CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218771Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	218771
Priority or Standard	Standard
Submit Date(s)	August 4, 2023
Received Date(s)	August 4, 2023
PDUFA Goal Date	June 4, 2024
Division/Office	Division of General Endocrinology (DGE)/Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)
Review Completion Date	May 31, 2024
Established/Proper Name	Teriparatide Injection
(Proposed) Trade Name	Teriparatide Injection
Pharmacologic Class	Parathyroid hormone analog
Code name	
Applicant	Almaject, Inc
Dosage form	injection
Applicant proposed Dosing Regimen	20 mcg subcutaneous injection daily
Applicant Proposed Indication(s)/Population(s)	• Treatment of osteoporosis in postmenopausal women at high risk for fracture (defined herein as having a history of osteoporotic fracture or multiple risk factors for fracture) or who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, teripraratide injection reduces the risk of vertebral and nonvertebral fractures. • To Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture or who have failed or are intolerant to other available osteoporosis therapy • Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy (daily dosage equivalent to 5 mg or greater of prednisone) at high risk for fracture or who have failed or are intolerant to other available osteoporosis therapy.
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	N/A
Recommendation on Regulatory Action	Approval

Recommended Indication(s)/Population(s) (if applicable)	No change in the indication language sought
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 daily subcutaneous injection

Table of Contents

Table of Tables

Table of Figures

No figures entries found.

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
CDRH=Center for Devices and Radiologic Health
OPEQ=Office of Product Quality and Evaluation
OHT3=Office of Health Technology 3

Signatures

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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
CBER	Center for Biologics Evaluation and Research
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
NME	new molecular entity
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
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

1 Executive Summary

1.1. Product Introduction

The subject of this NDA is teriparatide injection, 0.60 mg/2.40 mL (0.25 mg/mL) proposed for the treatment of osteoporosis in patients at high risk for fracture. The applicant, Almaject Inc., seeks approval pursuant to the 505(b)(2) regulatory pathway, relying on FDA's previous findings of safety and effectiveness of Forteo (teriparatide injection, NDA 021318). Almaject also requests a therapeutic equivalence evaluation between their product and Forteo.

Teriparatide is a peptide that is the bioactive portion of human parathyroid hormone (PTH). It can be manufactured using either recombinant DNA technology or chemical synthesis and has an identical sequence to the 34 N-terminal amino acid sequence of the 84-amino acid human PTH.

Human PTH regulates calcium and phosphate metabolism in bone and kidney, and its actions are mediated through binding to cell-surface receptors. Like its endogenous counterpart, teriparatide binds to PTH receptors where it exerts the same physiologic effects on bone and kidney as native PTH.

Among drugs indicated for treatment of osteoporosis, teriparatide is classified as an "anabolic agent" because it preferentially stimulates osteoblastic activity over osteoclastic activity. The net result is increased skeletal mass and bone strength.

There are currently two teriparatide injection products manufactrured by recombinant DNA technology and marketed in the U.S. – the originator product, Forteo (sponsor, Eli Lilly), and Bonsity[1] (sponsor, Alvogen) which was approved pursuant to the 505(b)(2) pathway. The two teriparatide products have the same amino acid sequence but use different genetically modified bacterial species for durg manufacturing – *E. coli* for Forteo and *Pseudonomas fluorescens* for Bonsity. Both teriparatide products are indicated for the following conditions:

- Treatment of osteoporosis in postmenopausal women at high risk for fracture (defined herein as having a history of osteoporotic fracture or multiple risk factors for fracture) or who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, [*drug*] reduces the risk of vertebral and nonvertebral fractures.
- To Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture or who have failed or are intolerant to other available osteoporosis therapy

[1] It should be noted that for NDA 211939, the Applicant removed the proprietary name Bonsity and product labeling refers to the product as Teriparatide Injection

- Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy (daily dosage equivalent to 5 mg or greater of prednisone) at high risk for fracture or who have failed or are intolerant to other available osteoporosis therapy.

The indications proposed for the current application are the same as those for which both Forteo and Bonsity are approved.

