

**Background Document for Meeting of Advisory Committee
for Reproductive Health Drugs (September 8, 2008)**

NDA 22-242

Lasofexifene Tartrate

(Proposed trade name: FABLYN)

Pfizer, Inc

Proposed Indication:

**“FABLYN is a selective estrogen receptor modulator indicated for
treatment of osteoporosis in postmenopausal women at increased
risk of fracture”**

Dosing regimen

0.5 mg tablet orally once daily

**Prepared by Division of Reproductive and Urologic Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration**

August 15, 2008

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1 BACKGROUND

1.1 Objective of Meeting and Overview of Development Program

The purpose of this Advisory Committee meeting is to review and discuss the safety, efficacy, and overall risk/benefit profile of lasofoxifene (a selective estrogen receptor modulator) for the treatment of osteoporosis in postmenopausal women at increased risk for fracture. The primary data in support of lasofoxifene treatment for the proposed indication were obtained from Study A2181002 (also referred to as PEARL [Postmenopausal Evaluation and Risk-reduction with Lasofoxifene]). Study A2181002 was a prospective, randomized, double-blind, multi-national clinical trial that compared 2 doses of lasofoxifene (0.25 mg/d and 0.5 mg/d) to placebo. All subjects were required to take supplemental calcium and Vitamin D. The clinical trial randomized 8,556 postmenopausal women at increased risk for fracture (2,852 to each of the 3 treatment groups).

The Study was initially designed to treat and follow all randomized subjects for up to 3 years. A study of 3-year duration is consistent with the FDA's guidance for establishing the efficacy of a drug product for the treatment of postmenopausal osteoporosis. The duration of Study A2181002 was subsequently extended to 5 years via a protocol amendment adopted prior to subjects reaching their 3-year (Month 36) visit. The primary efficacy endpoint of the original 3-year clinical trial is the risk of a subject developing a new or worsening radiographic vertebral fracture within 3 years of starting randomized treatment with study drug. This is the primary endpoint that the Committee members should focus upon in their assessment of the efficacy of lasofoxifene for the treatment of postmenopausal osteoporosis.

The original submission of NDA 22-242 included a 3-Year Interim Report for Study A2181002. During the course of the review of the original NDA submission by the Division of Reproductive and Urologic Products (hereafter referred to as DRUP or the Division), Pfizer (hereafter referred to as the Applicant) submitted selected 5-year safety and efficacy data from Study A2181002. (The 2-year extension of Study A2181002 has been completed, but a Final 5-Year Study Report has not been submitted by the Applicant). This Background Document will focus primarily on the 3-year data from Study A2181002 and the Applicant's analyses of these data. Data from the 2-year extension that are pertinent to the Committee's assessment of the safety and overall risk/benefit profile of lasofoxifene and analyses of these data also have been included in this Background Document.

1.2 Issues for Committee Consideration

Committee Members will find statements by the Division entitled "Issues for Consideration" throughout this Background Document. These statements identify issues that the Division believes to be of particular importance in the Committee's assessment of the safety and overall risk/benefit profile of lasofoxifene for the proposed indication of treatment of osteoporosis in postmenopausal women at increased risk for fracture.

The Issues for Consideration include the following:

- A trend toward an increase in all-cause mortality in lasofoxifene-treated subjects in the overall clinical development program and a statistically significant increase in all-cause mortality in the 0.25 mg dose group in pivotal Phase 3 Study A2181002 (see Section 5.3.1).
- A statistically significant increase in deep venous thromboses (DVTs) and pulmonary emboli (PEs) in lasofoxifene-treated subjects compared to placebo-treated subjects (see Section 5.4.1).
- A statistically significant increase in gynecologic adverse events including increased endometrial thickness (see Section 5.4.4.5) and increased vaginal bleeding (5.4.4.6) as well as an increased number of gynecologic (uterine) procedures (5.4.4.9) in lasofoxifene-treated subjects.

1.3 Postmenopausal Osteoporosis

Postmenopausal osteoporosis is a skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone leading to an increase in fragility and susceptibility to fracture.

Drug products currently approved in the U.S. for the treatment of osteoporosis include:

Bisphosphonates

- Alendronate (oral tablets and oral solution)
- Risedronate (oral tablets)
- Ibandronate (oral tablets; intravenous formulation)
- Zoledronic acid (intravenous formulation)

Selective estrogen receptor modulator (SERM)

- Raloxifene (oral tablet)

Calcitonin

- Calcitonin-salmon (intranasal spray; injection)

Parathyroid hormone (PTH)

- Teriparatide (injection)

Lasofoxifene, the focus of this Advisory Committee meeting, would be, if approved, the second SERM available in the U.S. for the treatment of postmenopausal osteoporosis. Currently, raloxifene is the only SERM approved in the U.S. for the treatment of postmenopausal osteoporosis.

1.4 Selective Estrogen Receptor Modulators

Selective Estrogen Receptor Modulators (SERMs) are pharmacologic agents which exert their activity by binding to estrogen receptors in different tissues in the body. The

pharmacologic effects of individual SERMs vary and are based on their relative agonistic and antagonistic effects in different tissues (e.g., bone vs. endometrium). SERMs have the potential advantage of being tailored to preserve the benefits of estrogenic medications in specific tissues while avoiding undesired effects of estrogens in other tissues.

The FDA-approved SERMs are listed below along with a brief description of their labeled indication(s)

- Raloxifene (treatment and prevention of postmenopausal osteoporosis, reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and who are at high risk for invasive breast cancer)
- Clomiphene (treatment of ovulatory dysfunction in women desiring pregnancy)
- Tamoxifen (multiple indications for breast cancer)
- Toremifene (treatment of metastatic breast cancer)
- Fulvestrant (treatment of metastatic breast cancer with disease that progresses following antiestrogen therapy)

A brief overview of safety concerns for SERMs is found in Section 5.1 of this document.

1.5 Regulatory Guidance for the Development of Products for Treatment of Osteoporosis

In 1994, the Division of Metabolic and Endocrine Drug Products issued a document entitled “Guidelines for Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis.” In their development program for lasofoxifene for the treatment of postmenopausal osteoporosis, the Applicant followed the most important and most relevant recommendations contained in this document. Among these recommendations for the development of a new drug product for the treatment of osteoporosis are: (1) demonstration of efficacy should be based on a reduction in the incidence of fractures (an increase in bone mineral density [BMD] is only supportive data) and (2) the benefit of treatment (i.e., a reduction in the incidence of fractures) should be shown at 3 years of treatment.

In 2006, the recommendations in a document entitled “Guideline on the Evaluation of Medical Products in the Treatment of Primary Osteoporosis” were adopted by Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA). This document, although not necessarily reflecting the official position of the FDA, provides relevant and useful information regarding the development of drug products for the treatment of postmenopausal osteoporosis. This document is provided in Appendix 3.

2 CLINICAL DEVELOPMENT OF LASOFOXIFENE

2.1 Overview of Clinical Studies

Although the Applicant has investigated the safety and efficacy of lasofoxifene treatment for other potential indications, the *treatment* of postmenopausal osteoporosis is the focus of this

Advisory Committee meeting. Some of these studies for other indications (e.g., *prevention* of postmenopausal osteoporosis) have contributed supportive efficacy data such as information on changes in BMD and markers of bone turnover. All of these studies have contributed to the overall safety database for lasofoxifene. In Section 2.2, a listing of the Applicant’s Phase 1 studies (types and number of studies) is provided. Sections 2.3 and 2.4 (and Appendix 1 [Phase 2 studies] and Appendix 2 [Phase 3 studies]) contain general information about the studies the Applicant conducted related to the prevention and/or treatment of osteoporosis.

2.2 Applicant’s Phase 1 Clinical Studies

The Applicant completed 23 Phase 1 studies that are listed in Table 1. These include standard pharmacokinetic and pharmacodynamic studies as well as numerous drug-drug interactions studies, a food effect study, and a hepatic impairment study.

Table 1 Summary of Phase 1 Studies for Lasofoxifene

Objective	Study Number
Pharmacokinetics in healthy volunteers (3)	218-001, 218-002, 218-004
Metabolism and excretion (1)	218-006
Pivotal bioequivalence of commercial formulation (2)	A2181018, A2181028
Food effect (1)	A2181036
Hepatic impairment (1)	A2181019
Drug interactions (7)	A2181020, A2181022, A2181023, A2181024, A2181027, A2181029, A2181035
Relative bioavailability and non-definitive bioequivalence (4)	218-003, 218-005, A2181007, A2181017
Pharmacokinetics in Japanese and Caucasian Women (4)	A2181006, A2181011, A2181025, 218-007

Source: Tabular Listing of Clinical Studies 5.2; NDA 22-242

2.3 Applicant’s Phase 2 Clinical Studies

The Applicant completed 11 Phase 2 studies, which are listed in Table 2. Information regarding the Phase 2 osteoporosis-related studies (overall design, treatment groups, number of subjects, and subject demographics) can be found in Appendix 1.

Table 2 Summary of Phase 2 Studies for Lasofoxifene

Objective	Study Number
Osteoporosis-related	218-101, 218-101E, 218-102, 218-103, A2181042 (LACE) A2181037 (JADE)
Other indications	A2181012, A2181014, A2181015, A2181016, A2181021

Source: Tabular Listing of Clinical Studies 5.2; NDA 22-242

2.4 Applicant's Phase 3 Clinical Studies

The Applicant completed the 6 Phase 3 clinical trials that are listed in Table 3. Additional information on the Phase 3 osteoporosis studies (overall design, treatment groups, number of subjects, and subject demographics) can be found in Appendix 2. The primary clinical trial in support of the safety and efficacy of lasofoxifene for the treatment of osteoporosis (Study A2181002) is described in detail in Section 3.

Table 3 Summary of Phase 3 Studies for Lasofoxifene

Objective	Study Number
Treatment of Osteoporosis	A2181002 (PEARL)*
Prevention of Osteoporosis	A2181003/A2181004 (OPAL), A2181030 (CORAL)
Vulvar Vaginal Atrophy	A2181031, A2181032

* 3-year interim final study for the PEARL Study was submitted with the original NDA; the 5-year study is complete but the study report is not finalized

Source: Tabular Listing of Clinical Studies 5.2; NDA 22-242

2.5 Dose Selection for Phase 3 Osteoporosis Studies

A range of daily doses of lasofoxifene have been investigated in the clinical development program as listed below:

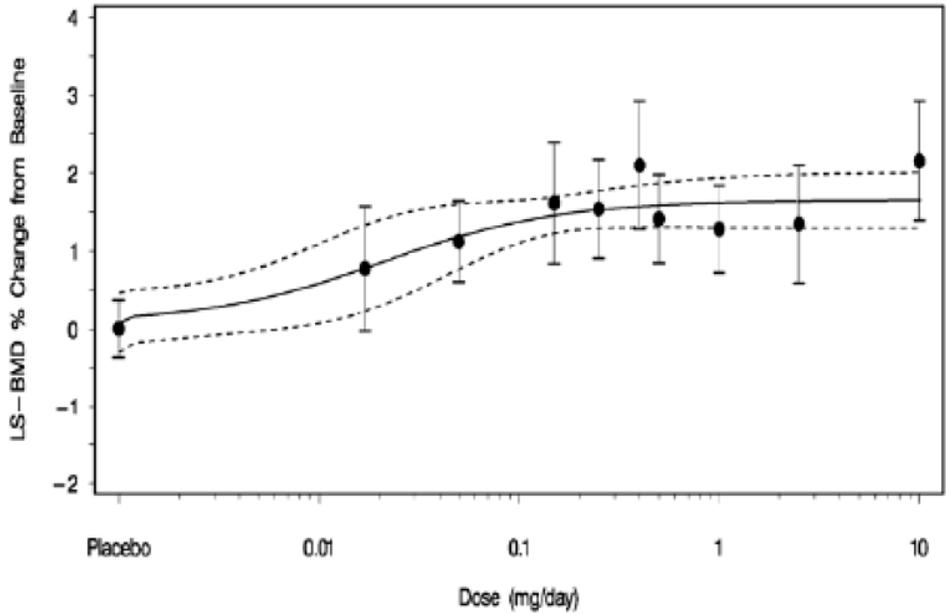
- Phase 1 Studies: 0.5 mg to 100 mg/day (single dose); 0.1 mg to 20 mg/day (multiple doses)
- Phase 2 Studies: 0.017 mg to 10 mg/day
- Phase 3 Osteoporosis Prevention Studies: 0.025 mg, 0.25 mg and 0.5 mg/day
- Phase 3 Osteoporosis Treatment Studies: 0.25 mg and 0.5 mg/day

The Applicant provided the following rationale for the 2 doses (0.25 mg/d and 0.5 mg/d) that were selected for study in Phase 3 osteoporosis treatment trial:

“Doses ranging from 0.017 mg to 10 mg were studied in Phase 2 osteoporosis prevention trials. The Month 6 lumbar spine BMD, Month 12 total hip BMD and Month 6 LDL-C results in these studies were analyzed to determine the lasofoxifene dose-response curves. The results of the dose-response analyses led to the selection of lasofoxifene 0.25 and 0.5 mg for the pivotal Phase 3 osteoporosis treatment trial (A2181002)..”

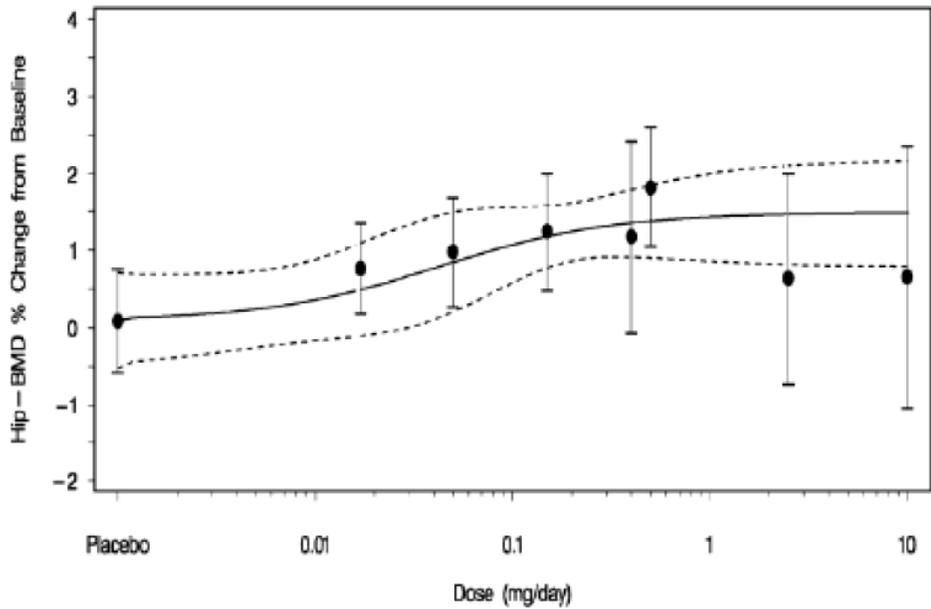
Dose-response relationship data for (1) lumbar spine BMD at Month 6 of treatment, (2) total hip BMD at Month 12 of treatment, and (3) LDL-cholesterol at Month 6 of treatment are shown in Figure 1, Figure 2, and Figure 3, respectively.

Figure 1 Dose-Response Relationship for Lumbar Spine BMD at 6 Months of Treatment (Phase 2 Studies)



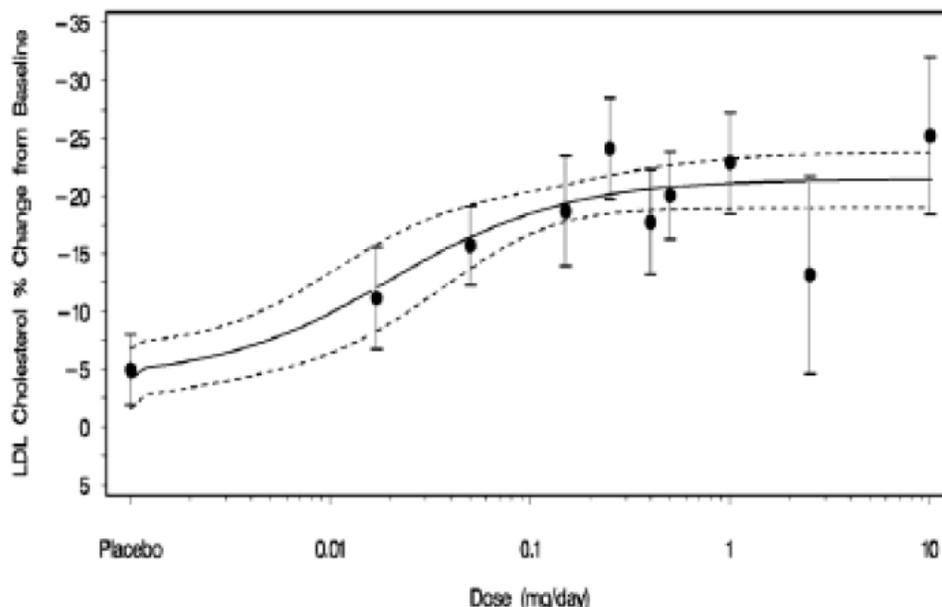
Source Figure 22, Pg 78, Prevention Efficacy Summary; NDA 22-242

Figure 2 Dose-Response Relationship for Total Hip BMD at 12 Months of Treatment (Phase 2 Studies)



Source: Figure 23, pg 78, Prevention Efficacy Summary; NDA 22-242

Figure 3 Dose-Response Relationship for LDL Cholesterol at 6 Months of Treatment (Phase 2 Studies)



Source: Figure 24, pg 79, Prevention Efficacy Summary; NDA 22-242

Data from Phase 2 Study 218-103 relating to lumbar spine BMD and total hip BMD (see Table 4) show that, of the doses studied, only treatment with the 0.5 mg/d dose produced a statistically significant increase in BMD at both the spine and hip relative to placebo at both time points (Month 6 and Month 12). It should be noted, however, that neither 0.25 mg/d nor 1.0 mg/d doses were investigated in Study 218-103.

Table 4 Statistical Significance of BMD Percent Change from Baseline (Least Squares Mean Difference) in Study A218-103

Endpoint	Lasofexifene Dose			
	0.017 mg	0.05 mg	0.15 mg	0.5 mg
Increased Lumbar Spine BMD at Month 6	—	—	+	+
Increased Lumbar Spine BMD at Month 12	+	+	+	+
Increased Total Hip BMD at Month 6	—	—	—	+
Increased Total Hip BMD at Month 12	—	—	—	+

+: statistically significant increase compared to placebo ($p < 0.05$ using Dunnett's procedure)

—: not statistically significantly different from placebo

BMD: bone mineral density

Source: Study A218-103; Tables 5.1.3, 5.1.4, 5.2.3, 5.2.4

In Phase 2 Study 218-102, 0.025 mg/d and 1.0 mg/d doses of lasofexifene were investigated (see Table 5). The changes in spine BMD for the 0.25 mg/d dose were significantly different from placebo from Month 6 through Month 24. The changes in total hip BMD, compared to

placebo, were significantly different at Months 6 and 24, but not at Month 12. The efficacy of the 1.0 mg/d dose did not appear to be better than that of the 0.25 mg/d dose.

Table 5 BMD Findings Compared to Placebo in Protocol 218-102

Endpoint	Lasofexifene Dose	
	0.25 mg	1.0 mg
Increased Lumbar Spine BMD at Month 6	+	+
Increased Lumbar Spine BMD at Month 12	+	+
Increased Lumbar Spine BMD at Month 24	+	+
Increased Total Hip BMD at Month 6	+	—
Increased Total Hip BMD at Month 12	—	+
Increased Total Hip BMD at Month 24	+	—

+: statistically significant increase compared to placebo ($p < 0.05$ using Dunnett's procedure)

—: not statistically significant different from placebo

BMD: bone mineral density

Source: Study A218-102; Tables 5.1.3, 5.1.4, 5.1.5, 5.2.3, 5.2.4, 5.2.5

Phase 3 Osteoporosis Prevention Trials (Studies A2181003 and A2181004). In the Phase 3 osteoporosis prevention program, 3 doses of lasofexifene (0.025 mg, 0.25 mg, and 0.5 mg) were studied. Among these 3 doses of lasofexifene, the 0.25 mg and 0.5 mg doses were found to be statistically superior to the 0.025 mg dose in regard to vertebral bone mineral density increases relative to placebo.

Phase 3 Osteoporosis Treatment Trial (Study A2181002-PEARL). In the single Phase 3 osteoporosis treatment study, only the 0.25 mg and 0.5 mg doses were investigated.

3 OBJECTIVES AND DESIGN OF PIVOTAL PHASE 3 TREATMENT TRIAL (STUDY A2181002 – PEARL)

3.1 Study Objectives and Overall Study Design and Assessments

Study Objectives

The primary objective of this study was to compare the risk of developing a new or worsening (radiographic) vertebral fracture in each of the 2 lasofexifene treatment groups (0.25 mg or 0.5 mg lasofexifene once daily) compared to that in the placebo treatment group within 3 years after the start of treatment with study drug. The principal secondary objectives were (1) to compare the incidence of multiple (radiographic) vertebral fractures between each dose of lasofexifene (0.25 mg and 0.5 mg) and placebo and (2) to compare the risk of clinical (symptomatic) vertebral fractures between each dose of lasofexifene (0.25 mg and 0.5 mg) and placebo through 3 years after the start of treatment.

Overall Study Design

This was a prospective, randomized, double-blind, multi-national study in postmenopausal women with osteoporosis (defined by low bone mineral density of the femoral neck or lumbar spine). The study was initially designed as a 3-year study, but in a protocol amendment the study was subsequently extended to 5 years with a prospectively defined 3-year interim analysis. Following consent, subjects entered a 6- to 8-week single-blind placebo and calcium/vitamin D screening/run-in period.

Treatment Groups. Following the screening period, eligible subjects were randomly assigned to 1 of 3 daily treatment groups: lasofoxifene 0.25 mg, lasofoxifene 0.5 mg, or matching placebo. Additionally, all subjects were provided with a daily supplement equivalent to approximately 1,000 mg calcium and 400-800 IU vitamin D.

Entry Criteria. Subjects entering the study were required to be ambulatory, outpatient women, 60-80 years of age (inclusive) who were at least 5 years postmenopausal. At screening, lumbar spine (L1-L4) or femoral neck bone mineral density had to be at least 2.5 standard deviations (SDs) below the mean for young adults (T-score \leq -2.5). A mammogram was required at screening or within the last 6 months that showed no evidence of cancer, or suspicion of cancer that warranted breast biopsy.

Efficacy Assessments

Principal Measures of Efficacy. Vertebral fractures were determined from X-rays of the lateral thoracic and lumbar spine (T4-L4) obtained at screening and at 1, 2, and 3 years in all subjects. Additionally, in subjects whose symptoms were suggestive of fracture, spine X-rays were taken at that time to aid in diagnosis. Clinical vertebral fractures were defined as radiographic fractures of the spine that were associated with symptoms of pain or discomfort that were volunteered by the subject. All vertebral X-ray films were centrally adjudicated for fracture assessment. All subjects were analyzed on an intent-to-treat (ITT) basis.

Secondary Measures of Efficacy (All Subjects). Bone mineral density of the hip and lumbar spine (L1-L4) were measured in all subjects pretreatment and at 1, 2, and 3 years by dual energy X-ray absorptiometry (DXA) using a Hologic or Lunar densitometer.

Secondary Measures of Efficacy (Subsets of Subjects). Additional BMD measurements at Month 3 and measurements of whole body bone mineral content (BMC) and forearm BMD at baseline and at Years 1, 2 and 3 were undertaken in a subset of subjects. Biochemical markers of bone turnover (C-telopeptide, procollagen type 1 N-propeptide, osteocalcin, and bone-specific alkaline phosphatase) also were evaluated from serum samples collected at pretreatment, and at Month 1, Month 3, Month 6, and Years 1, 2, and 3 in a subset of subjects.

Safety Assessments

Safety evaluations encompassed yearly physical examination and safety laboratory evaluations. Observed and spontaneously reported adverse events (AEs) were recorded at each visit. All subjects were required to have a gynecological examination at baseline and

Month 36. Cardiovascular events that were assessed for safety included venous thromboembolic events (VTEs), stroke events, major coronary events, and hospitalization for cardiovascular events. Independent endpoint classification committees were constituted for central adjudication of cardiovascular endpoints (including all deaths), breast cancer endpoints, and gynecological safety endpoints.

3.2 Schedule of Events

The general Schedule of Events for Study A2181002 is shown in Table 6.

