

Pfizer Inc

FABLYN® (lasofoxifene tartrate) 0.5 mg Tablets

Reproductive Health Drugs Advisory Committee Briefing Document, 08 September 2008

PFIZER INC

FABLYN® (lasofoxifene tartrate) 0.5 mg Tablets

NDA 22-242

**REPRODUCTIVE HEALTH DRUGS ADVISORY COMMITTEE
BRIEFING DOCUMENT**

08 SEPTEMBER 2008

01000007826140\1.0\Approved\05-Aug-2008 14:04

AVAILABLE FOR PUBLIC RELEASE WITHOUT REDACTION

TABLE OF CONTENTS

FABLYN® ADVISORY COMMITTEE BRIEFING DOCUMENT	13
1. SUMMARY	13
2. INTRODUCTION	21
2.1. Osteoporosis	21
2.2. Therapeutic Options	22
2.3. Product Description and Pharmacological Class	22
2.4. Proposed Indication	23
3. CLINICAL PHARMACOLOGY	24
4. PHASE 2/3 CLINICAL DEVELOPMENT PROGRAM OVERVIEW	25
4.1. Phase 2/3 Studies	25
4.2. Phase 2/3 Safety Database	27
4.3. Phase 2/3 Patient Population	29
5. CLINICAL EFFICACY	30
5.1. Introduction	30
5.2. Study Methodology	30
5.2.1. Study Design and Conduct	30
5.2.2. Selection of the Study Population	32
5.2.3. Efficacy Evaluations	32
5.3. Methods of Analysis	33
5.3.1. Analysis Populations	33
5.3.2. Efficacy Endpoints	34
5.3.2.1. Bone	34
5.3.2.2. Adjudicated Breast Cancer Efficacy Endpoints	36
5.3.2.3. Other Efficacy Endpoints	36
5.3.3. Multiple Comparison Considerations	36
5.3.4. Imputation of Missing Data	36
5.4. Selection of Dose Regimen	37
5.5. Demographics and Baseline Characteristics	38
5.6. Patient Disposition	40

5.7. Bone Fracture Results.....	40
5.7.1. Vertebral Fracture	40
5.7.1.1. New/Worsening Radiographic Vertebral Fracture	40
5.7.1.2. Incidence of Multiple Radiographic Vertebral Fracture.....	42
5.7.1.3. Time to First Clinical Vertebral Fracture	43
5.8. Nonvertebral Fracture.....	43
5.8.1. Risk of All Nonvertebral Fracture.....	43
5.8.2. Risk of Clinical Fracture	46
5.9. Other Bone Effects	47
5.9.1. Bone Mineral Density and Bone Mineral Content.....	47
5.9.2. Markers of Bone Turnover.....	49
5.10. Vulvar and Vaginal Atrophy Endpoints	49
5.11. Results in Subpopulations	51
5.12. Long-term Maintenance of Effects.....	51
5.13. Clinical Efficacy Summary of Results	52
6. CLINICAL SAFETY	53
6.1. Introduction	53
6.2. Safety Analyses	53
6.3. Adverse Events.....	55
6.3.1. Common Adverse Events.....	55
6.3.2. Discontinuations due to Adverse Events	59
6.3.3. Serious Adverse Events.....	59
6.3.4. Deaths.....	62
6.4. Breast Endpoints.....	71
6.4.1. ER+ Breast Cancer	71
6.4.2. All Breast Cancer	72
6.4.3. ER+ Invasive Breast Cancer	72
6.4.4. Invasive Breast Cancer.....	73
6.4.5. Ductal Carcinoma in Situ	73
6.4.6. Breast Density	73
6.5. Cardiovascular Safety Endpoints	74

6.5.1. Venous Thromboembolic Events	74
6.5.2. Stroke	79
6.5.3. Major Coronary Events	81
6.5.4. Lipids and Inflammation	83
6.5.5. Adjudicated Hospital Admission for Cardiovascular Events.....	84
6.5.6. QT Interval	85
6.6. Hepatic Safety	86
6.7. Serious Gallbladder Events	86
6.8. Cataracts	86
6.9. Gynecological Safety.....	87
6.9.1. Introduction	87
6.9.2. Endometrial Cancer.....	91
6.9.3. Endometrial Hyperplasia.....	94
6.9.4. Endometrial Effects of Lasofoxifene	95
6.9.4.1. Endometrial Cystic Changes.....	96
6.9.4.2. Endometrial Thickness	98
6.9.4.3. Benign Cystic Atrophy	104
6.9.4.4. Mechanism of Benign Cystic Change	109
6.9.4.5. Endometrial Polyps.....	110
6.9.5. Vaginal Bleeding.....	112
6.9.6. Pelvic Prolapse/Urinary Incontinence.....	113
6.9.7. Uterine Procedures	116
6.9.8. Beneficial Vaginal Changes	118
6.10. Safety in Other Groups and Situations	120
6.11. Long-term Safety.....	120
6.12. Clinical Safety Summary of Results.....	120
7. PROPOSED INDICATED DOSE.....	122
8. BENEFITS, RISKS AND RISK MANAGEMENT	122
REFERENCES	128

TABLES

Table 1.	Effect of Lasofoxifene on Fracture Endpoints through 3 Years in PEARL	16
Table 2.	Lasofoxifene 0.5 mg Benefits and Risks	20
Table 3.	Summary of Clinical Pharmacology Studies by Study Type	24
Table 4.	Summary of Phase 2/3 Studies by Study Type.....	25
Table 5.	Number of Patients Treated in the Lasofoxifene Phase 2/3 Clinical Development Program.....	27
Table 6.	Duration of Treatment – Lasofoxifene Phase 2/3 Clinical Program	29
Table 7.	Demographic and Baseline Characteristics – Lasofoxifene Phase 2/3 Clinical Program.....	30
Table 8.	Efficacy Endpoints in PEARL	34
Table 9.	Dose Response Analysis of Percent Change from Baseline in Lumbar Spine BMD, Total Hip BMD and LDL-C – Phase 2 Dose Response Set	37
Table 10.	Baseline Characteristics - PEARL.....	39
Table 11.	Patient Disposition – PEARL	40
Table 12.	Analysis of Time to First New/Worsening Radiographic Vertebral Fracture - PEARL – Full Analysis Set	41
Table 13.	Analysis of Time to First New/Worsening Radiographic Vertebral Fracture - PEARL – Women with or without Prevalent Fracture at Baseline	41
Table 14.	Analysis of Time to First New/Worsening Radiographic Vertebral Fracture – PEARL – Women with Baseline LS BMD T-Score ≤ -2.5 or Baseline LS BMD T-Score > -2.5	42
Table 15.	Analysis of Time to First Moderate or Severe Radiographic Vertebral Fracture – PEARL – Full Analysis Set	42
Table 16.	Frequency of New/Worsening Radiographic Vertebral Fractures – PEARL – Full Analysis Set	43
Table 17.	Analysis of Time to First Nonvertebral Fracture – PEARL – Full Analysis Set	44
Table 18.	Analysis of Time to First Nonvertebral Fracture – PEARL – Women with Baseline LS BMD T-Score ≤ -2.5 or Severe Osteoporosis	45
Table 19.	Analysis of Time to First Major Nonvertebral Fracture– PEARL – Full Analysis Set	45
Table 20.	Frequency of Major Nonvertebral Fractures by Anatomical Site – PEARL – Full Analysis Set	46
Table 21.	Analysis of Time to First Clinical Fracture –PEARL – Full Analysis Set.....	46

Table 22. Analysis of BMD by Site and Whole Body BMC: Percent Change from Baseline at Month 36 –PEARL – BMD Subgroup	48
Table 23. All Causality Adverse Events Reported in $\geq 5\%$ of Patients in Any Treatment Group (lasofoxifene 0.25 mg, lasofoxifene 0.5 mg, or placebo) - Phase 2/3 Clinical Program	56
Table 24. Selected* All Causality Adverse Events with $< 5\%$ Incidence in Any Treatment Groups (lasofoxifene 0.25 mg, lasofoxifene 0.5 mg) - Phase 2/3 Clinical Program	58
Table 25. All Causality Adverse Events Resulting in Discontinuation from Treatment Occurring in $\geq 0.3\%$ of Patients in Any Treatment Group (lasofoxifene 0.25 mg, lasofoxifene 0.5 mg) – Lasofoxifene Phase 2/3 Clinical Program	59
Table 26. All Causality Serious Adverse Events Occurring at ≥ 0.3 Events per 100 Patients in Any Treatment Group (placebo, lasofoxifene 0.25 mg, lasofoxifene 0.5 mg) - Phase 2/3 Clinical Program	61
Table 27. Cardiovascular Endpoint Classification Committee Cause of Death Categories	63
Table 28. Death Causality as Determined by External Endpoint Adjudication Committee – PEARL	63
Table 29. Adjudicated Cancer Deaths by Anatomical Site –PEARL	64
Table 30. Analysis of Time to All Cause Mortality –PEARL - Full Analysis Set	66
Table 31. Mortality Incidence Rates (95% CI) by Region - PEARL	70
Table 32. Time to First Adjudicated ER+ Breast Cancer–PEARL - Full Analysis Set	72
Table 33. Time to First Adjudicated All Breast Cancer –PEARL - Full Analysis Set	72
Table 34. Time to First Adjudicated ER+ Invasive Breast Cancer Endpoint –PEARL - Full Analysis Set	73
Table 35. Time to First Adjudicated Invasive Breast Cancer– PEARL - Full Analysis Set	73
Table 36. Analysis of Time to First On-Study Venous Thromboembolic Event, Deep Vein Thrombosis, Pulmonary Embolus, Retinal Vein Thrombosis at 3 Years –PEARL – Full Analysis Set	75
Table 37. Analysis of Time to First On-Study Venous Thromboembolic Event, Deep Vein Thrombosis, Pulmonary Embolus, Retinal Vein Thrombosis at 5 Years – PEARL – Full Analysis Set	76
Table 38. Deaths with Evidence of Pulmonary Embolism	77
Table 39. Analysis of Time to First Adjudicated Stroke –PEARL - Full Analysis Set	79
Table 40. Incidence of Adjudicated Strokes – PEARL – Full Analysis Set	80
Table 41. Hemorrhagic and Non-Hemorrhagic Stroke –PEARL	80
Table 42. Analysis of Time to First Adjudicated Major Coronary Event –PEARL - Full Analysis Set	81

Table 43. Incidence of Adjudicated Major Coronary Events – PEARL Full Analysis Set ..	83
Table 44. Lipids Median Percent Change from Baseline at 3 Years – PEARL – Lipids Subgroup	84
Table 45. Analysis of Time to First Adjudicated Hospital Admission for Cardiovascular Event - PEARL – Full Analysis Set	85
Table 46. Per Protocol Transvaginal Ultrasound Assessments - Lasofoxifene Phase 2/3 Studies 218-101/E, 218-102, 218-103, A2181002 (PEARL), A2181003/1004 OPAL, A2181002 (CORAL), A2181037 (JADE)	88
Table 47. Analysis of Incidence of Endometrial Cancer in Lasofoxifene Phase 2/3 Studies of at Least 1 Year in Duration	92
Table 48. Analysis of Incidence of Endometrial Cancer – PEARL – Full Analysis Set Excluding Patients with Pre-Treatment Hysterectomy	93
Table 49. Lasofoxifene Exposure in PEARL versus Raloxifene in MORE and Tamoxifen in NSABP P-1	94
Table 50. Analysis of Time to First Endometrial Hyperplasia – Lasofoxifene Phase 2/3 Clinical Program - Full Analysis Set Excluding Patients with Pre-treatment Hysterectomy	95
Table 51. Endometrial Morphology at End-of-Study –PEARL – TVU-I	96
Table 52. Heterogeneous Endometrial Echotexture at End-of-Study (All Patients without Polyps Confirmed by Histology) – Studies 218-101/E, 218-102, and 218-103	98
Table 53. Endometrial Thickness (mm) - Analysis of Change from Baseline to End-of-Study – PEARL – TVU-I	98
Table 54. Incidence of Endometrial Thickness Outliers –PEARL – TVU-I	99
Table 55. Benign Histological Changes – Lasofoxifene Phase 2/3 Clinical Studies -Patients at Risk for Centrally-Read Biopsy	104
Table 56. Analysis of Incidence of Adjudicated Endometrial Polyps – PEARL	111
Table 57. Analysis of Time to Vaginal Bleeding (Spontaneously Reported) –PEARL - FAS	112
Table 58. Analysis of Time to Treatment-Emergent Surgery for Either Pelvic Organ Prolapse or Urinary Incontinence - PEARL - Full Analysis Set	116
Table 59. Incidence of Follow-up Uterine Procedures - PEARL - Patients with No Planned TVU (Without Baseline Hysterectomy)	117
Table 60. Lasofoxifene 0.5 mg Benefits and Risks	124
Table 61. Activities to Monitor and Minimize Risk	126

FIGURES

Figure 1. Chemical Structure for Lasofoxifene Tartrate	23
Figure 2. Timeline of Lasofoxifene Clinical Development Program	26
Figure 3. Patient-years of Lasofoxifene Exposure in the Phase 2/3 Clinical Development Program.....	28
Figure 4. C-Telopeptide and Osteocalcin: Median Percent Change from Baseline –PEARL - BMD Sub-group	49
Figure 5. Change from Baseline in 4 Co-primary Endpoint Parameters – Phase 3 VVA Studies in Postmenopausal Women.....	50
Figure 6. Vaginal pH and Maturation Index in PEARL – TVU-I	51
Figure 7. Mortality Incidence by Region in PEARL	68
Figure 8. Cumulative Incidence of Mortality by Geographic Region – PEARL.....	69
Figure 9. Cumulative Incidence of First Adjudicated Major Coronary Event – Study A2181002 (PEARL) Full Analysis Set.....	82
Figure 10. A2181002 (PEARL): TVU-I Management Algorithm.....	89
Figure 11. Gynecological Surveillance by TVU - PEARL.....	91
Figure 12. All Patients with On-Study Cystic Echotexture - PEARL -TVU-I Subgroup.....	97
Figure 13. Endometrial Thickness and Echotexture for Lasofoxifene Patients with Maximum On-Study Endometrial Thickness ≥ 8 mm by the Year 1 Visit and no Endometrial Thickness Measurement Subsequent to a Polypectomy or D&C - PEARL.....	100
Figure 14. Endometrial Thickness and Echotexture for Lasofoxifene Patients with Maximum On-Study Endometrial Thickness ≥ 8 mm after the Year 1 Visit and by the Year 2 Visit and no Endometrial Thickness Measurement Subsequent to a Polypectomy or D&C - PEARL	101
Figure 15. Endometrial Thickness and Echotexture for Lasofoxifene Patients with Maximum On-Study Endometrial Thickness ≥ 8 mm after the Year 2 Visit and no Endometrial Thickness Measurement Subsequent to a Polypectomy or D&C - PEARL.....	102
Figure 16. Endometrial Thickness and Echotexture for Lasofoxifene Patients with Maximum On-Study Endometrial Thickness ≥ 8 mm and an Endometrial Thickness Measurement Subsequent to a Polypectomy or D&C - PEARL.....	103
Figure 17. Benign Endometrial Effects of Lasofoxifene – Cystic Changes and Benign Cystic Atrophy	105

Figure 18. Comparison of Benign Cystic Atrophy and Endometrial Hyperplasia – Low Power Photomicrographs (25x original magnification)	107
Figure 19. Comparison of Benign Cystic Atrophy and Endometrial Hyperplasia – High Power Photomicrographs (400x original magnification)	108
Figure 20. Endometrial Effects of Lasofoxifene and Estrogen.....	110
Figure 21. Uterine Prolapse Scores at Baseline and 3 Years –PEARL	114
Figure 22. Uterine Cystocele Scores at Baseline and 3 Years –PEARL	115

Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time profile
BL	Baseline
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
BrdU	Bromodeoxyuridine
CDER	Center for Drug Evaluation and Research
CECC	Cardiovascular Endpoint Classification Committee
CI	Confidence interval
cm	Centimeter
COPD	Chronic obstructive pulmonary disease
CORE	Continuing outcomes relevant to Evista
CT	Computed tomography
CHMP	Committee for Medicinal Products for Human Use
Cmax	Maximum plasma concentration
CORAL	Comparison of Raloxifene and Lasofoxifene (A2181030)
CRP	C-reactive protein
CTX	C-telopeptide
CVA	Cerebrovascular accident
CYP	Cytochrome p"450" monooxygenase enzymes
D&C	Dilation and curettage
DCIS	Ductal carcinoma in situ
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DVT	Deep vein thrombosis
DXA	Dual energy x-ray absorptiometry
ECG	Electrocardiogram
ED	Maximally effective dose
Emax	Estimated maximal drug effect
EMA	European Agency for the Evaluation of Medicinal Products
EOS	End of study
EQ-5D	Standardized instrument for measuring health outcome
ER	Estrogen receptor
ER+	Estrogen receptor positive
ET	Endometrial thickness
EU	European Union
Evista®	Raloxifene
FABLYN®	Lasofoxifene
FAS	Full analysis set
FDA	Food and Drug Administration
FN	Femoral neck
Fosamax®	Alendronate
FSD	Female sexual dysfunction
Fx	Fracture
GECC	Gynecological endpoint evaluation committee
h	Hour
HDL-C	High density lipoprotein cholesterol
HR	Hazard ratio
HR-QoL	Health Related Quality of Life
hs-CRP	High sensitivity C-reactive protein
HT	Hormone therapy
ICH	International Conference on Harmonisation
Inf	Infinity
IHD	Ischemic heart disease

IND	Investigational new drug application
IOF	International Osteoporosis Foundation
IR	Incidence rate
JADE	Japanese Asian Dose Evaluation (A2181037)
kg	Killogram
kg/m ²	Killogram per meter of height, squared
L1-L4	The first through fourth lumbar spine vertebrae
LACE	Lasofoxifene and Cytokine Evaluation (2181042)
LDL-C	Low density lipoprotein cholesterol
LOCF	Last observation carried forward
LS	Lumbar spine or least squares
MDS	MDS Pharma (CRO clinical trial service)
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MI	Maturation index or Myocardial infarction
µg	Microgram
min	Minutes
ml	Milliliter
mm	Millimeter
MORE	Multiple outcomes of raloxifene evaluation
MRHD	Maximum recommended human dosage
msec	Millisecond
NIH	National Institutes of Health
NDA	New drug application
ng	Nanogram
NNH	Number needed to harm
NNT	Number needed to treat
NOF	National Osteoporosis Foundation
NsABP	National surgical adjuvant breast and bowel project
OPAL	Osteoporosis Prevention and Lipid Lowering (A2181003 and A2181004)
OVX	Ovariectomized
PE	Pulmonary embolism
PEARL	Postmenopausal Evaluation and Risk-reduction with Lasofoxifene (A2181002)
PEPI	Postmenopausal estrogen/progestin intervention trial
P1NP	Procollagen type 1 N-terminal propeptide
PK	Pharmacokinetic
PYR	Patient-years
QD	Quaque die (every day)
QT	Time interval between Q and T events on electrocardiogram
QTc	QT interval corrected for heart rate
RMP	Risk management plan
RR	Relative risk
RVT	Retinal vein thrombosis
RUTH	Raloxifene use for the heart
SAE	Serious adverse event
s-CTX	Serum C-telopeptide
SD	Standard deviation
SERM	Selective estrogen receptor modulator
SIS	Saline infusion sonography
SOC	System organ class
T _{1/2}	Half life
TIA	Transient ischemic attack
Tmax	Time of C _{max} , hours
T-score	The number of standard deviations (SD) above or below the average BMD value for young healthy gender-matched controls
TVU	Transvaginal ultrasound
TVU-I	Transvaginal ultrasound – incidence (annual subgroup)
TVU-P	Transvaginal ultrasound – prevalence
ULN	Upper limit of normal
US	United States

Pfizer Inc

FABLYN® (lasofoxifene tartrate) 0.5 mg Tablets

Reproductive Health Drugs Advisory Committee Briefing Document, 08 September 2008

vs	Versus
VTE	Venous thromboembolic event
VVA	Vulvar and vaginal atrophy
WHI	Women's Health Initiative
yr	Year

01000007826140\1.0\Approved\05-Aug-2008 14:04

FABLYN® ADVISORY COMMITTEE BRIEFING DOCUMENT

1. SUMMARY

Introduction

New Drug Application (NDA) 22-242 was submitted by C.P. Pharmaceuticals International CV (with Pfizer Inc. acting as US agent) to request approval for FABLYN® (lasofoxifene tartrate, hereafter referred to as lasofoxifene) 0.5 mg Tablets, a selective estrogen receptor modulator (SERM), for the treatment of osteoporosis in postmenopausal women at increased risk of fracture.

The Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) Division of Reproductive and Urologic Products has asked that an Advisory Committee meeting be held on 8 September 2008 as part of the review process for the lasofoxifene NDA. This briefing document has been prepared to assist members of the committee in assessing the benefit-risk profile of lasofoxifene for the proposed indication.

Development Objectives

Lasofoxifene was developed by Pfizer to provide an effective treatment for postmenopausal osteoporosis, one that reduces the risk of both vertebral and nonvertebral fractures, as well as to address other postmenopausal conditions, including reduction in risk of breast cancer and treatment of vulvar and vaginal atrophy (VVA). Currently, no single medication addresses these needs together. Hence, there is a need for additional effective medications to prevent fractures in postmenopausal women that provides these additional benefits.

Product Description

Lasofoxifene belongs to the substituted tetrahydronaphthalenol class of SERM compounds. SERMs are chemically diverse and act by binding to the α and β isoforms of the estrogen receptor (ER α or ER β), which have distinct cellular functions. Depending upon the tissue type, SERMs demonstrate either agonist or antagonist activity at the estrogen receptor.

FABLYN®, the commercial dosage form of lasofoxifene, is a 0.5 mg, peach-colored, modified triangular, film-coated tablet.

Development Program

Pfizer has conducted an extensive development program comprised of 23 clinical pharmacology studies and 17 Phase 2/3 clinical studies. The development program was designed to support the use of lasofoxifene for the treatment of postmenopausal osteoporosis (the proposed indication of this NDA), the prevention of postmenopausal osteoporosis, and

the treatment of VVA. More than 10,000 women have received lasofoxifene in Phase 2/3 clinical trials, representing more than 27,000 patient-years of exposure.

Two NDAs were submitted in 2004 to the FDA: NDA 21-757 for the prevention of osteoporosis in postmenopausal women and NDA 21-843 for the treatment of moderate to severe symptoms of VVA in postmenopausal women with low bone mass. These NDAs contained data on approximately 3,000 patient-years of exposure to lasofoxifene. In Not Approvable letters issued in 2005 (NDA 21-757) and 2006 (NDA 21-843), the FDA acknowledged that efficacy had been demonstrated for both indications, but stated concerns regarding a hypothetical risk of endometrial cancer and an increased risk of invasive gynecological procedures.

Since the review of those submissions by the FDA, the lasofoxifene safety database has enlarged approximately 9-fold due to completion of Study A2181002 (Postmenopausal Evaluation and Risk-reduction with Lasofoxifene [PEARL]) at 5 years. PEARL is the large, multinational fracture trial that provides the pivotal efficacy and safety data for the proposed osteoporosis treatment indication. Enlargement of the safety database allows a more robust assessment of the benefit-risk profile of lasofoxifene for the treatment of osteoporosis in postmenopausal women at increased risk of fracture and has enabled Pfizer to address the specific concerns on gynecological safety previously raised by the FDA.

As agreed upon with the FDA, 5-year results are presented in this document for clinical safety endpoints, only, unless otherwise noted

Clinical Pharmacology Results

Results of the clinical pharmacology investigations show that lasofoxifene is extensively metabolized in humans via multiple pathways and is eliminated mainly through oxidative (CYP3A4 and CYP2D6) and conjugative (glucuronidation) metabolism. Lasofoxifene is highly bound to plasma proteins but binding does not appear to be affected by mild or moderate hepatic impairment.

Food does not affect the bioavailability of lasofoxifene; therefore, lasofoxifene can be dosed without regard to the timing of meals.

