degradation product
Met+O(8) teriparatide[b]	Degradation product
Met+O(18) teriparatide[b]	Degradation product
Met+O(8,18) teriparatide[b]	Degradation product

rhPTH = recombinant analog of human parathyroid hormone; USP = United States Pharmacopeia.
[a] = Specified in the teriparatide injection USP monograph.
[b] = Specified in the teriparatide USP monograph.
NOTE: The structure of the impurities is provided in *Table 3.2.P.5.5-6*.

<u>Safety margin (drug product impurities)</u>:

- The 30 µg/kg/day rat dose results in three of methionyl sulfoxides of teriparatide impurities: *Met+O(8)*, *Met+O(18)*, and *Met+O(8,18)*, which is approx. 9.6X, 7.2X, and 5.1X, respectively, higher than the maximum clinical impurity dose that would be administered at the (b) (4) %, respectively, drug product specification level for total methionyl sulfoxides of teriparatide in a 20 µg teriparatide dose.
- The 30 µg/kg/day rat dose results in a rhPTH (1-30) and teriparatide succinimide (30) impurity dose of 1.26 µg/m^2/day, which is 8.5X higher than the maximum clinical impurity dose that would be administered at the 1.2% drug product specification level for both rhPTH (1-30) and teriparatide succinimide (30) in a 20-µg teriparatide dose.

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Table 7 Impurities: Drug Product (Safety Margin)

Impurities	Acceptance Criteria NMT %	Impurity Dose at Max. Clinical Dose = 20 µg/day	Impurity Observed in Pen Injector Lot 1614-003A002 (Corresponding Cartridge Lot 1614-003)	Impurity Dose at 30 µg/kg/day in Rats	Safety Margin
Met+O(8)	(b) (4)%	(b) (4) µg/kg/day (b) (4) µg/m²/day In a 60 kg human	(b) (4)%	(b) (4) µg/kg/day (b) (4) g/m²/day	9.6X
Met+O(18)	(b) (4)%	(b) (4) µg/kg/day (b) (4) µg/m²/day In a 60 kg human	(b) (4)%	(b) (4) µg/kg/day (b) (4) µg/m²/day	7.2X
Met+O(8,18)	(b) (4)%	(b) (4) µg/kg/day (b) (4) µg/m²/day In a 60 kg human	(b) (4)%	(b) (4) µg/kg/day (b) (4) µg/m²/day	5.1X
rhPTH (1-30) <u>or</u> teriparatide succinimide (30)	1.2%	0.000 µg/kg/day (b) (4) µg/m²/day In a 60 kg human	(b) (4)%	0.21 µg/kg/day 1.26 µg/m²/day	8.5X

Unspecified product-related impurities were controlled under the largest other related impurity limit (NMT (b) (4)) established using lot analysis and stability data, and total impurities (NMT 7.0%) were set according to the USP teriparatide injection monograph.

There were no elemental impurities of concern at the 20-µg clinical dose. The drug product formulation is in direct contact with the primary container closure. The pen injector device does not contact the drug solution except for the attached needle during the injection. Extractable study (for primary container closure) showed that all elements were below the analytical threshold. Leachable study (for expired drug product cartridges) showed all results were below the specification listed in USP <232>. Biocompatibility testing for the PF708 pen injector (delivery device) showed that all test samples passed the required acceptance criteria per ISO 10993 for ≥ 30 days skin contact materials.

<u>Aggregate</u>

In Section 3.2.P.5.6, the justification and acceptance criterion for aggregate (HMM; impurities with molecular mass greater than that of teriparatide) was provided. The proposed limit for

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aggregate was (b) (4)%. A dimer of teriparatide was identified as major aggregated species. The observed level for 7 lots of PF708 Drug Product Cartridge, with age ranging from 8 to 36 months, was < LOQ (LOQ = (b) (4)%). The sum of all detectable aggregates was up to (b) (4)%.
CMC reviewer's note: RLD DP specification does not include testing for aggregate.