Table 6 Schedule of Events for Study A2181002 (Primary Study) through Year 3

Procedure	S-2	S-1	B	M3	M6	M12	M18	M24	M30	M36 EOS
Informed consent	X									
Medical history	X									
DXA left hip and lumbar spine	X					X		X		X
Lateral spine X-rays		X				X		X		X
Stadiometer height measurement		X				X		X		X
Physical examination		X				X		X		X
Complete blood count, chemistry	X					X		X		X
TSH	X									
25-OH Vitamin D			X							
DNA sample (optional)			X							
Serum/plasma aliquot for storage			X			X+pk				X
Cardiogram (resting 12-lead)		X								
Mammogram		X (a)				X		X		X
Pelvic and breast examination		X				X		X		X
Health care resource utilization log			X	X	X	X	X	X	X	X
Dispense medication	X		X		X	X	X	X	X	
Concomitant meds and non-drug treatments			X	X	X	X	X	X	X	X
Adverse-event reporting			X	X	X	X	X	X	X	X
TVU (b)										

Definitions: S = screening (extends overall for 6-8 weeks); M = month; EOS = end of study; DXA = dual energy X-ray absorptiometry; TSH = Thyroid stimulating hormone; pk = pharmacokinetics; TVU = transvaginal ultrasound

(a) Mammogram at this point or within the past 6 months (with no evidence of cancer and/or need for biopsy)

(b) TVU was not required in the main study but could be performed at the discretion of the study gynecologist or if country regulatory agencies or local practices requested or required.

Source: Page 7216 of 7454, Study Report A2181002

In addition to the primary study in which all subjects participated, several sub-studies also were conducted within the main study. The Schedules of Events for these sub-studies are provided in Table 7.

Table 7 Schedules of Events for Sub-studies within Study A2181002

Procedure/Assessment	B	M1	M3	M6	M12	M24	M36
Bone Sub-study							
DXA lumbar spine, left hip	X		X		X	X	X
Whole body DXA and forearm	X				X	X	X
Bone Quality	X				X		X
Biochemical markers (bone turnover)	X	X	X	X	X	X	X
Cardiovascular Sub-study							
Lipid profile	X	X		X	X	X	X
Inflammation markers	X				X	X	
Coagulation markers	X				X	X	
Quality of Life Sub-study							
EQ-5D	X			X	X	X	X
Pain and limited activity days (a)	X		X	X	X	X	X
Breast Density Sub-study							
Breast density (initial mammogram at screening)	X				X	X	X
Gynecological Safety Sub-study							
Transvaginal Ultrasound							
Prevalence study group							X
Incidence study group	X				X	X	X

Definitions: B = baseline; M= month; DXA = dual energy X-ray absorptiometry; TVU = transvaginal Ultrasound; EQ-5D = Quality of life instrument

(a) This analysis is also done at Month 18 and Month 30 (not shown in table)

Source: Page 7217 of 7454, Study Report A2181002

3.3 Entry Criteria

3.3.1 Inclusion Criteria

The inclusion criteria for Study A2181002 included:

- Ambulatory, outpatient women, 60-80 years of age who are at least 5 years postmenopausal and have an estimated life expectancy of at least 5 years with a self-rated health status of good or excellent.
- Screening bone mineral density (BMD) of the femoral neck must have a T-score ≤ -2.5 and ≥ -4.5 **or** screening bone mineral density (BMD) of the lumbar spine (L1-L4) must have a T-score ≤ -2.5 and ≥ -4.5 .
- Mammogram performed at screening, or within the last 6 months that shows no evidence of cancer, or suspicion of cancer, warranting a breast biopsy.
- Safety laboratory results (biochemistry and hematology) within the pre-specified limits as defined by the Central Laboratory.
- Normal gynecological examination including Papanicolaou (Pap) smear (cervical cytology) test. Minor abnormalities in cervical cytology (e.g., minor atypia such as

atypical squamous cells of undetermined significance [ASCUS], or inflammation) will not be grounds for exclusion.

3.3.2 Exclusion Criteria

The exclusion criteria for Study A2181002 included:

- Prior bilateral hip fracture or bilateral hip prostheses.
- Subjects with a clinical diagnosis of new vertebral fracture within the past 12 months.
- Subjects who have more than 3 vertebral fractures on X-ray by site read.
- Subjects with femoral neck or lumbar spine (L1-L4) BMD more than 4.5 S.D. below the mean for young adults (T-score ≤ -4.5) based on site read.
- History of breast cancer or intraductal carcinoma in situ (DCIS).
- Any prior localized endometrial cancer or endometrial hyperplasia (with or without atypia) unless treated by total hysterectomy. If any simple or complex hyperplasia or endometrial cancer is found during screening, the subject must be excluded.
- Any vaginal bleeding or spotting in the past year prior to screening.
- Any past history of venous thromboembolic disease, including deep vein thrombosis (DVT), pulmonary embolism (PE) or retinal vein thrombosis (RVT).
- A history of spontaneous superficial thrombophlebitis within the 5 years prior to screening.
- Medical disease that may be associated with the development of metabolic bone disease.
- Stroke, transient ischemic attack (TIA), or myocardial infarction (MI) in the previous 6 months.
- Atrial fibrillation if requiring anticoagulation therapy.
- Estrogen, calcitonin, tibolone, or raloxifene (within the last 3 months).
- If used for greater than one month any time during the past 2 years: bisphosphonates, parathyroid hormone, or sodium fluoride
- Tamoxifen, levormeloxifene, idoxifene, droloxifene, or toremifene (at any time in the past).

3.4 Efficacy Endpoints and Statistical Analysis

3.4.1 Primary Efficacy Endpoint

The primary objective for Study A2181002 was to compare the risk of a new or worsening radiographic vertebral fracture between each dose of lasofoxifene (0.25 mg/d and 0.5 mg/d) and the placebo control group within the first 3 years after the start of treatment. Because subjects could have multiple fractures, the subject, rather than fractures, was the analysis unit for the primary endpoint (and the other bone fracture endpoints).

The primary efficacy endpoint (new or worsening vertebral fracture) was assessed by X-rays of the lateral thoracic and lumbar spine (T4-L4). X-rays were obtained at screening and at 1, 2, and 3 years in asymptomatic subjects. Additionally, in subjects whose symptoms were suggestive of fracture, spine X-rays were taken at the time that symptoms were reported to

aid in the diagnosis. The X-rays were centrally read by SYNARC at one of two sites (San Francisco or Hamburg, Germany). The central reading sites also determined the adequacy of the X-rays and requested new X-ray assessment of the spine if needed.

Semiquantitative analyses for vertebral fracture determination were performed using the methodology described by Genant by readers blinded to treatment assignment. For this analysis, vertebrae were graded as 0 for no fractures, 1 for mild fractures, 2 for moderate fractures, and 3 for severe fractures. A new or worsening radiographic fracture was defined as a change in the semiquantitative score of ≥ 1 . To meet the protocol-defined criteria for a fracture, a presumptive fracture identified by the semiquantitative procedure required confirmation by (1) an independent review (assessed as the presence or absence of a fracture) and (2) quantitative morphometric analysis.

To qualify as an incident fracture by quantitative morphometric analysis, a decrease in anterior, mid, or posterior vertebral height of at least 20% and at least 4 mm was required.

3.4.2 Principal Secondary Endpoints

The principal secondary objectives included:

- The risk of a clinical vertebral fracture after 1, 2, and 3 years
- The risk of multiple (radiographic) vertebral fractures after 1, 2, and 3 years

As with the primary efficacy objective, the secondary endpoints in each lasofoxifene treatment group (0.25 mg/d and 0.5 mg/d) were compared to the respective endpoints in the placebo treatment group.

3.4.3 Primary Statistical Analysis

The Applicant's primary analysis used a time-to-event approach. Each dose of lasofoxifene was tested against placebo using a log-rank test stratified for geographic region and prevalent vertebral fracture at baseline. Data were censored at the date of the last radiograph. Hochberg's procedure was used to control the overall Type I error rate of 5% for testing the 2 doses of lasofoxifene against placebo¹. The hazard ratio for each lasofoxifene dose versus placebo was calculated using a Cox Proportional Hazards model with treatment group as a covariate and with stratification on vertebral fracture at baseline and geographic region. Kaplan-Meier methods were used to calculate annual incidence.

The hazard ratios and log-rank test statistics used by the Applicant address the time to occurrence of a new fracture rather than the risk of a new fracture at a prespecified time point. To further evaluate the ability of lasofoxifene to prevent fractures, the Division requested the Applicant to estimate the incidence of fractures at 1 year, 2 years and 3 years for each dose of lasofoxifene and placebo, to calculate relative risks using these estimates,

¹ The Hochberg procedure stipulates that if the larger p-value is less than 0.05, then both comparisons of lasofoxifene with placebo are statistically significant at 0.05. If the larger p-value is greater than 0.05, but the smaller is less than 0.025, then only the comparison associated with the smaller p-value is statistically significant at 0.05. If the larger p-value is greater than 0.05 and the smaller p-value is greater than 0.025, then neither comparison is statistically significant at 0.05.

and to use Cochran-Mantel-Haenszel test statistics to compare the incidence rates between each dose of lasofoxifene and placebo.

4 FINDINGS FROM PIVOTAL PHASE 3 TREATMENT TRIAL (STUDY A2181002-PEARL)

4.1 Subject Enrollment and Disposition

A total of 8,556 postmenopausal women with osteoporosis were randomized to treatment with study drug (2,852 to each of the 3 treatment groups). The countries in which the largest numbers of subjects were enrolled were Argentina (n = 1,054), India (n = 896), Croatia (n = 692), and the U.S. (n = 626). Subject disposition is summarized in Table 8.

In each treatment group, approximately 92% of subjects remained in the study through Month 36, and approximately 81% of subjects in each group remained on-treatment through Month 36. All of the randomized and treated subjects were analyzed for adverse events, and approximately 96% of subjects were analyzed for the primary endpoint.

Table 8 Subject Disposition in Study A2181002

Subject Disposition	Lasofoxifene		Placebo N (%)
	0.25 mg N (%)	0.5 mg N (%)	
Randomized	2852	2852	2852
Treated	2852	2852	2852
Discontinued study prior to Month 36	215 (7.5)	230 (8.1)	235 (8.2)
Completed Month 36	2637 (92.5)	2622 (91.9)	2617 (91.8)
• On treatment	2314 (81.1)	2308 (80.9)	2342 (82.1)
• Off treatment	323 (11.3)	314 (11.0)	275 (9.6)
Analyzed for primary endpoint	2733 (95.8)	2746 (96.3)	2742 (96.1)
Analyzed for adverse events	2852 (100.0)	2852 (100.0)	2852 (100.0)
Laboratory data analyzed	2670 (93.6)	2660 (93.3)	2673 (93.7)

Source: Table 5; Page 117 of 7454; A2181002 Study Report; 5.3.5.1.1; NDA 22-242

4.2 Demographic Data.

The mean age in Study A2181002 was approximately 67 years in each treatment group. White subjects comprised the largest percentage of the study population (approximately 74%, (see Table 9). Body mass index was similar across treatment groups as was the percentage of subjects who had hysterectomies in the past (approximately 19%). Lasofoxifene and placebo treatment groups were comparable with respect to baseline mean lumbar spine BMD T-scores (approximately -3.0) and baseline mean femoral neck BMD T-scores (approximately -2.25). The percentage of subjects with pre-existing vertebral fractures across the lasofoxifene and placebo groups was similar (28%).

Table 9 Subject Demographics and Bone Assessments at Baseline in Study A2181002

Parameter	Lasofloxifene		Placebo N=2852* (100%)
	0.25 mg N=2852* (100%)	0.5 mg N=2852* (100%)	
Mean age (SD)	67.5 (5.2)	67.3 (5.2)	67.5 (5.2)
Age range in years	60-80	60-80	59-80
Race (n, %)			
• White	2111 (74.0)	2108 (73.9)	2118 (74.3)
• Black	26 (0.9)	29 (1.0)	27 (0.9)
• Asian	530 (18.6)	519 (18.2)	521 (18.3)
• Hispanic	138 (4.8)	144 (5.0)	141 (4.9)
• Other	47 (1.6)	52 (1.8)	45 (1.6)
Prior Hysterectomy (n, %)	552 (19.4)	551 (19.3)	543 (19.0)

Body Mass Index (BMI)			
• Mean BMI (SD)	25.2 (3.8)	25.4 (3.7)	25.4 (3.8)
• BMI range	13.3-47.0	12.2-42.4	13.7-55.4

Time Since Menopause at Baseline			
• Mean years (SD)	19.5 (7.2)	19.4 (7.1)	19.5 (7.2)
• Range in years	2.0-52.0	2.0-57.0	5.0-55.0

Bone Assessments at Baseline			
Lumbar Spine Bone Mineral Density			
• T-score mean (SD)	-3.024 (0.735)	-3.020 (0.712)	-3.007 (0.735)
Femoral Neck Bone Mineral Density			
• T-score mean (SD)	-2.289 (0.699)	-2.229 (0.693)	-2.247 (0.714)
Pre-existing Vertebral Fractures (Fx)			
• Subjects with Fx (n, %)	807 (28.3%)	808 (28.4%)	803 (28.2%)

* Some assessments were not available for every subject
Source: Page 118 of 7454, Study report A2181002

4.3 Efficacy Findings

4.3.1 Primary Efficacy Endpoint and Analysis

The results of the Applicant's primary efficacy analysis (time-to-event analysis) are shown in Table 10. Based on the analysis, there was a statistically significant reduction in the risk of developing a new or worsening radiographic vertebral fracture through each of Years 1, 2, and 3. The reduction was observed for treatment with either dose of lasofloxifene (0.25 mg/d and the proposed to-be-marketed dose of 0.5 mg/d) compared to treatment with placebo.

Table 10 New or Worsening Radiographic Vertebral Fracture (Study A2181002: Time-to-Event Analysis)

Parameter	Lasofloxifene		Placebo
	0.25 mg	0.5 mg	
Total number of subjects	2733	2746	2742
Total subject-years of follow-up	7776.5	7788.8	7663.6
Through Year 1			
Number (%) of subjects with event	29 (1.1)	28 (1.0)	60 (2.2)
Hazard ratio (vs. placebo)	0.48	0.45	
95% CI	(0.31,0.75)	(0.29,0.71)	
P-value	0.0009*	0.0004*	
Through Year 2			
Number (%) of subjects with event	73 (2.7)	60 (2.2)	125 (4.6)
Hazard ratio (vs. Placebo)	0.57	0.47	
95% CI	(0.43,0.76)	(0.34,0.64)	
P-value	0.0002*	<0.0001*	
Through Year 3			
Number (%) of subjects with event	129 (4.7%)	105 (3.8%)	176 (6.4%)
Hazard ratio (vs. Placebo)	0.69	0.58	
95% CI	(0.55,0.87)	(0.45,0.73)	
Stratified P-value	0.0018*	<0.0001*	
Unstratified P-value	0.0035*	<0.0001*	

* P-value statistically significant, Hochberg procedure with overall alpha = 0.05

CI = confidence interval

Hazard ratio based on Cox proportional hazards model with treatment as a covariate and stratified on geographic region and prevalent vertebral fracture

Unstratified p-value is based on log rank test for lasofloxifene compared to placebo on time to first new radiographic vertebral fracture

Source: Table 10; Page 37 of 147; Summary of Clinical Efficacy; 2.73; NDA 22-242

Division Comment

- *The actual reductions in numbers of subjects with a new or worsening radiographic vertebral fracture in the lasofloxifene 0.5 mg/d group compared to the placebo group were 32, 65, and 71 subjects at years 1, 2, and 3, respectively.*

The Applicant also provided an analysis of cumulative incidence (relative risk) for first new or worsening vertebral fracture for subjects treated with study drug. The results of this analysis are shown in Table 11. Based on this analysis, the relative risk of developing a new or worsening radiographic vertebral fracture through each of Year 1, 2, and 3 was statistically significant in favor of lasofloxifene treatment. The calculated cumulative relative risk of developing a new or worsening vertebral fracture was 0.46, 0.49, and 0.59 through Year 1, Year 2, and Year 3, respectively, for the 0.5 mg lasofloxifene dose.

Table 11 Cumulative Relative Risk of First New or Worsening Radiographic Vertebral Fracture (Study A2181002)

Parameter	Lasofloxifene		Placebo N = 2742
	0.25 mg N = 2733	0.5 mg N = 2746	
Through Year 1			
Number of subjects with event (%)	29 (1.1%)	28 (1.0%)	60 (2.2%)
Relative risk (95% CI)	0.49 (0.31, 0.75)	0.46 (0.29, 0.72)	
p-value vs. placebo	0.0010*	<0.0001*	
Through Year 2			
Number of subjects with event	73 (2.7%)	60 (2.2%)	125 (4.6%)
Relative risk (95% CI)	0.58 (0.44, 0.78)	0.49 (0.35, 0.64)	
p-value vs. placebo	<0.0001*	<0.0001*	
Through Year 3			
Number of subjects with event	129 (4.7%)	105 (3.8%)	176 (6.4%)
Relative risk (95% CI)	0.73 (0.59, 0.91)	0.59 (0.47, 0.75)	
p-value vs. placebo	0.0050*	<0.0001*	

* P-values significant

P-values are based on Cochran-Mantel-Haenszel test controlling for geographic region and prevalent vertebral fracture

Source = Applicant response to FDA information request of July 30, 2008

Division Comment

- *A statistically significant benefit of treatment with lasofloxifene 0.25 mg/d or lasofloxifene 0.5 mg/d compared to placebo, in terms of a reduction in first new or worsening vertebral fracture, was demonstrated by both statistical analyses (a time-to-event approach or cumulative relative risk).*

The Applicant also explored the efficacy of lasofloxifene in subjects with and without a pre-existing (prevalent) vertebral fracture at baseline. The following table (Table 12) provides this information for those subjects with and those without a prevalent vertebral fracture. Lasofloxifene treatment was shown to have a statistically significant benefit in both subgroups.

Table 12 New or Worsening Radiographic Vertebral Fracture through Year 3 in Subjects With or Without a Prevalent Fracture (Study A2181002: Time-to-Event Analysis)

Parameter	Lasofloxifene		Placebo
	0.25 mg	0.5 mg	
With Prevalent Vertebral Fracture at Baseline			
Number of subjects	778	778	773
Number (%) of subjects with event	67 (8.6)	47 (6.0)	87 (11.3)
Hazard ratio (vs. Placebo)	0.70	0.52	
95% CI	(0.51,0.97)	(0.36,0.74)	
P-value	0.0288*	0.0003*	
Without Prevalent Vertebral Fracture at Baseline			
Number of subjects	1955	1968	1969
Number (%) of subjects with event	62 (3.2)	58 (2.9)	89 (4.5)
Hazard ratio (vs. Placebo)	0.68	0.63	
95% CI	(0.49,0.95)	(0.45,0.88)	
P-value	0.0249*	0.0067*	

* P-value significant, Hochberg procedure with overall alpha = 0.05

Source: Page 122 of 7454, Study report A2181002

To meet the recently adopted European regulatory guidelines for the development of new drug products for the treatment of osteoporosis, the Applicant also analyzed the vertebral fracture data after excluding those subjects who had only a worsening fracture. The efficacy analysis based only on those subjects who developed a new fracture is shown in Table 13. Based on this analysis, there was a statistically significant reduction in the risk of developing a new radiographic vertebral fracture through each of Years 1, 2, and 3 in each of the lasofloxifene treatment groups.

Table 13 New Radiographic Vertebral Fractures (Study A2181002 -Time to Event Analysis)

Primary Endpoint	Lasofexifene		Placebo
	0.25 mg	0.5 mg	
Total number of subjects	2733	2746	2742
Total subject-years of follow-up	7778.4	7791.6	7670.5
Through 1 Year			
Number (%) of subjects with event	29 (1.1)	27 (1.0)	57 (2.1)
Hazard ratio (vs. placebo)	0.51	0.46	
95% CI	(0.32,0.79)	(0.29,0.73)	
P-value	0.0024*	0.0007*	
Through 2 Years			
Number (%) of subjects with event	72 (2.6)	59 (2.1)	121 (4.4)
Hazard ratio (vs. Placebo)	0.58	0.48	
95% CI	(0.43,0.78)	(0.35,0.65)	
P-value	0.0003*	<0.0001*	
Through 3 years			
Number (%) of subjects with event	124 (4.5%)	104 (3.8%)	172 (6.3%)
Hazard ratio (vs. Placebo)	0.68	0.58	
95% CI	(0.54,0.86)	(0.46,0.75)	
Stratified P-value **	0.0013*	0.0001*	
Unstratified P-value ***	0.0027*	0.0001*	

* P-value significant, Hochberg procedure with overall alpha = 0.05

CI = confidence interval

** Hazard ratio based on Cox proportional hazards model with treatment as a covariate and stratified on geographic region and prevalent vertebral fracture

*** Unstratified p-value is based on log rank test for lasofexifene compared to placebo on time to first new radiographic vertebral fracture

Source: Table 9; Page 123 of 7454; A2181002 Study Report; 5.3.5.1.1; NDA 22-242

Division Comment

- *There were few cases of worsening fracture compared to the number cases of new fractures, and the analyses with or without worsening fractures were both statistically significant compared to placebo. In the lasofexifene 0.25 mg/d, lasofexifene 0.5 mg/d, and placebo groups, the Applicant reported only 5, 1, and 4 subjects with a first worsening vertebral fracture, respectively.*

4.3.2 Principal Secondary Endpoints

The applicant also specified two principal secondary endpoints in the protocol for Study A2181002:

- Risk of clinical (symptomatic) vertebral fractures after 1, 2, and 3 years
- Risk of multiple (radiographic) vertebral fractures after 1, 2, and 3 years

The risk of clinical (symptomatic) vertebral fracture, by time-to-event analysis, was numerically reduced in both lasofexifene treatment groups compared to placebo, but the reductions were not statistically significant, as shown in Table 14.

Table 14 First *Clinical* Vertebral Fracture through Year 3 (Study A2181002: Time-to-Event Analysis)

Parameter	Lasofloxifene		Placebo
	0.25 mg	0.5 mg	
Number of subjects at risk	2850	2847	2848
Subject-years of follow-up	8181.0	8185.5	8136.4
Number (%) of subjects with event	41 (1.4)	33 (1.2)	49 (1.7)
Hazard ratio (vs. placebo)	0.83	0.66	
95% CI	(0.55,1.26)	(0.43,1.03)	
P-value	0.37685	0.06764	

* P-value significant, Hochberg procedure with overall alpha = 0.05

CI = confidence interval

Source: Table 13; Page 126 of 7454; A2181002 Study Report; 5.3.5.1.1; NDA 22-242

The frequency distribution of subjects with a single or multiple new or worsening radiographic vertebral fractures (the other principal secondary endpoint) was significantly shifted toward fewer fractures for both doses of lasofloxifene at Years 1, 2, and 3 (Table 15).

Table 15 Proportions of Subject with New or Worsening Single and Multiple Radiographic Vertebral Fractures (Study A2181002)

Parameter	Lasofloxifene		Placebo
	0.25 mg	0.5 mg	
Through 1 Year			
Subjects at risk	2733	2746	2742
No new fractures	2704 (98.9%)	2718 (99.0%)	2682 (97.8%)
1 New fracture	26 (1.0%)	26 (0.9%)	53 (1.9%)
>1 New fracture	3 (0.1%)	2 (0.1%)	7 (0.3%)
P-value	0.0010*	<0.0001*	
Through 2 Years			
Subjects at risk	2733	2746	2742
No new fractures	2660 (97.3%)	2686 (97.8%)	2617 (95.4%)
1 New fracture	62 (2.3%)	50 (1.8%)	106 (3.9%)
>1 New fracture	11 (0.4%)	10 (0.4%)	19 (0.7%)
P-value	<0.0001*	<0.0001*	
Through 3 Years			
Subjects at risk	2733	2746	2742
No new fractures	2604 (95.3%)	2641 (96.2%)	2566 (93.6%)
1 New fracture	111 (4.1%)	85 (3.1%)	147 (5.4%)
>1 New fracture	18 (0.7%)	20 (0.7%)	29 (1.1%)
P-value	0.0060*	<0.0001*	

P-values are based on Cochran-Mantel-Haenszel row means test

* P-value significant, Hochberg with overall alpha = 0.05

Source: Table 12; Page 41 of 147; Summary of Clinical Efficacy; 2.73; NDA 22-242

Division Comment

- *Although the analysis represented in Table 15 shows a statistical benefit for treatment with lasofloxifene, few subjects in any treatment group suffered more than one new fracture. Therefore, the treatment benefit for lasofloxifene is largely driven by its impact on the incidence of single fractures.*

4.3.3 Supportive Efficacy Findings (Changes in Bone Mineral Density [BMD] and Biomarkers of Bone Turnover)

4.3.3.1 Bone Mineral Density

At Month 36 in the BMD Sub-study, there were statistically significant increases in BMD at each anatomic site evaluated (lumbar spine, total hip, femoral neck, greater trochanter, intertrochanteric area, Ward's triangle, and forearm) and in whole body bone mineral content (BMC) for both lasofloxifene treatment groups compared to the placebo group (Table 16). Because Japanese subjects in the BMD Sub-study did not have whole body or forearm BMD measurements or duplicate baseline measurements for any parameter, the analysis plan specified that these subjects were to be removed from the BMD analyses for this Sub-study.