Lasofoxifene has linear pharmacokinetics over a wide dose range (0.01 to 100 mg). The T_{\max} of lasofoxifene is approximately 6 hours and the half-life ($T_{1/2}$) is approximately 6 days.

Age, weight, race, mild to moderate hepatic impairment, mild to moderate renal impairment, or use of concomitant medications have not been associated with clinically meaningful differences in lasofoxifene pharmacokinetics. These observations obviate the need to make dosage adjustments for these patient-specific factors. Additionally, lasofoxifene is not expected to have clinically meaningful pharmacokinetic drug interactions. This is based on the results of studies of the effects of ketoconazole (CYP3A4 inhibitor), paroxetine (CYP2D6 inhibitor), and fluconazole (CYP2C9 inhibitor) on the pharmacokinetics of lasofoxifene, and on the results of studies of lasofoxifene's effects on the pharmacokinetics of drugs that it may

be co-administered with in an aging population, such as warfarin, dextromethorphan, chlorzoxazone, methylprednisone, and digoxin.

Clinical Efficacy Results

Demonstration of lasofoxifene's efficacy for the proposed indication is based on results from Study A2181002 (PEARL), the large, multinational, pivotal Phase 3 osteoporosis treatment study. PEARL was originally designed as a 3-year study, but was extended by 2 additional years via a protocol amendment prior to patients reaching their Month 36 visit. A prospectively defined 3-year analysis provides the pivotal efficacy and safety data for the proposed osteoporosis treatment indication. Subsequent to the submission of the NDA, final 5-year results from the extended completed study became available.

The PEARL study was a prospective, randomized, double-blind, placebo-controlled, osteoporosis treatment study in postmenopausal women at increased risk of fracture. Two doses of lasofoxifene were studied: lasofoxifene 0.25 mg and lasofoxifene 0.5 mg. The primary endpoint at 3 years was the risk of new/worsening radiographic vertebral fracture. The key secondary endpoints were the incidence of multiple radiographic vertebral fractures and time to first clinical vertebral fracture. Additional secondary endpoints at 3 years, which include other fracture endpoints, breast cancer endpoints, and indices of vaginal benefit, are described in greater detail in Section 5.3.

Extending the study through 5 years provided sufficient power to detect a difference in nonvertebral fractures and ER+ breast cancer; accordingly, the risk of nonvertebral fracture and the risk of ER+ breast cancer were selected as the 2 co-primary endpoints at 5 years. Five-year key secondary endpoints were the risk of clinical fracture and the risk of hip fracture. Additional secondary endpoints at 5 years included radiographic vertebral fractures, other fracture endpoints, and other breast cancer endpoints.

As agreed upon with the FDA, efficacy results for all endpoints, with the exception of major nonvertebral fractures, are presented in this document through 3 years. Results for major nonvertebral fractures are presented both through 3 years and through 5 years. Also, by agreement with the FDA, breast cancer results are discussed in the clinical safety section. An indication for breast cancer prevention is not sought in this application.

Results are summarized in Table 1 for the different fracture endpoints and patient populations evaluated in the PEARL study; those that are significantly different from placebo are shaded. Lasofoxifene 0.5 mg reduced radiographic vertebral and nonvertebral fractures in postmenopausal women, including those at highest risk of fracture: women with severe osteoporosis.

Table 1. Effect of Lasofoxifene on Fracture Endpoints through 3 Years in PEARL

	Lasofoxifene			
	0.25 mg		0.5 mg	
	HR (95% CI)	Reduction (%)	HR (95% CI)	Reduction (%)
Analysis of time to first				
Radiographic vertebral fracture				
new/worsening [†]	0.69 (0.55, 0.87)*	31	0.58 (0.45, 0.73)*	42
with prevalent at baseline	0.70 (0.51, 0.97)*	30	0.52 (0.36, 0.74)*	48
without prevalent at baseline	0.68 (0.49, 0.95)*	32	0.63 (0.45, 0.88)*	37
with LS BMD T-score <-2.5	0.67 (0.52, 0.86)*	33	0.65 (0.50, 0.84)*	35
moderate/severe	0.84 (0.62, 1.13)	16	0.68 (0.49, 0.94)*	32
Clinical vertebral fracture[‡]	0.83 (0.55, 1.26)	17	0.66 (0.43, 1.03)	34
Nonvertebral fracture	0.86 (0.70, 1.05)	14	0.78 (0.64, 0.96)*	22
with LS BMD T-score <-2.5	0.76 (0.61, 0.95)*	24	0.78 (0.63, 0.98)*	22
with severe osteoporosis ^a	0.76 (0.59, 0.98)*	24	0.73 (0.56, 0.94)*	27
Major nonvertebral fracture^b	0.89 (0.73, 1.10)	11	0.75 (0.60, 0.92)*	25
Clinical fracture	0.87 (0.72, 1.04)	13	0.77 (0.64, 0.93)*	23
Hip fracture	0.87 (0.48, 1.58)	13	0.78 (0.42, 1.44)	22

*P-value significant vs placebo.

[†]Primary endpoint

[‡]Key secondary endpoint

^aSevere osteoporosis defined as LS BMD T-score ≤-3.0 or ≤-2.5 plus baseline prevalent fracture.

^b5-year results.

Additionally, the frequency of multiple new/worsening radiographic vertebral fractures (a key secondary endpoint at 3 years) was significantly lower for both lasofoxifene dose groups compared to placebo at 3 years.

Lasofoxifene also significantly increased BMD of the lumbar spine, total hip, and components of the hip (femoral neck, greater trochanter, intertrochanteric area and Ward's triangle), and decreased markers of bone turnover, including C-telopeptide (CTX), procollagen type 1 N-propeptide (PINP), osteocalcin and bone-specific alkaline phosphatase, compared with placebo.

Lasofoxifene had favorable effects on endpoints associated with vaginal atrophy. In PEARL, lasofoxifene 0.25 mg and 0.5 mg significantly reduced vaginal pH and demonstrated favorable effects on the vaginal maturation index compared to placebo in postmenopausal women with osteoporosis. The effects in PEARL were consistent with those observed in the pivotal VVA studies in postmenopausal women with low bone mass, whose efficacy the FDA acknowledged in the 2006 Not Approvable letter for NDA 21-843.

Clinical Safety Results

The safety of lasofoxifene has been extensively studied and its safety profile well characterized. The data demonstrate that lasofoxifene is generally safe and well tolerated. There are 2 safety findings of note: an increase in venous thromboembolic events (VTEs) and an increased incidence of diagnostic uterine procedures, both of which are addressed in proposed risk management activities.

The safety database has shown the adverse event profile of lasofoxifene to be consistent with that observed with other SERMs. The most common adverse events associated with lasofoxifene treatment are muscle spasms and hot flush. Vaginal discharge is also reported more commonly on lasofoxifene, which may reflect beneficial changes in the vagina that associated with the efficacy of lasofoxifene in VVA. Most adverse events were mild to moderate in severity and infrequently associated with treatment discontinuation.

Serious adverse events more commonly observed on lasofoxifene were generally gynecologic or vascular in nature and occurred at low incidence. The gynecologic serious adverse events included uterine polyp and endometrial hypertrophy, both considered benign findings, and an increase in events of uterine prolapse. The small increased reporting of uterine prolapse was not confirmed by comprehensive and specific rating scales used to evaluate pelvic organ prolapse, nor was there a significant increase in prolapse surgery through 5 years of follow-up in the PEARL trial.

The lasofoxifene development program included a comprehensive evaluation of all reported deaths, the results of which indicate that lasofoxifene is not associated with an increase in mortality risk. The majority of deaths occurred in the PEARL trial, the longest trial in the program with the highest mean age of participants and the highest enrollment. The causes of death in PEARL were consistent with those generally observed in women of similar age.

Lasofoxifene was associated with a reduction in risk of breast cancer. Lasofoxifene 0.5 mg significantly reduced the risk of all breast cancer, ER+, invasive, and ER+ invasive breast cancer through 3 years and through 5 years; these effects were not consistently observed with lasofoxifene 0.25 mg. ER+ breast cancer was a co-primary endpoint in the PEARL study at 5 years.

VTEs, stroke, major coronary events, cataracts, and gallbladder events, which constitute general safety events of special interest for any SERM, were comprehensively evaluated in the PEARL study. The data show that lasofoxifene was associated with an approximate 2-fold increased risk of VTEs. The increased risk of VTEs was primarily driven by an increased risk of deep vein thrombosis. Pulmonary embolism occurred less frequently but was also significantly increased in lasofoxifene-treated patients compared to placebo-treated patients.

In PEARL, lasofoxifene was not associated with an increased risk of stroke. While the prospectively-defined analysis included transient ischemic attacks (TIAs), an analysis excluding TIAs, consistent with the way stroke is frequently analyzed, showed lasofoxifene

to be associated with a decreased risk of stroke. Most stroke events were ischemic in nature and were balanced across treatment groups. A review of all fatal stroke events did not indicate an increased risk associated with lasofoxifene.

Lasofoxifene 0.5 mg was associated with a significant reduction in major coronary events (a composite endpoint including coronary death, nonfatal myocardial infarctions, coronary revascularization procedures, documented new ischemic heart disease, and hospitalizations for unstable angina) through 5 years. Markers of cardiovascular risk that were measured through 3 years (i.e., total cholesterol, LDL-cholesterol, and high sensitivity C-reactive protein) were also significantly reduced on lasofoxifene compared to placebo. Lasofoxifene was not associated with adverse effects on cardiac function including vital signs, ECG findings, or QTc prolongation.

Lasofoxifene was not associated with an increase in gallbladder events or cataracts.

As previously noted, the FDA identified a concern with the theoretical risk of endometrial cancer in the Not Approvable letters received in 2005 and 2006. The larger clinical safety database does not show evidence of an increased risk of endometrial cancer associated with the use of lasofoxifene through 5 years. Further, there is no evidence of an increased risk of endometrial hyperplasia, considered a precursor of endometrial cancer, with lasofoxifene.

Lasofoxifene is associated with benign effects on the endometrium that are characterized by an approximate 1.5 mm mean increase in endometrial thickness and increased cystic echotexture on ultrasound, which are consistent with benign cystic atrophy on biopsy. These benign effects are attributed to increased vascular permeability by lasofoxifene, which results in uterine imbibition and accumulation of fluid in both the glands and stroma of the endometrium. Accumulation of glandular luminal fluid results in the cystic echotexture and increased endometrial thickness observed on ultrasound, together with the benign cystic atrophy observed on biopsy. Importantly, these effects occur in the absence of proliferative effects. Lasofoxifene, consistent with other SERMs, is associated with a small increased incidence of benign endometrial polyps.

In the PEARL study, vaginal bleeding was reported with low frequency, but was more common in lasofoxifene-treated patients compared to placebo (excess incidence of 3 patients/1000 patient-years). The small increase in vaginal bleeding, together with asymptomatic benign endometrial findings detected in unplanned transvaginal ultrasound, contributed to an increase in diagnostic uterine procedures. Endometrial biopsy was the most common diagnostic uterine procedure performed.

In summary, the lasofoxifene safety profile has been extensively studied, and 2 main risks have been identified: an increase in VTEs similar to that observed with other SERMs and an increase in diagnostic uterine procedures (primarily office-performed endometrial biopsies), mainly as a result of a small increase in vaginal bleeding and investigative follow-up of the benign asymptomatic findings encountered during uterine surveillance. Both risks are addressed in the proposed risk management activities.

Proposed Indicated Dose

Lasofloxifene 0.5 mg is the proposed indicated dose for the treatment of osteoporosis in postmenopausal women based on improved efficacy in reducing osteoporotic fractures throughout the skeleton and comparable safety compared to lasofloxifene 0.25 mg.

Benefit-Risk Profile and Risk Management

Lasofloxifene affords a unique benefit among SERMs for the treatment of osteoporosis in postmenopausal women at increased risk of fractures by reducing both radiographic vertebral and nonvertebral fractures as well as clinical fractures (vertebral and nonvertebral fractures associated with pain and discomfort). The efficacy of lasofloxifene on nonvertebral and clinical fractures is within scope of that achieved with bisphosphonates (Black et al, 2007). Nonvertebral fractures are an important clinical endpoint that account for a large portion of the clinical burden associated with osteoporosis (Simonelli et al, 2003), and clinical fractures are considered predictive of an increased mortality risk (Trone et al, 2007). Vertebral fractures are associated with loss of height, kyphosis, pain, mobility impairment, and limitations of activities of daily living (Lindsay, R. in Harrison's Online, 2001).

Lasofloxifene is unique among SERMs in demonstrating improvements in VVA. In addition, lasofloxifene has superior effects on BMD, markers of bone turnover, and serum lipid profiles compared to raloxifene (based on head-to-head osteoporosis prevention trials). The effect on reduction in risk of breast cancer observed with lasofloxifene has also been observed with raloxifene, which was recently approved in the US for the reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and for reduction in risk of invasive breast cancer in postmenopausal women at high risk of invasive breast cancer. An indication for the prevention of breast cancer is not being sought in the current application.

Lasofloxifene can also be differentiated from bisphosphonates in a number of ways. Firstly, lasofloxifene can be dosed at any time of day without regard to food or drink unlike bisphosphonates, which have strict dosing requirements due to low oral bioavailability. Additionally, lasofloxifene is not incorporated into the bone matrix and does not become embedded in the bone for long periods of time resulting in longterm concerns about bone quality. Finally, lasofloxifene provides extraskeletal benefits to postmenopausal women that bisphosphonates do not including a reduction in breast cancer and VVA.

The main general safety risk associated with lasofloxifene use is an increase in VTEs, consistent with other SERMs. There is no evidence that lasofloxifene increases the risk of stroke, and through 5 years of follow-up, lasofloxifene was associated with a decreased risk of stroke and major coronary events.

With respect to gynecological safety, there is no evidence to suggest that lasofloxifene increases the risk of endometrial cancer or endometrial hyperplasia. The exposure (patient-years) upon which the analysis was based is twice that of tamoxifen in the NSABP P-1 trial, in which an increased risk of endometrial cancer was evident by 3 years for subjects who

received tamoxifen. It also exceeds that used to establish that raloxifene does not increase the risk for endometrial cancer in the MORE Study (Grady et al, 2004).

While all SERMs have uterine effects to varying degrees, lasofoxifene's effects on the uterus in the clinical program were benign. The main gynecological risk associated with lasofoxifene use appears to be a small increase in diagnostic uterine procedures (primarily office endometrial biopsies), mainly as a result of a small increase in vaginal bleeding and investigative follow-up of benign asymptomatic endometrial findings encountered during uterine surveillance. In the community setting and according to current guidelines, Pfizer's proposed risk minimization activities are expected to limit this risk to women who experience vaginal bleeding. Women with vaginal bleeding would most likely first undergo Transvaginal Ultrasound (TVU) rather than an invasive diagnostic procedure per these guidelines (ACOG, 2006; Goldstein et al, 2001; NHS guidance, 1999; Sign, 2002).

The benefit-risk profile for lasofoxifene 0.5 mg, the proposed indicated dose, based on statistically significant effects is summarized in the following table.

Table 2. Lasofoxifene 0.5 mg Benefits and Risks

	Number of Patients Annualized Rate(%)			
	Placebo	Lasofoxifene 0.5 mg	NNT	NNH
Proposed Indicated Benefits				
Radiographic vertebral fracture	176 (2.14)	105 (1.27)	116	
Nonvertebral fracture	209 (2.44)	167 (1.95)	204	
Clinical fracture	246 (2.88)	193 (2.26)	161	
Additional Benefits				
VVA*	178 (5.97)	213 (7.37)	72	
Major coronary events	95 (0.67)	66 (0.46)	492	
Breast cancer (all types)	24 (0.18)	5 (0.04)	721	
ER+	21 (0.15)	4 (0.03)	806	
Risks				
VTE	18 (0.13)	37 (0.26)		751
DVT	13 (0.09)	28 (0.20)		951
PE	2 (0.01)	9 (0.06)		2037
Diagnostic uterine procedures	36 (0.53)	95 (1.40)		115

NNH=number needed to harm based on 1 year of treatment; NNT=number need to treat based on 1 year of treatment.

*Based on improvement from baseline in the most bothersome symptom in Phase 3 VVA studies; assumes maximal efficacy achieved and maintained after 12 weeks and 50% VVA in osteoporotic patients.

The risks that have been identified and characterized during the lasofoxifene clinical development program are addressed in the proposed prescribing information. To refine further the understanding of the lasofoxifene product profile, to optimize patient safety, and to realize the full therapeutic benefit of this product, Pfizer is committed to a program to manage actual and potential risk. In addition to appropriate prescribing information

(including a proposed patient package insert), this program will include routine and enhanced pharmacovigilance activities, and education of health care providers regarding (1) the risk factors, symptoms, and risk mitigation of VTE, (2) the benign endometrial changes that may occur in postmenopausal women on lasofoxifene, and (3) currently accepted guidelines for endometrial cancer surveillance. Pfizer also plans to conduct a large, 8-year, prospective cohort study that will assess gynecological and non-gynecological outcomes in women treated with lasofoxifene or raloxifene in a community setting.

With appropriate product labeling and risk management, lasofoxifene's unique benefits can provide a viable therapeutic option for postmenopausal women at increased risk of osteoporosis. Based on improved efficacy in reducing osteoporotic fractures throughout the skeleton and comparable safety compared to lasofoxifene 0.25 mg, lasofoxifene 0.5 mg is the proposed recommended dose.

2. Introduction

2.1. Osteoporosis

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing patients to an increased risk of fracture (National Institutes of Health [NIH] Consensus Panel, 2001). It occurs as the result of multiple mechanisms that together cause microarchitectural deterioration of the skeletal structure and loss of bone mass (Raisz, 2005). Failure to produce a skeleton of optimal mass and strength during growth, and an excess of bone resorption and inadequate bone formation throughout life, may all contribute to the development of the disease. However, the decline in circulating estrogen that occurs with the cessation of menses is the signal event resulting in an increased risk of the disease for postmenopausal women. In the first 5-7 years following menopause, women can lose up to 20% of their bone mass (National Osteoporosis Foundation [NOF], 2003).

As of 2002, 10 million people (7.8 million women) aged ≥ 50 years had osteoporosis, and almost 34 million (21.8 million women) more, who had low bone mass, were at increased risk for fractures in the United States (US) (NOF, 2007). Worldwide, osteoporosis affects 200 million people with 75 million of these in Europe, Japan, and the US (International Osteoporosis Foundation [IOF], 2007). With the aging of the world population, osteoporosis is a growing major public health threat.

Osteoporosis is considered a "silent disease" and is often diagnosed clinically only after the occurrence of a fracture (NOF, 2003). The risk for a 50-year-old American woman suffering an osteoporotic fracture in her remaining lifetime is estimated at 40% (Johnell & Kanis, 2005). The lifetime risk for a 50-year old British woman has been estimated at 53.2% compared to the estimated lifetime risk for a 50-year-old woman of 2.6% for endometrial cancer, 10% for breast cancer, 46% for coronary heart disease, and 20% for stroke (Dennison et al, 2006). In the US, osteoporotic fractures are responsible for approximately 500,000 hospitalizations, 800,000 emergency room visits, 2.6 million physician visits, and 180,000 nursing home placements each year (US Department of Health and Human Services, 2004.)

Nonvertebral fractures are an important clinical endpoint since these types of fractures account for most of the disability due to osteoporosis (Cummings, 2006; Simonelli et al, 2003). Hip fracture, a nonvertebral fracture considered among the most devastating consequences of osteoporosis, has an annual incidence of 1.5 million in the US and are projected to increase to about 6.3 million by 2025. Furthermore, 1 in 5 persons die during the first year following a hip fracture and nearly one-third of those with a hip fracture require nursing home placement (Lane 2006).

As a result, osteoporosis imposes a major economic burden on health-care systems world-wide. The combined annual costs of all osteoporotic fractures have been estimated to be \$20 billion (US) in the US and about \$30 billion (US) in the European Union (EU) (Cummings & Melton, 2002).

2.2. Therapeutic Options

The bisphosphonates (alendronate, risedronate, ibandronate, and zoledronate) are the most commonly prescribed medications for the treatment of osteoporosis. Their benefits are restricted to the skeleton where they decrease the risk of vertebral and nonvertebral fractures. They offer no additional benefits outside the skeleton. Furthermore, risks with bisphosphonate use have been identified and include: esophagitis, esophageal ulcers and erosion, hypocalcemia, bone, joint, and muscle pain, and osteonecrosis of the jaw, and, for zoledronate, acute phase reactions and atrial fibrillation.

Raloxifene, a selective estrogen receptor modulator, is also approved for the treatment of osteoporosis. It reduces the risk of vertebral fractures and breast cancer; however, it does not reduce the risk of nonvertebral fractures and no effect on VVA has been demonstrated. Risks associated with raloxifene include VTEs and an increased risk of death due to stroke in women at high risk for cardiovascular disease.

Despite the availability of approved therapies, osteoporosis remains an inadequately recognized, prevented and treated disease. Most postmenopausal women who have osteoporosis have not been diagnosed. Most postmenopausal women with osteoporosis are not receiving effective medication. Furthermore, noncompliance with available therapeutic regimens remains high (Jakob et al, 2006; Papaioannou et al, 2007).

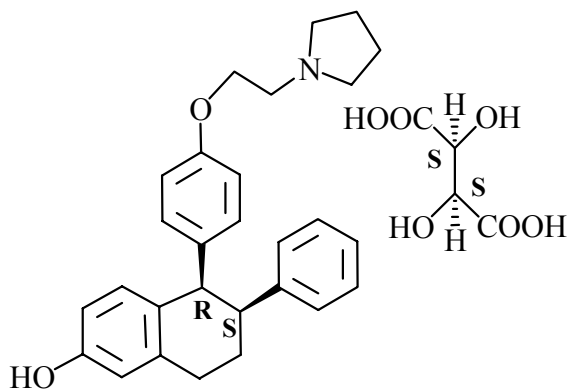
Hence, there is a need for additional effective and well-tolerated medications to prevent debilitating osteoporotic fractures, especially nonvertebral fractures, and extend the options for women not currently treated for osteoporosis. Additional benefits offered by osteoporosis treatment, besides reduction in fracture risk, may help ensure that postmenopausal women stay on therapy and derive long-term benefit.

2.3. Product Description and Pharmacological Class

Lasofoxifene is a tartrate salt with a white-off-white crystalline appearance, an aqueous solubility of 1.1 mg/ml, and a molecular weight of 563.64 daltons. Lasofoxifene tartrate is designated chemically as (5R,6S)-5,6,7,8-tetrahydro-6-phenyl-5-[4-[2-(1-

pyrrolidinyl]ethoxy] phenyl]-2-Naphthalenol, (2S,3S)-2-3-dihydroxybutanedioate. The structure of lasofoxifene tartrate is shown in Figure 1.

Figure 1. Chemical Structure for Lasofoxifene Tartrate



The commercial dosage form of lasofoxifene is a 0.5 mg, peach-colored, modified triangular, film-coated tablet.

Lasofoxifene belongs to the substituted tetrahydronaphthalenol class of SERM compounds. SERMs exert selective agonist and antagonist effects on different estrogen target tissues. SERMs are chemically diverse and act by binding to the α and β isoforms of the estrogen receptor (ER α or ER β), which have distinct functions in cells (McDonnell, 2003; Musa et al, 2007). The resultant conformational change and receptor dimerization allows interaction with coregulators and promoter regions on DNA.

The pharmacological uniqueness of SERM activity depends upon (1) the differential expression and distribution patterns of estrogen receptors (α and β) in target tissues, (2) the unique ligand-binding conformational changes of each receptor depending upon the particular SERM bound, (3) varying combinations of coregulator (coactivator and corepressor) proteins determined by the ligand-binding conformational change and depending upon the target tissue, and (4) differential gene activation via classic and non-classic estrogen response elements (Osborne et al, 2000; Riggs & Hartmann, 2003; Levy et al, 2007).

2.4. Proposed Indication

The indication sought in NDA 22-242 for FABLYN® (lasofoxifene tartrate 0.5 mg film-coated tablets) is the treatment of osteoporosis in postmenopausal women at increased risk of fracture.