Almaject is cross-referencing the modules for chemistry, manufacturing and controls, clinical and nonclinical studies from Alvogen Inc.'s teriparatide injection (NDA 211939, Teriparatide Injection (previously referred to as Bonsity); approved October 24, 2019). The only differences between the referenced NDA 211939 and this proposed NDA are in labeling and additional immunogenicity and analytical bridging studies to support a TE evaluation to the listed drug, Forteo. The Almaject drug substance and drug product use the same chemistry, manufacturing and controls as approved in NDA 211939. The applicant has provided a letter of authorization from Alvogen, Inc authorizing Almaject, Inc to incorporate by reference, rely upon, or otherwise use all of the relevant modules of NDA 211939 along with any amendments, supplements and annual reports.[2] The data from these modules were previously reviewed by FDA and the reviews are documented under NDA 211939. The review team for this application references the relevant prior FDA reviews for NDA 211939 and the prior NDA 211939 unireview will be included in this review appendix for reference.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This application relies on the FDA's previous findings of safety and effectiveness for Forteo for the proposed indications. By right of reference to NDA 211939, the applicant has demonstrated physiochemical comparability, and pharmacokinetic and immunogenic similarity between their teriparatide product and Forteo. Therefore, the applicant has established an adequate scientific bridge to Forteo and Teriparatide Injection is expected to have similar efficacy and safety as Forteo for the proposed indications.

This review is not intended to address the request for a Therapeutic Equivalence (TE) evaluation. Review of the TE request is ongoing.[3]

[2] This review considered information submitted to NDA 211939 as part of a supplement to the extent that such information was reviewed and such supplement was approved.

[3] As part of the original NDA submission, the applicant submitted a request for a therapeutic equivalence (TE) evaluation pursuant to section 505(j)(7)(A)(v)(I)(aa) of the FD&C Act. This provision provides, among other things, that evaluation of requests that meet applicable requirements will be made at the time of approval or not later than 180 days after the date of approval of such application. The Agency is considering the applicant's request, including whether it meets the applicable requirements under section 505(j)(7)(A)(v)(I)(aa) of the FD&C Act.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

This application relies on the FDA's previous findings of safety and effectiveness for Forteo for the proposed indications. By right of reference to NDA 211939, the applicant has demonstrated physiochemical comparability, and pharmacokinetic and immunogenic similarity between their teriparatide product and Forteo. Therefore, the applicant has established an adequate scientific bridge to Forteo and Teriparatide Injection is expected to have similar efficacy and safety as Forteo for the proposed indications. The risk-benefit profile of both Forteo and teriparatide injection are favorable in the treatment of osteoporosis in patients at high risk for fracture.

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) are due to typical age-related loss of bone. Secondary osteoporosis (e.g., glucocorticoid 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 and is a major source of morbidity and mortality among the elderly.
Current Treatment Options	Current pharmacologic treatment options for osteoporosis are anti-resorptive agents (i.e., medications that inhibit bone loss) and anabolic agents (i.e., medications that stimulate bone formation. The anti-resorptive agents include bisphosphonates, RANK ligand inhibitors (denosumab), estrogen agonists/antagonists, and calcitonin. Anabolic agents are parathyroid hormone related peptide analogs (teriparatide and abaloparatide) and a sclerostin inhibitor (romosozumab). Bisphosphonates are the most widely prescribed medications for	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. Therapies that are indicated only in patients with osteoporosis who are at high risk of fracture or who are intolerant to other available osteoporosis therapy are teriparatide, abaloparatide, denosumab and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	osteoporosis. Rare but serious side effects with bisphosphonates are osteonecrosis of the jaw and atypical femoral fractures. Denosumab is a RANK-ligand inhibitor that is also associated with osteonecrosis of the jaw and atypical femoral fractures, as well as an increased risk of fracture upon discontinuation. Teriparatide and abaloparatide are parathyroid hormone analogues. Their use is limited to two years because of the potential risk of osteosarcoma, which was noted in animal studies. Romosozumab is a sclerostin inhibitor that has the following risks: major adverse cardiac events, injection site reactions, hypersensitivity reactions, hypocalcemia, osteonecrosis of the jaw and atypical femoral fractures.	romosozumab.
Benefit	The applicant, by right of reference to NDA 211939, has adequately demonstrated comparability between Teriparatide injection and Forteo.	The clinical benefit of teriparatide injection is expected to be the same as that for Forteo.
Risk and Risk Management	The applicant, by right of reference to NDA 211939 has adequately demonstrated comparability between Teriparatide injection and Forteo.	The safety profile of teriparatide injection is expected to be the same as that for Forteo. Labeling alone is adequate to inform patients and prescribers of the risks.