Table 16 Change from Baseline to Month 36 in Bone Mineral Density (BMD) or Whole Body Mineral Content (BMC) (LOCF) – (BMD Sub-study – Study A2181002)

Parameter	Lasofloxifene		Placebo
	0.25 mg	0.5 mg	
Lumbar Spine BMD			
N	254	253	253
LS Mean change	4.623	4.677	1.331
95% CI	(4.056, 5.190)	(4.109, 5.245)	(0.762, 1.899)
LS Mean diff v. placebo	3.293	3.346	
95% CI	(2.489, 4.096)	(2.542, 4.151)	
P-value versus placebo	<0.001*	<0.001*	
Total Hip BMD			
N	254	252	253
LS Mean change	1.742	2.527	- 0.516
95% CI	(1.292, 2.191)	(2.075, 2.78)	(-0.968, -0.065)
LS Mean diff v. placebo	2.258	3.043	
95% CI	(1.620, 2.896)	(2.403, 3.683)	
P-value versus placebo	<0.001*	<0.001*	
Femoral Neck BMD			
N	254	252	253
LS Mean change	1.871	2.465	- 0.826
95% CI	(1.309, 2.432)	(1.901, 3.029)	(-1.389, -0.263)
LS Mean diff v. placebo	2.696	3.291	
95% CI	(1.900, 3.492)	(2.493, 4.089)	
P-value versus placebo	<0.001*	<0.001*	
Greater Trochanter BMD			
N	254	252	253
LS Mean change	2.184	3.469	- 0.122
95% CI	(1.596, 2.772)	(2.879, 4.059)	(-0.711, 0.468)
LS Mean diff v. placebo	2.306	3.591	
95% CI	(1.473, 3.139)	(2.756, 4.426)	
P-value versus placebo	<0.001*	<0.001*	
Intertrochanteric Area BMD			
N	254	252	253
LS Mean change	1.439	2.059	- 0.578
95% CI	(0.952, 1.925)	(1.570, 2.548)	(-1.067, -0.089)
LS Mean diff v. placebo	2.016	2.637	
95% CI	(1.326, 2.707)	(1.943, 3.330)	
P-value versus placebo	0.001*	<0.001*	

Parameter	Lasofloxifene		Placebo
	0.25 mg	0.5 mg	
Ward's Triangle BMD			
N	254	252	253
LS Mean change	1.416	2.894	- 2.957
95% CI	(0.209,2.623)	(1.692, 4.106)	(-4.167, -1.749)
LS Mean diff v. placebo	4.374	5.951	
95% CI	(2.665, 6.092)	(4.138, 7.565)	
P-value versus placebo	0.001*	<0.001*	
Forearm BMD			
N	215	210	216
LS Mean change	-0.445	0.085	- 1.713
95% CI	(-0.884, -0.006)	(-0.360, 0.530)	(-2.151, -1.275)
LS Mean diff v. placebo	1.268	1.798	
95% CI	(0.647, 1.888)	(1.173, 2.423)	
P-value versus placebo	0.001*	0.001*	
Whole Body BMC			
N	239	233	242
LS Mean change	1.877	2.054	- 0.729
95% CI	(1.333, 2.421)	(1.503, 2.605)	(-1.269, -0.188)
LS Mean diff v. placebo	2.606	2.783	
95% CI	(1.839, 3.373)	(2.010, 3.555)	
P-value versus placebo	<0.001*	<0.001*	

CI = confidence interval; diff = difference; v= versus; BMD = bone mineral density; BMD units = g/cm squared
BMC = bone mineral content; LS = least squares

P-values and LS means are based on an analysis of covariance on percent change from baseline with treatment, geographical region and baseline value as covariates

*P-value significant, Hochberg procedure with overall alpha = 0.05

Source: Pages 130, 2285 and 2288 of 7454; A2181002 Study Report; 5.3.5.1.1; NDA 22-242

4.3.3.2 Biomarkers of Bone Turnover

Both doses of lasofloxifene reduced biomarkers of bone turnover at each time point in the BMD Sub-study. These markers included bone resorption markers (CTx), and bone formation markers (osteocalcin, procollagen type 1 N-terminal propeptide, and bone specific alkaline phosphatase). The percent changes from baseline to Month 36 for these biomarkers are summarized in Table 17.

Table 17 Percent Change from Baseline to Month 36 in Serum Bone Markers (LOCF) (BMD Sub-study – Study A2181002)

Parameter	Lasofoxifene		Placebo
	0.25 mg	0.5 mg	
C-Telopeptide (CTx)			
N	371	367	367
Median change	-29.57	-29.02	11.27
95% CI	(-33.73, -24.19)	(-33.85, -23.66)	(3.09, 16.17)
Median diff v. placebo	-40.84	-40.29	
95% CI	(-48.38, -33.30)	(-47.83, -32.75)	
P-value versus placebo	<0.0001*	<0.0001*	
Osteocalcin			
N	371	367	367
Median change	-44.28	-43.82	-12.44
95% CI	(-46.86, -41.15)	(-46.66, -41.20)	(-16.57, -9.69)
Median diff v. placebo	-31.84	-31.38	
95% CI	(-36.76, -26.92)	(-36.36, -26.41)	
P-value versus placebo	<0.0001*	<0.0001*	
Bone-Specific Alkaline Phosphatase			
N	370	367	367
Median change	-19.02	-17.36	5.73
95% CI	(-21.66, -16.57)	(-19.65, -13.64)	(2.44, 9.65)
Median diff v. placebo	-24.76	-23.09	
95% CI	(-29.37, -20.15)	(-27.71, -18.47)	
P-value versus placebo	<0.0001*	<0.0001*	
Procollagen Type 1 N-propeptide			
N	372	367	367
Median change	-32.46	-34.32	-0.23
95% CI	(-35.82, -28.33)	(-37.31, -29.93)	(-4.32, 3.90)
Median diff v. placebo	-32.23	-34.09	
95% CI	(-38.38, -26.08)	(-40.29, -27.88)	
P-value versus placebo	<0.0001*	<0.0001*	

All parameters are reported in pmol/L; LOCF = last observation carried forward; BMD = bone mineral density

*P-value significant, Hochberg procedure with overall alpha = 0.05

Source: Table 21; Page 132 of 7454; A2181002 Study Report; 5.3.5.1.1; NDA 22-242

4.3.4 Bone Biopsy Data

Bone biopsies were performed in the Applicant's osteoporosis prevention trials (A2181003 and A2181004). At selected centers, trans-iliac bone biopsies were obtained at Month 24 in subjects who volunteered for the procedure and signed a separate Informed Consent Form. Biopsy samples were analyzed by a central lab (Creighton University) to assess bone quality and histomorphometric parameters of bone turnover. Parameters derived from these assessments are provided in Table 18 and Table 19.

Table 18 Bone Biopsy Data at Month 24 (Study A2181003)

Parameter	Lasofloxifene			Placebo (n=10)
	0.025 mg/d (n=11)	0.25 mg/d (n=10)	0.5 mg/d (n=14)	
Mean bone volume (%)	19.3	26.3	24.7	20.5
Mean osteoid volume (%)	1.2	1.3	1.3	1.5
Mean osteoid thickness (um)	5.2	5.2	5.4	5.8
Mean trabecular separation (um)	701.5	634.1	607.1	692.4
Mean mineral apposition rate (um/d)	0.5	0.5	0.5	0.6
Means bone formation rate (total surface reference)	0.008	0.008	0.007	0.012
Mean bone formation rate (total volume reference)	0.102	0.110	0.092	0.173

Source: Section 11, Item 11, Tables 71-77 on pgs 682-688; A2181003 Study Report

Table 19 Bone Biopsy Data at Month 24 (Study A2181004)

Parameter	Lasofloxifene			Placebo (n=6)
	0.025 mg/d (n=5)	0.25 mg/d (n=6)	0.5 mg/d (n=9)	
Mean bone volume (%)	21.8	25.4	20.4	24.8
Mean osteoid volume (%)	0.5	0.7	0.8	1.0
Mean osteoid thickness (um)	4.4	5.1	4.9	5.8
Mean trabecular separation (um)	629.8	663.0	590.3	568.7
Mean mineral apposition rate (um/d)	0.5	0.5	0.5	0.5
Means bone formation rate (total surface reference)	0.010	0.010	0.005	0.010
Mean bone formation rate (total volume reference)	0.148	0.114	0.073	0.134

Source: Section 11, Item 11, Tables 71-77 on pgs 1634-1640; A2181004 Study Report

Division Comment

- *No pathological bone findings were identified in the bone biopsies in studies A2181003 and A2181004. There were no reports of osteomalacia, marrow dyscrasia, marrow fibrosis, or woven bone. Of the evaluable samples, all bone was of normal lamellar mineralization and osteoid. As expected, the rate of bone formation was slightly lower in the lasofloxifene groups compared to placebo.*

4.4 Summary of Efficacy

The Applicant found that treatment with both doses of lasofloxifene (0.25 mg and 0.5 mg) significantly reduced the risk of a radiographic vertebral fracture compared to treatment with placebo. In the pivotal Phase 3 Study A2181002, the cumulative relative risk, compared to placebo treatment, for developing a new or worsening radiographic vertebral fracture through Year 3 was 0.73 (95% CI: 0.59, 0.91) in the lasofloxifene 0.25 mg group and

0.59 (95% CI: 0.47, 0.75) in the lasofoxifene 0.5 mg group. The percentages of subjects developing a new or worsening radiographic vertebral fracture within 3-years of the start of treatment were 4.7%, 3.8%, and 6.4% in the lasofoxifene 0.25 mg, lasofoxifene 0.5 mg, and placebo groups, respectively. The benefit of lasofoxifene treatment was also observed (1) when only new vertebral fractures were considered and (2) in subjects whether or not they had a pre-existing (prevalent) vertebral fracture.

5 SAFETY FINDINGS

5.1 Overview of Safety Concerns with Selective Estrogen Receptor Modulators (SERMs)

Since the publication of the Women's Health Initiative (WHI) studies^{2,3} the risks and benefits of estrogen therapy in postmenopausal women have been subject to heightened scrutiny. Selective Estrogen Receptor Modulators (SERMs) are pharmacologic agents which exert their activity by binding to estrogen receptors in different tissues in the body. The pharmacologic effects of individual SERMs vary and are based on their relative agonistic and antagonistic effects in different tissues (e.g., bone vs. endometrium).

Clomiphene citrate was the first available SERM, approved in the U.S. in 1967 for the treatment of anovulatory infertility. Although used in a very different patient population, clomiphene is associated with visual disturbances including spots or flashes, cataracts, scotomata, and changes in retinal cell function. The visual symptoms appear to be dose related.

Tamoxifen was approved in 1977 and its approved indications include treatment of metastatic breast cancer, adjuvant treatment of breast cancer, and the reduction of breast cancer incidence in high risk women. Tamoxifen is known to have adverse endometrial effects including carcinoma, hyperplasia, and polyps, as well as producing an unusual endometrial appearance on ultrasound. The current U.S. labeling for Nolvadex (tamoxifen citrate) has a Boxed Warning about uterine malignancies (endometrial adenocarcinoma and uterine sarcoma), stroke, and pulmonary embolism. Tamoxifen also has associated ocular disturbances, including corneal changes, decrement in color vision perception, retinal vein thrombosis, retinopathy, and an increased incidence of cataracts.

Raloxifene is a SERM that was approved in 1997 for the prevention and treatment of osteoporosis in postmenopausal woman. The current U.S. labeling for Evista (raloxifene) has a Boxed Warning about the increased risk of venous thromboembolism and fatal stroke. The increased risk of fatal stroke occurred in a trial of postmenopausal women with documented coronary heart disease or at increased risk for major coronary events.⁴ There

² The Women's Health Initiative Steering Committee, Effects of Conjugated Equine Estrogen in Postmenopausal Women with Hysterectomy, *JAMA*, 291: 1701-12, 2004

³ Writing Group for the Women's Health Initiative Investigators, Risks and Benefits of Estrogen plus Progestin in Healthy Menopausal Women, *JAMA*, 288: 321-33, 2002

⁴ Barrett-Connor E, Mosca L, Collins P, Geiger MJ, Grady D, Kornitzer M, McNabb MA, Wenger NK for the Raloxifene Use for The Heart (RUTH) Trial Investigators. Effects of Raloxifene on Cardiovascular Events and Breast Cancer in Postmenopausal Women. *N Engl J Med* 2006;355:125-37.

have been reports of uterine polyps with raloxifene, but treatment with raloxifene does not appear to have the same risk of uterine cancer and endometrial hyperplasia as does treatment with tamoxifen.⁵

Toremifene citrate was approved in 1997 for the treatment of metastatic breast cancer in postmenopausal women with estrogen-receptor positive or unknown receptor status tumors. Endometrial hyperplasia has been reported with toremifene, and some patients developed endometrial cancer, but circumstances (short duration of treatment or prior antiestrogen treatment or premalignant conditions) have made it difficult to establish a causal relationship. Thromboembolic events and visual events also have been reported in clinical trials.

Fulvestrant is an injectable SERM that was approved in 2002 for the treatment of hormone-receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. Thromboembolic events and vaginal bleeding have been reported with fulvestrant.

In summary, potential safety concerns that have been identified with use of the currently marketed SERMs include:

- Cardiovascular safety concerns including fatal stroke
- Endometrial hyperplasia, uterine cancer, and polyps
- Venous thromboembolic events
- Ocular events including cataracts, corneal changes, and other disturbances in vision

The safety database for lasofoxifene was closely scrutinized for evidence of these adverse effects.

5.2 Overview of the Safety Database for Lasofoxifene

The lasofoxifene safety database includes data from 23 clinical pharmacology studies, 11 Phase 2 studies, and 6 Phase 3 studies. Safety data were examined from the Phase 2/3 lasofoxifene clinical studies, which investigated lasofoxifene daily doses ranging from 0.017 mg to 10 mg. The Phase 2/3 clinical studies included other indications for lasofoxifene that are not being considered for approval in this application. The indications studied in the Phase 3 clinical trials included treatment of osteoporosis (1 study), prevention of osteoporosis (3 studies), and treatment of vulvar vaginal atrophy (2 studies).

As of the cut off-date for the 4-month Safety Update (December 3, 2007), the overall Phase 2/3 clinical program included safety data from 14,958 subjects in lasofoxifene clinical trials (see Table 20). Of these, 10,257 subjects had received lasofoxifene. Of these latter subjects, 4,547 had received lasofoxifene 0.25 mg daily and 4,308 received lasofoxifene 0.5 mg daily. Total subject-years of lasofoxifene treatment were 14,625 years and 14,101 years for lasofoxifene 0.25 mg and 0.5 mg daily, respectively.

⁵ Martino S, Disch D, Dowsett SA, Keech CA, and Mershon JL. Safety assessment of raloxifene over eight years in a clinical trial setting. *Current Medical Research and Opinion* 2005; Vol 21, (9), 1441–1452.

Table 20 Safety Exposure in the Overall Lasofoxifene Phase 2/3 Clinical Program (December 3, 2007, Cutoff)

Parameter	Lasofoxifene			Placebo
	0.25 mg	0.5 mg	Pooled**	
Number of subjects	4,547	4,308	10,257	4,701
Subject-years	14,625	14,101	30,316	14,567

** Pooled lasofoxifene includes 0.017 mg, 0.025 mg, 0.05 mg, 0.15 mg, 0.25 mg, 0.4 mg, 0.5 mg, 1.0 mg, 2.5 mg, and 10.0 mg lasofoxifene dose groups

Source: Modified from 4-Month safety update; page 25 of 84; NDA 22-242

The study which provides the majority of the safety data in this application is Study A2181002 (PEARL). The Applicant submitted safety data for Study A2181002 in the original 3-Year Interim Study Report, the 4-Month Safety Update, and in a preliminary 5-year abbreviated report. Subject exposure in Study A2181002 based on the preliminary 5-year abbreviated report is summarized in Table 21.

Table 21 Safety Exposure in Study A2181002 (PEARL) through Year 5

Parameter	Lasofoxifene			Placebo
	0.25 mg	0.5 mg	Pooled	
Number of subjects	2,852	2,852	5,704	2,852
Subject-years	12,883	12,850	25,733	12,818

Source: Preliminary 5-year report, NDA 22-242, modified from Table 19, page 20 of 58

Adverse events in Study A2181002 were captured by the study investigators (verbatim adverse event terms). The Applicant then coded these verbatim adverse event terms to preferred terms (PTs) in a medical coding dictionary. The medical coding dictionary used in this application was the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA is a hierarchical medical coding dictionary that is organized as follows:

- System Organ Class (SOC)
 - High Level Group Term (HLGT)
 - High Level Term (HLT)
 - Preferred Term (PT)

5.3 Safety Findings from the Lasofoxifene Clinical Development Program

5.3.1 Deaths

There have been 237 deaths reported in the overall lasofoxifene Phase 2/3 clinical development program (this includes 5-year data from Study A2181002). In the pivotal Phase 3 osteoporosis treatment study (Study A2181002), 228 deaths were reported through the end of Year 5 (Study Day 1876). There were a total of 9 deaths reported in the 9 other Phase 2/3 studies (1 death in each study). No deaths were reported in the 23 Phase 1 studies. A listing of the number of deaths in the overall lasofoxifene Phase 2/3 clinical development

program by study and treatment group (i.e., lasofoxifene dose group or placebo) is provided in Table 22.

Table 22 Number of Deaths by Study and Treatment Group in the Lasofoxifene Phase 2/3 Clinical Development Program

Study	Lasofoxifene				Placebo
	0.025 mg	0.25 mg	0.5 mg	2.5 mg	
2181002 – PEARL	*	90	73	*	65
Other Phase 2/3 Studies	1	4	3	1	0

* = dose was not studied in the respective study

Division Comment

- *As shown in the preceding table, there were no deaths in any of the placebo-treated subjects in any study other than Study A2181002.*

As of the December 3, 2007, cutoff for the 4-month Safety-Update, 235 deaths had occurred in the lasofoxifene clinical development program (Table 23). Most of the deaths occurred in Study A2181002 (see Section 5.3.1.1).

Table 23 All Cause Mortality in Overall Phase 2/3 Clinical Program (Data from 4-Month Safety Update)

	Lasofoxifene			Placebo N=4,701 SYR=14,566.9
	0.25 mg N=4,549 SYR=14,625.3	0.5 mg N=4,308 SYR=14,101.1	Pooled* N=10,259 SYR=30,316.3	
Number (%) of subjects with event	93 (2.0)	75 (1.7)	170 (1.7)	65 (1.4)
Incidence rate/100 subject-years (95% CI)	0.64 (0.51, 0.78)	0.53 (0.42, 0.67)	0.56 (0.48, 0.65)	0.45 (0.34, 0.57)
Hazard ratio versus Placebo (95% CI)	1.29 (0.97, 1.72)			
P-value	0.0799			

N=number of subjects, SYR=subject-years at risk, and CI=confidence interval

* Pooled lasofoxifene includes 0.017 mg, 0.025 mg, 0.05 mg, 0.15 mg, 0.25 mg, 0.4 mg, 0.5 mg, 1.0 mg, 2.5 mg, and 10.0 mg lasofoxifene dose groups

Source: 4-Month safety update; page 25 of 84; NDA 22-242

Division Comment

- *The lasofoxifene pooled data includes data from studies of a shorter duration than that of Study A2181002.*

5.3.1.1 Mortality Data from Study A2181002 (PEARL)

The Applicant included only 3-year safety with the original submission of NDA 22-242. During the ongoing review of the NDA, the Applicant submitted preliminary 5-year safety data that included data relating to all-cause mortality in Study A2181002. As noted in the following 2 mortality tables (Table 24 showing 3-year data and Table 25 showing 5-year data), the hazard ratio for “all-cause mortality” in subjects treated with

lasofoxifene 0.25 mg/d, compared to that in subjects treated with placebo, has increased from 1.20 to 1.38, and the hazard ratio of 1.38 is statistically significant (p-value = 0.0489) when considering the 5-year data.

Table 24 Analysis of Time to All-Cause Mortality (Study A2181002: 3-Year Data)

Parameter	Lasofloxifene		Placebo N=2,852
	0.25 mg N= 2,852	0.5 mg N=2,852	
Subject-years at risk	8231.3	8238.4	8217.1
Number (%) with event	45 (1.6)	47 (1.6)	38 (1.3)
HR	1.20	1.22	
95% CI	(0.78, 1.85)	(0.80, 1.88)	
P-value	0.4067	0.3621	

CI = confidence interval; HR = hazard ratio

Source: 3-year final interim report - Study A2181002, NDA 22-242, Table 30 page 142 of 7454

Table 25 Analysis of Time to All-Cause Mortality (Study A2181002: 5-Year Data)

Parameter	Lasofloxifene			Placebo N=2,852
	0.25 mg N= 2,852	0.5 mg N=2,852	Pooled N=5,704	
Subject-years at risk	12883.4	12849.7	25733	12817.8
Number (%) with event	90 (3.2)	73 (2.6)	163 (2.9)	65 (2.3)
HR	1.38	1.12	1.25	
95% CI	(1.00, 1.89)	(0.80, 1.56)	(0.94, 1.66)	
P-value	0.0489	0.5109	0.1311	

CI = confidence interval; HR = hazard ratio

Source: 5-year preliminary report - Study A2181002, NDA 22-242, Table 19 page 20 of 58

Review of the Applicant’s adjudicated cause of death data indicated that neoplasms and non-coronary vascular causes were important contributors to this relative increase in the number of deaths in subjects in the 0.25 mg/d lasofoxifene treatment group in the 5-year data. (Section 5.3.1.3, Table 27).

5.3.1.2 Determination and Classification of Causes of Death

The cause of death for each subject in Study A2181002 was determined by the Applicant in two ways: (a) death was attributed to one or more causes by the Study Investigator using MedDRA preferred terms and (b) death was assigned to a single cause by the Cardiovascular Endpoint Classification Committee (CECC). This Committee had the following 11 prospectively specified categories to choose from to attribute the death to a single cause:

Coronary Death

1. Sudden death (no known non-atherosclerotic cause, and death was either un-witnessed or witnessed and immediate)
2. Fatal myocardial infarction (definite or probable MI within 28 days of death)

3. Fatal ischemic heart disease (ischemic symptoms within 72 hours of death in the absence of valvular disease or non-ischemic cardiomyopathy)
4. Death from revascularization procedure (revascularization procedure within 28 days of death)

Non-coronary Death

5. Stroke (hemorrhagic, ischemic, embolic, and unknown type)
6. Other vascular (Well's scoring of 6 or greater if suspicion of pulmonary embolus without objective evidence)
7. Cancer
8. Suicide
9. Homicide
10. Other traumatic death
11. Other

5.3.1.3 Adjudicated Causes of Death for Subjects in Phase 2/3 Clinical Program

Most of the deaths in the lasofoxifene clinical program occurred in the pivotal osteoporosis treatment study (Study A2181002). The mean age in this study was approximately 67 years. The distribution of the adjudicated single causes of death in the study is presented separately by 3-year data (see Table 26) and 5-year data (see Table 27).

**Table 26 Causes of Death by External Endpoint Adjudication Committee
(Study A2181002: 3-Year Data)**

CAUSE of DEATH	Number (%) of Subjects		
	Lasofexifene		Placebo
	0.25 mg (n=2,852)	0.5 mg (n=2,852)	(n=2,852)
Coronary deaths	7 (0.2)	7 (0.2)	10 (0.4)
• Sudden death	5 (0.2)	4 (0.1)	8 (0.3)
• Fatal myocardial infarction	1 (<0.1)	2 (0.1)	1 (<0.1)
• Fatal ischemic heart disease	1 (<0.1)	1 (<0.1)	0 (0.0)
• Death from revascularization procedure	0 (0.0)	0 (0.0)	1 (<0.1)
Non-coronary deaths	38 (1.3)	40 (1.4)	28 (1.0)
Vascular	8 (0.3)	6 (0.2)	5 (0.2)
• Stroke	4 (0.1)	5 (0.2)	3 (0.1)
• Other vascular death	4 (0.1)	1 (<0.1)	2 (0.1)
Non-vascular	30 (1.1)	34 (1.2)	23 (0.8)
• Cancer	20 (0.7)	17 (0.6)	13 (0.5)
• Suicide	0 (0.0)	0 (0.0)	0 (0.0)
• Other traumatic death	2 (0.1)	3 (0.1)	1 (<0.1)
• Other	8 (0.3)	14 (0.5)	9 (0.3)
Total Deaths	45 (1.6)	47 (1.6)	38 (1.3)

Source: 3-Year Interim Report; Study A2181002-PEARL; page 146 of 7454

Division Comment

- *Two deaths were confirmed by autopsy results to be related to pulmonary emboli through 3 years of treatment.*

**Table 27 Causes of Death by External Endpoint Adjudication Committee
(Study A2181002: 5-Year Data)**

CAUSE of DEATH	Number (%) of Subjects		
	Lasofexifene		Placebo
	0.25 mg (n=2,852)	0.5 mg (n=2,852)	
Coronary deaths	18 (0.6)	18 (0.6)	21 (0.7)
• Sudden death	13 (0.5)	12 (0.4)	15 (0.5)
• Fatal myocardial infarction	3 (0.1)	3 (0.1)	3 (0.1)
• Fatal ischemic heart disease	2 (0.1)	3 (0.1)	1 (0.0)
• Death from revascularization procedure	0 (0.0)	0 (0.0)	2 (0.1)
Non-coronary deaths	72 (2.5)	55 (1.9)	44 (1.5)
Vascular	18 (0.6)	9 (0.3)	7 (0.2)
• Stroke	12 (0.4)	7 (0.2)	5 (0.2)
• Other vascular death	6 (0.2)	2 (0.1)	2 (0.1)
Nonvascular	54 (1.9)	46 (1.6)	37 (1.3)
• Cancer	34 (1.2)	25 (0.9)	20 (0.7)
• Suicide	0 (0.0)	1 (0.0)	0 (0.0)
• Other traumatic death	2 (0.0)	3 (0.1)	4 (0.1)
• Other	18 (0.6)	17 (0.6)	13 (0.5)
Total Deaths	90 (3.2)	73 (2.6)	65 (2.3)

*Reported through study day 1876 (365 x 5 = 1825)

Source: Preliminary 5-year report, NDA 22-242, Table 23 page 25 of 58

Division Comment

- *Noteworthy in the preceding table are the percentages of subjects in the lasofexifene 0.25 mg/d group whose deaths were attributed to non-coronary events (i.e., stroke and cancer).*

The Cardiovascular Endpoint Classification Committee also adjudicated the 9 deaths that occurred in the other clinical studies (non-PEARL studies). The adjudication results were as follows:

- Lasofexifene 0.025 mg – 1 subject (other traumatic death)
- Lasofexifene 0.25 mg – 4 subjects (1 sudden death, 1 traumatic death, 2 other)
- Lasofexifene 0.5 mg – 3 subjects (2 sudden death, 1 suicide)
- Lasofexifene 2.5 mg – 1 subject (sudden death)

5.3.1.4 Subjects with Cancer Who Died in Study A2181002

The following table (Table 28) lists the types and numbers of neoplasms reported in subjects whose deaths were attributed to cancer.

