CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office Director Decisional Memorandum

Date	April 27, 2017
From	Julie Beitz, MD
Subject	Office Director Decisional Memo
NDA #	208743
Applicant Name	Radius Health, Inc.
Date of Submission	March 30, 2016
PDUFA Goal Date	March 30, 2017; Extended to June 30, 2017
Proprietary Name / Established (USAN) Name	Tymlos (abaloparatide)
Dosage Forms / Strengths	Subcutaneous Injection by single-patient-use prefilled pen, 80 mcg delivered in 40mcL
Proposed Indication	Indicated for the 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. In postmenopausal women with osteoporosis, Tymlos reduces the risk of vertebral fractures and non-vertebral fractures.
Recommended Action:	Approval

Materials Reviewed/Consulted OND Action Package, including reviews from:	**Discipline Reviewers**
DBRUP / Medical Officer	Stephen Voss, MD
DBRUP / Medical Team Leader	Theresa Kehoe, MD
DBRUP / Pharmacology / Toxicology	Gemma Kuijpers, PhD / Mukesh Summan, PhD
DBRUP / Division Director	Hylton Joffe, MD
OB / Division of Biometrics III	Jia Guo, PhD / Mahboob Sobhan, PhD
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OSE / Division of Epidemiology II	Jie Li, PhD / Wei Liu PhD, MSc / CAPT David Money, RPh, MPH, USPHS
OSE / Division of Pharmacovigilance II	Samantha Cotter, PharmD, BCPS, FISMP / Neha Gada, PharmD, BCPS
OSE / Division of Risk Management	Jacqueline Sheppard, PharmD / Jamie Wilkins Parker, PharmD / Cynthia LaCivita, PharmD
OSE / DMEPA	Walter Fava, RPh, MSEd
Office of Scientific Investigations	Roy Blay, PhD

DBRUP = Division of Bone, Reproductive and Urologic Products
OB = Office of Biostatistics
OCP = Office of Clinical Pharmacology
DMEPA = Division of Medication Error Prevention and Analysis
OND = Office of New Drugs
OSE = Office of Surveillance and Epidemiology

1. Benefit-Risk Summary and Assessment

Tymlos (abaloparatide) is a synthetic human parathyroid hormone related peptide [(PTHrP(1-34)] analog which acts as an agonist at the PTH type 1 receptor (PTH1R) to activate the cAMP signaling pathway in target cells. In animal models of postmenopausal osteoporosis, abaloparatide had an anabolic effect on bone, demonstrated by increases in bone mineral density and bone mineral content that correlated with increases in bone strength at vertebral and/or non-vertebral sites.

Osteoporosis is the most common bone disease and represents a growing public health problem as the population ages. Reduction of fracture risk is the main goal of treatment for osteoporosis. Although several treatments for postmenopausal osteoporosis are commercially available in the U.S., additional therapeutic options are needed, particularly for women who do not respond to, or tolerate, existing treatments. Tymlos (abaloparatide) would offer an FDA-approved, safe and effective, alternative anabolic treatment for postmenopausal women *at high risk of fracture*.

I concur with the recommendation of the Division of Bone, Reproductive and Urologic Products to approve Tymlos (abaloparatide) for the treatment of postmenopausal women with osteoporosis *at high risk for fracture*. The recommended dose is 80 mcg taken subcutaneously once daily. Supplemental calcium and vitamin D should be taken if dietary intake is inadequate.

An FDA Advisory Committee Meeting was not held to discuss this application because the application did not raise significant safety or efficacy issues that were unexpected for a drug in this class.

Efficacy. Data submitted in the NDA supported the efficacy and safety of Tymlos (abaloparatide). Efficacy was established in postmenopausal women with osteoporosis randomized to receive 18 months of abaloparatide or placebo, followed by 6 months of alendronate. The assumption that PTH1R agonists have anabolic effects on bone that result in reduction of new vertebral and non-vertebral fractures and increases in bone mineral density has been borne out by the submitted clinical trial of abaloparatide. Qualitative and quantitative histology assessment of evaluable bone biopsy specimens confirmed normal bone architecture. I concur that the observed reductions in fracture risk with abaloparatide were statistically superior to placebo and that abaloparatide administration meets the primary goal of osteoporosis treatment, namely to reduce fracture risk. The absolute risk reduction of 3.6% for vertebral fracture with abaloparatide suggests that about 1 woman in 20 with postmenopausal osteoporosis will avoid a serious fracture with use of the drug.

