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APPLICATION NUMBER:

208743Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number	208743
Priority or Standard	Standard
Submit Date	3/30/2016
Received Date	3/30/2016
PDUFA Goal Date	3/30/2017
Division/Office	Division of Bone, Reproductive and Urologic Products/ Office of Drug Evaluation III
Reviewer Name	Stephen R. Voss M.D.
Review Completion Date	12/8/2016
Established Name	Abaloparatide
(Proposed) Trade Name	Tymlos
Applicant	Radius Health, Inc.
Formulation	2 mg/mL solution in glass cartridge, within a multi-dose pen injector
Dosing Regimen	80 mcg by subcutaneous injection daily, with a maximum duration (b) (4)
Applicant Proposed Indication/Population	Treatment of postmenopausal women with osteoporosis
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Postmenopausal women with osteoporosis at high risk of fracture

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Glossary

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ARR	absolute risk reduction
AUC	area under the curve
BMC	bone mineral content
BMD	bone mineral density
BMI	body mass index
BPM	beats per minute
BSAP	bone specific alkaline phosphatase
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CSR	clinical study report
CTCAE	Common Toxicity Criteria Grade for adverse events
CTX	C-telopeptides of Type 1 collagen crosslinks
DBRUP	Division of Bone, Reproductive and Urologic Products
DSMB	Data and Safety Monitoring Board
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
FRAX	Fracture Risk Assessment Tool
GCP	good clinical practice
HR	hazard ratio
HR	heart rate
Hct	hematocrit
Hgb	hemoglobin
HLGT	High Level Group Term
HLT	High Level Term
ICH	International Conference on Harmonization
IEC	independent ethics committee
IND	Investigational New Drug
IRB	institutional review board
ISE	integrated summary of effectiveness

ISS	integrated summary of safety
ITT	intent to treat
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NDA	new drug application
NVF	nonvertebral fracture
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
P1NP	procollagen type 1 N-propeptide
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMO	postmenopausal osteoporosis
PMR	postmarketing requirement
PP	per protocol
PPI	proton pump inhibitors
pQCT	peripheral quantitative computed tomography
PRO	patient reported outcome
PTH	parathyroid hormone
PTHrP	parathyroid hormone-related peptide
PTHR1	parathyroid hormone type 1 receptor
QTcB	QT interval corrected using Bazett formula
QTcF	QT interval corrected using Fridericia formula
REMS	Risk Evaluation and Mitigation Strategy
RRR	relative risk reduction
SC	subcutaneous
SAE	serious adverse event
SAP	statistical analysis plan
SMQ	standardized MedDRA queries
SOC	System Organ Class
SVT	supraventricular tachycardia
TEAE	treatment emergent adverse event
ULN	upper limit of normal
WNL	within normal limits

1 Executive Summary

1.1. Product Introduction

Parathyroid hormone (PTH) and parathyroid hormone-related peptide (PTHrP) are peptide hormones which participate in calcium and bone metabolism through parathyroid hormone receptor 1 (PTHR1). While continuous high levels of PTH or PTHrP stimulate osteoclastic bone resorption, intermittent administration generally has an anabolic effect on bone, with increases in bone mass and strength. Teriparatide (PTH 1-34, Forteo) 20 mcg by daily SC injection has been shown to reduce fractures in women with postmenopausal osteoporosis (PMO), and is currently the only anabolic agent among the drugs approved for treatment of osteoporosis.

Abaloparatide (previously designated BA058) is a synthetic 34-amino acid peptide analog of PTHrP which has 76% homology to the N-terminal 34-amino acid region of PTHrP, and 41% homology to the N-terminal region of PTH (i.e. teriparatide). Intermittent SC administration of abaloparatide has anabolic effects comparable to Forteo; the Applicant believes that it may have a lesser tendency to stimulate bone resorption and cause hypercalcemia. Based on demonstrated reductions in vertebral and nonvertebral fractures, abaloparatide (Tymlos) is proposed in this NDA for the indication of treatment of PMO, administered as a once-daily SC injection of 80 mcg via a multi-dose prefilled pen. As with all PMO treatments, Tymlos is intended to be used by women who have adequate intake of calcium and vitamin D.

Abaloparatide and teriparatide, as well as full-length PTH (1-84), have induced osteosarcoma in animal studies; although an increased incidence has not been shown in humans, this remains a safety concern. Due in part to this potential risk, Forteo is labeled for use by an individual patient for a lifetime maximum of 2 years. Abaloparatide has not been studied in treatment durations >18 months and should have similar labeling. The anabolic effects of these drugs decline after discontinuation, such that subsequent use of another (antiresorptive) osteoporosis drug may be appropriate.

Abaloparatide has not been studied in populations other than PMO (e.g. men with osteoporosis, glucocorticoid-induced osteoporosis). As with Forteo, pediatric use is likely to be unsafe because of the increased baseline risk of osteosarcoma associated with open epiphyses.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided the substantial evidence of effectiveness required by law, 21 CFR 314.126(a)(b), to support approval of Tymlos (abaloparatide) in the treatment of postmenopausal osteoporosis (PMO). The phase 3 studies BA058-05-003 and BA058-05-005 (extension) were adequate and well controlled studies that unequivocally establish the efficacy of abaloparatide in reducing PMO related fractures. The primary endpoint of morphometric (radiographically defined) vertebral fracture, which is the accepted efficacy standard in PMO studies, showed robust reductions for abaloparatide vs. placebo at month 18 (end of double blind treatment) and month 25 (following 6 months of open label alendronate in both groups). The secondary endpoints of nonvertebral fracture and bone mineral density (BMD) also demonstrated significant efficacy compared to placebo.

These studies included only 39 US women (1.6% of all participants), whose BMD data were inconsistent and who may not accurately represent the US PMO population. However, BMD data were highly consistent among other regions and other subgroups, including race and ethnicity. Also, Forteo (teriparatide), which has a mechanism of action similar to abaloparatide, has previously been shown to have similar efficacy between US and non-US patients; an active-control teriparatide arm in study BA058-05-003 demonstrated efficacy comparable to that previous Forteo study, and comparable to abaloparatide in the new study. Therefore, it appears reasonable to conclude that the overall findings of studies BA058-05-003 and BA058-05-005 are applicable to the US PMO population.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Osteoporosis is characterized by bone loss, disruption of bone architecture, compromised strength and increase in fractures. About 10 million Americans have osteoporosis, and several times as many are at risk because of low bone density. Post-menopausal osteoporosis (PMO), the most common type, is driven primarily by the hormonal changes beginning at menopause. Caucasian women are at highest risk; about half will experience an osteoporotic fracture in their lifetime. PMO causes no symptoms until fractures, usually with minimal trauma, develop in the later stages. Fractures of the vertebrae, the most common type, weaken the spine and lead to additional fractures, with potential irreversible loss of height and function. Hip fractures frequently impair the ability to walk and to live independently. Both vertebral and hip fractures are associated with increased mortality. A variety of effective treatments is available, such that many fractures are now preventable. However, PMO remains seriously under-diagnosed and under-treated in the US, and additional treatment options are needed.

Tymlos (abaloparatide) is an analog of PTHrP (parathyroid hormone-related peptide), indicated for the treatment of PMO in women at high risk of fracture. Similar to the PTH analog Forteo (teriparatide), abaloparatide is an anabolic agent that stimulates bone formation, increasing bone mass and strength, and is intended for a limited duration of use (for abaloparatide, (b) (4)). All other approved drugs for PMO act through a different mechanism, i.e. blocking resorption of bone tissue. In all cases, the aim of treatment is to reduce vertebral and other fractures. Adequate intake of calcium and vitamin D is also important for all postmenopausal women, especially those with osteoporosis.

In a large phase 3 study of postmenopausal women with moderate to severe osteoporosis, abaloparatide was highly effective in reducing fractures. After 18 months of treatment, new vertebral fractures were reduced by 86% in comparison to a placebo control group; absolute risk reduction was 3.6%. An active-control group, which was treated with teriparatide, showed similar results with an 80% reduction in vertebral fractures compared to placebo. Non-vertebral fractures (e.g. wrist, hip etc.) were reduced overall by 43% with abaloparatide vs. placebo, and by 28% with teriparatide vs. placebo. (The differences between abaloparatide and teriparatide were not significant, and should not be used to infer any differences in efficacy.) After month 18, abaloparatide and placebo recipients entered an extension study in which they were switched to alendronate (an anti-resorptive drug) and re-assessed at month 25; significant differences between the two initial groups in fracture incidence persisted. Abaloparatide also produced substantial increases in bone mineral density (BMD) of the spine and hip. Fracture reduction was consistent among different age groups (<65, 65-74, ≥75) and different levels of disease severity. Most women with fractures were Caucasian, which precludes any definitive conclusions about fracture efficacy in non-white women. However, because of consistent BMD increases among racial/ethnic, regional and other subgroups, abaloparatide is likely to be effective in all types of PMO patients. In most cases, an 18 month course of treatment with abaloparatide should be followed by treatment with an antiresorptive drug in order to maintain the

benefits, as was done and shown to be effective in these studies. These phase 3 studies were well designed and conducted, and the evidence provided met the accepted FDA standards for osteoporosis drugs. Comparisons between efficacy results of different PMO drugs in different studies should be interpreted cautiously, because of variations in the way that studies are conducted and in the types of patients enrolled; for example, reductions in absolute fracture risk vary widely with the baseline level of fracture risk in the population studied.

The most important safety concern with both abaloparatide and teriparatide is the potential risk for development of osteosarcoma, a rare bone malignancy, which is based entirely on studies in rats. Surveillance studies have been ongoing since Forteo was approved in 2002 and have not shown any evidence of an increased osteosarcoma risk in humans for teriparatide. However, because of the rarity of this tumor, it is unclear whether any studies could achieve statistical power to rule out a small increase in risk. In abaloparatide studies, no osteosarcoma cases have been reported to date. To minimize any risk, the cumulative lifetime duration of use of abaloparatide, teriparatide or other PTH agonists should be limited to a total of 2 years. Also, neither drug should be used by patients with increased risk for osteosarcoma, which includes all children and adolescents.

In clinical studies, abaloparatide was well tolerated except for an increase in symptoms of palpitations, tachycardia, dizziness and nausea. There was no evidence of serious cardiovascular adverse effects. Abaloparatide (like teriparatide) tends to increase serum and urine calcium levels, but the clinical impact of this is probably slight in the absence of an underlying calcium disorder. Because these are anabolic drugs, rare side effects of antiresorptive drugs (osteonecrosis of the jaw, atypical femoral fractures) have not been reported, and are not expected.

Because of the uncertainty about osteosarcoma risk, abaloparatide should be reserved (as is Forteo) for women with PMO who are at high risk for fracture, based on a history of fracture or other factors. For this intended population, the benefit of treatment with abaloparatide should well exceed the risks in most cases. The absolute risk reductions of 3.6% for vertebral fracture and 1.8% for non-vertebral fracture with abaloparatide in the phase 3 study indicate that about 1 woman in 20 with PMO will avoid a serious fracture by use of the drug, assuming a similar baseline level of risk. For women at higher risk, benefits of treatment would be greater. Because of the large size of the phase 3 study, the probability of unanticipated serious safety issues is expected to be low, particularly when considering the extensive experience with Forteo (nearly (b) (4) patients treated since 2002). In sum, approval of abaloparatide for the treatment of PMO is fully supported by the efficacy and safety demonstrated in this population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Postmenopausal osteoporosis (PMO) causes progressive loss of bone mass and strength • PMO is clinically silent until fractures occur, typically with a fall or other minor trauma • Caucasian women are at highest risk, but other groups are also at risk • One half of women in the US over 50 years old will have an osteoporosis-related fracture; risk increases with age • Vertebral fractures, the most common complication, may cause back pain, kyphosis (curvature), loss of height, impaired lung capacity or GI function • After hip fracture, only 40% of patients regain their previous level of independence; 20% require long term nursing home care • Women who have had low trauma fractures are at high risk of additional fractures • Vertebral and hip fractures are associated with increased mortality	PMO related fracture is one of the most common causes of serious morbidity and mortality among US women.
Current Treatment Options	• Many drugs are effective: bisphosphonates, denosumab, teriparatide, raloxifene • Different formulations, dosing schedules and routes of administration: oral tablets/solution, nasal spray, injection (subcutaneous, intravenous) • Treatment can reduce nonvertebral fractures by up to about 50%; vertebral fractures by up to 70% • Treatment is effective in patients with moderate or severe osteoporosis • Minor side effects are common, and contribute to poor compliance • Fear of rare, more severe side effects is a major obstacle to treatment • Even after a major fracture or with multiple risk factors, most patients do not receive appropriate treatment	Under-diagnosis and under-treatment of PMO is a critical public health issue in the US. Treatment is effective when used, but does not prevent all fractures. Availability of additional treatment options, especially those with high levels of fracture efficacy, will benefit PMO patients.

Benefit

- Abaloparatide is an analog of PTH related peptide (PTHrP), a hormone that plays an important role in calcium and bone metabolism
- Like teriparatide (Forteo), abaloparatide acts through the PTHR1 receptor and, when administered intermittently by injection, has an anabolic effect on bone, increasing bone mass and strength
- Abaloparatide was evaluated in a phase 3 study in 2463 women with PMO, in comparison to placebo injections (double blind), and to Forteo as an active control (open label)
- Mean age was 69 years; patients were 80% Caucasian, 16% Asian, 3% black or African American
- Patients were treated for 18 months, then patients who received abaloparatide or placebo were switched to open-label alendronate and re-evaluated at 25 months
- The primary efficacy endpoint was the reduction in vertebral fractures as seen on x-ray, which is the long-accepted FDA standard for efficacy of PMO treatments
- Secondary endpoints were non-vertebral fractures and bone mineral density (BMD)
- Abaloparatide significantly reduced fractures compared to placebo:

	Percent reductions in fractures		
		Abaloparatide vs. placebo	Teriparatide vs. placebo
Vertebral fractures	Month 18	86%*	80%*
Vertebral fractures	Month 25†	87%*	-
Non-vertebral fractures	Month 19‡	43%**	28%
Non-vertebral fractures	Month 25†‡	52%**	-

* p-value <0.0001; ** p-value <0.05
† following 6 months of alendronate in both groups
‡ time to event analysis

Abaloparatide vertebral fracture reduction evidence is very robust, and nonvertebral fracture and BMD improvement also clinically and statistically significant. Slightly greater percent fracture reductions with abaloparatide compared to teriparatide were not statistically significant and should not be used to make inferences about relative efficacy. Although percent fracture reductions were relatively high, comparison of efficacy data with other PMO drugs may not be valid because of differences between studies and study populations.

Because BMD data are consistent across subgroups, anti-fracture efficacy of abaloparatide is likely to apply to all types of women with PMO.

Anabolic bone drugs like abaloparatide are typically used for a limited time period, to build bone, followed by use of an antiresorptive drug to maintain the improvement in bone. Maintenance of efficacy at month 25 in these studies appears to validate this type of approach.

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Most fractures were in European/ Caucasian women; there were few fractures but similar trends in Asian, Hispanic women
Abaloparatide and teriparatide significantly increased BMD relative to placebo:
<table>
<tr><td></td><td colspan="2">Placebo corrected BMD increase from baseline at month 18</td></tr>
<tr><td></td><td>Abaloparatide</td><td>Teriparatide</td></tr>
<tr><td>Lumbar spine</td><td>8.7%</td><td>8.6%</td></tr>
<tr><td>Total hip</td><td>3.5%</td><td>2.9%</td></tr>
<tr><td>Femoral neck</td><td>3.3%</td><td>2.7%</td></tr>
<tr><td colspan="3">All p-values <0.0001</td></tr>
</table>

BMD increases were highly consistent across regions, racial and ethnic groups
Fracture and BMD data were consistent across subgroups of age and severity of osteoporosis
Abaloparatide BMD increases at month 18 were maintained at month 25, following 6 months of alendronate

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<td>Risk</td>
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Osteosarcoma is a potential risk factor for abaloparatide and teriparatide based on animal data
No evidence of increased osteosarcoma incidence in humans with teriparatide or abaloparatide
Increased incidence of adverse reactions of palpitations, tachycardia, dizziness and nausea post-injection caused excess in study discontinuation compared to placebo
No evidence of increase in serious adverse reactions, including cardiovascular
Potential for hypercalcemia or hypercalciuria had minimal clinical impact

</td>
<td>Osteosarcoma may be species-specific for rats, whose bone metabolism differs from humans, but has not been definitively ruled out as a risk for humans.

Adverse reactions are probably related to hemodynamic effects (increased heart rate, decline in blood pressure following injection).
Effects on calcium metabolism are less pronounced than teriparatide.</td>
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Risk Management	• Like Forteo, reserve for patients at higher fracture risk, to assure benefit > risk • Osteosarcoma risk can be mitigated by avoidance of prescribing to patients with osteosarcoma risk factors, including children or young adults because of actively growing bones, Paget's disease or previous radiation therapy • 97% of Forteo prescribers are aware of possible osteosarcoma risk, and 89% are aware of 2-year lifetime limitation of use • No predisposing factors for adverse reactions (e.g. palpitations) identified	Labeling similar to Forteo (including boxed warning) is probably adequate to communicate potential osteosarcoma risk to prescribers, patients. Abaloparatide should have labeled warnings for symptoms of orthostatic hypotension, hypercalcemia and hypercalciuria, similar to Forteo.

2 Therapeutic Context

2.1. Analysis of Condition

Osteoporosis is a systemic skeletal disease characterized by low bone mass and impaired bone quality, causing increased fragility and risk of fractures. The most common and clinically important type is postmenopausal osteoporosis (PMO). The hormonal changes of menopause (decline in estrogen, increase in gonadotropins) modify the physiologic bone remodeling processes such that bone resorption by osteoclasts exceeds bone formation by osteoblasts. This causes a progressive decline in bone mass and density that is especially rapid during the menopausal transition, as well as disruption of bone microarchitecture.

Fractures associated with PMO, typically occurring with minimal trauma such as a fall from standing height, are a major cause of morbidity and mortality in older women. Caucasian women are at highest risk and have a lifetime incidence of osteoporotic fracture of ~50%. The most common site of fracture in PMO is the spine, with a fracture prevalence of ~30% in women >50 years old. Although many vertebral compression fractures are not painful or otherwise clinically apparent, they indicate bone fragility, strongly predict subsequent fracture and may have deleterious effects on posture (height loss, kyphosis, restrictive lung disease), functional capacity and quality of life, and increased mortality. Hip fractures, which are also common (300K/year in the US), are the most devastating complication of PMO and frequently result in chronic pain, deformity, and disability; increased mortality; and great economic cost. Fractures at other characteristic skeletal sites in PMO (wrist, forearm, shoulder) also have significant, and sometimes irreversible, adverse effects on health, well-being and ability to function independently.

Unless there is a history of low-trauma hip or vertebral fracture, the clinical diagnosis of osteoporosis is generally based on measurement of bone mineral density (BMD), usually by dual-energy x-ray absorptiometry (DXA). Based on DXA-derived BMD T-scores (the number of SD above or below the healthy young adult mean) of the spine, hip or forearm, the WHO (1994) established the following definitions:

- Normal: T-score ≥ -1.0
- Low bone mass (osteopenia): T-score between -1.0 and -2.5
- Osteoporosis: T-score ≤ -2.5
- Severe or established osteoporosis: T-score ≤ -2.5 with one or more fractures

Although DXA is currently the best imaging predictor of fracture risk, more than half of all low-trauma fractures occur in patients with T-scores > -2.5, i.e. not osteoporotic by these

definitions. This is in part because bone "quality" (including architecture, turnover, microfractures, mineralization), which is no less important than bone mass and density, is not easily measured. (Risk for falls, another important factor, is also difficult to assess.) Therefore there is increasing interest in fracture prediction models such as the WHO-developed FRAX (Fracture Risk Assessment Tool), which incorporates validated non-BMD clinical risk factors: age, sex, race, height, weight, previous low-trauma fracture, family history of hip fracture, glucocorticoid use, rheumatoid arthritis, current smoking, alcohol use and secondary osteoporosis (e.g. premature menopause, hyperthyroidism etc.), as well as femoral neck BMD. Based on this information on a given individual (age 40-90 y/o), FRAX estimates their cumulative 10-year risk for hip fracture and for major osteoporotic fracture (hip, spine, forearm or shoulder). Such estimates may be used to guide treatment decisions (see below).

2.2. Analysis of Current Treatment Options

The National Osteoporosis Foundation (2013) currently recommends consideration of drug treatment of postmenopausal women with any of the following:

- Hip or vertebral (clinical or asymptomatic) fractures
- BMD T-scores of ≤ -2.5 by DXA of femoral neck, total hip or lumbar spine (i.e. osteoporosis by WHO definition)
- BMD T-score at one of these sites between -1.0 and -2.5 (low bone mass or osteopenia) and 10-year fracture probability (by FRAX) of ≥3% (hip fracture) or ≥20% (major osteoporosis-related fracture)

The following table lists all drug products (some also available as generics) currently approved for the treatment of postmenopausal osteoporosis (PMO). Most of these drugs inhibit bone resorption, which reduces bone loss. The exception is Forteo (teriparatide), which has an anabolic effect that increases bone mass. Among these products, the bisphosphonates and raloxifene are indicated for general treatment of PMO; for the others listed, the approved indications are currently narrowed (as detailed in the table footnotes) because of safety issues (Forteo, Prolia), or safety and efficacy issues (Miacalcin, Fortical).

Table 1 Approved products for treatment of postmenopausal osteoporosis

Drug class	Product name	Year of Approval	Dosing/ Administration	Important Safety and Tolerability Issues
Bisphospho-nates	Fosamax (alendronate)	1995	70 mg PO weekly (tablet or solution) 10 mg PO daily (tablet)	Osteonecrosis of the jaw (ONJ) Atypical femoral fractures (AFF) Hypocalcemia Upper GI AEs
	Fosamax Plus D (alendronate/ cholecalciferol)	2005	70 mg alendronate/2800 or 5600 IU cholecalciferol, 1 tablet weekly	
	Binosto (alendronate)	2012	70 mg PO weekly (effervescent tablet for oral solution)	
	Actonel (risedronate)	2000	Tablets: 5 mg PO daily 35 mg PO weekly 150 mg PO monthly	
	Atelvia (risedronate)	2010	35 mg PO weekly (delayed release tablet)	
	Boniva (ibandronate)	2003	150 mg PO monthly (tablet)	
	Boniva (ibandronate)	2006	3 mg IV q3 months	ONJ, AFF, hypocalcemia Renal toxicity Acute phase reactions
	Reclast (zoledronic acid)	2007	5 mg IV yearly	
Estrogen agonist/ antagonist	Evista (raloxifene)	1997	60 mg PO daily (tablet)	Venous thromboembolism Death due to stroke
PTH analog	Forteo* (teriparatide)	2002	20 mcg SC daily	Osteosarcoma (animal data) Hypercalcemia, hypercalciuria Orthostatic hypotension
RANK ligand inhibitor	Prolia* (denosumab)	2010	60 mg SC q6 months	ONJ, AFF, hypocalcemia Serious infections
Calcitonin-salmon	Miacalcin**	1986	SC or IM injection, 100 IU every other day	Hypersensitivity Hypocalcemia Malignancy
	Miacalcin**	1995	Nasal spray, 200 IU daily	
	Fortical**	2005	Nasal spray, 200 IU daily	

*approved only for osteoporotic patients at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy
**approved only for osteoporotic patients for whom alternative treatments are not suitable (e.g., patients for whom other therapies are contraindicated or for patients who are intolerant or unwilling to use other therapies)

Excluding the calcitonin products (which were approved based on total body calcium and/or BMD data), the 7 molecular entities represented in the above table were approved for treatment of PMO based on reduction of morphometric vertebral fractures, consistent with 1994 FDA guidelines on osteoporosis drug development. Such fractures are defined solely by

radiographic criteria. Although the clinical effects of such fractures vary, they are a strong predictor of subsequent fracture (vertebral and nonvertebral) and also are associated with increased mortality, therefore are considered by DBRUP to be a clinically relevant (rather than surrogate) endpoint.

The following table lists the absolute and relative risk reductions (ARR, RRR) in new morphometric vertebral fractures (the primary endpoint) in the PMO trials of approved drugs. Risk reductions were generally apparent within 1 or 2 years and maintained through 3 years (the Forteo trial was stopped at ~19 months for safety concerns – see below). Because the trial populations differed in baseline fracture risk, ARR is highly variable between drugs/trials while RRR is more consistent. For example, the FIT-1 trial of Fosamax enrolled a high risk population (women with baseline vertebral fractures) and FIT-2 a lower risk population (no baseline fractures); fracture rates in both treatment groups were much higher in FIT-1, but relative reduction in fracture risk was nearly identical in the two studies.

Table 2 PMO fracture trials: New morphometric vertebral fractures, risk reductions by year

	12 months		24 months		36 months	
	ARR (%) (95% CI)	RRR (%) (95% CI)	ARR (%) (95% CI)	RRR (%) (95% CI)	ARR (%) (95% CI)	RRR (%) (95% CI)
Teriparatide (Forteo)			9.3* (5.5, 13.1)	65 (45, 78)		
Denosumab (Prolia)	1.4 (0.8, 1.9)	61 (42, 74)	3.5 (2.7, 4.3)	71 (61, 79)	4.8 (3.9, 5.8)	68 (59, 74)
Zoledronic acid (Reclast)	2.2 (1.4, 3.1)	60 (43, 72)	5.5 (4.4, 6.6)	71 (62, 78)	7.6 (6.3, 9.0)	70 (62, 76)
Alendronate (Fosamax-FIT 1)			7.2	62	7.0	47
Alendronate (Fosamax-FIT-2)					2.3**	48
Risedronate (Actonel-NA)	4.0	65	5.9	55	5.0	41
Risedronate (Actonel-MN)	7.7	61	13.1	59	10.9	49
Ibandronate (Boniva PO)	0.6	58	2.3	61	4.9	62
Raloxifene (Evista) ≥1 baseline fx					6.1	30 (14, 44)
Raloxifene (Evista) no baseline fx					2.4	55 (29, 71)

ARR = Absolute Risk Reduction; RRR= Relative Risk Reduction
*Forteo trial = 19 months' median exposure
**Fosamax FIT-2 trial = 48 month assessment
Sources: Prescribing information (Forteo, RIS, ZOL, DEN, RAL); *Lancet* 1996,348:1535 (ALN); *JBMR* 2004, 19:1241 (IBD)

Other fracture types were evaluated as secondary endpoints in these trials e.g. nonvertebral or hip fractures, and where efficacy was shown this is included in the labeled indication statement. (Fracture reduction at such sites was not required for approval; reduction in vertebral fractures was sufficient to meet FDA guidelines.) The following table shows efficacy data for nonvertebral fractures, which were significantly reduced with some but not all of these drugs. (Note again that baseline fracture risk of participants varied between trials; also, definitions of nonvertebral fractures varied somewhat.)

Table 3 PMO fracture trials: Nonvertebral fractures, cumulative incidence and risk reductions

	Trial duration (months)	Placebo fx incidence (%)	Drug fx incidence (%)	ARR (%) (95% CI)	RRR (%) (95% CI)
Teriparatide (Forteo)	19	5.5	2.6	2.9	53
Denosumab (Prolia)	36	8.0	6.5	1.5 (0.3, 2.7)	20 (5, 33)
Zoledronic acid (Reclast)	36	10.7	8.0	2.7 (1.4, 4.0)	25 (13, 36)
Alendronate (Fosamax-FIT 1)	36			4.3	26
Alendronate (Fosamax-FIT-2)	48			3.3	22
Risedronate (Actonel- combined NA+MN)	36	11	7		36
Ibandronate (Boniva PO)	36	8.2	9.1		
Raloxifene (Evista, combined)	36	9.3	8.8		6 (2, 11)
Sources: Forteo FPI; *JCEM* 2000, 85:4118 (ALN); *JAMA* 1999, 282:1344, *Osteoporos Int* 2000, 11:83 and clinical review (RIS); *NEJM* 2007, 356: 1809 (ZOL); *NEJM* 2009, 361:756 (DEN); IBD: FPI					

Compared to vertebral fractures, nonvertebral fractures generally require a longer treatment duration to demonstrate benefit; in most PMO trials, RRRs were smaller at year 1 compared to years 2-3:

Table 4 PMO fracture trials: Nonvertebral fractures, risk reductions by year

	RRR (% vs. placebo)		
	Year 1	**Year 2**	**Year 3**
Alendronate (FIT-1/2)	15	26	26
Risedronate (VERT-NA)	41	35	38
Risedronate (VERT-MN)	15	37	32
Zoledronic acid	16	23	25
Denosumab	16	20	21
Sources: JCEM 2000, 85:4118 (ALN); JAMA 1999, 282:1344, Osteoporos Int 2000, 11:83 and clinical review (RIS); clinical review (ZOL); clinical review (DEN)			

Hip fractures are the most clinically significant PMO fracture type, but their low incidence may cause difficulty in detecting treatment effects. Significant reductions in hip fracture have been demonstrated in large trials of alendronate, zoledronic acid and denosumab. The Forteo phase 3 PMO trial was somewhat smaller than those trials and was shortened (see below); although the patient population was high-risk, the difference in low-trauma hip fractures (4 placebo patient vs. 1 teriparatide patient, 0.7% vs. 0.2%) was not statistically significant.

The optimal duration of osteoporosis treatment is unclear. Bisphosphonate treatment should be reassessed after 3-5 years, because the risk of certain side effects (ONJ, AFF) increases with treatment duration, and there is some residual BMD and anti-fracture benefit after discontinuation because of long term bisphosphonate retention in bone tissue. In contrast, discontinuation of Prolia leads to a rebound increase in bone resorption (above pre-treatment baseline), return of BMD to near baseline levels within 12 months, and an increased risk of multiple vertebral fractures.

Forteo, a drug with similarities to abaloparatide, is generally well tolerated but has a safety concern for osteosarcoma (OS) based on rat studies (see section 4.4). When this finding became known (1998), the phase 3 PMO trial (GHAC) was prematurely terminated as a safety precaution; as noted above, the fracture efficacy data were nonetheless sufficient for approval in 2002. The safety issue, which had not been completely allayed, was addressed in labeling with a black box warning (including statement that the drug should not be prescribed to patients with increased OS risk, e.g. Paget's disease, prior radiation therapy, or pediatric/young adults with open epiphyses); a narrowed indication for patients at high risk of fracture; limited 2-year lifetime duration of treatment; and Medication Guide (a REMS was later added). In addition a long-term phase 4 surveillance study was initiated in 2002, based on cancer registries and designed to estimate the OS incidence in Forteo recipients for comparison to the

background rate (which is ~4.2 cases/million/year in US adults >60 y/o). This study was supplemented in 2009 by a voluntary patient registry, and subsequently by Medicare claims data and national pharmacy database data. As of Sept. 2016, there have been 2 observed OS cases in the surveillance studies, and no cases in the registry (or in any Forteo clinical trials). The 2 observed cases are considered to be within the expected background rate for the population, (b) (4) in the ongoing postmarketing studies (b) (4) t to rule out an increased incidence, and is expected to remain so (final study reports are due in 2019 and 2022). In 2014, a FAERS search identified 4 postmarketing cases of teriparatide associated with adjudicated OS, which is also not inconsistent with the background incidence (though the extent of underreporting is unknown).

Given that bone metabolism differs between rats and humans, and that no clinical signal for OS with PTH or PTHrP analogs has emerged, it is widely believed that the effect may be species-specific to rats. Because of the rarity of OS in humans and presumed long latency, the potential risk to humans is difficult to evaluate and likely to remain uncertain. A counter-argument is that there is no known increased OS risk in patients with hyperparathyroidism, who may have elevated circulating PTH for many years; however, such patients do not experience the bone anabolic effects associated with intermittent administration of the peptide.

Following the labeled maximum 2 years of Forteo therapy, BMD tends to decline without further treatment; it is unknown to what extent and for how long the fracture benefits persist. Observational data suggest that, after stopping Forteo, switching to an antiresorptive drug such as alendronate preserves or may augment the BMD gains, therefore this is currently a common practice in treatment of PMO.

Despite the clear benefits of these various osteoporosis drugs in reducing fracture, many women in the US do not receive appropriate treatment for PMO, in many cases even after after a major fracture. In addition, medication adherence is poor: only ~40% of patients who are prescribed bisphosphonates remain on treatment at 1 year, mostly due to side effects, or fear thereof.

In addition to drug treatment, osteoporosis patients should have adequate calcium and vitamin D, which are essential to bone health generally. The Institute of Medicine recommended (2011) daily intakes of 1000 mg Ca for postmenopausal women, and vitamin D 600 IU (age ≤70 yr) to 800 IU (age >70 yr). Older persons frequently have inadequate intake or absorption, or insufficient exposure to sunlight, therefore Ca/Vit D supplements are widely used. Nearly all osteoporosis drug trials have included daily Ca/Vit D supplements for all enrollees (receiving active or placebo); adequate intake is routinely recommended in labeling.

Other general recommendations for postmenopausal women include: regular exercise, which improves bone density, muscle strength and balance and prevents falls; and avoidance of

smoking and excess alcohol. Because PMO is largely driven by loss of estrogen, women who have an indication for estrogen replacement (e.g. vasomotor symptoms) may also benefit from maintenance of BMD and potentially lower fracture rates. However for most women, the skeletal benefits alone are outweighed by the known safety concerns of hormone replacement therapy. Currently, estrogen is approved to prevent, but not to treat osteoporosis.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Abaloparatide is a new molecular entity (NME) drug that has never been marketed in the U.S. To date, development of this drug has been focused on the sole indication of treatment of postmenopausal osteoporosis, under IND 073176 and this NDA 208743; no other INDs or NDAs have been submitted.

3.2. Summary of Presubmission/Submission Regulatory Activity

Abaloparatide was initially developed by Beaufour Ipsen Pharma Group under the name BIM44058 or BIM44058C. The license was acquired by Nuvios Inc., which renamed the product BA058, and conducted a first in human phase 1a single dose study (#2-52-52127-001) in Germany.

Pre-IND meeting (12/14/05)
Based on the initial clinical data, a phase 1b study draft protocol BA058-05-001 was discussed. DMEP advised the sponsor that BA058 would likely have the same indication as Forteo, i.e. treatment of PMO in women at high risk for fracture. DMEP also advised that the animal carcinogenicity study should include teriparatide for comparison; and that any change in BA058 formulation during development or the to-be-marketed formulation should be addressed with a bioequivalence study.

IND 073176 submission (12/9/05)
After opening the IND, Nuvios (name changed to Radius Health Inc.) conducted phase 1b studies 001 and 001b in healthy postmenopausal women. These studies investigated daily dosing for 7 days of doses ranging from 5-120 mcg. On 12/21/06 the sponsor submitted a phase 2 protocol (study BA058-05-002) enrolling women with PMO and using BA058 doses of 20, 40 and 80 mcg, with active-control teriparatide 20 mcg and placebo; the primary endpoints were bone turnover markers and BMD. Study 002 was initially planned as a 3-month study, but upon DMEP advice was changed to a 6 month study, with optional extension in which patients would continue the blinded study drug for an additional 6 months. A total of 221 patients were randomized and treated in initial 6-month phase; 55 subsequently enrolled in the extension.

End of Phase 2 meeting (1/21/10)

The EOP2 meeting package included summaries of the above studies and a draft phase 3 protocol (BA058-05-003) for a fracture study comparing BA058 80 mcg to blinded placebo injection and active-control teriparatide 20 mcg, in postmenopausal women with severe osteoporosis (low BMD T-score and, for women ≤65 y/o, also a prior osteoporotic fracture). The study would enroll ~800 patients per arm and the treatment period duration would be 18 months. The decision to include the active-control teriparatide was the Applicant's, as this would not be required in a placebo-controlled study.

The planned 80 mcg dose was discussed at the EOP2 meeting. DBRUP advised studying two doses in phase 3, e.g. 40 mcg and 80 mcg, however the Applicant argued that in the phase 2 study, these two doses had similar safety data (BP, serum calcium), but there was greater efficacy (BMD of hip and spine, and biomarkers) with 80 mcg. DBRUP stated that week 48 data were sparse and that these differences may not apply to fracture outcomes, but that the choice of doses for phase 3 was the Applicant's option and risk.

The phase 3 protocol allowed a dose adjustment from 80 to 40 mcg in the event of hypercalcemia. DBRUP stated that a dose reduction algorithm could be used in the study, (b) (4)

DBRUP acknowledged that the active control Forteo could not be blinded and stated that:

> *…this may introduce bias which will be taken into account when considering what comparative data, if any, will be included in the full prescribing information….For inclusion in the product label, comparative fracture efficacy data is necessary.* (b) (4)

DBRUP agreed with the proposed study population; agreed with the primary endpoint of morphometric vertebral fractures for BA058 vs. placebo; stated that the secondary endpoints should include comparison of all BMD results between BA058 and placebo; and advised BMD of the mid-1/3 radius in at least a subset of patients.

DBRUP expressed concern about the findings of tissue mineralization seen in a 39-week monkey study, possibly in the absence of hypercalcemia, and advised that the Applicant should submit a proposal to adequately evaluate potential mineralization and renal function in the phase 3 study.

Other issues discussed at the EOP2 meeting:
DBRUP indicated that cardiovascular safety of BA058 is a potential issue, noting that a patient in the phase 1 study 12-52-52127-001 had experienced syncope, hypotension and dizziness with QTc prolongation. The Applicant agreed to conduct a thorough QT/QTc study.

Additional studies were recommended: a dose proportionality study (because the formulation had changed from (b) (4) in early phase 1 to solution); and a PK study in patients with impaired renal function, because of a concern for possible high exposure with reduced renal function.

Phase 3 study 003: original protocol version 1.0 submitted (12/17/10)
Based on the EOP2 meeting discussions, the Applicant submitted the phase 3 protocol. The more significant changes were the addition of a population PK study within study 003 to assess the interaction of baseline characteristics with study outcomes, including the interaction of renal function and study drug levels; a substudy in which ~300 patients would undergo end-of-study renal CT scans to assess potential tissue mineralization; and the addition of 1-hr-post-injection ECGs at every visit. The study began enrollment in March 2011.

In the same submission, the Applicant agreed to conduct the renal safety and thorough QT/QTc studies.

Type A Guidance meeting 3/21/12
After internal discussion, DBRUP advised the Applicant (letter 2/14/12) that a minimum of 24-month fracture data is necessary for PMO approval, even for anabolic drugs such as abaloparatide that are intended for a more limited treatment duration. Because study 003 was an 18-month study, the 3/21/12 meeting was held to discuss options for fulfilling the 24-month fracture data requirement. One option was to extend study 003 to 24 months, however the Applicant believed that 18 months was the optimal duration of BA058 therapy, and also that continuing placebo treatment beyond 18 months was not feasible because of ethical, logistical and non-US regulatory considerations. There was discussion of other designs for an extension (e.g. switch to bisphosphonate in one or more of the study arms) and timing of the primary endpoint (18 vs. 24 months). No agreement on these issues was reached in the meeting; the minutes state that:

> *The Division agrees that the 18 month assessment can be the primary endpoint and will form the basis for product labeling. The 24 month assessment is considered the "key" secondary endpoint and will require adequate enrollment for analysis…..The complete NDA submission should include the 24 month data.*

Protocol changes (July 2012)

Protocol amendment 2 (v. 3.0, 7/5/12) made 2 major changes to the study 003 protocol:

- Renal CT scans: in response to a DBRUP recommendation, these would now be required (at selected centers) for new enrollees both pre- and post-treatment
- Bone biopsies: previously required for abaloparatide and placebo arms only, were now required for some teriparatide subjects as well

Phase 3 extension study BA058-05-005 (original protocol dated 7/23/12) was also submitted. Interim rat carcinogenicity data had been submitted on 4/5/12, demonstrating osteosarcoma; DBRUP advised the sponsor (letter 6/4/12) that this finding reinforced the view that using bisphosphonate for the 6-month extension was most appropriate. This protocol stated that in study 005, study 003 patients who completed 18 months of BA058 or placebo would receive open-label alendronate 10 mg daily for 6 months if considered appropriate by the investigator, or if not, an alternative osteoporosis treatment.

Protocol changes (Feb. 2013)

In response to advice from DBRUP (letter 12/19/12) that (b) (4) in the 6-month extension was not acceptable, the first amendment to study protocol 005 (v.1, dated 2/13/13) stated that only alendronate 70 mg once a week could be used, and that patients on other osteoporosis therapies would be excluded. In addition, the extension study duration was extended from 6 to 24 months.

Protocol changes (March 2014)

Protocol 003 amendment 3 (v. 4.0) and protocol 005 amendment 2, both dated 3/31/14, reflected the API name change from BA058 to abaloparatide, and implemented other minor changes.

QT/QTc protocol

The thorough QT/QTc study protocol (012) was submitted 11/19/14. Following QTIRT consultation, comments and recommendations were communicated to the Applicant on 12/3/14.

Statistical Analysis Plan (SAP)

The last patient visit in study 003 was in Oct. 2014. DBRUP agreed to provide written responses to questions regarding a draft SAP. The Applicant submitted the draft SAP on 11/10/14 and then finalized the SAP on 12/8/14, prior to receiving DBRUP responses. DBRUP provided comments on 1/8/15 which included disagreement on the proposed primary endpoint (new (b) (4) vertebral fracture at month 18, while the currently accepted endpoint is new (b) (4) (b) (4) vertebral fracture); and a request for an integrated SAP for studies 003 and 005. These comments were addressed in a revised SAP for study 003 and draft SAP for study 005, submitted on 4/15/15.

Requests for Breakthrough Therapy Designation (BTD) (b) (4)

On 5/9/14 the Applicant submitted a BTD request, based on greater BMD response and safety (less hypercalcemia) in abaloparatide-treated patients compared to Forteo. This request was denied, as these data were not considered to establish a clinically significant improvement over approved therapy.

On 5/22/15 the Applicant submitted a second BTD request, citing phase 3 fracture data in addition to the benefits claimed previously. DBRUP responded that there was statistical overlap in vertebral fracture risk reduction between abaloparatide and teriparatide in study 003, and also statistical overlap with zoledronic acid and denosumab fracture data in previous studies. Thus, this request was also denied.

(b) (4)

Initial Pediatric Study Plan (iPSP)

As required by the Pediatric Research Equity Act (PREA), the Applicant submitted an iPSP on 3/20/15 requesting a full waiver of the requirement to conduct pediatric studies, given that PMO does not exist in this population and that abaloparatide is likely to be unsafe in children. DBRUP responded with written comments on 6/15/15; the Applicant submitted the Agreed iPSP on 10/2/15; the Pediatric Review Committee meeting on 10/21/15 concurred with the Applicant's plan for a full waiver; DBRUP communicated agreement to the Applicant on 10/30/15.

Pre-NDA meeting (5/28/15)

Significant areas of agreement at this meeting were as follows:

- The efficacy evaluation would be primarily based on study 003, and 6-month data from all enrollees in study 005. The 6-month interim report for study 005 would include complete datasets.
- DBRUP indicated agreement with the proposed analysis of the primary and secondary endpoints of both studies as defined in the respective SAPs, and emphasized the importance of the endpoint of new vertebral fractures at 24 months.
- The primary endpoint would be analyzed in the mITT; if the number of patients in the mITT differs significantly from the ITT, this would be a review issue.
- The ISE would include summaries of efficacy from studies 003/005, and supporting studies that inform the phase 3 dose.
- The ISS would mainly focus on pooled phase 2 and 3 safety data: all treatment groups in studies 002 and 003, and the placebo and abaloparatide 80 mcg SC groups from study 007 (b) (4) with upcoding to MedDRA v. 17.1.
- DBRUP requested a listing of all major and minor protocol violations and deviations, and a listing of all study discontinuations and temporary treatment suspensions in the phase 2 and 3 studies

- The completed and ongoing human PK, PD, Thorough QT/QTc and renal function studies were adequate to support filing and review of the NDA.
- The Applicant was advised that the potential risk of osteosarcoma would require (at minimum) a labeled boxed warning, Medication Guide and plan to mitigate this risk post-marketing; and was encouraged to submit a pharmacovigilance plan.
- As the proposed to-be-marketed drug-device combination product (using Unopen injector) differs from the product used in the Phase 3 trial (using BD Pen II injector), the Applicant was advised to conduct a bridging BE study prior to submission of the NDA.

Pre-NDA CMC meeting (6/3/15)

Final SAPs for studies 003 and 005 submitted (6/22/15)

3.3. Foreign Regulatory Actions and Marketing History

Abaloparatide has not been approved in any country to date. An application for marketing in Europe is currently under review by the EMA.

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

4.1. Office of Scientific Investigations (OSI)

Clinical site inspections were requested at sites #103 (Denmark), #121 (Brazil), #131 (Czech Republic) and #181 (Hong Kong). At this writing, inspections are completed and deemed NAI at 3 of these sites and the other (#131) inspection is pending.

4.2. Product Quality

The drug substance, abaloparatide, is a synthetic 34-amino acid peptide, which has 76% homology to hPTHrP(1-34), including 100% homology for the N-terminal 22 amino acids. Abaloparatide also has 41% homology to hPTH(1-34).

The drug product is a sterile solution (2 mg/mL) for SC administration, supplied in a (b) (4) mL glass cartridge for use with a pen-injector device, sufficient to provide 30 daily doses. Each mL contains 2000 mcg abaloparatide, 5 mg phenol, 5.08 mg sodium acetate trihydrate, 6.38 mg acetic acid, and water for injection.

See CMC reviews for product quality details.

4.3. Clinical Microbiology

There are no clinical microbiology issues with this product.

4.4. Nonclinical Pharmacology/Toxicology

Major findings are outlined here; for details please refer to nonclinical review by Dr. Gemma Kuijpers, DBRUP.

As is generally recommended for new osteoporosis drugs, bone quality studies were conducted in two animal models: ovariectomized rats and monkeys. These studies demonstrated significant BMD increases at multiple vertebral and nonvertebral sites which correlated with increased bone strength.

Osteosarcoma

The safety concern for osteosarcoma related to abaloparatide, as well as PTH analogs, is based entirely on animal data. The risk was initially identified with teriparatide in two rat carcinogenicity studies. In the first study, beginning at 2 months of age, Fischer 344 rats received daily SC injections of 0, 5, 30 or 75 mcg/kg for 2 years (exposure for ~75% of lifetime). These doses corresponded to about 3, 21 or 58x the systemic exposure in humans receiving the 20 mcg daily dose. Osteosarcomas developed at each dose (none with control), with incidence reaching ~50% at the highest dose (table below). The tumors became clinically apparent after 17-20 months of treatment.

Table 5 Teriparatide: Rat carcinogenicity study #1

	Males				Females			
Teriparatide dose (mcg/kg/day)	0	5	30	75	0	5	30	75
Treatment period (mos)	NA	2 to 26	2 to 26	2 to 26	NA	2 to 26	2 to 26	2 to 26
# examined	60	60	60	60	60	60	60	60
# w/ osteosarcoma	0	3	21	31	0	4	12	23
Multiple of human AUC*	-	3x	21x	58x	-	3x	21x	58x
* Comparison to 20 mcg daily clinical dose Source: NDA 021318, S-12 nonclinical review (DARRTS, 11/13/08)								

The second study confirmed the findings and demonstrated that they applied also to animals beginning treatment later, in adulthood. Female rats were begun on treatment at either 2 months of age (i.e. immature) or 6 months of age (mature), and treated with 5 or 30 mcg/kg, for 6 or 24 months' duration. Osteosarcoma incidence again tended to increase with dose, and also with treatment duration, in each group. In the mature rats, no tumors appeared at the lower dose (5 mcg/kg, ~3x human exposure), and it was concluded that mature animals may be less sensitive to the carcinogenic effects than younger animals.

Table 6 Teriparatide: Rat carcinogenicity study #2

	Treatment begun at 2 months of age				Treatment begun at 6 months of age			
Teriparatide dose (mcg/kg/day)	5	30	0 (control)	30	5	30	5	30
Treatment period (mos)	2 to 8*	2 to 8*	NA	2 to 26	6 to 12*	6 to 12*	6 to 26	6 to 26
# examined	60	60	60	60	60	60	60	60
# w/ osteosarcoma	1	2	1	9	0	2	0	5
Multiple of human AUC**	3x	21x	-	21x	3x	21x	3x	21x

* Animals dosed for 6 months were observed for an additional 18 months follow-up period
** Comparison to 20 mcg daily clinical dose
Source: NDA 021318, S-12 nonclinical review (DARRTS, 11/13/08)

PTH 1-84, which was approved in 2015 for treatment of hypoparathyroidism (Natpara, BLA 125511), exhibited similar findings in a 2-year rat study. The incidence of osteosarcoma in males was 22% at 50 mcg/kg/day (~20x the maximal recommended human dose or MHRD, based on AUC), and 45% at 150 mcg/kg/day (~50x MHRD). The incidence in females was somewhat lower, 8.3% and 22% respectively. At the lowest dose of 10 mcg/kg/day (~4x MHRD), there was no increased incidence.

For this abaloparatide NDA, the Applicant also conducted a carcinogenicity study in Fischer 344 rats. Abaloparatide doses of 10, 25 and 50 mcg/kg (approx. 4x, 18x and 30x the AUC of the clinical dose of 80 mcg) were used, with teriparatide 30 mcg/kg as positive control and also a vehicle control group. Animals were dosed for 2 years, beginning at about 6 weeks of age. As shown in the table below, osteosarcoma incidence and related mortality increased with abaloparatide dose, with the middle dose (25 mcg/kg) fairly comparable to teriparatide 30 mcg/kg; the Applicant considers these two regimens to be similar in regard to their respective multiples of the human AUC (~18x and 21x). Compared to the previous teriparatide studies, osteosarcoma incidence with both drugs was somewhat higher and also the tumors appeared somewhat earlier; the Applicant attributes this to the use of radiographs of the entire skeleton to detect small tumors in the new study. Benign bone proliferative findings (osteoblastomas, focal osteoblast hyperplasia) also occurred with both drugs, and there were large BMD increases with each dose.