The proposed indication is based primarily on a prospectively defined 3-year analysis from the pivotal Phase 3 Study A2181002 (Postmenopausal Evaluation and Risk-reduction with

Lasofoxifene [PEARL]); 5-year safety results from the extended recently completed study have also been included.

3. Clinical Pharmacology

The clinical pharmacology profile of lasofoxifene was characterized in a comprehensive Phase 1 program comprised of 23 studies. The studies were conducted predominantly in postmenopausal women using single or multiple doses of lasofoxifene ranging from 0.01 mg to 100 mg. The Phase 1 studies are listed by type in [Table 3](#). All studies were complete at the time of submission of NDA 22-242, and all data were included.

Table 3. Summary of Clinical Pharmacology Studies by Study Type

Study Type/Category	Study Number
Pharmacokinetics in healthy volunteers	218-001, 218-002, 218-004
Routes of metabolism and excretion	218-006
Pivotal bioequivalence of commercial formulation	A2181018, A2181028
Pivotal food effect	A2181036
Hepatic impairment	A2181019
Drug interactions	A2181020, A2181022, A2181023, A2181024, A2181027, A2181029, A2181035
Relative bioavailability and non-definitive bioequivalence	218-003, 218-005, A2181007 A2181017,
Pharmacokinetics in Japanese vs. Caucasian Women	A2181006, A2181011, A2181025, 218-007

The principal findings of the clinical pharmacology program are summarized below.

The bioavailability of lasofoxifene was not affected by food. Therefore, lasofoxifene can be dosed without regard to the timing of meals.

Lasofoxifene is extensively metabolized in humans via multiple pathways and is eliminated mainly through oxidative (CYP3A4 and CYP2D6) and conjugative (glucuronidation) metabolism. Less than 2% of lasofoxifene is excreted unchanged in the urine. Lasofoxifene is highly bound to plasma proteins with the fraction unbound consistently being less than 1%. Binding to plasma proteins does not appear to be affected by mild or moderate hepatic impairment.

Lasofoxifene exhibits linear pharmacokinetics over a wide dose range (0.01 to 100 mg). Steady-state pharmacokinetics are consistent with expectations from single-dose pharmacokinetics. The T_{max} of lasofoxifene is approximately 6 hours and the half-life ($T_{1/2}$) is approximately 6 days.

There are no clinically meaningful differences in lasofoxifene pharmacokinetics due to age, weight, race, mild to moderate hepatic impairment, or in women with estimated creatinine clearance as low as 32 mL/min. An assessment of lasofoxifene pharmacokinetics in patients with severe hepatic impairment has not been performed, and this would be reported in the proposed prescribing information.

Lasofoxifene has not demonstrated clinically meaningful pharmacokinetic drug interactions as either the object or precipitant of an interaction. The pharmacokinetics of lasofoxifene were not significantly affected ($\leq 35\%$ increase in AUC) by ketoconazole (CYP3A4 inhibitor), paroxetine (CYP2D6 inhibitor), or fluconazole (CYP2C9 inhibitor); therefore, other inhibitors of these CYP isoforms are unlikely to produce clinically meaningful alterations in lasofoxifene exposure and no dosage adjustments are required. Lasofoxifene did not alter the metabolism of dextromethorphan (CYP2D6 substrate) or chlorzoxazone (CYP2E1 substrate), or the pharmacokinetics of warfarin (CYP2C9 substrate), methylprednisolone (CYP3A4 substrate) or digoxin (MDR1 P-glycoprotein substrate). Based on these data, lasofoxifene is not expected to alter the pharmacokinetics of other drugs that are cleared by these CYP isoforms or by transport via MDR1 P-glycoprotein.

4. Phase 2/3 Clinical Development Program Overview

4.1. Phase 2/3 Studies

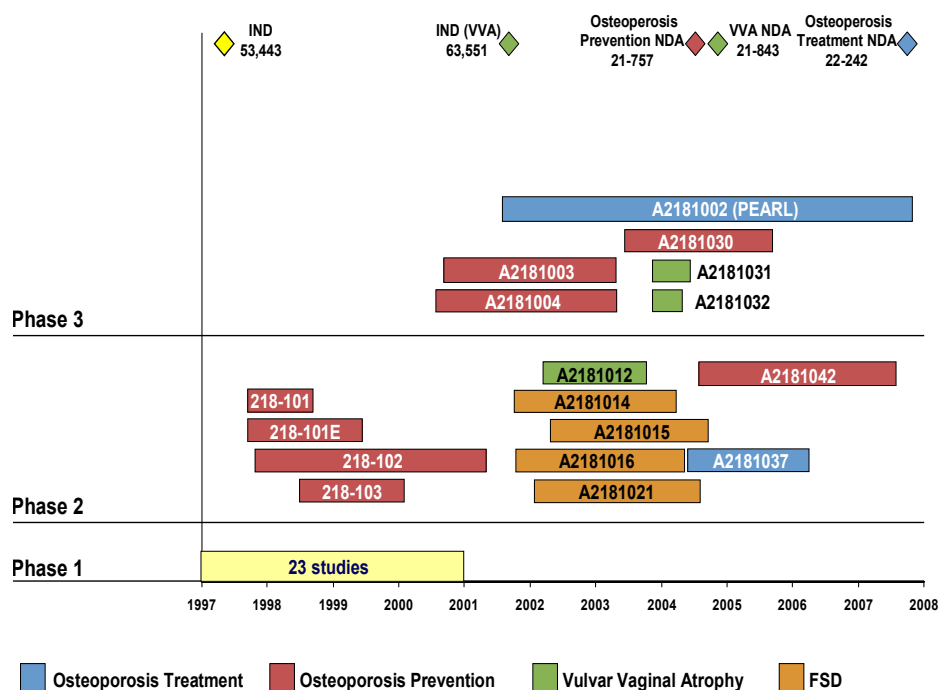
The Phase 2/3 program comprises 17 studies evaluating the effectiveness of lasofoxifene in the treatment of osteoporosis, the prevention of osteoporosis, the treatment of VVA, and the treatment of female sexual dysfunction (FSD). The studies are summarized by development phase in [Table 4](#).

Table 4. Summary of Phase 2/3 Studies by Study Type

Objective	Study
Phase 3 Studies	
Treatment of osteoporosis	A2181002 (PEARL)
Prevention of osteoporosis	A2181003/A2181004 (OPAL), A2181030 (CORAL)
Treatment of VVA	A2181031, A2181032
Phase 2 Studies	
Treatment of osteoporosis	A2181037 (JADE)
Prevention of osteoporosis	218-101, 218-101E, 218-102, 218-103, A2181042 (LACE)
Vulvar and vaginal atrophy	A2181012
Treatment of FSD	A2181014, A2181015, A2181016, A2181021

A timeline of the clinical development program is shown in [Figure 2](#).

Figure 2. Timeline of Lasofofifene Clinical Development Program



Two NDAs were submitted to the FDA in 2004: NDA 21-757 for the prevention of osteoporosis in postmenopausal women and NDA 21-843 for the treatment of moderate to severe symptoms of VVA in postmenopausal women with low bone mass. In Not Approvable letters issued in 2005 for osteoporosis prevention and 2006 for treatment of VVA, the FDA acknowledged that efficacy had been demonstrated for both indications, but stated concerns regarding a hypothetical risk of endometrial cancer and an increased risk of invasive gynecological procedures.

Study A2181002 (PEARL), is the the pivotal Phase 3 study to support the proposed osteoporosis treatment indication. The study was initially designed to last for 3 years with risk reduction of new/worsening radiographic vertebral fracture the prospectively defined primary efficacy endpoint in accord with FDA guidance. The protocol for this 3-year study was finalized in May 2001. The protocol was then amended in April 2004, prior to patients reaching their Month 36 visit and subsequent unblinding of 3-year data, to extend the study to 5 years. A separate analysis plan was prepared to support the analysis and reporting of data at 5 years. The co-primary endpoints at 5 years were risk reduction of ER+ breast cancer and risk reduction of nonvertebral fractures. Three-year data were included in the initial NDA 22-242 osteoporosis treatment submission. Five-year results from the study using a cutoff date of 16 April 2008 were submitted to the NDA in June 2008.

PEARL study design features are reviewed in Sections 5.2.1. Key features of the Phase 2/3 studies are summarized in [Appendix 1](#).

4.2. Phase 2/3 Safety Database

Over 10,000 women received lasofoxifene in the Phase 2/3 clinical development program, the majority of whom participated in the PEARL study ([Table 5](#)).

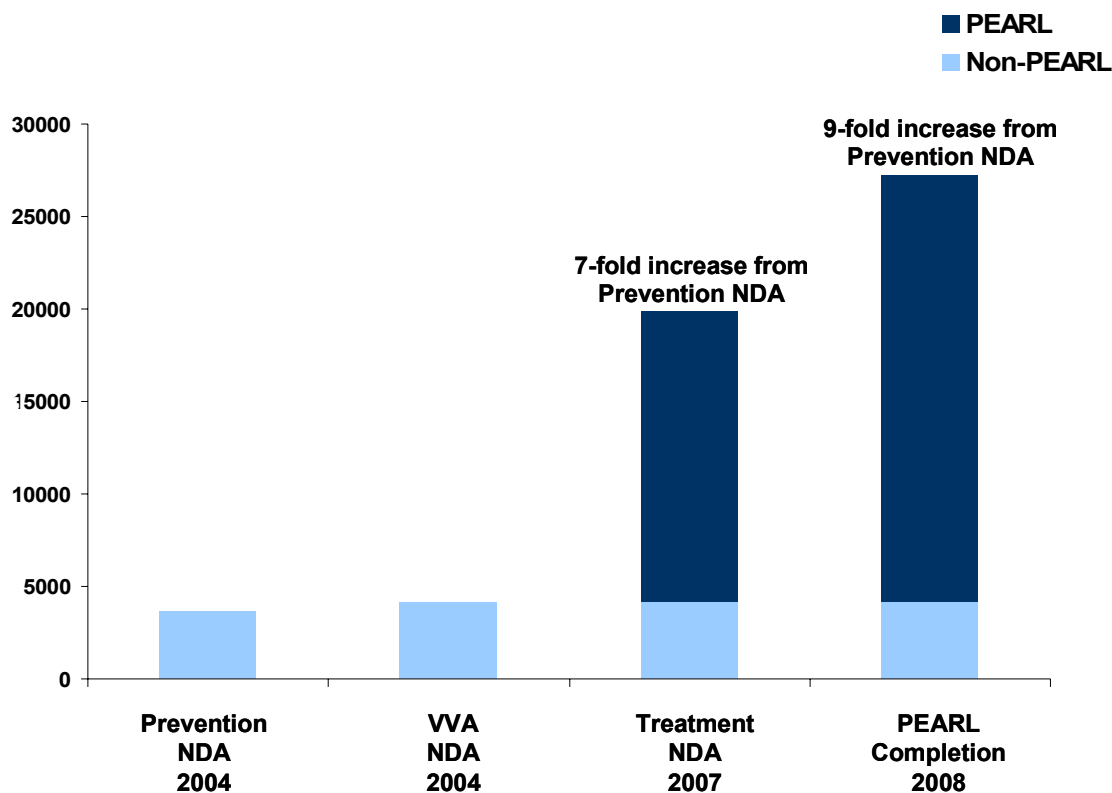
Table 5. Number of Patients Treated in the Lasofoxifene Phase 2/3 Clinical Development Program

	Number of Patients		Exposure (Patient-Years)	
	Overall	Lasofoxifene	Overall	Lasofoxifene
Total	15,404	10,257	42,143	27,910
Phase 3 Osteoporosis Treatment and Prevention Studies				
A2181002 (PEARL)*	8554	5702	34,868	23,169
A2181003/A2181004 (OPAL)	1894	1419	3193	2380
A2181030 (CORAL)	540	218	953	377
Other Phase 2/3 Studies				
Phase 2 Osteoporosis Treatment Study A2181037 (JADE)	497	372	452	340
Phase 2 Osteoporosis Prevention Study A2181042 (LACE)	51	26	94	49
Phase 2 Osteoporosis Prevention Studies 218-101/E, 218-102, 218-103	1125	675	1152	626
Phase 2/3 VVA Studies A2181012, A2181031, A2181032	1273	871	358	249
Phase 2 FSD Studies A2181014, A2181015, A2181016, A2181021	1470	974	1073	719

*Database cutoff 03 December 2007 – 4-month Safety Update.

Due to the reporting out of PEARL, the lasofoxifene safety database at the time of the NDA submission for the treatment of osteoporosis was about 7 time larger than that provided in the previously submitted osteoporosis prevention and VVA NDAs.

Figure 3. Patient-years of Lasofoxifene Exposure in the Phase 2/3 Clinical Development Program



In the Phase 2/3 Clinical Program, ~40% of patients received lasofoxifene for > 54 months (Table 6). The > 54 month exposure data were for patients in Study A2181002 (PEARL) only. Mean durations of exposure to study drug were 1,051, 1,077, and 1,096 days, respectively, for the placebo, lasofoxifene 0.25 mg, and 0.5 groups.

Table 6. Duration of Treatment – Lasofoxifene Phase 2/3 Clinical Program

Months of Exposure (Months)	Lasofoxifene			Pooled* N=10,257
	Placebo N=4701	0.25 mg N=4547	0.5 mg N=4308	
> 0-3	534	473	461	1125
> 3-6	273	276	253	714
> 6-12	553	399	459	1295
> 12-18	218	219	219	599
> 18-24	483	526	336	1191
> 24-30	233	262	191	552
> 30-36	190	202	211	413
> 36-42	159	159	157	316
> 42-48	69	76	62	138
> 48-54	63	83	68	151
> 54-60	1095	1042	1043	2085
≥ 60	831	830	848	1678
Mean duration (days)	1051	1077	1096	992
Median duration (days)	1040	1076	1103	736
Range (days)	1-2120	1-2105	1-2105	1-2105

* 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 participants in clinical pharmacology studies (N=814) received mainly single doses of study treatment, safety data from Phase 2/3 studies and from clinical pharmacology studies were integrated separately, and safety results from Phase 1 studies are not discussed in this document.

4.3. Phase 2/3 Patient Population

All patients in the full Phase 2/3 Clinical Program were postmenopausal women. The majority of women randomized to lasofoxifene received either 0.25 or 0.5 mg. The distribution of women in the placebo and lasofoxifene treatment groups was balanced with respect to age, weight, height, racial distribution, and years postmenopausal (Table 7).

Table 7. Demographic and Baseline Characteristics – Lasofoxifene Phase 2/3 Clinical Program

	Mean (SD)			
	Placebo	Lasofoxifene 0.25 mg	0.5 mg	Pooled*
Number of Patients	4701	4547	4308	10,257
Age (yrs)	63.7 (7.3)	64.3 (7.0)	64.1 (7.1)	63.4 (7.2)
Race (%)				
White	3665 (78.0)	3511 (77.2)	3304 (76.7)	7960 (77.6)
Black	88 (1.9)	74 (1.6)	74 (1.7)	184 (1.8)
Asian	666 (14.2)	666 (14.6)	655 (15.2)	1469 (14.3)
Hispanic	225 (4.8)	237 (5.2)	213 (4.9)	514 (5.0)
Other	57 (1.2)	59 (1.3)	62 (1.4)	130 (1.3)
Weight (kg)	64.5 (12.1)	64.0 (11.9)	64.0 (12.1)	64.4 (12.1)
Height (cm)	157.9 (7.5)	157.6 (7.3)	157.1 (7.3)	157.8 (7.4)
Body Mass Index (kg/m²)	25.8 (4.2)	25.7 (4.2)	25.8 (4.2)	25.8 (4.2)
Years Postmenopausal	16.0 (8.4)	16.2 (8.3)	16.2 (8.2)	15.6 (8.3)

*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.

5. Clinical Efficacy

5.1. Introduction

Results demonstrating the efficacy of lasofoxifene in the treatment of osteoporosis in postmenopausal women at increased risk of fracture are reviewed in this section. They derive from the prospectively defined 3-year analysis of the large, multinational pivotal Phase 3 PEARL study conducted in 8,556 postmenopausal women with osteoporosis. Five-year efficacy results are provided for major nonvertebral fractures only by agreement with the FDA. Also, by agreement with the FDA, breast cancer results are reviewed in Section 6 Clinical Safety.

5.2. Study Methodology

5.2.1. Study Design and Conduct

The PEARL study was a prospective, randomized, double-blind, placebo-controlled, osteoporosis treatment study. The study randomized 8,556 postmenopausal women in 32 countries to 1 of 3 treatment arms: lasofoxifene 0.25 mg, lasofoxifene 0.5 mg, or placebo. Study medication was taken once daily, and all patients were required to take supplemental calcium and Vitamin D during the run-in period and for the duration of the study.

The study was initially designed to follow all randomized patients for up to 3 years. The 3-year duration of the study was consistent with regulatory requirements for establishing efficacy in the treatment of osteoporosis at the time the study was designed and was agreed upon with the FDA. PEARL was subsequently extended by protocol amendment to 5 years, via a protocol amendment prior to patients reaching their Month 36 visit, in order to provide

long-term exposure data consistent with that emerging for other osteoporosis treatment agents. Patients who completed the initial 3 years of study and who signed informed consent were allowed to enter the extension and were then followed for an additional 2 years.

A 3-year statistical analysis plan (11 May 2006) was prepared to support the analysis and reporting of data at 3 years. A separate statistical analysis plan (11 May 2006) was prepared to support the analysis and reporting of data at 5 years. Both plans were finalized prior to unblinding of the 3-year data.

Appropriate steps to ensure the continued blinding of the ongoing study were described in the Study A2181002 (PEARL) Unblinding Plan. In accordance with the procedures outlined in the plan, all investigators, site and Pfizer personnel who were responsible for the management of the study remained blinded to the 3-year data through completion of the extended study at 5 years and database lock (April 2008). Other personnel, on a limited need-to-know basis, were unblinded for the preparation of the osteoporosis treatment NDA. They signed affidavits prior to reviewing any data, agreeing not to disclose any information except to other unblinded personnel.

The study was designed and conducted on an Intent-to-Treat basis and permitted patients to discontinue study medication while remaining in the study as non-drug participants. All protocol-mandated procedures were conducted, and these patients continued to be analyzed according to their randomized assessment, even those who terminated study medication.

Multiple substudies were conducted in PEARL for the assessment of specific endpoints during the first 3 years of the study. These substudies were conducted to assess bone density and biochemical markers of bone turnover (1126 patients at 33 centers), lipid profiles and inflammation markers (1014 patients at 38 centers), breast density (1236 patients at 24 centers), and health-related quality of life (3544 patients at 62 centers). Substudies conducted to assess uterine safety are described in Section 6.9. With the exception of the uterine safety substudies, patients could participate in more than one substudy.

All fractures (vertebral fractures, clinical fractures, nonvertebral fractures) were centrally adjudicated by external radiologists (Synarc) for fracture assessment. Three sponsor-independent expert committees were constituted for central adjudication of cardiovascular endpoints (including all deaths, major coronary events, hospitalization for cardiovascular events, VTEs, and stroke), breast cancer endpoints (breast cancer and DCIS), and gynecological safety endpoints (endometrial cancer, endometrial hyperplasia, ovarian cancer, cervical cancer, surgery for pelvic organ prolapse/urinary incontinence). Potential events were submitted by investigators and subsequently confirmed or rejected as endpoints by the blinded adjudication committee.

A data monitoring committee (DMC), not otherwise involved in the conduct of the trial was the primary data and safety advisory group for Pfizer. The DMC reviewed study results including the endpoint adjudication results, evaluated the treatments for excess adverse effects, determined whether the basic trial assumptions remained valid, judged whether the

overall integrity and conduct of the trial remained acceptable and made recommendations regarding the continued conduct of the trial.

5.2.2. Selection of the Study Population

Postmenopausal women entering the study were required to have a lumbar spine or femoral neck BMD T-score ≤ -2.5 . Exclusion criteria included more than 3 vertebral fractures on X-ray; known, suspected, or history of breast cancer; any untreated endometrial cancer or endometrial hyperplasia; abnormal vaginal bleeding in the past year; any past history of VTEs; a history of stroke in the past 6 months; and significant hepatic or renal events. Women were not allowed in the study if they were treated with: estrogen (alone or in combinations), calcitonin, tibolone, or raloxifene within 3 months of screening, or b) bisphosphonates, parathyroid hormone and sodium fluoride for more than 1 month within 2 years of screening. Gynecological examination (including Pap smear) was required to be normal before randomization. Minor abnormalities in cervical cytology (e.g., minor atypia such as atypical squamous cells of undetermined significance or inflammation) were not grounds for exclusion.

The enrollment criteria are consistent with those applied in the Evista (raloxifene) and bisphosphonate development programs in postmenopausal women with osteoporosis.

5.2.3. Efficacy Evaluations

Fracture Assessments

Vertebral fractures were determined using X-rays of the lateral thoracic and lumbar spine (T₄-L₄) obtained at screening and yearly, thereafter, in asymptomatic patients, and when a patient experienced symptoms suggestive of a fracture, by spine X-ray. All X-ray films were centrally adjudicated for fracture assessment.

The occurrence of an incident radiographic vertebral fracture was assessed through an initial screening of 2-year X-rays using the semi-quantitative scoring system (0 – no fracture, 1 – mild compression, 2 – moderate compression, 3 – severe compression) proposed by Genant (Genant et al, 1996).

If a fracture was not identified based on a change from baseline in the semi-quantitative score, no further action was taken.

If a fracture occurred at 2 years based on a change in the semi-quantitative score from baseline, all previous X-rays were evaluated for fracture using the semi-quantitative score (0 to 3). Then all X-rays were assessed using the following 2 scoring systems: (1) a binary semi-quantitative approach for the presence or absence of a fracture, (2) a quantitative assessment for which a fracture diagnosis required a decrease of 20% and at least 4 mm from baseline in vertebra height at either the anterior, medial, or posterior position. An incident fracture required 2 of the 3 independent assessments of fracture (change in semi-quantitative

score plus either the independent semi-quantitative assessment of fracture or a quantitative change).

Nonvertebral fractures were confirmed by X-ray and/or a copy of the site's radiologist report.

Bone Mineral Density

Lumbar spine (L₁-L₄) BMD and total hip BMD were measured in all patients pretreatment and at 1, 2, and 3 years by dual energy X-ray absorptiometry (DXA). More extensive BMD measurements of the lumbar spine and hip were performed in a subset of patients at baseline, 3 months, and at 1, 2, and 3 years. In the same subset, whole body bone mineral content (BMC) and forearm BMD were measured at baseline and at 1, 2 and 3 years.

Markers of Bone Turnover

C-telopeptide (CTX), procollagen type 1 N-propeptide (P1NP), osteocalcin and bone-specific alkaline phosphatase were evaluated from serum samples collected at pretreatment, and at 1 month, 3 months, 6 months, 1, 2, and 3 years in a subset of patients.

Breast Evaluations

Breast self-examination, clinical breast examination, and mammography were used to detect new or suspicious breast findings. Histological confirmation of breast cancer was the definitive measure for these endpoints, and breast cancer event endpoints were centrally adjudicated by an independent endpoint classification committee. Breast density was determined from centrally-read mammograms collected at baseline, 1, 2, and 3 years in a subset of patients.

Vaginal Atrophy Endpoint Evaluations

Vaginal maturation index and vaginal pH were assessed at 1, 2, and 3 years in a subset of patients.

Outcomes Research Evaluations

Health-related quality of life measures (via EQ-5D) were assessed at baseline, 6 months, and at 1, 2, and 3 years. Disability measures (Back Pain and Limited Activity Days) were assessed at baseline, 3 and 6 months, and every 6 months thereafter.

5.3. Methods of Analysis

5.3.1. Analysis Populations

Statistical analyses were performed on patient populations based on the efficacy endpoint and type of analysis.

Full analysis set (FAS): All randomized patients for whom there was a non-missing baseline (if applicable) and at least one postbaseline observation for the measurement of interest were included in the FAS. Patients were analyzed based on the treatment group to which they were randomized.