Safety. The safety profile of Tymlos (abaloparatide) is similar to that of another PTH1R agonist, Forteo (teriparatide). In postmenopausal

women with osteoporosis, treatment with abaloparatide was generally well tolerated. During the 18-month double-blind, placebo-controlled trial period, adverse reactions occurring more frequently in women treated with abaloparatide relative to placebo included: hypercalciuria, dizziness, nausea, headache, and palpitations. The most common adverse reactions leading to treatment discontinuation in the abaloparatide group were nausea, dizziness, headache, and palpitations.

The prescribers of Tymlos (abaloparatide) will likely be general practitioners and rheumatologists familiar with the need to reduce fracture risk in postmenopausal women with osteoporosis, and with the attendant risks of available treatments for osteoporosis, including those associated with teriparatide. The following serious safety risks have been associated with use of abaloparatide, as well as teriparatide, and can be adequately communicated in product labeling: 1) risk of osteosarcoma, 2) orthostatic hypotension, 3) hypercalcemia, and 4) hypercalciuria and urolithiasis.

In a 2-year carcinogenicity study, abaloparatide caused a dose-dependent increase in the incidence of osteosarcoma in male and female rats. It is unknown whether Tymlos (abaloparatide) will cause osteosarcoma in humans. To date, no signal for osteosarcoma has been identified in the postmarketing experience with teriparatide. Because of the uncertainty about this risk, abaloparatide should be reserved (as is teriparatide) for women with postmenopausal osteoporosis who are *at high risk for fracture*, based on a history of fracture or multiple risk factors for fracture. In addition, cumulative use of abaloparatide and other PTH1R agonists should not exceed 2 years during a patient's lifetime. I concur with the inclusion of a Boxed Warning recommending against the use of abaloparatide in patients at increased risk of osteosarcoma including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, open epiphyses, bone metastases, skeletal malignancies, hereditary disorders predisposing to osteosarcoma, or prior external beam or implant radiation therapy involving the skeleton.

Given the reported cases of orthostatic hypotension, I concur with the inclusion of a Warning in product labeling regarding this risk and with the recommendation that the first several doses of Tymlos (abaloparatide) be administered where the patient can sit or lie down.

Hypercalcemia can be expected to result from the effects of Tymlos (abaloparatide) on calcium metabolism. I concur with the inclusion of a Warning in the product labeling for abaloparatide regarding the risk of hypercalcemia, and with the recommendation that patients with pre-existing hypercalcemia or hypercalcemic disorders, such as primary hyperparathyroidism, not take the product because of the possibility of exacerbating hypercalcemia.

Tymlos (abaloparatide) may cause hypercalciuria. It is unknown whether abaloparatide may exacerbate urolithiasis in patients with active or pre-existing urolithiasis. I concur with the inclusion of a Warning in product labeling for regarding these risks, and with the recommendation that measurement of urinary calcium excretion be considered in patients with active urolithiasis or with pre-existing hypercalciuria.

A Risk Evaluation and Mitigation Strategy (REMS) will not be required for Tymlos (abaloparatide) to ensure that the benefits of the drug outweigh the risks. A Medication Guide will be required as part of approved labeling to provide important safety information to patients. Enhanced pharmacovigilance will be conducted in the postmarketing setting to improve the quality of spontaneous reports of osteosarcoma potentially associated with abaloparatide use. The results of the applicant's postmarketing study commitments will further inform product labeling regarding the immunogenicity of abaloparatide.