**Table 28 Types of Cancers and Numbers of Subjects with Cancer Who Died
(Study A2181002: 5-Year Data)**

Type of Cancer (n)	Lasofloxifene		Placebo
	0.25 mg	0.5 mg	
Abdominal	0	0	1
Bile Duct/Gallbladder	1	2	2
Bladder	0	1	0
Brain	4	1	1
Colorectal	5	3	2
Endometrial/Ovarian	0	0	1
Esophageal	3	0	0
Gastric	4	0	1
Leiomyosarcoma (thigh)	1	0	0
Leukemia	2	1	1
Liver	0	1	0
Lung	4	7	2
Lymphoma	1	1	1
Melanoma	2	1	1
Mesothelioma	0	1	0
Oral	0	0	1
Ovarian	0	0	2
Pancreatic	3	2	4
Peritoneal	1	0	0
Renal	1	1	0
Thyroid	0	1	0
Unknown	2	2	0
All Types	34	25	20

Source: Preliminary 5-year report, NDA 22-242, Table 24 page 26 of 58

Division Comments

- *Although some tumor types were found more commonly in the lasofloxifene treatment groups, the numbers of these specific types were small overall and do not appear to focus on any one organ system. The largest numeric differences between the lasofloxifene groups combined and the placebo group were observed for cancers of the brain (5 vs. 1), colon/rectum (8 vs. 2), and lung (11 vs. 2).*
- *Theoretically, a subject with cancer could be at greater risk for a thromboembolic event.*
- ***In summary**, there were numerically more deaths in the lasofloxifene-treated subjects compared to the placebo treated subjects, particularly through Year 5. The excess deaths are primarily in the cancer and non-coronary vascular categories. The number of deaths in the 0.25 mg lasofloxifene group exceeds those in the 0.5 mg group (90 vs. 73). The higher proportion of deaths in the 0.25 mg/d lasofloxifene group was statistically significant ($p = 0.0489$) compared to that in the placebo group, based on 5-year data from Study A2181002. The excess number of cancer-related deaths in the lasofloxifene-*

treated subjects does not appear to be focused on any specific organ system. Slightly more deaths were reported for brain, lung, and gastrointestinal systems in lasofoxifene-treated subjects.

Issues for Consideration

- **The Committee is asked to consider the finding of increased all-cause mortality in the lasofoxifene-treated subjects compared to placebo-treated subjects and the impact of this finding on the overall risk/benefit profile of lasofoxifene for the proposed indication. The Committee is also asked to assess the numerical increase in the adjudicated cases of cancer and non-coronary deaths in the lasofoxifene-treated subjects.**

5.3.2 Serious Adverse Events (Overall)

For subjects treated with lasofoxifene, there was a small numeric increase in reported serious adverse events (SAEs) compared to subjects treated with placebo in the 3-year interim analysis for Study A2181002 (Table 29).

Table 29 Summary of All-Causality Serious Adverse Events in Study A2181002 (3-Year Data)

3-Year Interim Analysis	Lasofoxifene		Placebo
	0.25 mg	0.5 mg	
Total SAEs			
Number of Subjects	2852	2852	2852
Number (%) of Subjects with SAEs	630 (22.1%)	617 (21.6%)	577 (20.2%)
Number of SAEs (Preferred Terms) Reported	1073	1044	986

SAE = Serious Adverse Event

Source: A2181002 Study Report, Table 34, page 148 of 7454, which includes data through the first 3 years of the PEARL study

During review of the NDA, the Applicant submitted preliminary 5-year data from Study A2181002 (Table 30). The analysis provided by the Applicant continued to show slightly more SAEs in subjects randomized to lasofoxifene treatment as compared to placebo treatment, particularly for SAEs classified as “treatment-related.”

Table 30 Summary of Serious Adverse Events in Study A2181002 (5-Year Preliminary Data)

	Lasofoxifene	Lasofoxifene	Placebo
	0.25 mg	0.5 mg	
Number of Subjects	2849	2852	2851
All Causality SAE			
Number (%) of Subjects with SAE	867 (30.4)	815 (28.6)	794 (27.8)
Number of SAEs (Preferred Terms) Reported	1608	1500	1506
Treatment-related SAE			
Number (%) of Subjects	208 (7.3)	167 (5.9)	95 (3.3)
Number of SAEs (Preferred Terms) Reported	253	200	106

SAE = Serious Adverse Event

Source: A2181002 Preliminary Study Report, Table 26, page 31 of 58, which includes preliminary 5-year data

Division Comment

- *Although the Applicant divides adverse events (AEs) into “all-causality” and “treatment-related,” the Division has historically focused on all AEs, without limitation to those the Applicant considers treatment-related. In a properly randomized trial, confounding factors that might affect the frequency of AEs unrelated to treatment should be balanced across treatment groups.*

For the 5-year preliminary data for Study A2181002, the most frequently reported all-causality SAEs for any treatment group were falls and osteoarthritis. All-causality SAEs with ≥ 10 events in any group that occurred more frequently in either lasofoxifene treatment group compared to placebo are summarized in Table 31. The most common SAEs in this selected listing were cataract, osteoarthritis, cholelithiasis, uterine polyp, endometrial hypertrophy, atrial fibrillation, and deep vein thrombosis.

**Table 31 Selected Listing of the Most Common All-Causality Serious Adverse Events (SAEs)
(Study A2181002, 5-Year Preliminary Data)**

Serious Adverse Event	Number of Subjects (%)		
	Lasofoxifene		Placebo N = 2851
	0.25 mg N = 2849	0.5 mg N = 2852	
Cardiac Disorders			
Atrial fibrillation	21 (0.7)	23 (0.8)	19 (0.7)
Cardiac failure congestive	13 (0.5)	6 (0.2)	9 (0.3)
Eye Disorders			
Cataract	35 (1.2)	39 (1.4)	33 (1.2)
Gastrointestinal disorders			
Inguinal hernia	5 (0.2)	10 (0.4)	3 (0.1)
General disorders and administrative site conditions			
Chest pain	8 (0.3)	15 (0.5)	11 (0.4)
Hepatobiliary Disorders			
Cholecystitis	7 (0.2)	11 (0.4)	9 (0.3)
Cholelithiasis	42 (1.5)	34 (1.2)	29 (1.0)
Infections and Infestations			
Bronchitis	7 (0.2)	10 (0.4)	6 (0.2)
Urinary tract infection	14 (0.5)	13 (0.5)	8 (0.3)
Injury, Poisoning and Procedural Complications			
Radius fracture	4 (0.1)	10 (0.4)	5 (0.2)
Musculoskeletal and Connective Tissue Disorders			
Osteoarthritis	45 (1.6)	39 (1.4)	37 (1.3)
Nervous System Disorders			
Syncope	8 (0.3)	11 (0.4)	4 (0.1)
Transient ischemic attack	15 (0.5)	9 (0.3)	12 (0.4)
Reproductive System			
Cystocele	12 (0.4)	13 (0.5)	9 (0.3)
Endometrial hypertrophy	21 (0.7)	24 (0.8)	4 (0.1)
Uterine polyp	33 (1.2)	25 (0.9)	12 (0.4)
Uterine prolapse	16 (0.6)	14 (0.5)	6 (0.2)
Respiratory, Thoracic and Mediastinal Disorders			
Chronic obstructive pulmonary disease	13 (0.5)	11 (0.4)	8 (0.3)
Pulmonary embolism	18 (0.6)	9 (0.3)	4 (0.1)
Vascular disorders			
Deep vein thrombosis	29 (1.0)	20 (0.7)	8 (0.3)

SAE = serious adverse event

* Events were selected if there were 10 or more events in any treatment group and more events in either lasofoxifene dose group than the placebo group

Source: Pearl 5 Year Preliminary Report, Table 27, page 32 of 58, which includes preliminary 5-year data

Division Comments

- *From the preceding table, it appears that percentages of subjects with cataracts are similar across the treatment arms.*

- *There were small numeric increases in the percentages of subjects with cholelithiasis in the lasofoxifene-treatment group, but there were no differences in the percentages of subjects with cholecystitis across the treatment arms.*
- *There was an increase in the percentages of subjects reporting the gynecologic adverse events of endometrial hypertrophy, uterine polyp, and uterine prolapse in the lasofoxifene-treatment groups. These are discussed in detail in Section 5.4.4 of this document.*
- *The percentages of subjects reporting pulmonary emboli and deep vein thromboses were increased in the lasofoxifene-treated subjects. These serious adverse events are discussed in detail in Section 5.4.1 of this document.*

Review of the SAEs from the overall lasofoxifene Phase 2/3 Clinical Program showed similar results. In the overall Phase 2/3 Clinical Program (in an analysis that included data only for Years 1-3 for Study A2181002), SAEs were more commonly reported for the 0.25 mg and 0.5 mg lasofoxifene-treated subjects, most notably for events classified as treatment-related (Table 32).

Table 32 Summary of Serious Adverse Events in Overall Phase 2/3 Clinical Program (Includes Data through Year 3 for Study A2181002)

	Number (%) of Subjects Who Experienced at Least 1 SAE			
	Lasofoxifene			Placebo N=4,676
	0.25 mg N=4,523	0.5 mg N=4,308	Pooled* N=10,233	
All Causality	728 (16.1)	697 (16.2)	1,501 (14.7)	657 (14.1)
Treatment-Related	181 (4.0)	145 (3.4)	340 (3.3)	108 (2.3)

*Pooled lasofoxifene includes 0.017 mg, 0.025 mg, 0.05 mg, 0.15 mg, 0.25 mg, 0.4 mg, 0.5 mg, 1.0 mg, 2.5 mg, and 10.0 mg lasofoxifene dose groups.

Source: Section 2.7.4 Summary of Clinical Safety, Table 35, page 58 of 112, which includes data only through the first 3 years of Study A2181002

In the overall Phase 2/3 Clinical Program, reported SAEs most frequently involved injuries (including fractures and falls) and cardiac events. All causality SAEs that were more frequently reported in the lasofoxifene group, as compared to the placebo group, included deep vein thrombosis (0.4% pooled lasofoxifene vs. 0.1% placebo), uterine polyps (0.4% pooled lasofoxifene vs. 0.2% placebo), and uterine hypertrophy (0.4% pooled lasofoxifene vs. 0.1% placebo).

5.3.3 Discontinuations Due to Adverse Events

In the lasofoxifene clinical development program, discontinuations from treatment with study drug and from the study entirely were recorded. For all studies except Study A2181002 (PEARL), a subject who permanently discontinued treatment also discontinued from the study. In Study A2181002, subjects who discontinued treatment were to remain in the study and continue to be monitored unless they withdrew consent.

In the first 3 years of Study A2181002, 256 subjects (9.0%) randomized to lasofoxifene 0.25 mg discontinued treatment because of an adverse event. Among the lasofoxifene 0.5 mg and placebo groups, 268 subjects (9.4%) and 211 subjects (7.4%), respectively,

discontinued treatment prematurely because of an adverse event. The most frequently reported AEs resulting in discontinuation from lasofoxifene treatment were muscle spasms and hot flushes. Muscle spasms were reported in 0.4% of subjects receiving lasofoxifene 0.25 mg, 0.8% receiving lasofoxifene 0.5 mg, and 0.3% receiving placebo who discontinued treatment. Hot flushes associated with premature discontinuation of treatment occurred more frequently in both lasofoxifene dose groups (1.0% of subjects in each group) compared with the placebo group (0.4% of subjects).

According to the preliminary 5-year data from Study A2181002, discontinuation of study drug due to an adverse event occurred in 396 (13.9%), 367 (12.9%) and 350 (12.3%) subjects in the lasofoxifene 0.25 mg, lasofoxifene 0.5 mg, and placebo groups, respectively. The most frequently reported adverse events that led to discontinuation of lasofoxifene treatment were hot flushes, deep vein thrombosis, and muscle spasms. The incidence of hot flushes leading to study drug discontinuation was similar in both lasofoxifene dose groups (each at 1.1% of subjects) compared with 0.4% of subjects in the placebo group. The incidence of deep venous thrombosis (DVT) leading to study drug discontinuation was 0.9% and 0.7% for lasofoxifene 0.25 mg and 0.5 mg, respectively, compared with 0.2% in the placebo group. Muscle spasms leading to discontinuation of treatment were reported most frequently among subjects in the lasofoxifene 0.5 mg group (0.9%), with only 0.5% of subjects randomized to lasofoxifene 0.25 mg or placebo reporting muscle spasms leading to study drug discontinuation. (The collective term “muscle spasm” included events related to extremity contracture, limb discomfort, pain in extremity, or muscle spasm.)

In the overall lasofoxifene Phase 2/3 Clinical Program (including data only through Year 3 for Study A2181002), the percentages of subjects discontinuing treatment were similar across treatment groups (Table 33). However, treatment discontinuations due to adverse events related to study drug were numerically slightly more common in the lasofoxifene treatment groups. The most common reasons for discontinuation from treatment in the pooled lasofoxifene treatment group were adverse events (all causality), followed by the categories “other” and “subject defaulted.” The “other” category included subjects who discontinued from treatment because they did not meet entrance criteria, had violated the protocol, or discontinued for other unspecified reasons. The “subject defaulted” category included subjects who withdrew consent for the study or were lost to follow-up or not willing to participate.

In the overall Phase 2/3 Clinical Program, a total of 606 subjects (5.9%) of subjects receiving lasofoxifene at any dose experienced adverse events considered related to study drug that led to discontinuation from treatment, as compared with 199 subjects (4.3%) receiving placebo (Table 33). Investigators categorized discontinuations as “related” or “not related” to study drug. A slightly higher percentage of subjects in the placebo group discontinued treatment for reasons not related to study drug (15.4% vs. 14.2% in the pooled lasofoxifene group). The placebo group also had a slightly higher percentage of subjects who discontinued treatment for reasons classified as “other” that were not related to study drug (6.5% of placebo subjects vs. 5.6% lasofoxifene subjects).

The specific treatment-related adverse events resulting in permanent discontinuation of study medication were reviewed. In the lasofoxifene 0.5 mg group, the most common adverse events resulting in discontinuation were hot flushes (1.6% of subjects in the lasofoxifene 0.5 mg group compared to 0.6% placebo-treated subjects) and leg cramps (0.8% of subjects in the lasofoxifene 0.5 mg group compared to 0.2% of placebo-treated subjects).

Table 33 Reasons for Discontinuation from Treatment in Overall Phase 2/3 Clinical Program (Includes Data through Year 3 for Study A2181002)

Reason for Discontinuation	Number (%) of Subjects			
	Lasofoxifene			Placebo N=4,676
	0.25 mg N=4,523	0.5 mg N=4,308	Pooled† N=10,233	
Subject Died**	23 (0.5)	23 (0.5)	47 (0.5)	25 (0.5)
Related to Study Drug*	257 (5.7)	234 (5.4)	606 (5.9)	199 (4.3)
• Adverse Event	254 (5.6)	234 (5.4)	600 (5.9)	199 (4.3)
• Laboratory Abnormality	3 (0.1)	0 (0.0)	6 (0.1)	0 (0.0)
Not related to Study Drug*	627 (13.9)	606 (14.1)	1,488 (14.2)	719 (15.4)
• Adverse Event	161 (3.6)	153 (3.6)	353 (3.4)	162 (3.5)
• Laboratory Abnormality	0 (0.0)	1 (< 0.1)	1 (< 0.1)	3 (0.1)
• Other	264 (5.8)	266 (6.2)	572 (5.6)	303 (6.5)
• Subject defaulted	202 (4.5)	186 (4.3)	522 (5.1)	251 (5.4)
Total	907 (20.1)	863 (20.0)	2,101 (20.5)	943 (20.2)

† Pooled lasofoxifene includes 0.017 mg, 0.025 mg, 0.05 mg, 0.15 mg, 0.25 mg, 0.4 mg, 0.5 mg, 1.0 mg, 2.5 mg, and 10.0 mg lasofoxifene dose groups

* As assessed by the clinical investigator

** Death occurring while still on therapy

Source: Clinical Safety Summary, Table 43, page 66 of 112, which includes data through the first 3 years of Study A2181002

Division Comment

- *In conclusion, when the discontinuations from the Phase 2/3 osteoporosis studies (which included data only through Year 3 of Study A2181002) were reviewed, the overall percentages of subjects who discontinued treatment prematurely were similar in the pooled lasofoxifene and placebo groups. Numerically more subjects in the pooled lasofoxifene group discontinued due to adverse events considered to be related to study medication. In the lasofoxifene 0.5 mg group, the most common adverse events resulting in premature discontinuation were hot flushes and leg cramps.*

5.3.4 Common Adverse Events (AEs)

A total of 10,233 subjects received lasofoxifene in the overall Phase 2/3 Clinical Program. As of the first 3 years of pivotal Study A2181002, 9,282 subjects (90.7%) reported all-causality adverse events as compared to 4,129 subjects (88.3%) randomized to placebo (see Table 34). Most AEs were mild or moderate in severity. A similar number of subjects in both treatment groups (lasofoxifene and placebo) reported severe all-causality AEs; however,

more subjects receiving lasofoxifene reported severe AEs considered treatment-related by the Applicant (5.3% of subjects receiving lasofoxifene and 3.5% of subjects receiving placebo).

Table 34 Summary of Adverse Events in Overall Phase 2/3 Clinical Program (Includes Data through Year 3 for Study A2181002)

	Number (%) of Subjects			
	Lasofoxifene			Placebo N=4,676
	0.25 mg N=4,523	0.5 mg N=4,308	Pooled† N=10,233	
All-Causality				
• Subjects with AEs	4,139 (91.5)	3,897 (90.5)	9,282 (90.7)	4,129 (88.3)
• Subjects with severe AEs	879 (19.4)	802 (18.6)	1,899 (18.6)	839 (17.9)
Treatment-Related				
• Subjects with AEs	2186 (48.3)	2,068 (48.0)	5,078 (49.6)	1,774 (37.9)
• Subjects with severe AEs	233 (5.2)	215 (5.0)	547 (5.3)	165 (3.5)

† Pooled lasofoxifene includes 0.017 mg, 0.025 mg, 0.05 mg, 0.15 mg, 0.25 mg, 0.4 mg, 0.5 mg, 1.0 mg, 2.5 mg, and 10.0 mg lasofoxifene dose groups

Source: Clinical Safety Summary, Table 20, page 40 of 112, which includes data through the first 3 years of Study A2181002

The most commonly reported all-causality AEs for subjects treated with lasofoxifene 0.25 mg or 0.5 mg that occurred more frequently in the lasofoxifene group, compared to the placebo group, were muscle spasms, hot flushes, and vaginal discharge (see Table 35).

Table 35 All-Causality Adverse Events Reported in ≥ 5% of Subjects in Any Treatment Group in Overall Phase 2/3 Clinical Program (Includes Data through Year 3 for Study A2181002)

System Organ Class • Preferred Term	Number (%) of Subjects			Placebo N=4,676
	0.25 mg N=4,523	0.5 mg N=4,308	Pooled† N=10,233	
Gastrointestinal Disorders				
• Constipation	299 (6.6)	309 (7.2)	704 (6.9)	291 (6.2)
General Disorders and Administration Site Conditions				
• Therapeutic response unexpected*	367 (8.1)	356 (8.3)	832 (8.1)	302 (6.5)
Infections and Infestations				
• Influenza	288 (6.4)	292 (6.8)	653 (6.4)	312 (6.7)
• Nasopharyngitis	388 (8.6)	372 (8.6)	858 (8.4)	358 (7.7)
• Upper respiratory tract infection	386 (8.5)	353 (8.2)	865 (8.5)	423 (9.0)
• Urinary tract infection	334 (7.4)	315 (7.3)	737 (7.2)	337 (7.2)
Musculoskeletal and Connective Tissue Disorders				
• Back pain	657 (14.5)	670 (15.6)	1431 (14.0)	745 (15.9)
• Muscle spasms	630 (13.9)	633 (14.7)	1411 (13.8)	322 (6.9)
• Osteoarthritis	234 (5.2)	233 (5.4)	490 (4.8)	264 (5.6)
• Pain in extremity	348 (7.7)	377 (8.8)	811 (7.9)	391 (8.4)
Nervous System Disorders				
• Dizziness	233 (5.2)	208 (4.8)	489 (4.8)	245 (5.2)
• Headache	240 (5.3)	234 (5.4)	565 (5.5)	338 (7.2)
Reproductive System and Breast Disorders				
• Vaginal discharge	286 (6.3)	250 (5.8)	648 (6.3)	124 (2.7)
Vascular Disorders				
• Hot flush	680 (15.0)	627 (14.6)	1601 (15.6)	297 (6.4)
• Hypertension	398 (8.8)	401 (9.3)	836 (8.2)	479 (10.2)

† Pooled lasofoxifene includes 0.017 mg, 0.025 mg, 0.05 mg, 0.15 mg, 0.25 mg, 0.4 mg, 0.5 mg, 1.0 mg, 2.5 mg, and 10.0 mg lasofoxifene dose groups

* Therapeutic response unexpected refers to positive effects of therapy, such as an improvement in back pain, hot flushes, or vaginal lubrication

Source: Clinical Safety Summary, Table 21, page 41 of 112, which includes data through the first 3 years of the PEARL study

Division Comments

- *In summary, in an analysis of the overall Phase 2/3 Clinical Program (which included only the first 3 years of data from Study A2181002), the most commonly reported all-causality AEs for subjects treated with lasofoxifene 0.25 mg or 0.5 mg (and which occurred more frequently in the lasofoxifene group compared to the placebo group) were muscle spasms, hot flushes, and vaginal discharge. These common adverse events were mostly mild or moderate in severity.*
- *In Study A2181002, the most commonly reported adverse events were very similar to those seen in the overall lasofoxifene Phase 2/3 Clinical Program. The most common*

all-causality AEs associated with lasofoxifene treatment were muscle spasms, hot flushes, endometrial hypertrophy, and vaginal discharge.

5.3.4.1 Leg Cramps

The following table (Table 36) taken from the Applicant’s 4-month safety update shows that lasofoxifene-treated subjects reported statistically significantly more leg cramps than placebo-treated subjects.

Table 36 Hazard Ratio for Subjects with Leg Cramps: Overall Phase 2/3 Clinical Program

Parameter	Lasofoxifene			Placebo
	0.25 mg (n=4,549)	0.5 mg (n=4,308)	Pooled* (n=10,259)	(n=4,701)
Subject-years at risk	12,678	12,005	26,167	13,436
Number (%) of subjects with event	728 (16.0)	755 (17.5)	1,605 (15.6)	431 (9.2)
Incidence rate/100 subject-years (95% CI)	5.74 (5.33, 6.18)	6.29 (5.85, 6.75)	6.13 (5.84, 6.44)	3.12 (2.91, 3.53)
Hazard Ratio versus Placebo (95% CI)	1.84 (1.66, 2.05)			
P-value	<0.0001			

*Pooled lasofoxifene includes 0.017 mg, 0.025 mg, 0.05 mg, 0.15 mg, 0.25 mg, 0.4 mg, 0.5 mg, 1.0 mg, 2.5 mg, and 10.0 mg lasofoxifene dose groups

Source: 4-Month Safety Update; Table 30 page 56 of 84; NDA 22-242

Division Comments

- *Leg cramps (muscle spasms) are also reported in the raloxifene drug product label.*
- *Because treatment with SERMs is associated with both deep venous thromboses of the leg and leg cramps, patients taking SERMs should be informed of both of these adverse events.*

5.3.4.2 Hot Flushes

The following table (Table 37) taken from the Applicant’s 4-month safety update shows that lasofoxifene-treated subjects reported statistically significantly more hot flushes than placebo-treated subjects.