Table 7 Abaloparatide: Rat carcinogenicity study (10RAD032)

	Males					Females				
	Vehicle	Abaloparatide			Teriparatide	Vehicle	Abaloparatide			Teriparatide
Dose (mcg/kg/day)	0	10	25	50	30	0	10	25	50	30
# examined	60	60	59	60	60	60	60	61	60	60
# w/ osteosarcoma related mortality	0	19	32	35	25	0	4	8	24	8
# w/ osteosarcoma – primary	1	31	46	52	39	1	11	22	37	24
# w/ osteosarcoma - metastasis	1	14	17	35	21	0	2	3	16	9
Multiple of human AUC*	-	4x	18x	30x	21x	-	4x	18x	30x	21x
* Comparison to abaloparatide 80 mcg or teriparatide 20 mcg daily dose Source: Expert Panel Report on rat carcinogenicity										

No osteosarcomas have been reported in long-term studies of monkeys (or humans) with teriparatide or abaloparatide. The Applicant believes that this difference from rodents may be related either to differences in bone metabolism, where the anabolic effect is less pronounced in primates, and/or to differences in exposure timing and duration relative to lifespan (e.g. ~70-80% of lifespan in rats vs. 2-3% in humans, the latter usually at advanced age).

Cardiovascular effects

Hemodynamic effects were evaluated in 6 anesthetized dogs (safety pharmacology study D01.381/3). Following IV doses of 0.1, 0.3, 1 and 3 mcg/kg, mean aortic BP decreased from baseline by 7, 13, 21 and 45% respectively within 1-2 minutes; and mean HR increased by 21, 48, 86 and 48% respectively within 1-5 minutes. Similarly, there were dose-related declines in total peripheral resistance and increases in cardiac output. It was concluded that abaloparatide exerted peripheral arteriolar vasodilatory effects as well as direct positive chronotropic and inotropic effects on the heart.

Mineralization

In 39-week monkey studies, soft tissue mineralization was seen at exposures 2-4x the human 80 mcg dose. Therefore, renal CT scans were required in the clinical phase 3 study (see section 8.5.3).

4.5. Clinical Pharmacology

Key findings will be outlined here; for details see Clinical Pharmacology review by Dr. LaiMing Lee.

4.5.1. Mechanism of Action

Abaloparatide is an analog of parathyroid hormone-related protein (PTHrP). PTHrP was originally identified by its role in humoral hypercalcemia of malignancy (HHM), a paraneoplastic complication of some malignancies. Unlike PTH, PTHrP generally functions in an autocrine or paracrine role, except in specific conditions such as HHM or during lactation, when PTHrP mobilizes calcium from the maternal skeletal for use by the neonate. PTHrP appears to play a critical role in growth plate function in long bones during development.

PTH (an 84 amino acid peptide) and PTHrP (secreted in various length peptides) share significant homology at the N-terminus, where 8 of the first 13 amino acids are identical. This N-terminus of PTH or PTHrP is necessary for interaction with the PTHR1 receptor. Two PTH receptors have been identified, PTHR1 and PTHR2, which belong to the Type II family of G-protein coupled receptors (GPCRs). PTH binds to both the PTHR1 and PTHR2, while PTHrP interacts only with PTHR1. Intermittent administration of PTH, PTHrP or abaloparatide stimulates osteoblastic bone formation, but effects on resorption may differ, perhaps because of different conformational states of the receptor.

4.5.2. Pharmacodynamics

Like teriparatide, abaloparatide by daily injection stimulates bone formation via osteoblasts, as reflected in an increase in bone formation markers. In the abaloparatide 80 mcg arm of phase 3 study (003), one such marker, serum P1NP, showed median increases of 81%, 59%, 58%, 44% and 29% above baseline at months 1, 3, 6, 12 and 18 respectively. In the teriparatide arm, median increases at these timepoints were somewhat greater: 84%, 94%, 135%, 140% and 103% respectively. In the placebo arm, median changes ranged from -6% to -19% at these points. As in earlier teriparatide studies, markers of bone resorption showed little change at 1 month with both drugs, followed by median increases of 16%, 10%, 6% and -2% for abaloparatide; and 50%, 45%, 45% and 30% for teriparatide at months 3, 6, 12 and 18 respectively (and -5% to -23% with placebo).

Also like teriparatide, abaloparatide is associated with increases in serum calcium levels. In the phase 3 study, mean serum calcium at 4 hrs post-dose increased by 0.20-0.41 mg/dL at various time points from baseline in abaloparatide patients, and by 0.24-0.50 mg/dL from baseline in teriparatide patients; pre-dose serum calcium rose by much smaller amounts. There were trends of higher incidence of hypercalcemia with increasing renal impairment (see section 8.5.1 of this review).

Like teriparatide, abaloparatide is associated with a transient increase in heart rate (HR). In the phase 3 study 003, mean HR (by ECG) 1 hr post-injection increased from baseline at various visits by 6.8-7.9/min for abaloparatide and 5.3-6.3/min for teriparatide, vs. 1.1-1.7/min for placebo. In the thorough QT/QTc study in younger adults, HR increases at earlier timepoints were more pronounced, with mean peak increases of 14.5/min and 20.4/min at 20 min post injection for abaloparatide 80 mcg and 240 mcg respectively.

4.5.3. Pharmacokinetics

Abaloparatide is rapidly absorbed from SC administration, with a median Tmax of ~20-30 min and elimination half-life of ~1.7 hr and negligible accumulation with daily injections. Compared to IV administration, the absolute bioavailability of an 80 mcg SC dose is 39%. Across doses of 20, 40 and 80 mcg SC, PK was dose-proportional.

Exposure increased with increasing degrees of renal impairment. In the dedicated phase 1 study (011), mean exposure ($AUC_{0\text{-}inf}$) was 1.7- and 2.1-fold higher in subjects with moderate and severe renal impairment, respectively, compared to subjects with normal renal function. In the phase 3 study (003), population PK modeling showed 20% and 30% increases in AUC in mild and moderate renal insufficiency.

Due to its peptide nature, lack of interference with CYP450 enzymes and rapid degradation, significant drug-drug interactions are not anticipated, and no formal studies have been conducted.

4.6. Devices and Companion Diagnostic Issues

In the phase 3 study (003), the drug-device combination product consisted of the multi-dose glass cartridge mounted in a BD Pen II, which was reusable. In the to-be-marketed version, the glass cartridge is pre-assembled into a disposable multi-dose pen (UnoPen). Both devices use an 8 mm, 31 gauge needle. (See device review by the Center for Devices and Radiological Health.) Because of the change in delivery device, the Applicant conducted study BA058-05-016 in order to demonstrate bioequivalence between the BD II and UnoPen. (See Clinical Pharmacology review.)

4.7. Consumer Study Reviews

Review by the Division of Medication Error Prevention and Analysis of the human factors validation study for the proposed multi-dose prefilled pen, identified areas of concern pertaining to priming the pen and difficulty with needle removal, which may prevent safe and effective use. The Applicant was advised to modify the Instructions for Use and conduct a

focused human factors study to validate the changes, prior to NDA approval. The validation study is pending at this writing.

5 Sources of Clinical Data and Review Strategy

Table of Clinical Studies

This NDA is primarily based on the efficacy and safety evaluation in the single pivotal phase 3 PMO study BA058-05-003, with an efficacy assessment of abaloparatide-SC vs. placebo and vs. teriparatide through 18 months of treatment; and the 6-month interim data from the extension study BA058-05-005 which evaluated the effect of abaloparatide-SC followed by alendronate, compared with placebo followed by alendronate, at 25 months. The total duration of these studies is 25 months: 18 months in study 003, then 1 month of no-treatment follow-up, then 6 months of alendronate treatment in study 005.

Supportive efficacy data are derived from the phase 2 PMO studies 002 and 007. Study 002 was the dose-finding study for abaloparatide-SC. Study 007 (b) (4) evaluates (b) (4) the SC formulation as active control; data from this SC arm are included in the ISS. There are 7 phase 1 studies of the SC formulation which evaluated PK, bioavailability, MTD, renal impairment, thorough QT and pen bioequivalence.

Table 8 Listing of clinical trials relevant efficacy and safety evaluation

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
BA058-05-**003**	Phase 3, R, placebo controlled (DB) and active controlled (OL)	ABL 80 mcg SC PLAC SC TPD 20 mcg SC (daily)	Fractures: vertebral and nonvertebral BMD Bone turnover markers	18 mos	2463	Women with PMO	28 centers 10 countries in Europe, S. America, Asia and N. America
BA058-05-**005**	Phase 3, OL extension of study 003	Alendronate 70 mg po weekly		24 mos (First 6 months data in NDA)	1139	Women with PMO who were assigned to ABL-SC or PLAC in study 003	Same as study 003
BA058-05-**002**	Phase 2, R, PC, dose finding DB for ABL/PLAC	ABL 20, 40, 80 mcg SC PLAC SC TPD 20 mcg SC (daily)	BMD of spine, total hip, fem neck, radius Bone turnover markers	48 wks (including 24wk extension w/ same assigned treatments)	222 (55 enrolled in 24 wk extension)	Women with PMO	30 centers 4 countries: US, UK, Argentina, India
BA058-05-**007**	Phase 2, R, PC, dose finding for (b) (4)	(b) (4) ABL-SC 80 mcg SC (daily)	BMD of spine, total hip, radius Bone turnover markers	6 mos	51 (ABL-SC arm)	Women with PMO	9 centers 4 countries: US, Denmark, Estonia, Poland
Studies to Support Safety							
BA058-05-**012**	Thorough QT study Phase 1, R, 3-way XO, partial DB	ABL 80 mg ABL 240 mg Moxifloxacin 400 mg Placebo	QT/QTc interval	Single doses	53	Healthy M/F subjects Median age 34 y/o	1 center (US)
ABL=abaloparatide; TPD=teriparatide; PLAC=placebo; R=randomized; DB=double blind; PC=placebo controlled; OL=open label; SD=single dose; XO=crossover							

5.2. Review Strategy

This review primarily concerns study BA058-05-003, the single pivotal phase 3 fracture study, and the initial 6 months' data from the extension study BA058-05-005. The data presented are derived from the study reports including tables/figures, CRF/narratives and datasets. Some of the analyses were conducted by this reviewer using JMP software, and others obtained from the statistical reviewer, Dr. Jia Guo (sources are indicated in table/figure footnotes).

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study BA058-05-003

6.1.1. Study Design

Overview and Objective

Title of study 003: A randomized, double-blind, placebo-controlled, comparative phase 3 multicenter study to evaluate the safety and efficacy of BA058 for injection for prevention of fracture in ambulatory postmenopausal women with severe osteoporosis and at risk of fracture

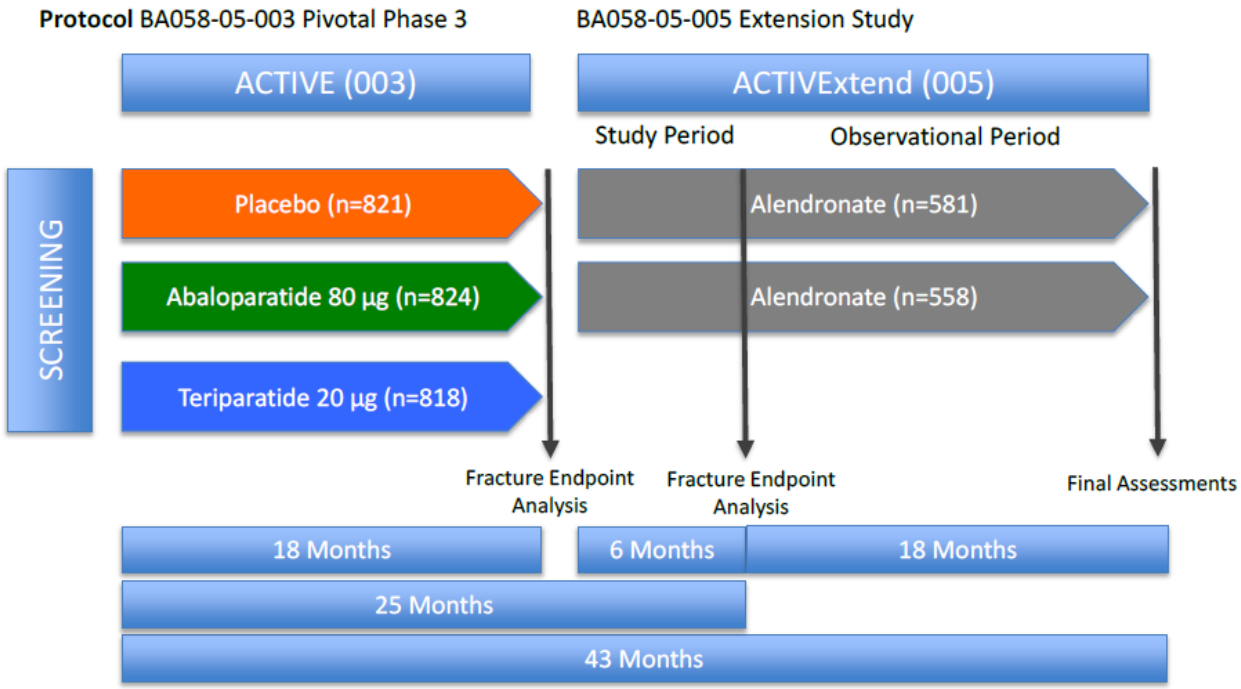
The primary objective of this pivotal study was to determine the safety and efficacy of abaloparatide (SC) relative to placebo in preventing new vertebral fractures, in ambulatory postmenopausal women with severe osteoporosis at risk of fracture. The secondary objectives were to evaluate efficacy relative to placebo in prevention of non-vertebral fractures and change in height; and to evaluate abaloparatide relative to teriparatide and placebo in BMD, safety (particularly hypercalcemia, ectopic mineralization and bone quality) and tolerability.

Trial Design

This phase 3 study was conducted between April 2011 and October 2014 at 28 centers in 10 countries. The study was planned to enroll ~2400 women age 50-85 who were ≥5 years post-menopause, with PMO and significant fracture risk, but otherwise healthy and ambulatory. Patients were randomized equally to 3 treatment arms: abaloparatide 80 mcg SC daily, matching placebo SC daily, and teriparatide 20 mcg SC daily (active control). The study was double blind with respect to abaloparatide vs. placebo, and open label with respect to the active control of commercially available teriparatide (with blinded assessments). The 18-month treatment period was followed by an additional month of observation off treatment. All patients received daily supplements of calcium and vitamin D during treatment.

Patients who were assigned to abaloparatide or placebo and completed study 003 could enroll in the extension study (005, reviewed separately below) to receive open label alendronate while remaining blinded to the original treatment assignment. This NDA includes the first 6 months' data from study 005; the primary analysis of fractures occurred both at month 18 (end of DB phase of study 003) and month 25 (after 6 months of study 005).

Figure 1 Design of Studies 003/005



Reviewer comment: *The use of double-blinded placebo as primary comparator is consistent with all previous PMO fracture trials. The active control (teriparatide) was included as a comparator for some secondary efficacy and safety outcomes, at the Applicant's option (not requested by FDA). While most PMO drugs have been evaluated in 3-year fracture trials, DBRUP believes that 2-year data are generally adequate. Anabolic drugs are generally considered to be appropriate for limited duration of use, and abaloparatide was planned for 18-month duration of use. Therefore the study 003 extension using alendronate was planned to fulfill the requirement for 2 year data (see section 3.2).*

The 80 mcg abaloparatide dose used in the study (dose reduction to 40 mcg was permitted for persistent hypercalcemia, see below) was chosen based on the phase 2 study, in which 80 mcg had significantly greater effects on BMD and bone markers than 20 or 40 mcg with comparable safety and tolerability, and with less hypercalcemia than teriparatide. Doses up to 120 mcg were studied in phase 1; based on an increase in nausea and one discontinuation due to vomiting at 120 mcg, the maximum tolerated dose was determined to be 100 mcg.

Eligibility criteria

The key inclusion criteria were as follows:

- Healthy ambulatory woman age 50-85 y/o
- Postmenopausal: amenorrhea ≥5 years and elevated FSH ≥30 IU/L
- Criteria for osteoporosis: BMD T-score ≤-2.5 to >-5.0 by DXA of L1-L4 spine or femoral neck, AND ≥2 mild or ≥1 moderate lumbar or thoracic vertebral fractures or history of low trauma fracture of forearm, humerus, sacrum, pelvis, hip, femur or tibia within the past 5 years
- Modified criteria for women >65 y/o: BMD T-score ≤-2.0 to >-5.0 if fracture criteria met; BMD T-score ≤-3.0 to >-5.0 if fracture criteria not met
- Good general health by H&P; BMI 18.5-33; no clinically significant abnormality of CBC or chemistry screen
- Serum Ca, Phos, ALP and PTH(1-84) all WNL (minor elevation or reduction in Ca allowed if ionized Ca is normal; elevated ALP acceptable if BSAP is normal; retesting allowed for minor PTH elevations)
- 25-OHD >15 ng/mL and <3xULN (if low, retesting allowed following supplementation)
- Systolic BP 100-155, diastolic BP 40-95, HR 45-100 (seated or supine)
- ECG without clinically significant abnormality and QTc ≤470 msec (Bazett's correction)

The key exclusion criteria were as follows:

- >4 spine fractures mild or moderate, or any severe fractures
- <2 vertebrae (L1-L4) evaluable by DXA
- S/P bilat hip replacement or otherwise unevaluable hip BMD
- History of bone disorders, other than PMO
- Potential osteosarcoma risk factors: Paget's disease, unexplained elevation of ALP, previous radiation, history of osteosarcoma
- History of chronic or recurrent renal, hepatic, pulmonary, allergic, cardiovascular, GI, endocrine, CNS, hematologic, metabolic or psychiatric conditions that may compromise safety or data interpretation
- History of Cushing's, hyperthyroidism, hypo- or hyperparathyroidism or malabsorptive syndrome within the past year
- Serum creatinine >2.0 mg/dL or eGFR <37 mL/min
- Cancer within 5 years, except basal cell or squamous skin Ca
- Nephrolithiasis or urolithiasis within 5 yrs
- Orthostatic hypotension (decrease ≥20 mm Hg systolic or ≥10 mmg Hg diastolic) or any symptomatic hypotension
- History of positive HBV, HCV or HIV (testing not required in absence of signs/symptoms)
- Prior treatment with PTH or PTHrP drugs including abaloparatide
- Prior bisphosphonates within 5 years, unless for <3 months and stopped because intolerant
- Prior denosumab, calcitonin, SERM, tibolone, androgens or anabolic steroids within 12

months (estrogen ± progestin replacement allowed)
- Prior fluoride or strontium within 5 yrs
- Daily corticosteroids (oral, intranasal or inhaled) within 12 months; occasional use of steroids for seasonal allergies or asthma was allowed (amendment 1)
- Anticonvulsants or anticoagulants within 6 mos
- General anesthesia within 12 wks
- Investigational drug within 12 mos
- Abnormal diet, excessive vitamin A or D, significant weight change
- Alcohol or drug abuse

Reviewer comment: *The study was designed to enroll a population at relatively high risk of osteoporotic fracture, thus the requirement for previous osteoporotic fracture in women ≤65 y/o, in addition to low BMD T-scores in all participants. The rationale for the slightly less restrictive criteria for women >65 y/o is that older age independently increases fracture risk.*

The study consisted of the following periods in succession:
- screening (up to 2 months)
- for eligible patients, a pretreatment period of 1 week for additional baseline procedures and training in self-injection, and beginning Ca/Vit D supplements
- treatment period (18 months)
- follow-up period (1 month): off treatment, but recommended to continue Ca/Vit D

Randomization was conducted on the first day of the treatment period using an interactive voice response system (IVRS) system in blocks of 6 for balance between treatment groups. There was no stratification.

Abaloparatide was supplied as a 2.0 mg/mL solution, in a (b) (4) mL glass cartridge designed to provide 30 daily doses, which was inserted into a reusable pen injector device. The placebo for injection was formulated and supplied similarly except for absence of abaloparatide, in an identical-appearing glass cartridge with reusable pen. The abaloparatide/placebo device could be adjusted to deliver half the dose as needed (see below). The active control teriparatide was supplied as commercial Forteo or Forsteo, in the manufacturer's non-reusable prefilled pen containing 28 daily doses, which was not masked, so there was no blinding for this study arm. Supplements of calcium (500-1000 mg/day) and Vitamin D (400-800 IU/day), "or a dose to be determined by investigator according to the patient's need", were supplied by the sites.

Injections were self-administered by patients (or another trained person as needed) in the morning at about the same time each day, in the periumbilical region, rotating the exact site. Ca/Vit D supplements were to be taken in the evening. Patients receiving abaloparatide/ placebo were instructed to change cartridges after 30 days and patients receiving teriparatide were instructed to change to a new pen after 28 days, regardless of any remaining volume of solution.

During the first 30 days of treatment, patients recorded every day the drug administration time, site of injection and any local reactions (redness, swelling, pain, tenderness on scales of 0-3, at 1 hr and 24 hr post injection) on patient diary cards; this was repeated during month 11. The diaries were collected and reviewed with the patient for treatment compliance and local adverse events at the month 1 and month 12 visits. In addition, patients maintained a diary throughout the study to summarize all study drug administration on a weekly basis. Site personnel were to review this information, record the reason for any missed dosing in the CRF and, as an additional compliance assessment, to measure the volume of residual fluid in returned cartridges.

Except for those listed in exclusion criteria (e.g. other osteoporosis treatments), most concomitant medications were allowed if approved by the investigator. Estrogens given as HRT prior to enrollment were allowed to be continued, but could not be initiated during the study, except for low dose vaginal estrogen. Occasional short term (≤3 month) use of corticosteroids for seasonal allergies or asthma was allowed.

During the treatment period, patients were seen at baseline and at months 1, 3, 6, 9, 12 and 18 (end of treatment). (At month 15, there was a brief visit for drug resupply and safety.) Study procedures during visits included the following:

- vital signs (including supine and standing BP, pre- and 1-hr-post-injection)
- ECGs (pre- and 1-hr-post-injection)
- labs including drug levels (at varying times post-injection) and anti-drug antibodies
- AEs and concomitant meds
- serum markers of bone turnover (also PTH1-84, 1,25OHD and 25OHD) and DXA at 6-month intervals
- spine x-rays for detection of fractures (the primary endpoint) at screening and month 18
- height at screening, baseline and month 18, measured standing using a stadiometer and standardized procedures

A month-19 end-of-study visit was scheduled 1 month after the last dose of study drug. Patients discontinuing prior to the end of the treatment period were to have all end-of-treatment and end-of-study evaluations performed. (see table of study procedures below).

The key efficacy assessments for vertebral fracture and BMD were coordinated by the central imaging contractor, (b) (4) These included AP and lateral thoracic/lumbar spine x-rays pre- and post-treatment; and DXA of spine and hip (and wrist in a subset). Lunar Prodigy DXA scanners were used at all sites except #132 (Czech Republic) and the US sites (#211, 212, 213, 214, 216) which used Hologic (total of 142 patients). Spine x-rays and DXA were conducted at screening, unless suitable films/scans were available within 3 months prior. Local spine x-ray and DXA readings were used to determine eligibility and fracture history. For purposes of data

analysis, all spine x-ray and DXA interpretations (treatment-blinded) were made centrally by (b) (4) which also coordinated longitudinal correction and cross calibration of DXA scanners. The submitted datasets include both raw and corrected BMD. Investigators were blinded to results of DXA scans during the treatment period.

Clinical fractures data (date, location, type and level of associated trauma) were recorded on dedicated eCRF pages. All source data pertaining to potential fracture events (x-rays or scans; radiology reports; ER, urgent care, hospital and/or surgery records) were sent to the Applicant for (treatment-blinded) adjudication.

At each treatment period visit, serum calcium (albumin-corrected) was measured both pre-dose (in chem panel) and 4 hours post-dose (estimated time of maximum Ca level), and 24-hr urine was collected for calcium and creatinine. The protocol included detailed algorithms regarding patients with hypercalcemia (defined as ≥10.7 mg/dL, or ≥0.3 mg/dL above ULN) or hypercalciuria (Ca/creat ratio >0.4 mg/mg). Predose hypercalcemia would result in temporary discontinuation of Ca/Vit D supplements and, if persistent or severe, also potentially a reduced dose of abaloparatide to 40 mcg daily (if on blinded abaloparatide/placebo), and/or discontinuation of study drug. Hypercalciuria would also cause suspension of supplements, but no change in study drug unless accompanied by hypercalcemia.

The following were assessed in subsets of patients:

- Iliac crest bone biopsies for quantitative bone histomorphometry to evaluate bone quality, using a double-labeling procedure, obtained between the month 12 and month 18 visits in up to 100 patients per group; all biopsies were read (treatment blinded) at a specialized facility (Osteoporosis Research Center, Creighton Univ., Dr. Robert Recker)
- Renal CT scans to investigate potential renal calcification: initially planned to occur only at month 18; following protocol amendment, at baseline and month 18 (all patients at selected centers)
- DXA of the wrist (in addition to spine and hip) at baseline and q6 mos (300 patients per group)
- Bone turnover markers (200 patients per group)

As a safety measure, any patient with a decline from baseline of >7% in BMD of spine or hip, confirmed by repeat DXA, was to be discontinued from the study. Patients experiencing a fracture (clinical vertebral, or non-vertebral fragility fracture) were to be re-consented if wishing to remain in the study. Discontinuation was required for persistent hypercalcemia; treatment-related SAEs; severe hypersensitivity to abaloparatide or teriparatide; or patient inability to complete procedures. Investigators also had discretion to withdraw patients from the study based on severe AEs or other illness, noncompliance or other protocol violations, or to temporarily suspend treatment when appropriate. Safety was monitored by an independent Data and Safety Monitoring Board (DSMB).

Table 9 Study 003: Schedule of visits and procedures

Study Period	Scree-ning	Pretreat-ment	Treatment								Follow-up
Visit:	1	2	3	4	5	6	7	8	V8R	9	10
Procedure *Study Day/ Month:*	1 to 2 months	-7 to -1	D1	1	3	6	9	12	15	18	19
Visit Window (Days)	NA	NA	± 1	± 3	± 7	± 7	± 7	± 14	± 7	± 14	± 3
Informed consent	X										
Review of entrance criteria	X	X									
Medical history	X										
Physical examination [1]	X									X	
Vital signs, weight and height measurements [2, 3]	X	X	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]		X	X
Electrocardiogram[4]	X		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]		X	X
Urinalysis (dipstick) [5,6]	X			X	X	X	X	X		X	
Chemistry blood collection [6]	X		X	X	X	X	X	X		X	
Hematology blood collection [6]	X			X	X	X	X	X		X	
Coagulation (PT and PTT) blood collection [6]	X									X	
FSH and serum estradiol [6]	X										
PTH(1-84) [6]	X					X		X		X	
25-hydroxy Vitamin D level [6]	X			X		X		X		X	
1,25-dihydroxy Vitamin D level [6]		X		X		X		X		X	
Serum markers of bone metabolism [6, 7]		X				X		X		X	
BA058 antibody levels [8]			X	X	X	X		X		X	
BA058 trough and peak (at randomized time) drug levels [9]			X[9]	X[9]	X[9]	X[9]		X[9]		X	
Calcium (4 hour post-injection) [10]			X	X	X	X	X	X			
24-hour urine collection [11] (for Calcium:Creatinine and Creatinine Clearance)			X	X	X	X	X	X		X	
Clinical and radiologic (spine, lumbar and thoracic vertebrae) fracture assessments	X									X	
Bone mineral density of hip and spine by DXA [13]	X					X		X		X	
Bone mineral density of wrist by DXA [12]			X			X		X		X	
Renal CT Scan (in subset of patients)[13]			X							X	
Quantitative Bone Histomorphometric Assessment (biopsy in subset of patients) [14]										X	
Calcium and Vitamin D supplements[15]			Daily Administration								
Injection training for patients [16]		X	X								
Study medication kit assignment via IVRS			X								
Study medication administration [3]			Daily Administration [3]								
Local tolerance (dermal reactions) assessment [17]			X	X	X	X	X	X		X	
Patient diary review [18]			X	X	X	X	X	X		X	
Document adverse events and concomitant medications			At any time; question patients at study visits								
Drug resupply									X		
Discuss possible participation in the Extension Study with BA058/Placebo patients										X	

	14.1	Schedule of Visits and Procedures (continued)
	1.	Interim or symptom directed physical examinations may be conducted at other time points to assess adverse events or clinical laboratory abnormalities.
	2.	Vital signs (orthostatic blood pressure, pulse rate, body temperature, and respiration rate) are to be recorded at each study visit. Height is to be measured at Visits 1, 2 and 9. Height will be measured at Visits 2 and 9 in the standing position using a medical stadiometer. Weight is to be measured during the Screening Period, at Visit 8, at the End-of-Treatment (Visit 9) and the Follow-up visit (Visit 10) only. Orthostatic blood pressure is to be measured initially after 5 minutes in the supine position and then again after standing for 3 minutes.
	3.	Study medication injections are to be administered under supervision in the study clinic during scheduled clinic visits. Assessments of orthostatic blood pressure will be done pre-dose and 60 minutes post-dose at Visits 3, 4, 5, 6, 7, and 8.
	4.	ECGs are to be obtained pre-dose and 1 hour post-dose on Visits 3, 4, 5, 6, 7 and 8.
	5.	On days of 24-hour urine collection, routine urinalysis will be performed on a sample freshly voided during the clinic visit.
	6.	These blood and urine samples are to be obtained under fasting conditions (N.P.O. for 8 hours; water is acceptable) in the morning of each scheduled study visit. They are to be collected prior to injection of the study medication during the Treatment Period.
	7.	Includes blood samples for PINP, bone-specific alkaline phosphatase, serum osteocalcin and CTX (subset of 600 patients).
	8.	Any patients who show presence of antibodies at End-of-Treatment (Visit 9) will have these additional time points tested to determine first occurrence of antibody positivity.
	9.	One peak level is to be drawn per patient per visit at the following varying post-injection times: 10 minutes to 30 minutes; 30 minutes to 1 hour; 1 hour to 2 hours; 2 hours to 3 hours; 3 hours to 4 hours. These draw times are to be randomized across Visits 3, 4, 5, 6, and 8. At the End-of-Treatment (Visit 9), only a trough level will be measured. No BA058 serum levels will be drawn for patients randomized to teriparatide.
	10.	These samples are to be drawn post-injection; the patient no longer needs to be fasting. The patient is to remain near the clinic for the post-injection blood collections.
	11.	This urine collection will be used for urinary calcium and urinary creatinine measurements. Patients will discard the 1st void and begin a 24-hour urine collection the day prior to the clinic visit. If a routine urinalysis is to be performed during the clinic visit, a separate sample freshly voided during the clinic visit will be used.
	12.	DXA is to be performed initially on the hip (femoral neck) and spine (L1-L4) during the Screening visit. A DXA of the wrist should be performed in a subset of patients on Day 1. Each DXA for a given patient must be performed on the same machine, preferably by the same technician.
	13.	In selected centers, a subset of patients in the BA058/Placebo and teriparatide groups enrolled prior to the effective date of Version 3 of the protocol, will be asked to undergo a single renal CT scan (obtained through standard abdominal/pelvic CT scan procedures) at the End-of-Treatment Visit (Visit 9). Patients in selected centers enrolled after the effective date of Version 3 of the protocol, will be asked to undergo two renal CT scans (obtained through standard abdominal/pelvic CT scan procedures), the first prior to treatment (Visit 3), and the second at the End-of- Treatment Visit (Visit 9).
	14.	Patients who agree to undergo the quantitative bone histomorphometric assessment will have additional clinic visits scheduled, as required, to prepare for the bone biopsy performed between Visit 8 and the End-of-Treatment visit (Visit 9).
	15.	Calcium and Vitamin D supplements begin at the Pretreatment Period visit and continue until the end of the Treatment Period; it will be recommended to patients that they continue these supplements through the Follow-up visit. A supply of supplements is provided for each patient. At each study visit, the patient's supply is to be assessed and the patient resupplied as necessary. Drug usage reconciliation is to be performed when a new supply is provided.
	16.	All patients will be trained on the use of the BA058/Placebo cartridge/pen delivery device at Visit 2; patients who are subsequently randomized to receive teriparatide will be trained on the use of the teriparatide pen at Visit 3.
	17.	The Investigator is to review and assess the injection sites at each Treatment Period visit.
	18.	Diaries will be provided to patients to record information regarding study medication injections (date/time/site of injection; local tolerance) for the first 30 days of treatment and for 30 days prior to Month 12 (Visit 8). In addition, the patient will also maintain a diary throughout the study to summarize all study drug administration on a weekly basis. The diaries are to be reviewed with the patient at each study visit.

Study Endpoints

The primary efficacy endpoint of study 003 is the percentage of abaloparatide-treated patients, compared to placebo, with new (incident) vertebral fractures (T4-L4) at end of treatment (month 18, or early termination). AP and lateral thoracic and lumbar spine x-rays were assessed by a central treatment-blinded radiologist (b) (4), in conjunction with screening films, according to the established semi-quantitative method of Genant (see table below). All potential new incident fractures (Genant grade 1-3 post-baseline, following grade 0 at baseline) were reviewed by a second radiologist; any disagreement was to be adjudicated by a third radiologist.

Table 10 Semi-quantitative scoring system for vertebral fractures (Genant)

Grade	Fracture severity	Definition
0	Normal	<20% reduction in anterior, mid and/or posterior vertebral height
1	Mild	20-25% reduction in height
2	Moderate	25-40% reduction in height
3	Severe	>40% reduction in height
Source: Genant et al (1993)		

Reviewer comment: *As discussed in section 2.2 of this review, incident vertebral fracture is the established efficacy standard for PMO drugs. This is in part due to the high incidence of such fractures relative to any other skeletal site in PMO patients. Among the vertebral fracture assessment methods available, the semi-quantitative Genant method has been used, by itself or in combination with quantitative measures, in most PMO fracture trials. Worsening of existing vertebral fractures (i.e. increase from baseline Genant grade 1 or 2 to a higher grade) has sometimes been used as a secondary endpoint, but is not considered by DBRUP to be appropriate for the primary endpoint. The initial SAP (12/8/14) for study 003 stated that "new and/or worsening" vertebral fracture would be the primary endpoint, but this was changed at DBRUP recommendation in the revised SAP (5/29/15) to new vertebral fractures only, consistent with the protocol.*

The protocol listed the following secondary efficacy endpoints:

- Incidence of non-vertebral fractures (defined only as "wrist, hip, rib etc."; no reference to level of trauma)
- Incidence of moderate and severe vertebral fractures
- Change in BMD of spine, hip, femoral neck and wrist
- Change in standing height
- Change in serum bone markers: P1NP, osteocalcin, BSAP, CTX

For non-vertebral fracture (NVF), the protocol-specified endpoint of incidence at month 18 was modified in the SAP to the time to first non-vertebral fracture (NVF) during the treatment and follow-up periods (to month 19), and this was designated a "key secondary" endpoint. Also, NVFs were defined in the SAP to include the following fracture types:

- fractures associated with low trauma, defined as a fall from standing height or less, or on stairs, steps or curbs
- fractures associated with minimal or moderate trauma other than a fall

and to exclude the following fracture types:

- spine, fingers, toes, skull, facial bones, sternum, patella
- fractures related to high trauma, including falls from a height equal to or higher than a stool, chair or first rung of a ladder (further defined in adjudication procedures manual as a height of ≥ 20 inches)
- pathologic fractures

The process for evaluation of each fracture as to location and degree of trauma using source data, and thereby the distinction of NVFs from other clinical fractures for analysis purposes, is described in imaging and procedures manuals. With all patient-specific identifiers redacted, these evaluations were carried out by medical staff of the Applicant, with expert radiologist consultation as needed.

Reviewer comment: *The NVF definition used is intended to include all non-spine fractures except for the types generally recognized as unrelated to osteoporosis/bone fragility, and not predictive of future fractures. This definition is generally consistent with literature studies of osteoporotic fractures and with previous PMO fracture trials; the endpoint is acceptable for labeling.*

The SAP also stated that exploratory analyses would compare treatment groups for each of the following time to event variables (not listed as endpoints in the protocol):

- Clinical fractures (not specifically defined in the SAP)
- NVF as defined above, but including any level of trauma
- Hip fracture
- Clinical spine fracture
- Wrist fracture
- Other clinical fracture (excluding hip, spine and wrist)
- Major osteoporotic fracture (FRAX definition: spine, hip, wrist, forearm, upper arm, shoulder)

Reviewer comment: *Among these exploratory endpoints, only hip fracture has been routinely considered appropriate for labeling of osteoporosis drugs. The category of clinical fractures, which would combine certain nonvertebral fractures with clinically apparent (not*

radiographically defined) vertebral fractures, (b) (4)

The SAP designated the following as "additional key secondary efficacy endpoints":

- Percent changes from baseline through month 18 in BMD of spine, total hip, femoral neck

Reviewer comment: *BMD of spine and hip are considered clinically relevant for osteoporosis drugs and are routinely included in labeling.*

Other efficacy endpoints were designated by the SAP as follows:

- Change and % change in height (baseline through month 18)
- Severity of incident (new and/or worsening) vertebral fractures through month 18
- Percent change in mid 1/3 radius BMD, baseline through month 18
- Percent changes in serum P1NP, BSAP, osteocalcin, CTX
- Incidence of new vertebral fractures through month 18, teriparatide vs. placebo

Reviewer comment: *These secondary endpoints are acceptable for providing supportive evidence of efficacy.*

Compliance with study drug, according to the protocol, was assessed through patient diaries, cartridge accountability, and site-assessment of remaining drug content of returned cartridges. The SAP described two methods of calculating compliance. The first would use the number of missed doses as recorded by patients in diaries, in conjunction with the number of days of study drug exposure. The second method would use measurement by site staff of returned drug quantities (based on total length of double blind study drug in a cartridge of 45.5 mm, and total length of open-label teriparatide in a pen of 37 mm). Because it was believed that the latter method would be subject to more uncertainties e.g. measurement errors, the Applicant chose the diary method for the primary compliance calculations, with the second method used only to confirm low compliance (<80%) in individual patients for exclusion from the per-protocol population. In response to DBRUP request, the Applicant also calculated compliance based on the second method.

Statistical Analysis Plan

The SAP defined the following analysis populations:

- Safety: all randomized patients who received ≥1 dose of study medication
- ITT: all randomized patients; used for all efficacy analyses except vertebral fracture
- Modified ITT (mITT): all ITT patients with evaluable pre- and post-treatment x-ray assessment for vertebral fractures; used for primary efficacy endpoint
- Per-protocol: mITT patients without protocol violations (including deviation from key enrollment criteria, treatment period <3 mos, compliance <80%, use of prohibited

concomitant medications, violations affecting data quality)
Reviewer comment: *The original protocol stated that the per-protocol population would be defined, in part, by compliance >90%; the SAP changed this to >80%.*

Additional analysis populations were defined for bone turnover markers, bone biopsies, renal CT scans and anti-abaloparatide antibodies, based on all patients with those respective assessments.

The primary endpoint of new vertebral fractures (VFs) was analyzed in the modified-ITT population. The Fisher's exact test was used to compare the abaloparatide and placebo treatment groups, with derivation of absolute and relative risk reductions for VF and 95% CI for the treatment difference. Supportive evidence was to be provided by analysis of VF in the per-protocol population and in a sensitivity analysis using a logistic regression model to impute missing VF data for ITT patients who were excluded from mITT, using 8 covariates and assuming that subjects were missing at random.

The proposed sample size of 800 patients per treatment arm, assuming a 20% dropout rate, was estimated to provide 90% power at a two-sided alpha of 0.05 to detect a difference of 4% between treatments in new VFs, assuming a fracture rate of 7% in placebo patients and 3% in abaloparatide-treated patients. The study was also adequately powered to evaluate BMD of the spine, hip and femoral neck, but the Applicant did not provide evidence that the study was adequately powered for non-vertebral fracture evaluation.

To control for multiplicity of efficacy endpoints analyzed (primary and key secondary), the SAP specified the following hierarchy of testing, with each step required to show 2-sided significance at the 5% level:

- Vertebral fracture, ABL vs. PLA (primary endpoint)
- BMD of total hip, ABL vs. PLA at month 18
- BMD of femoral neck, ABL vs. PLA at month 18
- BMD of lumbar spine, ABL vs. PLA at month 18
- Non-vertebral fractures, ABL vs. PLA by month 19
- BMD of total hip, ABL vs. TPD at month 6
- BMD of femoral neck, ABL vs. TPD at month 6
- Non-vertebral fractures, ABL vs. TPD
- BMD of lumbar spine, ABL vs. TPD at month 6

For the key secondary endpoint of non-vertebral fracture (NVF), the SAP stated that the time to first NVF between ABL/PLA and ABL/TPD groups would be analyzed using the log-rank test (ITT population), and the Cox proportional hazard model would be used to calculate the hazard ration (95% CI). Kaplan-Meier curves would be generated and used to estimate incidence rates at month 19.

BMD data were analyzed in the ITT population for subjects with baseline and ≥1 post-baseline value. For the BMD analyses listed in the hierarchy above (ABL vs. PLA at 18 months, ABL vs. TPD at 6 months), an ANCOVA model was used to compare treatment groups in percent changes from baseline in BMD using LOCF imputation, with a MMRM model used for the sensitivity analysis. Each model included fixed effects (including DXA manufacturer, Hologic vs. Lunar Prodigy; treatment; visit and treatment-by-visit interaction) and fixed covariate (including baseline BMD). Per protocol analyses were planned to support the ITT findings. Exploratory analyses were planned for BMD responders (>0%, >3% and >6% increase at each site, and at all sites), and for BMD comparisons other than those listed in the testing hierarchy (ABL vs. PLA at 6 and 12 months, and ABL vs. TPD at 12 months).

Reviewer comment: *The Applicant was informed at the end of phase 2 meeting that efficacy comparisons and claims between different drugs (e.g. abaloparatide/ teriparatide) must be based on fracture data, and that BMD data are not sufficient for this purpose.*

The following subgroup analyses for VF, NVF and BMD data were prespecified in the SAP:

- Age (<65, 65 to <75, ≥75 years)
- Years since menopause (<15, 15-<25, ≥25)
- Race (White, Black/African-American, Asian, Other)
- Region (N. America, S. America, Europe, Asia)
- Any prior fracture (yes/no)
- Any prior vertebral fracture (yes/no)
- Any prior non-vertebral fracture (yes, no)
- Prevalence of vertebral fracture at baseline (0, 1, ≥2)
- Severe disease (least BMD T-score ≤-2.5 and prevalent vertebral fx) at baseline (yes, no)
- Lumbar Spine BMD T-score at baseline (≤-2.5, >-2.5)
- Lumbar Spine BMD T-score at baseline (≤-3.0, >-3.0)
- Total hip BMD T-score at baseline (≤-2.5, >-2.5)
- Total hip BMD T-score at baseline (≤-3.0, >-3.0)
- Femoral neck BMD T-score at baseline (≤-2.5, >-2.5)
- Femoral neck BMD T-score at baseline (≤-3.0, >-3.0)

No interim analyses for efficacy were conducted.

Protocol Amendments

The original protocol for study 003 (v. 1.0, dated 12/2/10) was submitted to FDA on 12/17/10 and enrollment began in April 2011. There were 3 protocol amendments:

Amendment 1 (v. 2.0, 10/21/11 and 11/17/11) included minor changes to enrollment criteria, and clarification regarding assessments of calcium, 25OHD, and PTH.

Amendment 2 (v. 3.0, 7/5/12) included 3 major changes:

- Renal CT scans: previously required (at selected centers) only at end of treatment, were now required for new enrollees both pre- and post-treatment
- Bone biopsies: previously required for abaloparatide and placebo arms only, were now required for some teriparatide subjects as well
- Description of extension study (005): previously called for 6 additional months of abaloparatide (for a total of 24 months abaloparatide), was modified to the current design (abaloparatide and placebo subjects switched after 18 months to alendronate)

Amendment 3 (v. 4.0, 3/31/14) reflected the API name change from BA058 to abaloparatide; distinguished protocol violations vs. deviations, for defining the per-protocol population; and clarified that the hypercalcemia algorithms for dose modification or discontinuation were based on pre- (not post-) dose serum calcium.

As discussed above, the SAP modified the secondary endpoint of non-vertebral fracture from the method presented in the protocol (incidence of NVF at month 18) to a time-to-event analysis through month 19 (includes the 1-month follow-up period). The SAP also defined the specific fracture types to be included in the NVF endpoint and added exploratory analyses of other fracture categories (including clinical fracture, major osteoporotic fracture) and a responder analysis of BMD as discussed above.

Adjudication of clinical fractures based on source data was conducted by the Applicant prior to database lock in Dec. 2014. During finalization of the CSR in Sept. 2015, discrepancies were noted in locations of some fractures between the eCRF "fractures page" and the AE tables. Therefore, a complete re-adjudication (again, treatment-blinded) of all fractures was conducted, including review of all source data and x-ray re-interpretation. A total of 16 fractures were re-characterized for location (e.g. upper leg to hip, forearm to wrist); there were no changes in the determinations of associated trauma level or presence/absence of fracture.

Data Quality and Integrity: Sponsor's Assurance

The protocol stated that the study would be conducted and monitored in accordance with ICH-GCP requirements; and that study documentation and other source data would be maintained and made available for inspection upon request. The following assessments were to be made by treatment-blinded, independent assessors:

- Vertebral x-rays for fracture assessment
- DXA scans
- Renal CT scans
- Bone histomorphometry

Reviewer comment: *The procedures for these key assessments were appropriate.*

6.1.2. Study Results

Compliance with Good Clinical Practice

The study 003 protocol and patient informed consent for were reviewed and approved by an IEC or IRB for each site in accordance with 21 CFR part 56. The study was conducted in accordance with ethical principles of the Declaration of Helsinki and with current guidelines for Good Clinical Practice (GCP) in accordance with 21 CFR Parts 50, 54 and 312.

Financial Disclosure

Study 003 is a "covered clinical study" as defined in 21 CFR Part 54, for the purposes of financial disclosure review. Among the 38 Principal Investigators and 156 Sub-investigators who participated in the study, the Applicant received (as of 3/10/16) financial disclosure statements from 187; none had disclosable information. The Applicant certifies (Form 3454) that they have acted with due diligence to obtain the missing financial statements from the remaining 7 sub-investigators, 4 of whom never actually worked on the study, and that they have no reason to believe that bias was introduced into the study from their sites.

Patient Disposition

Study 003 was conducted at 28 sites in 6 European countries and the US, Brazil, Argentina and Hong Kong. There were 5268 patients screened; about half failed screening, most commonly for failing to meet inclusion criteria for vertebral fractures and/or BMD. There were 2463 women enrolled and randomized, comprising the ITT population (table below). The safety population is the same as ITT except for excluding 3 patients who were randomized but not treated. The mITT population for evaluation of the primary vertebral fracture endpoint and the per-protocol population comprised 86% and 78% of ITT patients respectively. About 70% of study 003 participants who were eligible (i.e. those in abaloparatide or placebo arms) subsequently entered the extension study (005).

Overall, 77% of patients completed the 18-month treatment period; there were fewer completers in the abaloparatide arm (74%) compared to the placebo and teriparatide arms (78% and 80%). This was attributed to higher rates of discontinuations in abaloparatide patients (11%, vs. 6% in each of the other arms) that were related to AEs, especially nausea, dizziness, headache and palpitations.

Table 11 Study 003: Patient Disposition and Analysis Populations

	Placebo n (%)	**Abaloparatide** n (%)	**Teriparatide** n (%)	**Overall** n (%)
Randomized (ITT)	821 (100)	824 (100)	818 (100)	2463 (100)
Safety population*	820 (100)	822 (100)	818 (100)	2460 (100)
Modified ITT (mITT)**	711 (87)	690 (84)	717 (88)	2118 (86)
Per-protocol population	643 (78)	625 (76)	649 (79)	1917 (78)
Completed study	637 (78)	606 (74)	658 (80)	1901 (77)
Early discontinuation	184 (22)	218 (27)	160 (20)	562 (23)
Primary reason for D/C‡				
Adverse event	53 (29)	89 (41)	53 (33)	195 (35)
Withdrew consent	48 (26)	47 (22)	45 (28)	140 (25)
Refusal of treatment	33 (18)	31 (14)	19 (12)	83 (15)
Lost to follow up	5 (3)	15 (7)	10 (6)	30 (5)
Inability to complete study procedures	7 (4)	11 (5)	5 (3)	23 (4)
Non-compliance	10 (5)	6 (3)	9 (6)	25 (4)
Serious illness	0	4 (2)	5 (3)	9 (2)
Protocol violation	4 (2)	4 (2)	5 (3)	13 (2)
Death	5 (3)	3 (1)	2 (1)	10 (2)
Treatment related SAE	0	0	2 (1)	2 (< 1)
Hypercalcemia or hypercalciuria	0	1 (< 1)	1 (< 1)	2 (< 1)
BMD decline ≥ 7%	12 (7)	1 (< 1)	1 (< 1)	14 (3)
Other	7 (4)	6 (3)	3 (2)	16 (3)
Enrolled in study 005‡‡	581 (71)	558 (68)	0	1139 (46)

* randomized patients who received ≥1 dose of study drug
** ITT patients with both baseline and a post-baseline spine x-ray assessment for vertebral fractures
‡ percentages based on all study 003 patients with early discontinuation
‡‡ percentages based on patients in study 003 safety population
Source: CSR Section 14, Table 14.1.1A

Reviewer comment: *The overall 77% study completion rate at 18 months is acceptable for a PMO trial, despite the higher AE-related dropout rate in abaloparatide patients.*

Among the 28 study sites, those with the highest enrollment are listed in the table below. As shown, the rate of early discontinuations varied from 15-33% at these sites. The highest-enrolling US site (#216) was North Miami (n=21 patients, 0.9% of overall ITT population); the 4 other US sites enrolled 2-8 patients each. Among the total of 39 US patients, 13 (33%) discontinued early, so only 27 (69%) are included in the mITT (vs. 86% in the overall study).

Table 12 Study 003: Highest-enrolling sites

Site	Investigator	Site #	Country	# enrolled/ # screened	# of patients enrolled	% of ITT patients	% premature discontinuation
Hong Kong	Lau	181	Hong Kong	59%	387	15.7	15
Rio de Janeiro	Russo	121	Brazil	60%	380	15.4	29
Pardubice	Hala	131	Czech Rep.	59%	290	11.8	18
Vejle	Alexandersen	103	Denmark	76%	155	6.3	15
Bucharest	Mustatea	161	Romania	37%	144	5.8	33
Aalborg	Nedergaard	102	Denmark	67%	124	5.0	15
Ballerup	Krogsaa	101	Denmark	59%	117	4.8	16
Brno	Slesinger	132	Czech Rep.	64%	103	4.2	22
Sao Paolo	Zerbini	123	Brazil	30%	101	4.1	33
Tallinn	Valter	111	Estonia	51%	85	3.5	28
Vilnius	Visockiene	151	Lithuania	21%	84	3.4	25
Warszaw	Jendrych	141	Poland	27%	79	3.2	24

Source: CSR Section 14, Table 14.1.2, response to OSI request (M 5.3.5.4)

Protocol Violations/Deviations

About 10% of mITT patients in each treatment group were excluded from the per-protocol population because of protocol violations, most commonly treatment duration <3 months or not meeting BMD inclusion criteria. Abaloparatide patients were somewhat more likely to have treatment duration <3 months or compliance <80%.