Dimension	Evidence, Uncertainties and Conclusions
Analysis of Condition	Osteoporosis is the most common bone disease and represents a growing public health problem as the population ages.[1] Osteoporosis is characterized by low bone mass, deterioration of bone tissue and disruption of bone architecture, compromised bone strength, and an increased risk of fractures, most commonly in the spine, hip and wrist. Osteoporosis is a multifactorial disease which has a complex pathophysiology involving genetic, endocrine, and nutritional factors. Several hormones are involved in bone health, including PTH, calcitonin, estrogen and vitamin D. An estimated 10.2 million U.S. adults aged 50 years and older had osteoporosis in 2010 and 43.4 million had low bone mass. Although most adults with osteoporosis or low bone mass were non-Hispanic white women, a substantial number of men and women from other racial and ethnic groups had osteoporosis or low bone mass.[2] In older Americans, osteoporosis is the most common cause of bone fracture; these fractures typically result from minimal injury. The clinical and economic burden of these fractures has been evaluated in a number of retrospective studies characterizing inpatient and/or ambulatory healthcare utilization, costs, and outcomes. A recent study of hospitalizations for osteoporosis-related fractures in individuals 50 years of age and older found that hip fractures accounted for 50% of hospital admissions, followed by vertebral fractures (14%). Femoral fractures accounted for only 5% of hospital admissions but were found to have the highest mean total cost and the longest hospital stay (5.8 days). Of note, while nearly 75% of individuals

[1] Bone Health and Osteoporosis: A Report of the Surgeon General. Office of the Surgeon General (US), Rockville (MD); 2004. Accessed March 2017 at http://www.ncbi.nlm.nih.gov/books/NBK45513/

[2] Wright NC, Looker AC, Saag KG, Curtis JR, Delzell ES, Randall S, Dawson-Hughes B. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. *J Bone Miner Res* 2014 Nov; 29(11):2520-2526.

Dimension	Evidence, Uncertainties and Conclusions
	were admitted from non-healthcare facilities, 53% were discharged to a skilled/long-term care facility and 14% were discharged to a rehabilitation facility.[3] ***Comment.*** Hospitalization, immobility, receipt of anesthesia, and fluid replacement can exacerbate underlying medical conditions (e.g., cardiovascular disease) or cause new ones to develop, such as thrombotic complications in patients with hip fractures. Fractures also can compound the pain experienced by patients, especially those with pre-existing musculoskeletal conditions, and lead to loss of muscle mass/strength, a need for extended physical therapy or admission to skilled nursing facilities. The availability of Tymlos (abaloparatide) would offer an FDA-approved, safe and effective alternative anabolic agent for the treatment of postmenopausal women with osteoporosis *at high risk for fracture*.
Current Treatment Options	Reduction of fracture risk is the primary goal of treatment for osteoporosis. The World Health Organization has developed an individual patient model known as FRAX to calculate individual fracture risk identifying patients at higher risk of fracture based on clinical risk factors and femoral neck bone mineral density. Treatment for postmenopausal women with osteoporosis is highly individualized. Lifestyle modifications include calcium and vitamin D supplementation, weight bearing activity, avoiding or stopping smoking, avoiding heavy alcohol consumption, and limiting caffeine intake. Pharmacological agents include anti-resorptive and anabolic agents. The primary action of anti-resorptive agents is to reduce bone resorption by inhibiting the activity of osteoclasts and include calcitonin formulations, bisphosphonates, selective estrogen-receptor modulators (e.g., raloxifene), and denosumab (a human IgG2 monoclonal antibody that inhibits RANK ligand). Anabolic agents can result in new bone formation by stimulating the function of osteoblasts. In 2002, FDA approved the first anabolic agent, Forteo (teriparatide), a recombinant human PTH analog (1-34), [rhPTH(1-34)]. Teriparatide regulates calcium metabolism by binding to the PTH1R. In monkey studies, teriparatide improved trabecular microarchitecture and increased bone mass and strength by stimulating new bone formation in both cancellous and cortical bone. In humans, the

[3] Weycker D, Li X, Barron R, Bornheimer R, Chandler D. Hospitalizations for osteoporosis-related fractures: Economic costs and clinical outcomes. *Bone Reports* 2016 (5): 186-191.

