CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208743Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Hylton V. Joffe, M.D., M.M.Sc.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	NDA 208743 000
Applicant	Radius Health, Inc.
Date of Submission	March 30, 2016
PDUFA Goal Date	March 30, 2017, extended to June 30, 2017
Proprietary Name / **Non-Proprietary Name**	Tymlos / Abaloparatide
Dosage Form(s) / Strength(s)	3120 mcg/1.56 mL (2000 mcg/mL) in a single-patient use pre-filled pen. The pre-filled pen delivers 30 doses, each containing 80 mcg of abaloparatide in 40 mcL.
Applicant Proposed Indication(s)/Population(s)	Treatment of postmenopausal women with osteoporosis
Action/Recommended Action for NME:	*Approval*
Approved/Recommended Indication/Population(s) (if applicable)	Treatment of postmenopausal women with osteoporosis at high risk of fracture defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy

Material Reviewed/Consulted Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Stephen Voss
Statistical Review	Jia Guo, Sonia Castillo, Mahboob Sobhan, Hepei Chen, and Karl Lin
Pharmacology Toxicology Review	Gemma Kuijpers and Mukesh Summan
Office of Pharmaceutical Quality Review	Xavier Ysern, Donna Christner, Hamid Shafiei, Moo-Jhong Rhee, Yuesheng Ye, Nallaperumal Chidambaram, Yeissa Chabrier-Rosello, Marla Riley-Stevens, Krishna Ghosh, Juandria Williams, Laura Pogue, Jingyue Yang, and Mark Seggel
Center for Devices and Radiological Health	Latoya Oliver-Powell, Robert Meyer, Ronald Swann, Alan Stevens
Clinical Pharmacology Review	LaiMing Lee, Fang Li, Jeffry Florian, Doanh Tran, and E. Dennis Bashaw
Interdisciplinary Review Team for QT Studies	Moh Jee Ng, Qianyu Dang, Chao Liu, Jiang Liu, Michael Li, and Christine Garnett
Immunogenicity Consult	Bruce Huang and Harold Dickensheets
Office of Prescription Drug Promotion	Jina Kwak
Office of Study Integrity and Surveillance	Michael Skelly, Seongeun (Julia) Cho, Hasan Irier, and Elise Murphy
Office of Scientific Investigations	Roy Blay, Janice Pohlman, and Kassa Ayalew
Cross-Discipline Team Leader Review	Theresa Kehoe
Office of Surveillance and Epidemiology (OSE)/ Division of Medication Error Prevention and Analysis	Loretta Holmes, Walter Fava, Lolita White, and QuynhNhu Nguyen
OSE/Division of Pharmacovigilance	Peter Waldron, Samantha Cotter, Neha Gada, and S. Christopher Jones
OSE/Division of Epidemiology II	Jie (Jenni) Li, Corinne Woods, Justin Mathew, Grace Chai, and Sukhminder Sandhu
OSE/Disk of Risk Management	Jacqueline Sheppard, Leah Hart, Jamie Wilkins Parker, and Cynthia LaCivita

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Abaloparatide, trade name Tymlos, is a synthetic analog of parathyroid hormone related peptide (PTHrP) proposed for the treatment of postmenopausal osteoporosis. The dosing regimen is 80 mcg administered subcutaneously once daily.

Osteoporosis is a skeletal disorder characterized by low bone mass, compromised bone strength, and an increased risk of fracture. While osteoporosis can occur in both men and women, studies in postmenopausal women represent the majority of the data defining the disease and its sequelae.

The efficacy of abaloparatide was evaluated in postmenopausal women with osteoporosis who were randomized to receive 18 months of double-blind treatment with abaloparatide 80 mcg or placebo. Patients also received daily supplemental calcium and vitamin D.

Compared to placebo, abaloparatide reduced the incidence of new morphometric (radiographically defined) vertebral fractures, prolonged the time to nonvertebral fracture, and increased bone mineral density at the lumbar spine and hip.

- After 18 months of treatment, the incidence of new vertebral fracture was 0.6% with abaloparatide and 4.2% with placebo ($p<0.0001$). The absolute risk reduction of new vertebral fracture was 3.6% (95% confidence interval 2.1%-5.4%) and the relative risk reduction was 86% (95% confidence interval 61%-95%). Based on the upper and lower bounds of the 95% confidence interval for the absolute risk reduction, the number needed to treat to prevent one vertebral fracture is 19-48.
- After 18 months of treatment, the percentage of patients with at least one nonvertebral fracture was 2.2% with abaloparatide and 4.0% with placebo. Abaloparatide prolonged the time to first incidence of nonvertebral fracture compared to placebo (hazard ratio 0.57; 95% confidence interval 0.32-1.00; log-rank $p=0.049$).
- After 18 months of treatment, the mean increase in bone mineral density with abaloparatide compared to placebo was greatest at the lumbar spine (8.7%) and more modest at the total hip (3.5%) and femoral neck (3.3%). The trial was underpowered to show an effect on hip fractures – there were only two hip fractures, both of which occurred on placebo. Therefore, the extent to which abaloparatide may reduce the risk of hip fracture is unknown.

The Phase 3 trial randomized only 30 patients from the United States to abaloparatide or placebo. These patients comprised less than 2% of the total patients randomized to abaloparatide and placebo and were too few to statistically analyze efficacy in this subgroup. However, it is reasonable to conclude that the foreign data from this trial are applicable to the United States population based on the totality of the data. These data include comparable pharmacokinetic exposures to abaloparatide between patients in the United States and patients across 23 foreign sites

and consistent bone mineral density changes across the various regions outside the United States despite their demographic differences.

The safety profile of abaloparatide is similar to that of teriparatide (trade name Forteo; another drug approved to treat postmenopausal osteoporosis) so their labeling will be similar. Both abaloparatide and teriparatide cause osteosarcoma in rats. The relevance to humans is unknown. Osteosarcoma is rare in humans. We will use enhanced pharmacoviligance to improve the quality of spontaneous reports submitted to the FDA Adverse Event Reporting System.

Because of the potential risk of osteosarcoma, we are requiring a Boxed Warning for abaloparatide, narrowing the indication to those at high risk of fracture, where the potential benefit more clearly outweighs the risk, and recommending at most two years of cumulative lifetime exposure to abaloparatide and/or teriparatide. A Medication Guide will explain the safety risks to patients.

Teriparatide has a Risk Evaluation and Mitigation Strategy (REMS) to mitigate the risk of osteosarcoma. This REMS has achieved its goals (there is good awareness of the osteosarcoma risk) and is being released. Although abaloparatide and teriparatide are not technically in the same class – abaloparatide is a PTHrP analog whereas teriparatide is a parathyroid hormone (PTH) analog – they both bind to the PTH-1 receptor and have a similar mechanism of action, both cause osteosarcoma in rats with uncertain relevance to humans, and both are expected to be used by a similar prescribing population. As we have determined that a REMS is no longer necessary to ensure the benefits of Forteo outweigh its risks, so too is it reasonable to conclude that labeling alone should be sufficient to ensure that the benefits of abaloparatide outweigh its risks.

Abaloparatide can cause hypercalcemia, hypercalciuria, nausea, dizziness and orthostasis (particularly tachycardia), hyperuricemia (without an apparent increase in gout) and injection site reactions. These risks can generally be monitored (e.g., with blood or urine testing) or mitigated with specific interventions (e.g., having the patient sit or lie down if orthostasis occurs), and can all be adequately handled with labeling. These adverse reactions usually did not lead to discontinuation from the trial, although it is possible that some patients treated in clinical practice may have more severe reactions. A large number of patients exposed to abaloparatide develop neutralizing anti-abaloparatide antibodies with some cross-reactivity to endogenous PTHrP, but these antibodies do not appear to reduce efficacy or cause safety concerns such as hypersensitivity reactions or hypocalcemia. Antibody formation was adequately assessed after patients had been treated with abaloparatide for 18 months, but was not comprehensively assessed at earlier timepoints in the trial. This additional assessment of antibody formation at earlier timepoints will be conducted as a postmarketing commitment.