Table 13 Study 003: Protocol violations (mITT)

	Placebo (N=711)	**Abaloparatide** (N=690)	**Teriparatide** (N=717)	**Overall** (N=2118)
Excluded from per-protocol for any reason	68 (9.6%)	65 (9.4%)	68 (9.5%)	201 (9.5%)
Most common reasons for exclusion*				
Treatment duration <3 mos	19 (28%)	27 (42%)	17 (25%)	63 (31%)
Did not meet BMD inclusion criteria	14	18	17	49 (24%)
Abnormal screening Ca, Phos, ALP or PTH level	8	6	10	24 (12%)
Prior treatment with fluoride, strontium or bisphosphonates	9	6	14	29 (14%)
Compliance <80%	3	7	4	14 (7%)
Concomitant systemic steroids >1 month during study	5	2	6	13 (7%)

* percentages based on patients excluded from per-protocol
Source: CSR Section 14, Table 14.1.1B

Table of Demographic Characteristics

The mITT and ITT populations, used for the primary and secondary efficacy endpoints respectively, were generally similar; demographics of these two populations are summarized in the tables below. The median age of patients was 68 years, with a median of 20 years post menopause. European patients made up 56% of the ITT population and were 99.8% white. South American patients (mostly Brazil) constituted 26% of the ITT and were 84% white, 11% black and 4% “other” race (descriptions included mulatto and multiracial); 83% of South American patients were described as Hispanic and 17% as non-Hispanic. The one Asian site (Hong Kong) enrolled 16% of ITT patients and 98% of Asian-race patients in the ITT. There were 39 North American (US) patients (1.6% of ITT), who were predominantly white (34, vs. 3 black, 2 other race) and mostly Hispanic (30). The median age was highest in South America (71) and Asia (70), compared to Europe (67) and the US (63). About 12% of patients overall had smoked in the past 5 years; the mean number of alcohol drinks was 0.9/week.

Table 14 Study 003: Demographic baseline characteristics (ITT)

	Placebo N=821	**Abaloparatide** N=824	**Teriparatide** N=818	**Overall** N=2463
Sex (% female)	821 (100)	824 (100)	818 (100)	2463 (100)
Age				
Mean years (SD)	68.6 (6.5)	68.8 (6.5)	68.7 (6.6)	68.7 (6.5)
Median (years)	68.0	68.0	68.0	68.0
Min, max (years)	50, 85	49, 85	50, 84	49, 85
Age Group, n (%)				
<65 years	163(20)	154 (19)	154 (19)	471 (19)
65 to < 75 years	514 (63)	519 (63)	504 (62)	1537 (62)
≥ 75 years	144 (18)	151 (18)	160 (20)	455 (19)
BMI (kg/m^2)				
Median	24.8	25.0	24.9	24.9
Min, Max	18.4, 34.9	18.5, 33.0	18.5, 33.2	18.4, 34.9
Race, n (%)				
White	655 (80)	663 (81)	645 (79)	1963 (80)
Asian	131 (16)	128 (16)	137 (17)	396 (16)
Black or African American	23 (3)	26 (3)	24 (3)	73 (3)
Other	12 (2)	7 (1)	12 (2)	31 (1.3)
Ethnicity, n (%)				
Hispanic or Latino	199 (24)	199 (24)	194 (24)	592 (24)
Not Hispanic or Latino	622 (76)	625 (76)	624 (76)	1871 (76)
Region				
North America (US)	13 (1.6)	17 (2.1)	9 (1.1)	39 (1.6)
South America	217 (26)	222 (27)	222 (27)	661 (27)
Europe	461 (56)	460 (56)	455 (56)	1376 (56)
Asia	130 (16)	125 (15)	132 (16)	387 (16)
Country				
Brazil	202 (25)	207 (25)	207 (25)	616 (25)
Czech Republic	157 (19)	146 (18)	153 (19)	456 (19)
Denmark	130 (16)	133 (16)	133 (16)	396 (16)
Hong Kong	130 (16)	125 (15)	132 (16)	387 (16)
Poland	67 (8)	70 (9)	62 (8)	199 (8)
Romania	46 (6)	51 (6)	47 (6)	144 (6)
Estonia	30 (4)	35 (4)	32 (4)	97 (4)
Lithuania	31 (4)	25 (3)	28 (3)	84 (3)
Argentina	15 (2)	15 (2)	15 (2)	45 (2)
USA	13 (2)	17 (2)	9 (1)	39 (1.6)

Source: CSR Section 14 Tables 14.1.2, 14.1.2.1A

Table 15 Study 003: Demographic baseline characteristics (mITT)

	Placebo N=717	**Abaloparatide** N=690	**Teriparatide** N=717	**Overall** N=2118
Sex (% female)	717 (100)	690 (100)	717 (100)	2118 (100)
Age				
Mean years (SD)	68.6 (6.2)	68.6 (6.5)	68.7 (6.3)	68.7 (6.3)
Median (years)	68.0	68.0	68.0	68.0
Min, max (years)	50, 86	49, 85	51, 84	49, 86
Age Group, n (%)				
<65 years	131(18)	126 (18)	133 (19)	390 (18)
65 to < 75 years	459 (65)	437 (63)	450 (63)	1346 (64)
≥ 75 years	121 (17)	127 (18)	134 (19)	382 (18)
BMI (kg/m^2)				
Median	25.0	25.0	25.1	25.0
Min, Max	18.4, 34.9	18.5, 33.0	18.5, 33.2	18.4, 34.9
Race, n (%)				
White	554 (78)	540 (78)	555 (77)	1649 (78)
Asian	126 (18)	123 (18)	132 (18)	381 (18)
Black or African American	20 (3)	22 (3)	18 (3)	60 (3)
Other*	11 (1)	5 (<1)	12 (2)	28 (1.3)
Ethnicity, n (%)				
Hispanic or Latino	163 (23)	154 (22)	155 (22)	472 (22)
Not Hispanic or Latino	548 (77)	536 (78)	562 (78)	1646 (78)
Region				
North America (US)	8 (1.1)	12 (1.7)	7 (1.0)	27 (1.3)
South America	183 (26)	177 (26)	183 (26)	543 (26)
Europe	395 (56)	381 (55)	400 (56)	1176 (56)
Asia	125 (18)	120 (17)	127 (18)	372 (18)
Country				
Brazil	170 (24)	167 (24)	171 (24)	508 (24)
Czech Republic	130 (18)	121 (17)	137 (19)	388 (18)
Denmark	125 (17)	119 (17)	128 (18)	372 (18)
Hong Kong	125 (17)	120 (17)	127 (18)	372 (17)
Poland	51 (7)	52 (8)	55 (8)	158 (7)
Romania	34 (5)	37 (5)	30 (4)	101 (5)
Estonia	28 (4)	30 (4)	24 (3)	82 (4)
Lithuania	27 (4)	22 (3)	26 (4)	75 (4)
Argentina	13 (2)	10 (1)	12 (2)	35 (2)
USA	8 (1)	12 (2)	7 (1)	27 (1.3)
Source: CSR Section 14 Tables 14.1.2, 14.1.2.1B, ADSL				

Reviewer comment: *Although the study population was predominantly white, the proportions of Asian and Hispanic patients were substantially higher than in most PMO studies. The low proportion of US patients continues a recent trend in PMO trials which is apparently related in part to IRB requirements and ethical issues involving placebo controlled studies.*

Among ITT patients, older patients (≥75 years) were less likely to complete the study (72%, vs. 80% for age <65 and 78% for age 65-75), mostly due to greater proportion with "withdrawal by subject". Study completion rates were lower in white compared to Asian patients (76% vs. 85%), Hispanics compared to non-Hispanics (70% vs. 80%), and South American patients compared to patients in Europe or Asia (72%, 78%, 85%). These differences were largely attributable to 67% completion rates at each of the two largest Brazilian sites (#121 and 123) and a 47% completion rate at the Argentinian site (#201). The small subset of US patients also had a low completion rate (67%).

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline osteoporosis status

As shown in the table below, the percentage of patients with baseline vertebral fractures differed markedly between the assessments by the imaging contractor (b) (4) (23.8%), and by the investigators (44.6%). The latter were apparently based on local radiologists' readings which were not standardized or described in the protocol. Another factor in the discrepancy is that the (b) (4) assessments were limited to T4-L4 vertebrae while investigators could assess any thoracic or lumbar vertebra (T1-L5).

Reviewer comment: *Differences between investigator ana (b) (4) assessments of baseline vertebral status varied widely between sites. The greatest discrepancy was at site #161 (Romania), where all 144 enrolled patients were considered by investigators to have baseline vertebral fractures, but only 16 were assessed as positive for baseline fracture by (b) (4). Investigator assessments at this site included 64 patients (44% of total) with fractures of L5 (not assessed by (b) (4)); 60 of these were "mild" and 4 were "moderate"). Mean baseline BMD T-scores at this site were -2.6 (lumbar spine) and -1.7 (femoral neck). This site had a somewhat lower than average rate of enrollment out of screened patients (37%).*

A history of clinical fracture (any skeletal location) was reported by 53% of ITT patients at screening. Prior nonvertebral fractures by SAP definition (excludes skull, fingers, toes etc.) were reported by 48% of ITT patients; the most common sites were wrist (20.7% of ITT), forearm (11.7%), ankle (4.4%), lower leg (4.2%), upper arm (3.3%) and foot (3.2%). Prior major osteoporotic fractures were reported by 38% of patients, also mostly wrist/forearm fractures; 1.7% of patients reported prior hip fractures. These percentages were similar in ITT and mITT patients and similar between treatment groups. White patients were somewhat more likely to have baseline vertebral or prior nonvertebral fractures (25%, 53%) compared to Asian patients (20%, 30%), while Asians had the lowest mean baseline T-scores (spine -3.1, femoral neck -2.7, total hip -2.3). US patients were around average in terms of baseline T-scores and prevalent vertebral fractures (23%), and had high rates of prior nonvertebral fractures (80%) and major osteoporotic fractures (82%). Mean baseline FRAX scores of US patients were 16.0% for major

osteoporotic fracture and 3.7% for hip fracture; corresponding scores were 14.0% and 4.5% (Europe); 8.7% and 3.7% (S. America); and 17.4% and 8.1% (Asia).

Table 16 Study 003: Baseline fracture and BMD status (ITT)

	Placebo N=821	**Abaloparatide** N=824	**Teriparatide** N=818	**Overall** N=2463
Prevalent vertebral fracture at baseline (b) (4), n (%)	188 (23)	177 (22)	220 (27)	585 (24)
Prevalent vertebral fracture at baseline (investigator), n (%)	366 (45)	356 (43)	376 (46)	1098 (45)
Prior nonvertebral fracture*, n (%)	416 (51)	405 (49)	371 (45)	1192 (48)
Prior major osteoporotic fracture**, n (%)	318 (39)	319 (39)	297 (36)	934 (38)
Lumbar spine BMD T-score, mean	-2.92	-2.87	-2.86	-2.88
Femoral neck BMD T-score, Mean	-2.15	-2.16	-2.12	-2.14
Total hip BMD T-score, mean	-1.89	-1.89	-1.85	-1.88
* excludes spine, skull, face, fingers, toes, sternum, patella ** fractures of upper arm, shoulder, forearm, wrist, hip, clinical spine Source: CSR Section 14, Tables 14.1.2.1A; 14.1.2.1.3				

Because fulfillment of enrollment criteria was determined by investigators' assessments (as per the protocol), inclusion criterion #3 (baseline BMD and fracture status) was nominally met by 99.4% of patients, as follows:

- <65 years; any prior osteoporotic fracture; any T-score ≤ -2.5: 18.4% of patients
- ≥65 years; any prior osteoporotic fracture; any T-score ≤ -2.0: 52.3% of patients
- ≥65 years; no prior osteoporotic fracture; any T-score ≤ -3.0: 28.7% of patients

However if the (b) (4) vertebral fracture assessments are used, this inclusion criterion was only fulfilled by 81.4% of patients:

- <65 years; any prior osteoporotic fracture; any T-score ≤ -2.5: 12.6% of patients
- ≥65 years; any prior osteoporotic fracture; any T-score ≤ -2.0: 42.5% of patients
- ≥65 years; no prior osteoporotic fracture; any T-score ≤ -3.0: 26.3% of patients

Using the (b) (4) assessments, a total of 111 patients (4.5%) had neither a prior osteoporotic fracture nor a T-score ≤ -2.5; all except 12 of these patients (0.5%) were ≥65 y/o, and all except 2 (0.1%) had at least one T-score ≤ -1.0. There were no major treatment group differences in these measures.

***Reviewer comment**:*
The above calculations by the Applicant overstate somewhat the percent of patients fulfilling inclusion criterion #3 because the designation "prior osteoporotic fracture" in this case includes any vertebral or nonvertebral fracture (excluding skull, fingers toes etc., regardless of trauma), whereas the inclusion criterion in the protocol was more restricted: ≥2 mild or ≥1 moderate lumbar or thoracic vertebral fractures or history of low trauma fracture of forearm, humerus, sacrum, pelvis, hip, femur or tibia within the past 5 years.

The protocol anticipated a study population with severe osteoporosis, which is defined by the WHO as a T-score < -2.5 and history of a fragility-related fracture. These criteria are somewhat more restrictive than the inclusion criteria used in other recent major PMO fracture trials. However, they were strictly met by only about half of the enrolled study 003 patients, and overall the study population was quite similar to, for example, the Prolia phase 3 trial, in which enrollees had baseline vertebral fracture prevalence of 23%, nonvertebral fracture history positive in 39%, and mean baseline BMD T-scores of -2.8 (lumbar spine), -2.2 (femoral neck), and -1.9 (total hip). These characteristics are consistent with a broad osteoporosis population. At least 95% of study 003 patients would have met current NOF recommendations for drug treatment (see section 2.2).

Except for osteoporosis, the most commonly reported medical conditions reported by patients in the baseline medical histories were hypertension (47%), osteoarthritis (28%), back pain (21%) and hypercholesterolemia (20%). The most frequent concomitant medications by class were statins (29%), NSAIDs (25%), ACE inhibitors (20%), proton pump inhibitors (21%), beta-blockers (18%), calcium channel blockers (16%), NSAIDs (14%), aspirin (13%), ARBs (11%), benzodiazepines (10%), and thyroid replacement (9%).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Based on patient recording of missed doses in the daily/weekly diaries, mean compliance with study medication was calculated at 97-98% of prescribed doses in each of the 3 treatment arms (table below). However, using the other method based on returned drug volumes, compliance appears to have been lower in the teriparatide group (84.9%) compared to the other groups (95.9%, 95.9%). This latter method also exhibited greater variability in compliance estimates within each arm, identifying more patients with low compliance estimates, and some with compliance >100% (which was not possible with the diary method).

Table 17 Study 003: Compliance with study medication (safety population)

	Placebo (N=820)	**Abaloparatide** (N=822)	**Teriparatide** (N=818)
Diary method: n with exposure data	793	782	789
Overall duration of exposure, days (mean)	467.5	450.3	476.2
Total number of doses taken based on diaries (mean)	460.5	440.3	468.5
Calculated % compliance (mean)	98.0	97.2	97.9
Drug dispense/return log method: n with drug dispensed/returned data	818	820	817
Total number of doses taken based on dispense/return volumes	443.6	416.9	403.0
Calculated % compliance (mean)	95.9	95.5	84.9
Sources: CSR Section 14, Table 14.3.5.12A and Response to IR 10/21/2016, Appendix Table 1			

Data for individual study sites (the table below lists the largest sites) show that compliance estimated by the diary method approached 100% for all 3 treatment arms at nearly all sites, while compliance estimated by returned drug volumes was also >90% for placebo and abaloparatide at most sites, but consistently lower for teriparatide.

Table 18 Study 003: Study drug compliance by site (higher-enrolling sites)

				Percent compliance* (mean)		
Site #	**Country**	**Enrollment**	**Method***	**Placebo**	**Abaloparatide**	**Teriparatide**
181	Hong Kong	387	Diaries	99	98	99
			Volumes	98	91	85
121	Brazil	380	Diaries	99	98	98
			Volumes	86	86	75
131	Czech Rep.	290	Diaries	98	97	98
			Volumes	98	101	88
103	Denmark	155	Diaries	99	99	99
			Volumes	93	93	88
161	Romania	144	Diaries	97	97	97
			Volumes	91	99	80
102	Denmark	124	Diaries	98	98	99
			Volumes	98	96	90
101	Denmark	117	Diaries	97	97	98
			Volumes	100	98	83
132	Czech Rep.	103	Diaries	98	97	99
			Volumes	96	96	89
123	Brazil	101	Diaries	96	97	94
			Volumes	89	95	84
111	Estonia	85	Diaries	95	92	95
			Volumes	90	92	86

* based on patient diaries, or dispensed/returned drug volumes
Source: Response to IR 10/21/2016, Appendix Table 1.1

Reviewer comment: *It is unclear which of the two methods of compliance assessment is more accurate. For the double-blind (placebo and abaloparatide) treatment arms, the compliance estimates are consistently high by either method, therefore compliance with these treatments appears to have been very good. The finding of lower teriparatide compliance with the returned-volumes method was consistent across study sites, suggesting that some aspect of the measurements or calculations with the teriparatide device may have caused systematic underestimation of use. Because teriparatide was open label, actual lower compliance cannot be ruled out, but the extent of any difference from the other groups would likely be too small to have a material impact on efficacy or safety conclusions.*

Efficacy Results – Primary Endpoint (Vertebral Fracture)

Study 003 met the primary efficacy endpoint, showing a highly significant 86% reduction in risk of new vertebral fractures at month 18 (4 vs. 30 patients, 0.58% vs. 4.22%), with abaloparatide compared to placebo. The absolute risk reduction in this population was 3.6%. The teriparatide active-control group showed a similar 80% reduction in new fractures (6 vs. 30 patients). Among these there were 4 patients (3 placebo, 1 abaloparatide) with >1 new vertebral fracture (in each case 2 new fractures). There were also 3 patients (1 in each treatment group) with worsening of a preexisting vertebral fracture (see below).

Table 19 Study 003: Incidence of new vertebral fracture (mITT)

	Placebo (N=711)	**Abaloparatide** (N=690)	**Teriparatide** (N=717)
Number of patients (%) with ≥1 new fracture	30 (4.22%)	4 (0.58%)	6 (0.84%)
95% CI*	2.97, 5.96	0.23, 1.48	0.38, 1.81
Absolute risk reduction vs. placebo (95% CI)**		-3.64 (-5.42, -2.10)	-3.38 (-5.18, -1.80)
Relative risk reduction vs. placebo (95% CI)***		-0.86 (-0.95, -0.61)	-0.80 (-0.92, -0.53)
P-value vs. placebo‡		<0.0001	<0.0001

* 95% CI for percentage based on the Wilson's Score method
** 95% CI based on Newcombe's method
*** 95% CI based on Wald's method
‡ p-values from Fisher's exact test
Source: CSR Table 13 and XE dataset

Results for the per-protocol population were similar to the mITT, with 25, 4 and 5 new vertebral fractures in placebo, abaloparatide and teriparatide treatment groups respectively, and an 84% risk reduction for abaloparatide vs. placebo (0.64% vs. 3.89%, p<0.0001). To assess the potential impact of data missing from the mITT, a prespecified sensitivity analysis was performed using the ITT population, using a multiple imputation method to account for the missing vertebral fracture data. The estimated incidence rates in this analysis were 0.78% for abaloparatide and 3.92% for placebo (RRR -0.81; 95% CI -0.93, -0.46).

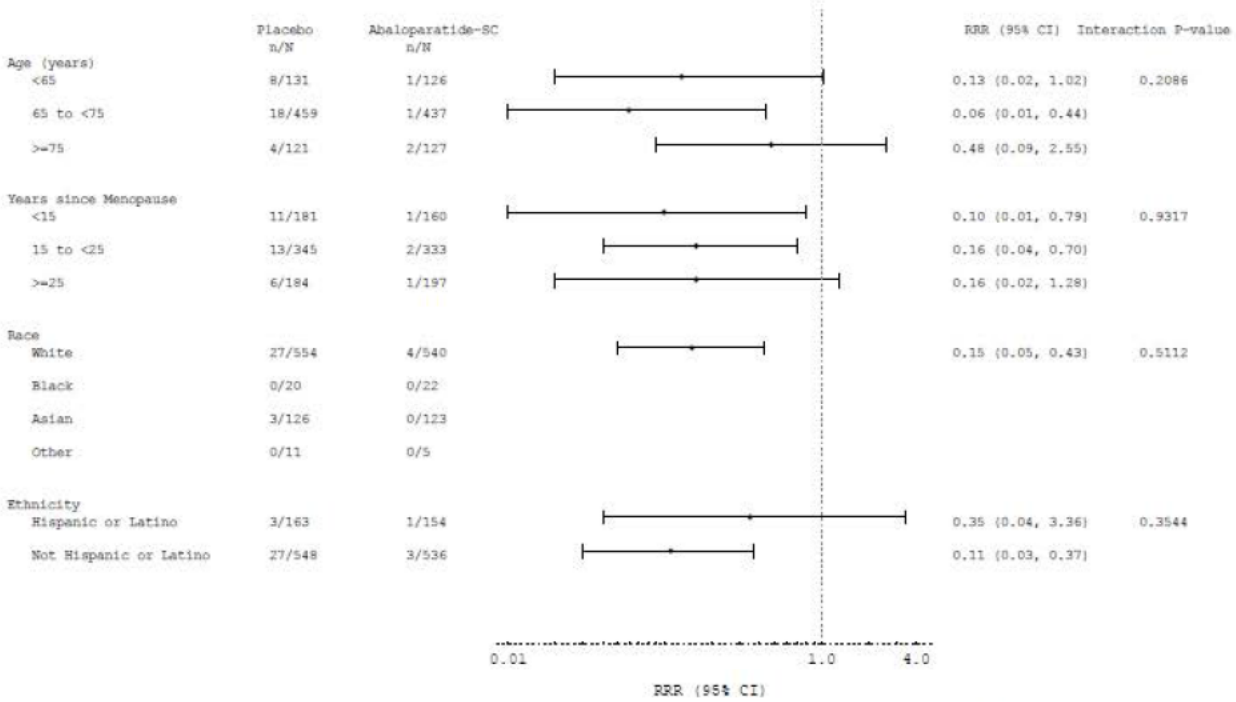
Reviewer comment: *The relative risk reduction of 86% in vertebral fractures with abaloparatide vs. placebo is the largest yet reported in a major PMO trial of any drug. The absolute risk reduction (3.6%), however, is smaller than some earlier trials which enrolled higher-risk patients and reported higher fracture rates in all treatment groups (see section 2.2). For example, 90% of patients in the previous Forteo pivotal PMO trial (GHAC) had a vertebral fracture at baseline, and during the study, new fractures developed in 14.3% of placebo and 5.0% of Forteo recipients, a 65% relative reduction and 9.3% absolute reduction. Because study 003 patients*

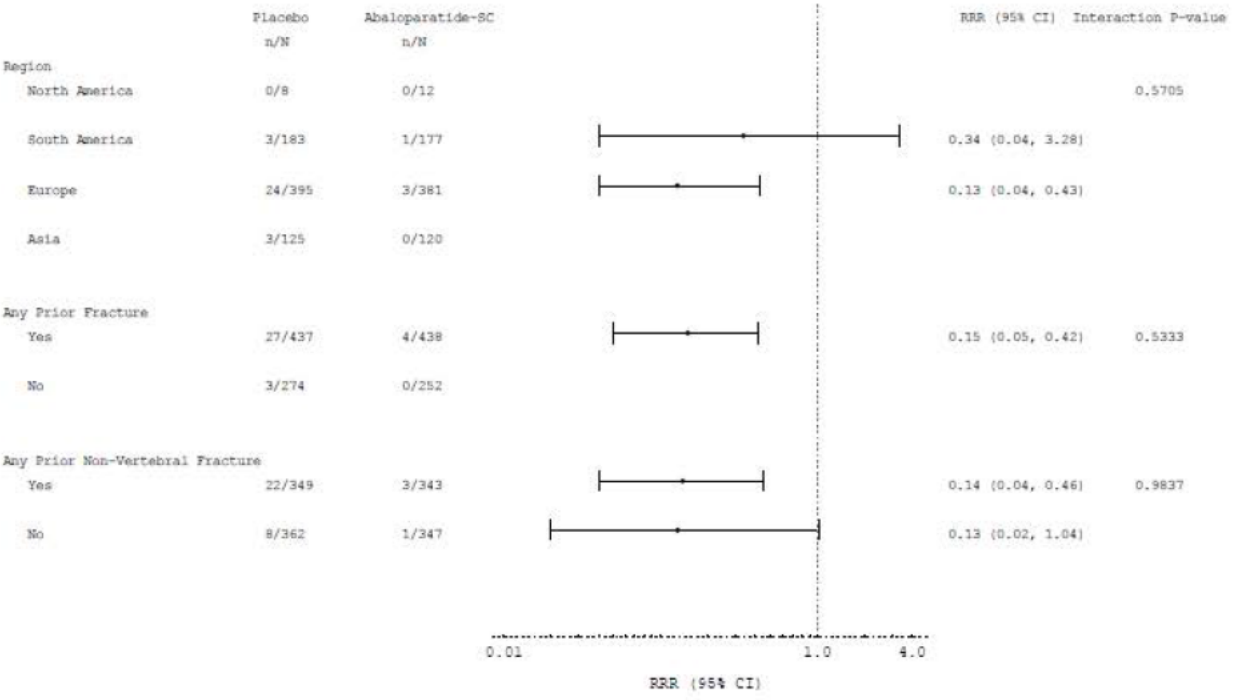
were lower risk and had far fewer fractures than in GHAC, it is difficult to compare the two studies or the two drugs, except to say that efficacy of both abaloparatide and teriparatide in 003 appears generally consistent with efficacy of Forteo in GHAC.

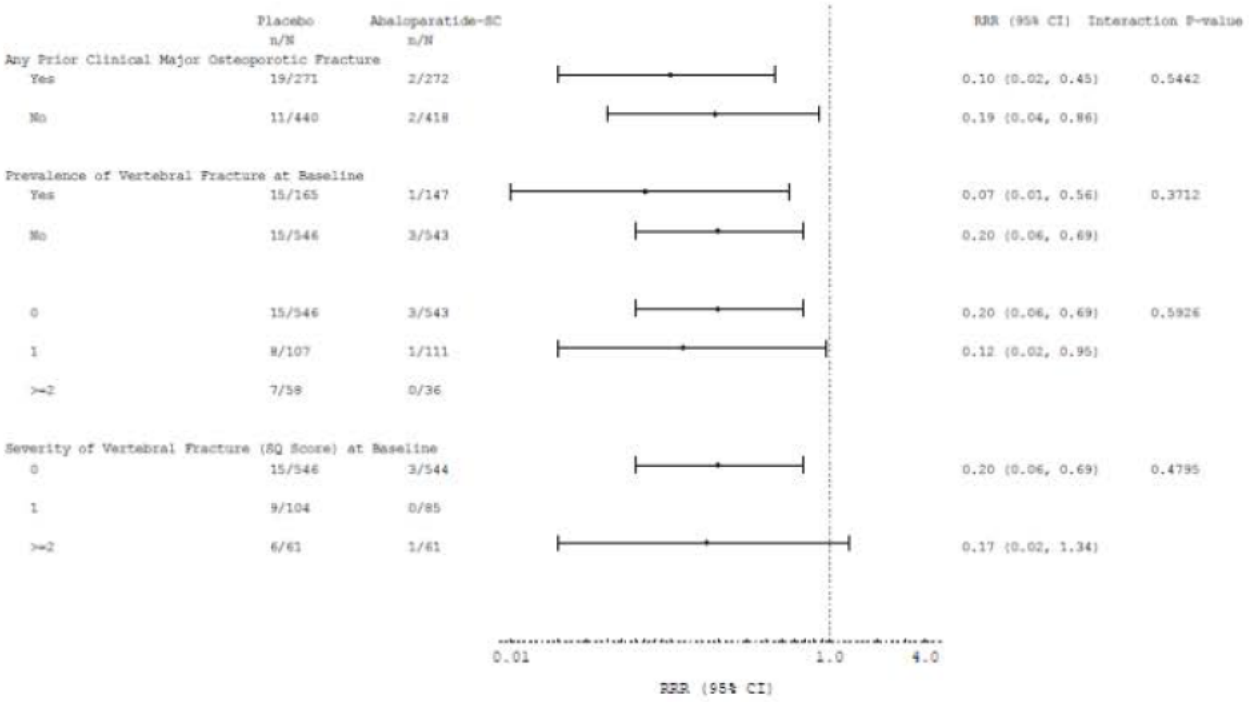
Vertebral fracture subgroups

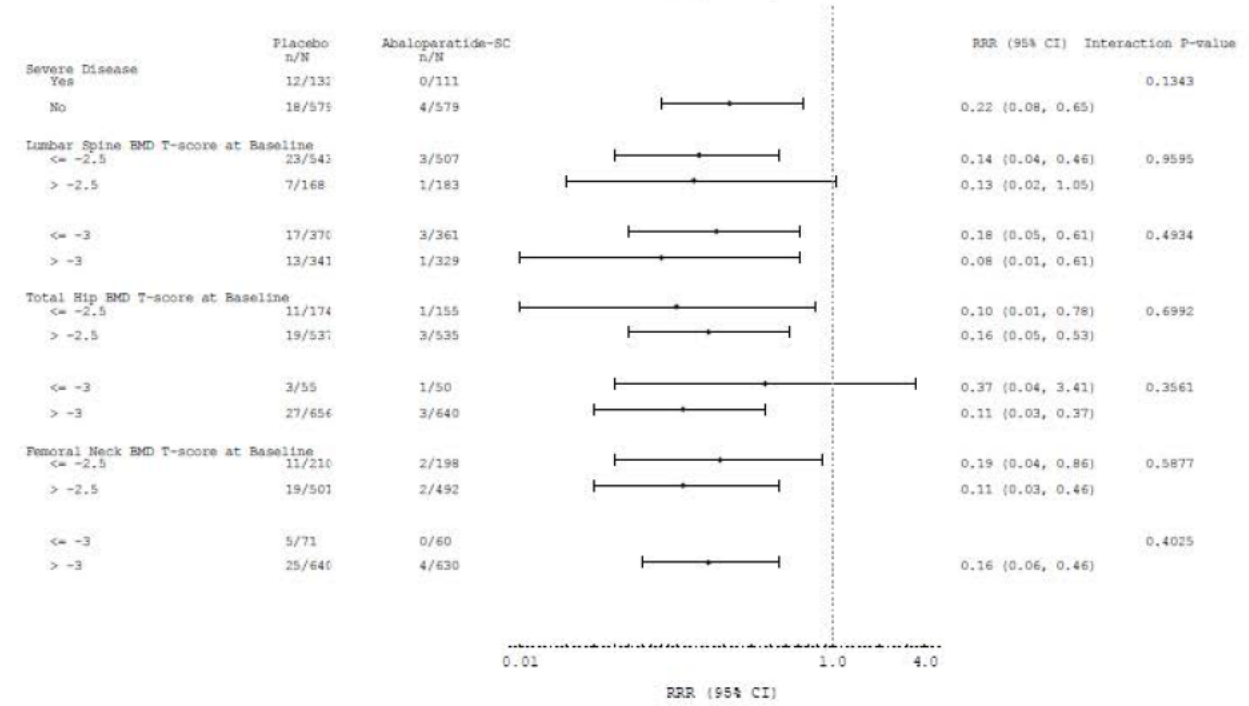
Examination of subgroups shows that, as expected, incidence of new vertebral fractures was generally higher in patients with prior fractures. The reduction in fractures with abaloparatide compared to placebo was consistent across multiple prespecified subgroups of age, years since menopause, presence or absence of prior fracture (vertebral or nonvertebral), and BMD at baseline (Forest plot below). However, white European patients comprised more than half of enrollees and had substantially higher rates of new vertebral fractures than patients in other racial groups and regions. Therefore, although non-white, Hispanic, and non-European patients showed similar trends in treatment effects, the number of fractures in these subgroups is insufficient to support any conclusions. (See below for discussion of applicability of data to the US population.)

Figure 2 Study 003: New vertebral fractures by treatment group (abaloparatide vs. placebo) and patient subgroup (mITT)









Interaction p-value was based on the Breslow-Day test.

Source: Response to IR 11/22/16, Figure 1.1

Data Quality and Integrity – Reviewers' Assessment

Pending the results of OSI inspections, this reviewer has not identified any inconsistencies in the data or other reason to question the validity of the results. In part this is because vertebral fracture is an objective endpoint, and analyses were conducted by treatment-blinded radiologists at an independent central facility.

Efficacy Results – Secondary and other relevant endpoints

Non-vertebral fractures:
There were 111 patients (4.5% of overall ITT) with a total of 129 adjudicated clinical fractures (any location) during study 003 (baseline to month 19). To meet the SAP definition of nonvertebral fractures (NVFs), the following fracture events were excluded:

- 32 fractures of spine (13), face (1), toes (8), fingers (5) or patella (5)
- 17 fractures attributed to trauma (e.g. car accident, fall off bike)

The remaining 80 NVFs occurred in 75 patients represented in the following table. There were trends of fewer fractures with both active treatments relative to placebo across most skeletal sites, with the notable exception of a large number of wrist fractures with teriparatide. There were only 2 patients (both placebo) with hip fractures.

Table 20 Study 003: Non-vertebral fracture*, incidence by location and treatment group (ITT)

	Placebo (N=821) n (%)	**Abaloparatide** (N=824) n (%)	**Teriparatide** (N=818) n (%)
Patients with any NVF skeletal location*	**33 (4.0)** (36 fractures)	**18 (2.2)** (18 fractures)	**24 (2.9)** (26 fractures)
Wrist	13 (1.6)	7 (0.8)	17 (2.1)
Forearm	4 (0.5)	1 (0.1)	0
Upper arm	3 (0.4)	1 (0.1)	2 (0.2)
Shoulder	1 (0.1)	0	0
Hand	0	0	1 (0.1)
Clavicle	0	1 (0.1)	1 (0.1)
Ribs	4 (0.5)	1 (0.1)	1 (0.1)
Pelvis	0	1 (0.1)	1 (0.1)
Hip	2 (0.2)	0	0
Upper leg (not hip)	1 (0.1)	0	0
Knee	0	1 (0.1)	0
Lower leg (not knee or ankle)	0	1 (0.1)	1 (0.1)
Ankle	4 (0.5)	1 (0.1)	1 (0.1)
Foot	2 (0.2)	3 (0.4)	0

* Source document verified; excludes fractures of skull, face, toes, fingers, sternum, patella, and high-trauma fractures
Source: CSR Section 14, Table 14.2.5.2, FRACLOG dataset

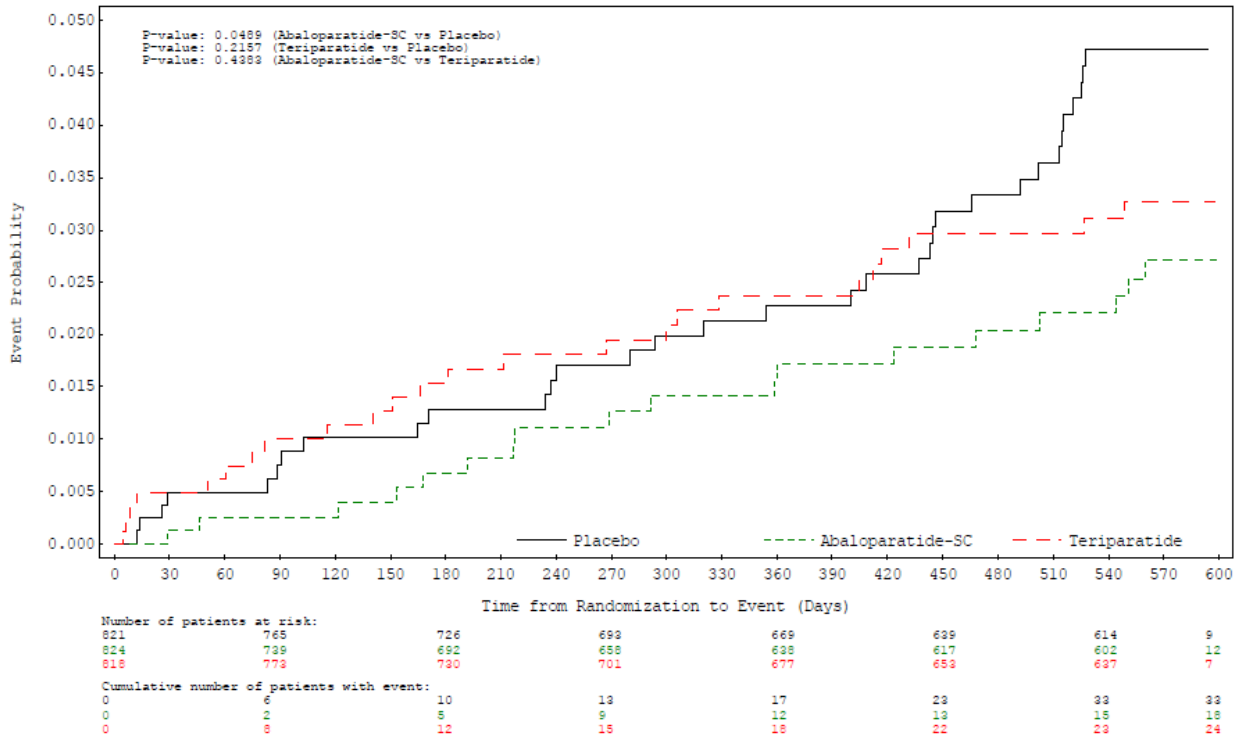
The secondary endpoint of time to first NVF in abaloparatide vs. placebo patients was met, with an estimated 43% hazard reduction (p=0.0489, see table below), and the respective K-M curves (figure below) showed separation throughout the treatment period. The absolute risk reduction was -1.84% (95% CI -3.60%, -0.15%) (from statistical reviewer). NVF incidence in the teriparatide group was intermediate between the other two groups. Although the K-M curves for abaloparatide and teriparatide were separate throughout the study, the differences between these groups were not statistically significant therefore the prespecified secondary endpoint for this comparison was not met. In the per-protocol population there were 4 fewer placebo patients with NVF (n=29) and the same number for abaloparatide patients (n=18), so this time-to-event comparison did not reach statistical significance in the per-protocol population.

Table 21 Study 003: Nonvertebral fracture, time to event (ITT)

	Placebo (N=821)	**Abaloparatide** (N=824)	**Teriparatide** (N=818)
Patients with NVF, n (%)	33 (4.0)	18 (2.2)	24 (2.9)
K-M estimated event rate at month 19 (%)	4.7	2.7	3.3
Hazard Ratio vs. placebo (95% CI)*		0.57 (0.32, 1.00)	0.72 (0.42, 1.22)
Hazard Ratio vs. teriparatide (95% CI)*		0.79 (0.43, 1.45)	
p-value vs. placebo**		0.0489	0.2157
p-value vs. teriparatide**		0.4383	

* Cox proportional hazard model
** log rank test
Source: CSR Section 14, Table 14.2.4.1A

Figure 3 Study 003: Nonvertebral fracture, Kaplan-Meier curve of time to first incidence, by treatment group (ITT)



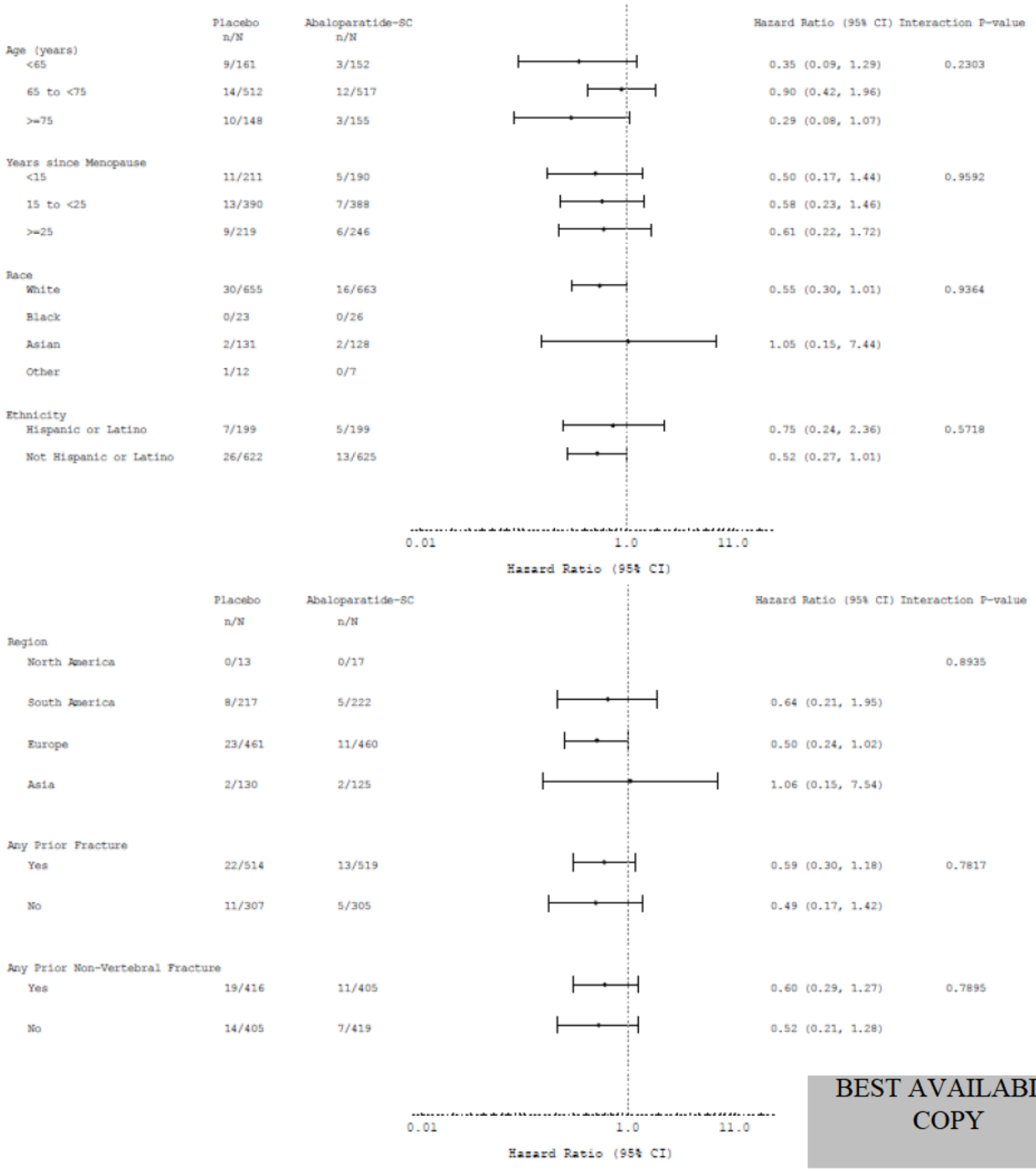
Source: CSR Section 14.2, Fig. 14.2.4.1

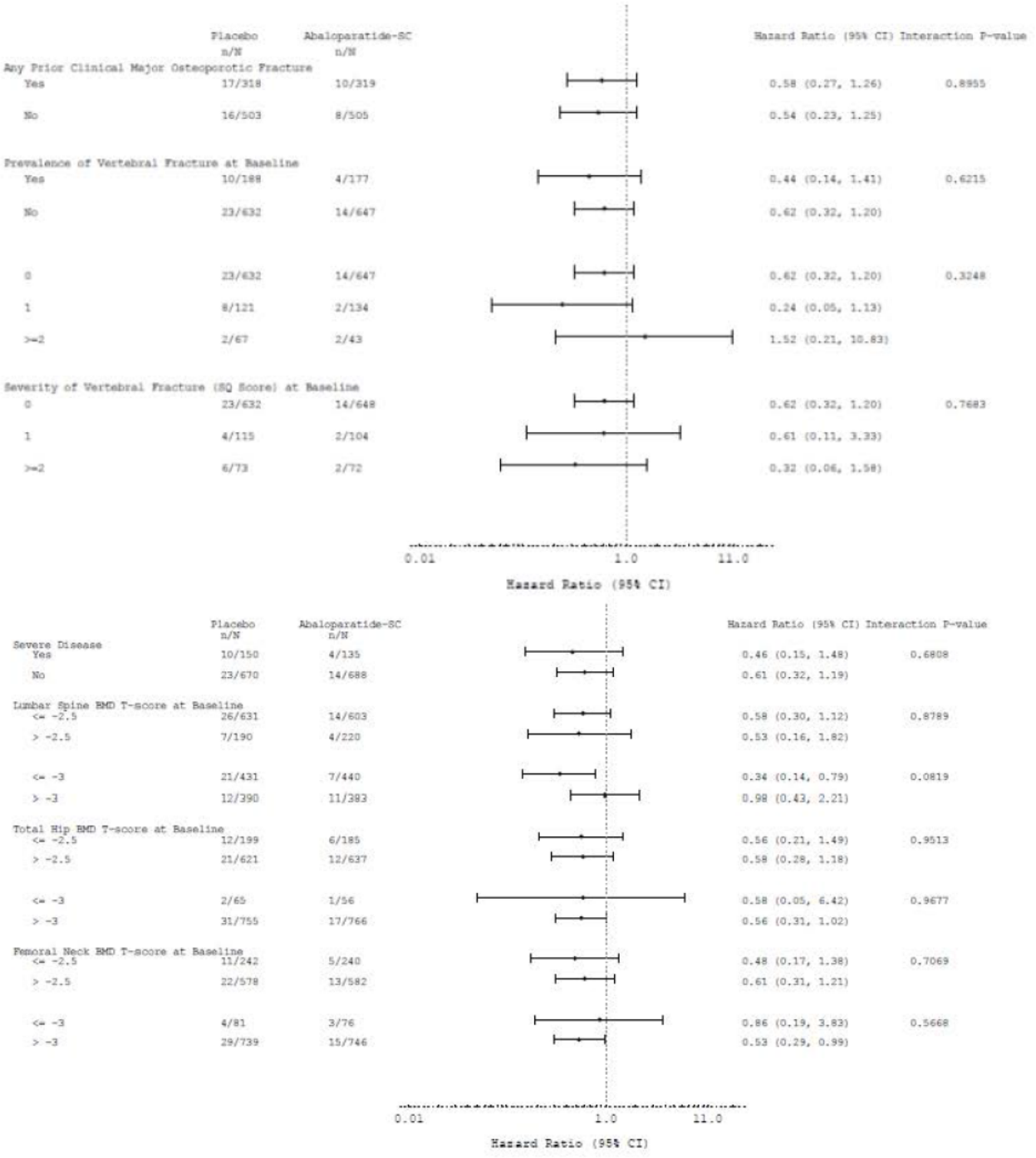
Reviewer comment:
Although the reduction in non-vertebral fractures with abaloparatide vs. placebo just reached statistical significance, the relative reduction (43%) compares favorably to other PMO fracture studies and was exceeded only by the GHAC (phase 3) study of Forteo, in which fragility NVFs were reported in 5.5% of placebo and 2.6% of Forteo recipients (RRR 53%; 95% CI: 12%, 75%; p<0.05). In that study the Forteo and placebo curves separated at ~9-12 months, but in study 003 (as shown) teriparatide and placebo curves only separate at ~15 months, and the risk reduction of 28% with teriparatide was not statistically superior to placebo. The reason for this is unclear and may reflect differences in the study populations such as baseline fracture risk. Another notable difference between these two studies is the opposing trends in wrist fractures, which in GHAC occurred in 1.3% of placebo and 0.4% of Forteo recipients (compare to 1.6% placebo, 2.1% teriparatide in study 003).

<u>Nonvertebral fracture subgroups:</u>
As with vertebral fractures, there was no evidence of an interaction between treatment (abaloparatide/ placebo) and any of the prespecified subgroups (Forest plot below). However, also similar to vertebral fractures, most NVFs were reported in European patients; there were

too few events to assess treatment effects in other regions, Hispanic or non-white patients, although trends were generally similar throughout.

Figure 4 Study 003: Nonvertebral fractures by treatment group (abaloparatide vs. placebo) and subgroup (ITT)





Interaction p-value was based on the Cox proportional hazard model that includes main effects of treatment, subgroup and treatment by subgroup interaction.

Source: Response to IR 11/22/16, Figure 1.4

Exploratory fracture analyses were conducted for several other fracture categories as specified in the SAP (though not in the protocol). The Applicant proposes (b) (4) these endpoints were not included in the fixed sequence of testing for multiple comparisons, were not previously discussed with the Agency, and are not routinely included in osteoporosis drug labeling.