Table 8 HMM Impurities

Impurities with Molecular Masses Greater than that of Teriparatide Specification Justification for PF708 Drug Product Cartridge and PF708 Finished Drug Product (Pen Injector)

Test Name	Method Number	Acceptance Criteria	Configuration	Stage Tested
Impurities with molecular masses greater than that of teriparatide	QCO.1902[a]	Sum of the peaks eluted before the principal peak is NMT (b) (4)%	DP cartridge	Release
			Finished DP (Pen Injector)	Stability
	Justification: Impurities with molecular masses greater than that of teriparatide are monitored for patient safety and product efficacy. Levels of impurities with molecular masses greater than that of teriparatide are measured using SE-HPLC. Below is a summary of the lots tested where analyses of PF708 drug product cartridge lots up to 36 months in age did not show higher molecular mass impurities above the LOQ (b) (4)%). Using batch analysis data, the proposed limit for the sum of higher molecular mass impurities is NMT (b) (4)%, which is (b) (4) times the method LOQ (ie, (b) (4). Safety and clinical studies which justify the acceptance criterion are reported in references 26, 27, and 28. The acceptance criteria (sum of the peaks eluted before the principal peak is NMT (b) (4)%) is also equivalent to the (b) (4) criteria.			

	Lot[a]	Result (%)	Sum of detectable HMM peaks[b] (%)	Age of lot[c]
	1542-200 (B0001D1)	< LOQ	(b) (4)	36 months
	1544-045 (B0002D1)	< LOQ		34 months
	1614-003 (B0003D1)	< LOQ		30 months
	1628-018 (B0004D1)	< LOQ		26 months
	1801-015 (B0004D2)	< LOQ		9 months
	1803-016 (B0002D2)	< LOQ		8 months
	1803-017 (B0003D2)	< LOQ		8 months

CMO = contract manufacturing organization; DP = drug product; HMM = high molecular mass; LOQ = limit of quantitation; NMT = not more than; SE-HPLC = size exclusion high-performance liquid chromatography.
[a] = CMO lot number listed with Pfenex lot number in parenthesis.
[b] = Sum of detectable peaks observed. All individual peaks were < LOQ (b) (4)%).
[c] = Age of lot in months from date of manufacture at the time of analysis.

4.2. 4-Week Rat Study

Study title: PF708 and Forteo®: A 4-Week Subcutaneous Injection Toxicity Study in Rats

Study no.:	PTLX-0011
Study report location:	\\CDSESUB1\evsprod\NDA211939\0001
Conducting laboratory and location:	(b) (4)
Date of study initiation:	01/26/18
GLP compliance:	Yes
QA statement:	Yes

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Drug, lot #, and % purity: Lot 1614-003, 93%

Summary for 4-week Nonclinical Bridging Study

Group	Treatment	Daily Doses			Number of Animals					
					Total on Study		Toxicity Study Terminal Necropsy		TK Study Days 1 and 28	
		Dose (µg/kg)	Volume (mL/kg)	Conc. (µg/mL)	M	F	M	F	M	F
1	Control	0	0.12	0	13	13	10	10	3	3
2	PF708	30	0.12	250	13	16	10	10	3	6
3	Forteo[a]	30	0.12	250	13	16	10	10	3	6

[a] US-Licensed Forteo

Abbreviations: TK = toxicokinetics, µg = microgram, kg = kilogram, mL = milliliter, M = male, F = Female

Parameters evaluated during the study were: viability, clinical observations, ophthalmology, body weights, food consumption, clinical pathology (termination), immunogenicity (pretest and Day 28), organ weights, gross pathology and histopathology.