In summary, the Division's assessment is that the benefits of abaloparatide on fracture risk reduction in postmenopausal osteoporosis outweigh the identified risks and uncertainties, all of which can be adequately mitigated with labeling alone.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Osteoporosis is characterized by low bone mass and compromised bone strength. Osteoporosis increases the risk of fracture. • Osteoporosis is underdiagnosed. About 50% of postmenopausal women over 50 years of age will have an osteoporotic fracture. • Vertebral fractures are the most common site of osteoporotic fracture and can cause kyphosis, back pain, height loss, and impaired lung function. • In older patients, hip fracture is associated with loss of independence and increased mortality	Osteoporosis increases the risk of fracture. Underdiagnosis of osteoporosis is a major public health issue. Vertebral fractures are the most common site of osteoporotic fracture. Fractures can cause morbidity. Hip fracture is associated with increased mortality in older patients.
Current Treatment Options	• Treatments include one drug that stimulates bone formation (teriparatide) and several drugs that inhibit bone loss (bisphosphonates, denosumab, estrogen agonists/antagonists, and calcitonin). • All approved treatments for postmenopausal osteoporosis except for calcitonin have been definitively shown to reduce the risk of fracture. • Bisphosphonates are the most widely prescribed osteoporosis medications, but use has declined because of fears related to the serious, but rare side effects of osteonecrosis of the jaw and atypical femoral fractures. • Teriparatide causes osteosarcoma in rats. Because human relevance cannot be excluded, teriparatide is indicated for patients at high risk of fracture and lifetime use beyond two years is not recommended.	Multiple therapies are available for the treatment of postmenopausal osteoporosis. Many patients with osteoporosis who would benefit from therapy remain untreated. Additional therapies, such as abaloparatide will expand the treatment options for osteoporosis.
Benefit	• In a randomized clinical trial of postmenopausal women with osteoporosis who were also receiving calcium and vitamin D supplementation, 18 months of treatment with abaloparatide reduced the incidence of new morphometric (radiographically defined) vertebral fractures, prolonged the time to nonvertebral fracture, and increased bone mineral density at the total hip, femoral neck and lumbar spine compared to placebo.	18 months of treatment with abaloparatide significantly increases bone mineral density at the lumbar spine and hip, and reduces vertebral and nonvertebral fractures in postmenopausal women. The number needed to treat to prevent

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The incidence of new vertebral fracture was 0.6% with abaloparatide and 4.2% with placebo ($p<0.0001$). The absolute risk reduction of new vertebral fracture was 3.6% (95% confidence interval 2.1%-5.4%) and the relative risk reduction was 86% (95% confidence interval 61%-95%). • Based on the 95% confidence interval for the absolute risk reduction, the number needed to treat to prevent one new vertebral fracture is 19-48. • The percentage of patients with at least one nonvertebral fracture was 2.2% with abaloparatide and 4.0% with placebo. Abaloparatide prolonged the time to first incidence of nonvertebral fracture compared to placebo (hazard ratio 0.57; 95% confidence interval 0.32-1.00; log-rank p=0.049). • After 18 months of treatment, the mean increase in bone mineral density with abaloparatide compared to placebo was greatest at the lumbar spine (8.7%) and more modest at the total hip (3.5%) and femoral neck (3.3%). The trial was underpowered to show an effect on hip fractures – there were only two hip fractures, both of which occurred on placebo. • The Phase 3 trial randomized only 30 patients from the United States to abaloparatide or placebo. There were too few patients from the United States to statistically analyze efficacy in this subgroup.	one vertebral fracture is 19-48. It is unknown whether abaloparatide reduces the risk of hip fracture because the trial was underpowered for this endpoint. The Phase 3 trial enrolled too few patients from the United States to statistically evaluate efficacy in this subgroup. However, based on the totality of data (e.g., pharmacokinetic exposures, consistent findings across diverse regions of the world), it is reasonable to conclude that the foreign data are applicable to the United States population. If approved, abaloparatide will be the second anabolic agent for osteoporosis and use will likely mimic that of teriparatide.
Risk	• Safety concerns with abaloparatide are similar to those for teriparatide, which has a similar mechanism of action. • Abaloparatide causes osteosarcoma in rats. The clinical relevance is unknown. Osteosarcoma is rare in humans. We will use enhanced pharmacovigilance to improve the quality of any spontaneous reports. • Abaloparatide can cause hypercalcemia, hypercalciuria, nausea, dizziness and orthostasis (particularly tachycardia), hyperuricemia, and injection site reactions. These adverse reactions usually did not lead to discontinuation from the trial.	Abaloparatide and teriparatide have similar safety concerns. Like teriparatide, abaloparatide causes osteosarcoma in rats and the risk to humans is unknown. We will use enhanced pharmacoviligance to improve the quality of any spontaneous reports. Adverse reactions include hypercalcemia, hypercalciuria, nausea, dizziness and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• About 50% of abaloparatide-treated patients developed anti-abaloparatide antibodies after 18 months of treatment, two-thirds of which were neutralizing. About 2% of patients with anti-abaloparatide antibodies developed cross-reactivity to endogenous parathyroid hormone related peptide (PTHrP). The antibodies did not reduce efficacy or raise safety concerns.	orthostasis, and injection site reactions, which usually did not lead to discontinuation from the trial, although it is possible that some patients treated in clinical practice may have more severe reactions. Anti-abaloparatide antibodies and cross-reacting antibodies to PTHrP do not appear to adversely affect efficacy or safety.
Risk Management	• Teriparatide has a Risk Evaluation and Mitigation Strategy (REMS) to mitigate the risk of osteosarcoma. This REMS has achieved its goals and is being released. Because of the similarities between abaloparatide and teriparatide it is reasonable to conclude that a REMS is also not needed for abaloparatide. • Labeling similar to that for teriparatide (e.g., narrowed indication, Boxed Warning, Warnings and Precautions, Medication Guide) is sufficient to ensure that the benefits of abaloparatide outweigh its risks.	Labeling, including a Medication Guide for patients, will be adequate to convey the important safety concerns with abaloparatide and ensure that the benefits outweigh the risks.

2. Background

Radius Health, Inc. submitted this New Drug Application (NDA) for abaloparatide (trade name Tymlos), a new molecular entity proposed for the treatment of postmenopausal osteoporosis. Abaloparatide is not approved in any country. The recommended daily dose is 80 mcg administered subcutaneously in the peri-umbilical region.

Abaloparatide is a 34-amino acid synthetic peptide analog of parathyroid hormone related peptide (PTHrP), with about 75% homology to the first 34 amino acids of PTHrP. Although PTHrP is a normal gene product expressed in a wide variety of tissues, it appears to have limited physiologic roles in humans, but is secreted by some tumors and is a well-recognized cause of hypercalcemia of malignancy. Abaloparatide also has about 40% homology to parathyroid hormone (PTH), which is a major modulator of calcium and phosphate hemostasis in humans. Both PTHrP and PTH activate the PTH-1 receptor. While continuous high concentrations of PTHrP or PTH stimulate bone resorption, intermittent administration has an anabolic effect on bone. Forteo (teriparatide), a recombinant PTH analog, is the only anabolic agent approved for the treatment of osteoporosis. Because of the similar mechanism of action, the expectation is that abaloparatide will have a similar efficacy and safety profile to Forteo.

This NDA was reviewed under the Prescription Drug User Fee Act (PDUFA) V "Program" because it contains a new molecular entity and was received after October 1, 2012. The PDUFA goal date was extended by three months after we requested and received additional immunogenicity data that required more time for review. This document summarizes the Division's recommendations on the application.