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.**			

2 Therapeutic Context

2.1. Analysis of Condition

Osteoporosis is a relatively common skeletal disorder characterized by low bone mass and structural deterioration of bone, which leads to fragility and increased fracture risk. It results from an imbalance between resorption of bone by osteoclasts and formation of new bone by osteoblasts during bone remodeling. Risk factors for development of osteoporosis include menopause, hypogonadism, smoking, inadequate calcium and vitamin D intake, immobility, and certain medications that adversely affect bone metabolism (e.g., glucocorticoids).

A clinical diagnosis of osteoporosis can be made in the presence of either of the following:

- Fragility fracture (i.e., those occurring spontaneously or from minor trauma)
- T-score <-2.5 standard deviations (SDs) at any site based upon bone mineral density measurement (BMD) by dual-energy x-ray absorptiometry (DXA).[4]

A BMD T-score is the difference between a patient's BMD and that of a young adult reference population.

2.2. Analysis of Current Treatment Options

Osteoporosis treatment consists of lifestyle changes (adequate vitamin D and calcium intake, weight- bearing exercise and smoking cessation) and pharmacologic therapy. There are two pharmacologic classes of drugs used to treat osteoporosis:

- anti-resorptive agents, which increase bone mineral density by reducing the rate of bone remodeling
- anabolic agents, which act by preferentially stimulating new bone formation.

Table 2 summarizes the currently approved pharmacologic therapies for postmenopausal osteoporosis (PMO), osteoporosis in men (MO) and glucocorticoid-induced osteoporosis (GIOP). In most cases, unless there is a contraindication, oral bisphosphonates are first-tine therapy because of their efficacy, ease of administration and long-term safety data. For patients who cannot tolerate a bisphosphonate, treatment options are the RANK ligand inhibitor denosumab, which is an anti-resorptive drug, or an anabolic agent (teriparatide, abaloparatide or romosozumab).

[4] Seeman E and TJ Martin. Antiresorptive and anabolic agents in the prevention and reversal of bone fragility. Nature Review Rheumatology 15, 225-236 (2019).

Table 2. FDA Approved Pharmacologic Treatment Options for Osteoporosis

Drug class	Product name	U.S. approval	Approved indications	Dose, dose form and route of administration	Important safety and tolerability issues
Antiresorptive agents					
Bisphosphonates	Fosamax (alendronate)	1995	Post-menopausal osteoporosis (PMO), male osteoporosis (MO), glucocorticoid induced osteoporosis (GIOP)	70 mg (tablets or solution) by mouth (PO) weekly 10 mg tablet PO daily	Hypocalcemia, osteonecrosis of the jaw (ONJ), atypical femoral fractures (AFF), gastrointestinal irritation
	FoxamasPlusD (alendronate/cholecalciferol)	2005	PMO, MO, GIOP	70 mg alendronate/2800 or 5600 IU cholecalciferol, 1 tablet PO weekly	
	Binosto (alendronate)	2012	PMO, MO	70 mg (effervescent tablet or solution) PO weekly	
	Actonel (risedronate)	2000	PMO, MO, GIOP	5 mg tablet PO daily; 35 mg tablet PO weekly; 150 mg tablet PO monthly	
	Atelvia	2010	PMO	35 mg delayed release tablet PO weekly	
	Boniva (ibandronate)	2003	PMO	150 mg PO monthly (tablet)	
	Reclast (zoledronic acid)	2007	PMO, MO, GIOP	5 mg IV yearly	Hypocalcemia, renal toxicity, acute phase reactions, ONJ, AFF
RANK-L antagonist	Prolia (denosumab)	2010	PMO, MO, GIOP at high risk for fracture	60 mg SC q 6 months	Hypersensitivity, hypocalcemia, ONJ, AFF, vertebral fractures following discontinuation, serious infections,