Additional analysis subpopulations were defined for some efficacy assessments and noted with the specific results.

5.3.2. Efficacy Endpoints

The primary and key secondary endpoints of the PEARL study are summarized in the following table.

Table 8. Efficacy Endpoints in PEARL

	Primary	Key Secondary
3 Years		
	New/worsening radiographic vertebral fracture	Multiple vertebral fractures Clinical vertebral fracture
5 Years		
	Nonvertebral fracture ER+ breast cancer	Clinical fracture Hip fracture

The following subsections focus on the efficacy endpoints defined for the initial 3-year study protocol.

5.3.2.1. Bone

Primary Endpoint

Risk of New/Worsening Radiographic Vertebral Fracture through 3 Years

The primary objective of PEARL was to compare the risk of new/worsening radiographic vertebral fracture for each lasofoxifene dose (0.25 mg and 0.5 mg) to placebo through 3 years. A new fracture was defined as significant compression in a vertebra, i.e., reduction in vertebral height, with no evidence of a fracture at baseline. A worsening vertebral fracture was defined as significant additional compression in a vertebra with a prevalent baseline fracture.

For the time-to-event analysis, each lasofoxifene treatment group was tested against placebo using the log-rank test stratified for geographic region and vertebral fracture at baseline. Censoring time was defined as the date of the last X-ray. The hazard ratio for each lasofoxifene treatment group versus placebo was calculated using a Cox proportional hazards model with treatment group as a covariate with stratification on vertebral fracture at baseline and geographic region.

Key Secondary Endpoints

Incidence of Multiple Radiographic Vertebral Fractures through 3 Years

The distribution of 0, 1, and >1 new/worsening vertebral fractures through 3 years was calculated for each treatment arm and compared to placebo. Each lasofoxifene group was tested against placebo using a Cochran-Mantel-Haenzel row mean score test in the FAS.

Time to First Clinical Vertebral Fracture through 3 Years

Clinical vertebral fracture was defined as any radiographic fracture of the spine associated with symptoms of back pain or discomfort. Each lasofoxifene treatment group was compared to placebo using an unstratified log-rank test. Censoring time was defined as the date of the last study visit. The hazard ratio and 95% CI were calculated using the Cox proportional hazards model with treatment as a covariate.

Other Secondary Endpoints

Statistical methodology similar to that utilized for the primary efficacy endpoint was employed for:

- The risk of new radiographic vertebral fracture (excluding worsening of previous fractures).
- The risk of new/worsening radiographic vertebral fracture in women with a prevalent fracture at baseline.
- The risk of all nonvertebral fractures. This was a co-primary endpoint at 5 years.
- The risk of all clinical fractures (vertebral and nonvertebral fractures associated with pain and discomfort).
- The risk of new/worsening radiographic vertebral fracture in women with lumbar spine (LS)-BMD T-score ≤ -2.5 and >-2.5 at baseline.
- The risk of a moderate or severe radiographic vertebral fracture.
- The risk of all nonvertebral fractures in women with severe osteoporosis at baseline.
- The risk of major nonvertebral fracture
- Percent change from baseline in BMD at various anatomical sites (lumbar spine, total hip, hip components, and forearm), whole body bone mineral content (BMC), and markers of bone turnover (osteocalcin, s-CTX, P1NP, bone-specific alkaline phosphatase).

5.3.2.2. Adjudicated Breast Cancer Efficacy Endpoints

The time to diagnosis of all breast cancers (a composite endpoint consisting of ER+, ER-, invasive and ductal carcinoma in situ [DCIS]), invasive breast cancers, and DCIS was compared between the pooled lasofoxifene group and placebo in PEARL. If the null hypothesis of no difference between the pooled lasofoxifene dose and placebo was rejected, each dose of lasofoxifene was compared to placebo. In addition, the time to first estrogen receptor positive (ER+) breast cancer and the time to first ER+ invasive breast cancer were compared between each lasofoxifene treatment group and placebo through 3 years. The time to ER+ breast cancer was a co-primary endpoint in the 5-year analysis.

In the breast density subgroup, the percent change from baseline in breast density within and between each dose of lasofoxifene and placebo after 1, 2, and 3 years was assessed with the Wald test using a linear model with treatment group, geographic region and baseline as covariates.

Breast cancer results are reviewed in Section 6 Clinical Safety.

5.3.2.3. Other Efficacy Endpoints

Analyses of additional efficacy endpoints were performed for VVA endpoints (vaginal pH and maturation index), and health-related quality of life (HRQoL) measures including back pain and vaginal health.

5.3.3. Multiple Comparison Considerations

The Hochberg procedure was used to control for multiplicity in comparison of each dose of lasofoxifene to placebo for the primary endpoint (time to first radiographic vertebral fracture). For the key secondary endpoints, time to first clinical vertebral fracture and multiple vertebral fractures, alpha was first divided equally among the endpoints using the Bonferroni approach (0.025 to each endpoint) followed by the use of the Hochberg procedure within each endpoint for the comparison of each dose of lasofoxifene to placebo.

For other secondary endpoints, the Hochberg procedure was used for the comparison of each dose of lasofoxifene to placebo within each endpoint unless a pooled dose was analyzed. The pooled dose was considered primary in some instances where a low event rate was anticipated. Individual doses were not considered significant unless the pooled dose was significant.

5.3.4. Imputation of Missing Data

Last observation carried forward (LOCF) was the default imputation methodology for analyses of those endpoints where it was considered necessary to impute a missing value at a given time for a patient's endpoint. If the endpoint had a value recorded at the most recent previous visit, that value was used to impute for the current visit. When no prior values were recorded, the imputation was not performed and the visit was considered to have a missing

value. The most recent (previous to the missing observation's time-point) non-missing post baseline observation was imputed. If no such value existed, the observation's value remained missing.

5.4. Selection of Dose Regimen

The 2 doses selected for PEARL were based on Phase 2 results of osteoporosis trials in postmenopausal women, where dose response studies evaluating lumbar spine and hip BMD showed maximal effects on BMD at these sites. Results for dose response modeling of 9 doses covering a 600-fold range showed that the 0.25 mg/day dose of lasofoxifene was expected to be the lowest fully effective dose for lumbar BMD while 0.5 mg would be the lowest fully effective dose for hip BMD.

The E_{MAX} model is a commonly employed tool for modeling dose-response relationships. This model fits a sigmoidal curve to the dose-response data, estimating the maximal drug effect (E_{MAX}) and the dose at which 50% of the maximal effect occurs (ED_{50}). Dose selection for Phase 3 studies was based on the estimate of ED_{90} , the dose at which 90% of the maximal effect occurs as determined in Phase 2 studies. As the dose response relationship is asymptotic by nature, the 90% effect level was chosen as a reasonable compromise to attain the lowest maximally effective dose.

Daily doses of 0.017 mg to 10 mg, providing a nearly 600-fold dose range, were studied in Phase 2 trials (Studies 218-101/101E, 218-102, and 218-103). The dose response modeling of percent change from baseline was performed using lumbar spine BMD at Month 6, total hip BMD at Month 12, and LDL-C at Month 6 to provide estimates of ED_{50} , ED_{90} and E_{MAX} for each of these endpoints. Since the hip is known to be slower than the spine to respond to anti-resorptive therapy, the 12-month data were used as more reflective of the likely "true" dose response in hip. Thus, lasofoxifene 0.25 mg and lasofoxifene 0.5 mg were selected for PEARL to ensure maximal efficacy in BMD at all critical sites in the skeleton that would translate into successful fracture outcomes.

Table 9. Dose Response Analysis of Percent Change from Baseline in Lumbar Spine BMD, Total Hip BMD and LDL-C – Phase 2 Dose Response Set

	ED_{50} mg/day (95% CI)	ED_{90} mg/day (95% CI)	E_{MAX} % Change (95% CI)
Lumbar spine BMD – Month 6	0.021 (0.000, 0.059)	0.191 (0.000, 0.529)	1.57 (1.07, 2.08)
Total hip BMD – Month 12	0.042 (0.000, 0.161)	0.381 (0.000, 1.445)	1.40 (0.52, 2.28)
LDL-cholesterol – Month 6	0.020 (0.000, 0.042)	0.183 (0.000, 0.381)	-17.3 (-20.7, -13.8)

ED_{50} = Dose at 50% of Maximal Response; ED_{90} = Dose at 90% of Maximal Response, E_{max} = maximal response, slope factor $n=1$ (fixed).

The analysis estimated the ED_{90} to be about 0.19 mg/day for both percent change from baseline in lumbar spine BMD and LDL-C. For percent change from baseline in total hip BMD, the estimated ED_{90} was 0.38 mg/day. Based on these results, the 0.25 mg/day dose was anticipated to be the lowest maximally effective dose for the lumbar spine BMD

endpoint and was chosen for the Phase 3 studies. However, the 0.38 mg/day ED₉₀ value for total hip BMD from these Phase 2 data seemed to suggest a dose higher than 0.25 mg/day would be required for optimal hip BMD response, and the 0.5 mg/day dosing regimen was thus included in the pivotal osteoporosis prevention trials (A2181003 and A2181004) and pivotal osteoporosis treatment trial (PEARL [A2181002]). This information was discussed at the End of Phase 2 meeting for the osteoporosis development program (June 2000) with FDA, and agreement was reached on these proposed doses.

5.5. Demographics and Baseline Characteristics

In PEARL the mean age at baseline was approximately 67 years in the lasofoxifene and placebo groups, and 74% of all subjects were white; 18.3% of all subjects were Asian. Mean body weight, height, and body mass index were similar across treatment groups, as was the percentage of subjects who were hysterectomized (approximately 19%) and the mean number of years postmenopausal (approximately 19.5). Lasofoxifene and placebo treatment groups were comparable with respect to mean lumbar spine BMD T-scores (approximately -3.0) and mean femoral neck BMD T-scores (approximately -2.25). The percentage of subjects with pre-existing vertebral fractures was consistent across the lasofoxifene and placebo groups (28%). Baseline characteristics are summarized in [Table 10](#).

Table 10. Baseline Characteristics - PEARL

	Placebo N=2852	Lasofoxifene	
		0.25 mg N=2852	0.5 mg N=2852
Age (years)			
Mean (SD)	67.5 (5.2)	67.5 (5.2)	67.3 (5.2)
Range	59-80	60-80	60-80
Race [n (%)]			
White	2118 (74.3%)	2111 (74.0%)	2108 (73.9%)
Black	27 (0.9%)	26 (0.9%)	29 (1.0%)
Asian	521 (18.3%)	530 (18.6%)	519 (18.2%)
Hispanic	141 (4.9%)	138 (4.8%)	144 (5.0%)
Other	45 (1.6%)	47 (1.6%)	52 (1.8%)
Weight (kg)			
Mean (SD)	61.6 (10.3) ^b	61.0 (10.1)	61.2 (9.9) ^a
Range	25.0-132.0	26.8-120.0	30.0-111.0
Height (cm)			
Mean (SD)	155.6 (6.9) ^c	155.5 (6.6)	155.3 (6.7) ^b
Range	132.3-178.0	131.0-177.4	134.0-181.5
Body Mass Index			
Mean (SD)	25.4 (3.8) ^c	25.2 (3.8)	25.4 (3.7) ^b
Range	13.7-55.4	13.3-47.0	12.2-42.4
Years Postmenopausal			
Mean (SD)	19.5 (7.2)	19.5 (7.2)	19.4 (7.1)
Range	5.0 - 55.0	2.0 - 52.0	2.0 - 57.0
Hysterectomized			
Number (%)	543 (19.0)	552 (19.4)	551 (19.3)
LS-BMD T-score			
Mean (SD)	-3.007 (0.735)	-3.024 (0.735)	-3.020 (0.712)
Femoral Neck BMD T-score			
Mean (SD)	-2.247 (0.714) ^c	-2.289 (0.699)	-2.229 (0.693)
Pre-existing Vertebral Fracture			
Number (%)	803 (28.2%) ^c	807 (28.3%) ^a	808 (28.4%) ^c

^aN=2843 for LS-BMD and femoral neck BMD T-scores and N=2850 for years postmenopausal and pre-existing vertebral fractures

^bN=2850 for weight and years postmenopausal, N= 2849 for height and BMI, N=2846 for LS-BMD T-score and pre-existing vertebral fracture, N=2847 for femoral neck BMD T-score

^cN=2849 for weight; N=2848 for height, BMI, femoral neck BMD T-score, and pre-existing vertebral fracture; N=2846 for LS-BMD T-score; N=2851 for years postmenopausal.

Approximately 28% of the women had a prevalent vertebral fracture at baseline, and approximately 84% of women had a baseline LS BMD T-score of ≤ -2.5 . This confirms that an appropriate patient population was studied to support the assessment of lasofoxifene for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. Additionally, a subject with the attributes of the average woman in PEARL would have an estimated 10-year fracture risk of 36% (FORE 10-year risk calculator), providing support for the women in PEARL being at high risk for fractures.

5.6. Patient Disposition

PEARL was originally designed as a 3-year Intent-to-Treat study. Overall, approximately 92% of patients in each treatment group completed the 3-year study. Most patients, approximately 81-82% in each treatment group, remained in the study on-treatment at 36 months. When the study was extended by 2 years (via a protocol amendment), patients were offered the opportunity at Month 36 to continue into the last 2 years of the study. Approximately 83% of patients provided written consent to continue in the study beyond 36 months. More than 75% of patients completed the study at 5 years and more than 62% of patients completed 5 years of treatment. Patient disposition is summarized in [Table 11](#).

Table 11. Patient Disposition – PEARL

	Number (%) of Patients		
	Lasofoxifene		
	Placebo	0.25 mg	0.5 mg
3 Years			
Randomized	2852	2852	2852
Treated	2852	2852	2852
Discontinued prior to Month 36	235 (8.2)	215 (7.5)	230 (8.1)
Completed Month 36	2617 (91.8)	2637 (92.5)	2622 (91.9)
On treatment	2342 (82.1)	2314 (81.1)	2308 (80.9)
Off treatment	275 (9.6)	323 (11.3)	314 (11.0)
5 Years			
Randomized	2,852	2852	2,852
Treated*	2,851	2849	2,852
Discontinued**	646 (22.7)	657 (23.0)	639 (22.4)
Completed	2206 (77.3)	2195 (77.0)	2213 (77.6)
On treatment	1820 (63.8)	1753 (61.5)	1777 (62.3)
Off treatment	386 (13.5)	442 (15.5)	436 (15.3)
Continued into last 2 years of study	2345 (82.2)	2379 (83.4)	2348 (82.3)

*Prior to database lock for 5-year analysis, it was discovered that 3 patients were randomized to but never treated with lasofoxifene 0.25 mg and 1 patient was randomized to but never treated with placebo.

**Includes patients who elected not to continue beyond Month 36.

The most common reason for discontinuation in the PEARL study was patients' defaulting (including withdrawal of consent or lost to follow up) from study.

5.7. Bone Fracture Results

5.7.1. Vertebral Fracture

5.7.1.1. New/Worsening Radiographic Vertebral Fracture

The risk for a new/worsening radiographic vertebral fracture, the primary endpoint at 3 years, was significantly reduced by 31% and 42% in the lasofoxifene 0.25 mg and 0.5 mg groups, respectively, compared with placebo ([Table 12](#)). This effect was observed as early as 1 year for both doses of lasofoxifene (lasofoxifene 0.25 mg HR=0.48; 95%CI [0.31, 0.75]; p=0.001; lasofoxifene 0.5 mg HR=0.45; 95%CI [0.29, 0.71]; p<0.001) and was sustained through 5 years.

Table 12. Analysis of Time to First New/Worsening Radiographic Vertebral Fracture - PEARL – Full Analysis Set

	Lasofoxifene		
	Placebo	0.25 mg	0.5 mg
3 Years			
Number of patients	2742	2733	2746
Number (%) with event	176 (6.4)	129 (4.7)	105 (3.8)
Hazard ratio (95% CI)		0.69 (0.55, 0.87)	0.58 (0.45, 0.73)
P-value		0.002*	<0.001*

*P-value significant versus placebo.

Analyses that excluded worsening of previous radiographic vertebral fractures analysis were virtually identical to those for the primary endpoint, confirming the robustness of lasofoxifene's efficacy in reducing the risk of new radiographic vertebral fracture. Through 3 years, lasofoxifene 0.25 mg and 0.5 mg were associated with statistically significantly reduced risks of 32% (HR=0.68; 95% CI [0.54, 0.86]; p=0.001) and 42%, (HR=0.58; 95% CI [0.46, 0.75]; p<0.001) respectively, compared with placebo.

A similar reduction in risk for a new/worsening radiographic vertebral fracture was seen with both lasofoxifene 0.25 mg and 0.5 mg through 3 years in women with or without a prevalent fracture at baseline compared to the full analysis set (Table 13).

Table 13. Analysis of Time to First New/Worsening Radiographic Vertebral Fracture - PEARL – Women with or without Prevalent Fracture at Baseline

	Lasofoxifene		
	Placebo	0.25 mg	0.5 mg
3 Years			
With prevalent vertebral fracture at baseline			
Number of patients	773	778	778
Number (%) with event	87 (11.3)	67 (8.6)	47 (6.0)
Hazard ratio (95% CI)		0.70 (0.51, 0.97)	0.52 (0.36, 0.74)
P-value		0.029*	<0.001*
Without prevalent vertebral fracture at baseline			
Number of patients	1969	1955	1968
Number (%) with event	89 (4.5)	62 (3.2)	58 (2.9)
Hazard ratio (95% CI)		0.68 (0.49, 0.95)	0.63 (0.45, 0.88)
P-value		0.025*	0.007*

*P-value significant versus placebo.

Additionally, lasofoxifene 0.25 and 0.5 mg significantly reduced the risk of radiographic vertebral fracture through 3 years in patients (N=7,170) with a baseline LS BMD T-score of ≤ -2.5. Lasofoxifene 0.5 mg, but not lasofoxifene 0.25 mg, significantly reduced the risk in patients (N=1,386) with baseline LS BMD T-score > -2.5, most of whom were eligible for the study on the basis of their baseline femoral neck BMD only (Table 14).

Table 14. Analysis of Time to First New/Worsening Radiographic Vertebral Fracture – PEARL – Women with Baseline LS BMD T-Score \leq -2.5 or Baseline LS BMD T-Score $>$ -2.5

	Placebo	Lasofoxifene	
		0.25 mg	0.5 mg
3 Years			
Baseline LS BMD T-Score ≤-2.5			
Number of patients	2365	2392	2413
Number (%) with event	143 (6.0)	104 (4.3)	98 (4.1)
Hazard ratio (95% CI)		0.67 (0.52, 0.86)	0.65 (0.50, 0.84)
p-value		0.002*	<0.001*
Baseline LS BMD T-Score >-2.5			
Number of patients	487	460	439
Number (%) with event	33 (6.8)	25 (5.4)	7 (1.6)
Hazard ratio (95% CI)		0.76 (0.45, 1.30)	0.22 (0.10, 0.51)
p-value		0.334	<0.001*

*P-value significant vs. placebo.

Lasofoxifene 0.5 mg significantly reduced the risk of moderate or severe radiographic vertebral fracture through 3 years (by 32%) compared to placebo (Table 15). The risk reduction observed with lasofoxifene 0.25 mg was not significantly different from placebo. Moderate and severe radiographic fractures were defined using standard validated criteria for fracture assessment (Genant et al, 1996).

Table 15. Analysis of Time to First Moderate or Severe Radiographic Vertebral Fracture –PEARL – Full Analysis Set

		Lasofoxifene	
	Placebo	0.25 mg	0.5 mg
3 Years			
Number of patients	2742	2733	2746
Number (%) with event	90 (3.3)	79 (2.9)	62 (2.3)
Hazard ratio (95% CI)		0.84 (0.62, 1.13)	0.68 (0.49, 0.94)
P-value		0.272	0.018*

*P-value significant vs. placebo.

5.7.1.2. Incidence of Multiple Radiographic Vertebral Fracture

The frequency of multiple new/worsening radiographic vertebral fractures (3-year key secondary endpoint) was significantly lower at 3 years for both lasofoxifene dose groups compared to placebo. The number (percentage) of patients with greater than 1 new fracture was 29 (1.1%), 18 (0.7%), and 20 (0.7%), for the placebo, lasofoxifene 0.25 mg, and lasofoxifene 0.5 mg groups, respectively. This effect was also observed for both doses at 1 year where 7 (0.3%), 3 (0.1%), and 2 (0.1%) patients in the placebo, lasofoxifene 0.25 mg, and lasofoxifene 0.5 mg groups, respectively, had more than 1 new fracture. The effect was sustained through 5 years.

Table 16. Frequency of New/Worsening Radiographic Vertebral Fractures – PEARL – Full Analysis Set

		Lasofoxifene	
	Placebo	0.25 mg	0.5 mg
3 Years			
Number of patients	2742	2733	2746
Number (%) with			
No new fractures	2566 (93.6)	2604 (95.3)	2641 (96.2)
1 new fracture	147 (5.4)	111 (4.1)	85 (3.1)
>1 new fracture	29 (1.1)	18 (0.7)	20 (0.7)
P-value		0.006*	<0.001*

*P-value significant vs. placebo.

5.7.1.3. Time to First Clinical Vertebral Fracture

The reduction in risk of a new clinical vertebral fracture through 3 years, a key secondary endpoint at 3 years, was not statistically significant for either lasofoxifene dose group. The hazard ratios versus placebo through 3 years were 0.83 (95% CI: [0.55, 1.26]; $p = 0.377$) and 0.66 (95% CI: [0.43, 1.03]; $p = 0.068$) in the lasofoxifene 0.25 and 0.5 mg groups, respectively. Although a statistically significant reduction in clinical vertebral fractures was not observed, lasofoxifene 0.25 mg- and 0.5 mg-treated patients experienced significantly fewer days of moderate or worse back pain compared to placebo based on analyses of the HRQoL subgroup of patients ($N=3,544$). Furthermore, patients in the HRQoL subgroup who received lasofoxifene 0.5 mg also experienced fewer days of severe or greater back pain, fewer days of bed rest for back pain, fewer days of limited activity due to back pain, and fewer days of hospitalization due to back pain compared to placebo at 1, 2, and 3, years.

5.8. Nonvertebral Fracture

5.8.1. Risk of All Nonvertebral Fracture

The risk of nonvertebral fracture was significantly reduced by 22% in the lasofoxifene 0.5 mg group through 3 years compared to placebo. This effect, observed as early as 1 year ($HR = 0.62$; 95%CI: [0.44, 0.87]; $p=0.006$) was maintained through 5 years. The risk of nonvertebral fractures was not significantly reduced in the 0.25 mg dose group at any time point.

Table 17. Analysis of Time to First Nonvertebral Fracture – PEARL – Full Analysis Set

		Lasofoxifene	
	Placebo	0.25 mg	0.5 mg
3 Years			
Number of patients	2852	2852	2852
Number (%) with event	209 (7.3)	181 (6.3)	167 (5.9)
Hazard Ratio (95% CI)		0.86 (0.70, 1.05)	0.78 (0.64, 0.96)
P-value		0.130	0.019*

*P-value significant vs. placebo.

Nonvertebral fracture sites included in the analysis were hip, pelvis, femur, knee, lower leg, ankle, calcaneus, foot, shoulder, humerus, elbow, forearm, wrist, scapula, clavicle, rib, sternum, and nonthoracic/nonlumbar spine. The analysis excluded fractures of the fingers, toes, face, and skull due to their lack of specificity for osteoporosis, and is consistent with that performed in the alendronate (Fosamax®) Phase 3 development program.

The overall incidence of hip fractures was low. At 3 years, there were 20 (HR=0.87: 95% CI: 0.48, 1.58) and 18 (HR= 0.78: 95% CI: 0.42, 1.44) hip fracture events in the lasofoxifene 0.25 mg and 0.5 mg groups, respectively, and 23 in the placebo group; the comparison with placebo was not statistically significant (p=0.647 and p=0.425 for lasofoxifene 0.25 and 0.5 mg, respectively).