3. Product Quality

The Office of Pharmaceutical Quality and the Center for Devices and Radiological Health recommend approval. See their reviews for details.

Tymlos is a drug-device combination product containing abaloparatide in a sterile solution within a glass cartridge and multi-dose, disposable pen injector. The pen injector, known as Ypsomed AG UnoPen, delivers 40 mcL (b) (4) of sterile product per injection. The cartridge contains sufficient solution for 30 once-daily injections plus priming. The pen injector is used with 8 mm, 31-gauge, mylife Clickfine Needles, which are not provided with the pen injector but can be obtained from a pharmacy with a prescription.

Each milliliter of abaloparatide solution contains 2 mg of abaloparatide and the following compendial, inactive ingredients: sodium acetate trihydrate and acetic acid (b) (4) phenol (b) (4) and water for injection. The abaloparatide solution is manufactured by (b) (4) The container closure system maintains product sterility.

The Applicant provided adequate data to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product, and has acceptable manufacturing processes. Specification tests and acceptance criteria for the drug product were also acceptable. The drug product is compatible with the glass cartridge based on leachables and extractables testing and stability and sterility studies.

Storage and expiration dating are primarily limited by the degradation of abaloparatide to the [redacted] impurity. This impurity [redacted], but was adequately qualified in nonclinical studies. The Chemistry reviewers concluded that the available data support a 24-month expiration dating period for the drug product stored at 2-8 degrees Celsius, followed by a 30-day in-use period at 25 degrees Celsius.

The Center for Devices and Radiological Health reviewed the Ypsomed UnoPen component and concluded that it is suitable for the intended use. Although the dose accuracy of the injector [redacted] the dose accuracy and specifications are comparable to those seen with the injector used in the Phase 3 trial.

Manufacturing inspections were acceptable. There will be a post-approval medical device Good Manufacturing Process (GMP) inspection of the German site that manufactures the drug product and performs the final pen assembly. This site had a pre-approval inspection covering drug and device GMPs in July 2016 and was found acceptable.

The Chemistry reviewers agree with the Applicant's request for a categorical exclusion from environmental assessment, because the estimated introduction concentrations are below the 1 parts per billion threshold with no extraordinary circumstances.

4. Nonclinical Pharmacology/Toxicology

The Nonclinical Pharmacology/Toxicology reviewers recommend approval. See their review for details.

In ovariectomized rats and monkeys (animal models of postmenopausal osteoporosis), abaloparatide increased bone mass and bone strength without negatively affecting bone quality.

The main safety concerns included:

- **Osteosarcoma and osteoblastoma**: Abaloparatide is not genotoxic, but caused osteosarcoma and osteoblastoma in the two-year rat carcinogenicity study. These tumors were expected based on previous findings with two related products, Forteo (teriparatide) and Natpara (human parathyroid hormone approved for the treatment of hypoparathyroidism). The rat carcinogenicity study tested three subcutaneous abaloparatide doses (10 mcg/kg/day, 25 mcg/kg/day, and 50 mcg/kg/day) and included a negative control (0 mcg/kg/day) and a teriparatide 30 mcg/kg/day positive control. The teriparatide dose in this study is the same as the mid-dose of teriparatide tested in the Forteo rat carcinogenicity study.

As shown in Table 1, abaloparatide caused tumors in both male and female rats in a dose-dependent manner, with a higher incidence in male rats compared to female rats. The overall incidence of osteosarcoma was 35% in the abaloparatide low-dose group, 57% in the mid-dose group, 74% in the high-dose group, 53% with teriparatide, and 2% with control.

In both sexes, these tumors were accompanied by large increases in bone mass (several fold-greater than the increases seen in humans), were considered treatment-related and were often fatal. The tumors are thought to occur from osteoblast stimulation or inhibition of osteoblast apoptosis.

Although the study included a head-to-head comparison to teriparatide, it is not possible to use these data to reliably determine which product has the stronger signal. This is because teriparatide systemic exposures (area under the concentration-time curve or AUC) were not assessed in this study, so calculations of exposure multiples would require cross-study comparisons to the Forteo data, and such cross-study comparisons are inherently limited. Therefore, the conclusion from this study is that both abaloparatide and teriparatide cause osteosarcomas and osteoblastomas in rats, that these findings are expected based on what has been observed with Forteo and Natpara, and that the human relevance of these findings is unclear. There are no additional nonclinical data that can be obtained at this time to inform on human risk.

Table 1. Osteosarcoma and Osteoblastoma Incidence in the Two-Year Rat Carcinogenicity Study (Adapted from the Table on Page 138 of the Nonclinical Pharmacology/Toxicology Review)

	Control	**Abaloparatide 10 mcg/kg/day**	**Abaloparatide 25 mcg/kg/day**	**Abaloparatide 50 mcg/kg/day**	**Teriparatide 30 mcg/kg/day**
Males	N=60	N=60	N=59	N=60	N=60
Osteosarcoma	2%	52%	78%	87%	65%
Osteoblastoma	0	2%	25%	33%	17%
Osteosarcoma/osteoblastoma[1]	2%	52%	81%	90%	72%
Exposure Multiple[2]	-	4x	14x	24x	Unknown[3]
Females	N=60	N=60	N=61	N=60	N=60
Osteosarcoma	2%	18%	36%	62%	40%
Osteoblastoma	0	13%	11%	15%	7%
Osteosarcoma/osteoblastoma[1]	2%	27%	44%	67%	45%
Exposure Multiple[2]	-	3x	12x	25x	Unknown[3]
Males Plus Females	N=120	N=120	N=120	N=120	N=120
Osteosarcoma	2%	35%	57%	74%	53%
Osteoblastoma	0	8%	18%	24%	12%
Osteosarcoma/osteoblastoma[1]	2%	39%	63%	78%	58%

[1]Includes animals who had osteosarcoma alone, osteoblastoma alone, or coexisting osteosarcoma and osteoblastoma
[2]Compares exposures in rats to exposures achieved in humans given the recommended clinical dose
[3]It is not possible to reliably calculate exposure multiples for teriparatide (see the main text)

- **Findings related to the pharmacologic action of the drug**, included hypercalcemia, hypercalciuria, decreases in blood pressure and increases in heart rate (due to peripheral vasodilation and inotropic and chronotropic effects on the heart) and soft tissue mineralization. These effects were seen in rats at exposures two-fold higher than the clinical dose, and in monkeys at exposures three-fold higher than the clinical dose. The Phase 3 trial assessed vital signs, serum and urine electrolytes, and, in a subset of patients, renal computed tomography (CT) scans for nephrolithiasis. See the Safety section for details.

Abaloparatide did not affect fertility in male rats and did not cause embryofetal toxicity in female rats mated with treated males. The Applicant did not conduct an embryofetal developmental toxicity study with treated female animals or a pre/post-natal development study because the intended population of postmenopausal women does not have reproductive potential.

5. Clinical Pharmacology

The Clinical Pharmacology and Pharmacometrics reviewers recommend approval. See their review for details. Key findings are summarized below:

- After subcutaneous injection of the 80 mcg dose, the median time to peak abaloparatide concentration is 31 minutes (range 15-31 minutes), with most of the systemic exposure occurring within the first five hours post-dose.

- Abaloparatide is degraded into smaller peptides by non-specific proteases then excreted renally. Abaloparatide is not metabolized by CYP enzymes, nor does it inhibit or induce those enzymes.

- Based on population pharmacokinetic modeling using the Phase 3 data and from the dedicated renal impairment pharmacokinetic study, abaloparatide exposures (AUC) increase about 1.2-fold in patients with mild renal impairment, 1.4- to 1.7-fold in patients with moderate renal impairment, and 1.4- to 2.1-fold in patients with severe renal impairment, compared to healthy controls. Effects on abaloparatide Cmax were more modest (increases up to 1.3- to 1.4-fold in patients with moderate or severe renal impairment). Based on these data, the reviewers are not recommending dosage adjustment in patients with renal impairment; however, in patients with severe renal impairment they recommend monitoring for adverse events that could potentially occur with the increased exposures.