Table 37 Hazard Ratio for Subjects with Hot Flushes: Phase 2/3 Clinical Program

Parameter	Lasodoxifene			Placebo (n=3,434)
	0.25 mg (n=3,544)	0.5 mg (n=3,325)	Pooled* (n=7,341)	
Subject-years at risk	12,245	11,827	24,728	12,979
Number (%) of subjects with event	524 (14.8)	495 (14.9)	1,136 (15.5)	239 (7.0)
Incidence rate/ 100 subject-years (95% CI)	4.28 (3.92, 4.66)	4.19 (3.82, 4.57)	4.59 (4.33, 4.87)	1.84 (1.62, 2.09)
Hazard Ratio versus Placebo (95% CI)	2.27 (1.97, 2.61)			
P-value	<0.0001			

*Pooled lasodoxifene includes 0.025 mg, 0.25 mg, 0.5 mg lasodoxifene dose groups
Source: 4-Month Safety Update; Table 29 page 55 of 84; NDA 22-242

Division Comment

- *Hot flushes are also reported as adverse events in the raloxifene label*

5.3.5 Treatment Related Adverse Events

The treatment-related adverse events more commonly reported in subjects receiving lasodoxifene 0.5 mg as compared with subjects receiving placebo in the overall Phase 2/3 Clinical Program included muscle spasms and hot flushes (see Table 38).

Table 38 Treatment-Related Adverse Events Reported in ≥ 5% of Subjects in Any Treatment Group in Overall Phase 2/3 Clinical Program (Includes Data through Year 3 for Study A2181002)

System Organ Class • Preferred Term	Number (%) of Subjects			Placebo N=4,676
	Lasodoxifene			
	0.25 mg N=4,523	0.5 mg N=4,308	Pooled† N=10,233	
Musculoskeletal and Connective Tissue Disorders				
• Muscle spasms	417 (9.2)	422 (9.8)	932 (9.1)	181 (3.9)
Vascular Disorders				
• Hot flush	609 (13.5)	549 (12.7)	1427 (13.9)	258 (5.5)

† Pooled lasodoxifene includes 0.017 mg, 0.025 mg, 0.05 mg, 0.15 mg, 0.25 mg, 0.4 mg, 0.5 mg, 1.0 mg, 2.5 mg, and 10.0 mg lasodoxifene dose groups
Source: Clinical Safety Summary, Table 22, page 42 of 112, which includes data through the first 3 years of Study A2181002

5.3.6 Less Common Adverse Events (Occurrence in <5% of Subjects)

Adverse events occurring with an incidence < 5% in the overall Phase 2/3 Clinical Program and occurring at a greater incidence among subjects receiving lasodoxifene 0.25 mg or 0.5 mg compared with placebo are listed in Table 39. The majority of these events are reproductive tract disorders (endometrial disorder, endometrial hypertrophy on sonogram, genital discharge, uterine polyp, vaginal disorder, and uterine leiomyoma) or reproductive tract infections (vaginal candidiasis, vulvovaginal mycotic infection, and vulvovaginitis).

These reproductive tract events are reviewed in detail in Section 5.4.4 (Gynecological Adverse Events).

The vascular events of superficial thrombophlebitis and deep vein thrombosis also were more commonly reported in the lasofoxifene treatment groups. Superficial thrombophlebitis occurred in 0.2% to 0.6% of subjects receiving lasofoxifene and deep vein thrombosis occurred in 0.4% to 0.6% of subjects receiving lasofoxifene, as compared with the occurrence of each event in only 0.1% of subjects receiving placebo. Venous thromboembolic events are reviewed in detail in Section 5.4.1.

Table 39 Selected All-Causality Adverse Events with < 5% Incidence and Occurring More Frequently among Subjects Receiving Lasofoxifene in Overall Phase 2/3 Clinical Program (Includes Data through Year 3 for Study A2181002)

System Organ Class • Preferred Term	Number (%) of Subjects			
	Lasofoxifene			Placebo N=4,676
	0.25 mg N=4,523	0.5 mg N=4,308	Pooled† N=10,233	
Infections and Infestations				
• Vaginal candidiasis	142 (3.1)	146 (3.4)	306 (3.0)	19 (0.4)
• Vulvovaginal mycotic infection	62 (1.4)	65 (1.5)	164 (1.6)	18 (0.4)
• Vulvovaginitis	36 (0.8)	35 (0.8)	80 (0.8)	18 (0.4)
Neoplasms Benign, Malignant and Unspecified				
• Uterine leiomyoma	45 (1.0)	70 (1.6)	142 (1.4)	38 (0.8)
Reproductive System and Breast Disorders				
• Endometrial disorder	39 (0.9)	44 (1.0)	94 (0.9)	11 (0.2)
• Endometrial hypertrophy	186 (4.1)	148 (3.4)	375 (3.7)	38 (0.8)
• Genital discharge	83 (1.8)	61 (1.4)	176 (1.7)	22 (0.5)
• Uterine polyp	69 (1.5)	77 (1.8)	185 (1.8)	26 (0.6)
• Vaginal disorder	48 (1.1)	44 (1.0)	106 (1.0)	23 (0.5)
Vascular Disorders				
• Deep vein thrombosis	26 (0.6)	18 (0.4)	47 (0.5)	6 (0.1)
• Thrombophlebitis superficial	7 (0.2)	24 (0.6)	31 (0.3)	7 (0.1)

† Pooled lasofoxifene includes 0.017 mg, 0.025 mg, 0.05 mg, 0.15 mg, 0.25 mg, 0.4 mg, 0.5 mg, 1.0 mg, 2.5 mg, and 10.0 mg lasofoxifene dose groups
Source: Clinical Safety Summary, Table 23, page 43 of 112, which includes data through the first 3 years of Study A2181002

5.3.7 Hepatic/Biliary Safety

The following information regarding hepatobiliary adverse events is based on 3-year safety data from pivotal Study A2181002 (PEARL):

- All-causality AEs classified as pertaining to the hepatobiliary system organ class (SOC) were reported for 3.6%, 4.4%, and 3.6 % of lasofoxifene 0.25 mg, lasofoxifene 0.5 mg, and placebo-treated subjects, respectively. The incidence of

discontinuations due to hepatobiliary adverse events was low ($\leq 0.1\%$) and similar across treatment groups.

- There was no increase in risk for serious gallbladder events in subjects in the pooled lasofoxifene treatment groups compared to placebo-treated subjects (hazard ratio: 0.961 [95% CI: 0.662, 1.395; $p=0.836$]). The cumulative incidences for serious gallbladder events were 1.4%, 1.4%, and 1.5% in the lasofoxifene 0.25 mg, lasofoxifene 0.5 mg, and placebo treatment groups, respectively.
- The incidence of elevated liver enzymes (> 3 x upper limit of normal) was low ($< 1.0\%$) across all treatment groups. Statistically significantly more subjects treated with lasofoxifene 0.25 mg (24 subjects; 0.9%) had elevated AST levels compared with placebo (9 subjects; 0.3%); although a numerically greater number of subjects treated with lasofoxifene 0.5 mg (16 subjects) had elevated AST levels compared with placebo (9 subjects), the difference was not statistically significant.
- The number of subjects with elevated ALT levels (> 3 x upper limit of normal) was 24, 17, and 18 in the lasofoxifene 0.25 mg, lasofoxifene 0.5 mg, and placebo groups, respectively. Among subjects with an abnormal baseline LFT, more subjects on lasofoxifene had abnormal LFTs (6% on 0.25 mg, 4% on 0.5 mg, and 1% on placebo).

Division Comment

- *Despite some increases in hepatic enzymes in the lasofoxifene treated subjects, no lasofoxifene-treated subject met the criteria for Hy's law (ALT or $AST \geq 3$ x ULN and concomitant total bilirubin ≥ 1.5 x ULN). One placebo-treated subject who had hepatic cancer met the criteria.*

5.4 Safety Issues of Particular Concern or Interest

5.4.1 Venous Thromboembolic Events (VTEs)

The Applicant conducted specific analyses and prepared additional summaries for venous thromboembolic events (VTEs) because of the known thromboembolic effects of therapy with estrogens and SERMs (e.g., raloxifene). The Applicant evaluated VTEs as a composite endpoint composed of the adjudicated endpoints of deep vein thrombosis (DVT), pulmonary embolus (PE), and retinal vein thrombosis (RVT) in Study A2181002 (PEARL). The Cardiovascular Endpoint Classification Committee (CECC) reviewed each potential event in a blinded manner to determine whether or not it met diagnostic criteria. In the other Phase 2/3 studies, the serious adverse event terms related to DVT, PE, or RVT were considered to be VTEs, but the events were not adjudicated. In the overall clinical development program to date, the Applicant has concluded that lasofoxifene treatment is associated with an approximate 2-fold increase in VTEs compared to placebo. The Applicant attributed the increase in the incidence of VTEs mainly to an increased incidence of DVTs in subjects being treated with lasofoxifene.

In the 3-year interim data from Study A2181002, there was a 2.6-fold increase (lasofoxifene 0.25 mg group) and a 2.2-fold increase (lasofoxifene 0.5 mg group) in the risk of any VTE compared to that in the placebo group (Table 40). The increases in risk were statistically

significant for both dose groups. The increase in risk was due largely to an increase in the number of reported DVTs.

Although pulmonary emboli did not occur frequently in the lasofoxifene treatment groups (0.1% to 0.2% of subjects), the hazard ratios for PE were 5.0 (lasofoxifene 0.25 mg group) and 4.0 (lasofoxifene 0.5 mg) compared to the placebo group. The confidence intervals about each ratio were wide, however, and neither value was statistically significant.

Table 40 Summary of First On-Study Venous Thromboembolic Event (VTE) in Study A2181002 (3-Year Interim Data)

Parameter	Lasofloxifene		Placebo N =2852
	0.25 mg N = 2852	0.5 mg N = 2852	
Any VTE			
No of cases (%)	26 (0.9)	22 (0.8)	10 (0.4)
Hazard Ratio	2.603	2.198	
95% C.I.	(1.255, 5.398)	(1.041, 4.641)	
P-Value	0.008*	0.034*	
Pulmonary Embolism			
No of cases (%)	5 (0.2)	4 (0.1)	1 (< 0.1)
Hazard Ratio	4.996	3.993	
95% C.I.	(0.584, 42.761)	(0.446, 35.727)	
P-Value	0.103	0.181	
Deep Vein Thrombosis			
No of cases (%)	22 (0.8)	18 (0.6)	8 (0.3)
Hazard Ratio	2.753	2.246	
95% C.I.	(1.226, 6.183)	(0.977, 5.166)	
P-Value	0.011*	0.050*	
Retinal Vein Thrombosis			
No of cases (%)	2 (< 0.1)	2 (< 0.1)	1 (< 0.1)
Hazard Ratio	1.996	1.994	
95% C.I.	(0.181, 22.015)	(0.181, 21.994)	
P-Value	0.565	0.566	

Confidence interval derived from Wald test; p-value derived from a log-rank test

*P-value significant, Hochberg procedure with overall alpha=0.05

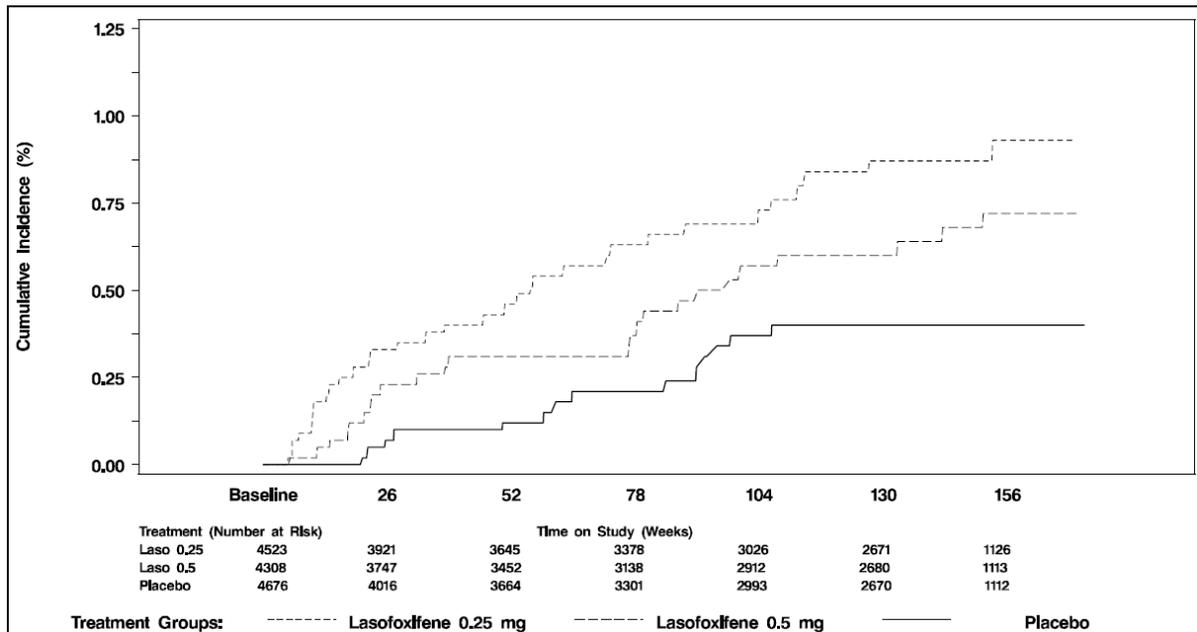
Source: A2181002 3-Year Interim Study Report, Table 39, page 154 of 7454

The Applicant calculated the rates of the first on-study VTE per 100 subject-years of treatment in each treatment group in Study A2181002 (3-year interim data). The values were:

- 0.33 (95% CI: 0.23, 0.46) for lasofoxifene 0.25 mg/d
- 0.25 (95% CI: 0.16, 0.37) for lasofoxifene 0.5 mg/d,
- 0.28 (95% CI: 0.22, 0.36) for the pooled lasofoxifene doses
- 0.14 (0.08, 0.23) for the placebo group

The Applicant also provided curves of the cumulative incidence of first on-study VTE versus time on study in each of the treatment groups in Study A2181002 (3-year interim data); see Figure 4. In Figure 4, the top line represents the cumulative incidence for 0.25 mg lasofoxifene, the middle line represents the cumulative incidence for lasofoxifene 0.5 mg, and the bottom line represents the cumulative incidence for placebo. The curves were compared using the log-rank and the Wilcoxon statistical tests. The p-values were statistically significant for the comparisons of lasofoxifene 0.25 mg versus placebo and for the pooled lasofoxifene 0.25 and 0.5 mg doses versus placebo by either statistical test, but not statistically significant for the comparison of 0.5 mg lasofoxifene versus placebo.

Figure 4 Cumulative Incidence of First on-Study Venous Thromboembolic Event (3-Year Interim data)



The top line represents 0.25 mg lasofoxifene, the middle line represents lasofoxifene 0.5 mg, and the bottom line represents placebo

Source: Figure 9, Submission #22, dated 07/11/08, Phase 2/3 Clinical Program, includes 3-year Interim Data for Study A2181002

Based on the preliminary 5-year data from Study A2181002, the hazard ratio for any VTE for lasofoxifene 0.5 mg/d compared to placebo was 2.055 (95% CI: 1.170, 3.609) (see Table 41). The hazard ratio for any VTE was higher for lasofoxifene 0.25 mg/d (HR = 2.667; 95% CI: 1.551, 4.584). The hazard ratios for PE were 4.493 (95% CI: 0.971, 20.796) for lasofoxifene 0.5 mg/d and 5.981 (95% CI: 1.339, 26.722) for lasofoxifene 0.25 mg/d.

Table 41 Summary of First On-Study Venous Thromboembolic Event (VTE) in the 5-Year Preliminary Data for Study A2181002

Parameter	Lasofoxifene		Placebo N =2852
	0.25 mg N = 2852	0.5 mg N = 2852	
Any VTE			
No of cases (%)	48 (1.7)	37 (1.3)	18 (0.6)
Hazard Ratio	2.667	2.055	
95% C.I.	(1.551, 4.584)	(1.170, 3.609)	
P-Value	0.001*	0.011*	
Pulmonary Embolism			
No of cases (%)	12 (0.4)	9 (0.3)	2 (< 0.1)
Hazard Ratio	5.981	4.493	
95% C.I.	(1.339, 26.722)	(0.971, 20.796)	
P-Value	0.008*	0.035*	
Deep Vein Thrombosis			
No of cases (%)	36 (1.3)	28 (1.0)	13 (0.5)
Hazard Ratio	2.767	2.152	
95% C.I.	(1.468, 5.217)	(1.115, 4.154)	
P-Value	0.002*	0.020*	
Retinal Vein Thrombosis			
No of cases (%)	4 (0.1)	3 (0.1)	4 (0.1)
Hazard Ratio	0.995	0.748	
95% C.I.	(0.249, 3.980)	(0.167, 3.341)	
P-Value	0.996	0.704	

Hazard ratio based on Cox proportional hazards model with treatment as covariate. P-value based on log-rank test

*P-value significant at ≤ 0.05 .

Source: A2181002 Amended Preliminary 5-Year Study Report, Table 32, page 37 of 58

For the overall Phase 2/3 Clinical Program (including 3-year interim data from Study A2181002), the hazard ratios for VTEs for each dose group were similar to those seen with Study A2181002.

Division Comments

- *The greater than 2-fold increase in the risk of any VTE and the greater than 4-fold increase in the risk of PE in subjects treated with either 0.25 mg/d or 0.5 mg/d of lasofoxifene are of concern.*
- *The Applicant has proposed a risk management plan for lasofoxifene to address VTEs, including a prospective epidemiological study examining cases of DVT, PE, stroke, and all-cause fatalities. In addition, the Applicant has proposed a web-based educational program on VTEs for healthcare providers.*
- *U.S. labeling for raloxifene states that during an average study-drug exposure of 2.6 years, VTEs occurred in about 1 out of 100 patients treated with raloxifene. According to labeling, 26 raloxifene-treated women had a VTE compared to 11 placebo-treated women. The hazard ratio was 2.4 (95% CI: 1.2, 4.5).*

Issues for Consideration

- **The Committee is asked to consider the finding of a statistically significant increase in overall VTEs in the lasofoxifene-treated subjects compared to placebo-treated subjects when evaluating the overall risk/benefit profile of treatment with lasofoxifene for the proposed indication. Of particular concern, is the increased risk for pulmonary emboli in the lasofoxifene-treated subjects.**

5.4.2 Stroke

As with overall VTEs, the Applicant evaluated strokes as a composite endpoint composed of adjudicated stroke events in Study A2181002 (PEARL). The CECC reviewed the potential event in a blinded manner to determine whether or not it met diagnostic criteria. Events that were confirmed by the committee to meet the inclusion criteria were further analyzed. In the other Phase 2/3 studies, MedDRA serious adverse event terms related to stroke were used for data analyses.

The risk of stroke through 3-years and 5-years of follow-up in Study A2181002 was numerically lower among subjects randomized to lasofoxifene compared to placebo, but the differences were not statistically significant (Table 42). Similar results were observed in the overall Phase 2/3 Clinical Program.

Table 42. Analysis of Time to First Stroke (Study A2181002: 3-Year Interim and 5-Year Preliminary Data)

Parameter	Lasofloxifene			Placebo
	0.25 mg	0.5 mg	Pooled*	
Study A2181002: 3-Year Interim Data ^a				
No. of Subjects	2852	2852	5704	2852
No. of Strokes	28 (1.0%)	32 (1.1%)	60 (1.1%)	35 (1.2%)
HR (95% CI)	0.80 (0.49, 1.31)	0.91 (0.56, 1.47)		
P-value	0.3714	0.7053		
Study A2181002: 5-Year Preliminary Data ^b				
No. of Subjects	2852	2852	5704	2852
No. of Strokes (%)	50 (1.8)	46 (1.6)	96 (1.7%)	61 (2.1)
HR (95% CI)	0.81 (0.56, 1.18)	0.75 (0.51, 1.10)		
P-value	0.276	0.140		

HR = Hazard Ratio

* Pooled lasofoxifene includes 0.017 mg, 0.025 mg, 0.05 mg, 0.25 mg, 0.4 mg, 0.5 mg, 1.0 mg, 2.5 mg, and 10 mg lasofoxifene dose groups

Source: ^a Study Report for A2181002 3-Year Interim Data, Table 44, page 158 of 7454; ^b Amended Preliminary Study Report for A2181002 5-Year Data, Table 35, page 39 of 58

Although numerically lower percentages of subjects randomized to lasofoxifene experienced strokes compared to placebo-treated subjects, the percentages of subjects with fatal strokes was slightly greater for the pooled lasofoxifene groups in Study A2181002. Of note, fatal strokes more frequently occurred with the lasofoxifene 0.25 mg dose, based on the 5-year preliminary data. No fatal strokes were identified in the other lasofoxifene clinical studies.

Table 43 Analysis of Time to First Stroke (Study A2181002: Fatal and Non-fatal Strokes)

Parameter	Lasofoxifene			Placebo
	0.25 mg	0.5 mg	Pooled*	
Study A2181002: 3-Year Interim Data ^a				
No. of Subjects	2852	2852	5704	2852
Total No. of Strokes	28 (1.0%)	32 (1.1%)	60 (1.1%)	35 (1.2%)
No. of Fatal Strokes (%)	4 (0.1%)	5 (0.2%)	9 (0.2%)	3 (0.1%)
Study A2181002: 5-Year Preliminary Data ^b				
No. of Subjects	2852	2852	5704	2852
Total No. of Strokes	50 (1.8)	46 (1.6)	96 (1.7%)	61 (2.1)
No. of Fatal Strokes (%)	12 (0.4%)	7 (0.2%)	19 (0.3%)	5 (0.2%)

* Pooled lasofoxifene includes 0.017 mg, 0.025 mg, 0.05 mg, 0.25 mg, 0.4 mg, 0.5 mg, 1.0 mg, 2.5 mg, and 10 mg lasofoxifene dose groups

Source: ^a Study Report for A2181002 3-Year Interim Data, Table 32, page 146 of 7454; ^b Amended Preliminary Study Report for A2181002 5-Year Data, Table 23, page 25 of 58

Division Comment

- *In summary, the percentages of subjects with stroke were numerically lower in the lasofoxifene groups compared to the placebo group. However, there is a suggestion of a small numeric excess in fatal strokes in the lasofoxifene group in the 5-year data. This may be of concern as this risk was recently identified as a safety signal for raloxifene⁶ and resulted in a Box Warning in the product labeling with a cautionary statement to consider the risk-benefit balance of raloxifene treatment in women at risk for stroke.*

5.4.3 Other Cardiovascular Events

5.4.3.1 Coronary Events

The Applicant categorized coronary endpoints of special interest as a composite endpoint composed of major coronary events including in Study A2181002 the adjudicated endpoints of coronary death, nonfatal myocardial infarction, new ischemic heart disease, hospitalization for unstable angina, and revascularization procedures. For all other studies, a series of MedDRA serious adverse event terms were used to identify coronary events for the analyses.

The risk of serious coronary events through 3 years and 5 years of follow-up in Study A2181002 was lower among subjects randomized to lasofoxifene compared to placebo (Table 44 and Table 45).

⁶ Barrett-Connor E, Mosca L, Collins P, Geiger MJ, Grady D, Kornitzer M, McNabb MA, Wenger NK for the Raloxifene Use for The Heart (RUTH) Trial Investigators. Effects of Raloxifene on Cardiovascular Events and Breast Cancer in Postmenopausal Women. N Engl J Med 2006;355:125-37.

Table 44 Analysis of Time to First Adjudicated Major Coronary Event (Study A2181002: 3-Year Interim Data)

	Lasofloxifene			
	0.25 mg	0.5 mg	Pooled	Placebo
Number of Subjects	2852	2852	5704	2852
Subjects Years of Follow-up	8174.5	8174.8	16349.3	8140.1
Number (%) of Subjects With Event	46 (1.6)	43 (1.5)	89 (1.6)	55 (1.9)
Hazard Ratio	0.83	0.78	0.81	
95% Confidence Interval	0.56, 1.23	0.52, 1.16	(0.58, 1.13)	
P-Value	0.3575	0.2142	0.2052	

Source: Study Report for A2181002 3-Year Interim Data, Table 40, page 155 of 7454

Table 45 Analysis of Time to First Adjudicated Major Coronary Event (Study A2181002: 5-Year Preliminary Data)

	Lasofloxifene			
	0.25 mg	0.5 mg	Pooled	Placebo
Number of Subjects	2852	2852	5704	2852
Subjects Years of Follow-up	12766	12715	25481	12641
Number (%) of Subjects With Event	73 (2.6)	66 (2.3)	139 (2.4)	95 (3.3)
Hazard Ratio (95% CI)	0.76 (0.56, 1.03)	0.68 (0.50, 0.93)	0.72 (0.55, 0.94)	
P-Value	0.0774	0.0161*	0.0135*	

Source: Amended Preliminary Study Report for A2181002 5-Year Data, Table 33, page 38 of 58

Results similar to those observed for Study A2181002 were noted for the overall Phase 2/3 Clinical Program (Table 46).