Methods

Doses:	30 µg/kg/day
Frequency of dosing:	Once daily
Route of administration:	Subcutaneous injection
Dose volume:	0.12 mL/kg/day
Formulation/Vehicle:	0.9% saline
Species/Strain:	Sprague Dawley CD rats
Number/Sex/Group:	10/sex/group
Age:	11-13 weeks
Weight:	Males: 303 g to 334 g Females: 205 g to 239 g
Satellite groups:	TK animals (3/sex in Group 1, 3 males/group in Groups 2 and 3 and 6 females/group in Groups 2 and 3)
Unique study design:	--
Deviation from study protocol:	Deviation from the study plan was listed on Page 36 of the final study report. The deviation was not considered to have compromised the validity or integrity of the study:

Observations and Results

- Mortality

All animals survived until the scheduled sacrifices.

- Clinical Signs

There were no treatment-related effects on clinical observations.

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- Body Weights

There were no treatment-related effects on body weight.

- Feed Consumption

There were no treatment-related effects on food consumption.

- Ophthalmoscopy

There were no treatment-related effects on ophthalmology parameters.

- ECG

Not applicable.

- Hematology

There were changes in hematology parameters observed with both PF708 and Forteo. However, there were no toxicologically significant differences between PF708 and Forteo, the RLD. PF708-related hematology changes included decreases in hemoglobin (0.97 × control; females only), hematocrit (0.96 × control; females only), and red blood cells (0.96 × control; females only); increases in red cell distribution (1.05 to 1.07 × control) and platelets (1.10 × control; males only); and decreases in neutrophils (0.74 × control; males only). Forteo-related hematology changes included increases in red cell distribution (1.04 to 1.06 × control) and platelets (1.16 × control; males only); and decreases in neutrophils (0.81 × control; males only).

- Coagulation

There were no treatment-related effects on coagulation parameters.

- Clinical Chemistry

There were changes in clinical chemistry parameters observed with both PF708 and Forteo. However, there were no toxicologically significant differences between PF708 and Forteo, the RLD. PF708-related clinical chemistry changes included increases in albumin (1.06 × control; males only) with corresponding increases in total protein (1.03 × control; males only); and increases in calcium (1.12 × control; males only). Forteo-related clinical chemistry changes included increases in albumin (1.06 × control; males only) with corresponding increases in total protein (1.05 × control; males only); and increases in calcium (1.05 × control; males only).

- Urinalysis

There were no treatment-related effects on urinalysis parameters.

- Gross Pathology

There were no treatment-related effects on gross pathology parameters.

- Organ Weights

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Slightly increased mean absolute and relative splenic weights were observed in female rats following administration of PF708 compared to controls. These treatment-related changes correlated microscopically with increased extramedullary hematopoiesis.

- Histopathology

Adequate Battery: Yes; Peer Review: Yes

Treatment-related microscopic findings (PF708 and Forteo) were present in the bone (sternum and femorotibial joint) and spleen in male and female rats.

Bone

Slight to moderate increases in trabecular and cortical bone were present in all PF708- and Forteo-treated males and females. Increased bone was observed in the sternum and in the distal femur and proximal tibia of the femorotibial joint, which was characterized by increased thickness of trabeculae and cortex.

Spleen

Extramedullary hematopoiesis was slightly increased in the spleen of PF708- and Forteo-treated males and females compared to the controls. The incidence and severity of these findings were similar in the PF708 and Forteo treated groups.

Treatment-related Microscopic Findings Observed in Rats Following Daily Subcutaneous Administration of PF708 or Forteo for 4 Weeks

		Male (10/group)			Females (10/group)		
Microscopic Findings	**Severity**	**Vehicle**	**PF708**	**Forteo**	**Vehicle**	**PF708**	**Forteo**
	Dose (mcg/kg/day)	**0**	**30**	**30**	**0**	**30**	**30**
Sternum							
Increased bone	Slight[a]	0	10	10	0	10	10
Femorotibial joint							
Increased bone	Slight[a]	0	9	8	0	7	8
	Moderate[b]	0	1	2	0	3	2
	Total	0	10	10	0	10	10
Spleen							
Increased extramedullary hematopoiesis	Slight[a]	0	8	10	0	7	4

[a] = The change is more noticeable but only evident as few/small foci or areas affected.
[b] = The chage is obviously present, and of appreciable size and/or number.