- Bone turnover markers were measured in about 200 patients in each treatment arm in the Phase 3 trial. Abaloparatide increased the bone formation marker, type 1 N-terminal procollagen (P1NP) and the bone resorption marker, collagen type 1 C-telopeptide (CTX), with greater increases in P1NP than CTX. Both markers peaked early in the trial (around one month for P1NP and three months for CTX) then declined over time. P1NP remained above baseline values until the end of the trial, whereas CTX returned to baseline values by the end of the trial. These data support that abaloparatide has both anabolic and resorptive effects on bone, with anabolic effects predominating.

- The Applicant conducted a six-month, dose-finding Phase 2 trial that randomized postmenopausal women with osteoporosis to abaloparatide 20 mcg (n=43), 40 mcg (n=43) or

80 mcg (n=45) per day, placebo (n=45) or teriparatide (n=45). There was a dose-related increased in bone mineral density with abaloparatide at the total hip and lumbar spine, but not at the femoral neck. Based on these data, the Applicant chose to carry the 80 mcg dose into the Phase 3 trial.

- The Applicant assessed the effects of age and race on abaloparatide exposures in a subset of postmenopausal women in the Phase 3 trial. Abaloparatide exposures were not affected by age among women 49 to 86 years old. Abaloparatide exposures were slightly higher in Asians (mean AUC 1550 pg*hr/mL; n=126) and Blacks (mean AUC 1616 pg*hr/mL; n=25) compared to Caucasians (AUC 1451 pg*hr/mL; n=650), but dose adjustment is not needed based on these minor differences.

- In the Phase 3 trial, abaloparatide was administered using multi-dose cartridges inserted into the Becton-Dickenson II pen injector, whereas the to-be-marketed product uses these same cartridges inserted into the UnoPen pen injector. The Applicant successfully bridged the Phase 3 and to-be-marketed products by showing that abaloparatide exposures with these products were bioequivalent.

- The Thorough QT Study tested single subcutaneous abaloparatide doses of 80 mcg and 240 mcg (three times the recommended dose). The largest upper bound for the 90% confidence interval for the mean difference between abaloparatide and placebo for QTcF was 9.7 msec for the 80 mcg dose and 12.5 msec for the 240 mcg dose. These upper bounds were close to or slightly exceeded the 10 msec threshold for regulatory concern used in the International Conference on Harmonization E14 guideline. The Interdisciplinary Review Team for QT studies concluded that the transient and marginal increases in the QTc interval were likely due to the increase in heart rate seen with abaloparatide, that the concentrations achieved with the supratherapeutic dose were above the predicted worst-case scenario (severe renal impairment), and that abaloparatide is not expected to cause QT interval prolongation of clinical concern at the therapeutic concentration range.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

This section briefly summarizes the design and key efficacy results of the single Phase 3 trial (BA-58-05-003, also known as Study 003) and its open-label extension (BA-58-05-005, also known as Study 005). See the clinical and statistical reviews and Cross-Discipline Team Leader memorandum for details.

Study 003 was a randomized, placebo-controlled, multinational trial designed to establish the efficacy of abaloparatide for the treatment of postmenopausal osteoporosis. Women at least five years postmenopause at increased risk of fracture were randomized to 18 months of blinded treatment with abaloparatide 80 mcg (n=824) or placebo (n=821), or to open-label treatment with

teriparatide 20 mcg, each administered as a daily subcutaneous injection in the morning. Patients also took calcium and vitamin D supplements in the evening.

The primary efficacy endpoint was the percentage of patients with at least one new morphometric (radiographically defined) vertebral fracture at the end of treatment with abaloparatide compared to placebo. This is the standard efficacy endpoint for drugs intended to treat postmenopausal osteoporosis. X-rays of the spine were obtained for the primary efficacy endpoint at screening and Month 18.

Key secondary endpoints comparing abaloparatide to placebo included the percentage change from baseline to Month 18 in total hip, femoral neck, and lumbar spine bone mineral density, as well as the time to first incident nonvertebral fracture by the follow-up visit (Month 19). Nonvertebral fractures were defined as low trauma fractures at sites other than the spine, fingers, toes, skull, face, sternum or patella – such as fractures of the wrist, hip and ribs. These secondary endpoints were tested sequentially to preserve the type I error rate.

The Applicant prespecified the following superiority comparisons of abaloparatide to teriparatide that were also tested sequentially to control type I error, and were to proceed if abaloparatide was superior to placebo on nonvertebral fractures:

- Change from baseline to Month 6 in total hip bone mineral density
- Change from baseline to Month 6 in femoral neck bone mineral density
- Nonvertebral fractures
- Change from baseline to Month 6 in lumbar spine bone mineral density

The Applicant chose the 6-month timepoint for these bone mineral density comparisons with the intent to show more rapid increases with abaloparatide than teriparatide.

All spine x-rays and bone mineral density images were read blindly at a central facility. Source data pertaining to potential fractures were sent to the Applicant for blinded adjudication.

The Intent-to-Treat population included all randomized patients who received the randomization kit. This population was used for the bone mineral density analyses with imputation of missing data using the last-observation-carried-forward method, and for the secondary endpoint of nonvertebral fractures. The modified Intent-to-Treat population included all patients with pre-treatment and post-baseline evaluable spine x-rays, and comprised 85% of the randomized population. This population was used for the primary efficacy endpoint.

Abaloparatide- and placebo-treated patients who completed Study 003 could choose to participate in Study 005, an ongoing 24-month extension trial that switched all participants to open-label alendronate 70 mg orally once weekly starting one month after completion of Study 003, and continued calcium and vitamin D supplementation. Patients and investigators remained blinded to prior treatment assignment through the first six months.

The primary efficacy endpoint in Study 005 was the percentage of patients with at least one new morphometric vertebral fracture from the baseline visit of Study 003 through Month 25 of treatment. These 25 months encompass the 18-month treatment period of Study 003, one-month

of no treatment after completion of Study 003, and the first six months of Study 005. Key secondary endpoints included the percentage change from baseline to Month 25 in total hip, femoral neck, and lumbar spine bone mineral density, as well as the time to first incident nonvertebral fracture by Month 25. These secondary endpoints were tested sequentially to control the type I error rate.

The Intent-to-Treat population for Study 005 included all patients who enrolled into Study 005. This population was used for the bone mineral density analyses with imputation of missing data using the last-observation-carried-forward method, and for the secondary endpoint of nonvertebral fractures. The modified Intent-to-Treat population for Study 005 included all patients with pre-treatment and Month 25 evaluable spine x-rays, and comprised 98% of the patients who entered Study 005. This population was used for the primary efficacy endpoint.

Results: Study 003 randomized 824 patients to abaloparatide, 821 patients to placebo, and 818 patients to teriparatide. The completion rate was 74% for abaloparatide, 78% for placebo, and 80% for teriparatide. None of the teriparatide-treated patients entered Study 005. About 90% of the patients who completed treatment with abaloparatide or placebo in Study 003 entered Study 005, representing about 70% of the patients originally randomized to either abaloparatide or placebo in Study 003. About 94% of the patients who entered Study 005 were continuing at six months. The most common reason for discontinuation in both trials was adverse events.