Table 46 Analysis of Time to First Coronary Event in Overall Phase 2/3 Clinical Program (Includes Data through Year 3 for Study A2181002)

	Lasofloxifene			
	0.25 mg	0.5 mg	Pooled*	Placebo
	N=4,523 SYR=10,035.9	N=4,308 SYR=9,594.5	N=10,233 SYR=21,216.0	N=4,676 SYR=10,011.4
Number (%) of subjects with event	52 (1.1)	47 (1.1)	105 (1.0)	62 (1.3)
Incidence rate/100 subject-years (95% CI)	0.52 (0.39, 0.68)	0.49 (0.36, 0.65)	0.49 (0.40, 0.60)	0.62 (0.47, 0.79)
Hazard ratio versus Placebo (95% CI)			0.81 (0.59, 1.11)	
P-value			0.1952	

SYR = Subject-years at risk

Source: Summary of Clinical Safety, Table 52, page 76 of 112, NDA 22-242, includes 3-year interim data for Study A2181002

When the specific adjudicated major coronary events of interest were examined, the incidence of these events in both dose groups of lasofloxifene was numerically lower than, or comparable to, that observed in the placebo group (Table 47).

Table 47 Incidence of Specific Adjudicated Major Coronary Events (Study A2181002: 5-Year Preliminary Data)

	Lasofloxifene 0.25 mg	Lasofloxifene 0.5 mg	Placebo
Number of Subjects	2852	2852	2852
Number (%) of Subjects With Event	73 (2.6)	66 (2.3)	95 (3.3)
Type of Major Coronary Event			
Coronary Death	18 (0.6%)	18 (0.6%)	21 (0.7%)
Non-Fatal Myocardial Infarction	17 (0.6%)	23 (0.8%)	28 (1.0%)
New Ischemic Heart Disease	21 (0.7%)	12 (0.4%)	23 (0.8%)
Hospitalization for Unstable Angina	21 (0.7%)	16 (0.6%)	27 (0.9%)
Revascularization Procedures	19 (0.7%)	19 (0.7%)	34 (1.2%)

Source: Amended Preliminary Study Report for A2181002 5-Year Data, Table 34, page 38 of 58

When fatal coronary events were examined in detail, there was no evidence of an increase in coronary-related fatalities among subjects treated with either dose of lasofloxifene compared to subjects treated with placebo (Table 48).

Table 48 Fatal Coronary Events (Study A2181002: 3-Year Interim Data and Preliminary 5-Year Data)

Parameter	Number (%) of Subjects		
	Lasofloxifene		Placebo
	0.25 mg	0.5 mg	
Study A2181002: 3-Year Interim Data ^a			
Number of subjects	2,852	2,852	2,852
Coronary deaths	7 (0.2)	7 (0.2)	10 (0.4)
• Sudden death	5 (0.2)	4 (0.1)	8 (0.3)
• Fatal myocardial infarction‡	1 (<0.1)	2 (0.1)	1 (<0.1)
• Fatal ischemic heart disease	1 (<0.1)	1 (<0.1)	0 (0.0)
• Death from revascularization procedure	0 (0.0)	0 (0.0)	1 (<0.1)
Study A2181002: 5-Year Preliminary Data ^b			
Number of subjects	2,852	2,852	2,852
Coronary deaths	18 (0.6)	18 (0.6)	21 (0.7)
• Sudden death	13 (0.5)	12 (0.4)	15 (0.5)
• Fatal myocardial infarction‡	3 (0.1)	3 (0.1)	3 (0.1)
• Fatal ischemic heart disease	2 (0.1)	3 (0.1)	1 (0.0)
• Death from revascularization procedure	0 (0.0)	0 (0.0)	2 (0.1)

Source: ^a Study Report for A2181002 3-Year Interim Data, Table 32, page 146 of 7454

^b Amended Preliminary Study Report for A2181002 5-Year Data, Table 23, page 25 of 58

Division Comment

- *There were no findings that indicated that treatment with lasofoxifene increased the incidence of fatal or non-fatal major coronary adverse events.*

5.4.3.2 Blood Pressure

The effect of lasofoxifene treatment on blood pressure was closely examined, particularly because of the suggestion of a possible increased risk of fatal strokes in lasofoxifene-treated subjects. In Study A2181002, vital signs were measured at screening and yearly thereafter. For this protocol, all vital signs were measured while the subject was seated. Median changes in vital signs from baseline to the last observation were summarized by the Applicant only for the 3-Year interim data. No clinically important median changes from baseline in systolic blood pressure, diastolic blood pressure, or heart rate were observed in any treatment group. The baseline vital signs and the median changes from baseline are provided in Table 49 for the 3-Year Interim data from Study A2181002.

Table 49 Vital Signs: Median at Baseline and Median Change at Last Observation (Study A2181002: 3-Year Interim Data)

Vital Signs**	Lasofoxifene		Placebo
	0.25 mg N = 2633*	0.5 mg N = 2620*	N = 2648*
Baseline Measurement (Median)			
Systolic BP (Q1, Q3)	132 (120.0, 145.0)	134.5 (120.0, 150.0)	132 (120.0, 148.0)
Diastolic BP (Q1, Q3)	80 (72.0, 90.0)	80 (74.0, 90.0)	80 (72.0, 90.0)
Heart Rate (Q1, Q3)	72 (66.0, 80.0)	72 (66.0, 80.0)	72 (66.0, 80.0)
Median Change from Baseline			
Systolic BP (Q1, Q3)	0 (-15.0, 10.0)	-2 (-15.0, 10.0)	0 (-14.0, 10.0)
Diastolic BP (Q1, Q3)	0 (-10.0, 5.0)	0 (-10.0, 4.0)	0 (-10.0, 5.0)
Heart Rate (Q1, Q3)	0 (-4.0, 8.0)	0 (-6.0, 8.0)	0 (-6.0, 6.0)

BP = blood pressure; Q1, Q3 represents the interquartile range which is from the 25th to the 75th percentile of the data

* Several subjects did not have heart rates recorded

** All vital signs for this protocol done in a sitting position, as noted A2181002 Study Manual, v.5.

Source: A2181002 Study Report, 3-Year Interim Analysis, Table 8, pages 3530-3531; NDA 22-242

In the overall Phase 2/3 Clinical program, changes in vital signs from baseline were available for subjects enrolled in the following protocols: 218-101, 218-101E, 218-102, A2181002, A2181012, A2181030, A2181031, A2181032, and A2181037. A review of these data did not show any clinically important median changes from baseline in seated systolic blood pressure, diastolic blood pressure, or heart rate were observed in any treatment group. The

baseline vital signs and the median changes from baseline are provided in Table 50 for the overall Phase 2/3 Clinical Program.

Table 50 Vital Signs: Median at Baseline and Median Change at Last Observation in Overall Phase 2/3 Clinical Program (Includes 3-year Interim Data for Study A2181002)

Vital Signs**	Lasofloxifene				Placebo N = 3001*
	0.025 mg N = 210*	0.25 mg N = 2922*	0.5 mg N = 2830*	Pooled N = 6237*	
Baseline Measurement (Median)					
Systolic BP (Q1, Q3)	124 (114.0, 132.0)	130 (120.0, 145.0)	130 (120.0, 147.0)	130 (120.0, 144.0)	130 (120.0, 145.0)
Diastolic BP (Q1, Q3)	76 (70.0, 81.0)	80 (70.0, 88.0)	80 (72.0, 90.0)	80 (70.0, 87.0)	80 (70.0, 86.0)
Heart Rate (Q1, Q3)	69 (64.0, 76.0)	72 (66.0, 80.0)	72 (66.0, 80.0)	72 (65.0, 78.0)	72 (66.0, 80.0)
Median Change from Baseline					
Systolic BP (Q1, Q3)	-2 (-10.0, 6.0)	0 (-14.0, 10.0)	-2 (-15.0, 10.0)	0 (-14.0, 10.0)	0 (-13.0, 10.0)
Diastolic BP (Q1, Q3)	-2 (-8.0, 5.0)	0 (-10.0, 5.0)	0 (-10.0, 4.0)	0 (-10.0, 5.0)	0 (-10.0, 5.0)
Heart Rate (Q1, Q3)	0 (-4.0, 7.0)	0 (-4.0, 8.0)	0 (-6.0, 8.0)	0 (-5.0, 8.0)	0 (-6.0, 6.0)

BP = blood pressure; Q1, Q3 represents the interquartile range which is from the 25th to the 75th percentile of the data

* Several subjects did not have all vital sign measurements recorded

** All vital signs for this protocol done in a sitting position (per A2181002 Study Manual, v.5)

Includes protocols: 218-101, 218-101E, 218-102, A2181002, A2181012, A2181030, A2181031, A2181032, A2181037

Source: Clinical Summary of Safety, Section 2.7.4, Appendix K.1.3, pages 11290-11292

Division Comment

- *In summary, treatment with lasofloxifene did not appear to have a clinically important effect on blood pressure or heart rate when compared to treatment with placebo.*

5.4.4 Gynecological Adverse Events

The gynecologic adverse event tables in this section are based on the 3 year interim data for Study A2181002 or data contained in the 4-month safety update.

5.4.4.1 Endometrial Carcinoma

The Applicant's analysis of the incidence of endometrial cancer is shown in Table 51. The percentages of subjects with endometrial cancer appear similar in the lasofloxifene-treated and placebo-treated subjects.

Table 51 Analysis of Incidence of Endometrial Cancer in Lasofoxifene Phase 2/3 Studies of at Least 1 Year Duration

Parameter	Lasofoxifene			Placebo
	0.25 mg	0.5 mg	Pooled*	
Number of subjects at risk	3,291	3,136	7,268	3,291
Total years at risk	11,523	11,237	23,813	11,523
Number (%) of subjects with event	4 (0.1)	2 (0.1)	7 (0.1)**	4 (0.1)
Incidence rate per 100 subject-years	0.03	0.02	0.03	0.03
95% CI	(0.01, 0.09)	(0.00, 0.06)	(0.01, 0.06)	(0.01, 0.09)
Hazard Ratio			0.84	
95% CI			(0.24, 2.86)	
P-value			0.7743	

CI = confidence interval

* Pooled lasofoxifene includes 0.017 mg, 0.025 mg, 0.05 mg, 0.15 mg, 0.25 mg, 0.4 mg, 0.5 mg, 1.0 mg, 2.5 mg, and 10.0 mg lasofoxifene dose groups

Includes Studies 218-101E, 218-102, 218-103, A2181002, A2181003, A2181004, A2181014, A2181015, A2181016, A2181021, A2181030, A2181037, A2181042

**Total includes 1 subject who received lasofoxifene 0.025 mg

Source: 4-Month Safety Update; NDA 22-242; page 75 of 84

Division Comments

- *These endometrial cancers ranged in stage from IB through IIIA. One of the central pathologists considered one of the tumors arising in the 0.25 mg group to be a serous carcinoma. Serous carcinomas have not typically been associated with hormonal factors.*
- *The 2 sarcomas identified in the lasofoxifene clinical development program are not included in the preceding table and are described in the following section.*

5.4.4.2 Uterine Sarcoma

The applicant provided information on the 2 uterine sarcomas (single case each of carcinosarcoma and endometrial stromal sarcoma) that were reported in Study A2181015, both occurring in lasofoxifene-treated subjects. This was the only study in the lasofoxifene program to report uterine sarcomas. Verbatim narrative summaries from the NDA submission are provided below for the 2 subjects:

Case 1 (carcinosarcoma). *“A 61-year-old white female, Subject 5217537, with a remote history of previously treated vaginal bleeding received lasofoxifene 0.025 mg for 162 days before discontinuing study medication due to vaginal bleeding. A total abdominal hysterectomy was performed and revealed Stage 1B, high grade uterine carcinosarcoma of the uterus with largely senescent adjacent endometrium, indicating no evidence of endometrial hyperplasia. In both the Investigator’s and Sponsor’s opinion, the carcinosarcoma was not related to study drug. Based on the calculation of tumor growth and applying conservative assumptions about aggressive tumor growth kinetics (Cotran 1999; Fingert, 1993), a minimal tumor growth time exceeding 1 year is estimated for a tumor of this histology and a size of 5.3 cm x 3.2 cm x 3.1 cm. Based on this estimate, the onset of the uterine tumor would have preceded lasofoxifene treatment (interval between first dose of lasofoxifene and surgical extraction of the uterine tumor was approximately 6.5 months).*

Therefore, a causal association between lasofoxifene and the tumor can be reasonably excluded.”

Division Comment

- *Based on the duration of therapy until the diagnosis of the carcinosarcoma and the size of the tumor at the time of hysterectomy, it is reasonable to conclude that the tumor was pre-existing at the start of lasofoxifene therapy.*

Case 2 (endometrial stromal sarcoma). *“A 59-year-old white female, Subject 0090619, without a significant past medical history, received lasofoxifene 0.25 mg for 125 days prior to experiencing vaginal bleeding for 6 days, followed by a similar 6-day episode after 155 days of study drug, both of which resolved spontaneously. Another episode of bleeding after 180 days of study drug resulted in study discontinuation after 249 days and hysteroscopy and myoma resection on post therapy Day 1. Vaginal bleeding resolved on postoperative Day 10. The local [REDACTED] histology report of this specimen revealed a leiomyoma with no signs of increased mitosis. Approximately 1 year following treatment discontinuation, the subject experienced another episode of vaginal bleeding. An ultrasound revealed an intrauterine mass and a second pathology review [REDACTED] [REDACTED] of the earlier myoma resection specimen first revealed the presence of a low-grade endometrial sarcoma as well as leiomyoma. Subsequently, on post therapy day 429, the subject underwent a total hysterectomy and bilateral oophorectomy at which point the condition was considered resolved. The local [REDACTED] postoperative histopathology results showed a Stage 1B, low-grade endometrial stroma cell sarcoma and benign leiomyoma, the bilateral adnexa were unremarkable.”*

Division Comments

- *It is theoretically possible that this tumor was pre-existing because of the slow growth of low grade endometrial stromal sarcoma. The tumor was first detected (retrospectively diagnosed by second pathology review) after the subject had been exposed to lasofoxifene for 249 days.*
- *Special consideration of uterine sarcomas is pertinent to safety discussion of SERMs because tamoxifen treatment has been associated with these tumors and the tamoxifen label mentions uterine sarcomas in a black box warning.*

Tamoxifen and Uterine Sarcoma

The SERM that has been associated with uterine sarcoma is tamoxifen. Sixty-eight (68) tamoxifen-associated uterine sarcomas in 33 literature case reports were summarized by Arenas et al.⁷ The author provided a table (see following) that divided the sarcomas into specific types.

Uterine Sarcomas in Patients Receiving Tamoxifen (Literature Survey)

Type of Tumor	No. of Cases
Carcinosarcoma/MMMT	43
Adenosarcoma	13
Endometrial stromal sarcoma	6
Leiomyosarcoma	5
Rhabdomyosarcoma	1

Source: Modified from Arenas et al.⁷

The mean time to appearance of these tumors was 68.6 months. Tamoxifen treatment duration varied from 6 to 144 months. The listing by Arenas did not specify whether the endometrial stromal sarcomas were high grade or low grade. From review of the cited articles it appears that 4 of the endometrial stromal sarcomas were low grade tumors, one was a high grade sarcoma, and the other was not graded in the literature reference.

The tamoxifen label discusses uterine sarcoma in a table derived from major outcomes of the NSABP P-1 Trial. There were 4 uterine sarcoma events in tamoxifen-treated women and no cases in placebo-treated women. The incidence rate of uterine sarcoma was 0.17 per 1,000 women years for tamoxifen.

Division Comments

- *It remains uncertain whether tamoxifen is causative in regard to uterine sarcomas as a group or to any sarcoma subgroups. These tumors are still very rare in the population. There is no known etiologic mechanism that links the different sarcomas.*
- *It is possible that both of the sarcomas found in the lasofoxifene studies were pre-existing. These tumors are very rare and would require an extremely large number of subjects to assess an association prospectively.*

5.4.4.3 Endometrial Hyperplasia

At the time of the 4-month safety update for NDA 22-242, there were 4 cases of endometrial hyperplasia in the lasofoxifene treatment groups and none in the placebo group. These 4 cases consist of 3 cases that were adjudicated by central pathology review and one case read locally (slides for this case were destroyed and not available for central review). The incidence rates and pooled lasofoxifene hazard ratio is shown in Table 52.

⁷ Arenas M, Rovirosa A, Hernandez V, Ordi J, Jorcano S, Mellado B, Biete A. Uterine sarcomas in breast cancer patients treated with tamoxifen. *Int J Gynecol Cancer* 2006;16:861-5.

Table 52 Analysis of Time to Endometrial Hyperplasia in Overall Lasofoxifene Phase 2/3 Clinical Program

Parameter	Lasofoxifene			Placebo
	0.25 mg	0.5 mg	Pooled*	
Number of subjects at risk	3,685	3,518	8,347	3,844
Total years at risk	11,731	11,398	24,399	11,772
Number (%) of subjects with event	2 (0.1)	2 (0.1)	4 (<0.05)	0 (0.0)
Incidence rate per 100 subject-years	0.02	0.02	0.02	0.00
95% CI	(0.00, 0.06)	(0.00, 0.06)	(0.00, 0.04)	(0.00, 0.03)
Hazard Ratio			Infinity	
95% CI			(0.00, Infinity)	
P-value			0.9932	

CI=confidence interval,

Includes Studies 218-101, 218-101E, 218-102, 218-103, A2181002, A2181003, A2181004, A2181012, A2181014, A2181015, A2181016, A2181021, A2181030, A2181031, A2181032, A2181037, A2181042

*Pooled lasofoxifene includes 0.017 mg, 0.025 mg, 0.05 mg, 0.15 mg, 0.25 mg, 0.4 mg, 0.5 mg, 1.0 mg, 2.5 mg, and 10.0 mg lasofoxifene dose groups

Source: 4-Month Safety Update; NDA 22-242; page 76 of 84

Division Comments

- *The percentage of subjects with endometrial hyperplasia (0.1%) in each of the lasofoxifene treatment groups is low and of minor clinical concern. Based on the FDA's guidance for estrogen/progestin drug products, a drug regimen is considered to be protective against estrogen-induced endometrial hyperplasia if the point estimate for the rate of hyperplasia in a one year study is $\leq 1.0\%$ and the upper bound of the one-sided 95% confidence interval is $\leq 4\%$.*
- *The Division had concerns when initially reviewing this NDA application because the numbers of cases of hyperplasia (based on local pathology readings) in the lasofoxifene treatment groups were considerably higher than those listed in Table 52. All locally diagnosed cases of endometrial hyperplasia were adjudicated by a group of 3 blinded pathologists on the Gynecologic Endpoint Classification Committee (GECC). To evaluate this discrepancy between the local and central diagnoses, a gynecologic pathologist in the Division of Reproductive and Urologic Products (DRUP) reviewed images (low and high power images) of the cases in question. The DRUP reviewer agreed with the 3 central pathologists on all cases that were adjudicated by the GECC as not containing hyperplasia. The DRUP reviewer felt that these cases represented cystic atrophy rather than hyperplasia.*
- *In summary, there is no evidence of a clinically significant increase in the incidence of endometrial hyperplasia in the lasofoxifene-treated subjects compared to placebo-treated subjects.*

5.4.4.4 Endometrial Polyps

The Applicant investigated the risk of developing endometrial polyps in lasofoxifene-treated subjects in 2 subgroups. The first population consisted of approximately 1,000 subjects who underwent transvaginal ultrasonography (TVU) examinations at the end of Year 3 (the TVU prevalence sub-study). In this population, subjects who had an increased endometrial

thickness underwent endometrial biopsy. The second population consisted of all subjects who received study drug and who had a uterus; these women were biopsied only for cause. The numbers of endometrial polyps in these 2 populations are shown in (Table 53). As shown in the table, both pooled analyses indicated that the percentage of subjects with endometrial polyps was increased (approximately doubled) in subjects taking lasofoxifene compared to subjects taking placebo.

Table 53 Incidence of Histologically Confirmed, Adjudicated Endometrial Polyps (Transvaginal Ultrasonography Prevalence Sub-Study and Study A2181002)

Parameter	Lasofoxifene			Placebo
	0.25 mg	0.5 mg	Pooled	
Study A2181002 (PEARL) – Transvaginal Ultrasound – Prevalence Sub-Study				
Number of subjects at risk	354	366	720	360
Total years at risk	1,545	1,615	3,160	1,634
Number (%) of subjects with event	31 (8.8)	20 (5.5)	51 (7.1)	12 (3.3)
Incidence rate per 100 subject-years	2.01	1.24	1.61	0.73
95% CI	(1.36, 2.85)	(0.76, 1.91)	(1.20, 2.12)	(0.38, 1.28)
P-value	0.003	0.163	0.014	
Study A2181002: Full Analysis Set (Excluding Subjects with Pre-treatment Hysterectomy)				
Number of subjects at risk	2,298	2,302	4,600	2,309
Total years at risk	9,144	9,291	18,435	9,387
Number (%) of subjects with event	51 (2.2)	34 (1.5)	85 (1.8)	18 (0.8)
Incidence rate per 100 subject-years	0.56	0.37	0.46	0.19
95% CI	(0.42, 0.73)	(0.25, 0.51)	(0.37, 0.57)	(0.11, 0.30)
P-value	0.001	0.025	0.001	

Source: 4-Month Safety Update: NDA 22-242; page 80 of 84

Division Comments

- *As anticipated, the percentage of polyps is greater in those subjects undergoing additional monitoring (i.e., those in the TVU prevalence sub-study).*
- *Although endometrial polyps have a low risk for developing malignant features (less than 2%) they are associated with vaginal bleeding.*

5.4.4.5 Endometrial Thickness

Measurements of endometrial thickness were obtained from centrally-read TVUs. Change in endometrial thickness in subjects treated with lasofoxifene or placebo was assessed in several clinical trials over treatment period ranging from 12 to 36 months (Table 54). The Applicant found that for all durations of treatment and both doses of lasofoxifene studied (i.e., 0.25 mg and 0.5 mg) the mean change from baseline endometrial thickness was significantly increased over those for placebo. Mean change from baseline for endometrial thickness in subjects treated with 0.5 mg lasofoxifene treatment ranged from 0.61 mm (pooled Phase 2 studies) to 1.44 mm (Study A2181002). Corresponding mean changes from baseline in the placebo-treated subjects were -0.23 mm and -0.71 mm, respectively.

**Table 54 Endometrial Thickness (mm): Change from Baseline to End-of-Study
(Lasofoxifene Phase 2/3 Osteoporosis Prevention and Treatment Studies)**

Study Drug	N	Mean baseline	LS Mean Change*
Study A2181002 (PEARL) – Month 36			
Lasofoxifene 0.25 mg	86	2.55	1.18
Lasofoxifene 0.5 mg	75	2.35	1.44
Placebo	85	2.59	-0.71
Study A2181037 (JADE) – 12 months			
Lasofoxifene 0.25 mg	99	2.01	1.26
Lasofoxifene 0.5 mg	98	2.03	1.14
Placebo	97	2.12	0.20
Study A2181030 (CORAL) – 24 months			
Lasofoxifene 0.25 mg	120	2.73	1.77
Placebo	63	2.72	0.18
Studies A2181003, A2181004 (OPAL) – 24 months			
Lasofoxifene 0.25 mg	279	2.78	1.44
Lasofoxifene 0.5 mg	273	2.77	1.16
Placebo	278	2.81	0.15
Osteoporosis Prevention Phase 2 Studies – 3-24 months			
Lasofoxifene 0.25 mg	54	2.34	1.36
Lasofoxifene 0.5 mg	54	2.66	0.61
Placebo	146	2.73	-0.23

* LS =least square; all changes are statistically significant
Source: Table 18 – Summary of Gynecological Safety; page 49

Division Comment

- *From a clinical standpoint, mean increases of 0.61 to 1.44 mm are not as important as the number of subjects who developed more marked increases in endometrial thickness (described by the applicant as endometrial thickness outliers).*

The number of subjects in each of the studies represented in the preceding table who had an endometrial thickness of 8 mm or greater is summarized in Table 55. In Study A2181002, 17.9% of subjects in the lasofoxifene 0.5 mg treatment, compared to 0% of subjects in the placebo group, had an endometrial thickness of ≥ 8 mm.

Table 55 Numbers of Subjects with Endometrial Thickness \geq 8 mm (Lasofloxifene Phase 2/3 Osteoporosis Prevention and Treatment Studies)

Parameter	Lasofloxifene		Placebo
	0.25 mg	0.5 mg	
Study A2181002 (PEARL) – Month 36			
No. of subjects with measurement	100	95	107
Number (%) of subjects \geq 8 mm	19 (19.0)	17 (17.9)	0
95% CI	(11.8, 28.0)	(10.7, 27.1)	(0.0, 2.7)
P-value vs. placebo	0.001	0.001	
Study A2181037 (JADE) – 12 months			
No. of subjects with measurement	103	101	99
Number (%) of subjects \geq 8 mm	3 (2.9)	3 (3.0)	1 (1.0)
95% CI	(0.6, 8.2)	(0.6, 8.4)	(0.0, 5.5)
P-value vs. placebo	0.622	0.622	
Study A2181030 (CORAL) – 24 months			
No. of subjects with measurement	128	-	63
Number (%) of subjects \geq 8 mm	13 (10.2)	-	0
95% CI	(5.5, 16.7)	-	(0.0, 4.6)
P-value vs. placebo	0.006	-	
Studies A2181003, A2181004 (OPAL) – 24 months			
No. of subjects with measurement	305	295	305
Number (%) of subjects \geq 8 mm	36(11.8)	28 (9.5)	10 (3.3)
95% CI	(8.4, 15.9)	(6.4, 13.4)	(1.5, 5.9)
P-value vs. placebo	0.001	0.003	
Osteoporosis Prevention Phase 2 Studies – 3-24 months			
No. of subjects with measurement	56	55	155
Number (%) of subjects \geq 8 mm	6 (10.7)	6 (10.9)	3 (1.9)
95% CI	(4.0, 21.8)	(4.1, 22.2)	(0.4, 5.5)
P-value vs. placebo	0.012	0.012	

Source: Table 18 – Summary of Gynecological Safety; page 49

Division Comments

- *In the preceding table it appears that the highest percentage of subjects with an endometrial thickness \geq 8 mm was noted at Month 36 in Study A2181002.*
- *The threshold of 8 mm was selected by the Applicant; in clinical practice, clinicians are likely to pursue further diagnostic evaluations for postmenopausal women with an endometrial thickness $>$ 4-5 mm.*

Issue for Consideration

- **The Committee is asked to consider the statistically significant increased percentage of lasofloxifene-treated subjects, as compared to placebo-treated subjects, who developed endometrial thickness of 8 mm or greater. The finding**

that 18-19% of subjects will have an endometrial thickness of 8 mm or greater is of clinical concern because healthcare providers for postmenopausal women will often initiate diagnostic and therapeutic procedures for an endometrial thickness of greater than 4-5 mm.