Dimension	Evidence, Uncertainties and Conclusions
	anabolic effects of teriparatide manifest as an increase in skeletal mass, an increase in markers of bone formation and resorption, and an increase in bone strength.[4] Because teriparatide caused an increase in the incidence of osteosarcoma in rats that was dependent on dose and treatment duration, teriparatide was indicated for the treatment of postmenopausal women *at high risk of fracture* and use of the drug for more than 2 years during a patient's lifetime was not recommended. At the time of approval, a Risk Minimization Action Plan was implemented to mitigate the risk of osteosarcoma. In 2009, a REMS was required, in part because a new approved indication (glucocorticoid-induced osteoporosis) was expected to expand the indicated population to include younger patients who may have a higher osteosarcoma risk, and because postmarketing studies had failed to resolve the uncertainty regarding risk to humans. Patients were also encouraged to enroll in the voluntary Forteo Patient Registry designed to collect information about any potential risk of osteosarcoma with use of the drug. Tymlos (abaloparatide) is a synthetic human PTH related peptide [PTHrP(1-34)] analog. Like teriparatide, abaloparatide acts as an agonist at the PTH1R and has demonstrated anabolic effects in nonclinical studies of postmenopausal osteoporosis. The drug also demonstrated dose-dependent increases in osteosarcoma in a 2-year rat carcinogenicity study. ***Comment.*** Although several treatments for postmenopausal osteoporosis are commercially available in the U.S., additional therapeutic options are needed, particularly for women who do not respond to, or tolerate, existing treatments. Tymlos (abaloparatide) would offer an FDA-approved, safe and effective, alternative anabolic treatment for postmenopausal women *at high risk of fracture*.
Benefit	The efficacy of Tymlos (abaloparatide) was established in a single randomized, double-blind, placebo-controlled clinical trial (Study BA058-05-003, hereafter referred to as Study 003) involving postmenopausal women with osteoporosis. Subjects were randomized 1:1 to either abaloparatide 80 mcg or placebo, administered subcutaneously once daily for 18 months (824 on abaloparatide and 821 on placebo).[5] The mean age of participants was 69 years and 80% were white. At baseline, mean T scores were: -2.9 at the lumbar spine, -2.1 at the femoral neck, and -1.9 at the total hip. Twenty-four percent had at least one

[4] *See* Forteo (teriparatide) Prescribing Information.
[5] A third group of 818 subjects was randomized to receive Forteo (teriparatide) 20 mcg administered subcutaneously once daily. The baseline characteristics of this group were similar to those of the abaloparatide and placebo groups; there were 9 U.S. subjects in this group.

Dimension	Evidence, Uncertainties and Conclusions
	prevalent vertebral fracture and 48% had at least one prior non-vertebral fracture. Subjects took daily supplemental calcium and vitamin D. After 18 months, 92% of study completers received no treatment for one month, then open-label treatment with alendronate 70 mg weekly, with calcium and vitamin D supplements, for 6 months (558 previously on abaloparatide and 581 previously on placebo). U.S. subjects were under-represented in this trial, with only 17 U.S. subjects randomized to abaloparatide and 13 to placebo. The primary efficacy endpoint was the incidence of new vertebral fractures in subjects treated with abaloparatide compared to placebo. At 18 months, the incidence of new vertebral fractures was 0.6% among abaloparatide-treated subjects vs. 4.2% among placebo-treated subjects, for an absolute risk reduction of 3.6% (95% CI: 2.1, 5.4). At 25 months, the incidence of new vertebral fractures was 0.6% among subjects treated with abaloparatide followed by alendronate, vs. 4.4% among subjects treated with placebo followed by alendronate, for an absolute risk reduction of 3.9% (95% CI: 2.1, 5.9). At both time points, the reduction in new vertebral fractures for abaloparatide-treated subjects was statistically superior to that for placebo-treated subjects. In addition, subjects who received abaloparatide had statistically significant reductions in non-vertebral fractures (absolute risk reduction of 2%), and increases in bone mineral density at the lumbar spine, total hip and femoral neck. The reductions in the risk of vertebral and non-vertebral fractures, and the increases in bone mineral density, were observed regardless of age, years since menopause, presence or absence of prior fracture, and bone mineral density at baseline. In evaluable bone biopsy specimens (27 in the abaloparatide group and 28 in the placebo group), normal bone architecture was observed, and there was no evidence of woven bone, marrow fibrosis, or mineralization defects after 12-18 months of treatment. ***Comment.*** The efficacy of Tymlos (abaloparatide) has been established in postmenopausal women with osteoporosis randomized to receive 18 months of abaloparatide or placebo, followed by 6 months of alendronate. The assumption that PTH1R agonists have anabolic effects on bone that result in reduction of new vertebral and non-vertebral fractures and increases in bone mineral density has been borne out by the submitted clinical trial of abaloparatide. Qualitative and quantitative histology assessment of evaluable bone biopsy specimens confirmed normal bone architecture. The absolute risk reduction of 3.6% for vertebral fracture with abaloparatide treatment indicates that about 1 woman in 20 with postmenopausal osteoporosis will avoid a serious fracture with use of the drug. I concur that the observed reductions in fracture risk with abaloparatide were statistically superior to placebo and that abaloparatide administration meets the primary goal of