- ADA/Immunogenicity

There were no detectable ADA findings before injection on day 1 and following multiple (Day 28) daily subcutaneous injection of PF708 or Forteo. There were no findings of immunogenicity for either PF708 or Forteo, despite the supraphysiological circulating levels of teriparatide following subcutaneous injection of either PF708 or Forteo.

- Toxicokinetics

Individual plasma teriparatide concentrations were highly variable across both treatments and

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sexes (n=3 male and female rats per time point). Teriparatide concentrations following a single or multiple daily dose of 30 µg/kg PF708 or Forteo were quantifiable starting at 0.25 hours through 1 hour postdose on Days 1 and 28. Mean overall concentrations were similar between Day 1 and Day 28 for both PF708 and Forteo. No sex differences were observed.

Day 1 mean C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, and $t_{1/2}$ values for PF708 appeared to be higher than Day 1 Forteo parameters, although, due to the high variability, no clear treatment difference can be attributed. On Day 28, mean TK parameters C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, and $t_{1/2}$ values for PF708 were comparable to parameters for Forteo. No clear gender differences in exposure were observed in either treatment.

Table 9 Study No PF-PTLG-0011: TK Data

Mean Toxicokinetic Parameters for Teriparatide in Sprague Dawley Rats Following Once Daily Subcutaneous Bolus Administration of PF708 or Forteo for 4 Weeks

Dose	C_{max} (ng/mL)		T_{max} (h)		AUC_{0-t} (ng·h/mL)		$AUC_{0-\infty}$ (ng·h/mL)		$t_{1/2}$ (h)	
(mcg/kg/day)	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
30 PF708										
Male	14.69	10.75	0.25	0.25	5.58	5.13	5.80	5.67	0.19	0.25
Female	5.82	8.62	0.25	0.25	2.20	3.60	2.26	3.80	0.16	0.20
30 Forteo										
Male	7.47	8.96	0.25	0.25	2.64	4.83	2.71	5.69	0.17	0.31
Female	6.27	9.46	0.25	0.25	2.59	3.75	2.65	3.85	0.14	0.16

$AUC_{0-\infty}$ = area under the plasma concentration-time curve extrapolated through infinity; AUC_{0-t} = area under the plasma concentration-time curve from time 0 to the last measurable plasma concentration; C_{max} = maximum observed concentration; h = hours; $t_{1/2}$ = terminal elimination half-life; T_{max} = time maximum observed concentration.
Note: Values are the mean of 3 animals/sex/time point.
Source: *Annex 4, Report PTLX-0011 [RPTX-0236].*

- Dosing Solution Analysis

No analysis was performed, the test, comparator and control items were used as provided and as characterized by their providers.

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4 Week Bridging Toxicity Study: Histopath Summary

Table 10 Study No PF-PTLG-0011: Microscopic Findings

Histopathology - group distribution of findings

	Vehicle Control	PF708	Forteo
Dose Group	1	2	3
Dose (µg/kg/day)		30	30

		Number of animals affected					
	Group/Sex	1M	2M	3M	1F	2F	3F
Tissue/Organ and Findings	No. of animals	10	10	10	10	10	10
Adrenals	No. examined	10	10	10	10	10	10
Aorta Thoracic	No. examined	10	10	10	10	10	10
Bone Marrow, Femoral	No. examined	10	10	10	10	10	10
Bone, Femur Including Joint	No. examined	10	10	10	10	10	10
Increased Bone, Trabecular	Slight	0	9	8	0	7	8
	Moderate	0	1	2	0	3	2
	Total	0	10	10	0	10	10
Bone, Sternum Including Marrow	No. examined	10	10	10	10	10	10
Increased Bone	Slight	0	10	10	0	10	10
	Total	0	10	10	0	10	10
Brain	No. examined	10	10	10	10	10	10
Cecum	No. examined	10	10	10	10	10	10
Congestion, Mucosal/Submucosal	Total	1	0	0	0	0	0