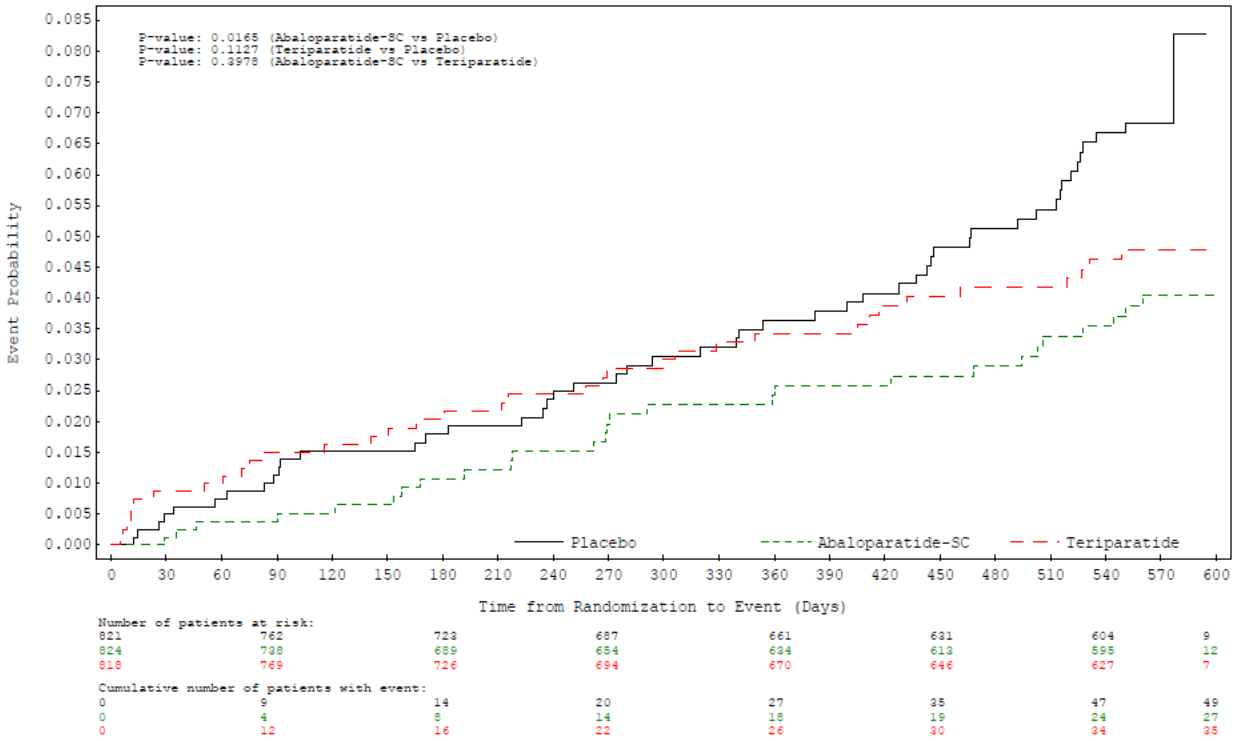
Clinical fractures included all verified clinical fractures regardless of site or level of trauma. Incidence through month 19 was lowest in the abaloparatide group, and because of an imbalance in clinical vertebral fractures (see below), the difference from placebo was greater than for nonvertebral fractures alone. Teriparatide was again intermediate between the two other treatments in incidence, and not significantly different from either.

Table 22 Study 003: Clinical fracture, time to event (ITT)

	Placebo (N=821)	**Abaloparatide** (N=824)	**Teriparatide** (N=818)
Patients with clinical fracture, n (%)	49 (6.0) (57 fractures)	27 (3.3) (33 fractures)	35 (4.3) (39 fractures)
K-M estimated event rate at month 19	8.3	4.0	4.8
Hazard Ratio vs. placebo (95% CI)*		0.57 (0.35, 0.91)	0.71 (0.46, 1.09)
Hazard Ratio vs. teriparatide (95% CI)*		0.81 (0.49, 1.33)	
p-value vs. placebo**		0.0165	0.1127
p-value vs. teriparatide**		0.3978	

* Cox proportional hazard model
** log rank test
Statistical comparisons (p-values) were not included in hierarchy of hypothesis testing and not adjusted for multiplicity
Source: CSR Section 14, Table 14.2.4.1A and 14.2.5.2

Figure 5 Study 003: Clinical fracture, Kaplan-Meier curve of time to first incidence, by treatment group (ITT)



Source: CSR Section 14.2, Fig. 14.2.5.1

Reviewer comment: *Unlike the NVF endpoint, this "clinical fracture" endpoint includes not only patients with vertebral fractures, which are relevant to PMO treatment, but also patients with fractures of toes (8), fingers (3), patella (3) and face (1), and several other trauma-related fractures that are of little or no relevance to treatment effects. The Applicant proposes* (b) (4) (b) (4) *fractures of fingers, toes and face were excluded from both the clinical fracture and non-vertebral fracture endpoints.*

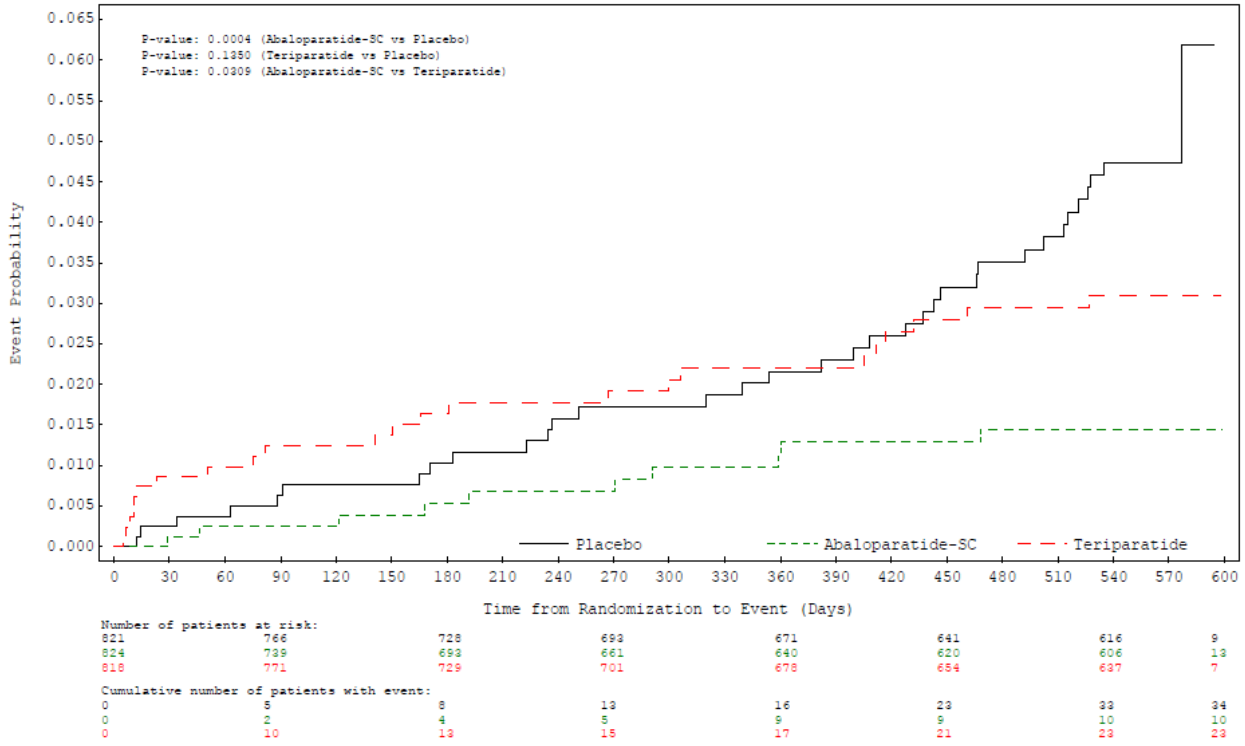
Major osteoporotic fractures: These included fractures of the wrist, forearm, shoulder, hip and clinical spine, i.e. the most common osteoporosis fracture types as defined by FRAX. Incidence was significantly lower (by nominal p-values) in abaloparatide patients, relative to the other groups.

Table 23 Study 003: Major osteoporotic fracture, time to event (ITT)

	Placebo (N=821)	**Abaloparatide** (N=824)	**Teriparatide** (N=818)
K-M estimated event rate at month 19	6.2	1.5	3.1
# of patients with event, n (%)	34 (4.1)	10 (1.2)	23 (2.8)
Hazard Ratio vs. placebo (95% CI)*		0.30 (0.15, 0.61)	0.67 (0.39, 1.14)
Hazard Ratio vs. teriparatide (95% CI)*		0.45 (0.21, 0.95)	
p-value vs. placebo**		0.0004	0.1350
p-value vs. teriparatide**		0.0309	

* Cox proportional hazard model
** log rank test
Statistical comparisons (p-values) were not included in hierarchy of hypothesis testing and not adjusted for multiplicity
Source: CSR Section 14, Table 14.2.4.1A

Figure 6 Study 003: Major osteoporotic fracture, Kaplan-Meier curve of time to first incidence, by treatment group (ITT)



Source: CSR Section 14.2, Fig. 14.2.5.1B

Reviewer comment: *Like the "clinical fracture" endpoint, major osteoporotic fracture was an exploratory endpoint not prespecified in the hierarchy of hypothesis testing,* (b) (4)

Clinical Vertebral Fractures

Clinically apparent vertebral fractures, another exploratory endpoint, were reported in 9 placebo, 1 abaloparatide and 3 teriparatide patients. Of these, two were adjudicated as related to high trauma: an abaloparatide patient in a severe auto accident, and a teriparatide patient who fell 2 meters down off a ladder.

Reviewer comment: *The treatment group difference in clinically apparent vertebral fractures is similar to the difference in morphometric vertebral fractures. This is consistent with other studies, e.g. in the FIT studies of alendronate there were similar 45-55% reductions in both clinically apparent and morphometric fractures.*

Vertebral fracture severity

The table below shows the severity score of new vertebral fractures, with somewhat more fractures in the more-severe categories (Genant 2-3) in the placebo group and possibly in the other groups, though with small numbers.

Table 24 Study 003: Severity of new vertebral fractures (mITT)

	Placebo (N=711)	**Abaloparatide** (N=690)	**Teriparatide** (N=717)
Subjects with new vertebral fractures	30	4	6
Semiquantitative (Genant) highest score			
1	4	0	2
2	14	2	1
3	12	2	3
Source: CSR Table 22, XE dataset			

There were only 3 patients, one in each treatment group, with "worsening" vertebral fractures (score of 1→2 in a teriparatide patient, 1→3 in an abaloparatide patient and a placebo patient).

Reviewer comment: *Previously, the Forteo phase 3 trial (GHAC) was able to show reductions in the proportion of patients with new moderate or severe vertebral fractures, and in patients with multiple new vertebral fractures, as the study population was more high-risk than study 003 and there were more fractures. There were 30 patients in study GHAC with >1 new vertebral fracture, and only 4 in this study 003.*

Bone mineral density

BMD of the hip and spine demonstrated progressive increases during treatment with abaloparatide and teriparatide, apparent within 6 months, which tended to be somewhat larger with abaloparatide, and minimal change from baseline with placebo (tables below). Comparisons between abaloparatide and placebo at month 18 (LOCF) for total hip, femoral neck and lumbar spine BMD (included in the prespecified statistical testing hierarchy) were each significant at the p<0.0001 level. As the Applicant sought to demonstrate more rapid BMD increases with abaloparatide compared to teriparatide, comparisons of these two drugs at month 6 were also included in the testing hierarchy, and were also significant at p<0.0001 for total hip and femoral neck. Compared to the ITT/LOCF data in the following tables, BMD percent increases at each of these bone sites were somewhat greater for the per-protocol population, and for the by-visit data at month 18.

Table 25 Study 003: Total hip BMD by visit (ITT, LOCF)

	Placebo (N=821)	**Abaloparatide** (N=824)	**Teriparatide** (N=818)
Baseline, n	820	822	818
Mean (g/cm^2)	0.767	0.766	0.773
Month 6, n	820	822	818
Mean % change from baseline (SD)	**0.29** (2.11)	**2.07** (2.55)	**1.33** (2.38)
p-value vs. teriparatide*		<0.0001	
Month 12, n	820	822	818
Mean % change from baseline (SD)	**0.10** (2.45)	**2.87** (3.06)	**2.03** (2.92)
Month 18, n	820	822	818
Mean % change from baseline (SD)	**-0.08** (2.77)	**3.44** (3.50)	**2.81** (3.33)
p-value vs. placebo*		<0.0001	

Missing BMD data were imputed using last observation carried forward (LOCF)
* p-values were derived from contrast tests based on ANCOVA model fitted using only the data of the two treatment groups to be compared
Source: CSR Table 14.2.7.1A

Table 26 Study 003: Femoral neck BMD by visit (ITT, LOCF)

	Placebo (N=821)	**Abaloparatide** (N=824)	**Teriparatide** (N=818)
Baseline, n	820	822	818
Mean (g/cm^2)	0.732	0.730	0.737
Month 6, n	820	822	818
Mean % change from baseline (SD)	**-0.12** (2.84)	**1.54** (3.07)	**0.80** (2.90)
p-value vs. teriparatide*		<0.0001	
Month 12, n	820	822	818
Mean % change from baseline (SD)	**-0.37** (3.09)	**2.21** (3.56)	**1.41** (3.38)
Month 18, n	820	822	818
Mean % change from baseline (SD)	**-0.44** (3.57)	**2.90** (4.21)	**2.26** (3.57)
p-value vs. placebo*		<0.0001	

Missing BMD data were imputed using last observation carried forward (LOCF)
* p-values were derived from contrast tests based on ANCOVA model fitted using only the data of the two treatment groups to be compared
Source: CSR Table 14.2.7.2A

Table 27 Study 003: Lumbar spine BMD by visit (ITT, LOCF)

	Placebo (N=821)	**Abaloparatide** (N=824)	**Teriparatide** (N=818)
Baseline, n	821	823	818
Mean (g/cm^2)	0.823	0.829	0.831
Month 6, n	821	823	818
Mean % change from baseline (SD)	**0.56** (3.34)	**5.90** (5.17)	**4.84** (4.31)
p-value vs. teriparatide*‡		0.0004‡	
Month 12, n	821	823	818
Mean % change from baseline (SD)	**0.39** (3.53)	**8.19** (6.72)	**7.40** (5.38)
Month 18, n	821	823	818
Mean % change from baseline (SD)	**0.48** (3.82)	**9.20** (7.54)	**9.12** (6.28)
p-value vs. placebo*		<0.0001	

Missing BMD data were imputed using last observation carried forward (LOCF)
* p-values were derived from contrast tests based on ANCOVA model fitted using only the data of the two treatment groups to be compared
‡ comparison of abaloparatide/teriparatide in lumbar spine BMD at 6 months was a prespecified endpoint, but in the testing sequence followed the abaloparatide/teriparatide comparison in nonvertebral fractures which did not achieve significance (see above), therefore this p-value is considered exploratory
Source: CSR Table 14.2.7.3A

Placebo-corrected increases in BMD at these sites are summarized in the following table.

Table 28 Study 003: Placebo-corrected BMD changes at month 18 (ITT)

	Placebo-corrected BMD increase Baseline to month 18	
	Abaloparatide	Teriparatide
Total hip	3.5%	2.9%
Femoral neck	3.3%	2.7%
Lumbar spine	8.7%	8.6%
All p-values <0.0001		

Reviewer comments:
Only the BMD changes at month 18 are appropriate for labeling. Although the Applicant believes that the changes at month 6 show a "faster" response to abaloparatide compared to teriparatide, the clinical significance of this is unclear.

Although the previous Forteo phase 3 study (GHAC) enrolled higher risk PMO patients, the hip and spine BMD percent increases with teriparatide 20 mcg at 18 months were very similar between the two studies. In both of these studies and others, the magnitude of the PTH effects was larger at the lumbar spine than the hip, probably because of the relative predominance of trabecular bone in the spine, while the hip contains much cortical bone. This PTH effect differs from bisphosphonates, where BMD changes are more balanced between cortical and trabecular bone.

BMD results by visit (not LOCF) and for the per-protocol population were similar. The prespecified exploratory analysis of responders (patients with BMD increases >0%, >3%, or >6% at lumbar spine, total hip and femoral neck) at months 6, 12 and 18 were consistent with the data for mean percent changes. Almost 90% of abaloparatide patients had a BMD increase >0% at all three of these sites, compared to 80% for teriparatide and 38% for placebo.

Other hip and spine DXA data (table below, post hoc analyses) demonstrated ~2% increases in bone projectional area at the spine with each of the two active drugs, therefore bone mineral content (BMC) increased to an even greater extent than areal BMD:

Table 29 Study 003: Hip and spine BMC and bone area, mean percent changes from baseline at month 18

	Placebo	Abaloparatide	Teriparatide
Total hip BMC	0.17%	4.56%	3.62%
Total hip bone area	0.32%	0.42%	0.40%
Lumbar spine BMC	0.91%	13.81%	13.03%
Lumbar spine bone area	0.33%	2.34%	2.32%
Observed data in patients with DXA at baseline and at month 18 Source: DEV_HIP and DEVSPINE datasets			

Reviewer comment: *It is not clear whether the increased bone area in L1-L4 means that there was actual bone enlargement e.g. from periosteal bone formation; it could also result from additional pixels meeting the DXA software's BMD threshold for bone detection, particularly in patients with severe osteoporosis.*

BMD of the mid-1/3 radius, a pure cortical bone site, was evaluated in a subset of patients, and demonstrated declines from baseline in all 3 treatment groups, with the largest declines in the teriparatide group (table below). BMD changes were significantly better for abaloparatide than teriparatide, though trending slightly worse than placebo. For BMD of ultradistal radius, a site with more trabecular relative to cortical bone, there were slight decreases with placebo and teriparatide, and a slight increase with abaloparatide.

Table 30 Study 003: Mid-1/3 Radius BMD by visit (MITT, LOCF)

	Placebo (N=821)	Abaloparatide (N=824)	Teriparatide (N=818)
Baseline, n	334	321	327
Mean (g/cm^2)	0.517	0.517	0.512
Month 6, n	334	321	327
Mean % change from baseline (SD)	**-0.15** (3.57)	**-0.01** (3.77)	**-0.93** (3.64)
Month 12, n	334	321	327
Mean % change from baseline (SD)	**-0.22** (3.87)	**-0.75** (4.49)	**-1.67** (4.12)
Month 18, n	334	321	327
Mean % change from baseline (SD)	**-0.62** (3.97)	**-1.02** (4.68)	**-2.27** (4.54)
Missing BMD data were imputed using last observation carried forward (LOCF) Source: CSR Table 14.2.7.4A			

Table 31 Study 003: Ultradistal radius BMD by visit (MITT, LOCF)

	Placebo (N=821)	Abaloparatide (N=824)	Teriparatide (N=818)
Baseline, n	334	321	327
Mean (g/cm^2)	0.257	0.258	0.258
Month 6, n	334	321	327
Mean % change from baseline (SD)	**0.05** (5.42)	**1.62** (5.36)	**0.74** (6.21)
Month 12, n	334	321	327
Mean % change from baseline (SD)	**-0.38** (5.63)	**1.31** (5.93)	**0.39** (5.79)
Month 18, n	334	321	327
Mean % change from baseline (SD)	**-1.21** (5.87)	**1.04** (6.14)	**-0.54** (6.32)

Missing BMD data were imputed using last observation carried forward (LOCF)
Source: CSR Table 14.2.7.5A

Other DXA data for the mid-1/3 and ultradistal radius show that BMC changed in parallel to BMD; unlike the lumbar spine, bone area did not increase with either drug:

Table 32 Study 003: Radius BMC and bone area, mean percent changes from baseline at month 18

	Placebo	Abaloparatide	Teriparatide
Mid-1/3 radius BMC	-0.78%	-2.12%	-3.13%
Mid-1/3 radius bone area	0.16%	-0.54%	-0.49%
Ultradistal radius BMC	-0.92%	1.52%	-0.28%
Ultradistal radius bone area	0.68%	0.54%	0.49%

Observed data in patients with DXA at baseline and at month 18
Source: DEVRAD datasets

Reviewer comment:
Previously in the Forteo phase 3 PMO trial (GHAC), teriparatide was similarly associated with decline in BMD at the mid-1/3 radius, with evident dose response (larger decline with 40 mcg compared to 20 mcg dose). This did not cause great concern with reviewers because there were numerically fewer low-trauma wrist fractures with 20 mcg or 40 mcg compared to placebo (2, 3, 7 patients respectively). Also, a possible explanation was provided by a peripheral quantitative CT (pQCT) substudy, which at the "proximal" (15%) radius showed trends of dose-related increases in periosteal and endosteal circumference and total bone area; no change in BMC; dose-related decreases in cortical vBMD; and dose-related increases in estimated strength indices. It was speculated that the enlarged cortical bone could explain the seeming paradox of decreased radius BMD, yet maintenance of BMC and bone strength. However, re-examination by this reviewer of the GHAC mid-1/3 radius DXA data at 12 months (table below) shows that

mean bone area declined slightly from baseline with teriparatide, and the decline in BMD was related to lower BMC, not an increase in bone area. The seeming discrepancy in findings between DXA and pQCT may reflect different cortical site examined (33% vs. 15% radius).

Study GHAC- Mid-1/3 radius DXA, month 12 vs. baseline

	Placebo	*Terip. 20 mcg*	*Terip. 40 mcg*
BMD	*-1.19%*	*-1.94%*	*-3.01%*
BMC	*-0.59%*	*-1.98%*	*-3.30%*
Bone area	*0.45%*	*-0.21%*	*-0.43%*

In the current study 003, the DXA data for teriparatide 20 mcg vs. placebo are consistent with GHAC DXA data in showing ~2% declines in mid-1/3 radius BMD and BMC, and smaller decline in bone area (pQCT was not conducted in 003). The BMD and BMC declines of teriparatide at this cortical site were mitigated somewhat with abaloparatide, which also showed favorable trends in wrist fractures relative to the other treatment groups: 7 patients, vs. 13 placebo and 17 teriparatide.

BMD subgroups

Spine and hip BMD response was highly consistent across the multiple subgroups (including age, years since menopause, race, ethnicity, prior fracture status, baseline BMD), and across regions with the exception of the US (see below). BMD of the mid-1/3 radius was also consistent across subgroups, showing greater declines in teriparatide recipients, relative to placebo or abaloparatide. Post hoc analyses of BMD data from the abaloparatide recipients, by renal function, showed hip and spine BMD increases in subgroups with baseline creatinine clearance of <60, 60-<90, and ≥90 mL/min that were generally similar, but with trends of slightly smaller increases in the ≥90 mL/min group.

Applicability of study 003 efficacy data to the US population

As noted above, there were only 39 US women enrolled in study 003 (1.6% of the study population). None of these women experienced any fracture during the study, and the subgroup is much too small to assess fracture efficacy in US patients. In the Filing Letter, DBRUP asked the Applicant for a detailed rationale to support extrapolation of overall study 003 results to the US target PMO population and US medical practice, including a discussion of possible regional differences in intrinsic and extrinsic factors, and regional differences in the BMD data.

The Applicant's response (submitted 8/15/16) cites the relative global consistency in definition of PMO and guidelines for treatment, based on BMD T-scores and FRAX risk scores developed by the WHO, although there are limited published data on the extent to which clinical practice follows guidelines in different regions. US and non-US participants in study 003 essentially all met US guidelines for PMO treatment.

Published data on calcium intake in the Czech Republic, Denmark, Hong Kong, Brazil and the US are presented by the Applicant, showing no evidence of substantial differences. In contrast, published data suggest that 25-OH-vitamin D levels may be higher in the US than in those countries, perhaps related in part to routine fortification of foods (e.g. milk, juice and cereals). This is consistent with study 003 data in which US women had higher baseline 25-OHD than non-US women (mean 98 vs. 66 nmol/L) [and also consistent with US/non-US differences (mean 93 vs. 73 nmol/L) in a recent multinational PMO trial of another drug (NDA 203149)]. Because study 003 participants were required to have 25-OHD >37.5 mmol/L and mean baseline levels were ~67 mmol/L, a level widely considered to establish vitamin D sufficiency, and all patients received supplements during the study, the Applicant believes that vitamin D status should not affect applicability of the data to the US PMO population.

In study 003, US patients were somewhat younger than non-US patients (mean 62.8 vs. 68.9 years), with fewer years since menopause (mean 14.3 vs. 20.4 years). This appears consistent with observational studies showing mean ages of postmenopausal women receiving treatment for osteoporosis of 63.8 years (US); 69 years (10 countries including the US); 68 years (5 European countries); and 68.4 years (Brazil). As indicated above, patients <65 and ≥65 years in study 003 experienced similar reductions in new vertebral and nonvertebral fractures with abaloparatide.

Study 003 participants overall were 80% white, 16% Asian, 3% black and 24% Hispanic. A published registry of US women receiving PMO treatment in clinical practice reported 89% as white (with no data on Hispanic ethnicity). This target US population may have lower Asian and Hispanic representation than study 003 overall, but is probably more diverse than European women (of whom 98% of those receiving PMO treatment in a published registry, and 99.8% of those enrolled in study 003, were described as white). The observed reductions in vertebral and nonvertebral fractures in study 003 occurred mainly in white European women, a demographic that has generally responded similarly to (predominantly white) US women in previous PMO drug trials.

Mean baseline BMI in study 003 was 25.1 kg/m^2 and was similar across sites except for Hong Kong where the mean was 22.5 kg/m^2. A published study reported a slightly higher mean BMI of 26.9 in US women receiving PMO treatment.

Study 003 participants consumed about 1 alcoholic drink per week on average, and 12.5% were smokers; based on published data, the US PMO population was not expected to be markedly different.

The Applicant compared data on concomitant medications in study 003 participants with a published observational study of US women receiving bisphosphonates. The most common drug classes (cholesterol meds, analgesics/NSAIDs, ACE inhibitors, diuretics, beta blockers,

calcium channel blockers, antisecretory drugs) were generally similar in frequency of usage between the two groups. An exception was that thyroid hormone replacement was somewhat less frequent in study 003 (9%, vs. 20%). As expected based on enrollment criteria, study 003 participants (compared to the US PMO population, based on published data) had lower prevalence of some comorbidities including COPD, asthma, angina, CHF, depression, cancer and rheumatoid arthritis.

As discussed above, study 003 data show no evidence that abaloparatide/placebo differences in vertebral or nonvertebral fractures varied between the 4 continental regions: p-values for treatment-by-subgroups interactions were 0.57 (vertebral) and 0.89 (nonvertebral). However, most patients with fractures were European: 27/34 patients with vertebral fractures and 34/51 patients with non-vertebral fractures within these two treatment groups. In other regions, the trends were similar but numbers very small, with no fractures in the 39 US patients.

BMD data in study 003 were analyzed by region and are summarized in the tables below, with figures representing US patients. Mean BMD increases at hip and spine were numerically lower in the US than in South America, Europe or Asia, for both abaloparatide and teriparatide. However, even among the small number of US patients, mean BMD increase was numerically greater at each skeletal site and each timepoint (month 6, 12, 18) with abaloparatide compared to placebo, with generally increasing trends over time. The treatment effect was greatest in lumbar spine BMD which increased 3-4% from baseline with abaloparatide in US women, with nominally significant p-values (<0.05) vs. placebo at months 6, 12 and 18. BMD changes with teriparatide in the US were generally similar to or lower than with abaloparatide at each skeletal site and timepoint (as in other regions), but are based on only 9 US patients who received teriparatide (vs. 17 abaloparatide, 13 placebo).

Table 33 Study 003: Total hip BMD, mean % change from baseline at month 18 by region (ITT, LOCF)

	Total N	**Placebo** (N=821)	**Abaloparatide** (N=824)	**Teriparatide** (N=818)
All regions	2463	-0.08	3.44	2.81
N. America (US)	**39**	**-0.56**	**0.94***	**-0.08**
S. America	661	0.45	3.46	3.21
Europe	1376	-0.21	3.58	2.72
Asia	387	-0.44	3.25	2.61

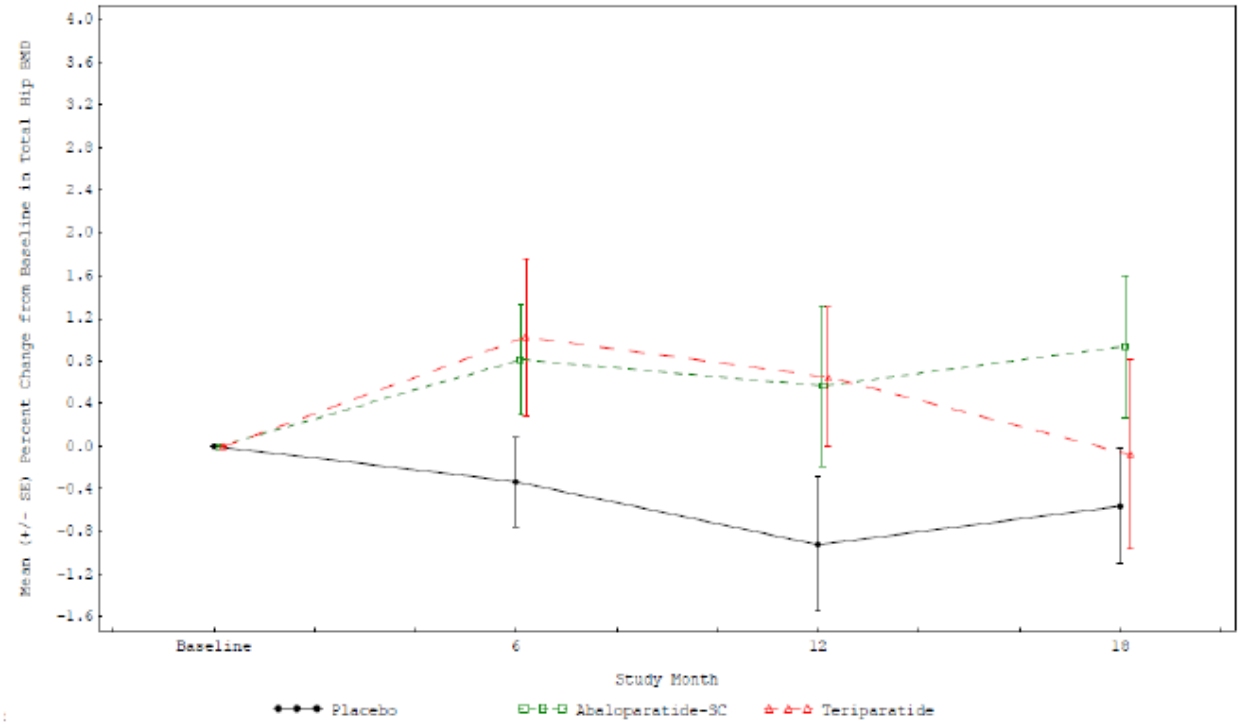
* p-value vs. placebo (US patients) = 0.09 (derived from contrast tests based on ANCOVA model fitted using only the data of the two treatment groups to be compared)
Source: CSR Section 14, Tables 14.2.7.1A and 14.2.8.1D

Results at the month 18 visit (not LOCF; only the 27/39 US patients with data at month 18) showed similar US/non-US differences:

Table 34 Study 003: Total hip BMD, mean % change from baseline at month 18 by region (ITT)

	Total N	**Placebo** (N=821)	**Abaloparatide** (N=824)	**Teriparatide** (N=818)
All regions	1926	-0.10	4.18	3.26
N. America (US)	**27**	**-0.94**	**1.07**	**-0.10**
S. America	479	0.55	4.33	3.55
Europe	1085	-0.28	4.34	3.10
Asia	335	-0.41	3.81	2.84
Observed data (not LOCF) Source: CSR Section 14, Tables 14.2.7.1C and 14.2.9.1D				

Figure 7: Study 003: Total hip BMD, mean (SE) % change over time in US patients (ITT, LOCF)



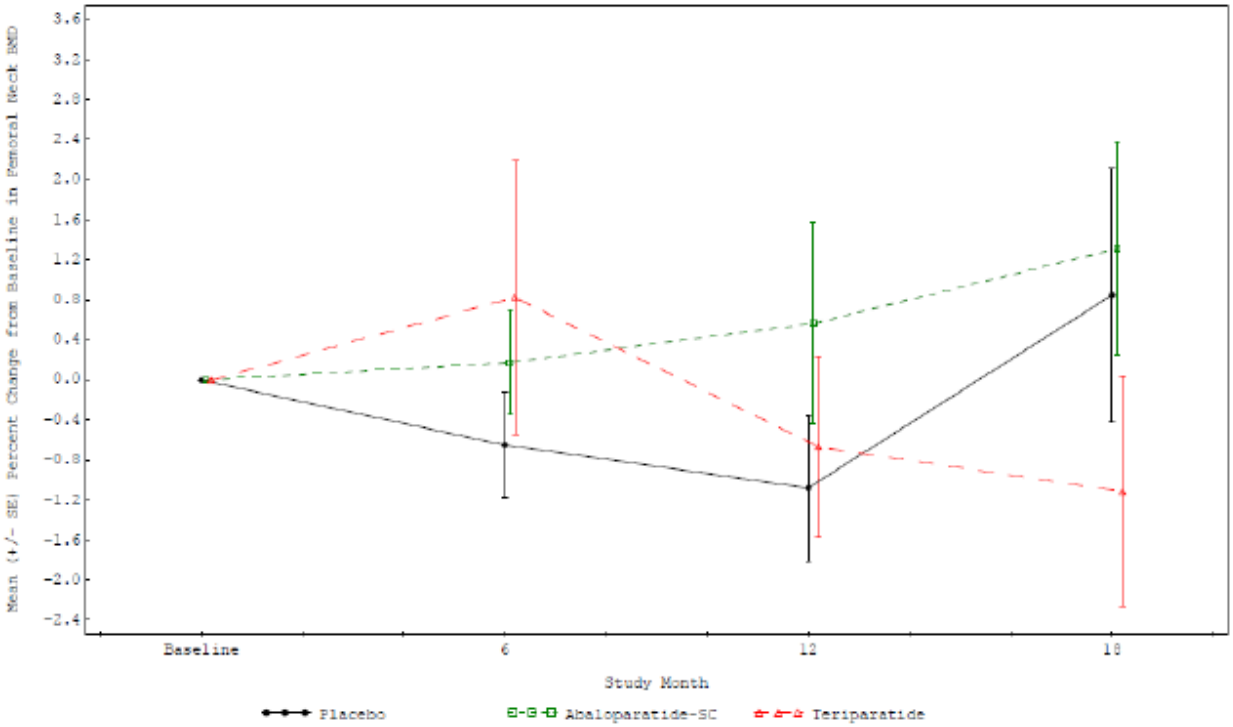
Source: Response to Filing Letter questions, submitted 8/15/16

Table 35 Study 003: Femoral neck BMD, mean % change from baseline at month 18 by region (ITT, LOCF)

	Total N	Placebo (N=821)	Abaloparatide (N=824)	Teriparatide (N=818)
All regions	2463	-0.44	2.90	2.26
N. America (US)	**39**	**0.85**	**1.31***	**-1.11**
S. America	661	-0.21	2.54	1.78
Europe	1376	-0.51	3.23	2.49
Asia	387	-0.70	2.56	2.52

* p-value vs. placebo (US patients) = 0.78 (derived from contrast tests based on ANCOVA model fitted using only the data of the two treatment groups to be compared)
Source: CSR Section 14.2, Tables 14.2.7.2A and 14.2.8.2D

Figure 8 Study 003: Femoral neck BMD, mean (SE) % change over time in US patients (ITT, LOCF)



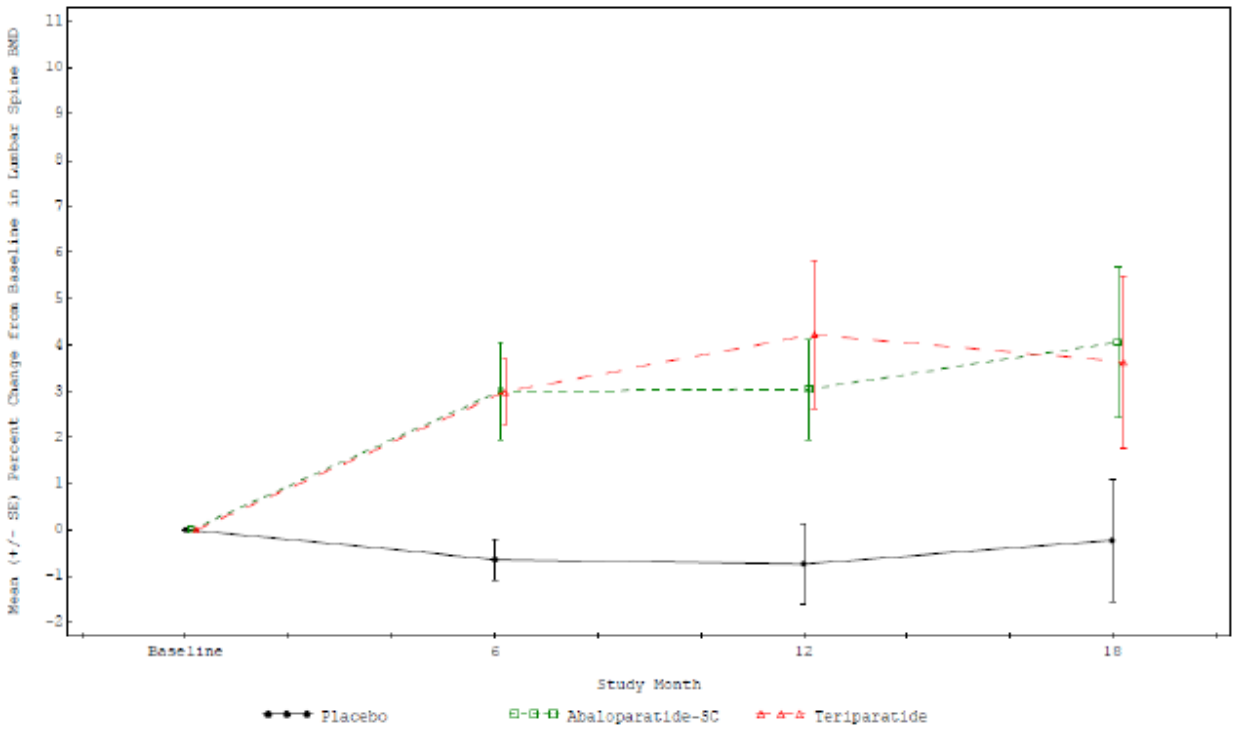
Source: Response to Filing Letter questions, submitted 8/15/16

Table 36 Study 003: Lumbar spine BMD, mean % change from baseline at month 18 by region (ITT, LOCF)

	Total N	Placebo (N=821)	Abaloparatide (N=824)	Teriparatide (N=818)
All regions	2463	0.48	9.20	9.12
N. America (US)	**39**	**-0.23**	**4.06***	**3.63**
S. America	661	1.03	8.69	8.67
Europe	1376	0.34	9.54	9.06
Asia	387	0.14	9.58	10.46

* p-value vs. placebo (US patients) = 0.01 (derived from contrast tests based on ANCOVA model fitted using only the data of the two treatment groups to be compared)
Source: CSR Section 14.2, Tables 14.2.7.3A and 14.2.8.3D

Figure 9 Study 003: Lumbar spine BMD, mean (SE) % change over time in US patients (ITT, LOCF)



Source: Response to Filing Letter questions, submitted 8/15/16

Reviewer comment: *Hip and spine BMD trending changes (abaloparatide vs. placebo) were qualitatively consistent between US and non-US despite the small number of US patients, and quantitatively consistent between the non-US regions despite marked demographic differences therein. Moreover, there was no evidence that abaloparatide was less effective in any region or any bone site than teriparatide, a drug with a similar mechanism of action approved in the US.*

The cause of the lower BMD response in the US is unclear. As noted above, one of the most notable differences between US and other patients was their higher baseline levels of 25-OH-vitamin D (mean 98 vs. 66 nmol/L), suggesting the possibility that regional differences in nutrition might modify the effects of treatment. However, BMD responses were similar in patients with higher (≥60 nmol/L) and lower (<60 nmol/L):

Table 37 Study 003: BMD, placebo-adjusted LS mean change by baseline vitamin D status and treatment group at month 18 (ITT, LOCF)

	Baseline 25-OH-vitamin D (nmol/L)	**Abaloparatide** (N=824)	**Teriparatide** (N=818)
Total hip	< 60	3.4	2.7
	≥ 60	3.6	3.0
Femoral neck	< 60	3.2	2.6
	≥ 60	3.5	2.8
Lumbar spine	< 60	8.8	9.4
	≥ 60	8.6	7.9
Source: NDA statistical reviewer			

Most (30/39) US patients were Hispanic or Latino, and BMD response in this group was less than in the 9 non-Hispanic US patients (see table below). Hispanic ethnicity was not among the subgroups evaluated by the Applicant, but reviewer analysis of South American patients shows that ethnicity did not appear to be a significant factor with respect to BMD. The following table presents these data for total hip BMD; femoral neck and lumbar spine BMD data show similar trends.

Table 38 Study 003: Total hip BMD, mean percent changes from baseline by ethnicity (Month 18, ITT, LOCF)

	Placebo	**Abaloparatide**	**Teriparatide**
US patients			
Hispanic (n=30)	-0.6	0.3	-1.1
Non-Hispanic (n=9)	-	2.2	1.9
South American patients			
Hispanic (n=550)	0.6	3.5	3.3
Non-Hispanic (n=111)	-0.1	3.4	2.9
Source: NDA statistical reviewer			

Among the 39 US patients, 21 were enrolled at one site (#216, N. Miami FL). BMD responses to abaloparatide and teriparatide were notably lower at this compared to the other US sites (table below), and account for most of the overall US/non-US difference in BMD changes. The reason for this finding is unclear. The 21 patients at site #216 were all Hispanic, with mean age of 61

years; 18 were white and 3 were black; their mean baseline BMD T-scores were similar to the overall study (-2.9 lumbar spine, -1.8 total hip, -2.2 femoral neck); all 21 had a history of prior nonvertebral fracture (mostly wrist or forearm); 7 had baseline vertebral fractures by investigator assessment, and 4 by (b) (4) assessment; few had notable medical histories (other than osteoporosis), concomitant medications or AEs. Exposure data were adequate at this site.

Table 39 Study 003: BMD mean percent changes from baseline at different US sites (US patients in ITT, month 18, LOCF)

	Placebo N=13	**Abaloparatide** N=17	**Teriparatide** N=9
Site 216, n	8	8	5
Total hip BMD	0.1	0.2	-1.6
Femoral neck BMD	0.7	0.2	-2.5
Lumbar spine BMD	0.8	0.9	-0.2
Sites 211/212/213/214, total n	5	9	4
Total hip BMD	-1.6	1.6	1.8
Femoral neck BMD	1.1	2.3	0.6
Lumbar spine BMD	-2.3	6.7	8.5
Source: NDA statistical reviewer			

In addition to the observed BMD data in the 39 US patients, the Applicant applied a statistical model using BMD data from non-US patients in the study and baseline covariates (baseline BMD; DXA manufacturer; age; race; ethnicity; years since menopause; BMI; prior fractures; prevalent vertebral fractures at baseline; alcohol and smoking; and baseline serum calcium and 25-OHD) to predict BMD response in US patients. The Applicant based the method on the draft ICH E17 guidance on planning and design of multi-regional clinical trials (dated 5/6/16). This guidance was not intended to address the analysis of trial data, and the statistical reviewer does not consider the findings to be valid (see separate review).

Reviewer comment: *Ultimately, the US data in study 003 are of limited value. The small US cohort (n=39) may not be adequately representative of the US PMO population, e.g. 20% of US women were "white/non-Hispanic" in 003, vs. 96% "Caucasian" in the Forteo study GHAC (see below), which is more typical of PMO drug trials. Also because of the inconsistent results especially at the largest US site (#216), unknown issues of study conduct cannot be ruled out. Therefore, assessment of abaloparatide efficacy in the US PMO population is largely dependent on foreign data (Europe, South America, Asia). The consistency of BMD increases with abaloparatide between these non-US regions, and across all subgroups including race and ethnicity, helps to support applicability of study 003 data to the US.*

Forteo study GHAC: efficacy data by region

Data from this pivotal phase 3 teriparatide study in women with PMO may also be informative in assessing possible US/non-US efficacy differences with abaloparatide, as teriparatide also acts through the PTHR1 receptor. Study GHAC enrolled 1637 women in 17 countries (54% Europe; 22% US; 11% Argentina; 6% Canada; 7% others), with mean age of 69 years, at least 5 years postmenopause; 99% were Caucasian. Among the 365 US patients, 349 (96%) were Caucasian; ethnicity (Hispanic/non-Hispanic) was not recorded. Compared to study 003, the study population was at greater fracture risk: about 90% met the entry criterion of ≥2 mild or ≥1 moderate vertebral fractures at baseline (Genant criteria).

Patients in this study were randomized (1:1:1) to receive daily SC injections of placebo, teriparatide 20 mcg or 40 mcg, each with calcium and vitamin D supplements. Originally planned as a 3-year study, GHAC was terminated early because of the osteosarcoma findings in animal studies; median treatment duration was 19.3 months (range 16-24 months). The closeout visits for each patient included vertebral x-rays and final DXA exams.

Compared to study 003, GHAC had higher rates of new vertebral fractures in all treatment groups and, despite the early termination, was able to demonstrate significant reductions in new vertebral and non-vertebral fractures for both 20 mcg and 40 mcg doses, relative to placebo (table below). US patients showed trends of fewer fractures with teriparatide, except for vertebral fractures with the 20 mcg dose.

Table 40 Study GHAC (Forteo): Incidence of new fractures, US patients compared to overall study

	Placebo	Teriparatide 20 mcg	Teriparatide 40 mcg
Patients with a new morphometric vertebral fracture			
Overall	64/448 (14.3%)	22/444 (5.0%)	19/434 (4.4%)
USA	9/99 (9.0%)	10/87 (11.5%)	4/92 (4.3%)
Patients with any new non-vertebral fracture			
Overall	53/544 (9.7%)	34/541 (6.3%)	32/552 (5.8%)
USA	16/124 (12.9%)	11/115 (9.6%)	6/126 (4.8%)
Patients with any new non-vertebral fragility* fracture			
Overall	30/544 (5.5%)	14/541 (2.6%)	14/552 (2.5%)
USA	9/124 (7.3%)	6/115 (5.2%)	4/126 (3.2%)

Fractures assessed among patients with data at early discontinuation visit and/or final vertebral x-ray, at median 21 months from randomization
* Any documented nonvertebral fracture where "the associated trauma would not have resulted in the fracture of a normal bone, in the opinion of the local investigator"
Source: GHAC, SPINXRAY and NVERFRAC datasets

BMD changes at various sites, assessed by DXA, were generally similar in US patients relative to the overall study:

Table 41 Study GHAC (Forteo): BMD, mean percent change from baseline*, US patients compared to overall study

	N‡	Placebo	Teriparatide 20 mcg	Teriparatide 40 mcg
Lumbar spine				
Overall	1122	1.32	10.09	15.02
USA	245	1.93	9.09	14.06
Total hip				
Overall	530	-0.77	2.73	4.11
USA	167	-1.03	2.82	4.36
Femoral neck				
Overall	1113	-0.42	3.01	5.88
USA	236	0.30	2.94	6.00
1/3 radius				
Overall	380	-1.21	-2.32	-3.45
USA	86	-0.72	-1.92	-2.42
Total body				
Overall	348	-0.63	0.62	1.73
USA	93	-0.17	1.03	1.64

* Lumbar spine DXA was conducted per protocol at month 18; % changes represented are from screening DXA to month 18. DXA at other sites was not scheduled at month 18 but was obtained at the closeout visit, generally between months 18-24. Percent changes represented for total hip and femoral neck are from screening to closeout visit; percent changes for 1/3 radius and total body BMD are from screening and/or baseline visit to closeout visit. All observed data only (not LOCF).
‡ Number of patients assessed was lower for total hip compared to femoral neck because of incomplete data for intertrochanteric region in many patients. BMD of 1/3 radius and total body were assessed only in subsets of patients.
Source: GHAC, DEXA dataset

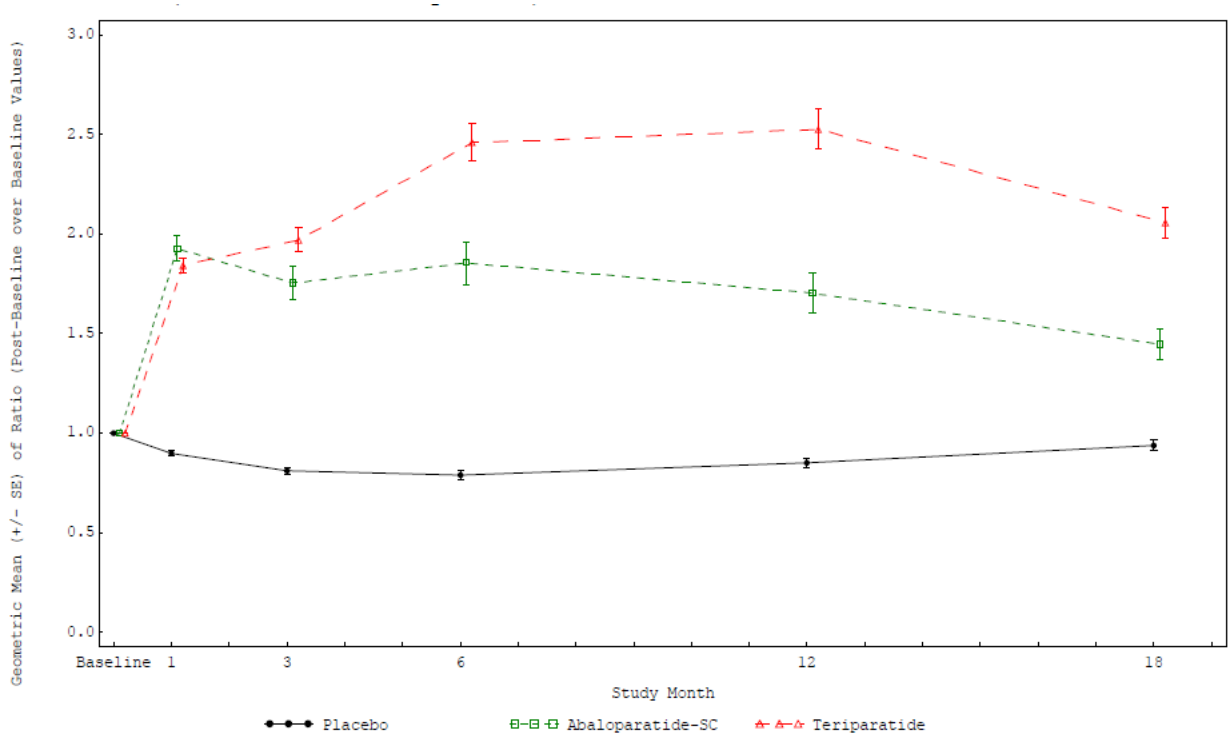
Reviewer comment: *As discussed above, teriparatide 20 mcg data in study 003 are similar to GHAC 20 mcg data with respect to vertebral fracture risk reductions (80% and 65% respectively), and percent increases in BMD at various sites. The nonvertebral fracture risk reduction is somewhat lower (28% vs. 53%) in study 003, but the 95% CI for this endpoint in the two studies overlap, and abaloparatide had more effect than teriparatide (43% vs. 28% reduction). Thus, it is reasonable, as the Applicant contends, to use the teriparatide 20 mcg arms to bridge the efficacy data from the two studies. The similarity in teriparatide efficacy between the US and other countries in study GHAC is strong evidence in favor of applicability of study 003 data to the US.*

Other efficacy endpoints in study 003:
Height decreased slightly from baseline to end of treatment in each study 003 arm. Mean changes were -0.13% (placebo), -0.10% (abaloparatide), and -0.12% (teriparatide); there were no significant differences between groups.