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	osteoporosis treatment, namely to reduce fracture risk. Although U.S. subjects were under-represented in Study 003 and none experienced a fracture, increases in bone mineral density with abaloparatide use were noted in all geographic regions, and pharmacokinetic analyses showed comparable exposures in U.S. and non-U.S subjects. I concur that it is reasonable to conclude that the abaloparatide efficacy findings in Study 003 are applicable to postmenopausal women with osteoporosis in the U.S.
Risk	**General Considerations.** Following subcutaneous administration, the median time to peak concentration of abaloparatide 80 mcg was 0.5 hr. The absolute bioavailability of abaloparatide in healthy women after subcutaneous administration of an 80 mcg dose was 36%. The mean half-life of abaloparatide was 1.7 hrs. The metabolism of abaloparatide is consistent with non-specific proteolytic degradation into smaller peptide fragments, followed by elimination by renal clearance. *In vitro* studies showed that abaloparatide, at therapeutic concentrations, does not inhibit or induce cytochrome P450 enzymes. No dosage adjustment is required for patients with mild, moderate or severe renal impairment. However, patients with severe renal impairment may have increased abaloparatide exposures that may increase the risk of adverse reactions. Abaloparatide is not indicated for use in females of reproductive potential. There are no human data on abaloparatide use in pregnant women to inform any drug associated risks. Animal reproduction studies with abaloparatide have not been conducted. There is no information on the presence of abaloparatide in human milk, the effects on the breastfed infant, or the effects on milk production. The safety and effectiveness of abaloparatide have not been established in pediatric patients. Abaloparatide is not recommended for use in pediatric patients with open epiphyses or hereditary disorders predisposing to osteosarcoma. In clinical trials, 82% and 19% of abaloparatide-exposed subjects were 65 years and over or 75 years and over, respectively. No differences in safety or effectiveness between these and younger subjects were observed. **Common Adverse Reactions.** In postmenopausal women with osteoporosis, treatment with abaloparatide was generally well tolerated. During the 18-month double-blind, placebo-controlled trial period, the most frequent adverse reactions in women treated with abaloparatide 80 mcg (N=822) once daily vs. placebo (N=820) included: hypercalciuria, 11% vs. 9%, dizziness, 10%

Dimension	Evidence, Uncertainties and Conclusions
	vs. 6%; nausea 8% vs. 3%; headache, 8% vs. 6%; and palpitations, 5% vs. 0.4%. The incidence of serious adverse events was 10% for abaloparatide-treated subjects and 11% in the placebo group. The most common adverse events leading to treatment discontinuation in the abaloparatide group were nausea, dizziness, headache, and palpitations. **Risk of Osteosarcoma.** In a 2-year carcinogenicity study, abaloparatide caused a dose-dependent increase in the incidence of osteosarcoma in male and female rats after subcutaneous injection at exposures 4 to 28 times the human exposure at the 80 mcg recommended dose. All dose groups were affected. Abaloparatide was not genotoxic or mutagenic in a standard battery of tests including the Ames test for bacterial mutagenesis, the chromosome aberration test using human peripheral lymphocytes, and the mouse micronucleus test. ***Comment.*** It is unknown whether Tymlos (abaloparatide) will cause osteosarcoma in humans. To date, no signal for osteosarcoma has been identified in the postmarketing experience with teriparatide.[6] Because of the uncertainty about this risk, abaloparatide should be reserved (as is teriparatide) for women with postmenopausal osteoporosis who are *at high risk for fracture*, based on a history of fracture or multiple risk factors for fracture. In addition, cumulative use of abaloparatide and other PTH1R agonists should not exceed 2 years during a patient's lifetime. I concur with the inclusion of a Boxed Warning recommending against the use of abaloparatide in patients at increased risk of osteosarcoma including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, open epiphyses, bone metastases, skeletal malignancies, hereditary disorders predisposing to osteosarcoma, or prior external beam or implant radiation therapy involving the skeleton. **Orthostatic Hypotension.** The incidence of orthostatic blood pressure decline $\geq$ 20 mm Hg systolic or $\geq$ 10 mm Hg diastolic at 1 hour after the first abaloparatide injection was 4% in the abaloparatide group and 3% in the placebo group. Associated symptoms may include dizziness, palpitations, tachycardia or nausea. ***Comment.*** Given the reported cases of orthostatic hypotension, I concur with the inclusion of a Warning in product labeling regarding this risk and with the recommendation that the first several doses of abaloparatide be administered where the patient can sit or lie down.