Drug class	Product name	U.S. approval	Approved indications	Dose, dose form and route of administration	Important safety and tolerability issues
					dermatologic reactions
Estrogen agonist/antagonist	Evista (raloxifene)	1997	PMO	60 mg daily (tablet)	Venous thromboembolism; cerebrovascular accident
Anabolic therapy					
PTH analog/PTHrP analog	Forteo (teriparatide)	2002	PMO, MO, GIOP at high risk for fracture	20 mg SC daily	
	Tymlos (abaloparatide)	2017	PMO, MO at high risk for fracture	80 mg SC daily	
	Bonsity (teriparatide)	2019	PMO, MO, GIOP at high risk for fracture	20 mg SC daily	
Sclerostin inhibitor	Evenity (romosozumab)	2019	PMO at high risk for fracture	210 mg SC monthly	Risk of myocardial infarction, stroke, cardiovascular death; hypersensitivity; hypocalcemia, ONJ, AFF; duration of use limited to 12 monthly doses

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

FDA approved NDA 021318 for Forteo (teriparatide injection for subcutaneous use) [Sponsor: Eli Lilly USA] in November 2002, for the treatment of osteoporosis in post-menopausal women at high risk for fracture and to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture. The product was later approved for treatment of men and women with glucocorticoid induced osteoporosis who are at high risk for fracture. The original presentation of Forteo was a 750 mg /3 mL single-patient-use prefilled pen delivery device containing 28 daily doses of 20 mcg teriparatide. That formulation was later discontinued in favor of a 600 mcg/2.4 mL prefilled pen. The Division has reviewed the regulatory file for 021318 and finds no evidence that the 3.0 mL formulation was discontinued for reasons of safety or effectiveness.

In October 2019, FDA approved a 505(b)(2) New Drug Application for another teriparatide injection product (approved tradename of Bonsity] [NDA 211939, Sponsor: Pfenex] for the same indications as those of the reference listed drug (RLD), Forteo. Ownership of NDA 211939 was transferred to Alvogen, Inc on 11/8/2019 and the product has been marketed as Teriparatide Injection. However, Alvogen continues to submit labeing supplements using the Bonsity product labeling. Both Forteo and Teriparatide Injection are sold as a single-patient-use prefilled pen containing 28 daily doses of 20 mcg teriparatide which is to be injected subfcutaneously once daily. The applicant is relying upon the 600 mcg/2.4 mL presentation of Forteo.

3.2. Summary of Presubmission/Submission Regulatory Activity

In April 2023, Almaject, Inc., a subsidiary of Alvogen, Inc., opened pre-IND 166626 for a proposed teriparatide injection product that was manufactured using the same chemistry, manufacuting and controls as Bonsity, and would be offered in the same dose form as Bonsity. A pre-IND written responses only (WRO) meeting occurred in May 2023, to discuss Almaject's planned submission of a new 505(b)(2) NDA for its teriparatide injection product to obtain approval as well as to support a therapeutic equivalence rating with Forteo under the new provisions set forth in 21 U.S.C. § 355(j)(7)(A).[5]

The current submission contains the 505(b)(2) NDA for Almaject's Teriparatide Injection, (b) (4) 0.60 mg/2.4 mL (0.25 mg/mL). The Applicant proposes to use Forteo as the listed drug relied upon and will rely on FDA's finding of safety and effectiveness for Forteo in treatment of

[5] See Footnote 2.

osteoporosis in patients at high risk for fracture. The Applicant has also submitted authorization to reference NDA 211939 (Teriparatide Injection) and is referencing CMC, clinical and non-clinical studies submitted to that application and which informed its approval. The only new information submitted with the current application are additional immunogenicity and analytical bridging data to support a TE evaluation to the listed drug, Forteo. This review focuses on the approval of teriparatide injection using the 505(b)(2) pathway. Review of the submitted package for determination of therapeutic equivalence will occur separately.

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

4.1. Office of Scientific Investigations (OSI)

No new clinical data were submitted requiring involvement of the Office of Scientific Investigastions.

4.2. Product Quality

The Office of Pharmaceutical Quality Review team has assessed the Chemistry, Manufacturing, and Controls (CMC) information for NDA 218771 and determined that the NDA meets all applicable standards to support the quality and purity of the drug product. As such, OPQ recommends approval of this NDA from a quality perspective.