	Vehicle Control	PF708	Forteo
Dose Group	1	2	3
Dose (µg/kg/day)		30	30

		Number of animals affected					
	Group/Sex	1M	2M	3M	1F	2F	3F
Tissue/Organ and Findings	No. of animals	10	10	10	10	10	10
Colon	No. examined	10	10	10	10	10	10
Duodenum	No. examined	10	10	10	10	10	10
Epididymides	No. examined	10	10	10	-	-	-
Sperm Granuloma	Moderate	1	0	0	-	-	-
	Marked	0	0	1	-	-	-
	Total	1	0	1	-	-	-
Esophagus	No. examined	10	10	10	10	10	10
Eyes	No. examined	10	10	10	10	10	10
Harderian Glands	No. examined	10	10	10	10	10	10
Heart	No. examined	10	10	10	10	10	10
Ileum	No. examined	10	10	10	10	10	10

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	Vehicle Control	PF708	Forteo
Dose Group	1	2	3
Dose (µg/kg/day)		30	30

		Number of animals affected					
	Group/Sex	1M	2M	3M	1F	2F	3F
Tissue/Organ and Findings	No. of animals	10	10	10	10	10	10
Jejunum	No. examined	10	10	10	10	10	10
Kidneys	No. examined	10	10	10	10	10	10
Nephropathy, Chronic Progressive	Minimal	9	1	5	1	2	4
	Total	9	1	5	1	2	4
Lacrimal Glands	No. examined	10	10	10	10	10	10
Liver	No. examined	10	10	10	10	10	10
Nodule, Hepatodiaphragmatic	Total	1	0	0	0	0	0
Lungs and Bronchi	No. examined	10	10	10	10	10	10
Alveolar Macrophage Aggregation	Minimal	0	1	1	1	0	0
	Total	0	1	1	1	0	0
Lymph Node, Axillary	No. examined	10	10	10	10	10	10
Lymph Node, Mandibular	No. examined	0	2	0	1	2	0
Erythrocytosis/Erythrophagocytosis, Sinuses	Minimal	0	2	0	1	2	0
	Total	0	2	0	1	2	0

	Vehicle Control	PF708	Forteo
Dose Group	1	2	3
Dose (µg/kg/day)		30	30

		Number of animals affected					
	Group/Sex	1M	2M	3M	1F	2F	3F
Tissue/Organ and Findings	No. of animals	10	10	10	10	10	10
Lymph Node, Mesenteric	No. examined	10	10	10	10	10	10
Lymph Node, Thymic	No. examined	0	0	0	1	0	0
Erythrocytosis/Erythrophagocytosis, Sinuses	Moderate	0	0	0	1	0	0
	Total	0	0	0	1	0	0
Mammary	No. examined	10	10	10	10	10	9
Nerve, Sciatic	No. examined	10	10	10	10	10	10
Ovaries	No. examined	-	-	-	10	10	10
Pancreas	No. examined	10	10	10	10	10	10
Parathyroids	No. examined	10	9	8	8	9	9
Peyer's Patches/GALT	No. examined	10	10	10	10	10	10

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	Vehicle Control	PF708	Forteo
Dose Group	1	2	3
Dose (µg/kg/day)		30	30