In Study 003, all patients were postmenopausal women. The age range was 49-86 years (median 68 years), and about 18% were at least 75 years old. Approximately 80% of the patients were Caucasian and 16% were Asian. The median body mass index was 24.9 kg/m^2 (range 18.4-34.9 kg/m^2). Most patients were from Europe (56%) and South America (27%), and only 39 patients (1.6%) were from the United States. Nearly 50% of patients reported a history of at least one nonvertebral fracture. At baseline, the percentage of patients with imaging-confirmed vertebral fractures of T4-L4 was 24% based on central read. Baseline mean T-scores were -2.9 at the lumbar spine, -2.1 at the femoral neck, and -1.9 at the total hip.

Primary endpoint of new vertebral fracture: As shown in Table 2, the incidence of new vertebral fracture was significantly ($p<0.0001$) lower with abaloparatide compared to placebo in Study 003 (0.6% vs. 4.2%). Twelve patients with vertebral fractures at Month 18 (one treated with abaloparatide and 11 treated with placebo) did not enroll in Study 005. In the first six months of Study 005, seven of the patients previously treated with placebo and none of the patients previously treated with abaloparatide developed new vertebral fractures. The incidence of new vertebral fracture was significantly ($p<0.0001$) lower with abaloparatide then alendronate compared to placebo then alendronate through Month 25 in Study 003 plus Study 005 (0.6% vs. 4.4%). The corresponding absolute risk reductions were 3.6% in Study 003 and 3.9% through Month 25 in Study 003 plus Study 005. The corresponding relative risk reductions were 86% in Study 003 and 88% through Month 25 in Study 003 plus Study 005.

As expected, the trial was considerably underpowered to show an effect on hip fractures. There were only two hip fractures in Study 003 (both on placebo) and one additional hip fracture in Study 005 (placebo then alendronate arm).

Table 2. Primary Efficacy Endpoint: Incidence of First Vertebral Fracture (Adapted from Tables 6 and 9 in the Statistical Review)						
	Patients in Study 003 Only		Patients in Both Study 003 + Study 005			
			Baseline to Month 18		Baseline to Month 25	
	Abaloparatide N=690	Placebo N=711	Abaloparatide N=544	Placebo N=568	Abaloparatide/ Alendronate N=544	Placebo/ Alendronate N=568
n (%)	4 (0.6%)[1]	30 (4.2%)	3 (0.6%)[1]	19 (3.4%)	3 (0.6%)[1]	25 (4.4%)
p-value[1]	<0.0001		<0.0001		<0.0001	
Absolute risk reduction[2]	-3.6% (-5.4%, -2.1%)		-2.8% (-4.7%, -1.2%)		-3.9% (-5.9%, -2.1%)	
Relative risk reduction[2]	-86% (-95%, -61%)		-84% (-95%, -45%)		-88% (-96%, -60%)	
[1]p-value for abaloparatide vs. placebo from Fisher's exact test [2]95% confidence interval in parentheses						

Bone mineral density changes: As shown in Table 3, abaloparatide significantly (p<0.0001) increased bone mineral density over placebo at the total hip, femoral neck, and lumbar spine in Study 003. Abaloparatide then alendronate also significantly increased bone mineral density at all three sites compared to placebo then alendronate through Month 25 in Study 003 plus Study 005. The largest treatment effects on bone mineral density were seen at the lumbar spine.

As noted in the clinical review, the Applicant assessed bone mineral density of the mid-one-third of the radius in about 40% of patients. This site is of interest because it is comprised of cortical bone, and shows bone loss in patients with hyperparathyroidism who are exposed to chronic, endogenous excess PTH. As expected, abaloparatide caused numerically greater bone loss at this site than did placebo (mean percentage change in bone mineral density at Month 18 of -1.0% vs. -0.6%), although this difference was small and numerically fewer patients had wrist fractures on abaloparatide than placebo (7 vs. 13 patients).

Table 3. Bone Mineral Density Changes (Adapted from Tables 7 and 10 in the Statistical Review)								
	Study 003 (at Month 18)				Study 003 + Study 005 (at Month 25)[1]			
	Baseline	Percent Change from Baseline	LS Mean Difference from Placebo (95% CI)	p-value	Baseline	Percent Change from Baseline	LS Mean Difference from Placebo (95% CI)	p-value
Total Hip								
Abaloparatide	0.77	3.4	3.5 (3.3, 3.8)	<0.0001	0.77	5.4	4.1 (3.7, 4.5)	<0.0001
Placebo	0.77	-0.1			0.77	1.4		
Femoral Neck								
Abaloparatide	0.73	2.9	3.3 (3.0, 3.7)	<0.0001	0.73	4.5	4.1 (3.6, 4.6)	<0.0001
Placebo	0.73	-0.4			0.73	0.5		
Lumbar Spine								
Abaloparatide	0.83	9.2	8.7 (8.2, 9.2)	<0.0001	0.83	12.8	9.2 (8.6, 9.9)	<0.0001
Placebo	0.82	0.5			0.83	3.5		
[1]Comparisons for Study 003 + Study 005 are abaloparatide then alendronate vs. placebo then alendronate CI=confidence interval								

Nonvertebral fractures: In Study 003, the percentage of patients with at least one nonvertebral fracture was 2.2% with abaloparatide and 4.0% with placebo. Abaloparatide prolonged the time to first incidence of nonvertebral fracture compared to placebo (hazard ratio 0.57; 95% confidence interval 0.32, 1.00; log-rank p=0.049). Similar findings were seen with abaloparatide then alendronate compared to placebo then alendronate through Month 25 in Study 003 plus Study 005 (hazard ratio 0.48; 95% confidence interval 0.26, 0.89; log-rank p=0.02).

Comparisons to teriparatide: In Study 003, abaloparatide was superior to teriparatide on bone mineral density changes at the total hip and femoral neck at Month 6, but was not superior to teriparatide with regard to the time to first incidence of nonvertebral fracture (hazard ratio 0.79; 95% confidence interval 0.43, 1.45; log-rank p=0.44). These were the only prespecified comparisons to teriparatide that were controlled for type 1 error and analyzed according to the hierarchical statistical testing procedure.

Subgroup analyses: As discussed in the statistical review, analyses of the primary efficacy endpoint were consistent across tested subgroups based on age and region (South America vs. Europe). There were too few patients to reliably assess subgroup results in North America or Asia or among races other than Caucasians.

Study 003 randomized only 30 patients from the United States to abaloparatide or placebo, none of whom developed vertebral fractures. Twenty four of these patients were Hispanic or Latino. We asked the Applicant to justify why the data from Study 003 – with 98.4% of participants enrolled outside the United States – apply to the intended United States population.

To support applicability of the foreign data, the Applicant analyzed bone mineral density based on geographic region. As shown in Table 4, the increase in bone mineral density at the total hip, femoral neck, and lumbar spine was smaller among the 17 patients with evaluable data from the United States compared to patients from the other geographic regions. As discussed by the clinical reviewer, there are no clear explanations for this discrepancy.

Table 4. Bone Mineral Density Treatment Effects (Abaloparatide minus placebo with 95% Confidence Intervals) in Study 003 by Geographic Region (Adapted from Table 13 in the Statistical Review)

	United States N=17	**South America N=222**	**Europe N=458[1]**	**Asia N=125**
Total Hip	1.5 (-0.2, 3.2)	3.0 (2.4, 3.5)	3.8 (3.4, 4.1)	3.8 (3.2, 4.4)
Femoral Neck	0.4 (-2.2, 3.0)	2.7 (2.1, 3.2)	3.7 (3.3, 4.2)	3.4 (2.6, 4.1)
Lumbar Spine	4.3 (1.0, 7.6)	7.7 (6.7, 8.7)	9.2 (8.5, 9.9)	9.4 (8.1, 10.7)
N=459 for lumbar spine				

The Phase 2 dose-finding trial enrolled only 14 patients from the United States, which is also too limited to inform on bone mineral density changes among the subgroup of patients from the United States.

Based on the above considerations, I agree with the statistical team that there are too few patients from the United States to permit evaluation of efficacy in this subgroup from a statistical perspective. The statistical team states that generalizability of the efficacy results to the United States population is a clinical decision.