Further analysis demonstrated that both doses of lasofoxifene significantly reduced the risk of nonvertebral fracture through 3 years compared to placebo in patients who had a baseline LS BMD T-score ≤ -2.5 . Additionally, in women with severe osteoporosis who were at greater risk of fracture (baseline LS BMD T-score ≤ -3.0 , or ≤ -2.5 plus baseline prevalent vertebral fracture), lasofoxifene 0.25 mg and 0.5 mg reduced the risk of nonvertebral fracture through 3 years by 24% and 27%, respectively, compared with placebo.

Table 18. Analysis of Time to First Nonvertebral Fracture – PEARL – Women with Baseline LS BMD T-Score \leq -2.5 or Severe Osteoporosis

	Placebo	Lasofoxifene	
		0.25 mg	0.5 mg
3 Years			
Baseline LS BMD T-Score ≤-2.5			
Number of patients	2365	2392	2413
Number (%) with event	176 (7.4)	137 (5.7)	144 (6.0)
Hazard ratio (95% CI)		0.76 (0.61, 0.95)	0.78 (0.63, 0.98)
P-value		0.015*	0.030*
Severe osteoporosis†			
Number of patients	1625	1699	1680
Number (%) with event	133 (8.2)	107 (6.3)	102 (6.1)
Hazard ratio (95% CI)		0.76 (0.59, 0.98)	0.73 (0.56, 0.94)
P-value		0.034*	0.015*

*P-value significant vs. placebo.

[†]Severe osteoporosis designation based on patients having a baseline lumbar spine T-score \leq -3.0 or \leq -2.5 plus prevalent baseline vertebral fracture.

In a separate analysis, the effect of lasofoxifene on fracture risk at the major nonvertebral sites was assessed. Seven major nonvertebral sites were defined as commonly accepted with osteoporosis: hip, pelvis, femur, lower leg, humerus, forearm/wrist, and rib (CHMP, 2006). The risk of major nonvertebral fractures was significantly reduced by 25% (HR=0.75; 95% CI: [0.60, 0.92]; p=0.007) in the lasofoxifene 0.5 mg group through 5 years compared to placebo, but not at 3 years. The risk reduction observed with lasofoxifene 0.25 mg through 3 or through 5 years was not statistically significant.

Table 19. Analysis of Time to First Major Nonvertebral Fracture– PEARL – Full Analysis Set

		Lasofoxifene	
	Placebo	0.25 mg	0.5 mg
3 Years			
Number of patients	2852	2852	2852
Number (%) with event	125 (4.4)	118 (4.1)	102 (3.6)
Hazard ratio (95% CI)		0.94 (0.73, 1.21)	0.80 (0.62, 1.04)
P-value		0.619	0.102
5 Years			
Number of patients	2852	2852	2852
Number (%) with event	192 (6.7)	173 (6.1)	145 (5.1)
Hazard ratio (95% CI)		0.89 (0.73, 1.10)	0.75 (0.60, 0.92)
P-value		0.275	0.007*

*P value significant vs. placebo.

Major nonvertebral fracture sites: hip, pelvis, femur, lower leg, humerus, forearm, wrist, and rib.

The number of patients at 3 and 5 years with fractures is shown by site in [Table 20](#).

Table 20. Frequency of Major Nonvertebral Fractures by Anatomical Site – PEARL – Full Analysis Set

		Lasofoxifene	
	Placebo	0.25 mg	0.5 mg
3 Years			
Number of patients	2852	2852	2852
Number (%) with event			
Hip	23 (0.8)	20 (0.7)	18 (0.6)
Pelvis	4 (0.1)	7 (0.2)	3 (0.1)
Femur	3 (0.1)	4 (0.1)	1 (0.0)
Lower Leg	3 (0.1)	5 (0.2)	2 (0.1)
Humerus	2 (0.1)	1 (0.0)	4 (0.1)
Forearm/Wrist	75 (2.6)	66 (2.3)	62 (2.2)
Rib	21 (0.7)	21 (0.7)	18 (0.6)
5 Years			
Number of patients	2852	2852	2852
Number (%) with event			
Hip	35 (1.2)	31 (1.1)	27 (0.9)
Pelvis	11 (0.4)	13 (0.5)	11 (0.4)
Femur	4 (0.1)	5 (0.2)	1 (0.0)
Lower Leg	4 (0.1)	7 (0.2)	4 (0.1)
Humerus	10 (0.4)	2 (0.1)	5 (0.2)
Forearm/Wrist	112 (3.9)	92 (3.3)	88 (3.1)
Rib	30 (1.1)	32 (1.1)	20 (0.7)

A patient may have clinical fractures at more than one anatomical site, but a patient is only counted once within each anatomical site.

5.8.2. Risk of Clinical Fracture

The risk of clinical fracture (vertebral and nonvertebral fractures associated with pain and discomfort) through 3 years was significantly reduced by 23% in the lasofoxifene 0.5 mg dose group as shown in Table 21. This effect was observed as early as through the first year (HR=0.61; 95% CI [0.45, 0.84]; p=0.002) and was maintained through 5 years. The risk reduction observed with the 0.25 mg dose through 3 years did not achieve statistical significance.

Table 21. Analysis of Time to First Clinical Fracture –PEARL – Full Analysis Set

		Lasofoxifene	
	Placebo	0.25 mg	0.5 mg
3 Years			
Number of patients	2852	2852	2852
Number (%) with event	246 (8.6)	216 (7.6)	193 (6.8)
Hazard ratio (95% CI)		0.87(0.72, 1.04)	0.77 (0.64, 0.93)
P-value		0.129	0.006*

*P-value significant vs. placebo.

5.9. Other Bone Effects

5.9.1. Bone Mineral Density and Bone Mineral Content

Measurements of bone mineral density have been shown to correlate strongly with load-bearing capacity of the hip and spine and with the risk of fracture. In a subset of patients in PEARL, BMD at the lumbar spine, hip and hip components, and forearm was shown to be significantly increased at 3 years (the last assessment timepoint for this analysis subset) by lasofoxifene 0.25 mg or 0.5 mg in comparison to placebo. Consistent numerically greater increases at all sites were observed with lasofoxifene 0.5 mg compared to lasofoxifene 0.25 mg. In addition, whole body BMC was significantly increased at 3 years for lasofoxifene-treated patients compared to placebo. These results are shown in [Table 22](#) below.

Table 22. Analysis of BMD by Site and Whole Body BMC: Percent Change from Baseline at Month 36 –PEARL – BMD Subgroup

	Placebo	Lasofoxifene	
		0.25 mg	0.5 mg
Lumbar spine BMD	N=253	N=254	N=253
LS mean	1.331	4.623	4.677
LS mean diff vs. placebo (95% CI)		3.293 (2.489, 4.096)	3.346 (2.542, 4.151)
P-value		<0.001*	<0.001*
Total hip BMD	N=253	N=254	N=252
LS mean	-0.516	1.742	2.527
LS mean diff vs. placebo (95% CI)		2.258 (1.620, 2.896)	3.043 (2.403, 3.683)
P-value		<0.001*	<0.001*
Femoral neck BMD	N=253	N=254	N=252
LS mean	-0.826	1.871	2.465
LS mean diff vs. placebo (95% CI)		2.696 (1.900, 3.492)	3.291 (2.493, 4.089)
P-value		<0.001*	<0.001*
Greater trochanter BMD	N=253	N=254	N=252
LS Mean	-0.122	2.184	3.469
LS mean diff vs. placebo (95% CI)		2.306 (1.473, 3.139)	3.591 (2.756, 4.426)
P-value		<0.001*	<0.001*
Intertrochanteric area BMD	N= 253	N= 254	N= 252
LS Mean	-0.578	1.439	2.059
LS mean diff vs. placebo (95% CI)		2.016 (1.326, 2.707)	2.637, (1.943, 3.330)
P-value		0.001*	<0.001*
Ward's triangle BMD	N= 253	N=254	N= 252
LS Mean	-2.957	1.416	2.894
LS mean diff vs. placebo (95% CI)		4.374 (2.665, 6.082)	5.851 (4.138, 7.565)
P-value		0.001*	<0.001*
Forearm BMD	N=216	N=215	N=210
LS Mean	-1.713	-0.445	0.085
LS mean diff vs. placebo (95% CI)		1.268 (0.647, 1.888)	1.798 (1.173, 2.423)
P-value		0.001*	0.001*
Whole Body BMC	N=242	N=239	N=233
LS Mean	-0.729	1.877	2.054
LS mean diff vs. placebo (95% CI)		2.606 (1.839, 3.373)	2.783 (2.010, 3.555)
P-value		<0.001*	<0.001*

LS = least squares; diff = difference; vs=versus

BMD was measured in g/cm²; BMC was measured in grams

*P-value significant versus placebo.

The statistically significant increase in lumbar spine and total hip BMD was evident at 3 months and sustained through 3 years. The effect on hip components and whole body BMC was evident at 12 months (the first time point for these evaluations) and sustained through 3 years.

The efficacy of lasofoxifene in improving BMD in postmenopausal women with osteoporosis was also evident in the significantly smaller proportion of lasofoxifene-treated patients who experienced severe bone loss compared to placebo: 3.3% placebo patients, 0.9% lasofoxifene 0.25 mg, and 0.9% lasofoxifene 0.5 mg. Severe bone loss was defined as any 1 of the following conditions: (1) $\geq 7\%$ BMD loss at lumbar spine or $\geq 10\%$ BMD loss at femoral

neck at Month 12, (2) $\geq 11\%$ BMD loss at lumbar spine or $\geq 14\%$ BMD loss at femoral neck at Month 24, or (3) ≥ 2 on-study radiographic vertebral fractures by Month 24. Patients meeting any of these conditions were referred to their physician with a recommendation that she be considered for treatment with a bisphosphonate or other appropriate bone active agent.

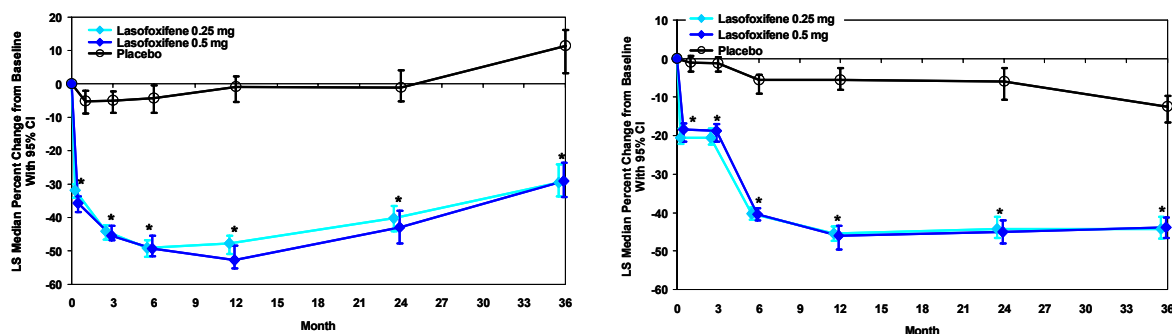
5.9.2. Markers of Bone Turnover

The effect of lasofoxifene on markers of bone resorption (CTX), and bone formation (osteocalcin, P1NP, and bone specific alkaline phosphatase) was evaluated in a subset of patients (N=1126) in PEARL through 3 years. Lasofoxifene-treated patients had significantly decreased levels of all markers of bone turnover compared to placebo from Month 1 through 3 years (with the exception of P1NP at Month 1). Representative results for a bone resorption marker (CTX) and a bone formation marker (osteocalcin) are shown in Figure 4.

Figure 4. C-Telopeptide and Osteocalcin: Median Percent Change from Baseline – PEARL - BMD Sub-group

C-Telopeptide

Osteocalcin



* P-value significant vs. placebo for both doses

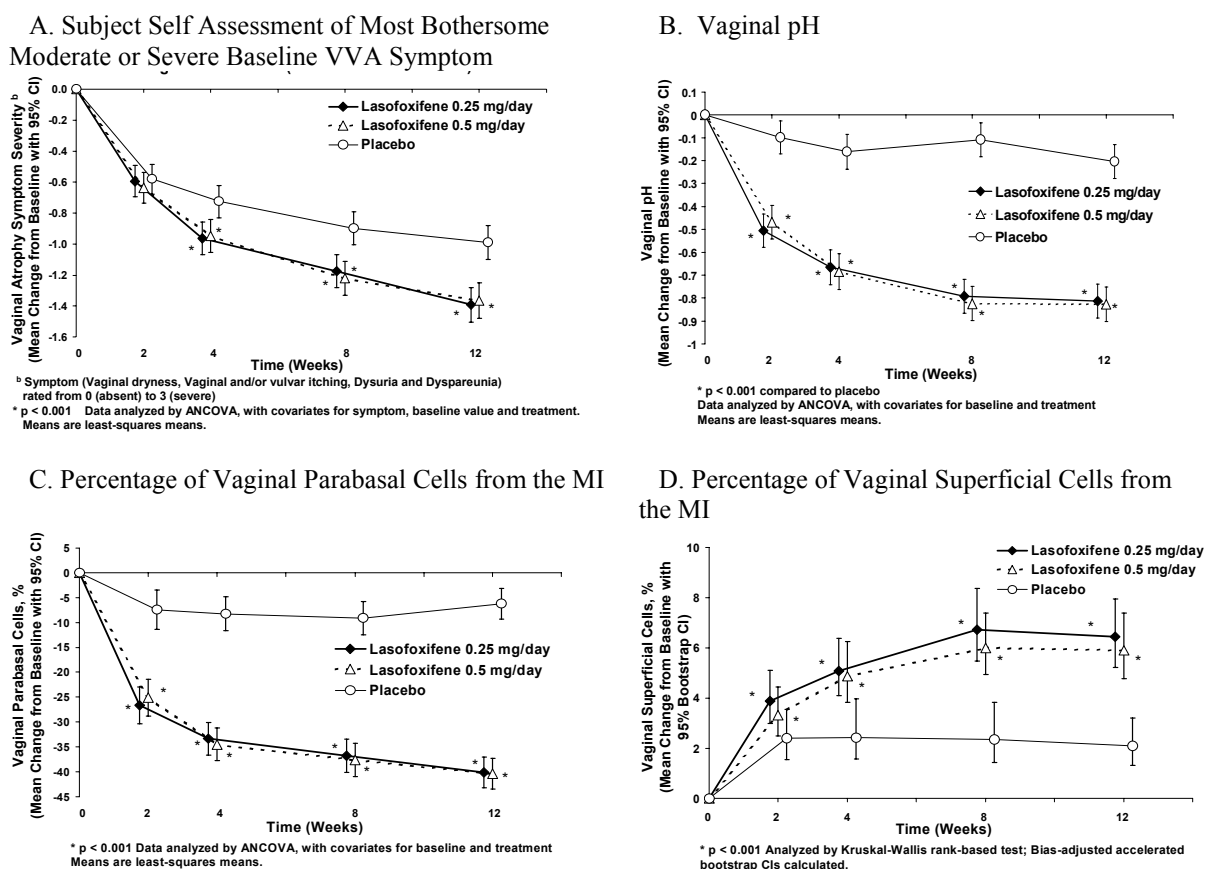
5.10. Vulvar and Vaginal Atrophy Endpoints

In VVA, the maturation index of the vagina shifts with a loss of superficial cells and an increase in parabasal and intermediate cells. These cellular changes are accompanied by an increase in pH and ensuing vaginal dryness. With this decreased lubrication, patient symptoms including vaginal discomfort, burning, soreness, and dyspareunia may occur.

NDA 21-843, for the treatment of moderate to severe symptoms of VVA in postmenopausal women with low bone mass, was submitted in 2004. The NDA included results from 2 pivotal, 12-week, Phase 3 trials (Studies A2181031 and A2181032) of identical design and one proof of concept Phase 2 trial (Study A2181012). Both Phase 3 studies evaluated

lasofoxifene 0.25 mg and 0.5 mg versus placebo in postmenopausal women for efficacy using four co-primary endpoints (measured as a change from baseline to Week 12): subject self-assessed most bothersome moderate or severe baseline VVA symptom, vaginal pH, percentage of vaginal parabasal cells and percentage of vaginal superficial cells. Based on the results of these studies, the FDA acknowledged in the 2006 Not Approvable letter for NDA 21-843 that lasofoxifene was efficacious in the treatment of VVA in postmenopausal women. Results from the Phase 3 studies are summarized in Figure 5.

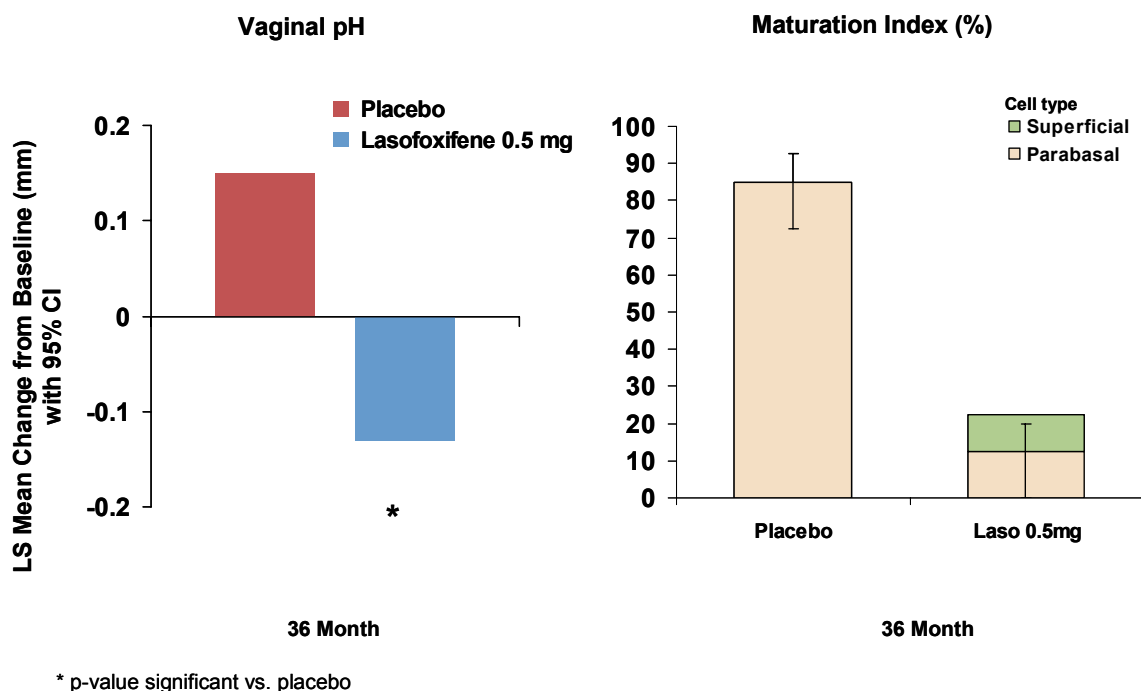
Figure 5. Change from Baseline in 4 Co-primary Endpoint Parameters – Phase 3 VVA Studies in Postmenopausal Women



MI = maturation index

Assessments of vaginal pH and Maturation Index were performed in the TVU-I subgroup (n=326) of PEARL. In these patients, lasofoxifene significantly reduced vaginal pH and demonstrated favorable effects on the vaginal maturation index. Results at 3 years are shown in Figure 6. These positive effects on signs of VVA, observed at 1 year and sustained through 3 years in these postmenopausal women with osteoporosis, were consistent with results from the Phase 2/3 VVA registration studies, which enrolled 1,276 postmenopausal women who were on average 5 to 10 years younger than those in PEARL.

Figure 6. Vaginal pH and Maturation Index in PEARL – TVU-I



The beneficial vaginal changes associated with lasofoxifene are further described in Section 6.9.8 together with results from nonclinical investigations into the mechanism of these changes.

5.11. Results in Subpopulations

Based on analyses of 3-year PEARL data, there was no evidence of a differential impact of demographic factors (age and race) on either fracture or BMD endpoints for lasofoxifene-treated patients compared to placebo.

5.12. Long-term Maintenance of Effects

Results from PEARL demonstrate that lasofoxifene 0.5 mg, the proposed indicated dose, significantly reduced the risk of new/worsening radiographic vertebral fracture, the risk of nonvertebral fracture, and the risk of clinical fracture in postmenopausal women with osteoporosis. Significant risk reduction for these parameters was seen as early as 1 year and was sustained through 5 years of treatment. These results show that lasofoxifene is an effective treatment for osteoporosis, a chronic disease that requires long-term therapy.

Additionally, the beneficial effect of lasofoxifene 0.5 mg in reducing the risk of breast cancer (ER+, all, ER+ invasive, and invasive) was sustained through 5 years. No new cases of breast cancer emerged between 3 years and 5 years in women treated with lasofoxifene 0.5 mg.

5.13. Clinical Efficacy Summary of Results

- Lasofoxifene is efficacious in the treatment of osteoporosis in postmenopausal women at increased risk of fracture.
- Lasofoxifene 0.5 mg/day is the most efficacious dose, based on the number of fracture endpoints and patient subsets in which fracture benefits were observed, compared to lasofoxifene 0.25 mg (Table 1).

Summary of Bone Effects

- Lasofoxifene 0.5 mg significantly:
 - Reduced the risk of new/worsening radiographic vertebral fractures by 42% through 3 years. Reductions in risk were observed:
 - As early as 1 year, and were sustained through 5 years.
 - In patients with LS BMD T-score ≤ -2.5 and in patients with LS BMD T-score > -2.5 .
 - In patients with and without prevalent fractures at baseline.
 - Reduced the risk of nonvertebral fractures by 22% through 3 years. Reductions in risk were observed:
 - As early as 1 year, and were sustained through 5 years.
 - In patients with LS BMD T-score ≤ -2.5 .
 - In patients with severe osteoporosis.
 - Reduced the risk of clinical fractures (vertebral and nonvertebral fractures associated with pain and discomfort) by 23% through 3 years. Reductions in risk were observed:
 - As early as 1 year, and were sustained through 5 years.
 - Reduced the risk of major nonvertebral fractures at 5 years, but not at 3 years.
 - Reduced the frequency of multiple new/worsening radiographic vertebral fractures
 - Reduced the risk of moderate or severe radiographic vertebral fractures.
 - Increased BMD of the lumbar spine, total hip and hip components, whole body BMC, and biochemical markers of bone turnover.

VVA Effects

- The efficacy of lasofoxifene for the treatment of VVA has previously been established in postmenopausal women with low bone mass with moderate or severe VVA signs and symptoms, regardless of osteoporosis status.
- In postmenopausal women with osteoporosis, lasofoxifene 0.5 mg demonstrated improvements in clinical signs of VVA (vaginal pH, and Maturation Index) that were consistent with those observed in the pivotal VVA studies.

6. Clinical Safety

6.1. Introduction

This section contains a review of the clinical safety data from 17 Phase 2/3 clinical studies, only. Pre-clinical toxicology and clinical pharmacology studies are not included as they did not identify any safety issues related to lasofoxifene use in the intended population (postmenopausal women). In the 23 clinical pharmacology studies in which the majority of participants received only single doses of lasofoxifene: no deaths or serious adverse events were reported, and the proportion of participants experiencing any adverse event was similar among treatment groups with most adverse events reported as mild.

6.2. Safety Analyses

Safety evaluation of lasofoxifene included assessment of adverse events (AEs), serious adverse events (SAEs) including deaths, premature discontinuation, laboratory test abnormalities, vital signs, electrocardiogram (ECG) parameters, and analyses of special endpoints with particular focus on gynecological and cardiovascular safety.

All patients who received at least one dose of study drug were included in the analysis of safety. Safety analyses were performed according to the treatment to which the patient was randomized. Subsets of the safety analysis set were used for safety evaluations of some endpoints, as appropriate.

Integrated data across the Phase 2/3 program are presented based on a cutoff of 03 December 2007, the date of the 4-Month Safety Update for general safety assessments.

For specific endpoint analyses, results are presented only for PEARL. PEARL results include those from the prospectively defined 3-year analysis as well as 5-year extended study results based on a cutoff date of 16 April 2008. As noted previously, the majority of lasofoxifene treatment exposure occurred in PEARL.