Reviewer comment: *This result is consistent with other PMO drug trials (teriparatide and bisphosphonates): loss of height generally occurs in all treatment groups, and active drug typically has only a modest effect in slowing the loss.*

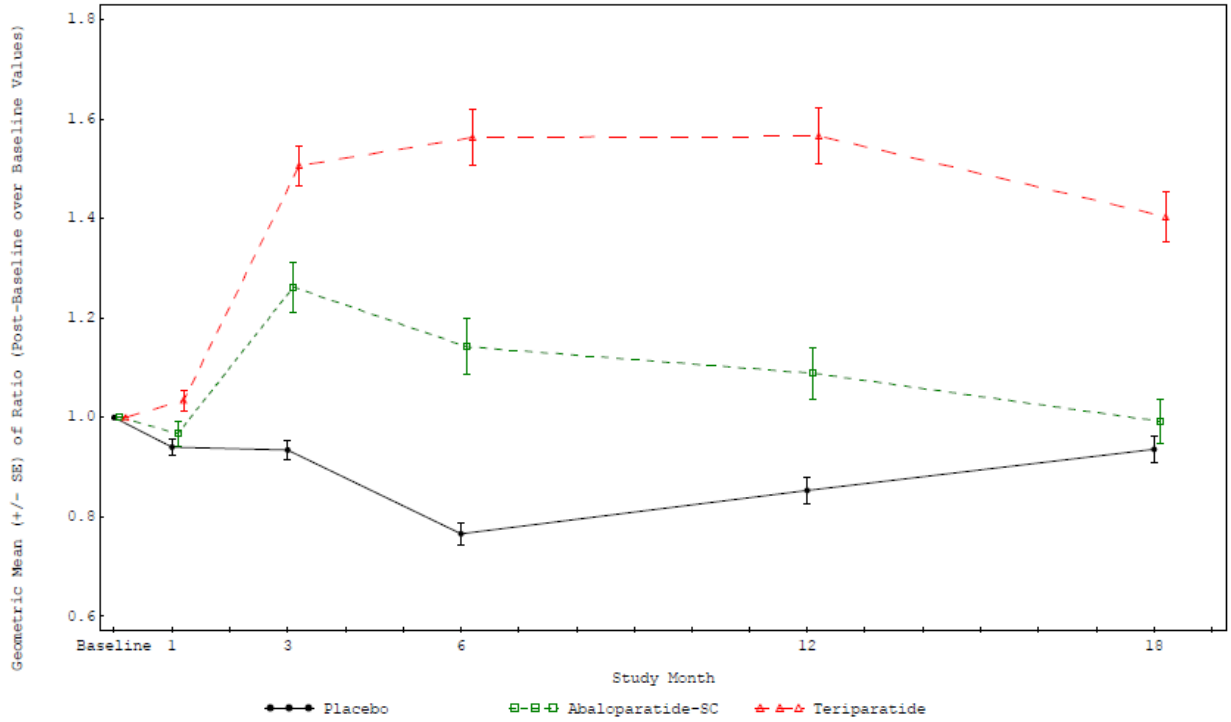
Bone turnover markers were measured in a subset of ~200 patients in each treatment group. Patients receiving abaloparatide and teriparatide showed increases in the bone formation marker P1NP starting at 1 month, and in the bone resorption marker CTX starting at 3 months. For both markers, increases were somewhat greater with teriparatide relative to abaloparatide.

Figure 10 Study 003: Serum P1NP by treatment group and visit



Source: CSR Section 14.2, Figure 14.2.13.1

Figure 11 Study 003: Serum CTX, by treatment group and visit



Source: CSR Section 14.2, Figure 14.2.13.4

Reviewer comment: *The Applicant believes that these changes are consistent with the BMD changes, with abaloparatide showing similar increase in P1NP to teriparatide in early months of treatment, with lesser increase in CTX, perhaps resulting in the more rapid BMD increases seen with abaloparatide.*

Examination of subgroups (age, years since menopause, race, region, prior fractures, baseline BMD) showed generally consistent patterns of change in bone turnover markers; the number of US patients (n=9) was too small for meaningful assessment of the data.

<u>Bone histology and histomorphometry:</u>
Bone biopsy data are discussed in section 8.5.6 below.

Dose/Dose Response

The 80 mcg dose used in study 003 was based on superior BMD and bone marker response compared to 20 mcg and 40 mcg in the phase 2 study 002 (see below, and separate Clinical Pharmacology review). The protocol included an option for dose reduction from 80 to 40 mcg for patients experiencing persistent hypercalcemia, however no patients met the criteria for this and therefore 40 mcg was not used in study 003 (b) (4)

(b) (4)

Durability of Response

Although levels of bone formation marker P1NP decline after 6-12 months with both abaloparatide and teriparatide, they remain above baseline at 18 months as BMD continues to increase (see above). Use of both of these drugs is likely to remain limited to ≤2 years, not based on efficacy considerations, but because of the potential safety issue of osteosarcoma.

Persistence of Effect

Off-treatment effects of abaloparatide were not evaluated. Previous observational data with teriparatide (see section 2.2) suggest that BMD declines after discontinuation, and that this may be prevented by switching to alendronate. Study 005 (see below) similarly shows that switching from abaloparatide to alendronate maintains BMD, as well as fracture reduction. This is relevant to clinical practice because a course of teriparatide is typically followed by a bisphosphonate, and this would probably become common practice with abaloparatide also.

Additional Analyses Conducted on the Individual Trial

Effects of anti-drug antibody development on efficacy parameters
About half of abaloparatide-treated patients who completed 18 months of therapy developed anti-drug antibodies (ADA), and most of those showed evidence of *in vitro* neutralizing antibodies (refer to section 8.4.10). Exploratory analyses by the Applicant showed that patients who developed antibodies experienced similar BMD increases and similar fracture incidence to patients without antibodies:

Table 42 Study 003: Incidence of new fracture by anti-abaloparatide antibody status*

	ADA negative N=310	ADA positive Neut-Ab neg N=96	ADA positive Neut-Ab pos N=201
Total hip BMD, % change‡	4.1	4.7	4.2
Femoral neck, % change ‡	3.6	4.2	3.4
Lumbar spine, % change ‡	11.1	11.9	11.1
New vertebral fracture, # of patients	3	1	0
Non-vertebral fracture, # of patients	10	3	3
Major osteoporotic fracture, # of patients	5	3	1

ADA = anti-drug antibodies
* mITT or ITT patients who were treated with abaloparatide and underwent antibody testing at month 18
‡ mean percent change from baseline to month 18 (LOCF)
Source: CSR Section 14, Table 14.2.2 and 14.2.10A-C

6.2. Study BA058-05-005

6.2.1. Study Design

Overview and Objective

Title of study 005: An extension study to evaluate 24 months of standard-of-care osteoporosis management following completion of 18 months of BA058 or placebo treatment in protocol BA058-05-003

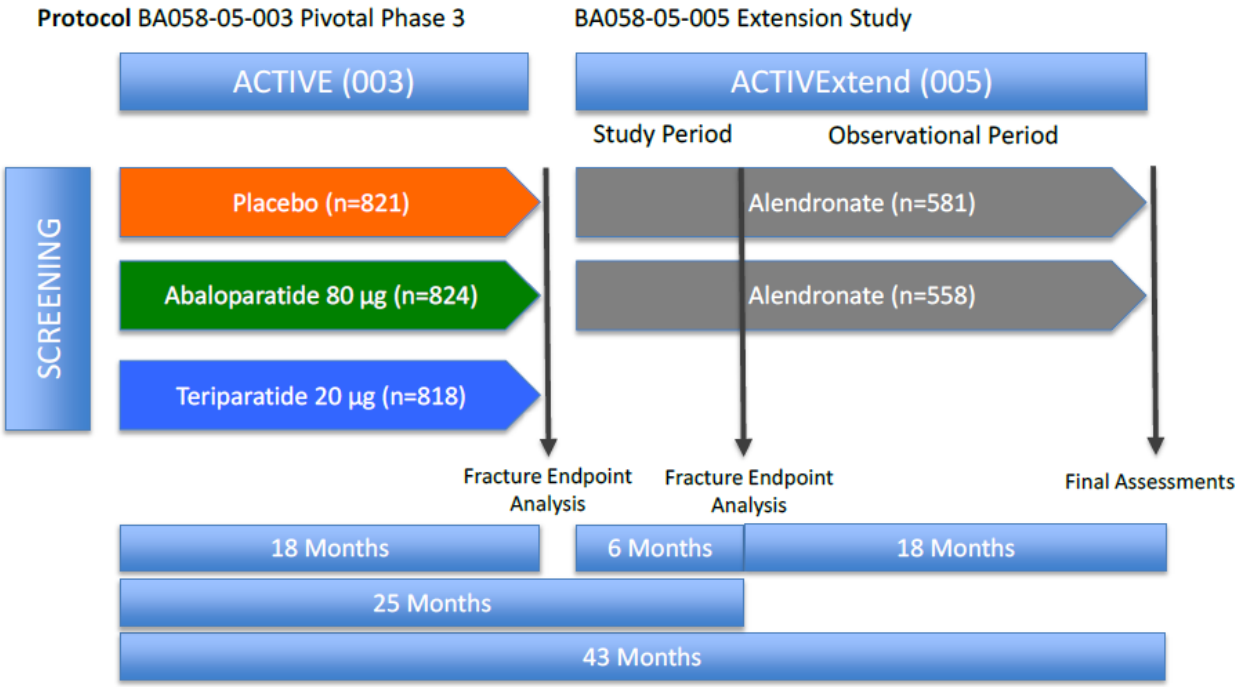
The 6-month interim report of this ongoing 24-month extension study is included in the original NDA as per agreement with DBRUP. The objectives of this study are to collect efficacy and safety data in patients who received 18 months of blinded treatment with abaloparatide or placebo in study 003, followed by 6 months of treatment with alendronate, including the cumulative rate of vertebral fractures and additional data on non-vertebral fractures and BMD changes; and to provide (which will occur at a later date) longer term efficacy data (BMD and osteoporosis status) following 24 months of alendronate.

Trial Design

Study 005 is an open-label extension of study 003, which enrolled women age 49-85 y/o with PMO and significant fracture risk, who were otherwise healthy and ambulatory (see section 6.1.1 of this review for 003 entry criteria). Patients who completed 18 months of blinded treatment with either abaloparatide or placebo in study 003 were eligible to enroll in study 005, unless they had experienced a treatment-related SAE. Patients who were assigned to Forteo (teriparatide) in study 003 were not eligible for the extension. The 003 end-of-study visit (month 19) serves as the baseline visit for study 005, and should be no more than 40 days from the end-of-treatment (month 18) visit of study 003.

At enrollment in study 005, all patients began treatment with oral alendronate (if deemed appropriate by the investigator), which is to be continued for the duration of the study (24 months). Alendronate is open label, however patients remain blinded to their previous study 003 treatment assignment (abaloparatide or placebo) during the first 6 months of study 005, in order to obtain a full 2 years of double-blinded efficacy and safety data to support the NDA.

Figure 12 Design of studies 003/005



The open label treatment, alendronate sodium 70 mg oral tablets, was begun within 1 week of the 005 baseline visit and taken once a week, according to labeled instructions, contraindications and precautions. Fosamax or a generic substitutable approved version may be used. Alendronate is sourced centrally except in South America, where it may be locally sourced. Patients also continue the supplements taken in study 003 of calcium (500-1000 mg daily) and vitamin D (400-800 IU daily). Patients record missed doses of alendronate or Ca/Vit D supplements weekly in a diary. Compliance is also assessed by returned doses of medication and supplements. As in study 003, estrogens are not to be initiated during the study, except for low dose vaginal estrogen. Patients requiring treatment with an anticonvulsant or chronic heparin are to be discontinued. Other concomitant medications are generally allowed if approved by the investigator, including occasional short term (≤3 month) use of corticosteroids for seasonal allergies or asthma.

In addition to the 005 baseline visit, clinic visits are scheduled at months 3, 6, 12, 18 and 24 (see table of study visits and procedures below). Vital signs are measured at each visit, and ECG at baseline and month 6. Routine labs (hematology, chemistry, urinalysis), and markers of bone turnover (P1NP, BSAP, osteocalcin, CTX) are assessed at baseline and every 6 months. Serum PTH (1-84), 25-OH-vitamin D, 1,25-OH-vitamin D and anti-abaloparatide antibody levels are checked at month 6. 24-hour urine for calcium and creatinine is collected at baseline and month 6.

Assessments for vertebral fracture (AP/lateral thoracic and lumbar x-rays) and BMD (DXA) at study 003 end-of-treatment (month 18) serve as the baseline assessments for study 005. Vertebral x-rays are then repeated at months 6 and 24 of the extension, and DXA at months 6, 12, 18 and 24 of the extension. In addition to DXA of spine and hip, DXA of the wrist is obtained in the subset of patients who had wrist DXA in study 003. Radiographic procedures are the same as in study 003 and coordinated by the same contractor (b) (4)). Vertebral x-ray interpretation is also the same, with blinded assessments and use of the Genant severity scale. Clinical fractures occurring at any time are confirmed and adjudicated according to the same treated-blinded assessment of source documents and imaging as in study 003.

As in study 003, any patient with a decline from baseline of >7% in BMD of spine or hip, or a treatment-related SAE, is to be discontinued from the study. Investigators also have discretion to withdraw patients from the study based on severe AEs or other illness, noncompliance or other protocol violations, or to temporarily suspend treatment when appropriate.

Table 43 Study 005: Schedule of visits and procedures

Procedure	*Visit*	1	2	3	4	5	6
	Study Day/Month:	Visit 10 003/ Visit 1[1] 005	Month 3	Month 6	Month 12	Month 18	Month 24
	Day	1	90	180	360	540	720
	Visit Window (Days)	N/A	± 5	± 14	± 14	± 14	± 14
Informed consent		X					
Review of entrance criteria		X					
Recent health status		X	X	X	X	X	X
Vital signs, weight and height measurements[2]		X	X	X	X	X	X
Electrocardiogram		X		X			
Urinalysis (dipstick)[3]		X		X	X	X	X
Chemistry blood collection[4]		X		X	X	X	X
Hematology blood collection[5]		X		X	X	X	X
Coagulation blood collection[5]		X		X			X
PTH(1-84)				X			
25-hydroxy vitamin D level				X			
1,25-dihydroxy vitamin D level				X			
Serum markers of bone metabolism[5]		X		X	X	X	X
BA058 antibody levels[6]				X			
24-hour urine collection (for calcium: creatinine and creatinine clearance)[7]		X	X[8]	X			
Clinical and radiologic (spine, lumbar and thoracic vertebrae) fracture assessments				X			X
Clinical assessment of *de novo* fractures[9]					X	X	
Bone mineral density of hip and spine by DXA[10]				X	X	X	X
Bone mineral density of wrist by DXA[11]				X	X	X	X
Calcium and vitamin D supplements			← Daily →				
Alendronate administration (if applicable)			← Dosing as per prescribing information →				
Study medication resupply (if applicable)			X	X	X	X	
Subject diary review[12]			X	X	X	X	X
Document adverse events and concomitant medications			← Daily →				

[1]The procedures for the Follow-up visit (Visit 10) for Study BA058-05-003 will serve as the procedures performed at Day 1 (for Study BA058-05-005). The consent form will need to be signed if it was not signed during the End-of-Treatment Visit (Visit 9) of Study BA058-05-003.
[2] Vital signs (blood pressure, pulse rate, body temperature, and respiration rate) are to be recorded at each study visit. Only the blood pressure assessment on Day 1 (Visit 10) needs to be orthostatic. Height is to be measured at each visit in the standing position using a medical stadiometer. Weight is to be measured at each visit. Orthostatic blood pressure is to be measured initially after 5 minutes in the supine position and then again after standing for three minutes.
[3] All routine urinalysis will be performed on a sample freshly voided during the clinic visit.
[4] These blood samples are to be obtained under fasting conditions (N.P.O. for 8 hours; water is acceptable) in the morning of each scheduled study visit.
[5] Includes blood samples for PINP, bone-specific alkaline phosphatase, serum osteocalcin and CTX.
[6]. Subjects who remain positive at the 6 month antibody draw will have samples drawn for antibodies every six months until the antibody titer is negative.
[7] Twenty-four hour urine collection will be used for urinary calcium and urinary creatinine measurements. Subjects will discard the 1st void and begin a 24-hour urine collection the day prior to the clinic visit.
[8] A 24-hour urine collection will be collected at Month 3 only if a sample was not collected for the Day 1 (Visit 10).
[9] Documentation should be obtained on all de novo fractures that occur during the Treatment Period. This documentation should be maintained in the source documents.
[10] Each DXA for a given subject should be performed on the same machine, and if available, preferably by the same technician
[11] Each DXA for a given subject should be performed on the same machine, and if available, preferably by the same technician. Only subjects who had wrist DXA assessments in Study BA058-05-003 will have wrist DXAs performed.
[12] The subjects will maintain a diary throughout the study to record missed doses of medication (including supplements) on a weekly basis; the diaries are to be reviewed with the subject at each study visit.

Study Endpoints

As delineated in the SAP, the efficacy endpoints of study 005 are similar to study 003 (see definitions and full discussion above, section 6.1.1), with each of the following assessed cumulatively at month 6 of study 005, i.e. month 25 of the combined studies, relative to study 003 baseline:

- New vertebral fracture (L1-L4), % of patients (primary endpoint)
- Nonvertebral fracture, time to first event
- BMD of total hip, femoral neck and lumbar spine, % change from baseline
- BMD of wrist (mid-1/3 radius and ultra-distal radius), % change from baseline
- Clinical fracture, major osteoporotic fracture and clinical wrist fracture, time to first event

Reviewer comment: *In study 003, the 3 fracture categories in this last bullet were not included in the study protocol, and were analyzed as exploratory endpoints (see above, section 6.1.2). In study 005, these categories were again not mentioned in the protocol (or discussed with FDA) but were designated secondary endpoints in the statistical plan.*

Other efficacy endpoints evaluated at month 25 (using 003 baseline) were the following:

- Change and % change in height
- Severity of incident (new and/or worsening) vertebral fractures
- Percent changes in serum P1NP, BSAP, osteocalcin, CTX

The statistical plan designated as exploratory efficacy endpoints most of the above endpoints using the study 005 (rather than 003) baseline.

Statistical Analysis Plan

The NDA includes all 6 month data from study 005, which are analyzed as follow-up to the data from study 003, based on each patient's randomized treatment in 003, i.e. either abaloparatide/ALN or placebo/ALN. A similar analysis of efficacy endpoints will occur at month 24 of study 005 (data not yet available).

Analysis populations for study 005 are similar to those of study 003:

- ITT: all 003 patients who enroll in 005, for efficacy analyses (except vertebral fracture)
- Safety: all 005 ITT patients who receive at least one dose of alendronate
- Modified ITT: all 003 mITT patients with a post-005-baseline evaluable vertebral x-ray at month 6 (month 25 of combined 003/005), for analysis of primary endpoint
- Per-protocol: 005 mITT patients with ≥80% compliance and without protocol violations (involving enrollment criteria, concomitant med restrictions, or other violations affecting safety or data integrity)

In addition there are analysis populations limited to each of the subsets of patients who had assessments of distal radius BMD, bone turnover markers, or anti-abaloparatide antibodies.

For the primary and secondary efficacy endpoints evaluations at month 6 of study 005, the SAP specified a fixed sequence of hypothesis testing to control for multiplicity of endpoints, with each step required to show 2-sided significance at the 5% level. The hierarchy, which is essentially the same as that of study 003 for the first 5 steps, is as follows:

- Vertebral fracture, ABL/ALN vs. PLA/ALN at month 25 (primary endpoint)
- BMD of total hip, ABL/ALN vs. PLA/ALN at month 25
- BMD of femoral neck, ABL/ALN vs. PLA/ALN at month 25
- BMD of lumbar spine, ABL/ALN vs. PLA/ALN at month 25
- Non-vertebral fracture, ABL/ALN vs. PLA/ALN by month 25
- Clinical fracture, ABL/ALN vs. PLA/ALN by month 25
- Clinical major osteoporotic fracture, ABL/ALN vs. PLA/ALN by month 25
- BMD of ultra distal radius, ABL/ALN vs. PLA/ALN at month 25
- Clinical wrist fracture, ABL/ALN vs. PLA/ALN by month 25
- BMD of mid-1/3 radius, ABL/ALN vs. PLA/ALN at month 25

Analysis methods for each endpoint are the same as in study 003: Fisher's exact test for new vertebral fractures in the mITT population; the log-rank test for time to first event testing for non-vertebral, clinical, clinical major osteoporotic and clinical wrist fractures (ITT); an ANCOVA model with LOCF imputation for each BMD endpoint (ITT). Subgroups for analysis are also the same as in study 003 (see section 6.1.1).

Protocol Amendments

The original protocol for study 005 was dated 7/23/12. Three protocol amendments were implemented during the conduct of study 005:

Amendment 1 (v.1, 12/13/13) extended the study from 6 to 24 months, and specified that only alendronate would be used for the study drug.

Amendment 2 (3/31/14) added further details about the study drug (alendronate).

Amendment 3 (3/3/15) clarified the timing of the starting dose of alendronate.

Amendment 4 (8/24/15) extended the time that patients with anti-abaloparatide antibodies would be followed.

The SAP (finalized 5/30/15) made some changes and clarifications to the protocol:

- The protocol stated that "the primary objective of this study is to collect clinical information…." and gave no specifics on the fracture or BMD endpoints. The SAP clarified the primary and secondary efficacy endpoints and hierarchy as described above.
- The ITT and safety populations were differentiated according to whether patients received any study medication (alendronate).
- The 3 subpopulations for analysis of radius BMD, bone turnover markers and antibodies were added.

Data Quality and Integrity: Sponsor's Assurance

The protocol states that the study will be conducted in accordance with ICH GCP requirements and ethical principles of the Declaration of Helsinki.

6.2.2. Study Results

Compliance with Good Clinical Practices

The protocol and patient informed consent form for this study were reviewed and approved by an IEC or IRB for each site in accordance with 21 CFR part 56. The study was conducted in accordance with ethical principles of the Declaration of Helsinki and with current guidelines for Good Clinical Practice (GCP) in accordance with 21 CFR Parts 50, 54 and 312.

Financial Disclosure

All of the Principal Investigators and nearly all the Sub-Investigators in study 005 also participated in study 003, and provided financial statements accordingly.

Patient Disposition

Patients enrolled in study 005 at 25 sites, comprising all study 003 sites with the exception of 3 sites with very low 003 enrollment (1 in Poland, 2 in the US). Among the 1243 patients assigned to abaloparatide or placebo in study 003 who completed that study and were therefore eligible, 1139 (92%) enrolled in study 005 (ITT). Of these, 98% had vertebral x-rays at 6 months and thereby comprised the 005 mITT. About 6% dropped out of study 005 by 6 months, mostly due to adverse events.

Table 44 Study 005: Patient Disposition and Analysis Populations

	Double-blind treatment group in study 003		
	Placebo n (%)	**Abaloparatide** n (%)	**Overall** n (%)
Study 003 ITT	821 (100)	824 (100)	1645 (100)
Completed study 003 (% of 003 ITT)	637 (78)	606 (74)	1243 (76)
Study 005 ITT population (% of 003 completers)	581 (91)	558 (92)	1139 (92)
Study 005 Safety population (% of 005 ITT)	580 (100)	553 (99)	1133 (100)
Study 005 Modified ITT population (% of 005 ITT)	568 (98)	544 (98)	1112 (98)
Study 005 Per protocol population (% of 005 mITT)	515 (91)	510 (94)	1025 (92)
Ongoing at 6 mos, or completed study 005 (% of 005 ITT)	544 (94)	529 (95)	1073 (94)
Discontinued study 005 (% of 005 ITT)	37 (6)	29 (5)	66 (6)
Primary reason for discontinuation (% of patients discontinuing)			
Adverse event	21 (57)	17 (59)	38 (58)
Withdrew consent	7 (19)	7 (24)	14 (21)
Others	9 (24)	5 (17)	14 (21)
Source: CSR Section 14.1, Tables 14.1.1A and 14.1.1B			

Reviewer comment: *Equally high proportions (>90%) of placebo and abaloparatide patients enrolled in the extension study. However, patients who had experienced fractures during 003, compared to those who did not, were much less likely to enroll in the extension (see below), which reduces the power of the combined 003/005 fracture data. At the time of 005 enrollment, patients and investigators remained blinded to the previous treatment assignment and also blinded to BMD data, so it is unlikely that there was any bias toward enrollment in study 005.*

Protocol Violations/Deviations

The Per-protocol population comprised 92% of the mITT; the most common reasons for exclusion from per-protocol were compliance <80% (68% of excluded patients), treatment duration <3 months (24%) and glucocorticoid use >1 month (10%).

Table of Demographic Characteristics

The study 005 population was not notably different from the overall study 003 population in regard to demographics at 003 baseline, and the two 005 groups (based on 003 treatment) were similar to each other. As in study 003, there were few US patients (n=16, 1.4% of total).

Table 45 Study 005: Demographic baseline characteristics (ITT)

	Placebo/ALN N=581	**Abaloparatide/ALN** N=558	**Overall** N=1139
Sex (% female)	581 (100)	558 (100)	1139 (100)
Age			
Mean years (SD)	68.5 (6.3)	68.6 (6.5)	68.6 (6.4)
Median (years)	68.0	68.0	68.0
Min, max (years)	50, 86	49, 85	49, 86
Age Group, n (%)			
<65 years	114 (20)	106 (19)	220 (19)
65 to < 74 years	370 (64)	351 (63)	721 (63)
≥ 74 years	97 (17)	101 (18)	198 (17)
BMI (kg/m^2)			
Median	24.7	24.9	24.9
Min, Max	18.4, 34.9	18.5, 33.0	18.4, 34.9
Race, n (%)			
White	447 (77)	433 (78)	880 (77)
Asian	106 (18)	101 (18)	207 (18)
Black or African American	18 (3)	19 (3)	37 (3)
Other	10 (2)	5 (1)	15 (1)
Ethnicity, n (%)			
Hispanic or Latino	139 (24)	124 (22)	263 (23)
Not Hispanic or Latino	442 (76)	434 (78)	876 (77)
Region			
North America (US)	7 (1.2)	9 (1.6)	16 (1.4)
South America	157 (27)	145 (26)	302 (27)
Europe	312 (54)	305 (55)	617 (54)
Asia	105 (18)	99 (18)	204 (18)
Country			
Brazil	148 (26)	140 (25)	288 (25)
Czech Republic	97 (17)	100 (18)	197 (17)
Denmark	105 (18)	98 (18)	203 (18)
Hong Kong	105 (18)	99 (18)	204 (18)
Poland	38 (7)	39 (7)	77 (7)
Romania	31 (5)	32 (6)	63 (6)
Estonia	22 (4)	22 (4)	44 (4)
Lithuania	19 (3)	14 (3)	33 (3)
Argentina	9 (1.5)	5 (0.9)	14 (1.2)
USA	7 (1.2)	9 (1.6)	16 (1.4)

Data based on study 003 baseline. Source: CSR Table 14.1.2 and 14.1.2.1A

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Study 005 patients were similar to the overall 003 population with regard to BMD and fracture status at 003 baseline. Study 005 patients who had completed 18 months of placebo vs. 18 months of abaloparatide were similar in BMD/fracture status at 003 baseline, but different (as expected) at 005 baseline, e.g. mean BMD T-scores -2.9 vs. -2.1 (spine), -1.9 vs. 1.6 (total hip). The 005 treatment groups were also similar to each other, and to the overall 003 population, in regard to medical history and concomitant medications.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Overall compliance with study drug (alendronate) was estimated at 98% for both groups. There were no notable differences between treatment groups in other concomitant medications. The most common medications were statins (29%) and PPIs (20%).

Efficacy Results - Primary Endpoint

In the study 005 population, during the previous study, new vertebral fractures had developed in 19/568 placebo-treated patients (3.35%) at 18 months, and in 3/544 abaloparatide-treated patients (0.55%). Following 6 months of alendronate treatment in study 005, new vertebral fractures developed in 7 former-placebo patients (1.2%), and in none of the former-abaloparatide patients. (One of the 7 placebo/ALN patients had a new fracture in 003 and also in 005.) The cumulative totals for patients who enrolled in both studies were 25 vs. 3 patients with new fractures at month 25 (4.40% vs. 0.55%), a significant difference (87% relative risk reduction) comparable to month 18 data. For the per-protocol population there were 22 vs. 2 patients with new fractures in these respective groups (4.27% vs. 0.39%, RRR -0.91, p<0.0001).

Table 46 Study 005: Incidence of new vertebral fracture at month 25 (mITT)

	Placebo/ALN N=568	**Abaloparatide/ALN** N=544
Number of patients (%) with ≥1 new fracture	25 (4.40%)	3 (0.55%)
95% CI*	3.00, 6.42	0.19, 1.61
Absolute risk reduction vs. placebo (95% CI)**	-3.85 (-5.90, -2.09)	
Relative risk reduction vs. placebo (95% CI)***	-0.87 (-0.96, -0.59)	
P-value ‡	<0.0001	

Cumulative total in studies 003 and first 6 months of 005, relative to 003 baseline
* 95% CI for percentage based on the Wilson's Score method
** 95% CI based on Newcombe's method
*** 95% CI based on Wald's method; ‡ p-value from Fisher's exact test
Source: CSR Table 11 and XE dataset

Reviewer comment: *The large treatment group difference in new vertebral fractures during 18 months of blinded treatment continued through the first 6 months of alendronate (7 vs. 0 patients with new fractures). Therefore the cumulative effect at month 25 was similar to month 18, despite the fact that 11 placebo patients with vertebral fractures at month 18 did not enroll in the extension, compared to just one abaloparatide patient with a vertebral fracture at month 18 who did not enroll.*

Vertebral fracture subgroups

Most vertebral fractures in the study 005 population, as noted above, occurred by month 18, and at month 25 there was no change in the lack of interaction between treatment and any subgroups including age, years since menopause, or baseline fracture or BMD status (see Fig. 2 in section 6.1.2 above for month 18 Forest plot). Also similar to month 18, there were too few vertebral fractures in non-white or non-European patients for evaluation of these subgroups, and no vertebral fractures in US patients.

Data Quality and Integrity - Reviewers' Assessment

Pending the results of OSI inspections, as with study 003, this reviewer has not identified any inconsistencies in the data or other reason to question the validity of the results. In part this is because vertebral fracture is an objective endpoint, and analyses were conducted by treatment-blinded radiologists at an independent central facility.

Efficacy Results - Secondary and other relevant endpoints

Non-vertebral fractures:

Among study 005 patients, during the previous study 003, adjudicated nonvertebral fractures (NVFs, excluding certain sites e.g. fingers/toes and excluding high-trauma) had occurred in 25 placebo and 12 abaloparatide patients. (There were also 8 placebo and 6 abaloparatide patients who experienced NVFs during study 003 who did not enroll in the extension.) During the first 6 months of study 005, 7 and 3 patients in these respective groups developed new NVFs listed in the following table.

Table 47 Study 005: Nonvertebral fracture*, incidence through first 6 months by location (ITT)

	Placebo/ALN N=581 n (%)	**Abaloparatide/ALN** N=558 n (%)
Patients with any NVF skeletal location*	**7 (1.2)** (8 fractures)	**3 (0.5)** (4 fractures)
Wrist	2	2
Upper arm	1	0
Hip	1	0
Lower leg (not knee or ankle)	1	1
Ankle	2	0
* Source document verified; excludes fractures of skull, face, toes, fingers, sternum, patella, and high-trauma fractures. Fractures occurring from study 005 baseline to month 6 (month 19 to 25 of combined studies 003/005) Source: CSR Table 14.2.5.1C		

Cumulatively through month 25, NVFs occurred in 32 placebo/ALN patients (5.5%) and 15 abaloparatide/ALN patients (2.7%). The treatment group difference appears to be consistent across various skeletal sites:

Table 48 Study 005: Nonvertebral fracture*, incidence at month 25 by location (ITT)

	Placebo/ALN N=581 n (%)	**Abaloparatide/ALN** N=558 n (%)
Patients with any NVF skeletal location*	**32 (5.5)** (35 fractures)	**15 (2.7)** (16 fractures)
Wrist	12 (2.1)	8 (1.4)
Forearm	4 (0.7)	1 (0.2)
Upper arm	3 (0.5)	1 (0.2)
Shoulder	1 (0.2)	0
Clavicle	0	1 (0.2)
Ribs	4 (0.7)	1 (0.2)
Hip	1 (0.2)	0
Lower leg (not knee or ankle)	1 (0.2)	1 (0.2)
Ankle	5 (0.9)	0
Foot	2 (0.3)	2 (0.4)
* Source document verified; excludes fractures of skull, face, toes, fingers, sternum, patella, and high-trauma fractures. Cumulative totals of fractures occurring during combined studies 003/005. Source: CSR Section 14, Table 14.2.5.2		

Reviewer comment: *During study 003 there were 2 patients with hip fractures, both placebo patients who dropped out after the fracture and did not enroll in the extension. If these two are considered together with a placebo/ALN patient who suffered a hip fracture ~3 months after*

enrollment in study 005, there were 3 placebo and 0 abaloparatide patients with hip fractures overall in both studies. On the other hand, there were 6 patients in each group with non-hip NVFs in study 003 who did not participate in the extension, and if considered together with 005 participants would have diluted somewhat the NVF relative risk difference.

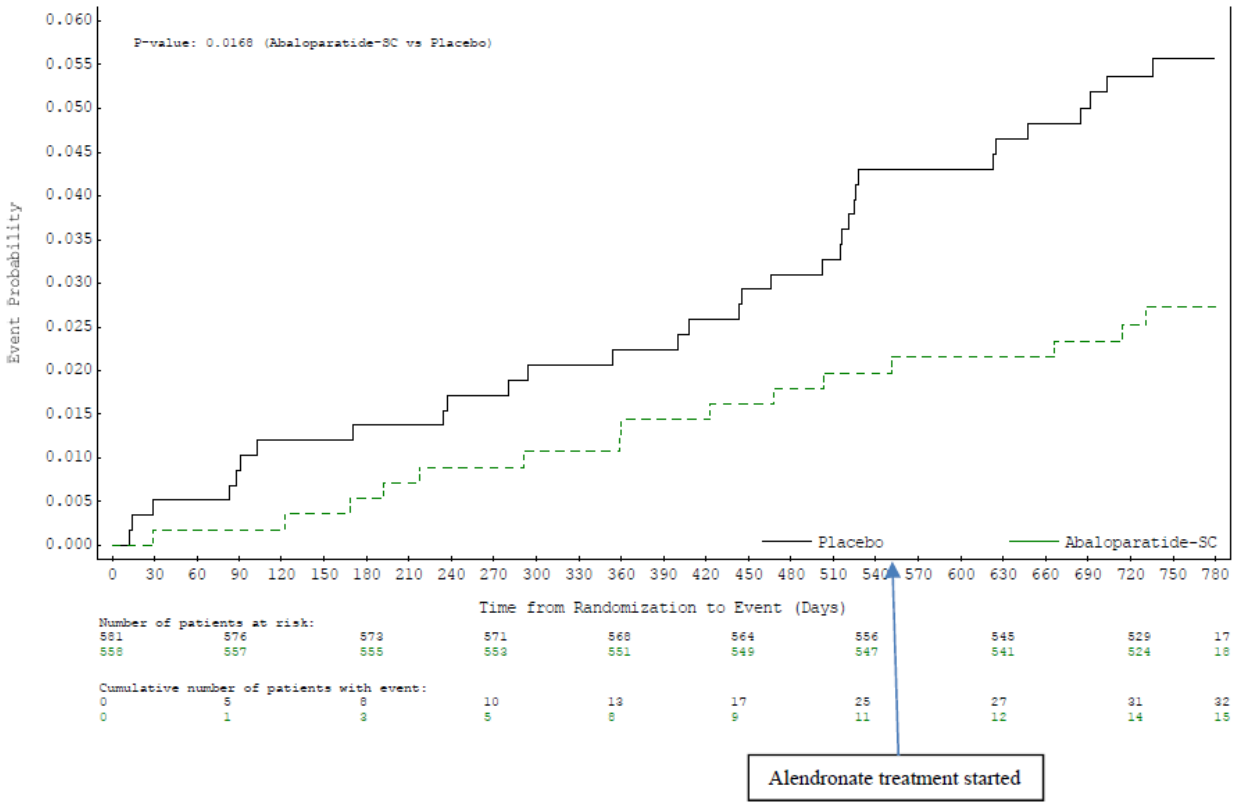
Time to event analysis (table and figure below) showed that the difference in NVF between the two study 005 groups that had developed during study 003 was maintained during study 005, with a significant difference at month 25 (HR 0.48, p=0.0168). The absolute risk reduction was -2.82% (95% CI -5.23%, -0.50%) (from statistical reviewer).

Table 49 Study 005: Nonvertebral fracture, time to event (ITT)

	Placebo/ALN N=581	**Abaloparatide/ALN** N=558
Patients with NVF*, n (%)	32 (5.5%)	15 (2.7%)
K-M estimated event rate at month 25 (%)	5.6%	2.7%
Hazard Ratio vs. placebo (95% CI)**	0.48 (0.26, 0.89)	
p-value vs. placebo***	0.0168	

* Source document verified; excludes fractures of skull, face, toes, fingers, sternum, patella, and high-trauma fractures. Cumulative total of fractures occurring during combined studies 003/005.
** Cox proportional hazard model
*** log rank test
Source: CSR Table 14.2.4A

Figure 13 Studies 003/005: Nonvertebral fracture, Kaplan-Meier curve of time to first incidence, by treatment group (ITT)



Source: CSR Section 14.2, Fig. 14.2.4.1

For the per-protocol 005 population, NVF time-to-event analysis was similar: 28 placebo/ALN vs. 12 abaloparatide/ALN patients with NVF, HR 0.43 (95% CI 0.22, 0.84), p=0.01.

Non-vertebral fracture subgroups:
As with vertebral fractures, nonvertebral fractures in study 005 showed no evidence of any subgroups interacting with treatment, with inadequate fractures to support conclusions in non-white and non-European populations, and no US patients with nonvertebral fractures. The month 25 Forest plot was similar to month 18 (see Fig. 4 above, section 6.1.2).

Clinical fractures:
Among study 005 patients, from study 003 baseline through month 25, there were 41 placebo/ALN and 22 abaloparatide/ALN patients with confirmed/adjudicated clinical fractures. This includes the patients with NVFs discussed above as well as another 16 patients (9 placebo/ALN and 7 abaloparatide/ALN) with confirmed fractures of toes (3); patella (3); facial bones (2); fingers (1); high-trauma fractures of ribs (2) or clavicle, pelvis, sternum or wrist (1

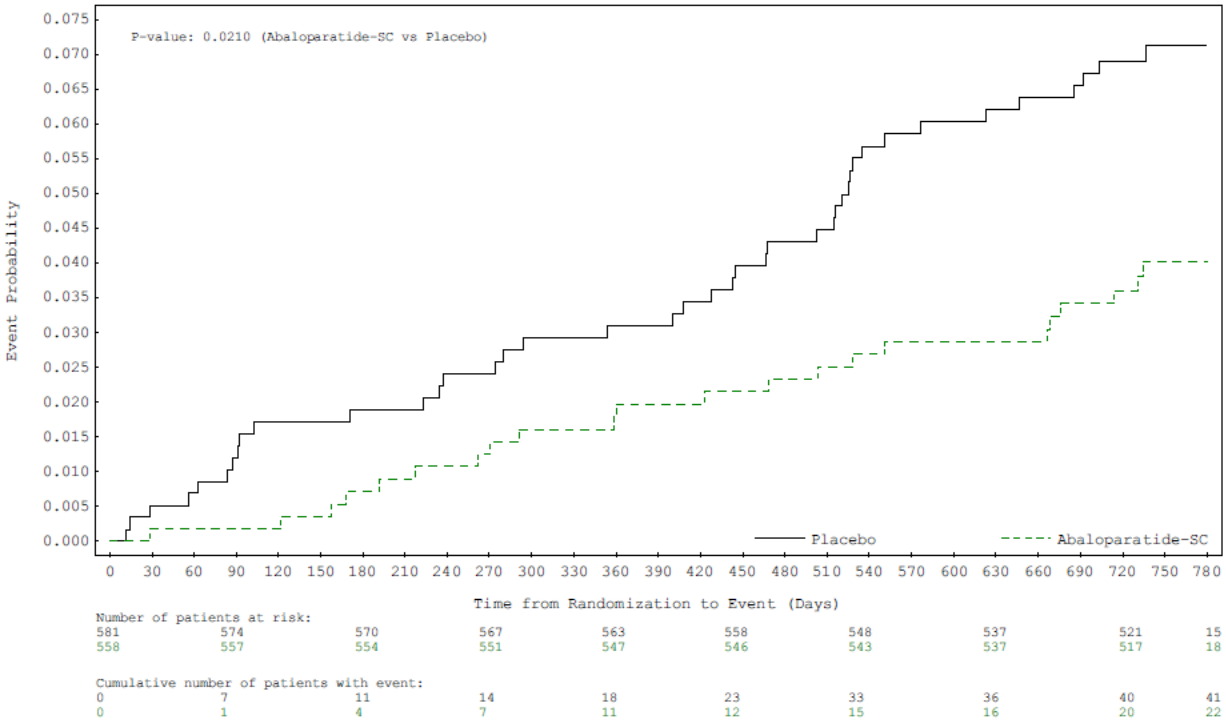
each); and/or clinical spine fractures (6). Most of these occurred during study 003, prior to enrollment in 005. Time to event analysis (table and figure below) showed that, similar to NVFs, the difference between treatment groups at the end of study 003 was maintained through month 25.

Table 50 Study 005: Clinical fracture, time to event (ITT)

	Placebo/ALN N=581	**Abaloparatide/ALN** N=558
Patients with clinical fracture*, n (%)	41 (7.1%)	22 (3.9%)
K-M estimated event rate at month 25 (%)	7.1%	4.0%
Hazard Ratio vs. placebo (95% CI)**	0.55 (0.33, 0.92)	
p-value vs. placebo***	0.021	

* Source document verified clinical fractures, any skeletal site and level of trauma. Cumulative total of fractures occurring during combined studies 003/005.
** Cox proportional hazard model
*** log rank test
Source: CSR Table 14.2.4A

Figure 14 Studies 003/005: Clinical fracture, Kaplan-Meier curve of time to first incidence, by treatment group (ITT)



Source: CSR Section 14.2, Fig. 14.2.5.1

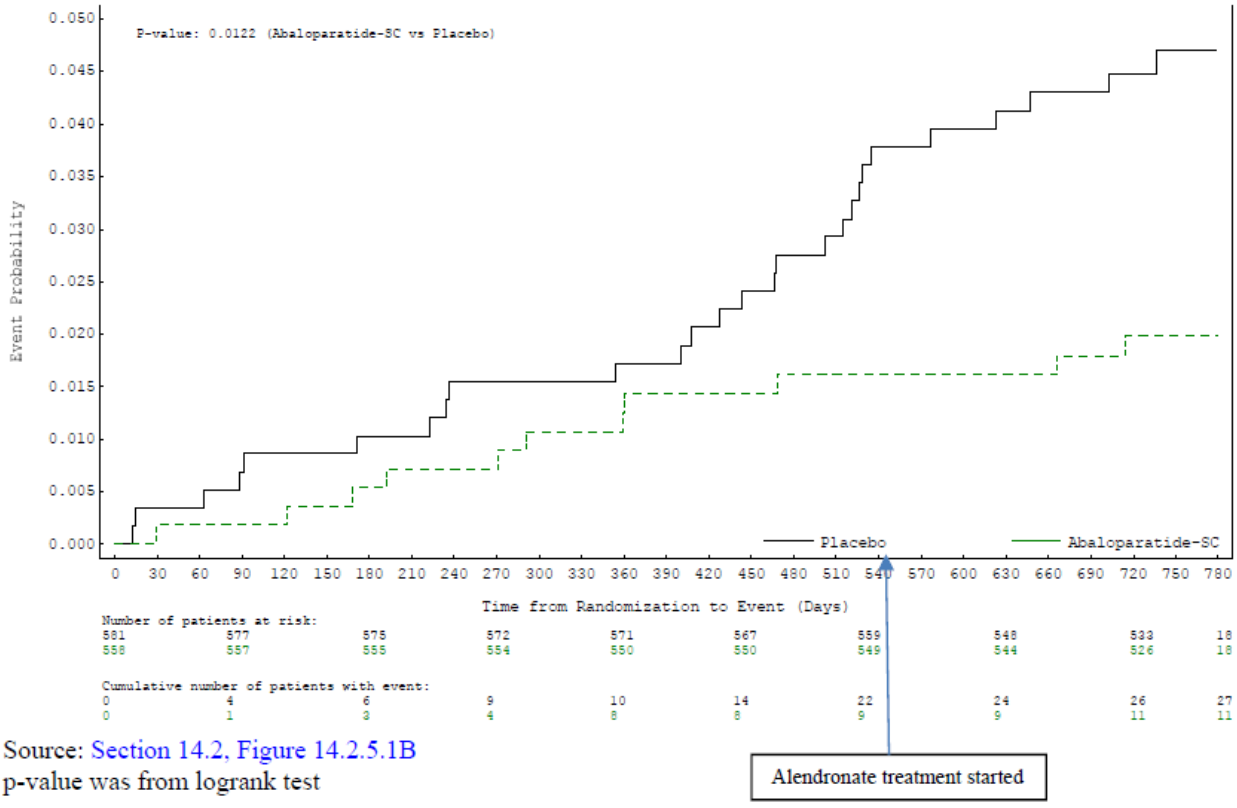
Major osteoporotic fractures: This category, encompassing fractures of the wrist, forearm, upper arm, shoulder, hip and clinical spine, also showed maintenance of treatment group differences in the extension study:

Table 51 Study 005: Major osteoporotic fracture, time to event (ITT)

	Placebo/ALN N=581	**Abaloparatide/ALN** N=558
Patients with major osteoporotic fracture*, n (%)	27 (4.6%)	11 (2.0%)
K-M estimated event rate at month 25 (%)	4.7%	2.0%
Hazard Ratio vs. placebo (95% CI)**	0.42 (0.21, 0.85)	
p-value vs. placebo***	0.012	

* Source document verified fractures of wrist, forearm, upper arm, shoulder, hip and clinical spine. Cumulative total of fractures occurring during combined studies 003/005.
** Cox proportional hazard model
*** log rank test
Source: CSR Table 14.2.4A

Figure 15 Studies 003/005: Major osteoporotic fracture, Kaplan-Meier curve of time to first incidence, by treatment group (ITT)



Source: Section 14.2, Figure 14.2.5.1B
p-value was from logrank test

Wrist fracture, also a prespecified endpoint in study 005, occurred in 13 placebo/ALN and 8 abaloparatide/ALN patients; there was no significant difference in time to event (p=0.31).

Reviewer comment: *Not included in these totals are 4 placebo patients and 1 abaloparatide patient with wrist fracture during study 003, who did not enroll in study 005.*

Clinical vertebral fractures, also prespecified, occurred in 5 placebo/ALN patients and 1 abaloparatide/ALN patient (p=0.11 for time to event).

Reviewer comment: *These vertebral fractures all occurred during study 003, and the totals do not include 4 placebo patients (and no abaloparatide patients) with vertebral fractures in 003 who did not enroll in 005.*

For all these various fracture categories, results for the per protocol population at month 25 are consistent with the ITT analyses.

Vertebral fracture severity

Among the 7 placebo/ALN patients with new vertebral fractures during study 005, there were 2, 3 and 2 patients with fractures of Genant SQ severity grades 1, 2 and 3 respectively, and cumulative month 25 totals of 3, 15 and 7 respectively. There were no abaloparatide/ALN patients with new vertebral fractures during study 005 and cumulative totals were 0, 2 and 1 respectively by SQ grade. There were no patients in either group with worsening of a fracture during study 005.

Bone mineral density

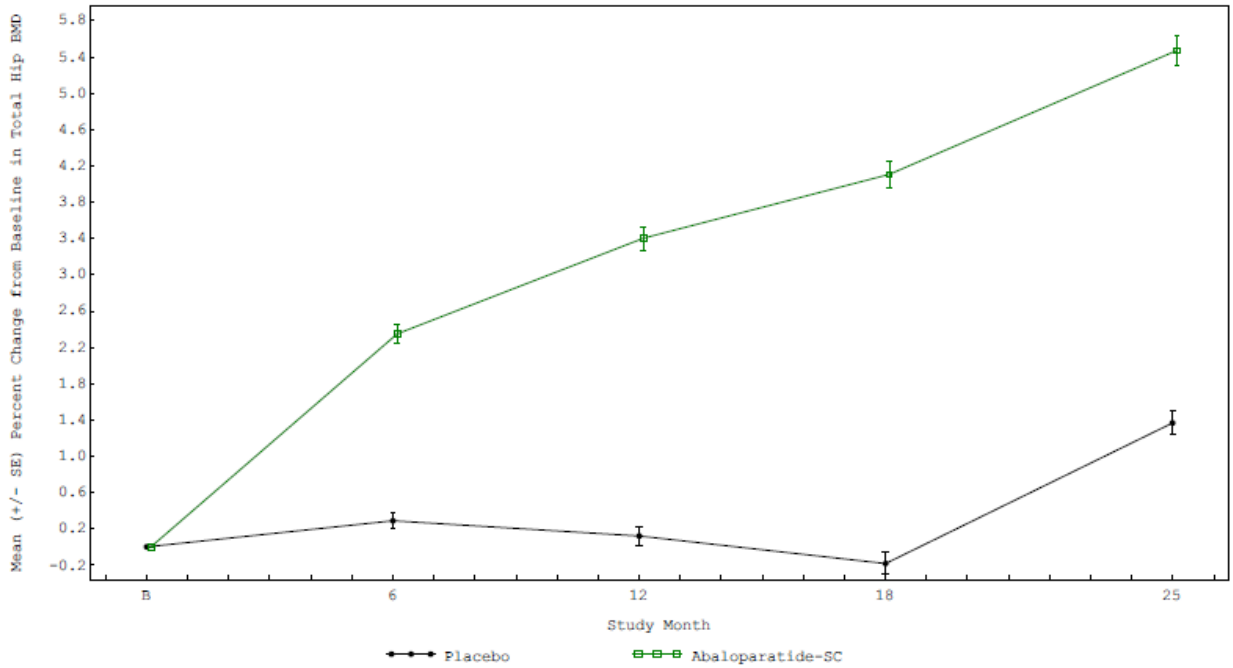
During the first 6 months of alendronate treatment in study 005, BMD of the hip and spine increased in placebo/ALN and abaloparatide/ALN patients, and the significant differences between groups at month 18 were maintained at month 25. These results were similar between ITT/LOCF (shown in table and figures below), ITT/MMRM and Per-protocol analyses. Measured from study 005 baseline, BMD increases at 6 months were similar between the two groups for total hip and femoral neck, but former-placebo patients had a larger 6-month increment in lumbar spine BMD (3.00% vs. 1.51%, p<0.0001).