I agree with the clinical reviewer and Cross-Discipline Team Leader that the totality of the data support applicability of the foreign data to the intended population in the United States. In Study 003, there were similar pharmacokinetic exposures to abaloparatide between patients from the United States (mean abaloparatide AUC 1474 pg*hr/mL) and patients across 23 foreign sites (mean abaloparatide AUC 1463 pg*hr/mL). In addition, bone mineral density changes with abaloparatide compared to placebo were consistent across regions outside the United States (Table 4), despite demographic differences between those regions. Lastly, the limited bone mineral density data among the 17 patients from the United States who were mostly Hispanic do not mirror what was seen in South America where bone mineral density increases were larger and comparable among Hispanic and non-Hispanic patients.

Immunogenicity: Abaloparatide has the potential to elicit an immune response that could neutralize the drug and affect efficacy because it contains a 14 amino acid sequence that is not identical to any known primate proteins. The Applicant developed validated assays to assess for this possibility. Samples for immunogenicity analyses were collected at baseline and at Months 1, 3, 6, 12 and 18 in Study 003, and every six months until return to baseline levels in Study 005. Anti-abaloparatide antibodies developed in 49% of the 610 evaluated patients at Month 18, two-thirds of whom tested positive for neutralizing antibodies to abaloparatide. The incidence of anti-drug antibodies declined to 27% at Month 6 in Study 005. As discussed in the Clinical Review, patients who developed non-neutralizing or neutralizing antibodies to abaloparatide had similar changes in bone mineral density and a similar incidence of fractures compared to abaloparatide-treated patients who were antibody negative. Therefore, this high incidence of anti-abaloparatide antibodies does not appear to have a deleterious effect on efficacy.

8. Safety

This section focuses on the key safety findings from Study 003 (Study 005 did not involve administration of abaloparatide, and the Phase 1 and 2 trials were small). See the Clinical review and Cross-Discipline Team Leader memorandum for a detailed discussion of safety.

Exposures: A total of 1,349 patients received at least one dose of abaloparatide, 918 of whom received the to-be-marketed dose of 80 mcg, and 640 of whom were treated for at least one year. These exposures are adequate, and meet or exceed the recommendations in the International Conference on Harmonization E1A guideline which states that, for drugs to treat chronic, non-life-threatening conditions, there should be about 1,500 patients exposed, with at least 300-600 patients exposed for six months at dose levels intended for clinical use, and 100 patients exposed for a minimum of one year.

Deaths: In Study 003, there were three deaths with abaloparatide (0.4%), five deaths with placebo (0.6%) and three deaths with teriparatide (0.4%). In Study 005, there have been two

deaths in the abaloparatide then alendronate group and three deaths in the placebo then alendronate group. Therefore, the incidence of death was numerically higher with placebo in Study 003 and with placebo then alendronate in Study 005. In addition, the underlying causes of death do not raise any particular concerns (see the Clinical Review for details).

Serious Adverse Events: In Study 003, serious adverse events were reported in 10% of abaloparatide- and teriparatide-treated patients and 11% of placebo-treated patients. As shown in the Clinical Review, for each of the preferred terms, there were generally very small imbalances between treatment groups (typically differences of two or fewer patients) that do not raise any safety concerns. The largest numerical imbalance between treatment groups was between teriparatide and placebo for serious adverse events of breast cancer – six (0.7%) with teriparatide and one (0.1%) with placebo (there were three (0.4%) with abaloparatide). There was no signal for breast cancer in the Forteo NDA, suggesting that this numerical imbalance is likely a chance finding.

Discontinuations due to Adverse Events: In Study 003, 10% of abaloparatide-treated patients discontinued due to an adverse event compared to 6% with placebo and 7% with teriparatide. This difference was predominantly driven by discontinuations due to nausea, dizziness, headache and palpitations, although each of these adverse events led to discontinuation in fewer than 2% of abaloparatide-treated patients. Patients rarely discontinued abaloparatide due to hypercalcemia or hypotension.

Common Adverse Events: In Study 003, 89% of abaloparatide- and teriparatide-treated patients reported at least one adverse event compared to 88% of placebo-treated patients. Common adverse events (those occurring in more than 2% of abaloparatide-treated patients) that had the most notable separation from placebo (an incidence at least 2% higher than with placebo) included:

- Palpitations (5.1% with abaloparatide, 0.4% with placebo, 1.6% with teriparatide)
- Nausea (8.3% with abaloparatide, 3.0% with placebo, 5.1% with teriparatide)
- Dizziness (10.0% with abaloparatide, 6.1% with placebo, 7.3% with teriparatide)
- Hypercalciuria (11.3% with abaloparatide, 9.0% with placebo, 12.5% with teriparatide)

Palpitations, dizziness and hypercalciuria are discussed in greater detail below.

Adverse Events of Interest: Adverse events of interest based on animal findings, the mechanism of action, or prior findings with Forteo include:

Osteosarcoma: No cases of osteosarcoma were reported in Study 003 and 005. This is not surprising – even if abaloparatide increased the risk for osteosarcoma – given the rarity of the tumor. Nonetheless, like Forteo, there is potential for abaloparatide to cause osteosarcoma in humans based on the findings in rats. The Applicant proposed a communication plan Risk Evaluation and Mitigation Strategy (REMS), a Medication Guide and enhanced pharmacovigilance to mitigate this risk. For the reasons explained in Section 13 of this memorandum, I do not recommend a REMS for abaloparatide.

I agree with the review team's recommendation for enhanced pharmacovigilance that will run for 15 years, after which it will be reassessed. This plan has been reviewed by the Division of Pharmacovigilance within the Office of Surveillance and Epidemiology. It is designed to improve the quality of adverse event reports of osteosarcoma cases associated with abaloparatide through the use of a targeted osteosarcoma questionnaire (b) (4) This plan will also require expedited reporting (15-day) of possible cases (based on a prespecified list of MedDRA preferred terms) and a yearly analysis of potential reports.

I do not recommend any required postmarketing studies for abaloparatide based on our experience with the Forteo required postmarketing studies that are attempting to assess osteosarcoma risk in humans. (b) (4)

(b) (4)

(b) (4) I do not recommend any required postmarketing studies for abaloparatide.

Hypercalcemia: Forteo can cause hypercalcemia, and is labeled with a Warning and Precaution stating that patients with hypercalcemic disorders have not been studied and should not receive the product.

Abaloparatide can also cause hypercalcemia. In a Phase 1 study, the Applicant determined that the peak serum calcium most commonly occurs four hours post-dose, with return to near baseline concentrations at 12-24 hours post-dose.

In Study 003, patients were required to have normal serum calcium at baseline (patients with minor elevations could be enrolled if the ionized serum calcium was normal). Serum calcium was then measured at each visit predose and at four hours post-dose. The post-dose serum calcium increased, on average, by 0.2-0.4 mg/dL from baseline with abaloparatide and by 0.2-0.5 mg/dL with teriparatide. The Applicant also analyzed the percentage of patients with at least one albumin-corrected serum calcium ≥10.7 mg/dL (≥0.3 mg/dL above upper limit of normal). The percentage of patients meeting this criterion was 3.4% with abaloparatide, 6.4% with teriparatide, and 0.4% with placebo. The highest reported serum calcium concentration was 11.9 mg/dL for abaloparatide, 12.7 mg/dL for teriparatide and 11.1 mg/dL for placebo. Two abaloparatide- and four teriparatide-treated patients discontinued due to hypercalcemia. Calcium

supplements were reduced or stopped due to hypercalcemia in 1.7% of abaloparatide-treated patients and 3.2% of teriparatide-treated patients.

Like with Forteo, this risk with abaloparatide can be managed with labeling.