		Number of animals affected					
	Group/Sex	1M	2M	3M	1F	2F	3F
Tissue/Organ and Findings	No. of animals	10	10	10	10	10	10
Pituitary	No. examined	10	10	10	10	10	10
Prostate	No. examined	10	10	10	-	-	-
Infiltrate, Inflammatory Cell, Perivascular	Minimal	2	2	3	-	-	-
	Total	2	2	3	-	-	-
Salivary Gland, Mandibular	No. examined	10	10	10	10	10	10
Seminal Vesicles	No. examined	10	10	10	-	-	-
Skeletal muscle, Rectus femoris	No. examined	10	10	10	10	10	10
Skin and Subcutis	No. examined	10	10	10	10	10	10
Spinal Cord Cervical	No. examined	10	10	10	10	10	10
Spinal Cord Lumbar	No. examined	10	10	10	10	10	10

	Vehicle Control	PF708	Forteo
Dose Group	1	2	3
Dose (µg/kg/day)		30	30

		Number of animals affected					
	Group/Sex	1M	2M	3M	1F	2F	3F
Tissue/Organ and Findings	No. of animals	10	10	10	10	10	10
Spinal Cord Thoracic	No. examined	10	10	10	10	10	10
Spleen	No. examined	10	10	10	10	10	10
Extramedullary Hemopoiesis, Increased	Slight	0	8	10	0	7	4
	Total	0	8	10	0	7	4
Tissue, Accessory Splenic	Total	0	0	0	0	0	1
Stomach	No. examined	10	10	10	10	10	10
Ulceration, Glandular Region	Moderate	1	0	0	0	0	0
	Total	1	0	0	0	0	0
Subcutaneous IS 1	No. examined	10	10	10	10	10	10
Infiltrate, Inflammatory Cell, Subcutis	Minimal	3	0	3	6	1	7
	Total	3	0	3	6	1	7
Needle Tract	Total	1	3	3	0	1	2
Hemorrhage, Subcutis	Total	0	2	0	0	1	0

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	Vehicle Control	PF708	Forteo
Dose Group	1	2	3
Dose (µg/kg/day)		30	30

		Number of animals affected					
	Group/Sex	1M	2M	3M	1F	2F	3F
Tissue/Organ and Findings	No. of animals	10	10	10	10	10	10
Subcutaneous IS 2	No. examined	10	10	10	10	10	10
Infiltrate, Inflammatory Cell, Subcutis	Minimal	0	1	1	2	0	2
	Total	0	1	1	2	0	2
Needle Tract	Total	0	0	0	5	1	0
Subcutaneous IS 3	No. examined	10	10	10	10	10	10
Needle Tract	Total	1	1	2	2	0	0
Infiltrate, Inflammatory Cell, Subcutaneous	Minimal	0	1	0	2	0	5
	Total	0	1	0	2	0	5
Subcutaneous IS 4	No. examined	10	10	10	10	10	10
Infiltrate, Inflammatory Cell, Subcutis	Minimal	2	0	2	5	3	2
	Total	2	0	2	5	3	2
Needle Tract	Total	0	2	1	1	3	1
Hemorrhage, Subcutaneous	Total	0	1	0	1	0	1

	Vehicle Control	PF708	Forteo
Dose Group	1	2	3
Dose (µg/kg/day)		30	30

		Number of animals affected					
	Group/Sex	1M	2M	3M	1F	2F	3F
Tissue/Organ and Findings	No. of animals	10	10	10	10	10	10
Testes	No. examined	10	10	10	-	-	-
Thymus	No. examined	10	10	10	10	10	10
Thyroids	No. examined	10	10	10	10	10	10
Trachea	No. examined	10	10	10	10	10	10
Urinary Bladder	No. examined	10	10	10	10	10	10
Uterus and Cervix	No. examined	-	-	-	10	10	10
Dilatation, Luminal	Total	-	-	-	1	3	2
Vagina	No. examined	-	-	-	10	10	10

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4.3. Sponsor's Proposed Labeling

(b) (4)

[redacted]

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

MIYUN M TSAI-TURTON
09/19/2019 11:54:04 AM

KIMBERLY P HATFIELD
09/19/2019 01:46:36 PM
I concur with the evaluation and conclusions of Dr. Tsai-Turton.