A range of lasofoxifene doses (0.017 mg to 10 mg /day) was used across the Phase 2/3 studies, most commonly 0.25 mg/day and 0.5 mg/day. For cross Phase 2/3 program data presentations, results are shown for the placebo, lasofoxifene 0.25 mg, lasofoxifene 0.5 mg,

and all lasofoxifene doses pooled groups. The pooled dose group includes all dose treatment groups in Phase 2/3 studies (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).

Statistical analysis of incidence rates was generally not performed for routine safety analyses; however, a time-to-event analysis of all cause mortality was performed in which each lasofoxifene treatment group was compared against placebo using a log-rank test; censoring time was defined as the date of the last study visit. Hazard ratios and 95% CIs were calculated using a Cox proportional hazards model with treatment as a covariate. The Hochberg procedure was used to control Type I error. Cumulative incidence was estimated using Kaplan-Meier methods.

Nongynecological events of interest included hot flush, leg cramps, venous thromboembolic events, stroke, coronary endpoints, hepatic safety, gallbladder events, blood lipids, markers of cardiovascular safety risk, and cataracts because they have been observed with other SERMs such as raloxifene and tamoxifen. Time-to-event analyses comparing the pooled dose of lasofoxifene versus placebo were performed for a number of these endpoints (VTE, stroke, coronary endpoints of special interest, gallbladder, leg cramps, hot flush) using a Cox proportional hazards model with treatment as a covariate, and stratified by protocol. The log-rank statistic was used to test the pooled dose of lasofoxifene versus placebo. For cataracts, a logistic regression model with treatment and protocol as covariates was used to compare the pooled lasofoxifene group with placebo. Laboratory results (high sensitivity c-reactive protein (hs-CRP)), blood lipids were analyzed using an analysis of covariance on rank-transformed percent change from baseline, with treatment, geographic region, and rank-transformed baseline value as fixed covariates, and protocol as a random covariate, to allow comparison of the treatment groups with placebo.

Gynecological events of special interest included endometrial cancer, endometrial hyperplasia, endometrial polyps, endometrial thickness and cystic changes, benign endometrial histological changes, vaginal bleeding, prolapse, and uterine procedures.

Time-to-event analyses comparing the pooled lasofoxifene group versus placebo were performed for a number of these endpoints (endometrial cancer, endometrial hyperplasia, vaginal bleeding, prolapse) using a Cox proportional hazards model with treatment as a covariate, and stratified by protocol. The log-rank statistic was used to test the pooled dose of lasofoxifene versus placebo. For change from baseline in endometrial thickness, a linear mixed model with treatment, time, treatment by time interaction, and baseline thickness as fixed covariates and protocol as a random effect was used to compare the pooled lasofoxifene group with placebo. The incidence of uterine polyps and uterine procedures in each lasofoxifene treatment group was compared to the incidence in the placebo group using a Cochran-Mantel-Haenszel test.

6.3. Adverse Events

6.3.1. Common Adverse Events

The general adverse event profile for lasofoxifene is consistent with that seen for other SERMs.

Reports received from the Phase 2/3 Clinical Program show the following: the incidence was comparable among treatment groups (89% in the placebo, 92% in the 0.25 mg, 92% in the lasofoxifene 0.5 mg groups, and 92% for the pooled doses group, respectively), and most adverse events were mild or moderate in intensity.

The most commonly reported adverse events that appeared to be associated with lasofoxifene 0.5 mg treatment (i.e., that occurred with higher incidence compared to placebo) were hot flush, muscle spasms, and vaginal discharge ([Table 23](#)). Hot flush was reported for 7% of patients who received placebo compared to 15% who received lasofoxifene 0.5 mg. Muscle spasms were reported for 8% of patients who received placebo compared to 16% of patients who received lasofoxifene 0.5 mg.

Table 23. All Causality Adverse Events Reported in ≥ 5% of Patients in Any Treatment Group (lasofoxifene 0.25 mg, lasofoxifene 0.5 mg, or placebo) - Phase 2/3 Clinical Program

SOC Preferred Term	Number (%) of Patients			
	Placebo N=4701	Lasofoxifene		Pooled N=10,257
		0.25 mg N=4547	0.5 mg N=4308	
Eye Disorders				
Cataract	287 (6.1)	276 (6.1)	269 (6.2)	562 (5.5)
Gastrointestinal Disorders				
Constipation	325 (6.9)	321 (7.1)	338 (7.8)	755 (7.4)
General Disorders /Administration Site Conditions				
Therapeutic response unexpected	310 (6.6)	377 (8.3)	363 (8.4)	849 (8.3)
Infections and Infestations				
Bronchitis	318 (6.8)	326 (7.2)	308 (7.1)	681 (6.6)
Influenza	363 (7.7)	331 (7.3)	340 (7.9)	744 (7.3)
Nasopharyngitis	403 (8.6)	425 (9.3)	419 (9.7)	942 (9.2)
Upper respiratory tract infection	476 (10.1)	450 (9.9)	409 (9.5)	985 (9.6)
Urinary tract infection	392 (8.3)	404 (8.9)	388 (9.0)	880 (8.6)
Musculoskeletal/Connective Tissue Disorders				
Arthralgia	808 (17.2)	726 (16.0)	690 (16.0)	1550 (15.1)
Back pain	851 (18.1)	757 (16.6)	776 (18.0)	1637 (16.0)
Muscle spasms	356 (7.6)	676 (14.9)	673 (15.6)	1498 (14.6)
Musculoskeletal pain	269 (5.7)	274 (6.0)	253 (5.9)	553 (5.4)
Osteoarthritis	328 (7.0)	289 (6.4)	292 (6.8)	604 (5.9)
Pain in extremity	466 (9.9)	430 (9.5)	453 (10.5)	969 (9.4)
Nervous System Disorders				
Dizziness	305 (6.5)	299 (6.6)	248 (5.8)	595 (5.8)
Headache	364 (7.7)	264 (5.8)	260 (6.0)	615 (6.0)
Reproductive System/Breast Disorders				
Vaginal discharge	134 (2.9)	296 (6.5)	265 (6.2)	673 (6.6)
Respiratory Disorders				
Cough	184 (3.9)	231 (5.1)	205 (4.8)	489 (4.8)
Vascular Disorders				
Hot flush	309 (6.6)	690 (15.2)	631 (14.6)	1615 (15.7)
Hypertension	601 (12.8)	514 (11.3)	508 (11.8)	1059 (10.3)

SOC=system organ class
Safety data cutoff 3 December 2007

Vaginal discharge was reported for 3% of patients who received placebo compared to 6% of those who received lasofoxifene 0.5 mg. Vaginal discharge may reflect the beneficial effect of lasofoxifene on the vulva and vagina; as noted in Section 6.9.8, lasofoxifene significantly improves postmenopausal vulvovaginal atrophy symptoms by decreasing vaginal pH, increasing vaginal lubrication, and improving vaginal cell maturation index.

All causality AEs that occurred at an incidence of < 5% in the lasofoxifene 0.25 mg or lasofoxifene 0.5 mg treatment groups in the Phase 2/3 Clinical Program and that also occurred at a higher incidence among lasofoxifene 0.5 mg- compared with placebo-treated patients are listed in [Table 24](#).

Table 24. Selected* All Causality Adverse Events with < 5% Incidence in Any Treatment Groups (lasofoxifene 0.25 mg, lasofoxifene 0.5 mg) - Phase 2/3 Clinical Program

SOC Preferred Term	Number (%) of Patients			
	Placebo N=4701	0.25 mg N=4547	0.5 mg N=4308	Pooled N=10,257
Blood and Lymphatic System Disorders				
Thrombocytopenia	4 (0.1)	5 (0.1)	11 (0.3)	17 (0.2)
Hepatobiliary Disorders				
Hepatic steatosis	24 (0.5)	46 (1.0)	41 (1.0)	90 (0.9)
Hepatic cyst	7 (0.1)	16 (0.4)	15 (0.3)	32 (0.3)
Infections and Infestations				
Tracheitis	7 (0.1)	6 (0.1)	11 (0.3)	20 (0.2)
Vaginal candidiasis	24 (0.5)	151 (3.3)	159 (3.7)	328 (3.2)
Vulvovaginal mycotic infection	18 (0.4)	67 (1.5)	69 (1.6)	173 (1.7)
Investigations				
Blood triglycerides increased	6 (0.1)	13 (0.3)	13 (0.3)	31 (0.3)
Hepatic enzyme increased	7 (0.1)	13 (0.3)	17 (0.4)	33 (0.3)
Musculoskeletal and Connective Tissue Disorders				
Sensation of heaviness	5 (0.1)	16 (0.4)	12 (0.3)	32 (0.3)
Nervous System Disorders				
Reproductive System and Breast Disorders				
Cervical cyst	3 (0.1)	11 (0.2)	13 (0.3)	31 (0.3)
Colpocele	11 (0.2)	28 (0.6)	24 (0.6)	54 (0.5)
Endometrial disorder†	11 (0.2)	41 (0.9)	52 (1.2)	105 (1.0)
Endometrial hypertrophy‡	48 (1.0)	225 (4.9)	182 (4.2)	448 (4.4)
Genital discharge	28 (0.6)	95 (2.1)	70 (1.6)	197 (1.9)
Postmenopausal hemorrhage	6 (0.1)	16 (0.4)	14 (0.3)	33 (0.3)
Uterine polyp	36 (0.8)	109 (2.4)	109 (2.5)	257 (2.5)
Vaginal disorder	28 (0.6)	68 (1.5)	68 (1.6)	150 (1.5)
Vascular Disorders				
Deep vein thrombosis	9 (0.2)	35 (0.8)	24 (0.6)	62 (0.6)
Flushing	3 (0.1)	21 (0.5)	12 (0.3)	37 (0.4)
Phlebitis	3 (0.1)	14 (0.3)	17 (0.4)	34 (0.3)
Thrombophlebitis	3 (0.1)	10 (0.2)	13 (0.3)	24 (0.2)
Thrombophlebitis superficial	10 (0.2)	10 (0.2)	27 (0.6)	37 (0.4)

SOC=System Organ Class

*Events with at least a 2-fold difference (3-fold if 1 incidence below 0.5%) in incidence between the lasofoxifene 0.5 mg and placebo groups.

†Endometrial disorder identifies cystic change

‡Endometrial hypertrophy events based on investigator reporting of endometrial thickness findings.

Safety data cutoff 3 December 2007

Cardiovascular safety and gynecological safety are discussed further in Sections 6.5 and 6.9, respectively.

No notable effects of lasofoxifene on adverse events by geographic region, age or race category, or time on study were seen.

6.3.2. Discontinuations due to Adverse Events

Discontinuation of study treatment due to an adverse event occurred in 443 (9.4%), 515 (11.3%), 464 (10.8%), 1132 (11.0%) patients in the placebo, lasofoxifene 0.25 mg, lasofoxifene 0.5 mg, and pooled lasofoxifene treatment groups, respectively (Table 25). The most frequent causes of discontinuation from lasofoxifene treatment were hot flushes, muscle spasms and deep vein thrombosis (DVT). Hot flushes, DVT, and muscle spasm leading to discontinuation from treatment occurred more frequently among lasofoxifene-treated patients compared to placebo.

Table 25. All Causality Adverse Events Resulting in Discontinuation from Treatment Occurring in ≥ 0.3% of Patients in Any Treatment Group (lasofoxifene 0.25 mg, lasofoxifene 0.5 mg) – Lasofoxifene Phase 2/3 Clinical Program

SOC	Preferred Term	Number (%) of Patients			
		Placebo N=4701	Lasofoxifene		
			0.25 mg N=4547	0.5 mg N=4308	Pooled N=10,257
	Any adverse event	443 (9.4)	515 (11.3)	464 (10.8)	1132 (11.0)
	Gastrointestinal Disorders				
	Nausea	9 (0.2)	10 (0.2)	12 (0.3)	29 (0.3)
	Musculoskeletal and Connective Tissue Disorders				
	Muscle spasms	17 (0.4)	32 (0.7)	40 (0.9)	77 (0.8)
	Nervous System Disorders				
	Headache	20 (0.4)	16 (0.4)	12 (0.3)	32 (0.3)
	Vascular Disorders				
	Deep vein thrombosis	6 (0.1)	30 (0.7)	18 (0.4)	51 (0.5)
	Hot flush	35 (0.7)	79 (1.7)	74 (1.7)	190 (1.9)

SOC=System Organ Class.

Safety data cutoff 3 December 2007

6.3.3. Serious Adverse Events

All causality serious adverse events were reported in 876 (18.6%), 962 (21.1%), 888 (20.6%), and 1926 (18.8%) patients in the placebo, lasofoxifene 0.25 mg, lasofoxifene 0.5 mg and pooled lasofoxifene groups, respectively.

Falls, cholelithiasis, osteoarthritis, cataract, and pneumonia were the most common all causality serious adverse events for lasofoxifene- and placebo-treated patients. These events occurred with generally comparable incidence across treatment groups.

Most of the events which occurred at greater incidence among lasofoxifene 0.5 mg- than placebo-treated patients were reported under the Reproductive System and Breast Disorders

SOC and the Vascular Disorders SOC, and included uterine polyp, endometrial hypertrophy (sonographic endometrial thickness), uterine prolapse, pulmonary embolism, and DVT.

Uterine polyps and endometrial hypertrophy (sonographic endometrial thickness findings) are both considered benign findings. Reporting of endometrial hypertrophy and polyps was driven by per protocol surveillance; review of these serious adverse events showed that most of these events were categorized as serious due to hospitalization for procedures generally performed in an outpatient setting. The small increased reporting of serious adverse events for prolapse was not confirmed by the comprehensive and specific rating scales used in the development program to assess anatomical prolapse, and there was no significant increase in the occurrence of uterine/vaginal prolapse surgery or surgery for urinary incontinence at the proposed dose. Adverse event data are not considered to provide an accurate reflection of the incidence of vaginal and uterine prolapse, since the investigator criteria for reporting these events do not mandate that they represent a change in symptoms, anatomical signs, or a combination of both. Gynecological findings are discussed in more detail in Section 6.9.

In addition, SAEs of pulmonary embolism and DVT were more common among lasofoxifene- than placebo-treated patients. These events are discussed in Section 6.5.

All causality serious adverse events are summarized in Table 26.

Table 26. All Causality Serious Adverse Events Occurring at ≥ 0.3 Events per 100 Patients in Any Treatment Group (placebo, lasofoxifene 0.25 mg, lasofoxifene 0.5 mg) - Phase 2/3 Clinical Program

SOC Preferred Term	Number of Events (Incidence [Events per 100 Patients])			
	Placebo N=4701	0.25 mg N=4549	0.5 mg N=4308	Pooled N=10,257
Cardiac Disorders				
Acute myocardial infarction	14 (0.3)	11 (0.2)	11 (0.3)	22 (0.2)
Angina pectoris	18 (0.4)	17 (0.4)	11 (0.3)	30 (0.3)
Angina unstable	16 (0.3)	15 (0.3)	13 (0.3)	29 (0.3)
Atrial fibrillation	22 (0.5)	25 (0.5)	24 (0.6)	50 (0.5)
Cardiac failure congestive	10 (0.2)	14 (0.3)	7 (0.2)	22 (0.2)
Coronary artery disease	12 (0.3)	10 (0.2)	7 (0.2)	20 (0.2)
Myocardial infarction	25 (0.5)	19 (0.4)	20 (0.5)	44 (0.4)
Myocardial ischemia	9 (0.2)	7 (0.2)	11 (0.3)	18 (0.2)
Eye Disorders				
Cataract	33 (0.7)	35 (0.8)	37 (0.9)	72 (0.7)
General Disorders and Administration Site Conditions				
Chest pain	12 (0.3)	13 (0.3)	16 (0.4)	31 (0.3)
Hepatobiliary Disorders				
Cholecystitis	8 (0.2)	9 (0.2)	12 (0.3)	22 (0.2)
Cholelithiasis	31 (0.7)	50 (1.1)	41 (1.0)	96 (0.9)
Infections and Infestations				
Bronchitis	7 (0.1)	6 (0.1)	11 (0.3)	17 (0.2)
Gastroenteritis	14 (0.3)	7 (0.2)	8 (0.2)	15 (0.1)
Pneumonia	34 (0.7)	30 (0.7)	31 (0.7)	66 (0.6)
Urinary tract infection	9 (0.2)	16 (0.4)	14 (0.3)	30 (0.3)
Injury, Poisoning and Procedural Complications				
Fall	75 (1.6)	67 (1.5)	52 (1.2)	119 (1.2)
Femoral neck fracture	15 (0.3)	13 (0.3)	6 (0.1)	19 (0.2)
Femur fracture	15 (0.3)	10 (0.2)	5 (0.1)	15 (0.1)
Hip fracture	19 (0.4)	17 (0.4)	15 (0.3)	33 (0.3)
Humerus fracture	12 (0.3)	4 (0.1)	8 (0.2)	12 (0.1)
Radius fracture	5 (0.1)	4 (0.1)	12 (0.3)	17 (0.2)
Wrist fracture	15 (0.3)	9 (0.2)	7 (0.2)	17 (0.2)
Musculoskeletal and Connective Tissue Disorders				
Osteoarthritis	41 (0.9)	51 (1.1)	40 (0.9)	94 (0.9)
Neoplasms Benign, Malignant and Unspecified				
Breast cancer	18 (0.4)	15 (0.3)	6 (0.1)	22 (0.2)
Nervous System Disorders				
Cerebrovascular accident	25 (0.5)	22 (0.5)	22 (0.5)	45 (0.4)
Syncope	5 (0.1)	8 (0.2)	11 (0.3)	19 (0.2)
Transient ischemic attack	16 (0.3)	14 (0.3)	11 (0.3)	26 (0.3)
Reproductive System and Breast Disorders				
Cystocoele	9 (0.2)	11 (0.2)	13 (0.3)	24 (0.2)
Endometrial hypertrophy*	4 (0.1)	23 (0.5)	24 (0.6)	47 (0.5)

Ovarian cyst	13 (0.3)	11 (0.2)	8 (0.2)	20 (0.2)
Uterine polyp	13 (0.3)	36 (0.8)	28 (0.6)	64 (0.6)
Uterine prolapse	7 (0.1)	16 (0.4)	14 (0.3)	30 (0.3)
Respiratory, Thoracic and Mediastinal Disorders				
Pulmonary embolism	5 (0.1)	18 (0.4)	11 (0.3)	31 (0.3)
Vascular Disorders				
Deep vein thrombosis	11 (0.2)	33 (0.7)	22 (0.5)	58 (0.6)
Hypertension	22 (0.5)	11 (0.2)	13 (0.3)	24 (0.2)

SOC=System Organ Class

*Endometrial hypertrophy events based on investigator reporting of endometrial thickness findings.

Safety data cutoff 3 December 2007

6.3.4. Deaths

The lasofoxifene clinical development program has included a comprehensive evaluation and analysis of all reported deaths. The results indicate that lasofoxifene was not associated with an increased mortality risk.

Introduction

The majority of deaths (228 out of 237) occurred in the PEARL study, as would be anticipated based on study design (largest number of patients, longest duration of follow-up both on and off treatment, and highest mean age), hence, the evaluation of deaths in the clinical development program is provided in greatest detail for PEARL. PEARL is unique in that patients could discontinue blinded study therapy but remain in the study, providing much longer follow-up off drug than is usual in clinical trials, including those for other osteoporosis treatments. Patients in PEARL represent the proposed osteoporosis treatment population for lasofoxifene, i.e., postmenopausal women at increased risk of fracture.

The PEARL Cardiovascular Endpoint Classification Committee (CECC), a blinded endpoint adjudication committee of external experts, reviewed every death in PEARL. The CECC assigned each death event to a single cause of death from 11 prospectively defined categories (Table 27).

Table 27. Cardiovascular Endpoint Classification Committee Cause of Death Categories

Coronary death	Noncoronary death
Sudden death	Vascular
Fatal myocardial infarction	Stroke
Fatal ischemic heart disease	Other vascular
Death from revascularization procedure	Nonvascular
	Cancer
	Suicide
	Homicide
	Other traumatic death
	Other ^a

^aOther includes any death not covered by any of the other 10 pre-specified categories.

PEARL

Death Causality

The overall pattern and distribution of deaths was generally comparable among the lasofoxifene and placebo groups (Table 28). The most common causes of death in the PEARL study were consistent with those observed in the elderly population at large, i.e. cancer deaths and coronary deaths (WHO, 2007; National Centre for Health Statistics, 2001).

Table 28. Death Causality as Determined by External Endpoint Adjudication Committee –PEARL

	Placebo N=2852	Number (%) of Patients	
		Lasofoxifene	
		0.25 mg N=2852	0.5 mg N=2852
All Deaths	65 (2.3)	90 (3.2)	73 (2.6)
Coronary death	21 (0.7)	18 (0.6)	18 (0.6)
Sudden death	15 (0.5)	13 (0.5)	12 (0.4)
Fatal myocardial infarction	3 (0.1)	3 (0.1)	3 (0.1)
Fatal ischemic heart disease	1 (0.0)	2 (0.1)	3 (0.1)
Death from revascularization procedure	2 (0.1)	0	0
Noncoronary death	44 (1.5)	72 (2.5)	55 (1.9)
Vascular	7 (0.2)	18 (0.6)	9 (0.3)
Stroke	5 (0.2)	12 (0.4)	7 (0.2)
Other vascular	2 (0.1)	6 (0.2)	2 (0.1)
Nonvascular	37 (1.3)	54 (1.9)	46 (1.6)
Cancer	20 (0.7)	34 (1.2)	25 (0.9)
Suicide	0 (0.0)	0 (0.0)	1 (0.0)
Homicide	0 (0.0)	0 (0.0)	0 (0.0)
Other traumatic death	4 (0.1)	2 (0.1)	3 (0.1)
Other cause of death	13 (0.5)	18 (0.6)	17 (0.6)

Cancer was the most common cause of death, comprising 35% of all deaths in the study. Cause of death adjudicated as cancer occurred in 20 (0.7%), 34 (1.2%), and 25 (0.9%) of patients in the placebo, lasofoxifene 0.25 mg, and lasofoxifene 0.5 mg groups, respectively. The lasofoxifene 0.25 mg group included one patient who was randomized to treatment but did not take any dose of study drug

The distribution of adjudicated cancer deaths by anatomical site based on clinical review is summarized in [Table 29](#).

Table 29. Adjudicated Cancer Deaths by Anatomical Site –PEARL

	Placebo	Lasofoxifene	
		0.25 mg	0.5 mg
All locations	20	34	25
Abdominal	1	0	0
Bile Duct/Gallbladder	2	1	2
Bladder	0	0	1
Brain	1	4	1
Colorectal ^a	2	5	3
Endometrial/Ovarian ^b	1	0	0
Esophageal	0	3	0
Gastric/Stomach	1	4	0
Leiomyosarcoma	0	1	0
Leukemia	1	2	1
Liver	0	0	1
Lung	2	4	7
Lymphoma/Lymphoma non-Hodgkin	1	1	1
Melanoma	1	2	1
Mesothelioma	0	0	1
Oral	1	0	0
Ovarian	2	0	0
Pancreatic	4	3	2
Peritoneal	0	1	0
Renal	0	1	1
Thyroid	0	0	1
Unknown	0	2	2

^aColorectal includes colon, rectal, and bowel

^bEndometrial and ovarian in origin.

The sites in the body where cancer was identified as the cause of death were diverse and not consistent with cancers associated with modulation of the estrogen receptor. The most frequently reported cancer events resulting in death and their occurrence in the placebo, lasofoxifene 0.25 mg, and lasofoxifene 0.5 mg groups, respectively, were lung cancers (2, 4, and 7); colorectal cancers (2, 5, and 3); pancreatic cancers (4, 3, and 2); brain cancers (1, 4, and 1); gastric/stomach cancers (1, 4, and 0); and esophageal cancers (0, 3, and 0). There were no events of breast cancer that resulted in death during 5 years of follow-up.