5.4.4.6 Vaginal Bleeding

The Applicant's analysis of vaginal bleeding from the 4-month safety update is shown in Table 56. The number (and percentage) of subjects reporting vaginal bleeding in the lasofoxifene treatment groups, compared to the placebo group, was statistically significantly greater. In the 0.5 mg lasofoxifene treatment group, 2.5% of subjects reported vaginal bleeding compared to 1.3% of subjects in the placebo group.

Table 56 Vaginal Bleeding - Spontaneously Reported (Study A2181002, 4-Month Safety Update)

Parameter	Lasofoxifene			Placebo
	0.25 mg	0.5 mg	Pooled*	
Number of subjects at risk	2,852	2,852	5,704	2,852
Total years at risk	12,544	12,484	25,027	12,548
Number (%) of subjects with event	62 (2.2)	72 (2.5)	134 (2.3)	37 (1.3)
Incidence rate per 100 subject-years	0.49	0.58	0.54	0.29
95% CI	(0.38, 0.63)	(0.45, 0.73)	(0.45, 0.63)	(0.21, 0.41)
Hazard Ratio			1.82	
95% CI			(1.26, 2.61)	
P-value			0.0014**	

CI=confidence interval

* Pooled includes lasofoxifene doses 0.017 mg, 0.025 mg, 0.05 mg, 0.15 mg, 0.25 mg, 0.4 mg, 0.5 mg, 1.0 mg, 2.5 mg, 10 mg

**P-value significant versus placebo ≤ 0.05

Source: 4-Month Safety Update: NDA 22-242; page 78 of 84

The Applicant stated in the 4-month safety update that 15 (0.3%), 7 (0.2%), and 4 (0.1%) of lasofoxifene 0.25 mg, lasofoxifene 0.5 mg, and placebo subjects, respectively, discontinued treatment because of vaginal bleeding across the Phase 2/3 clinical program.

Division Comment

- *Vaginal bleeding, along with increased endometrial thickness and increased endometrial polyps, will lead to more gynecologic procedures.*

Issues for Consideration

- **The Committee is asked to consider the overall finding of increased vaginal bleeding in the lasofoxifene-treated subjects. The Committee also is asked to consider recommendations regarding clinical management of patients with vaginal bleeding if lasofoxifene were to be approved for the proposed indication.**

5.4.4.7 Uterine Leiomyomata

The numbers (percentages) of subjects with uterine leiomyomata in Study A2181002 are shown in Table 57. Although the percentages of subjects with uterine leiomyomata in the lasofoxifene treatment groups are slightly increased compared to the placebo group, the differences were not statistically significant.

Table 57 Number (%) of Subjects with Uterine Leiomyomata (Study A2181002: 3-Year Data)

Parameter	Lasofoxifene		Placebo
	0.25 mg	0.5 mg	
Number of subjects at risk	354	366	360
Total years at risk	1,059	1,096	1,077
Number (%) of subjects with event	38 (10.7)	35 (9.6)	26 (7.2)
Incidence rate per 100 subject-years	3.59	3.19	2.41
95% CI	(2.54, 4.93)	(2.23, 4.44)	(1.58, 3.54)
Odds Ratio	1.54	1.36	
95% CI	(0.92, 2.60)	(0.80, 2.31)	
P-value	0.101	0.257	

Source: Table 5.14.14; page 2468 of 7454; Study A2181002

5.4.4.8 Pelvic Prolapse / Urinary Incontinence

The numbers (%) of subjects with pelvic organ prolapse/urinary incontinence for the overall Phase 2/3 clinical program are shown in Table 58. The percentages of subjects with pelvic organ prolapse/urinary incontinence were numerically slightly higher in the lasofoxifene treated subjects, but the increases were not statistically significant relative to the placebo group.

Table 58 Number (%) of Subjects with Pelvic Organ Prolapse/Urinary Incontinence (Overall Lasofoxifene Phase 2/3 Clinical Program)

Parameter	Lasofoxifene			Placebo
	0.25 mg	0.5 mg	Pooled*	
Number of subjects at risk	4,549	4,308	10,259	4,701
Total years at risk	14,503	14,008	30,099	14,489
Number (%) of subjects with event	45 (1.0)	37 (0.9)	83 (0.8)	29 (0.6)
Incidence rate per 100 subject-years	0.310	0.264	0.276	0.200
Hazard Ratio			1.418	
95% CI			(0.929, 2.165)	
P-value			0.104	

CI=confidence interval

* Pooled includes lasofoxifene doses 0.017 mg, 0.025 mg, 0.05 mg, 0.15 mg, 0.25 mg, 0.4 mg, 0.5 mg, 1.0 mg, 2.5 mg, 10 mg

Event = adjudicated surgery in Study A2181002 and serious adverse events in other studies
MedDRA preferred terms contributing to the analysis: enterocele, rectocele, bladder prolapse, stress incontinence, stress urinary incontinence, urinary incontinence, colpocele, cystocele, genital prolapse, pelvic prolapse, rectocele, uterine prolapse, uterovaginal prolapse, vaginal prolapse, colporrhaphy

Source: 4-Month Safety Update: NDA 22-242; page 81 of 84

Division Comments

- *The Applicant also performed an analysis of surgeries for pelvic organ prolapse and/or urinary incontinence, as adjudicated by an independent committee, for Study A2181002. The risk of surgery for pelvic organ prolapse or urinary incontinence was not significantly increased in subjects assigned to lasofoxifene (pooled dose groups) compared to placebo.*
- *In Study A2181002 the Applicant monitored for pelvic organ prolapse at screening and at 12 months, 24 months, and 36 months. Specific grades (0-4) were assigned to urethrocele, cystocele, rectocele, vaginal enterocele, and uterine prolapse. There was no evidence of any significant increase in these types of prolapse in the lasofoxifene treatment arms compared to placebo.*

5.4.4.9 Gynecological Uterine Procedures

The numbers (%) of subjects undergoing at least 1 uterine procedure and the numbers of specific types of gynecologic procedures performed in Study A2181002 are presented in Table 59. Subjects represented in this table are those women who were not being monitored routinely by transvaginal ultrasounds (i.e., they underwent TVU only when indicated by symptoms). Within each lasofoxifene treatment group, at least twice the number of women in the lasofoxifene group, compared to that in the placebo group, underwent one or more uterine procedures.

Table 59 Number (%) of Subjects Undergoing ≥ 1 Uterine Procedures and Types of Procedures Performed (Study A2181002: Women not Monitored by Transvaginal Ultrasound; 5-Year Preliminary Data)

Parameter or Procedure	Lasofoxifene		Placebo
	0.25 mg	0.5 mg	
Number of subjects at risk	1348	1351	1354
Number (%) of subjects with at least 1 uterine procedure	115 (8.5)	103 (7.6)	46 (3.4)
95% CI	(7.0%, 10.2%)	(6.2%, 9.2%)	(2.4%, 4.5%)
P-value	0.001*	0.001*	
Procedure*	No. of Events (I.R./100 Subject-years)		
Hysteroscopy	43 (0.71)	30 (0.50)	10 (0.17)
Saline-infused sonohysterogram	3 (0.05)	1 (0.017)	0 (0.00)
Endometrial biopsy	72 (1.20)	80 (1.33)	31 (0.52)
Polypectomy	18 (0.30)	15 (0.25)	2 (0.03)
Dilation and curettage	58 (0.96)	42 (0.70)	17 (0.28)
Hysterectomy	33 (0.55)	16 (0.27)	16 (0.27)
Other	1 (0.02)	3 (0.05)	1 (0.02)

CI = confidence interval; IR = Incidence Rate

*Subjects may have more than one procedure or more than one type of procedure

Source: Study A2181002 Preliminary 5-year report; page 47

Division Comments

- *As shown in the prior table, the number of uterine-related procedures performed in a population not closely monitored was approximately 2-fold greater in the lasofoxifene-treatment groups compared to the placebo group.*
- *In a “real world” scenario, this increase in number of procedures would most likely be driven by lasofoxifene-treated women complaining of vaginal bleeding. An increase in vaginal bleeding was observed in lasofoxifene-treated subjects in Study A2181002 (see Section 5.4.4.6).*

Issues for Consideration

- **The Committee is asked to consider the finding of increased uterine procedures in the lasofoxifene-treated subjects compared to placebo-treated subjects when evaluating the risk/benefit profile of lasofoxifene for the treatment of postmenopausal osteoporosis. Consider the likelihood that lasofoxifene treatment may lead to procedures that are not always office-based and may require anesthesia, especially for postmenopausal women who have some degree of cervical stenosis.**

5.4.4.10 Other Gynecological Adverse Events

In the 4-month safety update, the most commonly reported events (those reported in at least 2% of subjects in the lasofoxifene group that also were more common in the lasofoxifene treatment group included vaginal discharge, endometrial hypertrophy, vaginal candidiasis, and uterine polyp.

Division Comment

- *The specific adverse events of most concern (i.e., endometrial hypertrophy and uterine polyps) have been described previously in Sections 5.4.4.4 and 5.4.4.5.*

5.5 Summary of Safety

The lasofoxifene safety database includes data from 23 clinical pharmacology studies, 11 Phase 2 studies and 6 Phase 3 studies. As of the cut-off for the 4-month safety update for NDA 22-242, there were safety data from 14,958 subjects in lasofoxifene clinical trials. Of these, 10,257 subjects received lasofoxifene, including 4,549 subjects who received lasofoxifene 0.25 mg daily and 4,308 who received lasofoxifene 0.5 mg daily. The number of subject-years at risk was 14,625 years and 14,101 years for the lasofoxifene 0.25 mg and 0.5 mg treatment groups, respectively.

General Safety Findings

In Study A2181002 (5-year preliminary data), the percentages of subjects with SAEs was 30.4%, 28.6%, and 27.8% in the lasofoxifene 0.25 mg, lasofoxifene 0.5 mg, and placebo treatment groups, respectively. The percentages of subjects who discontinued from treatment due to an adverse event in Study A2181002 (based on 5-year preliminary data) were 13.9%, 12.9%, and 12.3% in the lasofoxifene 0.25 mg, lasofoxifene 0.5 mg, and placebo treatment groups, respectively. The most commonly reported all-causality AEs in subjects treated with lasofoxifene 0.25 mg or 0.5 mg that also occurred more frequently in the lasofoxifene

treatment groups, compared to the placebo group, were muscle spasms (usually categorized as leg cramps), hot flushes, and vaginal discharge.

Principal Safety Concerns

The principal safety concerns identified during review of the lasofoxifene clinical trials were:

- An increased percentage of subjects who died (all-cause mortality) in the lasofoxifene treatment group compared to the placebo treatment group
- An increased percentage of subjects with serious venous thromboembolic events in the lasofoxifene treatment group compared to the placebo treatment group
- An increased percentage of subjects (1) with gynecological adverse events (i.e., endometrial polyps, increased endometrial thickness, and vaginal bleeding) or (2) undergoing uterine surgical procedures in the lasofoxifene treatment group compared to the placebo treatment group

Deaths

A greater percentage of lasofoxifene-treated subjects died compared to placebo-treated subjects based on both the 3-year and 5-year safety data from Study A2181002.

Unexpectedly, the percentage of subjects who died in the 0.25 mg lasofoxifene group exceeded that in the 0.5 mg group and was statistically greater than that in the placebo-treated subjects based on 5-year data from Study A2181002. The excess number of deaths were found primarily in the cancer and non-coronary vascular categories. The excess cancer deaths did not appear to be focused in any specific organ system. Slightly more cancer deaths occurred in the brain, lung, and gastrointestinal system in the lasofoxifene-treated subjects.

Venous Thromboembolic Events

Subjects treated with lasofoxifene in Study A2181002 experienced more than a 2-fold increase in venous thromboembolic events (VTEs) compared to subjects treated with placebo. Based on the preliminary 5-year data, this increase was statistically significant in both the 0.25 mg and 0.5 mg lasofoxifene groups for the occurrence of any VTE, deep venous thrombosis (DVT), and pulmonary embolus (PE). There was a 4-fold increase in the risk of a PE (0.25 mg lasofoxifene group) and a 6-fold increase in the risk of a PE (0.5 mg lasofoxifene group) compared to placebo.

Gynecological Adverse Events

There was no evidence of increased endometrial carcinoma or endometrial hyperplasia in the lasofoxifene-treated subjects compared to placebo-treated subjects. Two cases of uterine sarcoma were reported in lasofoxifene-treated subjects. It is possible that both were pre-existing; however, treatment with another SERM, tamoxifen, has been associated with uterine sarcomas.

There was a statistically significant increase in the percentage of lasofoxifene-treated subjects reporting vaginal bleeding compared to placebo-treated subjects. In subjects monitored by yearly transvaginal ultrasonography, 18-19% of subjects treated with lasofoxifene were found to have an endometrial thickness of ≥ 8 mm at Year 3. In addition, there was a statistically significant increase in the percentage of lasofoxifene-treated subjects

who underwent uterine diagnostic and/or therapeutic procedures compared to placebo-treated subjects.

Issues for Consideration

- **The Committee is asked to consider if the overall safety profile for lasofoxifene is acceptable for the demonstrated benefit in the treatment of postmenopausal women with osteoporosis. The Committee also is asked to consider the proportion of treated women who are likely to derive benefit from treatment with lasofoxifene (i.e., prevention of a vertebral fracture) relative to the proportion of treated women who may develop a clinically significant adverse event.**

6 APPENDICES

Appendix 1

Overview of Phase 2 Osteoporosis Studies

Study protocol number and number of country sites Start date/ Status	Study design	Treatment groups	Number of subjects by treatment groups	Demographics Number of M/F subjects Mean age (Age range) Race W/B/A
A218-101 US (19) Started 14 Oct 1997 Completed	Phase 2, multi-center, randomized, double-blind, placebo- and active treatment-controlled, multidose study Duration of treatment = 3 mo Prevention of osteoporosis	<u>Lasofoxifene</u> 0.4 mg QD (1.25 mg every third day) 2.5 mg QD 10 mg QD Conjugated equine estrogen/MPA 0.625/2.5 mg QD Placebo QD	Randomized: 65 Treated: 65 Completed: 59 Randomized: 64 Treated: 64 Completed: 58 Randomized: 67 Treated: 67 Completed: 56 Randomized: 68 Treated: 68 Completed: 62 Randomized: 57 Treated: 57 Completed: 50	Sex: 0 M/65 F 56.8 (44/68) years 57/0/8 Sex: 0 M/64 F 56.2 (50/65) years 60/0/4 Sex: 0 M/67 F 56.6 (48/65) years 59/0/8 Sex: 0 M/68 F 56.3 (44/68) years 60/0/8 Sex: 0 M/57 F 57.2 (48/68) years 52/0/5

F = Female; M = Male; W = White; B = Black; A = Asian

Source: eCTD 5.2 Tabular listing of all clinical studies; page 19

Overview of Phase 2 Osteoporosis Studies

Study protocol number and number of country sites Start date/ Status	Study design	Treatment groups	Number of subjects by treatment groups	Demographics Number of M/F subjects Mean age (Age range) Race W/B/A
A218-101E US (19) Started 15 Oct 1997 Completed	Phase 2, multi-center, randomized, double-blind, placebo- and active treatment-controlled, multidose study Extension of study 218-101 Total duration of treatment = 12 mo (3 months in 218-101 and 9 months in 218-101E) Prevention of osteoporosis	<u>Lasofexifene</u>		
		0.4 mg QD (1.25 mg every third day)	Randomized: 46 Treated: 46 Completed: 40	Sex: 0 M/46 F 57.3 (48/68) years 41/0/5
		2.5 mg QD	Randomized: 38 Treated: 38 Completed: 29	Sex: 0 M/38 F 55.7 (50/64) years 37/0/1
		10 mg QD	Randomized: 34 Treated: 34 Completed: 30	Sex: 0 M/34 F 57.2 (49/65) years 31/0/3
		Conjugated equine estrogen/MPA 0.625/2.5 mg QD	Randomized: 36 Treated: 36 Completed: 32	Sex: 0 M/36 F 55.7 (44/67) years 34/0/2
	Placebo QD	Randomized: 36 Treated: 36 Completed: 29	Sex: 0 M/36 F 57.3 (50/68) years 33/0/3	
A218-102 US (26) Started 18 Nov 1998 Completed	Phase 2, 2-year duration randomized, double-blind, placebo- and active treatment-controlled multi-dose study with 4 parallel groups	<u>Lasofexifene</u>		
		0.25 mg QD	Randomized: 82 Treated: 82 Completed: 51	Sex: 0 M/82 F 59.0 (50/74) years 74/1/7
		1 mg QD	Randomized: 82 Treated: 82 Completed: 56	Sex: 0 M/82 F 57.7 (49/72) years 77/2/3
		<u>Raloxifene</u>		
		60 mg QD	Randomized: 163 Treated: 163 Completed: 116	Sex: 0 M/163 F 57.5 (49/73) years 140/5/18
	Placebo QD	Randomized: 83 Treated: 83 Completed: 56	Sex: 0 M/83 F 57.5 (47/71) years 77/4/2	

F = Female; M = Male; W = White; B = Black; A = Asian

Source: eCTD 5.2 Tabular listing of all clinical studies; pages 20 and 21

Overview of Phase 2 Osteoporosis Studies

Study protocol number and number of country sites Start date/ Status	Study design	Treatment groups	Number of subjects by treatment groups	Demographics Number of M/F subjects Mean age (Age range) Race W/B/A
A218-103 US (24) Started 06 Jul 1998 Completed	Phase 2, multi-center, randomized, double-blind, placebo-controlled, multi-dose 12 month study with 5 parallel groups	<u>Lasofexifene</u> 0.017 mg (0.05 mg every third day) 0.05 mg QD 0.15 mg QD 0.5 mg QD Placebo QD	Randomized: 77 Treated: 77 Completed: 61 Randomized: 75 Treated: 75 Completed: 59 Randomized: 83 Treated: 83 Completed: 54 Randomized: 80 Treated: 80 Completed: 62 Randomized: 79 Treated: 79 Completed: 69	Sex: 0 M/77 F 57.5 (50/72) years 72/3/2 Sex: 0 M/75 F 58.0 (50/69) years 67/3/5 Sex: 0 M/83 F 58.2 (50/72) years 73/2/8 Sex: 0 M/80 F 59.3 (50/72) years 71/2/7 Sex: 0 M/79 F 58.2 (50/74) years 74/1/4

F = Female; M = Male; W = White; B = Black; A = Asian
Source: eCTD 5.2 Tabular listing of all clinical studies; page 22

Study protocol number and number of country sites Start date/ Status	Study design	Treatment groups	Number of subjects by treatment groups	Demographics Number of M/F subjects Mean age (Age range) Race W/B/A
A2181037 (JADE) Korea (3) Japan (11) Taiwan (3) Started 28 June 2004 Completed	A Phase 2 double-blind, randomized, placebo controlled, parallel group, multicenter, dose-response study. One year duration osteoporosis treatment study	<u>Lasofexifene</u> 0.05 mg (one 0.025 mg tablet every other day) 0.25 mg QD 0.5 mg QD Placebo QD	Randomized: 125 Treated: 125 Completed: 108 Randomized: 123 Treated: 123 Completed: 108 Randomized: 124 Treated: 124 Completed: 114 Randomized: 125 Treated: 125 Completed: 108	Sex: 125 F 63.6 (50-79) years 0/0/125 Sex: 123 F 63.9 (50-79) years 0/0/123 Sex: 124 F 62.6 (44-78) years 0/0/124 Sex: 125 F 63.2 (46-79) years 0/0/125

F = Female; M = Male; W = White; B = Black; A = Asian
Source: eCTD 5.2 Tabular listing of all clinical studies; page 27

Overview of Phase 2 Osteoporosis Studies

Study protocol number and number of country sites Start date/ Status	Study design	Treatment groups	Number of subjects by treatment groups	Demographics Number of M/F subjects Mean age (Age range) Race W/B/A
A2181042 (LACE) UK (1) Started 07 Sept 2004 Ongoing	A Phase 3 prospective, double-blind, randomized, placebo-controlled, parallel group single center study-	<u>Lasofoxifene</u> 0.25 mg QD Placebo	All Subjects Blinded: Randomized 51 Treated: 51 Completed:	All Subjects Blinded: Sex: 0 M/51 F

F = Female; M = Male; W = White; B = Black; A = Asian

Source: eCTD 5.2 Tabular listing of all clinical studies; page 26

Appendix 2

Overview of Phase 3 Studies

Study protocol number and number of country sites Start date/ Status	Study design	Treatment groups	Number of subjects by treatment groups	Demographics Number of M/F subjects Mean age (Age range) Race W/B/A
A2181030 (CORAL) US (27) Started 23 May 2003 Completed	A Phase 3, double-blind, randomized, placebo and active controlled, prospective study Duration of treatment = 2 yrs Prevention of osteoporosis	<u>Lasofoxifene</u>	Randomized: 218 Treated: 218 Completed: 177	Sex: 0 M/218 F 62.2 (49-76) years 179/2/37
		0.25 mg QD		
		<u>Raloxifene</u>		
		60 mg QD	Randomized: 215 Treated: 215 Completed: 186	Sex: 0 M/215 F 61.8 (47-77) years 173/2/40
		<u>Placebo</u>	Randomized: 107 Treated: 107 Completed: 90	Sex: 0 M/107 F 61.3 (47-74) years 85/3/19
		QD		

F = Female; M = Male; W = White; B = Black; A = Asian
Source: eCTD 5.2 Tabular listing of all clinical studies; page 16

Study protocol number and number of country sites Start date/ Status	Study design	Treatment groups	Number of subjects by treatment groups	Demographics Number of M/F subjects Mean age (Age range) Race W/B/A		
A2181003 (OPAL) US (29) Argentina (2) Brazil (2) Canada (3) France (1) UK (3) Started 12 Sept 2000 Completed	Phase 3, prospective, double-blind randomized, placebo-controlled, parallel group, multicenter Duration of treatment = 2 yrs Prevention of osteoporosis	Lasofoxifene	Randomized: 230 Treated: 229 Completed: 185	Sex: 0 M/229 F 58.3 (42/75) years 217/4/8		
		0.025 mg (0.05 mg every other day)				
		0.25 mg QD			Randomized: 228 Treated: 226 Completed: 171	Sex: 0 M/226 F 59.6 (43/74) years 208/6/12
		0.5 mg QD			Randomized: 233 Treated: 230 Completed: 178	Sex: 0 M/230 F 58.3 (40/75) years 207/7/16
		Placebo QD	Randomized: 233 Treated: 230 Completed: 195	Sex: 0 M/230 F 59.0 (45/73) years 203/11/16		

F = Female; M = Male; W = White; B = Black; A = Asian
Source: eCTD 5.2 Tabular listing of all clinical studies; page 17

Overview of Phase 3 Studies

Study protocol number and number of country sites Start date/ Status	Study design	Treatment groups	Number of subjects by treatment groups	Demographics Number of M/F subjects Mean age (Age range) Race W/B/A
A2181004 (OPAL) US (29) Argentina (2) Denmark (2) Mexico (2) Norway (2) Started 23 Aug 2000 Completed	Phase 3, prospective, double-blind randomized, placebo-controlled, parallel group, multicenter Duration of treatment = 2 yrs Prevention of osteoporosis	<u>Lasofoxifene</u> 0.025 mg (0.05 mg every other day) 0.25 mg QD 0.5 mg QD Placebo QD	Randomized: 243 Treated: 243 Completed: 194 Randomized: 249 Treated: 248 Completed: 210 Randomized: 245 Treated: 243 Completed: 196 Randomized: 246 Treated: 245 Completed: 193	Sex: 0 M/243 F 58.0 (40/75) years 204/2/37 Sex: 0 M/248 F 58.9 (45/74) years 205/7/36 Sex: 0 M/243 F 58.5 (43/74) years 202/5/36 Sex: 0 M/245 F 57.9 (42/73) years 204/7/34

F = Female; M = Male; W = White; B = Black; A = Asian

Source: eCTD 5.2 Tabular listing of all clinical studies; page 18

Appendix 3

Guideline on the Evaluation of Medical Products in the Treatment of Primary Osteoporosis (European Medicines Agency)



**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

**GUIDELINE ON THE EVALUATION OF MEDICINAL PRODUCTS IN THE TREATMENT
OF PRIMARY OSTEOPOROSIS**

DRAFT AGREED BY THE EFFICACY WORKING PARTY	27 September 2005
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	15 December 2005
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 June 2006
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This guideline replaces NfG on Post Menopausal Osteoporosis in Women CPMP/EWP/552/95 Rev. 1

KEYWORDS	osteoporosis; guidance; osteopenia; "bone mineral density"; fractures; postmenopausal
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**GUIDELINE ON THE EVALUATION OF MEDICINAL PRODUCTS IN THE TREATMENT
OF PRIMARY OSTEOPOROSIS**

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EXECUTIVE SUMMARY

This Guideline is intended to provide guidance for the evaluation of new medicinal products in the treatment of primary osteoporosis, principally in postmenopausal women but also in men. This Guideline should be read in conjunction with Directive 2001/83/EC, as amended, and all other pertinent elements outlined in current and future EU and ICH guidelines and regulations, especially those on:

- Studies in Support of Special Populations: Geriatrics CPMP/ICH/379/99 (ICH E7)
- Dose-Response Information to Support Drug Registration CPMP/ICH/378/95 (ICH E4)
- Statistical Principles for Clinical Trials CPMP/ICH/363/96 (ICH E9)
- Choice of Control Group in Clinical Trials CPMP/ICH/364/96 (ICH E10)
- Note for Guidance on the Investigation of Drug Interactions CPMP/EWP/560/95
- Guideline on the Choice of the Non-Inferiority Margin CPMP/EWP/2158/99
- The Extent of Population Exposure to Assess Clinical Safety for Drugs CPMP/ICH/375/95 (ICH E1A)

This Guideline is intended to assist applicants during the development of antiosteoporotic medicinal products. It is only guidance; any deviation from guidelines should be explained and discussed in the Clinical Overview.