Table 52 Study 005: BMD of hip and spine, mean percent changes from 003 baseline (005 ITT, LOCF)

	Placebo/ALN N=581	Abaloparatide/ALN N=558	p-value‡
Total hip			
Month 18	-0.18	4.10	<0.0001
Month 25	1.37	5.47	<0.0001
Femoral neck			
Month 18	-0.57	3.58	<0.0001
Month 25	0.46	4.51	<0.0001
Lumbar spine			
Month 18	0.55	11.13	<0.0001
Month 25	3.51	12.79	<0.0001

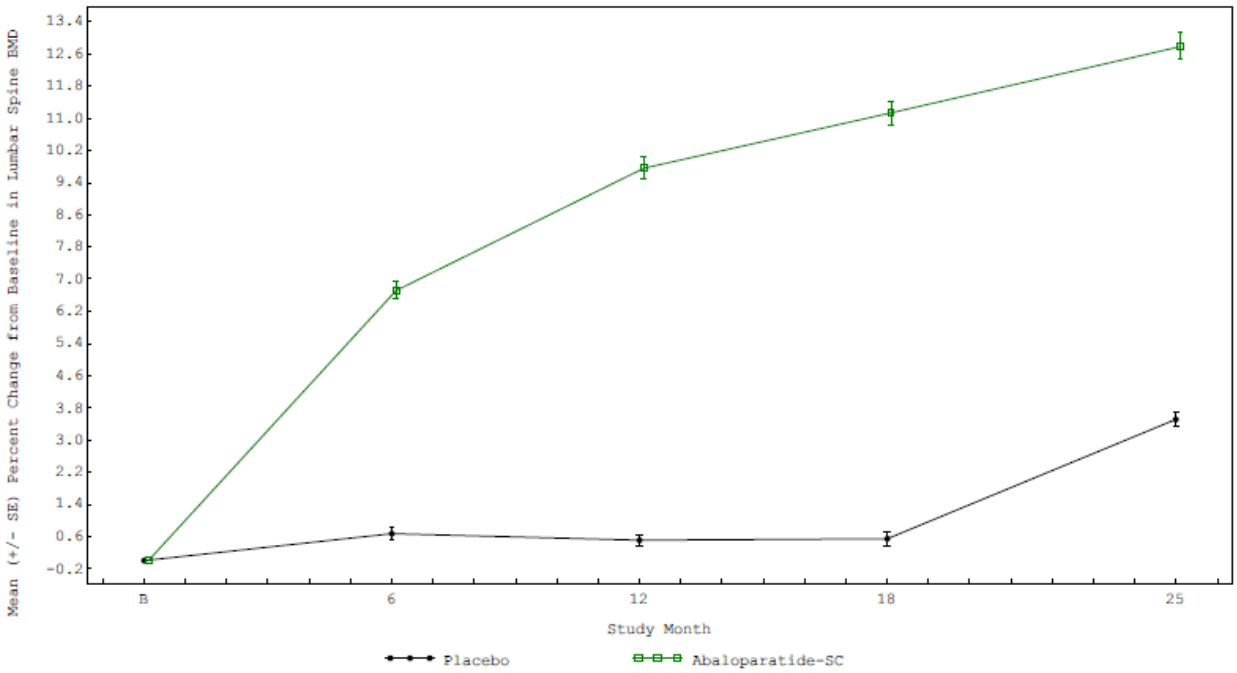
Missing BMD data were imputed using last observation carried forward (LOCF)
‡ p-values were based on ANCOVA model with % change from baseline as response and fixed effects of DXA manufacturer, treatment, and baseline BMD
Source: CSR Table 14.2.7.1A through 14.2.7.3A

Figure 16 Studies 003/005: Total hip BMD, mean percent change from 003 baseline (005 ITT)



Source: CSR Section 14.2 Fig. 14.2.10.1A

Figure 17 Studies 003/005: Lumbar spine BMD, mean percent change from 003 baseline (005 ITT)



Source: CSR Section 14.2, Fig. 14.2.10.3A

The analysis of responders (patients with BMD increases >0%, >3%, or >6% at lumbar spine, total hip and femoral neck) at month 25 was consistent with the data for mean percent changes; 83% of abaloparatide/ALN and 40% of placebo/ALN patients had increases from 003 baseline at all 3 of these skeletal sites (p<.0001).

In the subset of study 005 patients also undergoing radius DXA, cortical BMD at mid-1/3 radius, which had declined with both placebo and abaloparatide at month 18, recovered slightly with alendronate at month 25 but remained below baseline. Ultradistal radius BMD also increased slightly in both groups during alendronate treatment.

Table 53 Study 005: BMD of radius, mean percent changes from 003 baseline (005 ITT, LOCF)

	Placebo/ALN N=233	Abaloparatide/ALN N=213	p-value‡
Mid-1/3 radius			
Month 18	-0.81	-1.62	0.07
Month 25	-0.70	-1.00	0.50
Ultradistal radius			
Month 18	-1.57	1.00	<0.0001
Month 25	-0.83	1.14	0.001

Missing BMD data were imputed using last observation carried forward (LOCF)
‡ p-values were based on ANCOVA model with % change from baseline as response and fixed effects of DXA manufacturer, treatment, and baseline BMD
Source: CSR Tables 14.2.7.4A and 14.2.7.5A

BMD subgroups

BMD changes at month 25, similar to month 18, were consistent across the various prespecified subgroups (including age, years since menopause, race, prior fracture status, baseline BMD, renal function group) and region with the exception of the very small group of US patients (7 placebo/ALN, 9 abaloparatide/ALN). This group, compared to other regions, continued to show lesser mean BMD increases for hip and spine with abaloparatide/ALN, and also with placebo/ALN:

Table 54 Study 005: Total hip BMD, mean % change from 003 baseline at month 25 by region (005 ITT, LOCF)

	Total n	Placebo/ALN N=581	Abaloparatide/ALN N=558
All regions	1139	1.37	5.47
N. America (US)	**16**	**-1.49**	**0.53**
S. America	302	1.89	5.20
Europe	617	1.17	5.64
Asia	204	1.38	5.81

Source: CSR Table 14.2.8.1D

Table 55 Study 005: Femoral neck BMD, mean % change from 003 baseline at month 25 by region (005 ITT, LOCF)

	Total N	Placebo/ALN N=581	Abaloparatide/ALN N=558
All regions	1139	0.46	4.51
N. America (US)	**16**	**-1.53**	**1.61**
S. America	302	0.41	3.29
Europe	617	0.37	4.89
Asia	204	0.95	5.41

Source: CSR Table 14.2.8.2D

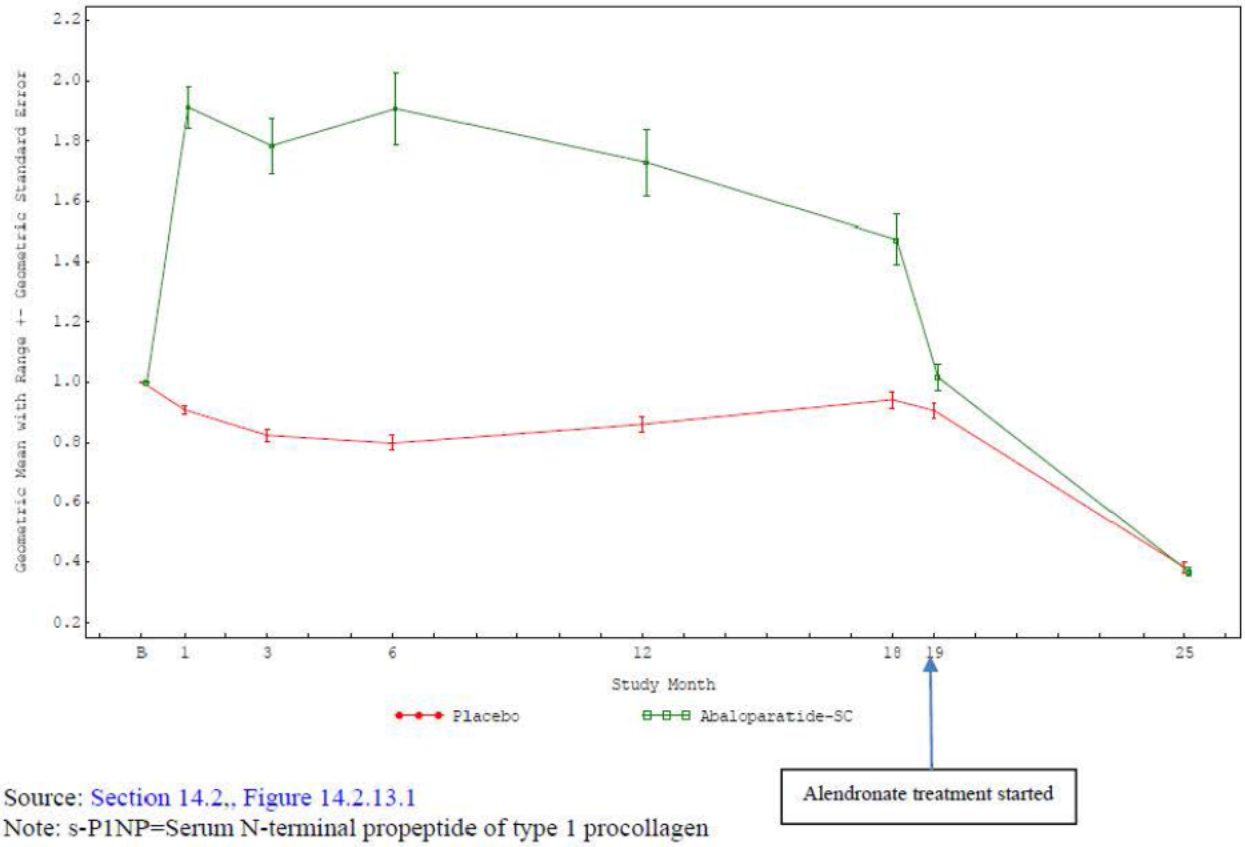
Table 56 Study 005: Lumbar spine BMD, mean % change from 003 baseline at month 25 by region (005 ITT, LOCF)

	Total N	**Placebo/ALN** N=581	**Abaloparatide/ALN** N=558
All regions	1139	3.51	12.79
N. America (US)	**16**	**0.43**	**3.32**
S. America	302	3.45	12.37
Europe	617	3.42	12.84
Asia	204	4.10	14.11
Source: CSR Table 14.2.8.3D			

Other efficacy endpoints:
Height decreased slightly from 005 baseline to month-6 of alendronate in both groups. Cumulative mean changes from 003 baseline to month 25 were -0.19% for placebo/ALN and -0.16% for abaloparatide/ALN (p=0.16).

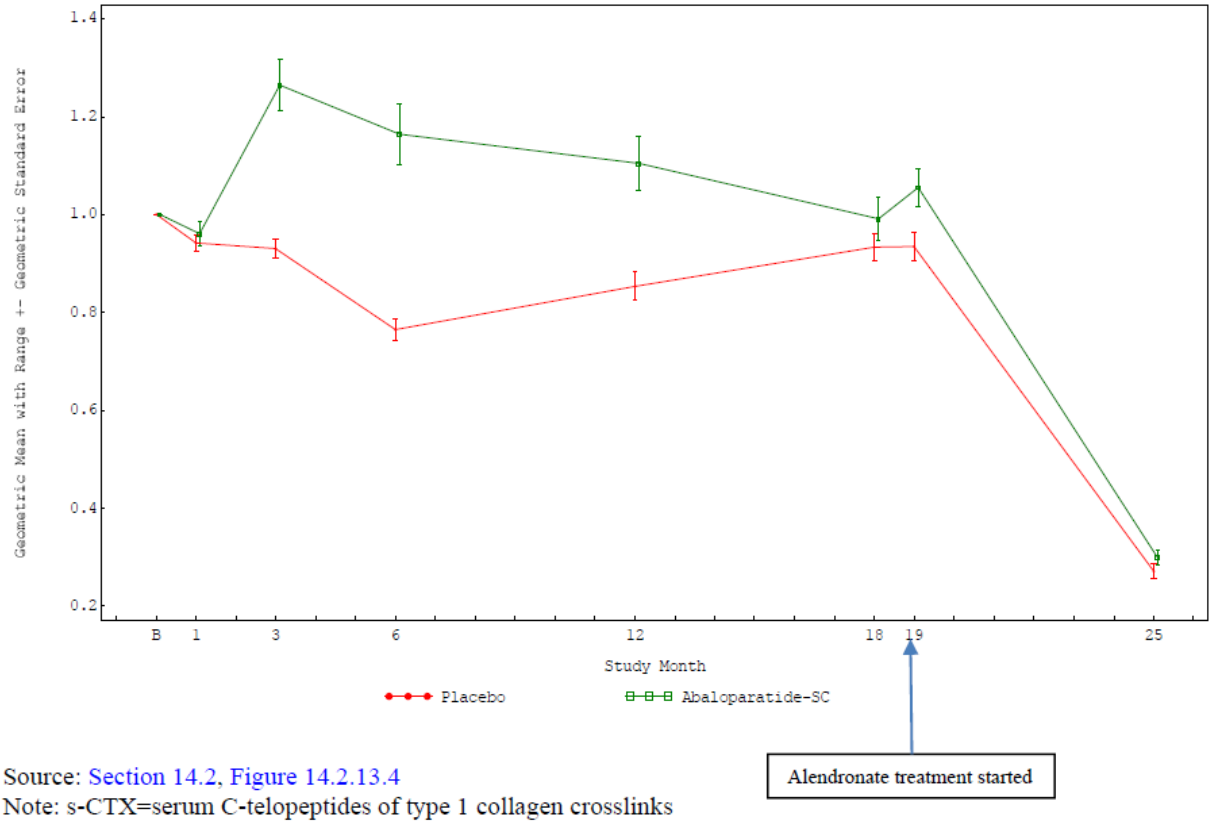
Bone turnover markers were measured in a subset of study 003 and 005 patients. The bone formation marker, serum P1NP, remained ≥50% above baseline through 18 months of abaloparatide, then returned to baseline after stopping (month 19), then declined further after 6 months of alendronate as expected (figure below). The bone resorption marker, serum CTX, increased to a lesser extent with abaloparatide, returned to baseline during continued treatment (month 18), then similarly declined with alendronate. Patients receiving placebo in study 003 had small transient declines in markers (probably due to Ca/Vit D supplements), followed in study 005 by the expected larger declines with alendronate.

Figure 18 Studies 003/005: Serum P1NP by treatment group and visit



Source: Section 14.2., Figure 14.2.13.1
Note: s-P1NP=Serum N-terminal propeptide of type 1 procollagen
B: Study BA058-05-003 Baseline (Visit 2 in Study BA058-05-003)

Figure 19 Studies 003/005: Serum CTX by treatment group and visit



Source: Section 14.2, Figure 14.2.13.4
Note: s-CTX=serum C-telopeptides of type 1 collagen crosslinks
B: Study BA058-05-003 Baseline (Visit 2 in Study BA058-05-003)

Dose/Dose Response

The same alendronate 70 mg (the recommended dose for PMO) is administered to all study 005 patients, in order to optimize comparisons of abaloparatide and placebo in study 003.

Durability of Response

As described above, durability of the abaloparatide/placebo differences after 18 months was maintained through 6 months of open label alendronate, and will continue to be observed through a total of 24 months of alendronate (data to be submitted later).

Persistence of Effect

Persistence of effect following discontinuation of alendronate has been evaluated previously, and is not relevant to this NDA.

Additional Analyses Conducted on the Individual Trial

Following 18 months of abaloparatide in study 003, anti-abaloparatide antibodies (ADA) were present in 300/610 (49%) evaluable patients. Following the 1 month follow-up and 6 months of alendronate in study 005, 143/557 (26%) remained ADA positive, as expected following discontinuation of abaloparatide.

6.3. Study BA058-05-002

6.3.1. Study Design

Overview and Objective

Title of study 002: A randomized, parallel-group, phase 2 dose-finding study to evaluate the effects of BA058 in the treatment of postmenopausal women with osteoporosis

The objectives of the initial 24-week treatment period of this study were to determine, in otherwise healthy women with PMO, the effects of abaloparatide relative to placebo upon serum markers of bone turnover; BMD of the spine, hip and forearm; and safety and tolerability. The objective of the 24-week extension period of the study was to determine longer term safety and tolerability. The ultimate purpose was to select a dose to be carried forward in development.

Trial Design

Study 002 was conducted at 30 study sites (10 in the US, 10 in Argentina, 4 in the UK, 6 in India). Eligible patients were randomized to one of 5 treatment groups:

- Abaloparatide 20 mcg SC
- Abaloparatide 40 mcg SC
- Abaloparatide 80 mcg SC
- Placebo SC
- Teriparatide 20 mcg SC

The first 4 groups listed were double blinded and teriparatide was open label. Study drugs were self-administered daily by patients. Calcium 500-1000 mg and Vitamin D 400-800 IU daily supplements were given. There were algorithms for stopping supplements and/or discontinuing from the study in the event of hypercalcemia. The study was planned to randomized 225 women (45/group).

There was a 2-4 week screening period was followed by a 4-week pretreatment period during which patients were instructed in self-injection, and a 24-week treatment period. Post-baseline visits were at weeks 1, 2, 4 and then every 4 weeks. Patients at certain sites who completed 24

weeks of treatment could participate in an extension with 24 additional weeks of the same (still blinded) treatment. Following either 24 or 48 weeks of treatment, patients were followed for an additional 4 weeks.

Eligibility criteria
Patients were ambulatory, generally healthy postmenopausal women age 55-85 years, postmenopausal for ≥5 years, with osteoporosis defined as lumbar spine or total hip BMD T-score ≤ -2.5; or T-score ≤ -2.0 and an additional risk factor (age ≥65; prior low-trauma fracture of forearm, humerus, vertebra, sacrum, pelvis, hip, femur or tibia within 5 years; or a maternal history of osteoporotic fracture). There were exclusion criteria similar to study 003 (as listed above) for baseline VS, orthostatic BP change, QTc, Paget's or other osteosarcoma risk factors, and low vitamin D (<15 ng/mL). Serum creat. >1.5 mg/dL was also an exclusion criterion.

Study Endpoints

Efficacy was assessed by determination of BMD of the spine, hip and wrist by DXA; and by serum levels of PINP, PICP, BSAP, osteocalcin, and CTX; and urine levels of NTX.

Statistical Analysis Plan

The primary population for efficacy analyses was patients who completed the study with >90% treatment compliance based on diaries and no major protocol violations. The primary population for safety data analysis was the ITT i.e. all patients who received at least 1 dose of study treatment.

6.3.2. Study Results

Patient Disposition

There were 221 patients randomized and treated in the initial 24 week period; 184 (83%) completed the first 6 months. Participation in the second 24 weeks was limited to certain centers, thus included only 55 patients (25% of participants in the first part).
Table 57: Study 002: Patient disposition

	Placebo	Abaloparatide			Teriparatide	Total
		20 mcg	40 mcg	80 mcg	20 mcg	
Randomized/ treated	**45**	**43**	**43**	**45**	**45**	**221**
Completed 6 months	42	33	36	34	39	184
D/C during first 6 months	4	10	7	11	6	38
D/C due to AE first 6 months	0	1	1	3	2	7
Continued beyond 6 months	**11**	**13**	**10**	**7**	**14**	**55**
Completed 12 months	10	11	8	6	13	48
D/C due to AE 6-12 months	0	0	1	1	0	2
Source: CSR Table 10-1						

Demographic Characteristics

The mean patient age was 65 y/o, with range of 54-84 y/o; 62% were Caucasian; baseline T-scores were in the osteoporotic range; treatment groups were well balanced.

Table 58 Study 002: Demographic and baseline characteristics (ITT)

	Placebo	Abaloparatide			Teriparatide	Total
		20 mcg	40 mcg	80 mcg	20 mcg	
	N=45	N=43	N=43	N=45	N=45	N=221
Age (mean, yrs)	65	66	65	65	65	65
Race						
Caucasian	28 (62%)	25 (58%)	27 (63%)	27 (60%)	29 (65%)	136 (62%)
African American	0	0	0	0	0	0
Asian	11	9	10	11	9	50 (23%)
Other	6	9	6	7	7	35 (16%)
Lumbar spine T-score (mean)	-2.9	-2.9	-3.1	-3.0	-2.9	-2.9
Source: CSR Tables 11-2 and 11-8						

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Median compliance with study medication was ~99% in each treatment group. Except for calcium, vitamin D and analgesic/NSAIDs, the only concomitant meds taken by >10% of patients were enalapril (14%) and atorvastatin (12%).

Efficacy Results

Efficacy results were analyzed in the Efficacy Analysis Set, i.e. patients with week-24 assessments and >90% compliance, which represented 70% of the ITT. BMD increased dose-dependently in the abaloparatide treatment groups and in the teriparatide group at weeks 12 and 24 in the main 24-week phase of the study (Table 59). Results were similar in the ITT (not shown). In the relatively small group of patients who also participated in the extension, BMD was more variable but generally continued to increase between weeks 24 and 48 (Table 60).

Table 59 Study 002: BMD, mean percent change from baseline (24-week efficacy analysis set, N=155)

	Placebo	Abaloparatide			Teriparatide
		20 mcg	40 mcg	80 mcg	
	N=37	N=29	N=29	N=28	N=32
Lumbar spine					
Week 12	1.6	2.5	3.3	4.6	3.5
Week 24	1.4	3.5	4.9	6.7	6.0
Total hip					
Week 12	0.4	1.1	1.5	1.4	0.5
Week 24	0.2	1.3	1.5	2.9	0.6
Femoral neck					
Week 12	1.0	1.9	1.4	1.9	0.6
Week 24	0.4	2.3	1.5	2.9	0.6
Soruce: CSR Tables 11-12, 11-17, 11-25					

Table 60 Study 002: BMD, mean percent change from baseline (extension population, N=55)

	Placebo	Abaloparatide			Teriparatide
		20 mcg	40 mcg	80 mcg	
	N=11	N=13	N=10	N=7	N=14
Lumbar spine					
Week 12	0.6	2.1	4.5	5.8	3.0
Week 24	1.0	2.5	5.5	7.5	5.8
Week 48	0.7	5.1	9.8	12.9	8.6
Total hip					
Week 12	1.1	1.3	1.1	1.6	0.7
Week 24	1.6	1.1	3.3	2.2	1.0
Week 48	0.7	2.0	2.1	2.7	1.3
Femoral neck					
Week 12	2.0	2.2	1.0	2.1	1.2
Week 24	2.2	2.1	2.3	2.3	2.0
Week 48	1.0	3.9	1.8	4.1	2.2
Source: CSR Tables 11-14, 11-19, 11-27					

Markers of bone turnover also increased dose-dependently. At Week 24, mean percent changes in serum PINP were -11%, 14%, 96% and 103% in the placebo, abaloparatide 20 mcg, 40 mcg and 80 mcg groups. The test for a linear trend (dose response) was statistically significant ($p<0.001$). Mean percent change in the teriparatide group at this visit was 174%.

Based on the bone marker and especially on the BMD data, the Applicant concluded that 80 mcg was appropriate for the phase 3 study, and also exhibited significantly less hypercalcemia effect than teriparatide.

7 Integrated Review of Effectiveness

Assessment of Efficacy Across Trials

The assessment of abaloparatide efficacy in the treatment of PMO is based entirely on the 18-month phase 3 study BA058-05-003, supplemented by the initial 6-month data from the extension study BA058-05-005 demonstrating that efficacy is maintained through 2 years. These studies are individually discussed above (sections 6.1 and 6.2 respectively) and efficacy data are summarized below (section 7.3).

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The study 003/005 population is broadly representative of the global PMO population (see below re applicability of data to the US), and unlikely to differ substantially from PMO patients treated in the postmarket setting. Because of the consistency of BMD data across all subgroups including age, race/ethnicity and severity of osteoporosis, significant variability in efficacy postmarketing is not anticipated. It is unclear to what extent abaloparatide may be prescribed off-label in populations not studied (e.g. men with osteoporosis, patients with glucocorticoid-induced osteoporosis), however based on experience with teriparatide, there do not appear to be major efficacy concerns regarding possible use in such groups.

7.2.2. Other Relevant Benefits

N/A

7.3. Integrated Assessment of Effectiveness

The submitted evidence meets the statutory standard for "substantial evidence of effectiveness" to support approval of Tymlos (abaloparatide) in the treatment of postmenopausal osteoporosis (PMO). The phase 3 studies BA058-05-003 and BA058-05-005

were adequate and well controlled studies that establish unequivocal efficacy in reducing PMO related fractures.

Fracture is the only clinically meaningful outcome of PMO; there is to date no valid surrogate (e.g. bone density) that has been adequately shown to predict fractures. Morphometric (radiographically identified) vertebral fracture is a useful endpoint because of its relatively high frequency relative to other fracture types in PMO, and since 1994 has been considered by FDA as the efficacy standard for treatment of PMO. All drugs currently approved for this indication have met this primary vertebral fracture endpoint (with the exception of calcitonin-salmon products, approved under pre-1994 standards that did not require fracture data, see section 2.2). Ideally, nonvertebral fractures would also be reduced with any given treatment, but this is generally a secondary endpoint, not considered essential for FDA approval in this indication. A significant increase in bone mineral density (BMD) of the spine and/or hip has also been demonstrated with all approved drugs and is generally also considered a requirement for establishment of efficacy in osteoporosis.

In study 003, 2463 women with PMO were enrolled at 28 centers in 10 countries. By protocol, the patients were age 50-85 years, at least 5 years postmenopausal, with significant fracture risk, but otherwise generally healthy and ambulatory. Women ≤65 y/o were required to have a T-score (spine or femoral neck) ≤ -2.5 as well as a previous low trauma fracture; women >65 y/o could qualify with a T-score ≤-2.0 with a previous fracture, or T-score ≤ -3.0 without a fracture. Patients were randomized (1:1:1) to receive daily injections of abaloparatide 80 mcg, matching placebo, or an active control (Forteo/teriparatide, which is approved for this indication). As is routine for PMO studies, all patients received calcium and vitamin D supplements. The abaloparatide and placebo injections were double blinded; Forteo was open-label because of the infeasibility of masking the manufacturer's device and labeling. The use of Forteo as active control was the choice of the Applicant, for the purpose of some secondary endpoint comparisons (efficacy and safety). FDA did not request use of an active control, which would not be required in a placebo-controlled study, and informed the Applicant that comparative efficacy claims in this indication can only be based on comparative fracture data.

The primary endpoint of study 003, new morphometric vertebral fracture, was assessed at end of treatment i.e. 18 months (or early discontinuation), by the standard method of lateral thoracic and lumbar vertebral x-rays (Genant semi-quantitative scale), compared to screening/ baseline x-rays at a central reading facility. The key secondary endpoint of non-vertebral fracture was defined similarly as in previous PMO fracture trials, i.e. with the exclusion of fractures of the spine, fingers, toes, face, sternum or patella, and also exclusion of fractures associated with high trauma, such as a fall from at or above chair height. BMD by DXA of the lumbar spine, total hip and femoral neck was conducted at 6 month intervals. All of these assessments were made with blinding to treatment assignments.

Overall, 77% of patients completed the 18-month treatment period. There were fewer completers in the abaloparatide arm (74%) compared to the placebo and teriparatide arms (78% and 80%), due to higher rates of AE-related discontinuations with abaloparatide. Compliance with the double blinded treatments (abaloparatide/ placebo) was apparently very good, estimated at a mean of 97-98% based on patient diaries, and 95-96% based on measured quantities of returned medication.

The mean age of participants was 69 years. Most patients (56%) enrolled at sites in Europe; 26% were South American (mostly Brazil); 16% enrolled at a center in Hong Kong; 1.6% enrolled at one of 5 sites in the US. Patients were 80% white, 16% Asian, 3% black or African American and 1% "other" race; 24% were Hispanic. Mean baseline T-scores were -2.9 (lumbar spine), -2.1 (femoral neck) and -1.9 (total hip); 24% had a baseline vertebral fracture by x-ray and 48% had a history of non-vertebral fracture. Mean FRAX fracture probability estimates at baseline were 13.2% for major osteoporotic fracture and 4.8% for hip fracture.

The primary endpoint of new morphometric fracture was assessed in the modified ITT (patients with a baseline and post-baseline x-ray), which constituted 86% of the ITT (which was all randomized patients). During the treatment period of 18 months, new morphometric vertebral fractures occurred in 4 abaloparatide, 30 placebo and 6 teriparatide patients (0.6%, 4.2%, 0.8%). Compared to placebo, the relative risk reductions were 86% for abaloparatide and 80% for teriparatide, each with $p<0.0001$. Vertebral fracture risk reductions were similarly robust in the per-protocol population, and in a sensitivity analysis of the ITT population to assess the impact of missing data. The relative risk reduction of 86% in vertebral fractures compares favorably to all previous PMO drug studies. The absolute risk reduction of 3.6% is somewhat smaller than some previous drug studies; this can be attributed to the somewhat lower baseline fracture risk, and thereby lower fracture rates on treatment, compared to some previous studies.

Nonvertebral fractures were also reduced by 43% for abaloparatide relative to placebo ($p=0.0489$ for time to event analysis), with an absolute risk reduction of -1.84%; there was a smaller 28% relative reduction in nonvertebral fractures for teriparatide vs. placebo. The comparison between abaloparatide and teriparatide in nonvertebral fractures was a prespecified endpoint (unlike with vertebral fractures, where it was not). This endpoint was not met, as abaloparatide was not statistically superior to teriparatide, therefore no statements can be made regarding comparative efficacy of these two drugs. Abaloparatide and teriparatide both demonstrated substantial increases in BMD, with significant placebo-corrected month-18 increases at lumbar spine (8.7% and 8.6% respectively); total hip (3.5% and 2.9%); and femoral neck (3.3% and 2.7%). At the cortical bone site of mid-1/3 radius, at which teriparatide was previously known to cause bone loss, BMD decline was slightly less with abaloparatide compared to teriparatide.

Because FDA requires 2 years of efficacy and safety data for new osteoporosis drugs, patients who completed the 18 months of randomized treatment could, after an off-treatment interval of ≤ 1 month, enroll in an open label extension study (BA058-05-005), in which all patients received open label alendronate 70 mg PO weekly (teriparatide patients in 003 were not eligible). There were 1139 patients enrolled (92% of study 003 completers; 558 who received abaloparatide and 581 who received placebo). The fracture and BMD efficacy benefits in the abaloparatide group relative to placebo were maintained during the initial 6 months of this study. At month 25 (of the combined studies), abaloparatide/ alendronate patients, compared to placebo/ alendronate patients, maintained significant 87% and 52% relative reductions in vertebral and nonvertebral fractures respectively. BMD of the hip and spine increased about equally in both groups during treatment 6 months of alendronate, with the abaloparatide/ alendronate group maintaining a significant advantage.

These studies were not adequately powered to evaluate hip fracture, a relatively infrequent event. There were 2 patients (both placebo) who incurred a hip fracture in study 003 (and did not enroll in study 005). There was one additional patient (placebo/ alendronate) who had a hip fracture in study 005.

Nearly half of all abaloparatide recipients developed antibodies to the drug, but there was no evidence of any adverse effect on efficacy (fractures or BMD).

Reductions in vertebral and non-vertebral fractures were consistent across subgroups of age, years since menopause, baseline fracture status and baseline BMD. Because white European patients comprised more than half of participants and had disproportionately higher fracture rates than other regions within each treatment group, there was an insufficient number of fractures to allow definitive conclusions about fracture efficacy in other regions or groups (nonwhite, Asian, Hispanic), although trends went in the same direction. However as hip and spine BMD were measured in all patients, data are adequate to conclude that BMD changes were highly consistent across all regional, racial and ethnic groups, with one caveat regarding US patients.

Study 003 included only 39 US women (1.6% of all participants), none of whom had any fracture during the study, therefore assessment of abaloparatide efficacy in the US PMO population is largely dependent on foreign data (Europe, South America, Asia). BMD increases with abaloparatide were consistent between these non-US regions, and across other subgroups as noted above. US participants, compared to non-US, exhibited numerically lower percent increases in hip and spine BMD with both abaloparatide and teriparatide (although with positive trends over time vs. placebo). The most likely explanation is that this small group was not optimally representative of the US PMO population in demographic and/or other characteristics.

It is appropriate to make some comparisons of study 003 and the previous phase 3 Forteo PMO study (GHAC), as BMD and fracture data in the teriparatide 20 mcg arms of these two studies were comparable. About 22% of GHAC enrollment was at US centers, and BMD and fracture data were similar for US compared to non-US participants in that study. Because abaloparatide efficacy was at least comparable to teriparatide throughout study 003, including at US sites, and the mechanism of action of both drugs involves the same PTHR1 receptor, it is reasonable to conclude that the overall study 003 and 005 findings are applicable to the US PMO population.

8 Review of Safety

8.1. Safety Review Approach

This review will mainly focus on the phase 3 study (003) of women with postmenopausal osteoporosis (PMO). Study 003 contains the bulk of the safety data for abaloparatide, both in number of patients and duration of treatment, and should be the basis of safety labeling in section 6.1. The phase 2 studies (002 and 007) also enrolled women with PMO, therefore as agreed at the Pre-NDA meeting, the Applicant's ISS focuses on the Pooled Safety Population consisting of all PMO patients who received abaloparatide-SC 80 mcg in studies 003, 002 and 007, and the placebo and teriparatide dose groups from studies 003 and 002. (b) (4) .

Because enrollment of patients in the phase 3 extension study (005) occurred ~1 month after the last dose of abaloparatide/placebo in study 003, and alendronate was the only study drug in 005, the study 005 safety data are reviewed separately from the other clinical data.

The most important safety issue for abaloparatide is the potential for development of osteosarcoma with this and other PTH-related drugs, as shown in animal studies (see section 4.4). Based on extensive clinical experience with teriparatide, the risk in humans, if any, is expected to be too low to become apparent in abaloparatide clinical studies, and should be monitored closely after marketing (see section 12). Other *a priori* safety concerns, based on the mode of action of PTH and PTHrP and clinical experience with teriparatide, are the potential for hypercalcemia or hypercalciuria, ectopic tissue mineralization and orthostatic hypotension; all of these were evaluated in study 003. Bone quality was not expected to be adversely affected by abaloparatide, based on experience with teriparatide and biomechanical studies with both

of these drugs, but is routinely assessed with all osteoporosis drugs via bone biopsies; these were conducted in a subset of study 003 patients.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

A total of 1349 individuals have received abaloparatide-SC in completed trials ((b) (4) (b) (4) This includes 1004 women with PMO exposed to abaloparatide-SC in the phase 2 and 3 studies (002, 003, 007), of whom 918 received the to-be-marketed dose of 80 mcg; 43 patients in these studies received 40 mcg, and 43 patients received 20 mcg.

Table 61 Abaloparatide safety population, size and denominators

	Numbers of exposed individuals in clinical studies*			
	Placebo (N=957)	**Abaloparatide-SC (N=1349)**	**Teriparatide (N=863)**	**All arms (N=3119)**
Phase 1: Healthy adults Healthy postmenopausal women Adults with renal impairment	92	345	0	387
Controlled trials conducted for this indication (Women with PMO), Phase 2/3 studies (003, 002, 007)	865**	1004	863	2732
Phase 2/3 PMO studies, 80 mcg abaloparatide dose only ("Pooled safety population")	865**	918	863	2646
Phase 3 study 003 (b) (4)	820	822	818	2460
All other than controlled trials conducted for this indication	0	0	0	0
Controlled trials conducted for other indications	0	0	0	0

* Exposed individuals in clinical studies included in ISS, and also 30 subjects in study 016 (bioequivalence) completed after ISS cutoff date
** Includes placebo-SC in studies 002 and 003, (b) (4)
Source: ISS Table 1.1.2

Among the 1349 abaloparatide-SC recipients, 640 received the 80 mcg dose for ≥1 year, almost all (n=633) in study 003. Total exposure to 80 mcg in the phase 2/3 studies was 1021 person-years.

Table 62 Abaloparatide phase 2/3 studies: duration of exposure to abaloparatide-SC

Number of patients exposed to abaloparatide-SC*			
<3 months	3 to <6 months	6 to <12 months	12 months or longer
N = 462	N = 128	N = 79	N = 640
* any dose (20, 40 or 80 mcg); excludes 40 patients in study 003 with unknown exposure stop date Source: ISS Table 4.1.1			

Reviewer comment: *According to the ICH guideline The extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions, a cohort of ~300-600 patients exposed to the study drug at the intended dose for ≥6 months, including ≥100 patients exposed for ≥1 year, should be adequate to characterize the pattern of adverse events over time. The abaloparatide safety database meets this standard.*

In study 003, the rate of study completion was somewhat lower for abaloparatide 80 mcg recipients compared to placebo or teriparatide recipients (74%, 78%, 80% respectively), attributed to higher rates of AE-related discontinuations. As a result, mean study drug exposure was somewhat less in abaloparatide patients (15.0 months, vs. 15.6 and 15.9 months for placebo and teriparatide respectively).

As discussed above (section 6.1.2), compliance was 97-98% in the abaloparatide/placebo arms based on patient diary data, or 95-96% based on study drug volumes dispensed/returned. Compliance in the open-label teriparatide arm was similar based on patient diaries, but possibly lower (~85%) based on drug volumes.

8.2.2. Relevant characteristics of the safety population:

See section 6.1.2 of this review for discussion of demographics of the ITT population of study 003, which is the same as the safety population with addition of 3 enrollees who were not dosed (Table 14). All patients received the correct (assigned) study drug.

8.2.3. Adequacy of the safety database:

In general, the safety database is adequate in regard to the number of exposed patients, duration of treatment, demographics and disease characteristics appropriate to the intended PMO population. As discussed above (section 6.1.2), the number of US patients in study 003 was small (39), however data from the overall study population appears to be applicable to the target US population.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Reporting frequency for TEAEs was generally >80% across different countries and study sites, with the exception of site #216 (US) where AEs were reported for 7/21 patients, and site #146 (Poland), with AEs for 7/13 patients.

For serious TEAEs however, there were some notable differences, with SAE reporting frequency by country as follows: Czech Rep. 15.4%; Hong Kong 13.4%; Estonia 13.4%; Argentina 13.3%; Romania 13.2%; Lithuania 11.9%; Denmark 8.9%; Brazil 6.0%; USA 5.1%; Poland 4.0%. Among individual higher-enrolling sites the SAE incidence was highest at the two largest Czech Rep. sites #131 and #132 (each 15.5%), slightly lower at Hong Kong site #181 (13.4%), and lowest at the two largest Brazilian sites #121 and #123 (4.2% and 6.9%). Deaths were also most numerous at Czech Republic sites with 4 of the 11 study deaths.

Reviewer comment: *The difference in SAE incidence does not appear to be explained by the age of enrolled patients; mean age was lower at the Czech Republic sites #131 and #132 (66.7 and 63.1 years) than at the Brazilian sites #121 and #123 (71.6 and 71.5 years). The difference may reflect regional differences in patterns of clinical practice (e.g. propensity to hospitalize patients for certain illnesses).*

8.3.2. Categorization of Adverse Events

In study 003, an adverse event (AE) was defined as any symptom or unfavorable/unintended sign (including a clinically relevant abnormal lab value), including worsening of a preexisting condition, regardless of potential relationship to the study drugs. Serious AEs were defined as those which (regardless of potential causality) were life-threatening or resulted in death; required hospitalization or caused prolongation of a hospitalization; resulted in persistent or significant disability/ incapacity; were a congenital anomaly/ birth defect; or constituted an "important medical event" requiring intervention to prevent a serious outcome.

AEs were also classified for severity by investigators, based on definitions in the protocol:

- Mild: awareness of sign or symptom, but easily tolerated
- Moderate: Discomfort enough to cause interference with normal daily activities
- Severe: inability to perform normal daily activities

AEs were collected in study 003 beginning at visit 2 (pre-screening period, up to 1 week prior to first injection) through end of study (month 19), including open ended questioning at each visit or other encounter. Treatment-emergent AEs were defined as those occurring after the first injection and up to 30 days after the last injection, and for patients enrolling in the extension study (005), AEs prior to the first dose of alendronate in that study; and also AEs that were

considered drug-related occurring at any time. It should be noted that abaloparatide and placebo were double-blinded but teriparatide treatment was open label.

Study 003 was coded in MedDRA version 13.1 for SOC and PT and up-coded to 17.1 after database lock. As agreed at the Pre-NDA meeting, all datasets were upcoded to this version, including phase 2 studies 002 (originally v. 11.1) and 007 (originally v. 15.1). The study 003 protocol initially specified the WHO Toxicity Criteria; amendment #2 (July 2012) changed this to the Eastern Cooperative Oncology Group common toxicity criteria.

8.3.3. Routine Clinical Tests

In study 003, routine lab testing (hematology, chemistry, urinalysis) was collected fasting/ predose at each regular visit during treatment (see schedule of procedures, section 6.1.1 above). Serum calcium was also collected 4 hours post dose at clinic visits because this was expected to be the approximate time of maximum serum calcium; hypercalcemia (abaloparatide vs. teriparatide) was designated a key safety endpoint. Pre- and post-dose hypercalcemia were to be summarized separately per the protocol and SAP, which defined hypercalcemia as an albumin-corrected level of ≥10.7 mg/dL, based on ≥0.3 mg/dL above the ULN of 10.4 mg/dL. Hypercalciuria was also prespecified as a safety endpoint and assessed by 24-hr urine collection at each visit.

Vital signs were recorded at all study 003 visits. Because of the potential for symptomatic hypotension with PTH related drugs, all blood pressure measurements were recorded both supine (after 5 minutes lying) and then after standing for 3 minutes. During the treatment period, these BP measurements were done both pre-dose and 60 minutes post-dose. Orthostatic hypotension was defined in the protocol as a decline from supine to standing of ≥20 mmHg systolic or ≥10 mmHg diastolic, and was used as an exclusion criterion if detected at screening or pre-screening.

ECGs were conducted at all study 003 visits during treatment, both pre-dose and 1 hour post-dose. Renal safety and potential tissue mineralization were assessed by blood and urine testing (creatinine clearance) and renal CT scans in a subset (see section 8.5.3). Local tolerance was self-assessed by patients via daily diary entries during months 1 and 11. Other safety evaluations included potential immunogenicity (antibody levels) and bone histomorphometry (bone biopsies), discussed in sections 8.4.10 and 8.5.7 respectively. Separately, a Thorough QT study was also conducted (section 8.4.9).

Reviewer comment: *The clinical testing conducted in study 003 appears to have been adequate to evaluate safety.*

8.4. Safety Results

8.4.1. Deaths

There were 11 deaths in study 003: 5 in placebo patients (0.6%), 3 in abaloparatide patients (0.4%) and 3 in teriparatide patients (0.4%); clinical features are summarized in the following table. Based on the narratives, it appears that death was sudden and unexpected in 1 abaloparatide patient (#1810423), 1 teriparatide patient (#1610011) and 2 placebo patients (#1310115, #1330031).

Table 63 Study 003: Deaths

Patient #	Site	Age/ race	Day of onset	Cause of death (Preferred term)	Narrative
Abaloparatide					
1240030	124/ Brazil	83/ white	317	Sepsis Craniocerebral injury	History: labyrinthitis x2mos, hypercholesterolemi Screening visit: bacteriuria, mild hyperglycemia Days 2, 89, 208 and 228: UTIs Rx antibiotics Day 317: found on floor convulsing; hospitalized for "traumatic brain injury", during hospitalization developed severe bronchopneumonia complicated by sepsis Death on day 347,attributed to head trauma and bronchopneumonia/sepsis Relationship to drug: "unlikely" for sepsis, "none" for craniocerebral injury ECGs normal
1810423	181/ Hong Kong	82/ Asian	136	Myocardial ischemia	History: HTN, hyperlipidemia, CVA (2004), dizziness (since 2009) Screening BP 151/64 supine, 153/65 standing HR 62 Screening ECG: NSR, R-S transition zone in V leads displaced to the right, QTc 430 ms Baseline, Month1, Month3: BP and HR stable, no change ECG, all QT and QTc <450 ms Day 136: found collapsed at home, DOA in ER Autopsy: 80% stenosis of 2 coronary aa. Rel. to drug "none"
1810276	181/Hong Kong	81/ Asian	421	Bronchiectasis	History: TB, pneumonia (2010), bronchiectasis (since 2010, followed in pulm. clinic), HTN Screening: VS normal, ECG=L atrial abnormality Day 1 of treatment: dizziness, "possibly related" Last visit (Month 12): no clin sig labs per

Patient #	Site	Age/ race	Day of onset	Cause of death (Preferred term)	Narrative
					investigator Site informed that pt had died on day 473, death certificate=bronchiectasis cause of death Rel. to drug "none"
Teriparatide					
1210259	121/ Brazil	76/ white	459	Pancreatic carcinoma	History: HTN Day 429: jaundice Day 459: pancreatic CA dx by CT scan Day 534: died at home Rel. to drug "unlikely"
1310425	131/ Czech Rep.	80/ white	537	General physical health deterioration	History: chronic bronchitis/asthma, HTN Day 228: dx with Lyme disease, treated PCN Day 431: fell, fractured wrist and tibial plateau Day 494-510: UTI, crural thrombosis of RLE, lymphedema of lower extremities/ erysipelas, ischemic heart disease, exacerbation of asthma Day 535: while "in hospital under complex care…suffered general physical health deterioration", died on day 544 Discontinued study treatment on day 506 Rel. to drug "none"
1610011	161/ Romania	74/ white	171	Cardio-respiratory arrest	History: HTN, dyslipidemia, CAD, vertebrobasilar insufficiency Site informed that on day 170, pt had C/O intense chest pain, DOA at ER, death certificate= cardio-respiratory arrest Rel. to drug "unlikely" ECGs ess. normal
Placebo					
1330031	133/ Czech Rep.	78/ white	341	Sudden death	History: HTN, myocardial ischemia Site informed that on day 340, patient died suddenly at home, no autopsy
1210307	121/ Brazil	70/ white	173	Intestinal obstruction	History: SBO, HTN, DM type 2 Day 172: hosp. for severe bowel obstruction Postop peritonitis/sepsis, died day 176
1320113	132/ Czech Rep.	77/ white	413	Dissecting aortic aneurysm	History: AFib, HTN, hypercholesterolemia Day 413: surgery for dissecting aneurysm Postop: multiple complications, died day 457
1310115	131/ Czech Rep.	60/ white	320	Myocardial infarction	History, HTN, DM type 2 Day 320: found dead at home Autopsy conclusion=MI
1210211	121/ Brazil	68/ white	433	Gastrointestinal carcinoma	Family history of cancer Died of "bowel cancer"
Sources: narratives summaries, table 14.3.1.5, listing 14.3.2.1					

In the first 18 months of extension study 005, there were 5 deaths (table below). Two of these (patients #1310163 and #1210344, one each treatment group) occurred during the initial 6 months, and the others were reported in the Safety Update. Only one of these 5 deaths (#1310163) is considered by the Applicant to be treatment-emergent, because the last dose of study drug (alendronate) was 7 months prior to death in one case and was unknown in the other 3.

Table 64 Study 005: Deaths

Patient #	Site	Age/ race	Day of onset*	Cause of death (Preferred term)	Comment
Placebo/ALN					
1310163	131/ Czech Rep.	74/ white	56	Acute myocardial infarction	History: MI with stent placement 2011, T2DM, HTN, dyslipidemia, CVA (1980) Day 45: acute MI Day 56: acute MI, cardiac arrest during PCI
1310441	131/ Czech Rep.	59/ white	523	Myocardial infarction	History: HTN, smoking Day 213: acute MI Day 521: Surgery for lung carcinoma 2 days postop: acute MI, cardiac arrest Date of last ALN dose unknown
1210123	121/ Brazil	71/ white	767	Septic shock	Day 238: Dx sigmoid colon adenoCa Day 747: hosp. for UTI Day 766: hosp. for pneumonia Day 767: death due to septic shock Date of last ALN dose unknown
Abaloparatide/ALN					
1210344	121/ Brazil	85/ white	132	Pancreatic carcinoma	Day 131: Hosp. for severe abdominal pain Day 148: Died of pancreatic cancer Date of last ALN dose unknown
1210121	121/ Brazil	67/ white	635	Diverticulitis	Stopped study med (ALN) on day 420 Day 641: perforated colon from diverticulitis, led to septicemia and death
* days from start of study 005 Source: narratives, 120-day safety update					

Reviewer comment: *There is no good evidence that any of these deaths in studies 003 or 005 were related to the study treatments.*

There were no deaths studies 002 or 007.