Coronary events were the second most common cause of death in PEARL, accounting for 25% of all deaths. There was no difference between lasofoxifene- and placebo-treated

patients in the number of coronary deaths, which occurred in 18 (0.6%) patients in each lasofoxifene dose group compared to 21 (0.7%) of placebo-treated patients.

Deaths adjudicated to ‘other cause of death’, which included those events that could not be attributed to a coronary, cancer, vascular or traumatic cause (i.e. suicide, homicide, or other trauma), collectively represented the third most common category. This included events such as sepsis, bronchopneumonia, chronic lung diseases (e.g. asthma, COPD, pulmonary fibrosis), worsening diabetes, respiratory failure and ‘death cause unknown’. Deaths in this category occurred in 13 (0.5%), 18 (0.6%), and 17 (0.6%) of patients in the placebo, lasofoxifene 0.25 mg, and lasofoxifene 0.5 mg groups, respectively. The individual causes of death in this category were diverse and no single cause was predominant.

Deaths adjudicated as stroke comprised 11% of all PEARL deaths and occurred in 5 (0.2%), 12 (0.4%), and 7 (0.2%) and patients in the placebo, lasofoxifene 0.25 mg, and lasofoxifene 0.5 mg groups, respectively. Fatal stroke events are described in further detail in Section 6.5.2, in the discussion of all stroke events in the PEARL study.

Noncoronary deaths adjudicated to ‘other vascular’ occurred in 2 (0.1%), 6 (0.2%), and 2 (0.1%) patients and in the placebo, lasofoxifene 0.25 mg, and lasofoxifene 0.5 mg groups, respectively. Of the 6 deaths in the lasofoxifene 0.25 mg dose group, pulmonary embolism was a primary or contributing factor to cause of death in 3 patients; of the remaining 3 patients, 1 patient experienced a fatal subarachnoid hemorrhage; 1 patient experienced an abdominal aneurysm; and in 1 patient cause of death was attributed to dilated cardiomyopathy. In the lasofoxifene 0.5 mg group, the 2 deaths were attributed to pulmonary embolism; 1 event occurred in the setting of recent surgery and the second event occurred in a patient immobilized following a fall that resulted in a fracture of the pelvis. For the 2 ‘other vascular’ deaths in the placebo group, 1 was attributed to a cerebral aneurysm and the second to an abdominal aneurysm. The 5 adjudicated deaths of pulmonary embolism are described in further detail in Table 39, Section 6.5.1 (Venous Thromboembolic Events).

Finally, deaths attributed to suicide, homicide or other traumatic events were infrequent and balanced across the three treatment groups, occurring in 4, 2 and 4 patients on placebo, lasofoxifene 0.25 mg and lasofoxifene 0.5 mg, respectively.

Analysis of All Cause Mortality through 3 and 5 Years

An analysis of All Cause Mortality is presented for the first 3 years of the study as reported in the NDA, and through 5 years (following completion of the 2-year study extension). The Hochberg procedure was used to control for multiple comparison at each time point, in accordance with the prospectively-defined analysis plan.

In the first 3 years of the study, 130 deaths were reported [38 on placebo (1.3%), 45 on lasofoxifene 0.25 mg (1.6%), and 47 on lasofoxifene 0.5 mg (1.6%)] (Table 30).

Through 5 years, there were 228 deaths [65 on placebo (2.3%), 90 on lasofoxifene 0.25 mg (3.2%), and 73 on lasofoxifene 0.5 mg (2.6%)]. The SAE-reporting process identified 2

additional deaths in the lasofoxifene 0.25 mg group. These occurred beyond the pre-specified cutoff for the 5-year analyses; consequently, they are not included in the analyses discussed below.

The mortality hazard ratio for the first 3 years was 1.20 (p=0.407) for lasofoxifene 0.25 mg compared to placebo and 1.22 (p=0.362) for lasofoxifene 0.5 mg, indicating that mortality risk was not increased for either lasofoxifene dose group.

Through 5 years of follow-up, the corresponding hazard ratios were 1.38 (p=0.049) for lasofoxifene 0.25 mg and 1.12 (p=0.511) for lasofoxifene 0.5 mg. The 5-year data suggest increased mortality in the lasofoxifene 0.25 mg group compared to placebo, but no evidence of increased hazard for the lasofoxifene 0.5 mg group. This apparent difference between the 2 treatment groups is explored in more detail below.

Table 30. Analysis of Time to All Cause Mortality –PEARL - Full Analysis Set

		Lasofoxifene	
	Placebo N=2852	0.25 mg N=2852	0.5 mg N=2852
3 Years			
Patient-years	8217	8231	8238
Number (%) with event	38 (1.3)	45 (1.6)	47 (1.6)
Incidence rate/1000 patient-years (95% CI)	4.6 (3.3, 6.4)	5.5 (4.0, 7.3)	5.7 (4.2, 7.6)
Hazard ratio (95% CI)		1.20 (0.78, 1.85)	1.22 (0.80, 1.88)
P-value		0.407	0.362
5 Years			
Patient-years	12,818	12,883	12,850
Number (%) with an event	65 (2.3)	90 (3.2)	73 (2.6)
Incidence rate/1000 patient-years (95% CI)	5.1 (3.9, 6.5)	7.0 (5.6, 8.6)	5.7 (4.5, 7.1)
Hazard ratio (95% CI)		1.38 (1.00, 1.89)	1.12 (0.80, 1.56)
P-value		0.049	0.511

Other 5-Year Mortality Analyses

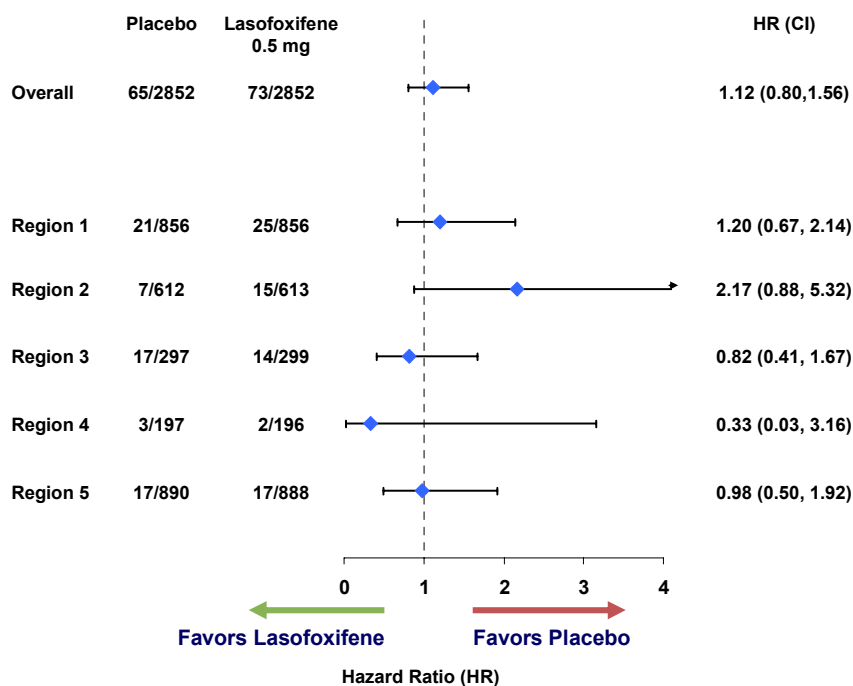
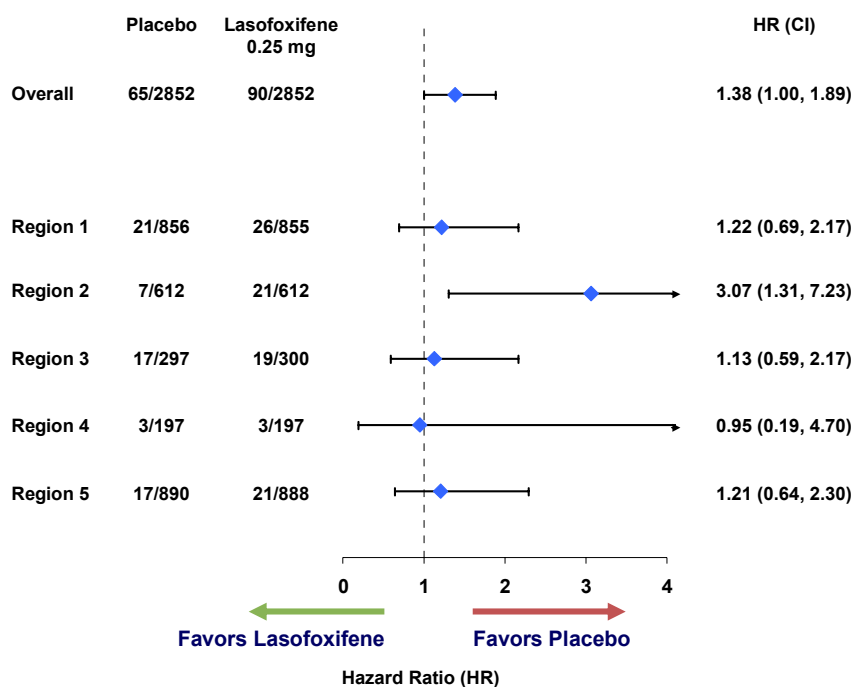
At 5 years, many of the patients had discontinued study treatment but had been followed for other on-study procedures including mortality status; approximately half of the total recorded deaths occurred more than 30 days since the last dose of study drug.

Because different regional standards of care following discontinuation of protocol-specified study treatment could have had an impact on mortality rates, mortality results were also analyzed for the full study population according to pre-specified geographic regions. The 5 pre-defined regions were:

1. USA, Canada, Western Europe, Australia, and South Africa
2. Mexico, Central, and South America
3. India
4. Asia (Japan, Hong Kong, and Korea)
5. Central and Eastern Europe, Egypt, and Turkey

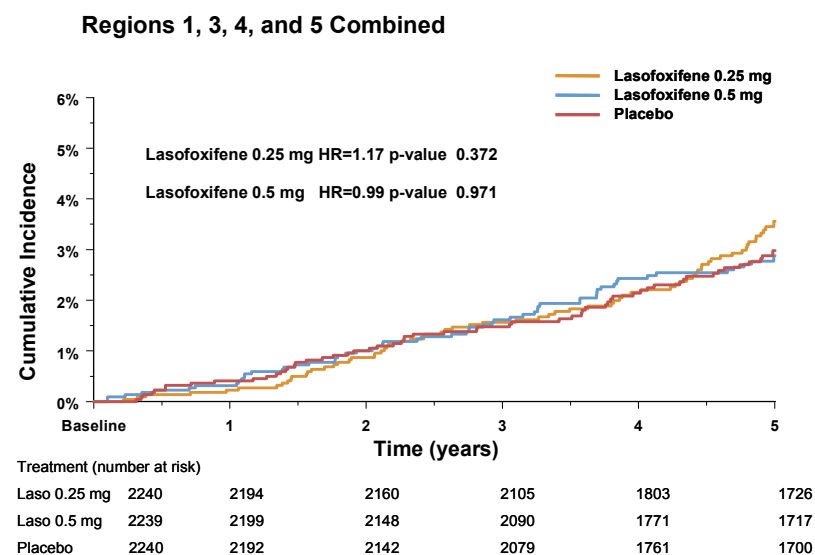
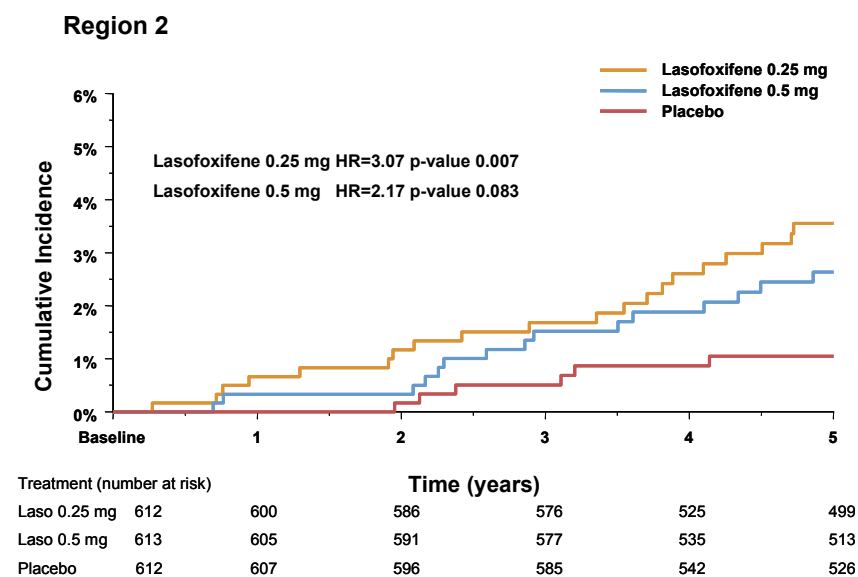
In Regions 1, 3, 4, and 5, which together account for 79% of the PEARL study population, mortality rates were similar across the placebo, lasofoxifene 0.25 mg, and lasofoxifene 0.5 mg treatment groups. In Region 2 (Mexico, Central, and South America), lasofoxifene 0.25 mg was associated with a statistically significantly higher mortality rate ($p=0.007$) compared to placebo. In addition, lasofoxifene 0.5 mg was associated with an observed increase in mortality events in Region 2 (2.4%) compared to placebo (1.1%) which, although not statistically significant, was consistent with a lower mortality rate for the placebo group. These results are summarized in [Figure 7](#).

Figure 7. Mortality Incidence by Region in PEARL



The cumulative incidence of mortality is shown for Region 2 and the other regions combined in [Figure 8](#).

Figure 8. Cumulative Incidence of Mortality by Geographic Region – PEARL



Mortality incidence rates are shown by region in [Table 31](#).

Table 31. Mortality Incidence Rates (95% CI) by Region - PEARL

	Placebo	Lasofoxifene	
		0.25 mg	0.5 mg
Region 1	5.55 (3.43, 8.48)	6.80 (4.44, 9.96)	6.66 (4.31, 9.83)
Region 2	2.44 (0.98, 5.03)	7.47 (4.63, 11.42)	5.27 (2.95, 8.70)
Region 3	13.22 (7.70, 21.16)	14.89 (8.96, 23.25)	10.89 (5.95, 18.27)
Region 4	3.55 (0.73, 10.36)	3.39 (0.70, 9.91)	2.33 (0.28, 8.41)
Region 5	4.22 (2.46, 6.75)	5.14 (3.18, 7.85)	4.14 (2.41, 6.63)

Incidence rate=number of deaths/1000 patient-years.

In summary, there was no suggestion of increased mortality on lasofoxifene through the first 3 years of the study. Although the 5-year data did suggest increased mortality hazard in the lasofoxifene 0.25 mg group compared to placebo, there was no suggestion of increased hazard for lasofoxifene 0.5 mg. No dose-response relationship, pattern of death causality, or plausible mechanistic explanation accounts for the observed differences in numbers of deaths on lasofoxifene 0.25 mg group compared to placebo. Rather, the observed difference appears to be due to an unusually low mortality rate for the placebo group in Region 2, suggesting that the apparent increase in deaths in the lasofoxifene 0.25 mg group Region 2 may be due to chance. In Regions, 1, 3, 4, and 5, which together account for 79% of the PEARL study population, mortality rates were similar across the placebo, lasofoxifene 0.25 mg, and lasofoxifene 0.5 mg treatment groups.

Phase 2/3 Clinical Studies excluding PEARL

Among the 16 other Phase 2/3 clinical studies (i.e. excluding PEARL), 9 deaths (9/4555 [0.2%]) were reported, 1 each in 9 separate studies. All deaths were adjudicated by the PEARL CECC. Three of the 9 deaths were trauma-related (lasofoxifene 0.025 mg; 0.25 mg; 0.5 mg), 2 were attributed to other illness (both in lasofoxifene 0.25 mg treated patients with concomitant respiratory disease) and 4 were attributed to sudden death (2 lasofoxifene 0.25 mg patients; one 0.5 mg patient and one 2.5 mg patient). Sudden Death was defined by the CECC as “no known non-atherosclerotic cause, and the death was either unwitnessed, or witnessed and immediate”. The 4 deaths adjudicated as Sudden Death were reported by the Investigator as asphyxia due to drowning (lasofoxifene 2.5 mg), coronary arteriosclerosis (lasofoxifene 0.5 mg), cardiovascular disease with obstructive sleep apnea (lasofoxifene 0.25 mg) and cardiac arrhythmia (lasofoxifene 0.25 mg). There were no deaths on placebo.

Mortality Summary and Conclusions

The lasofoxifene clinical development program has included a comprehensive evaluation of all reported deaths, the results of which indicate that overall, lasofoxifene was not associated with an increased mortality risk.

Nearly all of the mortality data in the Phase 2/3 development program comes from the PEARL study. The pattern of distribution of deaths in PEARL was consistent with the leading causes of death in the elderly population at large, i.e, cancer deaths and coronary deaths (WHO, 2007; National Center for Health Statistics, 2001).

Cancer was the most common cause of death in PEARL and represented 35% of all deaths in the study. The cancer sites in the body were diverse and not consistent with cancers associated with modulation of the estrogen receptor. Deaths attributed to coronary events were the second most common cause of death and were balanced across treatment groups. The proportion of fatal hemorrhagic and non-hemorrhagic stroke was similar across treatment groups. There were 5 deaths in which pulmonary embolism was indicated to be a primary or contributing factor to cause of deaths: 3 patients on lasofoxifene 0.25 mg and 2 on lasofoxifene 0.5 mg.

There was an observed difference in the number of deaths on lasofoxifene 0.25 mg compared to placebo at 5 years, which was not seen with lasofoxifene 0.5 mg. No dose response relationship, pattern of death causality, or plausible mechanistic explanation accounts for this observed difference. The difference appears to be due to an unusually low mortality rate for the placebo group in Region 2 (Mexico, Central and South America), suggesting that the apparent increase in deaths observed for lasofoxifene 0.25 mg in Region 2 may be due to chance. In all other regions, mortality rates were similar across the placebo, lasofoxifene 0.25 mg, and lasofoxifene 0.5 mg treatment groups.

In the other Phase 2/3 studies (i.e. excluding PEARL), death causality was disparate across the 9 reported events and did not suggest a treatment association. No deaths were reported in the Phase 1 Clinical Pharmacology program.

In summary, the results of Phase 2/3 the clinical program do not indicate an increased mortality risk associated with lasofoxifene treatment.

6.4. Breast Endpoints

PEARL was the only lasofoxifene study to prospectively define a reduction in risk of breast cancer as an efficacy endpoint. Treatment-emergent breast cancer was adjudicated by an independent expert endpoint committee and required histological confirmation. Three patients with pre-existing breast cancer were excluded from the analyses discussed in this section.

6.4.1. ER+ Breast Cancer

Both lasofoxifene 0.25 mg and 0.5 mg significantly reduced the risk of ER+ breast cancer (84% lasofoxifene 0.25 mg, 67% lasofoxifene 0.5 mg) through 3 years; through 5 years, lasofoxifene 0.5 mg significantly reduced the risk of ER+ breast cancer by 81% compared with placebo. The 48% reduction in risk observed with lasofoxifene 0.25 mg compared with placebo was not statistically significant.

Table 32. Time to First Adjudicated ER+ Breast Cancer–PEARL - Full Analysis Set

		Lasofoxifene	
	Placebo	0.25 mg	0.5 mg
3 Years			
Number of patients	2738	2729	2743
Number (%) with event	12 (0.4%)	2 (0.1)	4 (0.1)
Hazard ratio (95% CI) vs. placebo		0.16 (0.04, 0.73)	0.33 (0.11, 1.02)
P-value		0.007*	0.042*
5 Years			
Number of patients	2740	2729	2745
Number (%) with event	21 (0.8%)	11 (0.4)	4 (0.1)
Hazard ratio (95% CI) vs. placebo		0.52 (0.25, 1.08)	0.19 (0.07, 0.56)
P-value		0.076	<0.001*

*P-value significant vs placebo.

Time to first ER+ breast cancer was a co-primary endpoint (together with time to first nonvertebral fracture) for the 5-year analysis of PEARL.

6.4.2. All Breast Cancer

Lasofoxifene 0.5 mg significantly reduced the risk of all breast cancer (a composite endpoint consisting of ER+, ER-, invasive, and ductal cancer in situ [DCIS] breast cancer) by 65% compared to placebo through 3 years and by 79% through 5 years. Lasofoxifene 0.25 mg did not significantly reduce the risk of all breast cancer through 3 years or 5 years.

Table 33. Time to First Adjudicated All Breast Cancer –PEARL - Full Analysis Set

	Placebo	Lasofoxifene	
		0.25 mg	0.5 mg
3 Years			
Number of patients	2738	2729	2743
Number (%) with event	14 (0.5)	8 (0.3)	5 (0.2)
Hazard ratio (95% CI)		0.56 (0.23, 1.33)	0.35 (0.13, 0.98)
P-value		0.187	0.036*
5 Years			
Number of patients	2740	2729	2745
Number (%) with event	24 (0.9)	20 (0.7)	5 (0.2)
Hazard ratio (95% CI) vs. placebo		0.82 (0.45, 1.49)	0.21 (0.08, 0.55)
P-value		0.515	<0.001*

*P-value significant vs. placebo.

6.4.3. ER+ Invasive Breast Cancer

Both lasofoxifene 0.25 mg and 0.5 mg significantly reduced the risk of ER+ invasive breast cancer through 3 years (82% lasofoxifene 0.25 mg, 73% lasofoxifene 0.5 mg). Lasofoxifene 0.5 mg also significantly reduced the risk (by 83%) of ER+ invasive breast cancer through 5 years. The risk reduction observed with lasofoxifene 0.25 mg through 5 years was not significantly different from placebo.

Table 34. Time to First Adjudicated ER+ Invasive Breast Cancer Endpoint –PEARL - Full Analysis Set

	Placebo	Lasofoxifene	
		0.25 mg	0.5 mg
3 Years			
Number of patients	2738	2729	2744
Number (%) with event	11 (0.4%)	2 (0.1%)	3 (0.1%)
Hazard ratio (95% CI)		0.18 (0.04, 0.80)	0.27 (0.07, 0.96)
P-value		0.012*	0.030*
5 Years			
Number of patients	2740	2729	2746
Number (%) with event	18 (0.7)	9 (0.3)	3 (0.1)
Hazard ratio (95% CI) vs. placebo		0.50 (0.22, 1.11)	0.17 (0.05, 0.57)
P-value		0.082	0.001*

*P-value significant vs. placebo.

6.4.4. Invasive Breast Cancer

Lasofoxifene 0.5 mg significantly reduced the risk of invasive breast cancer by 75% compared to placebo through 3 years and by 85% through 5 years. Lasofoxifene 0.25 mg did not significantly reduce the risk of invasive breast cancer through 3 years or 5 years.

Table 35. Time to First Adjudicated Invasive Breast Cancer– PEARL - Full Analysis Set

	Placebo	Lasofoxifene	
		0.25 mg	0.5 mg
3 Years			
Number of patients	2738	2729	2744
Number (%) with event	12 (0.4)	6 (0.2)	3 (0.1)
Hazard ratio (95% CI)		0.48 (0.18, 1.29)	0.25 (0.07, 0.87)
P-value		0.146	0.018*
5 Years			
Number of patients	2740	2729	2746
Number (%) with event	20 (0.7)	16 (0.6)	3 (0.1)
Hazard ratio (95% CI) vs. placebo		0.79 (0.41, 1.52)	0.15 (0.04, 0.50)
P-value		0.474	<0.001*

*P-value significant vs. placebo.

6.4.5. Ductal Carcinoma in Situ

No treatment differences were observed for DCIS. Two patients in each treatment group experienced DCIS through 3 years. Through 5 years, 4, 4, and 3 patients in the placebo, lasofoxifene 0.25 mg, and lasofoxifene 0.5 mg groups, respectively, experienced DCIS.

6.4.6. Breast Density

Breast density (the percent of the mammographic image area designated as dense tissue) was measured in a subset of patients. Breast density increases through 3 years (final assessment

time point) for lasofoxifene-treated patients were smaller but not statistically significantly different compared to placebo.