Teriparatide is a 34 amino acid peptide. The amino acid sequence of teriparatide is identical to N terminal (1-34) portion of the human parathyroid hormone. The proposed product, teriparatide injection, 600mcg/2.4 mL (250mcg/mL) is a sterile solution filled in a multi-dose single patient use prefilled pen and intended for delivering a daily dose of 20mcg subcutaneously. For the proposed drug product, the Applicant, Almaject Inc is also requesting therapeutic equivalence designation to the listed drug, Forteo (teriparatide) injection, 600mcg/2.4 mL (250mcg/mL). The TE evaluation is not the subject of this review.[6]

The applicant, Almaject Inc. has referenced Alvogen's approved NDA 211939, Bonsity (teriparatide) injection, for all CMC information. The applicant states that that the drug substance and drug product for NDA 218771 uses the same chemistry, manufacturing and controls as the drug substance and drug product approved in NDA 211939. Almaject Inc. is a subsidiary of Alvogen Inc. (the owner of the approved NDA 211939) and share resources and quality system documentation.

[6] See Footnote 2.

Drug Substance: Since this NDA references NDA 211939 for all CMC information about the drug substance teriparatide and FDA's review of that information concluded it supports approval of NDA 211939, it is concluded, the applicant has provided sufficient information about the drug substance to support approval of this NDA. It is to be noted that the limit used for total methionyl sulfoxides (NMT (b) (4)%, sum of Met^{8}, Met^{18} and $Met^{8,18}$) in drug substance specification (b) (4) specified in USP Teriparatide monograph (NMT 0.5%). The limits specified for total impurities and other impurities in drug substance specification meets the USP monograph for teriparatide.

Regarding (b) (4)
(b) (4)

Drug Product: The proposed product formulation is similar to the formulation used in Forteo. Each milliliter of proposed drug product contains 250 mcg teriparatide, 0.41 mg glacial acetic acid, 0.10 mg sodium acetate provided as 0.16mg sodium acetate trihydrate, 45.4 mg mannitol, 3 mg metacresol, and water for injection. The target pH of the product is 4.0. Forteo and the proposed Almaject drug products contain teriparatide as an active ingredient. The drug product is provided as a solution for injection in a prefilled pen with, a product strengthof 600mcg/2.4mL, product concentration of 250 mcg/mL, and dose strength of 20 mcg per dose.

The applicant's drug product and finished product specification includes tests for appearance/visual inspection, color, pH, particulate matter by light obscuration, sterility, bacterial endotoxins, identification, and assay (teriparatide), metacresol content, product-related impurities (specified, each unspecified, and total impurities), impurities with molecular masses greater than that of teriparatide, bioidentity, container content for injections, break loose and sustaining force, and essential performance requirement tests such as dose (volume) accuracy, injection force and dose button pull force.

To support the proposed application, the applicant provided purity profile comparison between Forteo and the proposed drug product using multiple lots of Forteo and proposed Alvogen drug product. The applicant identified the impurities present in Forteo lots and Bonsity batches.

Bonsity batches used in the study were used in phase 3 studies and non-clinical immunogenicity studies.

Both the proposed drug product and Forteo are formulated in (b) (4)

The results from the purity profile comparison study indicated that major impurities observed in both Forteo, and the proposed drug product are (b) (4)
These impurities are present in both drug products at (b) (4)% to (b) (4)% level.
The USP monograph for teriparatide injection specifies limits for teriparatide succinimide (30), and rhPTH (1-30) and all the remaining impurities present in the product are considered as unspecified impurities. The unspecified impurities are controlled with a limit of NMT (b) (4)%.

Based on the impurity profile comparison, it is concluded that the individual impurity levels and total impurity levels present in the proposed drug product and Forteo drug product are comparable or within limits specified in USP drug product monograph.

Device: Like, Forteo, the proposed pen is intended for delivering subcutaneously a daily dose of 20 mcg for 28 days with labeling instruction to discard any unused portion 28 days after first use. The applicant provided dose accuracy comparison between the proposed drug product and Forteo® injection. The mean delivered dose data results are close to the label claim dose of 20mcg and statistically equivalent to 20mcg using an equivalence test with (b) (4)% error margin and (b) (4)% confidence interval.