Hypercalciuria: Forteo can increase urinary calcium, although the trials showed a similar incidence of hypercalciuria (>300 mg urinary calcium/day) with Forteo and placebo, and a similar incidence of urolithiasis. A Warning and Precaution in the Forteo labeling recommends caution in patients with active or recent urolithiasis and measurement of urinary calcium excretion if hypercalciuria is suspected.

Study 003 excluded patients with nephrolithiasis or urolithiasis within the previous five years then assessed 24-hour urinary calcium excretion at each clinic visit. At baseline, the mean 24-hour urine calcium/creatinine ratio was about 210 mg/g. Mean increases with abaloparatide were small (up to 14 mg/g). There were numerically larger mean increases with teriparatide (up to 39 mg/g) and mean reductions with placebo (up to 7 mg/g). The percentage of patients with a calcium/creatinine ratio above 300 mg/g was 46% with abaloparatide, 54% with teriparatide and 36% with placebo. As noted in the Clinical Review, the hypercalciuria may have contributed to a slight imbalance in the incidence of urolithiasis (2.1% with abaloparatide, 2.3% with teriparatide and 1.7% with placebo based on the MedDRA High Level Group Term "Urolithiases"). Most of the patients with nephrolithiasis or nephrocalcinosis (13/16 with abaloparatide, 14/17 with teriparatide, and 5/12 with placebo) had at least one documented episode of hypercalciuria (>300 mg/g creatinine) during the trial.

Like with Forteo, this risk with abaloparatide can be managed with labeling.

Hyperuricemia: Hyperuricemia is a known adverse effect of Forteo, and also occurs with abaloparatide. As noted in the Clinical Review, mean uric acid concentrations increased about 20% from baseline with both abaloparatide and teriparatide, and were unchanged with placebo. Among patients with normal uric acid concentrations at baseline, at least one elevated concentration occurred in 25% of abaloparatide-treated patients, 30% of teriparatide-treated patients, and 6% of placebo-treated patients. These increases in uric acid did not increase the incidence of gout (one patient per treatment group) but might have contributed to the slight imbalance in urolithiasis discussed above if some of the patients experienced uric acid stones, although this is difficult to ascertain because other factors (e.g., hypercalciuria) might have led to this minor imbalance.

Like with Forteo, this risk with abaloparatide can be managed with labeling.

Blood Pressure and Heart Rate Changes: Abaloparatide, like Forteo, can cause a transient post-dose decrease in blood pressure or increase in heart rate, which can cause orthostatic hypotension, dizziness, palpitations or tachycardia.

Patients with orthostatic hypotension were excluded from Study 003. Orthostatic blood pressure measurements were then obtained pre-dose and at 60 minutes post-dose. At each visit, heart rate

was assessed pre-injection (with other vital signs) and post-injection (on electrocardiograms obtained pre-dose and one hour post-dose).

In Study 003, the percentage of patients with at least one episode of orthostatic hypotension (defined as a blood pressure decline of ≥20 mmHg systolic or ≥10 mmHg diastolic) one-hour post-dose was 17.1% with abaloparatide, 16.4% with placebo and 15.5% with teriparatide. In addition, there were numerical imbalances in some adverse events that could be consistent with orthostatic hypotension (e.g., dizziness, nausea) as well as increases in heart rate (see below). The Clinical Reviewer notes that in many cases, these types of symptoms were reported within a few minutes to a few hours post-dose, with standing systolic blood pressure in the 60 mmHg range in some cases, and that more abaloparatide-treated patients discontinued due to these types of events compared to placebo or teriparatide. In addition, data from earlier studies also support the potential for orthostatic hypotension. For example, in the Phase 2 dose-finding trial, the percentage of patients with orthostatic hypotension, as defined above, was 31% with abaloparatide 80 mcg, 36% with teriparatide and 20% with placebo.

In Study 003, there were no meaningful changes from baseline in heart rate based on the pre-dose measurements. However, based on the electrocardiogram data obtained at one hour post-dose, there was a median increase from baseline (prior to the first dose) in heart rate of 6-8 beats per minute with abaloparatide, 5-6 beats per minute with teriparatide and 1-2 beats per minute with placebo. The percentage of patients who had an increase of more than 10 beats per minute in heart rate from pre-dose to one-hour post-dose based on the electrocardiogram data was 68% with abaloparatide, 59% with teriparatide, and 30% with placebo. The corresponding percentages for an increase of more than 20 beats per minute was 20%, 11%, and 3%, and the corresponding percentages for an increase of more than 30 beats per minute was 4%, 1% and 0%.

These data in Study 003 probably underestimate the maximal post-dose increase in heart rate with abaloparatide. The Thorough QT Study obtained electrocardiograms at earlier timepoints after dosing (15 minutes, 30 minutes, 45 minutes) as well as one hour post-dose and at additional timepoints to 24 hours post-dose. In that study, the median heart rate increase with the 80 mcg dose was greatest at 15 minutes after dosing (15 beats per minute), then declined but remained notably increased over baseline at 30 minutes (13 beats per minute), 45 minutes (11 beats per minute) and one-hour timepoints (9 beats per minute). In the placebo arm, the median heart rate changes were 0-1 beats per minute at these timepoints.

These heart rate changes did not appear to precipitate angina, as the incidence of the MedDRA High Level Term of Ischemic Coronary Artery Disorders in Study 003 was similar across treatment groups (0.9% with abaloparatide, 1.1% with teriparatide and 1.0% with placebo), as was serious adverse events within the High Level Group Term of Coronary Artery Disorders (0.4% with abaloparatide, 0.4% with teriparatide, and 0.5% with placebo). Imbalances, however, were noted for rate and rhythm disorders (1.8% with abaloparatide, 1.2% with teriparatide and 1.0% with placebo), driven predominantly by differences in the incidence of tachycardia (1.3% with abaloparatide, 0.7% with teriparatide, and 0.4% with placebo), and not due to an imbalance in the incidence of supraventricular or ventricular arrhythmias. While these findings are reassuring, it is important to note that the trials did not enroll many patients with pre-existing

coronary artery disease. Such patients could be more vulnerable to adverse effects from tachycardia (e.g., demand myocardial ischemia).

Like with Forteo, this risk with abaloparatide can be managed with labeling.

Tissue Mineralization: The Applicant obtained Month 18-19 renal CT scans in 208 patients at selected sites in Study 003 to assess for nephrocalcinosis. An additional 133 patients underwent renal CT scans at baseline and study end. As shown in the Clinical Review, the number of patients with post-treatment urinary tract calcifications was similar across treatment groups. The ability of these scans to assess tissue mineralization is unclear, but it is somewhat reassuring that there were no meaningful changes in renal function in any of the treatment groups over the course of the trial.

Other Safety Findings:

Immunogenicity: Abaloparatide could potentially elicit an immune reaction because of its foreign amino acid sequence. In Study 003, there were no reports of anaphylaxis or angioedema, but slight imbalances of pruritis (15 patients on abaloparatide, 8 patients on teriparatide and 9 patients on placebo) and urticaria (3 patients with abaloparatide, 5 patients with teriparatide, and 1 patient with placebo).

Antibodies to abaloparatide could also potentially cross-react and neutralize endogenous PTHrP or PTH. This could potentially lead to hypoparathyroidism, with hypocalcemia and hyperphosphatemia. The Applicant developed adequately validated assays to assess for cross-reactivity to PTHrP and PTH. None of the abaloparatide-treated patients developed cross-reactivity to PTH. However, at Month 18 in Study 003, seven of the 297 evaluable patients with anti-abaloparatide antibodies (2.4%) had developed cross-reactive antibodies to PTHrP. There was no apparent effect of these cross-reactive antibodies on calcium homeostasis.