[6] As of September 30, 2016, interim estimates from the Forteo manufacturer's U.S. Osteosarcoma Surveillance study suggest that the number of spontaneous reports of pathology-confirmed osteosarcoma does not exceed what is expected based upon the background incidence rate of osteosarcoma.

Dimension	Evidence, Uncertainties and Conclusions
	Hypercalcemia. Elevations in serum calcium (defined as albumin-corrected serum calcium ≥ 10.7 mg/dL) at 4 hours following injection was 3% in the abaloparatide group and 0.1% in the placebo group. Two (0.2%) subjects in the abaloparatide group discontinued treatment due to hypercalcemia vs. no subject in the placebo group. The incidence of hypercalcemia with abaloparatide was higher in subjects with mild or moderate renal impairment (4%) compared to those with normal renal function (1%). ***Comment.*** Hypercalcemia can be expected to result from the effects of abaloparatide on calcium metabolism. I concur with the inclusion of a Warning in the product labeling for abaloparatide regarding the risk of hypercalcemia, and with the recommendation to avoid use in patients with pre-existing hypercalcemia or hypercalcemic disorders, such as primary hyperparathyroidism, because of the possibility of exacerbating hypercalcemia in these patients. **Hypercalciuria and Urolithiasis.** Abaloparatide may cause hypercalciuria. The incidence of urine calcium:creatinine ratio > 400 mg/g was higher in the abaloparatide group compared to the placebo group (20% vs. 15%). Urolithiases were reported in 2% of subjects in both groups. ***Comment.*** It is unknown whether Tymlos (abaloparatide) may exacerbate urolithiasis in patients with active or a history of urolithiasis. I concur with the inclusion of a Warning in the product labeling for abaloparatide regarding these risks, and with the recommendation that measurement of urinary calcium excretion be considered in patients with active urolithiasis or with pre-existing hypercalciuria. **Immunogenicity.** Of subjects receiving abaloparatide for 18 months, 49% developed anti-abaloparatide antibodies; of these, 68% developed neutralizing antibodies to abaloparatide. Of the subjects with anti-abaloparatide antibodies tested for cross-reactivity, 2.3% developed cross-reactivity to PTHrP, 43% developed neutralizing antibodies to PTHrP, and none developed cross-reactive antibodies to PTH. Antibody formation did not appear to have any clinically significant impact on bone mineral density response, fracture reduction, or the occurrence of immune-related hypersensitivity or allergic reactions. Eighty-five percent of subjects with anti-abaloparatide antibodies had follow-up antibody measurements six months after completion of abaloparatide treatment; of these, 56% remained antibody positive. ***Comment.*** Anti-abaloparatide antibodies have the potential to bind to and neutralize the drug, thereby adversely affecting