1. INTRODUCTION

1.1. Background and scope of this guideline

Osteoporosis is a systematic skeletal disorder characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.

Osteoporotic fractures cause substantial clinical and economic burden for society. Vertebral and hip fractures have been, for many years, associated with increased morbidity and mortality. More recently, an association has been shown between increased mortality and a collective group of other major nonvertebral fractures (i.e. pelvis, distal femur, proximal tibia, multiple ribs and proximal humerus). Hip, vertebral, forearm and humerus fractures also reduce, to various extents, health-related quality of life with deleterious effects lasting up to several years after the fracture event.

Primary or involutional osteoporosis develops as a result of excessive age-related bone loss. Age and menopause are the two main determinants of osteoporosis. The cessation of ovarian production of oestrogen, at the time of the menopause, results in an accelerated rate of bone loss in women.

Secondary osteoporosis, resulting from immobilisation, diseases (hyperthyroidism, hyperparathyroidism, rheumatoid arthritis) or drugs, especially glucocorticoid therapy and hormonal ablative therapies, in both genders, will not be covered by this guideline.

Hormone replacement therapy (HRT) has been shown to reduce the risk of fracture, but increases the risk of breast cancer and cardiovascular diseases. Oestrogens have been used for prevention of bone loss. However, due to recent discussions/developments, there has been a shift in thinking about the use of medicinal products in osteoporosis. New developments only for prevention of bone loss after menopause are no longer seen as a goal. The use of estrogens in this indication is left to local treatment guidelines, which will take into account both existing data for efficacy and safety. Indication for prevention of osteoporosis or postmenopausal bone loss will not be specifically granted to new products.

1.2. Risk of osteoporotic fractures in women and men

The risk of osteoporotic fractures is determined by several independent factors in addition to low bone mass. Age, prior fractures, a family history of hip fractures, high bone turnover, low body mass index, tobacco use, and alcohol abuse, are the most important factors to be considered. Genetic and nutritional factors (e.g. calcium intake and vitamin D repletion) play significant roles.

A quantitative predictor of osteoporotic fractures in postmenopausal women without a previous fracture is bone mineral density (BMD). The WHO operational definition defines an osteoporotic

woman on the basis of a BMD measurement (spine or hip) showing a T-score below -2.5. The term “severe or established osteoporosis” habitually denotes a T-score below -2.5 in the presence of one or more fragility fractures. Osteopenia is defined as a BMD T-score between -1 and -2.5.

However, BMD alone has a limited value to predict the risk of fractures. The incidence of osteoporotic fractures increases with age. The predictive value of BMD becomes weaker with age. It has become evident that fracture risk is also driven by parameters including bone size and shape, bone turnover, micro-architecture, damage accumulation (micro cracks), and degree of mineralisation or collagen structure, all playing a role in bone strength, and hence in the risk of osteoporotic fractures. Several epidemiological studies showed that a large proportion of incident fragility fractures occur in postmenopausal women who have a BMD T-score above -2.5. The use of bone-related independent risk factors for fractures combined with BMD values provides a global assessment of future fracture risk, allowing the identification of women who should benefit from a treatment to prevent the occurrence of osteoporotic fractures.

Most osteoporotic fractures occur in women because they have lower peak bone mass than men, the effect of menopause increases the risk of fracture at any given age and women have a higher life expectancy. However, the life-time risk of fragility fractures in men is also considered as a significant public health issue. No WHO definition for osteoporosis exists for men. However, in clinical practice the same cut-off for the diagnosis of osteoporosis in men, i.e. BMD below -2.5 standard deviations of the female reference range, has been used. Epidemiological studies have shown a similar relationship between BMD and fracture risk in men and in postmenopausal women, i.e. the predictive value of BMD for the occurrence of fractures is similar in men and in women. Prevalent fractures also predict the risk of future fractures to the same extent in both genders. Other independent risk factors (e.g. family history of hip fracture, alcohol or tobacco use) have not, however, been validated to the same extent in men than in women. Clinical trials of pharmacological intervention in osteoporotic men have shown BMD increases and changes in biochemical markers of bone turnover similar to those observed in postmenopausal women. The limited available fracture data in men show that, when observed, the degree of reduction in vertebral fractures and height loss in men was consistent with that observed in postmenopausal women.

Several chemical entities with original modes of action have been approved for the treatment of postmenopausal osteoporosis after demonstration of an anti-fracture efficacy at the level of the axial skeleton (spine) or appendicular skeleton (all non-vertebral, major non-vertebral, or hip). These products include bisphosphonates with daily or intermittent dosing formulations, selective oestrogen receptor modulators, calcitonin, active vitamin D metabolites, teriparatide, and strontium ranelate. Some of them have also been approved for the treatment of osteoporosis in men. Studies with these different products demonstrated that the relative reduction of fracture risk does not differ between women with different levels of baseline risk of future fractures. Therefore, there is no rationale to make any distinction in the indication between treatment and prevention or between osteoporosis and established osteoporosis. However, the absolute risk reduction of fractures and hence the expected benefit of therapy will be different depending on the basal risk for fractures.

These general principles apply to all classes of anti-osteoporotic agents including hormone replacement therapies.

2. AIM OF TREATMENT

The aim of the pharmacological intervention is to decrease the incidence of fractures. From the regulatory viewpoint, the therapeutic indication will generally be the treatment of osteoporosis in postmenopausal women at increased risk of fracture, or, secondarily, the treatment of osteoporosis in men at increased risk of fracture. The applicant will be requested to demonstrate the effect of the investigated medicinal product on both spinal and non-spinal fractures. For non-spinal fractures, either femoral (hip) or major non-vertebral (pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip) fractures should be assessed. This should be done in properly designed and adequately powered studies. The nominal results of the studies on the axial and appendicular skeleton will be described in the SmPC section on “Pharmacodynamic properties”.

3. PRE-CLINICAL STUDIES

These notes provide guidance for preclinical studies to assess bone architecture and bone strength. In conjunction, other guidelines for standard preclinical testing should be considered, such as Single-dose Toxicity, Repeated Dose Toxicity, Testing of Medicinal Products for their Mutagenic Potential, Carcinogenic Potential, Detection of Toxicity to reproduction for Medicinal Products, and Safety Pharmacology Studies.

Valid techniques for non-invasive in vivo assessment of bone architecture and strength in humans are currently not available. Documentation of drug-induced effects on these variables in animals is, thus, an important component of the initial efficacy and safety assessment.

3.1. Animal models

There are no completely satisfactory models of human osteoporosis, but a number of useful models exist. For drugs that are aimed for use in the treatment of postmenopausal osteoporosis in women, an evaluation of bone quality should be performed in two species, one of which should be the adult ovariectomised rat and the other an animal with oestrogen deficiency induced by ovariectomy and characterised by evaluable cortical bone remodelling. The primate, sheep, adult rabbit or pigs are possible suggestions. As a prerequisite to their clinical development, new chemical entities (NCEs) considered for the treatment of osteoporosis in men should be extensively investigated in the relevant animal models to identify potential gender-specific skeletal toxicity and efficacy.

In addition, it is mandatory for stimulators of bone formation to have a preclinical package demonstrating safety of the tested drug in terms of bone biomechanics at the exposure selected for Phase III clinical trials.

This information should be made available at the time of the file submission.

3.2. Methods of assessing efficacy and safety in animals

To allow relevant inference on long-term bone safety in humans, the study duration should take into account the relative rates of bone turnover between animal and human and the proposed regimen. Normally, studies should be of a sufficiently long duration to ensure their objectives are fully met (e.g. 6 remodelling cycles).

The time of initiation of treatment should reflect the clinical indication. When it is desired to demonstrate an ability to halt bone loss, it is recommended to use animals in which acute oestrogen deficiency is induced to cause bone loss. When it is desired to demonstrate an ability to add bone to an osteopenic skeleton, it is recommended to use animals in which oestrogen deficiency has already induced bone loss.

It is recommended that studies in the adult ovariectomised rat and in the second animal model are timed so as to provide guidance for the Phase II trials and support for the Phase III trials, respectively.

For these studies on bone quality, three exposure levels are normally needed. A low dose should aim at half-maximal response and the middle dose at the optimal response. The high dose should be a reasonable multiple of the middle dose. Where detrimental effects are observed, a clear no-effect dose should be established.

3.2.1. Bone mass/density measurements

Bone mass/density measurements may be made by validated non-invasive methods.

3.2.2. Bone architecture/histology/histomorphometry

The bone histology should be examined using undecalcified histological sections.

3.2.3. Biomechanical testing of bone strength

Validated biomechanical tests should be used. Preferably the same bone should be used for bone density and biomechanical testing. Both long bones and vertebrae should be tested.

4. CLINICAL TRIALS

4.1 General considerations

The studies should aim at defining a treatment schedule, define the optimal effect on the disease progression and explore the safety of the product. Clinical trials should be conducted in patients with characteristics that are representative of those of the population for whom the treatment is intended.

4.2. Populations to be studied

Postmenopausal osteoporosis

The clinical significance of osteoporosis lies in the fractures that occur. In order to encompass the complex relationship between BMD, independent risk factors and the individual 10-year fracture risk (as described in section 1), the suitable population for the clinical trials would be postmenopausal women at increased risk of experiencing osteoporotic fractures based on the known skeletal independent risk factors such as age, BMD, prior fractures, a family history of hip fracture, high bone turnover, low body mass index, current tobacco use, and alcohol abuse, that result in an increased 10-year probability of fractures, regardless of the time elapsed since menopause. Patients with various levels of BMD (i.e. osteopenia or osteoporosis) may be included provided their 10-year risk of fracture is increased.

In order to properly assess the benefit of treatment, the absolute risk of fractures of the included population should be considered. All known factors that determine the fracture risk should be carefully recorded and defined levels of risk for fractures should be prospectively defined on that basis. Based on the fracture rates observed in the placebo arms of the previous pivotal studies of drugs licensed for the treatment of osteoporosis, a 10-year probability of a first fracture can be calculated. For women to be included in a trial a probability range of 15-20% for spine, 5-7.5% for hip and 10-15% for major non-vertebral fractures would be a clinically relevant inclusion criterion. Consistency of the effects versus risk factors at baseline should be evaluated.

It is preferable to include, in a specific trial, patients with a similar basal risk for fractures. All known factors that determine the fracture risk should be carefully recorded and if groups of patients with different levels of estimated basal risk are included, the therapeutic effect should be consistent in all groups.

It is the Applicant's responsibility to provide substantial evidence confirming the validity of the chosen independent risk factor(s) and the characterisation of the population with regard to the absolute fracture risk. Overall, the indication may be expressed as "treatment of osteoporosis in postmenopausal women at increased risk of fracture".

Osteoporosis in men

No WHO definition for osteoporosis exists for men. However, in clinical practice the same cut-off for the diagnosis of osteoporosis in men, i.e. T-score below -2.5 of the female reference range, has been used. Epidemiological studies have shown a similar relationship between BMD and fracture risk in men and in postmenopausal women. However, since the other independent risk factors for fractures have not been as extensively validated in men as in women it is the Applicant's responsibility to justify that the criteria chosen for the inclusion of men in the pivotal study, including BMD, will generate a fracture risk of a magnitude similar to that of postmenopausal osteoporotic women, especially if the indication "treatment of osteoporosis in men at increased risk of fracture" is to be granted based on bridging studies (see 5.3.3). Other potential risk factors for fractures could also be taken into account in men.

4.3. Criteria of efficacy and their assessment

All endpoints to assess efficacy in clinical trials must be defined prior to the start of the trial and included in the study protocol.

4.3.1. Fractures

Fractures should be validated according to pre-defined criteria and the site and time of fracture recorded. Data regarding height and deformities also provide important efficacy information. The primary variable should be based on the occurrence of new axial and peripheral fractures (not on

worsening of previous fractures). Vertebral (clinical or morphometric) fractures and non-vertebral (hip or major non-vertebral) fractures are to be studied separately, preferably but not necessarily in separate studies. If they are studied in a single study, appropriate statistical measures should be applied. In the analysis the patient (not the fracture) should be the sampling unit. The primary variable should be assessed as incidence of patients with new fractures, which may be expressed as vertebral fractures or as a composite of hip fractures and the rest of major non vertebral fractures.

The baseline number of prevalent fractures/deformities must be recorded.

Serial X-rays, performed once a year, should be used to assess vertebral fractures and deformities. Provisions should be made for additional radiographic examinations to identify symptomatic vertebral fractures. A standardisation of procedures for obtaining X-rays is mandatory in order to minimise differences due to variations in the film to focus distance and to centring of X-rays. Prevalent and incident vertebral fractures/deformities should be determined by using morphometric and/or semiquantitative assessments (radiographic assessments). Since it is difficult to assess vertebral fractures accurately, a carefully validated method with predefined criteria for diagnosis of fractures must be used. The assessment should be made at a central facility with blinding to the treatment assignment of the patient. Radiographs should be kept available for possible re-analysis by an independent expert. Patients who wish to withdraw from the study should have an x-ray taken at the time of withdrawal, if more than 6 months have elapsed since the last X-ray.

4.3.2. Bone Mineral Density (BMD)

BMD may be the primary end point in exploratory studies but it is not an appropriate surrogate for fracture reduction. The current usual method for assessing BMD is dual energy X-ray absorptiometry. For all techniques, instrument precision and accuracy are very important. Careful quality control and assurance are required. The use of central BMD quality assurance centres is recommended.

It is desirable to measure BMD in the axial and appendicular skeleton at several different locations, taking into account trabecular and cortical bone. Measurements are mandatory at those sites where osteoporotic fractures most commonly occur, i.e. the spine (measurements can be taken at L₁ to L₄ or L₂ to L₄) and the hip (measurements of total hip and femoral neck BMD). Documentation of the effect on the forearm and/or total body may provide additional valuable information. In elderly subjects, values of spinal BMD should be analysed with caution due to the potential presence of osteophytes. The presence of a fracture in a given vertebra can also affect the analysis of BMD in that region.

4.3.3. Stature/deformity

Secondary endpoints may include stature. Height loss is a well-recognised clinical consequence of vertebral fracture. Measurements of stature should be performed with a validated measuring tool and appropriate quality control.

4.3.4. Biochemical markers

Biochemical markers of bone turnover are used to evaluate the mechanism of action of drugs and the integrated effect on bone. Appropriate biochemical markers of bone turnover include osteocalcin, bone-specific alkaline phosphatase, urine and serum N- or C-telopeptide of type I collagen, and N-propeptide of type I procollagen. In response to treatment, short-term changes (three to six months) in markers of bone remodelling have been demonstrated, along with changes in BMD and/or fractures after a longer period (2 to 3 years). However, the causal link (surrogacy) between the markers and longer term endpoints has not been unequivocally proven. Although BMD and biochemical markers used hitherto are not considered appropriate surrogates in therapeutic confirmatory treatment studies, they should be measured in the pivotal studies, at least in a subset of patients. They should be considered as primary variables in Phase II dose finding trials (see 5.2).

4.4. Criteria of safety and their assessment

All adverse experiences occurring during the course of clinical trials should be fully documented with separate analysis of adverse drug events, dropouts and patients who died while on therapy. Any information available concerning clinical features and therapeutic measures in accidental overdose or deliberate self-poisoning should be provided.

Laboratory tests usually performed in the safety evaluation of all drugs should be performed. Serum levels of calcium, PTH, and 25-OH vitamin D, and for some products also calcium excretion in the urine should be followed.

Radiographs or ultrasound examinations to detect soft tissue calcifications may be indicated with certain drugs.

Quantitative bone histomorphometry on undecalcified sections should be performed in a subset of patients in Phase III trials unless there is pre-clinical justification for not doing so. At least a representative subset of patients should be studied with the aim to disclose any potentially negative effects of the drug on bone remodelling as well as in an attempt to characterise its effects on bone remodelling balance, degree of mineralisation and hardness. Biopsies should demonstrate that bone formed during treatment with the agent is of normal lamellar structure and that there is no evidence of osteomalacia or other defects. The biopsies should be read at a central facility with appropriate expertise. Paired biopsies should be collected whenever possible. However, considering the technical and ethical constraints linked to repeatedly exposing patients to invasive procedures, unpaired biopsies may be acceptable providing the Applicant justifies the relevance of the number of biopsies analysed.

5. STUDY DESIGN

5.1. Human pharmacology

Studies involving the first administration of anti-osteoporotic agents do not differ from the first administration of drugs in general.

5.1.1. Pharmacodynamics

The initial studies should determine the general safety of the compound and should provide an indication of doses of potential clinical relevance.

5.1.2. Pharmacokinetics

The pharmacokinetic information required is stated in detail in the guideline on “Pharmacokinetic Studies in Man”. Apart from the pharmacokinetic studies in healthy volunteers, studies should be performed in the elderly (> 65 years old) and the very elderly (> 75 years old), and in patients with varying degrees of renal dysfunction and hepatic dysfunction.

The difficulty with regard to patients with osteoporosis results from the study of the bone compartment, which varies depending on the state of bone turnover. The possibility that binding of the NCE to bone may not correlate with plasma and urine levels can make interpretation of pharmacokinetic constants difficult.

5.1.3. Interactions

The guideline on the investigation of drug interactions (CPMP/EWP/560/95) should be followed, apprehending that the study population is elderly.

5.2. Dose response studies

A parallel-group, fixed dose, double-blind, placebo-controlled study design should be used in Phase II. Evaluation of at least three doses is recommended. If conclusive data are not obtained, at least two doses should be studied in Phase III studies.

Studies should be designed to allow robust evaluation of dose response. The treatment duration required evaluating significant effects may vary depending on the drug. The duration of treatment should be clearly justified by the applicant in the protocol and the primary analysis performed at this time point.

It is recommended to use co-primary variables including BMD measured at the spine and/or the hip and appropriate biochemical markers of bone turnover. The variables should be specified in the protocol and the study should be powered to detect significant effects on each variable. The mean change from baseline to the end of treatment is an appropriate primary parameterisation for each variable, but responders should also be assessed. The expected mean differences in BMD between active and control group must be predetermined. For inhibitors of bone resorption, BMD responders are patients with changes above baseline at the end of treatment. For stimulators of bone formation,

the responders are patients, with increases in BMD above a threshold that integrates the variability of the DXA technique. The primary BMD site should be the spine, with an absence of deleterious effect documented at other skeletal sites including hip, distal forearm, and/or total body. For biochemical markers the definition of responders should be based on robust scientific evidence.

5.3. Main therapeutic studies

5.3.1. General considerations

Parallel-group, double-blind, placebo-controlled and/or comparator-controlled studies are necessary. The studies must be carefully designed and dimensioned to maintain acceptable power in the face of anticipated dropouts. The use of an active control requires extra precaution in planning and conducting the study (ICH E10).

In principle, placebo-controlled trials should be performed whenever possible. However, if properly justified, non-inferiority trials versus active comparators could be considered if a clear justification of the margin of non-inferiority (CPMP/EWP/2158/99) is provided before the trial has started. In this case, the differences in target populations, the consistency of the effect size, and the assay sensitivity should all be taken into account. Consequently, a placebo arm might be needed. The choice of the comparator should be adequately documented and justified. Similarly, in case of a placebo-controlled superiority trial, the relevance of the findings, compared to currently registered medications, might have to be established.

Sample size calculation must provide assurance that the study will enrol enough patients for the hypothesis (superiority or non-inferiority) proposed. Any supplementation with calcium and/or vitamin D should be consistent in all patient groups and should be clearly documented. Dietary and relevant life style factors should be summarised.

5.3.2. Treatment of osteoporosis in women at increased risk of fracture

The population to be studied (osteoporosis and osteopenia with risk factors for fracture) and the criteria of efficacy and safety and their assessment have been detailed above. The primary variable should be the incidence of patients with new fractures. BMD from areas studied for fracture incidence usually provides important secondary efficacy data. Measurements of suitable biochemical variables reflecting bone turnover could be included among secondary efficacy variables.

Treatment to prevent fractures may be regarded as a long-term treatment although efficacy demonstration will depend on clinical trials of shorter duration. In order to provide fracture and bone safety data, duration of randomised treatment of at least two years is usually appropriate. The efficacy at first year should be considered as a secondary variable and the maintenance of the effect during the second year should be addressed.

With long-term treatment, loss of effect on fracture prevention due to altered bone structure or other changes is a matter of concern. The maintenance of effect after the second year (e.g. 3-5 years) should be studied, although data may be submitted after registration.

Catch up bone loss after withdrawal of treatment has been described with some drugs. Data that show what occurs after withdrawal should be submitted after registration.

5.3.3. Bridging studies

For compounds having demonstrated anti-fracture efficacy and for which the indication “treatment of osteoporosis in postmenopausal women at increased risk of fracture” has been previously granted for a specific dose, formulation or route of administration, an extension of the indication could be given for a new dose, route of administration or formulation on the basis of the demonstration of non-inferiority in terms of BMD changes (differences in the means and percentage of responders) between the original and the new doses, formulations or routes of administration, in a study of minimum one year. Alternative surrogate endpoints like biochemical markers of bone turnover should also be used in bridging studies after a thorough analysis of historical studies showing a good correlation between pharmacokinetic exposures, the pharmacodynamic response and the reduction in fracture risk. To avoid having to conduct separate fracture studies, the time-course of changes in surrogate markers should recapitulate the time-course observed for the original dosing regimen. This should apply to any

surrogate endpoint that is known to be associated with fracture risk, such as BMD and/or a biochemical marker.

Equivalence or non-inferiority can be tested in a bridging study. Equivalence or non-inferiority margins need to be clinically meaningful and should be selected carefully as described in the Guideline on the Choice of the Non-Inferiority Margin (CPMP/EWP/ 2158/99).

5.3.4. Minimal requirement to be granted a marketing indication for the treatment of osteoporosis in men at increased risk of fracture

Taking into consideration the different pathophysiology of osteoporosis in males and in females and the limited knowledge of the mechanism of action of products that have demonstrated efficacy in women, the gold standard for being granted a marketing authorisation for the treatment of osteoporosis in men at increased risk of fracture remains the demonstration of anti-fracture efficacy (spine and/or non-spine fractures) during a 2-year minimum, placebo-controlled, prospective study. However, once an initial marketing authorisation has been granted to a NCE for the treatment of postmenopausal osteoporosis in women at high risk of fracture, a separate bridging study of the same NCE, using the same formulation, dose, and route of administration in male osteoporotic patients could be sufficient for being granted a marketing authorisation with the indication “treatment of osteoporosis in men at increased risk of fracture” provided that:

- the duration of the study is at least one year;
- the dosage is justified
- the applicant justifies that the cut-off of BMD, age and any other risk factor chosen for the inclusion of men in the pivotal study will generate a fracture risk of a similar magnitude compared with postmenopausal women that were recruited in the studies used to obtain the indication “Treatment of postmenopausal osteoporosis in women at increased risk of fracture” (see 4.2 – Populations to be studied)
- the magnitude of the changes in BMD versus placebo is similar to that observed in postmenopausal osteoporotic women treated with the same compound and is proportional to the decreased incidence of fractures in treated women.

If these conditions are not fulfilled, or if the mechanism of action of the NCE is gender specific, a bridging strategy will not be acceptable and a therapeutic study with fracture endpoints will be required in a separate trial in men.