The immunogenicity review team noted that the Applicant's immunogenicity testing scheme might have under-reported anti-drug antibodies at timepoints before Month 18 in Study 003. This is because patients who tested negative for anti-drug antibodies at Month 18 were not analyzed for anti-drug antibodies at earlier timepoints, and could have had transient antibodies during the course of treatment. While the existing data are sufficient for approval, the immunogenicity review team recommends additional testing of samples for anti-drug antibodies as a postmarketing commitment. This is reasonable and is summarized further under Section 13.

Injection Site Reactions: During the first month of treatment, the Applicant assessed injection site reactions daily one-hour after dosing. Injection site redness was common, reported in 58% of abaloparatide-treated patients, 64% of teriparatide-treated patients and 28% of placebo. Less common injection site reactions during this first month included edema (10% with abaloparatide and teriparatide compared to 3% with placebo), pain (9% with abaloparatide, 8% with teriparatide and 7% with placebo), and tenderness (12% with abaloparatide, 11% with teriparatide and 7% with placebo). Severe reactions were uncommon (severe redness occurred in fewer than 3% of patients; severe swelling, pain or tenderness each occurred in fewer than 0.5% of patients).

Bone Histomorphometry: The Applicant obtained transiliac bone biopsies with tetracycline labeling in 105 patients in Study 003 between months 12-18, and analyzed these data blinded to treatment. These biopsies did not raise safety issues as none of the 78 evaluable specimens had marrow fibrosis, woven bone, osteomalacia or a mineralization defect.

9. Advisory Committee Meeting

This application was not taken to advisory committee. We did not identify efficacy or safety issues requiring input from an advisory panel.

10. Pediatrics

This Application triggers the Pediatric Research Equity Act (PREA) because of the new active ingredient. The Pediatric Review Committee agreed with a full waiver. Pediatric studies would be impossible because postmenopausal osteoporosis does not occur in children.

11. Other Relevant Regulatory Issues

Trade Name: The Division of Medication Error Prevention and Analysis (DMEPA) has concluded that the proposed trade name "Tymlos" is acceptable. See their review for details.

Inspections: The Office of Study Integrity and Surveillance (OSIS) inspected the bioanalytical portion of the pivotal bioequivalence study conducted to bridge abaloparatide administered with the pen injector used in the Phase 3 trials to the to-be-marketed product. The inspector issued an FDA Form 483 because of issues with the quality control samples and wider limits for accepting bioanalytical runs than recommended in FDA guidance. These issues impacted one of the runs in the audited study. However, the two products remained bioequivalent even after excluding the data from this run. See the OSIS memorandum for further details.

The Office of Scientific Investigations inspected the Applicant and four clinical sites. The Applicant was classified as Voluntary Action Indicated (VAI) because the transfer of obligations to a contract research organization was not described in writing for Study 003 and some clinical sites screened patients prior to approval of the monitoring guidelines. The Office of Scientific Investigations concluded that these deficiencies do not preclude use of the data to support the efficacy and safety assessment of abaloparatide. The four clinical sites were all classified as No Action Indicated (NAI). (b) (4) (Dr. Hala in the Czech Republic who randomized 290 (12%) patients in Study 003 and 136 patients in Study 005) and noted discrepancies between documents at the clinical site and medical records from the referring hospital. These discrepancies could have impacted patient eligibility for the trial. As shown in the Cross-Discipline Team Leader Memorandum, exclusion of data from this site did not change the efficacy conclusions.

Human Factors: In the Human Factors validation study, some subjects failed to prime the pen prior to use or unnecessarily re-primed the pen with subsequent use. Some patients also experienced needlestick injuries because of difficulty removing the needle from the device. We raised these concerns during the review cycle, prompting the Applicant to revise the Instructions for Use and conduct another validation study. This second study continued to identify failures related to the priming step and needlestick injury with removal of the needle. The priming errors appeared to be related to confusion with the stop sign symbol in the Instructions for Use, and the needlestick injuries appeared to be related to confusion with the instructions and graphics for removal of the needle. The Applicant made further edits to clarify these sections of the Instructions for Use. DMEPA found these revisions to be adequate without the need for additional validation testing. DMEPA also reviewed the Applicant's Use Related Risk Analysis to ensure that the revisions did not introduce new risks. See the DMEPA reviews for further details.

12. Labeling

Abaloparatide has a similar safety profile to Forteo and, therefore, the approach to labeling will be similar to that for Forteo, including an indication narrowed to patients at high risk of fracture, inclusion of a Boxed Warning for osteosarcoma, and Warnings and Precautions for orthostatic hypotension, hypercalcemia, and hypercalciuria. Because abaloparatide and Forteo each carry a risk for osteosarcoma, labeling will state that the cumulative lifetime use of abaloparatide (b) (4) (b) (4). This recommendation will be incorporated into the Boxed Warning, and (b) (4).

The Applicant proposed to include the (b) (4) However, I agree with the review team not to do sc (b) (4)

The Prescribing Information has been reviewed by all scientific disciplines for accuracy and by our Associate Director for Labeling for consistency with the Physician's Labeling Rule format. The Carton and Container labeling has been reviewed by DMEPA for areas of vulnerability that could lead to medication errors. The Medication Guide and Instructions for Use have been reviewed by the Division of Medical Policy Programs to ensure consistency with the Prescribing Information and readability for the layperson. We have also addressed comments from the Office of Prescription Drug Promotion that ensure labeling is not promotional. All outstanding labeling issues have been resolved. See the labeling reviews for details.

13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

Osteosarcoma is the only identified risk with abaloparatide that could potentially rise to the level of needing a REMS. Forteo has a REMS to mitigate the risk of osteosarcoma that includes a communication plan and Medication Guide. The Forteo REMS warns healthcare providers and patients about the risk of osteosarcoma, informs healthcare providers about the two-year maximum lifetime duration of use and proper patient selection, and informs healthcare providers and patients about the voluntary patient registry. The Division of Risk Management has determined that the Forteo REMS has met its goals, and that the level of knowledge about osteosarcoma has remained stable over time even though the Forteo communication plan ended in 2011. The most recent Forteo REMS assessment showed that almost all (97%) of the sampled health care providers who had prescribed Forteo were aware of the potential risk for osteosarcoma and 89% were aware of the two-year maximum lifetime duration of use. Drug utilization data show that only about 3-5% of patients use Forteo for longer than two years. Therefore, I agree with the Division of Risk Management that the Forteo REMS is no longer needed because there is good awareness of the osteosarcoma risk, and that the benefits of Forteo should continue to outweigh its risks with labeling alone (a narrowed indication, a Boxed Warning and Medication Guide). We will be discontinuing the Forteo REMS around the time we approve abaloparatide.

I also agree with the Division of Risk Management that a REMS is not needed to ensure that the benefits of abaloparatide outweigh the risk of osteosarcoma. Although abaloparatide and Forteo are technically in different classes (abaloparatide is a PTHrP analog whereas Forteo is a PTH analog), both drugs have similar mechanisms of action, both share the same narrowed indication, both cause osteosarcoma in rats with uncertain relevance to humans, both have similar adverse effects, and both are expected to be used by a similar prescribing population. As we have determined that a REMS is no longer necessary for Forteo, so too is it reasonable to conclude that labeling alone should be sufficient to ensure that the benefits of abaloparatide outweigh its risks. Therefore, I do not recommend a REMS for abaloparatide.

- Other Postmarketing Requirements and Commitments

We are requesting a postmarketing commitment to more comprehensively assess the extent to which anti-drug antibodies develop during the course of treatment with abaloparatide. The Applicant agrees with this request and with the associated timelines for completing the protocol and submitting the results for review. We are asking the Applicant to test existing samples from Study 003 for anti-drug antibodies (b) (4) This will include an assessment of cross-reactivity to PTHrP and PTH. This is not a required postmarketing study because we have not identified a serious safety concern based on the existing immunogenicity data.

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/s/

HYLTON V JOFFE
04/27/2017