CDRH reviewed the essential performance requirements testing of the finished drug device combination product. CDRH review concluded that it is adequate to support the NDA. Refer to CDRH review dated April 29, 2024, in DARRTS. We note that CDRH reviewed other aspects of the applicants NDA submission, including information incorporated by reference to NDA 211939, that was beyond this NDA review (and will be considered as part of the TE evaluation).

The storage conditions and shelf-life for the proposed product is the same as that recommended for Alvogen's teriparatide injection. The recommendation from process/facility, microbiology, drug product, labeling and drug substance reviewers for this NDA is adequate. For details please refer to OPQ integrated quality assessment fo NDA 218771 in DARRTS dated May 14 , 2024. All manufacturing facilities associated with the application are acceptable. The overall manufacturing inspection recommendation in Panorama for NDA 218771 is approve as of May 8th, 2024.

Overall, the NDA 218771 is recommended for APPROVAL from OPQ perspective.

4.3. Clinical Microbiology

Not Appplicable

4.4. Devices and Companion Diagnostic Issues

CDRH reviewed the essential performance requirements testing of the finished drug device combination product. CDRH review concluded that it is adequate to support the NDA. Refer to CDRH review dated April 29, 2024, in DARRTS.

5 Nonclinical Pharmacology/Toxicology

No new nonclinical data are submitted, refer to the nonclinical review of NDA 211939

6 Clinical Pharmacology

6.1. Executive Summary

No new clinical pharmacology studies were conducted to support the current application.

The applicant, Almaject Inc., seeks approval of teriparatide injection, (b) (4) 0.6 mg/2.4 mL (0.25 mg/mL) through the 505(b)(2) regulatory pathway, relying on FDA's finding of safety and effectiveness for Forteo (teriparatide injection, NDA 021318)..

The applicant has provided a letter of authorization that allows the applicant "to incorporate by reference, rely upon, or otherwise use, all relevant modules of NDA 211939."

As a result, Alvogen's NDA 211939 for Teriparatide Injection (tradename Bonsity), (b) (4) 0.6 mg/2.4 mL (0.25 mg/mL) is referenced for chemistry, manufacturing and controls, clinical and nonclinical studies.

In this NDA (NDA 218771), the applicant references Study PF708-101, which demonstrated the bioequivalence between Alvogen's teriparatide (Bonsity) and Forteo, and was previously reviewed under NDA 211939, supports the bioequivalence between Almaject's teriparatide and Forteo (See Section 6.2).

A Double-Masked, Randomized, Two-Treatment Cross-over Study Comparing the Pharmacokinetics of PF708* and Forteo Administered by Subcutaneous Injection in Healthy Adult Subjects	PF708-101 Study Report (previously reviewed by FDA for NDA 211939 approval)

6.2. Summary of Clinical Pharmacology Assessment

The referenced 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 (Alvogen's teriparatide or Bonsity) and Forteo in healthy subjects. The 90% confidence intervals (CI) of the PK parameters, maximum observed concentration (Cmax) and area under the concentration-time curve (AUC) values, were within the specified no-effect boundary of 80% to 125% (Table 3). This finding demonstrated the PK bioequivalence between Bonsity and Forteo, and supports the approval of the current product, i.e., Almaject's teriparatide.

Table 3. PK Parameters of Teriparatide Following a Single Dose of PF708 (Bonsity) 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)
AUCt and AUCinf: AUC from time 0 to time of last observed concentration and from time 0 to infinity, respectively.
Source: Table 6 of Multi-Discipline Review of NDA 211939

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

No new clinical studies were conducted to support the current application. The applicant is relying on FDA's finding of safety and effectiveness for Forteo as well as referencing the bioequivalence and immunogenicity data which supported approval of NDA 211939. All data that support this 505(b)(2) application are shown in Table 4.