8.4.2. Serious Adverse Events

SAEs were reported in 10-11% of study 003 patients with no apparent imbalances between treatment groups:

Table 65 Study 003: Incidence of serious adverse events occurring in ≥2 patients overall and in ≥1 abaloparatide patient (safety population)

System organ class Preferred term	**Placebo** (N=820) n (%)	**Abaloparatide** (N=822) n (%)	**Teriparatide** (N=818) n (%)
Patients with ≥1 serious TEAE	90 (11.0)	80 (9.7)	82 (10.0)
Cardiac disorders	7 (0.9)	8 (1.0)	8 (1.0)
Myocardial ischemia	0	2	1
Supraventricular tachycardia	0	2	1
Myocardial infarction	2	1	0
Cardio-respiratory arrest	0	1	1
Palpitations	0	1	1
Ear and labyrinth disorders	0 (0.0)	1 (0.1)	2 (0.2)
Vertigo	0	1	1
Endocrine disorders	1 (0.1)	1 (0.1)	3 (0.4)
Goiter	1	1	2
Eye disorders	2 (0.2)	2 (0.2)	1 (0.1)
Cataract	2	0	1
Gastrointestinal disorders	13 (1.6)	10 (1.2)	5 (0.6)
Gastric ulcer	0	2	1
Abdominal pain	3	1	0
Hemorrhoids	1	1	1
Intestinal obstruction	1	1	0
General disorders and administration site conditions	5 (0.6)	2 (0.2)	2 (0.2)
Chest pain	2	1	1
Pyrexia	1	1	0
Hepatobiliary disorders	3 (0.4)	4 (0.5)	2 (0.2)
Cholelithiasis	0	3	1
Infections and infestations	8 (1.0)	8 (1.0)	8 (1.0)
Sepsis	0	2	0
Urinary tract infection	1	2	0
Pneumonia	1	1	1
Bronchopneumonia	0	1	1
Appendicitis	0	1	1

System organ class Preferred term	**Placebo** (N=820) n (%)	**Abaloparatide** (N=822) n (%)	**Teriparatide** (N=818) n (%)
Injury, poisoning and procedural complications	18 (2.2)	10 (1.2)	10 (1.2)
Joint dislocation	2	1	0
Ligament rupture	1	1	0
Patella fracture	1	1	0
Spinal compression fracture	0	1	2
Upper limb fracture	2	1	1
Investigations	2 (0.2)	1 (0.1	2 (0.2)
Metabolism and nutrition disorders	0	3 (0.4)	2 (0.2)
Hypoglycemia	0	2	0
Musculoskeletal and connective tissue disorders	8 (1.0)	8 (1.0)	8 (1.0)
Osteoarthritis	1	3	3
Back pain	3	2	1
Foot deformity	0	1	1
Neoplasms benign,malignant and unspecified (incl. cysts and polyps)	9 (1.1)	10 (1.2)	15 (1.8)
Breast cancer	1	3	6
Adenocarcinoma of colon	0	2	0
Pancreatic carcinoma	0	2	2
Nervous system disorders	10 (1.2)	9 (1.1)	7 (0.9)
Transient ischemic attack	2	2	2
Radicular syndrome	0	1	1
Syncope	1	1	0
Renal and urinary disorders	1 (0.1)	1 (0.1)	0
Reproductive system and breast disorders	3 (0.4)	7 (0.9)	6 (0.7)
Ovarian cyst	0	2	1
Uterine prolapse	2	2	1
Postmenopausal hemorrhage	0	2	0
Respiratory, thoracic and mediastinal disorders	0	4 (0.5)	5 (0.6)
Dyspnea	0	1	1
Pulmonary embolism	0	1	1
Surgical and medical procedures	4 (0.5)	4 (0.5)	4 (0.5)
Colporrhaphy	1	1	0
Vascular disorders	3 (0.4)	1 (0.1)	6 (0.7)
Intermittent claudication	0	1	1
Sources: CSR Table 14.3.1.5			

In study 002, 2 SAEs were reported in abaloparatide-treated patients: ovarian cancer (20 mcg) and diverticulitis (80 mcg). Among the 51 abaloparatide 80 mcg SC-treated patients in study 007, there were 4 SAEs: breast cancer; coronary artery disease; osteoarthritis; and abdominal pain.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

AE-related discontinuations occurred more frequently in the abaloparatide arm (9.9%) relative to placebo (6.1%) or teriparatide (6.8%) arms. This difference resulted from apparent excesses in the abaloparatide group of discontinuation due to nausea (1.6% of patients), dizziness (1.2%), headache (1.0%) and palpitations (0.9%). There were also 2 patients each in the abaloparatide group who discontinued due to tachycardia or hypotension, and none in the other two groups (see discussion of orthostatic hypotension and cardiac disorders AEs below, sections 8.5.4 and 8.5.5).

Discontinuation due to hypercalcemia was most frequent with teriparatide (4 patients), followed by abaloparatide (1 discontinued due to hypercalcemia, 1 due to blood calcium increased) and no such discontinuations with placebo. There were no abaloparatide patients who met the protocol criterion for reducing dose (80 to 40 mcg) because of hypercalcemia.

Table 66 Study 003: Incidence of discontinuation due to AEs occurring in ≥2 patients overall and in ≥1 abaloparatide patient (safety population)

System organ class Preferred term	**Placebo** (N=820) n (%)	**Abaloparatide** (N=822) n (%)	**Teriparatide** (N=818) n (%)
Patients with ≥1 AE leading to discontinuation	**51 (6.1)**	**81 (9.9)**	**56 6.8)**
Cardiac disorders	**3 (0.4)**	**14 (1.7)**	**2 (0.2)**
Palpitations	**1 (0.1)**	**7 (0.9)**	**0**
Myocardial ischemia	1	3	0
Tachycardia	**0**	**2 (0.2)**	**0**
Eye disorders	0	2 (0.2)	1 (0.1)
Visual impairment	0	1	1
Gastrointestinal disorders	**7 (0.9)**	**18 (2.2)**	**9 (1.1)**
Nausea	**2 (0.2)**	**13 (1.6)**	**3 (0.4)**
Abdominal pain upper	0	1	2
Dyspepsia	1	1	1
General disorders and administration site conditions	6 (0.7)	7 (0.9)	7 (0.9)
Asthenia	1	2	2
Malaise	4	1	0
Infections and infestations	0	3 (0.4)	2 (0.2)
Injury, poisoning and procedural complications	1 (0.1)	2 (0.2)	1 (0.1)
Post procedural discomfort	0	1	1
Investigations	5 (0.6)	9 (1.1)	4 (0.5)
Electrocardiogram QT prolonged	2	3	1
Blood pressure increased	0	2	0

System organ class Preferred term	**Placebo** (N=820) n (%)	**Abaloparatide** (N=822) n (%)	**Teriparatide** (N=818) n (%)
Blood PTH increased	0	1	1
Metabolism and nutrition disorders	0	1 (0.1)	4 (0.5)
Hypercalcemia	**0**	**1 (0.1)**	**4 (0.5)**
Musculoskeletal and connective tissue disorders	14 (0.7)	3 (0.4)	3 (0.4)
Back pain	1	2	0
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	4 (0.5)	5 (0.6)	8 (1.0)
Pancreatic carcinoma	0	2	1
Breast cancer	0	1	3
Nervous system disorders	**7 (0.9)**	**19 (2.3)**	**13 (1.6)**
Dizziness	**3 (0.4)**	**10 (1.2)**	**8 (1.0)**
Headache	**2 (0.2)**	**8 (1.0)**	**4 (0.5)**
Psychiatric disorders	3 (0.4)	4 (0.5)	0
Restlessness	0	2	0
Depression	1	1	0
Respiratory, thoracic and mediastinal disorders	1 (0.1)	2 (0.2)	1 (0.1)
Skin and subcutaneous tissue disorders	5 (0.6)	4 (0.5)	5 (0.6)
Rash pruritic	0	2	0
Urticaria	1	1	1
Vascular disorders	2 (0.2)	6 (0.7)	3 (0.4)
Hypertension	1	3	2
Hypotension	**0**	**2 (0.2)**	**0**
Soruce: CSR Table 14.3.1.6			

8.4.4. Significant Adverse Events

The incidence of severe TEAEs was comparable among placebo (7.3%), abaloparatide (6.6%) and teriparatide (6.1%) treatment groups. There were no notable treatment group imbalances in severe TEAEs for specific SOC classes or preferred terms, including palpitations, nausea and dizziness.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

TEAEs were reported by 88-89% of study 003 patients, with slightly higher rates with the two active drugs relative to placebo (table below). There were higher rates in the abaloparatide arm in the SOC classes of Cardiac disorders, Gastrointestinal disorders and Nervous system disorders which were attributable to individual AE terms of palpitations, nausea, dizziness and headache. Vomiting was reported in 8 abaloparatide, 12 teriparatide and 5 placebo patients. The abaloparatide and teriparatide groups had higher rates than placebo of anemia and hypercalciuria.

Muscle spasms were also more frequent with abaloparatide and teriparatide relative to placebo (2.7%, 3.1%, 2.0% respectively) which was also true for myalgia (1.7%, 2.3%, 0.4%) and fibromyalgia (0.5%, 0, 0); however most other common musculoskeletal AEs (e.g. arthralgia, back pain, pain in extremity, musculoskeletal pain) as well as overall AEs in this SOC were somewhat more frequent with placebo.

Table 67 Study 003: Treatment emergent AEs occurring in >2% of abaloparatide patients and more frequent than placebo

System organ class Preferred term	**Placebo** (N=820) n (%)	**Abaloparatide** (N=822) n (%)	**Teriparatide** (N=818) n (%)
Patients with at least 1 TEAE	718 (87.6)	735 (89.4)	727 (88.9)
Blood and lymphatic system disorders	34 (4.1)	52 (6.3)	38 (4.6)
Anemia	**15 (1.8)**	**23 (2.8)**	**23 (2.8)**
Cardiac disorders	47 (5.7)	89 (10.8)	51 (6.2)
Palpitations	**3 (0.4)**	**42 (5.1)**	**13 (1.6)**
Ear and labyrinth disorders	21 (2.6)	31 (3.8)	34 (4.2)
Vertigo	15 (1.8)	17 (2.1)	20 (2.4)
Gastrointestinal disorders	200 (24.4)	221 (26.9)	184 (22.5)
Nausea	**25 (3.0)**	**68 (8.3)**	**42 (5.1)**
Dyspepsia	19 (2.3)	22 (2.7)	18 (2.2)
Abdominal pain upper	19 (2.3)	21 (2.6)	18 (2.2)
General disorders and administrative site conditions	110 (13.4)	111 (13.5)	108 (13.2)
Fatigue	13 (1.6)	21 (2.6)	18 (2.2)
Infections and infestations	326 (39.8)	317 (38.6)	317 (38.8)
Upper respiratory tract infection	63 (7.7)	68 (8.3)	73 (8.9)
Influenza	39 (4.8)	52 (6.3)	34 (4.2)
Urinary tract infection	38 (4.6)	43 (5.2)	41 (5.0)
Cystitis	25 (3.0)	28 (3.4)	25 (3.1)
Musculoskeletal and connective tissue disorders	300 (36.6)	276 (33.6)	272 (33.3)
Osteoarthritis	31 (3.8)	34 (4.1)	23 (2.8)
Muscle spasms	16 (2.0)	22 (2.7)	25 (3.1)
Nervous system disorders	152 (18,5)	193 (23.5)	150 (18.3)
Dizziness	**50 (6.1)**	**82 (10.0)**	**60 (7.3)**
Headache	49 (6.0)	62 (7.5)	51 (6.2)
Renal and urinary disorders	140 (17.1)	149 (18.1)	152 (18.6)
Hypercalciuria	**74 (9.0)**	**93 (11.3)**	**102 (12.5)**
Vascular disorders	80 (9.8)	98 (11.9)	81 (9.9)
Hypertension	54 (6.6)	59 (7.2)	41 (5.0)
Source: CSR Table 14.3.1.2			

In the phase 2 dose-finding study 002, headache and dizziness appeared to increase in frequency with increasing doses of abaloparatide.

8.4.6. Laboratory Findings

Treatment-related changes in serum and urine calcium are discussed below in sections 8.5.1 and 8.5.2 respectively.

In previous clinical trials of Forteo, serum uric acid levels increased above ULN in 3% of patients compared with 1% of placebo patients; there was no apparent increase in gout, arthralgia or urolithiasis. In study 003, mean serum uric acid levels increased about 20% from baseline with both abaloparatide and teriparatide (table below). Among patients with normal baseline levels, at least one elevated (>ULN) level was found in 5.5%, 25.4% and 29.7% of placebo, abaloparatide and teriparatide patients, respectively. There was no increase in arthralgia AEs (9.8%, 8.6%, 8.6% respectively); one patient in each of the 3 groups developed gout during the study.

Table 68 Study 003: Serum uric acid: mean changes from baseline by visit (safety)

	Placebo (N=820)	Abaloparatide (N=822)	Teriparatide (N=818)
Baseline, mean (µmol/L)	278.3	278.7	284.5
Month 1	-0.1	46.1	51.5
Month 6	-2.7	62.2	65.9
Month 18	-1.7	44.5	55.7
Source: CSR Table 14.3.4.3			

Consistent with the PTH mechanism of increasing renal 1α-hydroxylase activity, there were mean increases from baseline levels of 1,25-OH-vitamin D in abaloparatide and teriparatide arms of study 003 that were comparable to each other at each timepoint, and maximal at month 1. There were substantial decreases from baseline in serum levels of intact (endogenous) PTH in both of these groups, with a smaller PTH decline in placebo; the latter is probably related to calcium and vitamin D supplements.

25-hydroxyvitamin D increased ~15-25% over baseline in placebo patients, presumably from supplements. In the teriparatide arm there were small mean declines from baseline 25-OHD at each timepoint. In the abaloparatide arm there were small mean declines at months 1 and 6, then small increases at months 12 and 18.

Mean serum phosphorus did not change significantly from baseline in any of the 3 treatment arms of study 003; there were no patients in any treatment group who had a level below the lower limit of normal; and there were no AEs of hypophosphatemia.

Liver function tests (LFTs) showed no mean changes from baseline during study 003, except for mild increase in alkaline phosphatase in abaloparatide and teriparatide compared to placebo, which is attributable to the PTHR1-mediated bone effects.

The Applicant examined incidence of LFT elevations according to various cutoff levels specified in the Drug-Induced Liver Injury Guidance. There were 10 patients with ALT or AST ≥3xULN during treatment, listed in the following table. Two of these patients (#1020109 and #1310343) are discussed in more detail below. For the other 8 patients in the table, the ALT ≥3xULN threshold was met only at the one timepoint listed; 7 of these 8 patients completed the study and ALT/AST normalized, the other patient (#1210311) had partial improvement in ALT/AST 11 days later but discontinued the study (withdrew consent). Bilirubin remained WNL in these 8 patients except a teriparatide patient (#2010111) with 1.6x ULN.

Table 69 Study 003: Patients with ALT or AST ≥3x ULN, or bilirubin ≥2x ULN

		Multiples of ULN			
Patient ID	Study day	ALT	AST	ALP	Bilirubin
Placebo					
1010071	265	3.4	1.3	0.7	0.5
1020109	92	4.8	6.2	4.1	3.6
Abaloparatide					
1310228	97	3.0	2.1	0.8	0.4
1310343	(Separate table below)				
1810397	282	3.5	1.9	2.5	0.5
2140008	364	3.3	3.3	1.2	0.2
Teriparatide					
1210311	33	3.8	2.7	0.9	0.3
1310139	1	3.0	2.2	1.4	0.4
1810612	177	5.8	2.1	1.7	0.7
2010111	179	1.7	4.1	1.0	1.6
Source: Listing 16.2.8.5					

Patient #1020109: A 68 y/o white woman (assigned to placebo) with no history of liver disease and concomitant simvastatin, had mildly elevated LFTs at screening (ALT 1.8xULN, AST 1.4xULN, ALP and Bili WNL) but all were WNL at baseline and at study day 31. Between the day 31 and day 92 visits she was using acetaminophen up to 3 g/day. LFTs were markedly elevated at day 92 and she was hospitalized; CT and ultrasound showed an enlarged fatty liver; testing for hepatitis A, B, C was negative. Simvastatin, acetaminophen and study drug were stopped. LFTs

gradually declined to normal 1 month later. The patient discontinued the trial due to this SAE of liver function test abnormal.
Reviewer comment: *Had this patient received active treatment, she would not qualify as a Hy's Law case because of the 4x elevation of ALP, and the possible role of other hepatotoxic drugs.*

Patient #1310343: This 71 y/o white woman with no history of liver disease, had normal LFTs at screening and slightly elevated at baseline and day 31, then more elevated at day 91 (see table below). The study drug (abaloparatide) was stopped on day 170 but LFTs continued to increase with a peak ALT of 1404 U/L (28x ULN) and mild increased bilirubin (1.8xULN) at 1 month after stopping treatment. She reportedly had no related symptoms during the study. The patient was discontinued from the study due to AE of liver function test abnormal. Subsequently she was evaluated by a hepatologist, diagnosed with autoimmune hepatitis type 1 based on a liver biopsy finding of chronic hepatitis and positive (+++) antibodies to ANA, and treated with prednisone. According to limited information from subsequent follow-up (22-31 months after stopping the study) provided in the narrative, the patient had "persistent fatigue, difficulty in moving and joint pain", normal to mildly elevated LFTs (table below) and remained on prednisone.

Table 70 Study 003: Patient #1310343 liver function tests (multiples of upper limit of normal)

Study day	ALT	AST	ALP	Bili
-22 (screening)	0.8	0.7	0.6	0.5
1 (baseline)	1.9	1.3	0.6	0.5
31	1.1	0.9	0.6	0.8
91	4.6	2.6	0.7	0.6
Day 170: abaloparatide stopped				
181	12.2	6.8	1.0	0.8
202	28.1	15.0	1.6	1.8
Post-study follow-up				
+ 22 months	3.7	1.8	0.3	0.9
+ 26 months	1.3	0.8	0.3	0.9
+ 31 months	0.6	0.7	0.3	0.9
Source: Narrative of AE				

Reviewer comment: *The degree of ALT elevation (1404 U/L) in this case is somewhat concerning, however the bilirubin did not meet the ≥2x ULN criterion for Hy's Law, the patient had an apparent non-drug-related cause (autoimmune hepatitis), and there was no overall treatment group imbalance in patients with ≥3-fold aminotransferase elevations.*

The Applicant summarized the incidence by treatment group of clinically notable high or low values for key chemistry and hematology parameters, and used Eastern Cooperative Oncology Group (ECOG) criteria to create tables for shifts in grade from baseline to worst post-baseline point, and to end of study. For other data, shifts from baseline to highest, lowest and end of

study values were presented. There were no major differences between treatment groups except for calcium and uric acid, and the one patient with elevated LFTs discussed above.

Previously in studies of Forteo, renal function was identified in nonclinical studies as a potential safety concern, however there was no evidence of renal malfunction in clinical studies.

Hematology testing showed small declines from baseline in Hgb/Hct in each group. Mean Hct at various visits declined by 0.5-0.8% with placebo, 1.2-1.4% with abaloparatide and 1.1-1.4% with teriparatide. There were 10 placebo, 22 abaloparatide and 24 teriparatide patients with a post baseline ECOG-CTCAE grade ≥2 for hemoglobin. As listed in Table 67 above, AEs of anemia were reported in 1.8% of placebo, and 2.8% of abaloparatide or teriparatide patients, and were more common at lower levels of baseline renal function within each treatment group. One abaloparatide patient discontinued treatment on day 313 with SAE of severe anemia, attributed to chronic GI bleeding; there were no other anemia-related SAEs or discontinuations.

***Reviewer comment**: Previously, the pivotal Forteo PMO trial (GHAC) also observed an increase in anemia, with incidence of 0.2%, 2.5% and 2.7% with placebo, teriparatide 20 mcg and 40 mcg respectively as well as a small but statistically significant decrease (<1%) in median Hgb in the teriparatide groups. As in the current study, anemia was generally mild in the Forteo study.*

There were no notable treatment group differences in white blood cell or platelet counts, or in coagulation parameters.

8.4.7. Vital Signs

Abaloparatide, like teriparatide, tends to cause a transient drop in BP and/or increase in HR, which may lead to symptoms of orthostatic hypotension, dizziness, palpitations or tachycardia. Please see discussions below, sections 8.4.8 (HR response), 8.5.4 (BP response, AEs related to orthostatic hypotension) and 8.5.5 (palpitations and other cardiac AEs). In addition, there was an excess of hypertension AEs with both active drugs compared to placebo (section 8.5.6).

8.4.8. Electrocardiograms (ECGs)

Pre-marketing studies of Forteo did not include systematic ECG evaluation, therefore this was done in a phase 4 study (B3D-MC-GHBQ); the review (2003) concluded that except for "a modest tachycardia, mostly at about 30 minutes after injection", the drug had no clinically important adverse effects on the ECG, including the QTc interval.

Abaloparatide tends to cause an increase in HR that is similar to, and somewhat greater than, teriparatide. In study 003, ECGs were obtained at every visit, both pre- and 1-hr-post-injection (unlike HR collected with other vital signs, which was only assessed pre-injection). Mean post-injection HR, by ECG, was 6.8-7.9 bpm above baseline (day 1 pre-injection) for abaloparatide at

various visits. For teriparatide and placebo, the corresponding mean changes from baseline at 1 hr post-injection were 5.3-6.3 bpm and 1.1-1.7 bpm respectively. Pre-injection mean changes from baseline were much smaller: -0.3 to 0.1 bpm (placebo); -0.1 to 0.2 bpm (abaloparatide); 0.1 to 0.5 bpm (teriparatide). These data were consistent over the course of the study. The table below shows median post-injection changes from baseline.

Table 71 Study 003: Heart rate by ECG at 1 hr post-injection, median change from baseline by visit (safety)

Visit	**Placebo** (N=820) Median (min, max)	**Abaloparatide** (N=822) Median (min, max)	**Teriparatide** (N=818) Median (min, max)
Baseline* (bpm)	64 (41, 102)	65 (45, 99)	65 (43, 106)
Day 1	1.0 (-39, 25)	7.0 (-33, 42)	5.0 (-34, 38)
Month 1	2.0 (-31, 26)	7.0 (-27, 41)	5.0 (-27, 37)
Month 3	1.5 (-29, 33)	7.0 (-31, 56)	6.0 (-25, 39)
Month 6	1.0 (-32, 33)	6.0 (-23, 43)	6.0 (-19, 37)
Month 9	1.0 (-34, 48)	7.0 (-25, 49)	6.0 (-31, 48)
Month 12	2.0 (-37, 27)	7.0 (-24, 50)	6.0 (-22, 44)

* Baseline = pre-injection HR at baseline visit
Source: CSR , Table 14.3.5.6

The following table shows the number of patients with different levels of HR increase after injections, which was consistently greatest with abaloparatide and least with placebo. These increases occurred throughout the treatment period, with slight trends of fewer abaloparatide and teriparatide patients in each category over time. The data were similar for patients in different age categories; patients with or without cardiac-related medical history or risk factors; and patients with or without cardiac AEs.

Table 72 Study 003: Heart rate, proportion of patients with categorical increase from pre-dose to 1 hr post-dose ECG at any visit (safety)

	Placebo (N=820) n (%)	**Abaloparatide** (N=822) n (%)	**Teriparatide** (N=818) n (%)
>5 BPM	521 (64)	736 (90)	705 (86)

>10 BPM	246 (30)	561 (68)	484 (59)
>15 BPM	81 (10)	344 (42)	242 (30)
>20 BPM	22 (3)	165 (20)	87 (11)
>25 BPM	5 (1)	65 (8)	29 (4)
>30 BPM	0	32 (4)	11 (1)
>40 BPM	0	6 (1)	0
Source: response to mid-cycle review issues, submitted 11/22/16			

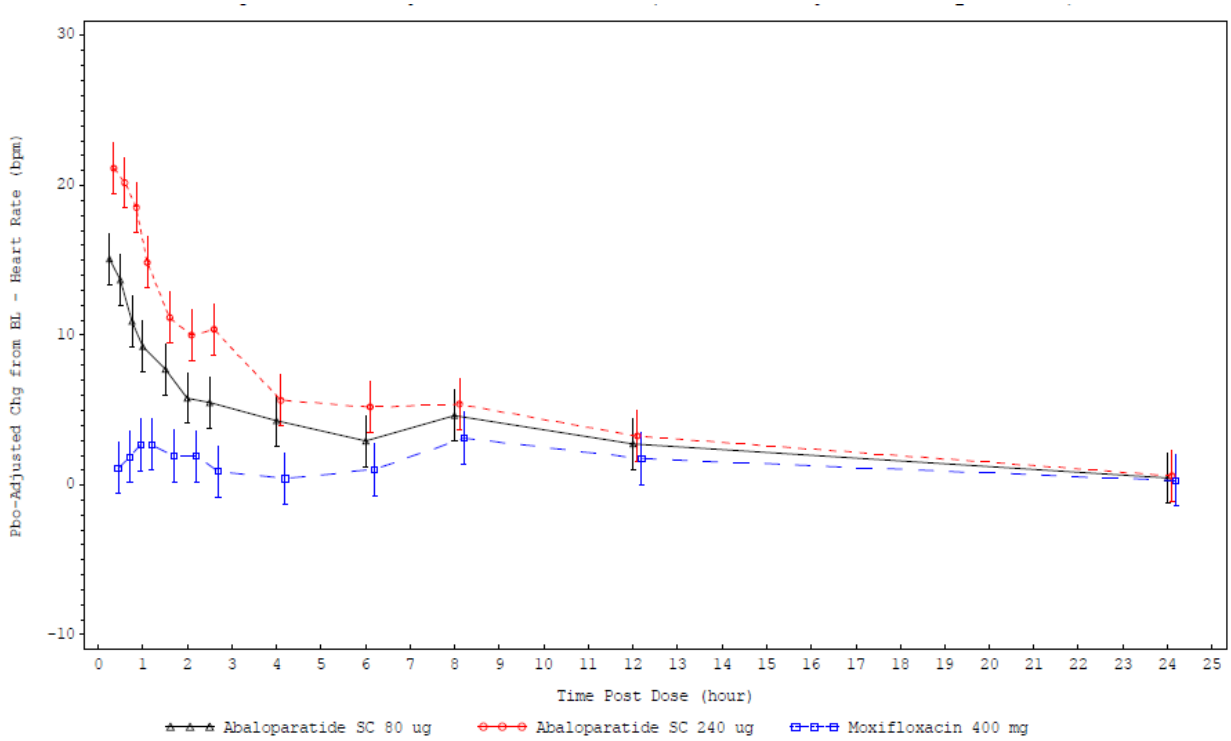
Among the 6 abaloparatide patients with >40 BPM increase in HR, 3 had related AEs but completed the study: one had AEs of hypotension at day 59 and palpitations at day 216; one had an AE of sinus tachycardia on day 277; and one (1510209) had AEs of sinus tachycardia on day 359 and atrial fibrillation on day 569 (29 days after last dose; ECG 4 days later at month 19 visit showed normal sinus rhythm).

In contrast to study 003 which measured HR only pre- and 1-hr-post-injection, the thorough QT/QTc study BA058-05-012 (see section 8.4.9) included ECG at frequent intervals. Following abaloparatide 80 or 240 mcg, HR peaked at the first post-dose time point (15 minutes) at ~15 and 20 bpm above baseline respectively. The effect abated gradually over about 6-12 hr.

Table 73 Study 012 (TQT study): Heart rate by ECG, median change from baseline by time point

Time post dose	**Abalo 80 mcg SC** N=52 Median (min,max)	**Abalo 240 mcg SC** N=52 Median (min,max)	**Placebo SC** N=51 Median (min,max)	**Moxifloxacin 400 mg PO** (active control) N=50 Median (min,max)
Baseline (bpm)	52 (48, 80)	52 (46, 86)	51 (48, 72)	50 (46, 100)
15 min	14.6 (4.0, 29.1)	19.9 (5.4, 41.2)	0.3 (-5.8, 5.0)	0.1 (-9.1, 7.4)
30 min	12.6 (0.8, 32.2)	19.5 (5.4, 36.9)	-0.1 (-7.1, 6.8)	1.7 (-10.0, 12.4)
45 min	10.6 (-2.1, 31.4)	17.2 (4.7, 45.2)	-0.4 (-5.8, 11.8)	2.3 (-10.0, 13.7)
1 hr	8.6 (0.6, 39.3)	14.8 (6.0, 30.4)	1.3 (-6.7, 6.8)	2.9 (-14.4, 14.5)
4 hr	3.4 (-9.5, 31.6)	4.4 (-8.6, 33.7)	1.3 (-14.1, 14.4)	2.3 (-31.3, 12.1)
8 hr	8.3 (-6.5, 26.7)	8.2 (-8.3, 32.7)	3.4 (-2.0, 13.1)	5.8 (-10.0, 29.1)
12 hr	9.5 (-9.4, 26.9)	9.6 (-6.4, 25.3)	7.7 (-11.4, 21.7)	8.7 (-23.0, 45.2)
Source: Study 012 Expert Cardiac Report, Table 5.1				

Figure 20 Study 012 (TQT study): Heart rate: Placebo-adjusted mean change from baseline



Source: response to mid-cycle review issues, submitted 11/22/16

Reviewer comment: *This study enrolled healthy young adults (male/female, mean age of 34 y/o) with lower baseline HR, so is not entirely comparable to study 003 (PMO). However, the median HR increase at 1 hr post-abaloparatide 80 mcg (8.6 bpm) in this TQT study was similar to the median increase at 1 hr in study 003 (~7 bpm), and PK does not differ substantially by age (mean Cmax ≈ 20-30 min), therefore postmenopausal women receiving the 80 mcg dose probably also experience the largest HR increases before 1 hr, which were not captured in study 003.*

In study 003, 1-hr-post-abaloparatide ECGs showed small mean decreases in PR and QT intervals, presumably related to the increase in HR. Mean QTcB at 1 hr post-abaloparatide increased by 5.1 to 7.0 msec from baseline at various visits, compared to 1.6 to 5.0 msec for teriparatide and -0.4 to 3.0 msec for placebo. However as noted in the E14 guidance, QTcB tends to overcorrect the QT at higher HR, and QTcF provided the best QT correction for HR in the TQT study, therefore is probably more accurate in study 003. At each study 003 visit (at 1 hr post-injection), QTcF showed minimal changes from baseline in mean or median values (table below). On day 1 post-injection there was an imbalance in patients with QTcF ≥60 msec from baseline (4 placebo, 13 abaloparatide, 10 teriparatide); but at other visits post injection, this QTcF threshold was reached by about equal numbers of patients in each group. The numbers of

patients with post-injection QTcF >450 msec, >480 msec or >500 msec, both in total and by shifts from baseline category, were similar between treatment groups at each visit.

Table 74 Study 003: QTcF at 1 hr post-injection, median change from baseline by visit (safety)

Visit	Placebo (N=820) Median (min, max)	Abaloparatide (N=822) Median (min, max)	Teriparatide (N=818) Median (min, max)
Baseline* (msec)	414 (320, 556)	414 (317, 534)	415 (235, 490)
Day 1	0.0 (-165, 105)	0.0 (-182, 87)	0.0 (-121, 225)
Month 1	0.0 (-115, 89)	0.0 (-129, 95)	-1.0 (--176, 169)
Month 3	1.0 (-84, 152)	0.0 (-121, 101)	-1.0 (-119, 157)
Month 6	1.0 (-117, 247)	0.0 (-124, 99)	0.0 (-125, 133)
Month 9	0.0 (-124, 104)	-1.0 (-122, 98)	-2.0 (-96, 108)
Month 12	2.0 (-153, 132)	0.0 (-126, 139)	-2.0 (-119, 171)

* Baseline = pre-injection ECG at baseline visit
Source: CSR , Table 14.3.5.6

In study 003, there were no treatment group imbalances in AEs of ECG QT prolonged (7 placebo patients, 8 abaloparatide, 6 teriparatide), or in discontinuations due to ECG QT prolonged (2, 3, 1). Two of the 3 abaloparatide QT-related discontinuations occurred after the first dose: a patient with post-dose palpitations and HR 91-96 (#1030132) and a patient with post-dose bigeminy (#1030055); QTcB reached 485 and 474 msec in these two patients respectively, but QTcF remained ≤450 msec for each. Another patient (#2010029) had a maximal QTcF of 475 msec on day 32 (baseline was 439 msec) which led to discontinuation. Patients with AEs of prolonged QT were distributed evenly among renal function subgroups.

The Applicant also presents tables for shifts from baseline to worst on study ECG and baseline to end of study ECG, classified as normal, abnormal or abnormal/clinically significant. There were no differences between the 3 treatment groups in these changes.

8.4.9. QT

The thorough QT/QTc study protocol (BA058-05-012) and results were reviewed by the QT Interdisciplinary Review Team (see separate QTIRT review). There was a 4-way crossover design

in which subjects received in random order four single doses: abaloparatide 80 mcg and 240 mcg, moxifloxacin 400 mg (positive control) and placebo, separated by 5 day washout periods. There were 55 healthy male and female subjects (median age 34) who enrolled; 51 received both abaloparatide doses.

As discussed above, HR increased dose-dependently with abaloparatide in the TQT study. With doses of 80 mcg and 240 mcg, there were maximal mean increases in the QTcF of 6.9 msec and 9.7 msec at 30 min, with 90% CI upper bound of 9.7 msec and 12.5 msec respectively (QTIRT analysis; findings of Applicant's expert report were similar). There were no subjects with QTcI or QTcF >480 sec or with increase >60 msec. The moxifloxacin data met pre-specified criteria for validation. PK data showed that the mean Cmax for the 240 mcg dose was 2.2x the Cmax for 80 mcg, which is higher than the predicted worst case scenario for 80 mcg dosing (severe renal impairment). The QTIRT concluded that the small QTc increases were related to the increased heart rate and, based on PK-QTc modeling, are not of clinical concern for the 80 mcg dose.

8.4.10 Immunogenicity

In study 003, pre-dose samples for anti-abaloparatide antibody assessment were obtained at baseline and months 1, 3, 6, 12 and 18. Among patients who received abaloparatide for 18 months, 49% developed antibodies, including 33% with neutralizing antibodies based on in vitro assays. There was no evidence of any significant impact on safety, such as hypersensitivity reactions. Six months after abaloparatide discontinuation, the proportion of antibody positive patients had declined to 26%.

8.5. Analysis of Submission-Specific Safety Issues

This section discusses several abaloparatide safety issues, some of which were prespecified by the Applicant as events of special interest based on experience with teriparatide and/or nonclinical findings. No cases of osteosarcoma were reported; none were expected based on the rarity of this malignancy.

8.5.1. Hypercalcemia

Previously in Forteo clinical studies, there were dose-dependent increases in serum calcium that peaked at about 4-6 hours post injection with a median increase of ~0.4 mg/dL, and returned to near baseline at 16-24 hours. In the phase 3 PMO study with frequent monitoring, postdose hypercalcemia occurred in 2% of placebo recipients vs. 11% with teriparatide 20 mcg. Because of hypercalcemia, calcium supplements and teriparatide doses were reduced per protocol in 7.2% and 2.8% of patients respectively among women receiving the 20 mcg dose; only one patient (0.2%) required teriparatide discontinuation. Significant clinical adverse events

related to hypercalcemia did not occur. The Forteo label includes a W&P stating that patients with hypercalcemic disorders have not been studied and should not receive Forteo; (b) (4) In postmarketing, hypercalcemia >13.0 mg/dL has been reported.

In the phase 1 abaloparatide study BA058-05-001B, doses of 80-120 mcg with frequent monitoring of serum calcium showed that the most common timepoint for peak levels was at 4 hours post-dose, with return to near baseline at 12-24 hours. Peak serum Ca was not dose proportional.

In the phase 2 study BA058-05-002, serum Ca levels ≥10.5 mg/dL at any time in the initial study period were observed in 4%, 12%, 19%, 18% and 40% of patients in the placebo, abaloparatide 20 mcg, 40 mcg and 80 mcg, and teriparatide 20 mcg groups respectively.

In study 003, serum calcium was measured at each visit both predose (~24 hr following the last dose, except at baseline) and 4 hr post-dose. Mean post-dose serum calcium increased by 0.20-0.41 mg/dL at various time points from baseline in abaloparatide patients, and by 0.24-0.50 mg/dL from baseline in teriparatide patients; pre-dose serum calcium rose by much smaller increments. There was no progressive increase in serum calcium during the 18 month treatment period.

Table 75 Study 003: Serum calcium: mean changes from baseline by visit (safety)

Serum calcium (mg/dL)	**Placebo** (N=820)	**Abaloparatide** (N=822)	**Teriparatide** (N=818)
Baseline, mean	9.1	9.1	9.1
Day 1 post-dose	**-0.00**	**0.20**	**0.24**
Month 1 pre-dose	-0.03	-0.03	0.01
Month 1 post-dose	**-0.04**	**0.27**	**0.34**
Month 3 pre-dose	-0.02	0.08	0.10
Month 3 post-dose	**-0.01**	**0.38**	**0.46**
Month 6 pre-dose	-0.04	0.14	0.14
Month 6 post-dose	**-0.05**	**0.41**	**0.50**
Month 9 pre-dose	-0.01	0.10	0.12
Month 9 post-dose	**-0.03**	**0.40**	**0.48**
Month 12 pre-dose	-0.05	0.08	0.14
Month 12 post-dose	**-0.06**	**0.36**	**0.47**
Month 18 pre-dose	-0.01	0.12	0.08
Source: CSR Table 14.3.4.3			

The number of patients with hypercalcemia (defined as albumin-corrected Ca ≥10.7 mg/dL, i.e. ≥0.3 mg/dL above ULN) at any point was designated a key safety endpoint, primarily for the

comparison of abaloparatide to teriparatide. By this criterion, almost twice as many teriparatide patients had hypercalcemia at any time compared to abaloparatide (52 vs. 28, 6.4% vs. 3.4%, p=0.0055), with most events at 4-hr post-dose and few at pre-dose. The difference between the two drugs was apparent at day 1 and month 1 but not at later time points.

Table 76 Study 003: Incidence of hypercalcemia by lab criterion* (safety)

Patients with Ca ≥10.7 mg/dL	**Placebo** (N=820)	**Abaloparatide** (N=822)	**Teriparatide** (N=818)
Overall incidence, n/m (%)	3/817 (0.4)	28/820 (3.4)	52/816 (6.4)
p-value, abaloparatide vs. teriparatide		0.0055	
Pre-injection incidence, n/m (%)	1/745 (0.1)	2/715 (0.3)	8/741 (1.1)
p-value, abaloparatide vs. teriparatide		0.0647	
Post-injection incidence, n/m (%)	1/816 (0.1)	28/818 (3.4)	50/816 (6.1)
p-value, abaloparatide vs. teriparatide		0.0104	
Day 1 post-injection, n	0	1	5
Month 1 post-injection, n	0	1	12
Month 3 post-injection, n	0	12	8
Month 6 post-injection, n	1	12	16
Month 9 post-injection, n	0	13	13
Month 12 post-injection, n	0	7	7

* Albumin-corrected Ca≥10.7 mg/dL
p-value from Chi-square test
Source: CSR Table 14.3.4.9A

The Applicant also analyzed patients with Ca ≥10.4 mg/dL (≥ ULN), with similar findings: greater numbers of teriparatide patients met this criterion compared to abaloparatide at each timepoint, with overall incidence of 13.5% and 7.8% respectively, vs. 1.1% placebo. Using another prespecified analysis cutoff (Ca ≥11.4 mg/dL), there were 4 patients each in the abaloparatide and teriparatide groups and none in placebo. The highest individual levels per arm were 11.1 mg/dL at month 18 (placebo), 11.9 mg/dL at month 3 post-dose (abaloparatide), and 12.7 mg/dL at month 3 post-dose (teriparatide).

A subset of these patients with elevated Ca were reported as having AEs, representing the investigator's assessment of potential clinical significance. The Applicant analyzed hypercalcemia as an AESI using a list of 7 preferred terms that were prespecified in the SAP; two of these (hypercalcemia and blood calcium increased) appeared in the AE dataset. As shown in the table below, frequency was highest with teriparatide. There were 2 abaloparatide and 4 teriparatide patients who discontinued due to hypercalcemia; this included one SAE in which a teriparatide patient was hospitalized for Ca=11.4 mg/dL. Calcium supplements were reduced or stopped, per protocol, for hypercalcemia in 1.7% of abaloparatide and 3.2% of teriparatide patients. There were no abaloparatide patients who met the protocol criterion for reducing dose (80 to 40 mcg).

Table 77 Study 003: Incidence of hypercalcemia as AESI event (safety)

	Placebo (N=820) n (%)	Abaloparatide (N=822) n (%)	Teriparatide (N=818) n (%)
Any AESI PT	5 (0.6)	15 (1.8)	34 (4.2)
Hypercalcemia	3 (0.4)	11 (1.3)	29 (3.5)
Blood calcium increased	2 (0.2)	4 (0.5)	5 (0.6)
SAE of hypercalcemia	0	0	1 (0.1)
Leading to discontinuation of study‡	0	2 (0.2)	4 (0.5)
Leading to interruption of study drug	0	1	2
Leading to dose reduction of study drug	0	0	N/A
Leading to changes in calcium supplements*	1 (0.1)	14 (1.7)	26 (3.2)

‡ Discontinuations were due to hypercalcemia, except for one abaloparatide patient with D/C due to blood calcium increased
* calcium dose reduced, interrupted and/or stopped according to algorithm
Source: CSR Table 14.3.1.15 and 14.3.1.23, Listing 16.2.5.5

Evaluation of renal function subgroups showed trends of higher incidence of serum calcium ≥10.7 mg/dL with increasing renal impairment among abaloparatide and teriparatide recipients (table below). Hypercalcemia AEs showed a similar trend (not shown).

Table 78 Study 003: Incidence of hypercalcemia* by baseline renal function (safety)

Patients with Ca ≥10.7 mg/dL	Placebo (N=820) n/m (%)	Abaloparatide (N=822) n/m (%)	Teriparatide (N=818) n/m (%)
Overall incidence*	3/817 (0.4)	28/820 (3.4)	52/816 (6.4)
CrCl ≥ 90 mL/min‡	2/218 (0.9)	3/224 (1.3)	8/213 (3.8)
CrCl 60 to <90 mL/min‡	1/433 (0.2)	19/428 (4.4)	23/411 (5.6)
CrCl <60 mL/min‡	0/166 (0.0)	6/168 (3.6)	21/192 (10.9)

* Albumin-corrected Ca≥10.7 mg/dL
‡ Cockcroft-Gault Estimated Creatinine Clearance
Source: CSR Table 28

Reviewer comment:
Abaloparatide appears to have less tendency for hypercalcemia than teriparatide, at least in the first month of treatment. The clinical significance of this is not clear; hypercalcemic symptoms (nausea, mental status changes etc.) do not generally occur at the mild elevations seen in this study, and have not been previously associated with Forteo treatment. In regard to the hypercalcemia AEs which reflect the investigators' assessments of clinical significance, the open label nature of the teriparatide arm may have introduced some bias against this drug.

Essentially all of the studies of abaloparatide and teriparatide have excluded patients with hypercalcemia. The Forteo-labeled warning against treatment of patients with pre-existing hypercalcemia should apply to both drugs.

In study 005 during treatment with alendronate, slight decreases in serum calcium occurred as expected in placebo/ALN and abaloparatide/ALN patients. AEs of hypocalcemia or blood calcium decreased occurred in 5 and 7 patients in these respective groups.

8.5.2. Hypercalciuria

Consistent with the PTH mechanism of action, previous studies of Forteo showed increased urinary calcium excretion, but the frequency of hypercalciuria (defined as >300 mg/day) in clinical trials was similar to placebo, and frequency of urolithiasis was also similar. A Forteo W&P states that patients with active urolithiasis have not been studied, and advises caution in patients with active or recent urolithiasis or suspected pre-existing hypercalciuria.

In study 003, similar to the previous Forteo studies, a history of nephrolithiasis or urolithiasis within the previous 5 years was an exclusion criterion. Mean 24-hr urine calcium:creatinine ratio showed no marked changes from baseline in the placebo or abaloparatide groups and small increases in the teriparatide group, with however a return to baseline at month 18.

Table 79 Study 003: Urine calcium/creatinine ratio: mean changes from baseline by visit (safety)

Ca/creat, 24 hrs (mmol/mmol)	Placebo (N=820)	Abaloparatide (N=822)	Teriparatide (N=818)
Baseline, mean	0.59	0.59	0.57
Month 1	-0.01	-0.01	0.06
Month 3	-0.01	0.01	0.10
Month 6	-0.01	0.03	0.11
Month 9	-0.00	0.04	0.06
Month 12	-0.02	0.00	0.04
Month 18	-0.02	-0.02	0.01
Source: CSR Table 14.3.4.10			

In this study, hypercalciuria was a designated safety endpoint and two cutoffs for event analysis were specified in the statistical plan: urine calcium:creatinine ratios of >400 mg/g and >300 mg/g. Both of these analyses (only the latter presented here) showed the highest incidence with teriparatide at all timepoints, with abaloparatide generally intermediate between teriparatide and placebo.

Table 80 Study 003: Incidence of hypercalciuria by lab criterion* (safety)

Patients with urine Ca:creat ratio >300 mg/g (>0.848 mmol/mmol)	**Placebo** (N=820) n/m (%)	**Abaloparatide** (N=822) n/m (%)	**Teriparatide** (N=818) n/m (%)
Overall incidence	283/786 (36.0)	361/784 (46.1)	424/793 (53.5)
Day 1	2/13 (15.4)	11/28 (39.3)	11/23 (47.8)
Month 1	135/770 (17.5)	124/747 (16.6)	179/776 (23.1)
Month 6	126/706 (17.9)	154/670 (23.0)	231/718 (32.2)
Month 18	116/700 (16.6)	133/685 (19.4)	142/694 (20.5)
* urine Ca:creat ratio >300 mg/g (>0.848 mmol/mmol) Source: CSR Table 14.3.4.11B			

Hypercalciuria was overall the most common AE term in study 003. The incidence in the abaloparatide group (11.3%) was intermediate between placebo (9.0%) and teriparatide (12.5%) (table below). Each subgroup of renal function (<60, 60-90, >90 mL/min) showed a similar pattern. There was a slight imbalance in patients with nephrolithiasis and/or nephrocalcinosis (12 placebo, 16 abaloparatide and 17 teriparatide patients); most of these (5, 13, 14 respectively) were patients with hypercalciuria (>300 mg/g creat ratio at any time).

Table 81 Study 003: Incidence of TEAEs potentially related to hypercalciuria (safety)

Preferred term	**Placebo** (N=820) n (%)	**Abaloparatide** (N=822) n (%)	**Teriparatide** (N=818) n (%)
Hypercalciuria	74 (9.0)	93 (11.3)	102 (12.5)
Urine calcium increased	2 (0.2)	1 (0.1)	3 (0.4)
(HLGT) Urolithiases	14 (1.7%)	17 (2.1%)	19 (2.3%)
(HLT) Renal lithiasis	12 (1.5%)	16 (2.0%)	17 (2.1%)
Nephrolithiasis	9 (1.1)	11 (1.3)	16 (2.0)
Nephrocalcinosis	4 (0.5)	6 (0.7)	2 (0.2)
Calculus urinary	1	1	1
Calculus bladder	1	0	0
Calculus ureteric	1	0	0
Calculus urethral	0	0	1
SAE or discontinuation due to any of the above	0	0	0
Leading to interruption of study drug	1	2	3
Leading to dose reduction of study drug	0	0	0
Leading to changes in calcium supplements*			
* calcium dose reduced, interrupted and/or stopped according to algorithm Source: CSR Tables 14.3.1.2, 14.3.1.5, 14.1.3.6, 14.3.1.27, 14.3.1.28			

Reviewer comment: *Although there was not a substantial increase in patients with urolithiasis with the two active drugs, it is important to note that patients with recent urolithiasis were excluded, and that a number of patients interrupted or stopped calcium supplements due to hypercalcemia and/or hypercalciuria.*

8.5.3. Tissue mineralization and renal function

At selected centers, a subset of patients underwent renal CT scans to assess the renal parenchyma and collecting system for calcifications. A total of 376 patients underwent at least one renal CT scan, with a mean age of 69 years; 52% were white and 43% were Asian; 12% were Hispanic. Mean exposure was ~17 months and estimated compliance was ~97-98% across treatment groups.

Per the original protocol, there were 208 patients at selected sites who underwent renal CT only post-treatment, i.e. between the month 18 and month 19 visits. Calcifications in any urinary tract location were found in 6/71 placebo, 7/71 abaloparatide and 9/66 teriparatide patients. All were located in the renal calyces with the exception of ureteral stones in 2 placebo patients and 1 abaloparatide patient; a ureterovesical junction stone in 1 abaloparatide patient; and bladder stones in 2 placebo patients.

After implementation of protocol version 3, patients enrolling at these sites underwent pre-treatment as well as post-treatment scans (table below). There were 4 patients (2 abaloparatide, 2 teriparatide) found to have a post-treatment calculus at a location where none had been present at baseline (in each case a renal calyx); both of the abaloparatide patients had a prior history of nephrolithiasis. In each treatment group there were also patients with calculi at baseline that were not apparent at end of study.

Table 82 Study 003: Urolithiasis by renal CT (patients with baseline and end-of-study scans)

	Placebo N=45		Abaloparatide N=42		Teriparatide N=46	
# of patients with calcifications at:	BL	EOS	BL	EOS	BL	EOS
Any location	8	5	6	7	2	5
Left kidney calyx	6	4	2	2	0	3
Right kidney calyx	6	4	4	5	1	1
Left kidney renal pelvis	0	0	0	0	0	0
Right kidney renal pelvis	0	0	1	1	0	0
Ureters/ ureterovesical junctions/bladder	0	0	0	0	1	1

BL=baseline, EOS=end of study
Source: Renal CT substudy report, Table 14.3.5.10B, CSR Appendix 16.1.14)

The substudy report concludes that there was no pattern of increased renal calcification at any location across treatment groups over 18 months of treatment.

There were small increases from baseline in mean serum creatinine and BUN in each treatment group that were generally similar between abaloparatide and teriparatide, and smaller with placebo, at each visit. The worst post baseline ECOG CTCAE grades for serum creatinine were grade 1 in 0, 4 and 6 patients (placebo, abaloparatide and teriparatide groups); grade 2 in 0, 1, 1; and grades 3 or 4 in none. Relevant AEs are listed in the following table, indicating a moderate excess in lab elevations of BUN/creatinine with abaloparatide. None of the AEs represented by the PTs in the table were serious or led to study discontinuation. One event (renal failure in a placebo patient) was deemed "severe".

Table 83 Study 003: Incidence of AEs related to renal impairment (safety)

Preferred term	Placebo N=820 n (%)	Abaloparatide N=822 n (%)	Teriparatide N=818 n (%)
SOC Renal and urinary disorders	140 (17.1)	149 (18.1)	152 (18.6)
HLT Renal failure and impairment	9 (1.1)	8 (1.0)	6 (0.7)
Renal failure	4 (0.5)	6 (0.7)	2 (0.2)
Renal impairment	4 (0.5)	2 (0.2)	3 (0.4)
Renal failure chronic	1 (0.1)	0	1 (0.1)
SOC Investigations/HLT Renal function analyses			
Blood urea increased	8 (1.0)	14 (1.7)	12 (1.5)
Creatinine renal clearance decreased	4 (0.5)	16 (1.9)	9 (1.1)
Blood creatinine increased	0	1 (0.1)	0
Glomerular filtration rate decreased	1 (0.1)	1 (0.1)	1 (0.1)
Source: AE dataset, CSR Table 14.3.1.2			

Reviewer comment: *Although abaloparatide and teriparatide appear to be associated with trends of mild declines in lab parameters of renal function, this appears to be of minimal or no clinical significance.*

8.5.4. Orthostatic hypotension

Hemodynamic effects were observed previously with teriparatide (NDA 021318), with phase 1 studies showing dose related decline in BP and increase in HR occurring within 6 hours after the SC injection. Symptomatic orthostatic hypotension and dizziness appeared as AEs in subsequent studies. There was no apparent increase in serious or severe events. In the Forteo phase 3 PMO study, syncope occurred in 1.7% of placebo, 3.1% of teriparatide 20 mcg and 0.7% of teriparatide 40 mcg patients. Episodes of syncope occurred throughout the study with no change over time, and many of these patients had identifiable causes of syncope unrelated to treatment (e.g. vasovagal reaction, epilepsy). Low baseline blood pressure was associated with syncope in all 3 treatment groups. Forteo was given a labeled W&P for orthostatic hypotension,

stating that episodes may occur with the first few doses and may require the patient to sit or lie down, but that most patients can continue treatment.