Dimension	Evidence, Uncertainties and Conclusions
	drug efficacy. There is also the potential risk that anti-abaloparatide antibodies may cross-react with and/or neutralize endogenous proteins, e.g., PTHrP or PTH, resulting in a *de facto* deficiency syndrome. The applicant has developed adequate assays for monitoring the development of anti-abaloparatide antibodies and their ability to cross-react with endogenous proteins. Antibody formation was assessed in subjects treated with abaloparatide for 18 months in Study 003, but was not comprehensively assessed at earlier time points. Postmarketing study commitments will characterize anti-abaloparatide antibody (b) (4) in Study 003.
Risk Management	**Labeling.** The prescribers of Tymlos (abaloparatide) will likely be general practitioners and rheumatologists familiar with the need to reduce fracture risk in postmenopausal women with osteoporosis, and with the attendant risks of available treatments for osteoporosis, including those associated with teriparatide. Product labeling for abaloparatide will address the serious safety risks associated with use of PTH1R agonists, including: • Risk of osteosarcoma (the subject of a Boxed Warning) • Orthostatic hypotension • Hypercalcemia • Hypercalciuria and urolithiasis In addition, a Medication Guide will be required as part of approved labeling of abaloparatide to provide important safety information to patients. **Risk Assessment.** Enhanced pharmacovigilance will be conducted by the applicant in the postmarketing setting to improve the quality of spontaneous reports of osteosarcoma potentially associated with abaloparatide through the use of a targeted questionnaire, expedited reporting of possible cases, and an annual analysis of case reports. The effectiveness of the program will be reassessed after 15 years. **Risk Mitigation.** The applicant proposed a communication plan REMS to mitigate the risk of osteosarcoma. I concur with the recommendation from DRISK that a REMS is not required for Tymlos (abaloparatide) to ensure that its benefits outweigh the risk of osteosarcoma. At the time of approval in 2002, a Risk Minimization Action Plan was implemented for Forteo (teriparatide) to mitigate the risk of osteosarcoma. With the passage of the Food and Drug Administration Amendments Act,

Dimension	Evidence, Uncertainties and Conclusions
	Forteo was deemed to have a REMS; the REMS was approved in 2009 and consisted of a Communication Plan, a Medication Guide, and a timetable for submission of assessments of the REMS. The Agency's Year 7 assessment of the Forteo REMS concluded that prescribers are familiar with the risk of osteosarcoma, with the maximum lifetime duration of treatment and with the need for proper patient selection. Moreover, the level of prescriber knowledge remained stable over time, even after the Communication Plan was eliminated from the Forteo REMS in 2011.[7] Thus, prescribers of abaloparatide, another PTH1R agonist, are likely to have good awareness of the osteosarcoma risk associated with this drug class. **Postmarketing Required Studies.** ***Pediatric Research Equity Act (PREA)*** The Agency is waiving the pediatric study requirement for this application. The required studies are impossible or highly impractical as the approved indication applies to conditions that do not occur in the pediatric population. ***Food and Drug Administration Amendments Act (FDAAA)*** The potential human risk of osteosarcoma with use of Forteo (teriparatide) has been the subject of postmarketing assessment since the drug's approval. A retrospective case-series study and a voluntary prospective patient registry were initiated in 2004 and 2009, respectively. No evidence of increased risk has emerged from these studies, (b) (4) (b) (4) Thus, these studies (b) (4) no definitive conclusions on the risk of osteosarcoma may be drawn. (b) (4) ***Postmarketing Study Commitments***

[7] On March 2, 2017, FDA notified the manufacturer of Forteo (teriparatide) that the approved REMS for Forteo was no longer required to ensure that the benefits of the drug outweigh the risk of osteosarcoma. A proposed REMS modification letter, as requested by FDA, was submitted on March 8, 2017.

Dimension	Evidence, Uncertainties and Conclusions
	The applicant has developed adequate assays for monitoring the development of anti-abaloparatide antibodies and their ability to cross-react with endogenous proteins. Antibody formation was assessed in subjects treated with abaloparatide for 18 months in Study 003, but was not comprehensively assessed at earlier time points. Postmarketing study commitments will characterize positive serum samples (b) (4) with respect to 1) anti-abaloparatide antibody titer, 2) abaloparatide neutralization, and 3) ability to cross-react with and/or neutralize endogenous PTHrP or PTH. ***Comment.*** The safety concerns identified with use of Tymlos (abaloparatide) can be adequately managed by professional labeling, a Medication Guide that will be required as part of approved labeling to communicate important safety information to patients, and enhanced pharmacovigilance in the postmarketing setting to improve the quality of spontaneous reports of osteosarcoma potentially associated with abaloparatide use. The results of postmarketing study commitments will inform product labeling regarding the immunogenicity of abaloparatide.

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/s/

JULIE G BEITZ
04/27/2017