Table 4. Documentation to support the scientific bridnging of the proposed teriparatide injection to Forteo

Study Description	Study report Number (review status)
Bioequivalence Studies	
A Double-Masked, Randomized, Two-Treatment Cross-over Study Comparing the Pharmacokinetics of PF708* and Forteo Administered by Subcutaneous Injection in Healthy Adult Subjects	PF708-101 Study Report (previously reviewed by FDA for NDA 211939 approval)
Studies assessing comparative immunogenicity	
A randomized, multi-center, parallel-group, open-label study to compare the effects of PF708 and Forteo after 24 weeks of treatment in 181 female and male patients with osteoporosis.	PF708-301 Study Report (previously reviewed by FDA for NDA 211939 approval)

*PF708 – previous name of Alvogen's teriparatide injection product

7.2. Review Strategy

A clinical review was not required since no new clinical data were submitted.
Referenced clinical data that supported comparability between Bonsity and Forteo to support reliance of Forteo efficacy and safety data are summarized in Section 8.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. A Double-Masked, Randomized, Two-Treatment Cross-over Study Comparing the Pharmacokinetics of PF708* and Forteo Administered by Subcutaneous Injection in Healthy Adult Subjects (study PF708-101)

Results of this referenced study were previously reviewed by FDA in the multi-disciplinary evaluation of NDA 211939 dated October 2, 2019. To summarize, 70 healthy male and female volunteers aged 20-53 years received single doses of each study drug (i.e., Forteo 20 mcg or PF708 20 mcg) separated by a three-day washout. Dose sequence assignment was randomized in a 1:1 ratio.

As summarized in Section 6 of this review and based on the multi-disciplinary review of NDA 211939, the findings of study RF708-101 demonstrated PK bioequivalence between PF708 and Forteo. The review team for NDA 211939 concluded that PF708 is expected to have similar clinical efficacy to Forteo and that it is acceptable to rely on FDA findings of Forteo's efficacy for the proposed indicaitons.

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

Referenced study PF708-301 was a comparative clinical study in a total of 182 female subjects with postmenopausal osteoporosis and male subjects with primary osteoporosis. Subjects were randomized in a 1:1 ratio to receive single doses of PF708 20 mcg or Forteo 20 mcg. The primary endpoint was the incidence of anti-drug antibodies (ADA) twenty-four weeks after dose administration. All positive ADA cases were also assessed for neutralizing activity.

ADA formation occurred in 2.3% and 2.2% of subjects in the PF708 and Forteo groups, respectively. One of the ADA-positive subjects in the PF708 group alsohad detectable neutralizing antibodies. The pharmacological responses of PF708 (i.e., bone turnover markers, serum calcium and phosphorous levels and BMD compared to baseline) and safety of PF708 in these subjects were not different from those in the non-ADA subjects in both treatment groups (PF708 and Forteo). There was also no findings of cross-reactivity against endogenous PTH (1-84) in any of the ADA-positive samples. The review team concluded that PF708 demonstrated similar safety and immunogenicity to Forteo and therefore, it would be acceptable to rely on FDA's findings of Forteo's safety for the proposed indications.

9 Advisory Committee Meeting and Other External Consultations

Not applicable.

10 Pediatrics

Teriparatide is not indicated for use in pediatric patients with open epiphyses. A full waiver of pediatric assessment was granted for both Forteo (NDA 021318) and for Bonsity (NDA 211939) and is appropriate for this NDA.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

Prescribing information is similar to Forteo. As outlined in Section 4.2 of this review, several oxidized impurities (b) (4) specified in the USP monogragh. (b) (4)

(b) (4)

(b) (4)

No proprietary name was proposed for the drug product; therefore, "Teriparatide Injection" was used in sections of labeling (i.e., Highlights Product Title, Full Prescibining Information subsections 2.1, 5.2, 8.4) where the proprietary name would typically be used to associate the drug with dosing recommendations, adverse reactions, pediatric use, and other product information.

For Section 3 Dosage Forms and Strengths, the strength was revised from (b) (4) to 600 mcg/2.4 mL and updated the solution description (e.g.,teriparatide in clear, colorless solution) was included.

For Section 12, half-life information was revised to only include the proposed subcutaneous route of administration in subsection 12.3 and immunogenicity beginning paragraph was updated in subsection 12.6.

Other Prescription Drug Labeling
The Medication Guide and Instructions for Use labeling have been reviewed and agreed upon labeling has been reached with the Applicant.

12 Risk Evaluation and Mitigation Strategies (REMS)

Not applicable as there is no REMS in place for the reference product.

13 Postmarketing Requirements and Commitment

Not applicable.

14 Appendices

14.1. NDA 211939 Unireview

97 Pages Have Been Withheld as A Duplicate Copy of NDA 211939 Unireview. Which can be found in Drugs@FDA. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211939Orig1s000TOC.cfm.

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/s/

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