In abaloparatide phase 1 study 2-52-52127-001 (80 M/F healthy subjects age 55-75 years), there were overall only small changes in mean BP and HR. However, a few subjects reported orthostatic hypotension symptoms, including one who received 80 mcg and experienced 92 minutes of dizziness, a 2 minute syncopal episode and inability to obtain standing BP measurements. It was concluded that "at 30 min to 3 hours post-dose, there may be a dose-dependent decrease in BP, associated with a moderate increase in HR".

In the abaloparatide phase 1 study BA058-05-001B, in which abaloparatide doses of 80, 100 and 120 mcg SC were given daily for 7 days to postmenopausal women, HR increases were noted, and several patients experienced dizziness and/or orthostatic hypotension after dosing.

In the phase 2 study BA058-05-002, orthostatic BP changes (decline ≥20 mmHg systolic or ≥10 mmHg diastolic) were observed at any time in 20%, 33%, 35%, 31% and 36% of patients in the placebo, abaloparatide 20, 40 and 80 mcg and teriparatide 20 mcg groups respectively.

In the phase 3 study (003), blood pressure was evaluated at every visit with supine and standing BP and, on days with study drug dosing, both pre- and 1-hr-post-dose. There was not an increase in patients with standing systolic BP <80 mmHg at any post-baseline visit in the abaloparatide group (n=2) compared to placebo (n=7) or teriparatide (n=4). Orthostatic hypotension was defined for analysis as a decline of ≥20 mmHg systolic or ≥10 mmHg diastolic from supine to standing. There was a mild imbalance in the number of patients meeting this criterion post-injection on day 1 (3.2% placebo, 4.1% teriparatide). Among patients who did not meet the criteria at baseline (pre-injection on day 1), 2.9% of placebo and 4.0% of abaloparatide patients met the criteria post injection on day 1. At later time points there was generally little or no difference between treatment groups, or between pre- and post-injection.

Table 84 Study 003: Orthostatic hypotension 1 hour post-injection by visit (safety)

	Placebo (N=820)	**Abaloparatide** (N=822)	**Teriparatide** (N=818)
Patients with at least one event post-injection at any visit	16.4%	17.1%	15.5%
Day 1	3.2%	4.1%	3.6%
Month 1	4.0%	4.2%	3.4%
Month 3	3.4%	4.2%	4.2%
Month 6	5.3%	3.7%	3.7%
Month 9	4.2%	3.8%	4.1%
Month 12	4.8%	5.6%	3.1%
Source: CSR Table 14.3.5.4			

The SAP included a list of 29 preferred terms in MedDRA v17.1 to be used to evaluate the AESI of orthostatic hypotension. Abaloparatide patients were much more likely to experience one or more of these events (26.8%, vs. 14.3% placebo and 19.7% teriparatide). This was driven largely by an excess of events coded as dizziness, nausea and palpitations in the abaloparatide group. There was much overlap of terms, e.g. the 82 abaloparatide patients with dizziness also had AEs of nausea (n=16); headache (11); palpitations (11); tachycardia (2); and presyncope, loss of consciousness or hypotension (1 each); though none had AEs of syncope, orthostatic hypotension or fall. Narratives in many cases describe these symptoms as occurring a few minutes to a few hours after injections, with standing systolic BP in the 60s systolic in some cases. Many more abaloparatide patients (28) discontinued due to one of these events compared to placebo (7) or teriparatide (13); this was also driven mainly by events of dizziness, nausea and palpitations.

Table 85 Study 003: Incidence of TEAEs potentially associated with orthostatic hypotension* (safety)

Preferred term	Placebo (N=820) n (%)	Abaloparatide (N=822) n (%)	Teriparatide (N=818) n (%)
Patients with any AE*	117 (14.3)	220 (26.8)	161 (19.7)
Patients with any severe AE*	5	7	0
Patients with any SAE*	2	3	4
Patients with any AE* related discontinuation	7	28	13
Dizziness	**50 (6.1)**	**82 (10.0)**	**60 (7.3)**
Nausea	**25 (3.0)**	**68 (8.3)**	**42 (5.1)**
Palpitations	**3 (0.4)**	**42 (5.1)**	**13 (1.6)**
Vertigo	15 (1.8)	17 (2.1)	20 (2.4)
Tachycardia	**3 (0.4)**	**11 (1.3)**	**6 (0.7)**
Tinnitus	3 (0.4)	10 (1.2)	4 (0.5)
Orthostatic hypotension	**4 (0.5)**	**7 (0.9)**	**3 (0.4)**
Muscular weakness	2 (0.2)	6 (0.7)	5 (0.6)
Syncope	9 (1.1)	6 (0.7)	8 (1.0)
Fall	2 (0.2)	4 (0.5)	4 (0.5)
Loss of consciousness	2 (0.2)	2 (0.2)	2 (0.2)
Presyncope	0	2 (0.2)	0
Sinus tachycardia	2 (0.2)	2 (0.2)	0
Vision blurred	2 (0.2)	2 (0.2)	2 (0.2)
Visual impairment	0	2 (0.2)	2 (0.2)
Arrhythmia	4 (0.5)	1 (0.1)	2 (0.2)
Balance disorder	0	1 (0.1)	0
Gait disturbance	1 (0.1)	1 (0.1)	1 (0.1)
Blood pressure orthostatic decreased	0	0	1 (0.1)
Confusional state	1 (0.1)	0	0
Visual acuity reduced	1 (0.1)	0	3 (0.4)
* PTs listed in the table			

There were 9 patients with SAEs potentially related to orthostatic hypotension, summarized in the following table.

Table 86 Study 003: SAEs potentially associated with orthostatic hypotension (safety)

Patient #	Age/ race	Day of onset	Preferred term	Comment
Abaloparatide				
1310212	68/white	263	Syncope	History: HTN, dyslipidemia Concom meds: nitrendipine, metipranolol, atorvastatin, gabapentin, clonazepam Baseline BP 140/80, HR 55, ECG WNL Day 263: walking felt cold and thirsty, then had syncope during dinner at restaurant Hospital W/U essentially neg., doses of gaba and clonazepam adjusted Continued abalo, completed study Investigator assessment "unlikely related"
1810143	70/Asian	387	Palpitation	History: HTN, DM Meds: nifedipine, perindopril, gliclazide, cinnarizine Baseline BP 124/75, HR 66 ECG NSR, incomplete RBBB, R-S transition zone in V leads displaced to the right Day 382: syncope in sitting position, hospitalized for worsening of DM, Na 127, gliclazide dose adjusted Day 387: hosp. again for palpitations, breathing difficulty, weakness, HR 110, BP 130/70, Holter normal, symptoms resolved, abalo interrupted
2010188	68/white	41	Vertigo	History: HTN, transient cerebral ischemia since 2008, Meds: enalapril, clonazepam Day 41: hosp. for vertigo, nausea, vomiting Dx=benign positional vertigo (peripheral) Discontinued study
Placebo				
1210447	68/white	426	Syncope	Day 426: fainted after a bone biopsy, head contusion Day 436: surgery for epidural hematoma
1810498	76/Asian	11	Dizziness	HTN, valsartan, nifedipine Day 11 hosp for dizziness, resolved
Teriparatide				
1610291	66/white	275	Vertigo	Day 298: hosp for vertigo, dx cervical spondylosis
1810175	83/Asian	330	Dizziness	Day 330 hosp for dizziness, CT brain WNL
1810645	78/Asian	532	Palpitation	HTN nifedipine, olmesartan, atenolol Day 532 hosp for palpitations and BP 210/88 BP meds adjusted, sx resolved
2010036	75/white	44	Dizziness Loss of consciousness	Day 44 dizziness, LOC ECG normal, sx resolved

8.5.5. Cardiac disorders

Previously, teriparatide studies demonstrated dose-related increase in HR within 6 hours after the SC injection. In the Forteo pivotal PMO trial (GHAC) there was an increase in cardiovascular disorders with teriparatide which was primarily related to coronary artery disease, but with no dose relationship: 17 placebo patients (4.1%), 34 patients at 20 mcg (7.8%) and 20 patients at 40 mcg (4.9%).

As discussed above (section 8.4.8), abaloparatide causes an increase in HR that is similar to, or somewhat greater than, teriparatide. This increase occurs within ~15-30 minutes of dosing and gradually abates over ~6-12 hrs.

In study 003, there was an increase in AEs of cardiac disorders in abaloparatide patients compared to placebo or teriparatide. As listed in the following table, most of these events were nonserious AEs of palpitations and tachycardia. If AEs of palpitations, tachycardia and sinus tachycardia are excluded, the incidence of cardiac SOC AEs was similar between placebo (n=41, 5.0%), abaloparatide (n=39, 4.7%), and teriparatide, (n=33, 4.0%). There was also a possible increase in cardiac conduction disorders with abaloparatide, but no apparent overall imbalances in other arrhythmias, coronary disease or CHF.

Table 87 Study 003: Cardiac AEs by selected MedDRA categories (safety)

System organ class Preferred term	**Placebo** (N=820) n (%)	**Abaloparatide** (N=822) n (%)	**Teriparatide** (N=818) n (%)
SOC Cardiac disorders	**47 (5.7)**	**88 (10.7)**	**50 (6.1)**
HLGT Cardiac disorder signs and symptoms	**3 (0.4)**	**41 (5.0)**	**13 (1.6)**
PT Palpitations	**3**	**41**	**13**
HLGT Cardiac arrhythmias	**29 (3.5)**	**38 (4.6)**	**27 (3.3)**
HLT Rate and rhythm disorders NEC	**8 (1.0)**	**15 (1.8)**	**10 (1.2)**
PT Tachycardia	**3**	**11**	**6**
PT Arrhythmia	4	1	2
PT Extrasystoles	2	3	1
PT Bradycardia	0	0	1
HLT Supraventricular arrhythmias	17 (2.1)	16 (1.9)	13 (1.6)
PT Sinus tachycardia	2	2	0
PT Supraventricular tachycardia	0	2	1
PT Supraventricular extrasystoles	5	3	2
PT Atrial fibrillation	5	5	4
PT Atrial flutter	0	1	2
HLT Ventricular arrhythmias and cardiac arrest	3 (0.4)	4 (0.5)	5 (0.6)
PT Ventricular extrasystoles	4	3	4
PT Cardio-respiratory arrest	0	1	1

System organ class Preferred term	**Placebo** (N=820) n (%)	**Abaloparatide** (N=822) n (%)	**Teriparatide** (N=818) n (%)
HLT Cardiac conduction disorders	**2 (0.2)**	**6 (0.7)**	**2 (0.2)**
PT Arterioventricular block first degree	1	3	1
PT Atrioventricular block	0	1	0
PT Bundle branch block right	0	2	0
HLGT Coronary artery disorders	10 (1.2)	10 (1.2)	11 (1.3)
HLT Coronary artery disorders NEC	3 (0.4)	3 (0.4)	2 (0.2)
HLT Ischemic coronary artery disorders	8 (1.0)	7 (0.9)	9 (1.1)
PT Myocardial ischemia	2	6	5
PT Myocardial infarction	2	1	1
PT Angina pectoris	4	2	2
PT Angina unstable	1	1	1
PT Acute coronary syndrome	0	0	1
PT Acute myocardial infarction	0	0	1
HLGT Heart failures	4 (0.5)	1 (0.1)	1 (0.1)
SOC investigations			
HLT ECG investigations	9 (1.1)	13 (1.6)	12 (1.5)
Electrocardiogram QT prolonged	7	8	6
MedDRA v17.1 Source: CSR Tables 14.3.1.23 and 14.3.1.20			

Patients with palpitation AEs (study 003)

Among the 42 abaloparatide patients with palpitations in study 003, many had other associated AEs (with the same onset date): headache (6); dizziness (7); nausea (5); tachycardia (1); prolonged QT (1); presyncope (1); fatigue (2); sleepiness (1); dyspnea (1); shivering (1). Numerous comments entered into CRFs indicate that palpitations typically occurred soon after injection (as early as 5-10 minutes), lasted up to 1-2 hours and often recurred, in some cases "every morning". Of the 42 abaloparatide patients with AEs of palpitations, 7 discontinued the study as a result, including 3/32 patients with "mild" palpitations; 4/9 patients with "moderate" palpitations and 0/1 with "severe" palpitations. Among the 13 teriparatide and 3 placebo patients with AEs of palpitations, 1 (a placebo patient) discontinued the study. Two patients (1 abaloparatide, 1 teriparatide) had SAEs of palpitations where the symptoms led to hospitalization; in both cases the symptoms resolved with no other cardiac AEs identified.

Among the 42 abaloparatide patients with palpitations, there were 3 patients (#1010144, #1210039, #1810254) whose postdose ECG showed sinus tachycardia (max HR 111, 124, 103 bpm respectively) associated with the symptoms; the remaining patients appear to have had HR <100 at all times on ECGs. Other ECG findings include one patient (#1030132) who experienced post-dose palpitations, HR 91-96 and AEs of QT prolongation (max QTcB=485 msec, max QTcF=450 msec) and ST segment depression (evaluated as not clinically significant by the investigator); these events all occurred on Day 1 and led to her discontinuation. Three

other patients with palpitations AEs (#1110031, 1310006, 1510300) also had reported AEs of sinus bradycardia, ventricular extrasystoles and extrasystoles respectively (although with onset dates different from the palpitations AEs). Aside from these patients, none of the abaloparatide patients with palpitations AEs had any documented arrhythmias, or other AEs in the cardiac disorders SOC.

As noted above, abaloparatide (and teriparatide) exposure generally increases with renal impairment. However, worsening renal function was not associated with a higher incidence of palpitations in study 003:

Table 88 Study 003: Incidence of palpitation AEs by baseline renal function (safety)

	Placebo (N=820) n/m (%)	**Abaloparatide** (N=822) n/m (%)	**Teriparatide** (N=818) n/m (%)
Overall incidence	3/820 (0.4)	42/822 (5.1)	13/818 (1.6)
CrCl ≥ 90 mL/min‡	0/218 (0.0)	14/226 (6.2)	2/213 (0.9)
CrCl 60 to <90 mL/min‡	3/435 (0.7)	22/428 (5.1)	5/413 (1.2)
CrCl <60 mL/min‡	0/167 (0.0)	6/168 (3.6)	6/192 (3.1)
‡ Cockcroft-Gault Estimated Creatinine Clearance Source: CSR Table 28, 14.3.1.2.1			

Patients with tachycardia AEs (study 003)

There were 11 abaloparatide patients with AEs of tachycardia in study 003, listed in the following table; none were SAEs or considered "severe", and the highest HR recorded was 111 bpm; no new arrhythmias were reported among these patients. As with palpitations AEs, the symptoms tended to occur after injections in some patients. Three discontinuations (patients #1010144, #1210342, #1310412) from abaloparatide were attributed to tachycardia. Another patient (#1020147) discontinued due to an AE of myocardial ischemia detected by ECG on day 30; HR was 88 at that point and the tachycardia AE (on day 5) was considered resolved. There was no apparent association between abaloparatide-associated tachycardia and mild/moderate renal impairment, though the number of events was small.

Table 89 Study 003: Abaloparatide patients with AEs of tachycardia

Patient ID	**Age**	**Relevant history, concomitant meds**	**AE start/ end day**	**ECG/ heart rate**	**Severity**	**Associated symptoms, outcome**
1010144	81	HTN Metoprolol moduretic	1/1	Started 10 min after injection HR 111 sinus tach	Moderate	Concurrent AEs: palpitations, headache, hypertension, flushing, pain in neck/back D/C from study, AEs resolved

Patient ID	Age	Relevant history, concomitant meds	AE start/ end day	ECG/ heart rate	Severity	Associated symptoms, outcome
1020113	66		2/80	ECGs normal, max HR 100 Recurrent sx of tachycardia ½ hr after injections	Moderate	AE resolved, completed study
1020147	72	HTN enalapril	5/5	Max HR = 97 post-dose on day 1 Day 30 ECG: myocardial ischemia (T wave abnormality in anterolateral leads, HR 88	Mild	Concurrent AE of dizziness on day 5, symptoms resolved D/C from study on day 30 because of AE myocardial ischemia
1110015	66		324/565	ECGs normal Max HR 98	Mild	Resolved, completed study
1110071	70	HTN metoprolol	177/542	Max HR 104 Day 365: AE of QT prolongation QTcB = 476 QTcF= 434	Mild	AEs of tachycardia and prolonged QT resolved, completed study
1210342	71	HTN chlorthalidone amlodipine atenolol	14/14	Max HR at visits = 60	Moderate	D/C study, sx resolved
1210615	65		Day 108/ ongoing	ECGs normal Max HR 80	Mild	Sx ongoing, completed study
1310028	65	metoprolol	11/30	1 hr after injections: HR 90-100	Mild	Resolved, completed study
1310412	69	HTN, chronic AFib HCTZ/ amiloride rilmenide for HTN	Day 11 resolved, day 149 ongoing	AFib Max HR 98	Mild	Dizziness day 27 D/C drug day 168 b/c tachycardia
1420091	74		268/357	1 hr after injection Max HR 86	Mild	Resolved, completed study
1450022	74		31/34	Max HR 101	Mild	D/C from study "withdrew consent"
Sources: Narratives; AE, ECG, MH and CONMED datasets; Listings 16.2.7.1						

Patients with cardiac disorder histories (study 003)

The Applicant provided a summary of cardiac and vascular AEs in the study 003 subset of 380 patients with a medical history of any cardiac disorder. Cardiac SOC TEAEs were reported in 13 placebo, 15 abaloparatide and 10 teriparatide patients (10.7%, 11.0%, 8.2%). The only apparent imbalances were in palpitations (2, 4, 2 patients respectively), tachycardia (1, 2, 0) and supraventricular tachycardia (0, 2, 0). There was no apparent relationship of cardiac AEs in this group to baseline renal function. In the vascular disorders SOC, there were an excess of events with abaloparatide and teriparatide compared to placebo, which was attributable to hypertension (see section 8.5.6 below).

Patients with hypertension history (study 003)

Patients with a previous history of hypertension (47% of all study patients) were similar to the overall population in that they had a larger number of patients with palpitations or tachycardia with abaloparatide, but otherwise a similar incidence across treatment groups of cardiac and vascular disorders, including SAEs, AEs leading to discontinuation or death.

Serious cardiac AEs (study 003)

In study 003, cardiac AEs, as listed in the following table, did not exhibit any notable treatment group differences. Three of these events were fatal (see also section 8.4.1): an abaloparatide patient (#1810423) with myocardial ischemia; a teriparatide patient (#1610011) with cardio-respiratory arrest; and a placebo patient (#1310115) with myocardial infarction. The other event of cardio-respiratory arrest represented in the table (patient #1210306, abaloparatide) occurred during hospitalization for sepsis and was precipitated by vomiting and bronchial aspiration; the patient subsequently recovered. Another fatal, possibly cardiac event was a placebo patient (#1330031) with history of ischemic heart disease who died suddenly, with SAE coded as “sudden death” (therefore not represented in the table).

Table 90 Study 003: Cardiac SAEs by MedDRA categories (safety)

System organ class Preferred term	**Placebo** (N=820) n (%)	**Abaloparatide** (N=822) n (%)	**Teriparatide** (N=818) n (%)
SOC Cardiac disorders	7 (0.9)	8 (1.0)	8 (1.0)
HLGT Cardiac disorder signs and symptoms	0 (0.0)	1 (0.1)	1 (0.1)
PT Palpitations	0	1	1
HLGT Cardiac arrhythmias	1 (0.1)	4 (0.5)	3 (0.4)
PT Supraventricular tachycardia	0	2	1
PT Atrial fibrillation	0	0	1
PT Sinus bradycardia	1	0	0
PT Cardio-respiratory arrest	0	1	1
PT Atrioventricular block	0	1	0

System organ class Preferred term	Placebo (N=820) n (%)	Abaloparatide (N=822) n (%)	Teriparatide (N=818) n (%)
HLGT Coronary artery disorders	4 (0.5)	3 (0.4)	3 (0.4)
PT Coronary artery stenosis	1	0	0
PT Myocardial ischemia	0	2	1
PT Myocardial infarction	2	1	0
PT Angina pectoris	1	0	0
PT Angina unstable	1	0	0
PT Acute coronary syndrome	0	0	1
PT Acute myocardial infarction	0	0	1
HLGT Heart failures	1 (0.1)	0 (0.0)	0 (0.0)
PT Cardiac failure congestive	1	0	0
HLGT Myocardial disorders	1 (0.1)	0 (0.0)	0 (0.0)
PT Cardiomyopathy	1	0	0
HLGT Cardiac valve disorders	0 (0.0)	0 (0.0)	1 (0.1)
PT Mitral valve stenosis	0	0	1

MedDRA v17.1
Source: CSR Tables 14.3.1.23 and 14.3.1.20

Within the subset of patients with a previous cardiac history, cardiac SAEs were reported in 3 placebo patients (angina unstable, cardiac failure congestive, myocardial infarction); 2 abaloparatide patients (both SVT); and 2 teriparatide patients (cardio-respiratory arrest, mitral valve stenosis). Two of these events were fatal: myocardial infarction in a placebo patient, and cardiorespiratory arrest in a teriparatide patient. For the 2 abaloparatide patients with SAEs of SVT, one had a history of coronary artery disease. The other (#1020051) had a history of SVT since 2000 had worsening of the condition, with episodes 3-4x weekly, beginning at day 63 of treatment and culminating in ablation therapy on day 560.

Cerebrovascular events did not demonstrate any safety signals for abaloparatide. Ischemic stroke or CVA were reported in 6 placebo, 0 abaloparatide and 1 teriparatide patients.

In the extension study (005), cardiovascular events were similar between placebo/ alendronate and abaloparatide/alendronate patients.

8.5.6. Hypertension

In study 003, 47% of patients reported a history of hypertension at baseline. During the study, the incidence of hypertension AEs was similar between treatment groups. However among the subset of patients with a medical history of a cardiac disorder, hypertension AEs were increased among teriparatide and especially abaloparatide patients (table below). Most of these patients had a previous history of hypertension; incidence in patients without such history was 2/122 (placebo); 7/136 (abaloparatide); and 6/122 (teriparatide). There were 3 patients (1 placebo, 2

teriparatide) with hypertensive crisis. The mean and range of heart rate and blood pressure readings in patients with hypertension AEs were similar to those without hypertension AEs.

Table 91 Study 003: AEs of hypertension

Preferred term	Placebo n (%)	Abaloparatide n (%)	Teriparatide n (%)
Overa l study population, N	820	822	818
Hypertension	54 (6.6)	59 (7.2)	41 (5.0)
Essential hypertension	0	0	1 (0.1)
Systolic hypertension	0	0	1 (0.1)
Blood pressure increased	4 (0.5)	7 (0.9)	5 (0.6)
Hypertensive crisis	1 (0.1)	0	2 (0.2)
SAE of hypertension	2 (0.2)	0	2 (0.2)
Discontinuation due to hypertension AE	1 (0.1)	3 (0.4)	2 (0.2)
Patients with cardiac history, N	122	136	122
Hypertension	**6 (4.9)**	**19 (14.0)**	**11 (9.0)**
Systolic hypertension	0	0	1 (0.8)
Hypertensive crisis	0	0	1 (0.8)
SAE of hypertension	1 (0.8)	0	0
Discontinuation due to hypertension AE	1 (0.8)	1 (0.7)	1 (0.8)
Source: response to mid-cycle review issues, submitted 11/22/16; and CSR Table 14.3.1.2			

8.5.7. Bone histomorphometry

Previously in the Forteo phase 3 PMO trial (GHAC), transiliac bone biopsies were performed in 102 patients at baseline (37 placebo; 31 teriparatide 20 mcg; 34 teriparatide 40 mcg). These were paired with biopsies at 12 months (total n=21) or at 24 months (total n=40). There were no findings of marrow fibrosis, woven bone or osteomalacia in any biopsy. At month 12 there were no differences in histomorphometry parameters between treatment groups with the exception of an increase in cortical porosity in the 40 mcg group. At month 24, there was no longer an increase in cortical porosity but there were some dose-related increases in trabecular bone volume and mineral apposition rate.

In study 003, transiliac bone biopsies with tetracycline labeling were performed in 105 patients (35 placebo, 36 abaloparatide, 34 teriparatide) at between 12-18 months of treatment (there were no baseline or paired biopsies). Patients undergoing biopsies had a mean age of 66-68 years; were 94% white; and were similar to the overall study population and similar across treatment groups at baseline with respect to BMI, prevalent fracture status and BMD. Study drug compliance was estimated at 98-99% in biopsied patients; BMD increases on treatment in biopsied abaloparatide and teriparatide patients were similar to or slightly greater than those in

the overall study population. Specimens were evaluated, blinded to treatment, by Dr. Robert Recker.

Among the 105 specimens, none exhibited marrow fibrosis, woven bone or evidence of osteomalacia. There were 78 specimens evaluable for quantitative histomorphometry; 66 of these exhibited double tetracycline labels and the remaining 12 contained only single label. All static and dynamic variables were normal and most showed no differences between the 3 treatment groups. There were no indices (osteoid thickness/volume, mineralization lag time) suggestive of a mineralization defect. Cortical porosity was slightly increased in abaloparatide and teriparatide patients (each with mean 6.8% of cortical bone) compared to placebo patients (5.1%) (each with $p<0.04$). However, other indices (e.g. activation frequency, eroded surface, mineralization surface, mineral apposition rate, bone formation rate) showed no evidence of the expected increase in bone remodeling with the two active drugs. There were increases in trabecular bone volume (BV/TV) and trabecular thickness (Tb.Th) with the two drugs compared to placebo, but p-values were not significant. Dr. Recker's interpretation of the findings is that the anabolic effect is probably largely confined to the periosteal surfaces rather than trabeculae, therefore histomorphometry is insensitive to the changes, e.g. relative to BMD. Unlike the equivocal findings with respect to efficacy, it was concluded that there were no bone safety issues raised by the biopsies.

Reviewer comment: *The bone histology and histomorphometry data do not raise any issues about bone quality. Abaloparatide and teriparatide increased cortical porosity to a similar extent; this reflects the increase in bone resorption and does not appear consistent with the Applicant's view that abaloparatide has a lesser effect on bone resorption.*

8.5.8. Injection site reactions

In study 003, local tolerance was assessed systematically by patients with diaries. The following table, representing daily entries during the first month at 1 hour after the injection, shows that symptoms were more common with abaloparatide and teriparatide compared to placebo, especially for redness, the most common symptom. The incidence and severity of symptoms were generally lower at 24 hr compared to 1 hr post-injection, and during month 12 compared to month 1 (not shown).

Table 92 Study 003: Local reactions to injection reported by patients during the first month‡ (safety population)

Percent of patients reporting symptom	Placebo N=820	Abaloparatide N=822	Teriparatide N=818
Redness	28	58	64
Severe redness*	0.4	2.9	2.8
Swelling	3	10	10
Severe swelling*	0.3	0.4	0
Pain	7	9	8
Severe pain*	0.1	0.4	0.4
Tenderness	7	12	11
Severe tenderness*	0.3	0.3	0

‡ Symptoms recorded at 1 hr post-injection every day
*Categories for each symptom were none, mild, moderate, severe. "Severe" represents >1 inch diameter for redness or swelling, "severe pain, similar to a bee sting" for pain, or "severe tenderness, withdraws to touch" for tenderness
Source: CSR Table 14.3.6.2

AEs of injection site reactions did not differ substantially between treatment groups except for injection site pain (3 placebo, 8 abaloparatide, 6 teriparatide; injection site pruritis (2, 5, 1); and injection site hemorrhage (0, 4, 0); injection site hematoma (5, 0, 4). Two abaloparatide patients (#1020040, #1810553)may have discontinued due to injection site reactions.

8.5.9. Hypersensitivity

In study 003, hypersensitivity was evaluated as an AESI using primarily the standardized MedDRA queries (SMQs) for anaphylactic reaction and angioedema. One or more of the identified terms were reported in 10.1% of placebo, 12.0% of abaloparatide and 11.7% of teriparatide patients. Some of the pertinent AEs were pruritis (9, 15, 8 patients respectively); rash (10, 8, 10); rash pruritic (5, 5, 7); dyspnea (2, 9, 8); urticaria (1, 3, 5); drug hypersensitivity (2, 2, 0); and hypersensitivity (3, 0, 3). There were no reports of anaphylaxis or angioedema. Overall there is no evidence of any increase in hypersensitivity AEs.

8.6. Safety Analyses by Demographic Subgroups

Among abaloparatide-treated patients, Asian women had a much higher incidence of palpitations compared to white women; however this was also the case for teriparatide and possibly for placebo treated patients (table below), therefore no evidence of interaction between these treatment and racial groups for this particular adverse reaction. In contrast, incidence of palpitations was not markedly different between age subgroups within any of the treatment groups.

Table 93 Study 003: Incidence of palpitation AEs for racial and age subgroups by treatment group

	Placebo	Abaloparatide	Teriparatide
Asian	2/131 (1.5%)	17/128 (13.3%)	7/137 (5.1%)
White	1/655 (0.2%)	25/663 (3.8%)	6/645 (0.9%)
Age <65 years	0/163 (0.0%)	8/154 (5.2%)	1/154 (0.6%)
Age 65 to <75 years	3/514 (0.6%)	30/519 (5.8%)	8/504 (1.6%)
Age ≥ 75 years	0/144 (0.0%)	4/151 (2.6%)	4/160 (2.5%)
Source: AE dataset			

8.7. Specific Safety Studies/Clinical Trials

N/A

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

As noted above, there is a safety concern for PTH- and PTHrP-related products based on the finding of osteosarcoma in rats, which is biologically plausible based on the mechanism of action (see section 4.4). In humans, there is no evidence to date of an increased risk with any of these drugs, but the data are not conclusive (see section 2.2). Because of the rarity of osteosarcoma and the probable long latency period, no cases have been reported in, or are expected in, clinical trials. There has been no evidence of increase in other neoplasms in teriparatide trials; in the phase 3 PMO study (GHAC), there were numerically fewer patients with cancer in the teriparatide groups compared to placebo.

In study 003, incidence of overall neoplasms, and of malignant or unspecified neoplasms, was slightly lower in the abaloparatide arm compared to placebo or teriparatide (table below). The number of events was not sufficient to discern any patterns with regard to specific types of neoplasms. There were no osteosarcomas and, except for a hemangioma of bone in a placebo patient, no other bone tumors.

Table 94 Study 003: Incidence of neoplasms malignant/unspecified (safety population)

HGLT Preferred term	**Placebo** (N=820) n (%)	**Abaloparatide** (N=822) n (%)	**Teriparatide** (N=818) n (%)
Any event in SOC of neoplasms benign, malignant and unspecified (incl cysts and polyps)	29 (3.5)	20 (2.4)	31 (3.8)
Any event in HGLTs of neoplasms malignant and unspecified (as listed below)	15 (1.8)	13 (1.6)	19 (2.3)
Breast neoplasms malig./unspec.	2 (0.2)	4 (0.5)	8 (1.0)
Breast cancer	1	3	6
Breast cancer stage II	0	1	0
Invasive ductal breast carcinoma	1	0	1
Breast neoplasm	0	1	2
Endocrine neoplasms malig./unspec.	2 (0.2)	2 (0.2)	1 (0.1)
Adrenal neoplasm	1	1	0
Thyroid neoplasm	1	1	1
Gastrointestinal neoplasms malig./unspec.	3 (0.4)	5 (0.6)	2 (0.2)
Adenocarcinoma of colon	0	2	0
Adenocarcinoma gastric	1	0	0
Gastric neoplasm	1	0	0
Pancreatic carcinoma	0	2	2
Pancreatic neoplasm	0	1	0
Gastrointestinal carcinoma	1	0	0
Hepatobiliary neoplasms, malig./unspec.	1 (0.1)	0 (0.0)	0 (0.0)
Bile duct adenocarcinoma	1	0	0
Leukemias	1 (0.1)	0 (0.0)	0 (0.0)
Chronic leukemia	1	0	0
Misc. and site unspecified neoplasms, malig./unspec.	1 (0.1)	0 (0.0)	0 (0.0)
Metastatic squamous cell carcinoma	1	0	0
Nervous system neoplasms, malig./unspec. NEC	0 (0.0)	1 (0.1)	0 (0.0)
Cerebellopontine angle tumor*	0	1	0
Reproductive neoplasms female malig./unspec.	1 (0.1)	0 (0.0)	1 (0.1)
Borderline ovarian tumor	1	0	0
Uterine cancer	0	0	1
Respiratory and mediastinal neoplasms malig./unspec.	1 (0.1)	0 (0.0)	1 (0.1)
Lung adenocarcinoma	1	0	0
Lung neoplasm malignant	0	0	1
Skin neoplasms malig./unspec.	3 (0.4)	1 (0.1)	6 (0.7)
Malignant melanoma	1	0	0
Melanoma recurrent	0	0	1
Metastatic malignant melanoma	0	0	1
Basal cell carcinoma	1	1	2
Skin cancer	1	0	3

* Benign, per narrative
Source: CSR Table 14.3.1.2
MedDRA v. 17.1

During the initial 6 months of extension study 005 (table below), there were more patients with AEs of potential malignancies in the abaloparatide/ALN group compared to the placebo /ALN group (6 vs. 0, if 2 patients with basal cell Ca and thyroid nodule are excluded). All neoplasm AEs within the initial 6 months are included in this table with the exception of an AE of malignant pleural effusion, which involved the patient with lung neoplasm malignant.

Table 95 Study 005: Incidence of neoplasms malignant/unspecified at 6 months (005 safety population)

Preferred term	**Placebo/ALN** (N=580) n (%)	**Abaloparatide/ALN** (N=553) n (%)	**Overall** (N=1133) n (%)
Any PT of neoplasm malignant/unspecified	2 (0.3)	6 (1.1)	8 (0.7)
Basal cell carcinoma	1	0	0
Brain neoplasm*	0	1	1
Colon cancer	0	1	1
Intestinal adenocarcinoma**	0	1	1
Leiomyosarcoma	0	1	1
Lung neoplasm malignant	0	1	1
Renal cancer	0	1	1
Thyroid neoplasm‡	1	0	0

* Histology= grade 4 glioblastoma, per narrative
** Diagnosis later changed to ovarian epithelial cancer (see table below)
‡ Verbatim term=thyroid nodule
Source: CSR Table 14.3.1.2

The 120-Day NDA Safety Update report (submitted 7/28/16) included an additional 12 months of study 005 data (i.e. the 12 and 18 month interim analyses). Compared with the 6 months' data in the above table, malignancies are more evenly distributed between the two treatment groups:

Table 96 Study 005: Incidence of neoplasms malignant/unspecified at 18 months (005 safety population)

Preferred term	Placebo/ALN (N=580) n (%)	Abaloparatide/ALN (N=553) n (%)	Overall (N=1133) n (%)
Any PT of neoplasm malignant/unspecified	10 (1.7)	11 (2.0)	21 (1.9)
Basal cell carcinoma	3	2	5
Brain neoplasm	0	1	1
Colon cancer	0	1	1
Colorectal adenocarcinoma	1	0	1
Leiomyosarcoma	0	1	1
Lung neoplasm malignant	1	1	2
Ovarian epithelial cancer*	0	1	1
Pelvic neoplasm**	0	1	1
Peritoneal neoplasm‡	1	0	1
Rectal cancer	1	0	1
Renal cancer	0	1	1
Squamous cell carcinoma of skin	1	0	1
Thyroid neoplasm	2	1	3
Vulval cancer	0	1	1

* Diagnosis changed from intestinal adenocarcinoma after 6-month database lock (see table above)
** Verbatim term=pelvic tumor unknown etiology
‡ Per IND safety report=advanced cancer
Source: 18-month CSR Table 14.3.1.2 and Listing 16.2.7.1

8.8.2. Human Reproduction and Pregnancy

There are no human data available regarding pregnancy, as the drug is intended for postmenopausal women.

8.8.3. Pediatrics and Assessment of Effects on Growth

Abaloparatide, like teriparatide, has not been studied in pediatric patients because of the likelihood that patients with open epiphyseal growth plates would be at higher risk of osteosarcoma.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Abaloparatide has been administered SC in single doses up to 320 mcg, and up to 120 mcg/day for 7 days. An accidental overdose of 400 mcg resulted in moderate asthenia, headache, nausea and vertigo. Adverse events of hypercalcemia, tachycardia, orthostatic hypotension, dizziness, nausea, vomiting and headache may be dose related and could occur in overdose. Based on extensive experience with teriparatide, it is very unlikely that any safety issues would be associated with abuse, withdrawal or rebound phenomena.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Abaloparatide has not been marketed in any country to date.

8.9.2. Expectations on Safety in the Postmarket Setting

In the phase 3 study (003), 19% of the patients were ≥75 y/o, although among the exclusion criteria were "history of chronic or recurrent renal, hepatic, pulmonary, allergic, cardiovascular, gastrointestinal, endocrine, central nervous system, hematologic or metabolic diseases, or immunologic, emotional and/or psychiatric disturbances…", or the presence at screening of orthostatic hypotension (decline of ≥20 mmHg systolic or ≥10 mmHg diastolic). After marketing, it is possible that abaloparatide would be prescribed to a wider population of patients with cardiovascular disease, use of potent diuretics, autonomic neuropathy etc. that could increase susceptibility to the hemodynamic effects of lower BP and/or increased heart rate. Therefore, a labeled warning is indicated (see section 10.2).

8.10. Additional Safety Issues From Other Disciplines

N/A

8.11. Integrated Assessment of Safety

Abaloparatide has an extensive safety database; 918 women with PMO received the drug at the recommended 80 mcg dose in phase 2/3 studies, including 640 with exposure >1 year. In study 003 there were 5 deaths with placebo (0.6%) and 3 deaths each with abaloparatide and teriparatide (0.4%). Serious AEs occurred in 11% of placebo recipients and 10% of abaloparatide or teriparatide recipients, with no apparent predominance of any specific type of event. Overall AEs occurred in 88% of placebo and 89% of abaloparatide or teriparatide treated patients.

There were imbalances in four specific AEs, with incidence in placebo/ abaloparatide/ teriparatide groups as follows: palpitations (0.4%, 5.0%, 1.6%); tachycardia or sinus tachycardia (0.6%, 1.6%, 0.7%); dizziness (6.1%, 10.0%, 7.3%); and nausea (3.0%, 8.3%, 5.1%). Many abaloparatide recipients experienced more than one of these symptoms simultaneously, typically within a few hours following an injection, and some reported repeated episodes after multiple injections. Few patients reported "severe" events and most completed the study, however because of these specific events there was an overall imbalance in AE-related discontinuations (6.1% placebo, 9.9% abaloparatide, 6.8% teriparatide) (see section 8.4.3).

These symptoms appear to be related to a tendency for abaloparatide to increase heart rate and/or cause postural changes in blood pressure (orthostatic hypotension), mainly within a few hours of an injection. Teriparatide has similar effects, but to a somewhat lesser extent. In study

003, heart rate 1 hour after injection averaged about 7-8 BPM above baseline for abaloparatide, compared to ~5-6 BPM for teriparatide and ~1-2 BPM for placebo. This study probably did not capture the maximal increase in heart rate: in the TQT study, heart rate peaked 15 min after injection, at ~15 BPM above baseline. Orthostatic hypotension was also monitored with supine to standing BP differences 1 hour after injection in study 003; slight increases in incidence of significant changes were seen with abaloparatide vs. placebo. Because of the AEs that are apparently related to these hemodynamic effects, labeling for abaloparatide should include a W&P for orthostatic hypotension similar to Forteo (sections 8.4.8, 8.5.4, 8.5.5).

There was no evidence in clinical studies of any apparent increase in serious cardiovascular events including arrhythmias or coronary artery disease related events. Analysis of study 003 patients with history of a cardiac disorder (~15% of all patients) showed excesses of palpitations AEs (similar to other patients) and a possible increase in hypertension AEs, but no evidence of increase in serious events. Although abaloparatide exposure is higher with declining renal function, there was no apparent relationship of palpitations or other cardiac AEs to baseline renal function, overall or within the group of patients with a cardiac history. The thorough QT study (012) and phase 3 study (003) provided no evidence of significant QT prolongation section 8.4.9).

Serum and urine calcium were carefully studied because of the known safety issues for teriparatide (sections 8.5.1 and 8.5.2). Phase 3 data showed that abaloparatide may cause hypercalcemia at 4 hours post injection, but with a significantly lower incidence than teriparatide (3.4%, vs. 6.4% with teriparatide and 0.4% with placebo). There were 2 abaloparatide patients (0.2%) who discontinued the study due to hypercalcemia (vs. 4 with teriparatide and none with placebo). The protocol provided for possible abaloparatide dose reduction (to 40 mcg) for persistent hypercalcemia, but this was not done for any patients. Abaloparatide and teriparatide patients showed a moderate increase in hypercalcemia incidence with declining levels of renal function (CrCl <60, vs. 60-90 or >90). Hypercalciuria incidence with abaloparatide was also intermediate between teriparatide and placebo. Urolithiasis incidence was 1.7% for placebo, 2.1% for abaloparatide and 2.3% for teriparatide. The 003 protocol excluded patients with baseline hypercalcemia or recent urolithiasis, therefore the relevant precautions in Forteo labeling should be included in abaloparatide labeling as well. Because of ectopic mineralization seen in animal studies, renal CT scans were conducted in a subset of 003 patients, and showed no evidence of increase in nephrocalcinosis or nephrolithiasis.

Like teriparatide, there was an increase in uric acid levels with abaloparatide, but no apparent increase in gout. Both drugs showed slight declines in hemoglobin vs. placebo and more AEs of anemia, but clinical impact was insignificant. There was no evidence of significant effects on renal or hepatic function (section 8.4.6).

A large number of abaloparatide patients (49%) developed antidrug antibodies, including 33% with neutralizing antibodies, but there was no evidence of an impact on safety (nor any effect on fracture incidence or BMD) (section 8.4.10).

Adverse reactions of injection site pain were reported by 1% of patients with TYMLOS and 0.4% of patients with placebo. No injection site reactions were severe or led to discontinuation of treatment. There were no reports of anaphylaxis, angioedema or other evidence of hypersensitivity reactions (section 8.5.9).

The most important safety issue, osteosarcoma, was not reported in any studies, and was not expected because of its rarity. There was no evidence of increase in any other malignancies with abaloparatide (see section 8.8.1).

As is routine for any osteoporosis drug, transiliac bone biopsies were performed in 105 patients between 12-18 months of treatment. There was no evidence of woven bone or marrow fibrosis. Cortical porosity was slightly increased in abaloparatide and teriparatide patients (each with mean 6.8% of cortical bone, vs. 5.1% for placebo). There were trending increases in trabecular bone volume and trabecular thickness with both drugs; remaining quantitative histomorphometry parameters were normal (see section 8.5.7).

9 Advisory Committee Meeting and Other External Consultations

This application does not raise any specific issues that require the input of an Advisory Committee, therefore no meeting is planned.

10 Labeling Recommendations

10.1. Prescribing Information

While labeling has not been discussed with the Applicant at this writing and final labeling will require much additional discussion, the following are comments from this reviewer regarding major content changes needed to the Applicant's proposed Prescribing Information:

Black box warning
The osteosarcoma warning for Forteo has been modified for abaloparatide.

Reviewer comment: *Two further changes are appropriate: addition of the 2-year limitation, and addition of "hereditary disorders predisposing to osteosarcoma".*

1. Indications and Usage

The Applicant proposed language is that [redacted] In postmenopausal women with osteoporosis, Tymlos reduces the risk of vertebral fractures and nonvertebral fractures".

Reviewer comment: *The indication [redacted] for patients "at high risk of fracture defined as….." to be consistent with the Forteo indication, because of the similar potential risk of osteosarcoma. A 2-year lifetime Limitation of Use is also appropriate, not only for consistency with Forteo but also because of the potential for patients to be treated with both drugs, for up to 4 years, which I would not recommend.*

4. Contraindications

The Applicant proposes a contraindication [redacted]

Reviewer comment: [redacted] *this should be changed to "none" (at least for now).*

5. Warnings and Precautions

In addition to changes to the osteosarcoma warning (as above), the Applicant proposes W&P for Bone Metastases and Skeletal Malignancies [redacted] which will be incorporated into the Osteosarcoma W&P (5.1); and a W&P for Pre-Existing Hypercalcemia. [redacted]

Reviewer comment: *Although hypercalcemia and hypercalciuria/urolithiasis issues probably are less important with abaloparatide than with teriparatide, the warnings for prescribers should apply. The orthostatic hypotension warning should as well, as this is significantly more common with abaloparatide compared to teriparatide.*

6. Adverse Reactions

The Applicant proposes to include safety data [redacted]

Reviewer comment: *After internal discussion,* [redacted] *and should be removed. In addition, section 6.1 requires extensive re-writing, including expansion of the Common Adverse Reactions table, and added information on orthostatic hypotension, tachycardia, injection site reactions and hypercalcemia.*

8. Use in Specific Populations

Reviewer comment: *Extensive re-writing is needed according to PLLR guidance, and to add*

findings of the dedicated renal impairment study.

12. Clinical Pharmacology
Reviewer comment: *Extensive changes are needed; see Clinical Pharmacology review.*

14. Clinical Studies
As in section 6.1, the Applicant proposes to include (b) (4) to this section. In addition to data on the primary and key secondary endpoints (vertebral and non-vertebral fractures), they also propose to (b) (4) . Some repetitive information is included (both table and K-M curve to portray non-vertebral fracture data), and very detailed BMD data.

Reviewer comment: *This section is far too long and will have much information deleted:* (b) (4)

17. Patient Counseling Information
Reviewer comment: *Additional information is needed regarding counseling of patients with respect to hypercalcemia and orthostatic hypotension.*

10.2. Patient Labeling

A proposed Medication Guide and Instructions for Use have been submitted by the Applicant and are under review.

10.3. Nonprescription Labeling

N/A

11 Risk Evaluation and Mitigation Strategies (REMS)

11.1. Safety Issue(s) that Warrant Consideration of a REMS

Based on the safety finding of osteosarcoma in animals, Forteo is approved under a Risk Evaluation and Mitigation Strategy (REMS). The REMS was first required in 2009, in part because a new approved indication (glucocorticoid-induced osteoporosis) (b) (4)
The goals of the Forteo REMS are to mitigate the potential risk of osteosarcoma by alerting

healthcare providers and patients about the potential risk, and to inform healthcare providers of the 2-year maximum lifetime duration of treatment with Forteo and of proper patient selection. The REMS consists of Medication Guide, communication plan and assessments. The latest assessment (dated 7/13/16) showed that among a random sample of physicians who had prescribed Forteo, 97% were aware of the potential risk for osteosarcoma, and 89% were aware of the 2-year maximum lifetime duration of therapy. A recent OSE study found that about 3-5% of patients use Forteo for longer than 2 years. Because it appears that the Forteo REMS may no longer be necessary, there are currently plans for it to be removed.

Abaloparatide appears to have a similar propensity to induce osteosarcoma in rats as teriparatide, therefore a similar level of uncertainty about potential risk to humans as teriparatide. Considering the many similarities between the two drugs that will be reflected in labeling (including black box warning), it is likely that prescriber awareness will be high, though probably somewhat less than the 97% for Forteo, at least initially.

11.2. Conditions of Use to Address Safety Issue(s)

As stated in the proposed black box warning for abaloparatide, the potential risk can be mitigated by avoidance of prescribing to patients with osteosarcoma risk factors, and possibly by observance of the lifetime 2-year limitation of use.

11.3. Recommendations on REMS

I believe that the potential osteosarcoma risk of abaloparatide, and appropriate steps to mitigate the risk, can probably be communicated adequately through labeling. While a REMS may have some value in promoting awareness, FDA can only require a REMS when it is considered necessary to ensure that a drug's benefits outweigh its risks. In this reviewer's opinion, this does not apply to abaloparatide, for which the benefits appear to outweigh the risks in the intended population, with or without a REMS. Therefore, I do not believe that a REMS should be required.

12 Postmarketing Requirements and Commitments

As noted above (section 2.2), the potential human risk of osteosarcoma with Forteo has been the subject of a postmarketing surveillance study since approval in 2002, which has since been expanded and supplemented by a patient registry. No evidence of increased risk has emerged to date, (b) (4) to rule out an increased risk of this rare malignancy. OSE is (b) (4) also considering different options for abaloparatide, including an enhanced pharmacovigilance program, similar to the one implemented for Natpara (NDA 125511) at the time of approval in 2015 for treatment of hypoparathyroidism. A PMR could also be considered with regard to assessing adherence to the recommended 2-year limitation of use, but this can probably be done through Sentinel. Therefore although discussions continue, it appears that no PMRs will be necessary for approval. I agree with this approach.

13 Appendices

13.1. References

Clinician's Guide to Prevention and Treatment of Osteoporosis, *National Osteoporosis Foundation* (2013), released 2/25/14

Genant HK et al, Vertebral fracture assessment using a semiquantitative technique, *J Bone Miner Res* (1993), 8: 1137-1148

13.2. Financial Disclosure

The Applicant provided financial disclosure information for the phase 3 clinical study (003) and for the phase 2 studies 002 and 007. Note that in the phase 3 extension study (005), all principal investigators, and nearly all sub-investigators, also participated in study 003.

Covered Clinical Study (Name and/or Number): BA058-05-003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 38 Principal Investigators, 156 Sub-investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details	Yes ☐	No ☐ (Request details from

of the disclosable financial interests/arrangements:		Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 7		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): BA058-05-002

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 42 Principal Investigators, 135 Sub-investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)

Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 5		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): BA058-05-007

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 11 Principal Investigators, 28 Sub-investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)

Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STEPHEN R VOSS
12/08/2016

THERESA E KEHOE
12/08/2016