6.5. Cardiovascular Safety Endpoints

A number of cardiovascular endpoints was assessed in the lasofoxifene development program and were a particular focus of the PEARL study. The risk of major coronary events and the risk of hospitalization for cardiovascular events were originally defined as secondary efficacy endpoints in the PEARL study. These were redefined as safety endpoints in view of cardiovascular data from studies such as from the Women's Health Initiative (Writing group for the Women's Health Initiative Investigators, 2002) and the raloxifene RUTH trial (Barret-Connor et al, 2006) which emerged after the PEARL study was designed.

6.5.1. Venous Thromboembolic Events

Venous Thromboembolic Event (VTE), which includes deep vein thrombosis (DVT), pulmonary embolism (PE) and retinal vein thrombosis (RVT), was identified as an important safety endpoint that merited careful monitoring in the development program based on the increased incidence of VTE seen with other SERMs (raloxifene and tamoxifen) and Hormone Therapy (HT).

The analysis of VTE in the lasofoxifene clinical development program, which excluded women with a history of VTE, was based on a composite endpoint composed of adjudicated endpoints of DVT, PE, and RVT in PEARL.

The risk of VTEs was significantly increased in both lasofoxifene treatment groups compared to placebo through 3 years ([Table 36](#)). This was due to the significantly increased risk for DVT (the predominant VTE) in both lasofoxifene treatment groups compared to the placebo group. The overall number of pulmonary embolic events was low (n=10), with the majority occurring in lasofoxifene treated patients (1 on placebo, 5 on lasofoxifene 0.25 mg; and 4 on lasofoxifene 0.5 mg). Similarly, the number of adjudicated RVT was low (n=5) with 1 event in the placebo cohort and 2 events in each lasofoxifene treatment cohort.

Table 36. Analysis of Time to First On-Study Venous Thromboembolic Event, Deep Vein Thrombosis, Pulmonary Embolus, Retinal Vein Thrombosis at 3 Years –PEARL – Full Analysis Set

	Placebo N=2852	0.25 mg N=2852	Lasofoxifene 0.5 mg N=2852
VTE			
Total years	8200	8187	8205
Number (%) with event	10 (0.4)	26 (0.9)	22 (0.8)
Incidence rate/1000 patient-years (95% CI)	1.2 (0.6, 2.2)	3.2 (2.1, 4.7)	2.7 (1.7, 4.1)
Hazard ratio (95% CI)		2.60 (1.25, 5.40)	2.20 (1.04, 4.64)
P-value		0.008*	0.034*
DVT			
Total years	8204	8192	8214
Number (%) with event	8 (0.3)	22 (0.8)	18 (0.6)
Incidence rate/1000 patient-years (95% CI)	1.0 (0.4, 1.9)	2.7 (1.7, 4.1)	2.2 (1.3, 3.5)
Hazard ratio (95% CI)		2.75 (1.23, 6.18)	2.25 (0.98, 5.17)
P-value		0.011*	0.050*
PE			
Total years	8213	8222	8230
Number (%) with event	1 (<0.1)	5 (0.2)	4 (0.1)
Incidence rate/1000 patient-years (95% CI)	0.1 (0.0, 0.7)	0.6 (0.2, 1.4)	0.5 (0.1, 1.2)
Hazard ratio (95% CI)		5.00 (0.58, 42.76)	3.99 (0.45, 35.73)
P-value		0.103	0.181
RVT			
Total years	8212	8229	8232
Number (%) with event	1 (<0.1)	2 (<0.1)	2 (<0.1)
Incidence rate/1000 patient-years (95% CI)	0.1 (0.0, 0.7)	0.2 (0.0, 0.9)	0.2 (0.0, 0.9)
Hazard ratio (95% CI)		2.00 (0.18, 22.02)	1.99 (0.18, 21.99)
P-value		0.565	0.566

*P-value significant vs. placebo

Through 5 years, the risk of VTEs remained significantly increased in both lasofoxifene treatment groups compared to placebo (Table 37) and comparable to that reported at 3 years. DVT continued to be the most common VTE, reported in 13, 36, and 28 patients treated with placebo, lasofoxifene 0.25 mg, and lasofoxifene 0.5 mg, respectively. Pulmonary emboli were reported in 2, 12, and 9 patients treated with placebo, lasofoxifene 0.25 mg, and lasofoxifene 0.5 mg, respectively. The risk of both DVT and PE was significantly increased compared to placebo. The number of adjudicated RVT events was low (n=11) reported in 4, 4, and 3 patients treated with placebo, lasofoxifene 0.25 mg, and lasofoxifene 0.5 mg, respectively.

Table 37. Analysis of Time to First On-Study Venous Thromboembolic Event, Deep Vein Thrombosis, Pulmonary Embolus, Retinal Vein Thrombosis at 5 Years – PEARL – Full Analysis Set

		Lasofoxifene	
	Placebo	0.25 mg	0.5 mg
	N=2852	N=2852	N=2852
VTE			
Total years	12,784	12,779	12,775
Number (%) with event	18 (0.6)	48 (1.7)	37 (1.3)
Incidence rate/1000 patient-years (95% CI)	1.4 (0.8, 2.2)	3.8 (2.8, 5.0)	2.9 (2.0, 4.0)
Hazard Ratio (95% CI)		2.67 (1.55, 4.58)	2.06 (1.17, 3.61)
P-value		0.001*	0.011*
DVT			
Total years	12,800	12,798	12,794
Number (%) with event	13 (0.5)	36 (1.3)	28 (1.0)
Incidence rate/1000 patient-years (95% CI)	1.0 (0.5, 1.7)	2.8 (2.0, 3.9)	2.2 (1.5, 3.2)
Hazard ratio (95% CI)		2.77 (1.47, 5.22)	2.15 (1.12, 4.15)
P-value		0.002*	0.020*
PE			
Total years	12,817	12,868	12,840
Number (%) with event	2 (<0.1)	12 (0.4)	9 (0.3)
Incidence rate/1000 patient-years (95% CI)	0.2 (0.0, 0.6)	0.9 (0.5, 1.6)	0.7 (0.3, 1.3)
Hazard ratio (95% CI)		5.98 (1.34, 26.72)	4.49 (0.97, 20.80)
P-value		0.008*	0.035*
RVT			
Total years	12,808	12,884	12,847
Number (%) with event	4 (0.1)	4 (0.1)	3 (0.1)
Incidence rate/1000 patient-years (95% CI)	0.3 (0.1, 0.8)	0.3 (0.1, 0.8)	0.2 (0.1, 0.7)
Hazard ratio (95% CI)		1.00 (0.25, 3.98)	0.75 (0.17, 3.34)
P-value		0.996	0.704

*P-value significant vs. placebo

There were 7 deaths (1 in a placebo-treated patient, 3 in patients who received lasofoxifene 0.25 mg, and 3 in patients who received lasofoxifene 0.5 mg) that occurred with evidence of PE. These included patients for whom the investigator reported the cause of death as PE or thromboembolism and patients for whom death causality was adjudicated to be “other vascular” by the CECC and which was determined to be a PE-associated death based on clinical review. The incidence rate in all 3 groups was low: 0.1, 0.2, 0.2 events per 1000 patient-years for placebo, lasofoxifene 0.25 mg, and lasofoxifene 0.5 mg, respectively. All cases with 2 exceptions were associated with coexistent risk factors for VTE, and 4 had discontinued study drug for >3 weeks at the time of death. In 4 cases, the PE event was not confirmed by imaging or autopsy. The 7 cases are summarized in [Table 38](#) with risk factors for VTE highlighted in red. No deaths with evidence of a PE event occurred in any studies other than PEARL.

Table 38. Deaths with Evidence of Pulmonary Embolism

SID	Age	Treatment	Therapy Stop	Death	Investigator Death Causality	^Adjudication Death Causality	Comments
0024 942* (Finland)	78	Lasofoxifene 0.25 mg	Study day 753	Study day 753	Pulmonary embolism	Other vascular death	On study day 752 subject experienced nausea/chest pain and nitroglycerin was prescribed. The following day the subject experienced difficulty breathing and died prior to the arrival of an ambulance. Autopsy confirmed PE and DVT. Investigator causality: PE due to DVT, and DVT was related to treatment.
5068 42* (Brazil)	74	Lasofoxifene 0.25 mg	Study day 63	Post-therapy day 36	Acute respiratory insufficiency	Other vascular death	Right kidney nodule identified on Study Day 36, and study treatment discontinued on Day 63. Surgery performed 21 days post-therapy and histology confirmed renal cell carcinoma . Subject experienced worsening dyspnea 4 days post-surgery. Subject's dyspnea again worsened 15 days post-surgery, she developed syncope and was diagnosed with PE and died on route to the hospital (36 days post-therapy). Investigator causality: Respiratory failure due to PE, and PE was related to treatment.
5074 799* (Canada)	73	Lasofoxifene 0.5 mg	Study day 104	Post-therapy day 25	Pulmonary embolism	Other vascular death	Study treatment was discontinued on study Day 104 in preparation for elective surgery. Surgery performed 15 days post-therapy, and anticoagulation was given. Two days post-surgery the subject complained of right thigh pain and was discharged 5 days post-surgery. Ten days post-surgery the subject complained of pain and swelling in the thigh and died at home. Autopsy confirmed PE and DVT. Investigator causality: PE due to DVT, and DVT was related to treatment.

Table 38. Deaths with Evidence of Pulmonary Embolism

SID	Age	Treatment	Therapy Stop	Death	Investigator Death Causality	^Adjudication Death Causality	Comments
0026 1574 (Finland)	79	Placebo	Study day 1537	Post-therapy day 43	Brain contusion; subdural hematoma of the brain; brain edema; pulmonary thrombosis; DVT in legs	Other traumatic death	Head injury: subject fell and developed hemiparesis / loss of consciousness and was hospitalized; CT scan showed subdural hematoma; surgery successfully removed clots; subject subsequently developed cerebral edema and died. Autopsy confirmed brain hemorrhage, bilateral DVTs and PE. Investigator causality: Thrombosis and DVT due to hemorrhage, coma and immobilization , not related to treatment.
0027 19101 (Croatia)	82	Lasofoxifene 0.25 mg	Study day 1668	Post-therapy day 69	Pulmonary embolism; cardio-respiratory failure	Other vascular death	Admitted to psychiatric hospital post-therapy day 1; died 68 days later; PE listed as primary cause on death certificate. No autopsy. Investigator causality: PE due to cardio-respiratory failure, not related to treatment.
0009 16660 (Russia)	79	Lasofoxifene 0.5 mg	Study day 1391	Post-therapy day 14	Thromboembolism	Other [†]	Subject immobilized following fall and fractured pelvis ; subject died at home; no autopsy. Investigator causality: Thromboembolism related to treatment.
5039 3602 (Argentina)	79	Lasofoxifene 0.5 mg	Study day 1583	Post-therapy day 1	Pulmonary embolism	Other vascular death	Subject immobilized following fall and fractured pelvis ; developed sudden onset dyspnea 9 days later and died. No autopsy. Investigator causality: PE was due to pelvic fracture and not related to treatment.

All subjects were in Study A2181002 (PEARL)

SID=Subject identification number, CT=computed tomography, DVT=deep vein thrombosis, PE=pulmonary embolism, and CVA=cerebrovascular accident.

*PE-associated deaths previously reported in the Summary of Clinical Safety.

[†]Adjudicated cause of death: Other; committee indicated that cause is unknown. Insufficient documentation to conclude thromboembolism as a possible cause of death.

[^]Adjudicated cases of fatal PE are within the other vascular category

Risk factor for VTE highlighted in **red**.

6.5.2. Stroke

In PEARL, stroke was a prespecified composite endpoint that included TIA, ischemic stroke, embolic stroke, hemorrhagic stroke, and strokes of unknown type. All stroke events were adjudicated by the Cardiovascular Endpoint Classification Committee.

Lasofoxifene was not associated with an increased risk of stroke (including transient ischemic attacks) in PEARL through 3 years or 5 years of follow-up in a pre-specified analysis. Through 3 years, 35 (1.2%), 28 (1.0%), and 32 (1.1%) patients who received placebo, lasofoxifene 0.25 mg, or lasofoxifene 0.5 mg, respectively had a stroke. Through 5 years, 61 (2.1%), 50 (1.8%), and 46 (1.6%) patients who received placebo, lasofoxifene 0.25 mg, or lasofoxifene 0.5 mg, respectively had a stroke.

Results were similar for a non-prespecified analysis of adjudicated stroke excluding TIA through 3 years. In the analysis of stroke excluding TIA events through 5 years, the risk of all stroke events was significantly reduced in both dose groups of lasofoxifene compared to placebo (HR=0.61; 95% CI: [0.39, 0.96]; p=0.031 for lasofoxifene 0.25 mg; and HR=0.64; 95% CI: [0.41, 0.99]; p=0.043 for lasofoxifene 0.5 mg as shown in [Table 39](#).

Table 39. Analysis of Time to First Adjudicated Stroke –PEARL - Full Analysis Set

	Placebo	Lasofoxifene	
		0.25 mg	0.5 mg
N	2852	2852	2852
3 Years			
Total years	8184	8208	8216
Number (%) with event	28 (1.0)	17 (0.6)	22 (0.8)
Incidence rate/1000 patient-years (95% CI)	3.4 (2.3, 4.9)	2.1 (1.2, 3.3)	2.7 (1.7, 4.1)
Hazard ratio (95% CI)		0.61 (0.33, 1.11)	0.78 (0.45, 1.37)
P-value		0.099	0.389
5 Years			
Total years	12,746	12,853	12,815
Number (%) with event	50 (1.8)	31 (1.1)	32 (1.1)
Incidence rate/1000 patient-years (95% CI)	3.9 (2.9, 5.2)	2.4 (1.6, 3.4)	2.5 (1.7, 3.5)
Hazard ratio (95% CI)		0.61 (0.39, 0.96)	0.64 (0.41, 0.99)
P-value		0.031*	0.043*

*p-value significant vs. placebo

The incidence of adjudicated strokes was ≤1.2 % for each event type (transient ischemic attack, ischemic, embolic, hemorrhagic, unknown) and was similar across all treatment groups both through 3 years and through 5 years ([Table 40](#)).

Table 40. Incidence of Adjudicated Strokes – PEARL – Full Analysis Set

		Number (%) of Patients	
		Lasofoxifene	
	Placebo N=2852	0.25 mg N=2852	0.5 mg N=2852
3 Years			
Number (%) with event	35 (1.2)	28 (1.0)	33 (1.2)
Stroke type			
Transient ischemic attack	8 (0.3)	11 (0.4)	12 (0.4)
Ischemic	16 (0.6)	11 (0.4)	15 (0.5)
Embolic	1 (<0.1)	1 (<0.1)	2 (0.1)
Hemorrhagic	8 (0.3)	3 (0.1)	5 (0.2)
Unknown	3 (0.1)	2 (0.1)	1 (<0.1)
5 Years			
Number (%) with event	61 (2.1)	50 (1.8)	47 (1.6)
Stroke type			
Transient ischemic attack	14 (0.5)	19 (0.7)	15 (0.5)
Ischemic	25 (0.9)	21 (0.7)	23 (0.8)
Embolic	6 (0.2)	1 (<0.1)	2 (0.1)
Hemorrhagic	14 (0.5)	8 (0.3)	6 (0.2)
Unknown	5 (0.2)	2 (0.1)	2 (0.1)

The incidence of hemorrhagic and non-hemorrhagic stroke was numerically lower in the lasofoxifene 0.25 and lasofoxifene 0.5 mg groups compared with placebo both at 3 years and at 5 years. Based on an analysis of the pooled lasofoxifene dose groups at 5 years, the risk of hemorrhagic stroke was not significantly reduced compared to placebo (placebo (HR=0.50; 95% CI: [0.24, 1.04]; p=0.060).

Table 41. Hemorrhagic and Non-Hemorrhagic Stroke –PEARL

	Placebo	Number (%) of Patients	
		Lasofoxifene	
		0.25 mg	0.5 mg
3 Years			
Hemorrhagic stroke	8 (0.3)	3 (0.1)	5 (0.2)
Non-hemorrhagic stroke	28 (1.0)	25 (0.9)	27 (0.9)
5 Years			
Hemorrhagic stroke	14 (0.5)	8 (0.3)	6 (0.2)
Non-hemorrhagic stroke	48 (1.7)	43 (1.5)	40 (1.4)

The number of fatal stroke events was comparable across treatment groups through 48 months in PEARL. Subsequent to Month 48, a greater number of patients in the lasofoxifene 0.25 mg group experienced fatal stroke compared to placebo; this observed difference was not seen for lasofoxifene 0.5 mg. The occurrence of fatal stroke events on study treatment (i.e., fatal stroke event on treatment or within 30 days of last dose) was comparable across treatment groups. The timing of some fatal stroke events relative to time off study treatment, the presence of significant stroke risk factors in all fatal cases, the comparable distribution of hemorrhagic and non-hemorrhagic stroke across treatment groups, and the comparable number of fatal stroke in the placebo and lasofoxifene 0.5 mg treatment groups do not

suggest an increased stroke mortality risk associated with lasofoxifene treatment. There were no fatal stroke events outside of the PEARL study.

6.5.3. Major Coronary Events

Major coronary events was a prespecified secondary endpoint of coronary death, nonfatal myocardial infarctions [MIs], coronary revascularization procedures, documented new ischemic heart disease [IHD], and hospitalizations for unstable angina. The CECC adjudicated all events.

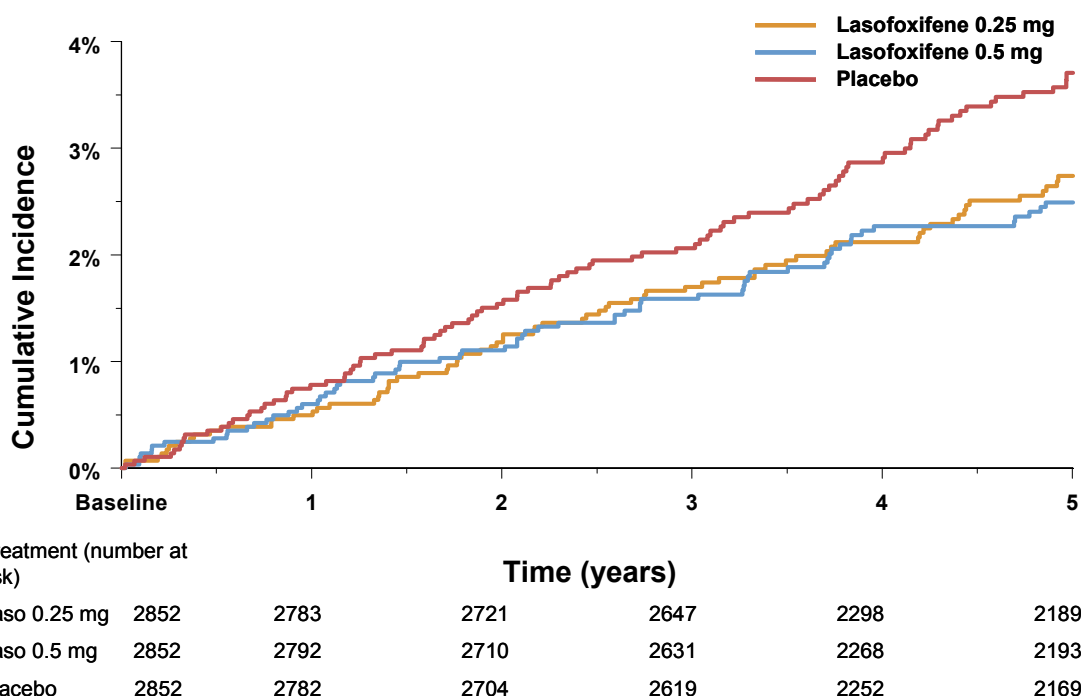
Lasofoxifene 0.5 mg was not associated with a reduction in risk for major coronary events at 3 years but was associated with a significant reduction at 5 years. After 3 years, the reduction in risk for major coronary events in the pooled lasofoxifene treatment groups compared to the placebo treatment group (i.e. the primary comparison for this endpoint) did not reach statistical significance (HR=0.81; 95% CI: [0.58, 1.13]; p=0.205). After 5 years, lasofoxifene 0.5 mg was associated with a statistically significant 32% reduction in major coronary events (Table 42, Figure 9).

Table 42. Analysis of Time to First Adjudicated Major Coronary Event –PEARL - Full Analysis Set

	Placebo N=2852	Lasofoxifene	
		0.25 mg N=2852	0.5 mg N=2852
3 Years			
Patient-years	8140	8175	8175
Number (%) with event	55 (1.9)	46 (1.6)	43 (1.5)
Incidence rate/1000 patient-years (95% CI)	6.8 (5.1, 8.8)	5.6 (4.1, 7.5)	5.3 (3.8, 7.1)
Hazard ratio (95% CI)		0.83 (0.56, 1.23)	0.78 (0.52, 1.16)
P-Value		0.358	0.214
5 Years			
Patient-years	12,641	12,766	12,715
Number (%) with event	95 (3.3)	73 (2.6)	66 (2.3)
Incidence rate/1000 patient-years (95% CI)	7.5 (6.1, 9.2)	5.7 (4.5, 7.2)	5.2 (4.0, 6.6)
Hazard ratio (95% CI)		0.76 (0.56, 1.03)	0.68 (0.50, 0.93)
P-Value		0.077	0.016*

*P-value significant vs. placebo

Figure 9. Cumulative Incidence of First Adjudicated Major Coronary Event – Study A2181002 (PEARL) Full Analysis Set



Cumulative incidence based on Kaplan-Meier estimation.

The incidence of adjudicated major coronary events was <1% for each event type and was similar across all treatment groups after 3 years. After 5 years, the incidences of adjudicated major coronary events ranged from 0.4% to 1.2% for each event type and were lower in the lasofoxifene treatment groups compared with the placebo group (Table 43).

Table 43. Incidence of Adjudicated Major Coronary Events – PEARL Full Analysis Set

	Placebo	Lasofoxifene	
		0.25 mg	0.5 mg
Number of patients	2852	2852	2852
Number (%) with event	95 (3.3)	73 (2.6)	66 (2.3)
Type of major coronary event			
Coronary death	21 (0.7)	18 (0.6)	18 (0.6)
Non-fatal myocardial infarction	28 (1.1)	17 (0.6)	23 (0.8)
New ischemic heart disease	23 (0.8)	21 (0.7)	12 (0.4)
Hospitalization for unstable angina	27 (0.9)	21 (0.7)	16 (0.6)
Revascularization procedures	34 (1.2)	19 (0.7)	19 (0.7)

6.5.4. Lipids and Inflammation

Lipids and markers of inflammation were assessed following 3 years of treatment in a subgroup of patients (N=1014) in PEARL. Total cholesterol, LDL-C, Apolipoprotein A-1, and Apolipoprotein B100 were significantly reduced in patients taking both doses of lasofoxifene compared to placebo. Lasofoxifene treatment was not associated with consistent changes in HDL-C. Lasofoxifene treatment resulted in a small but significant increase in serum triglyceride levels compared with placebo. The triglyceride changes reported with lasofoxifene treatment were not associated with adverse clinical outcomes of coronary events or pancreatitis through 5 years of follow-up. Hs-CRP, a marker of cardiovascular inflammation that has been associated with an increased risk of stroke, myocardial infarction, peripheral arterial disease, and sudden cardiac death (Ridker et al, 2002), was also significantly reduced in both lasofoxifene treatment arms compared to placebo. These results are summarized in [Table 44](#).

Table 44. Lipids Median Percent Change from Baseline at 3 Years – PEARL – Lipids Subgroup

		Lasofoxifene	
	Placebo	0.25 mg	0.5 mg
LDL-C			
N	334	338	334
Median % change	-1.01	-17.19	-16.80
(95% CI)	(-3.04,1.27)	(-20.18,-15.23)	(-18.64,-15.12)
P-value vs. placebo		<0.001*	<0.001*
HDL-C			
N	334	338	334
Median % change	1.55	1.30	2.00
(95% CI)	(-0.54,3.94)	(-1.55,3.57)	(0.00,3.66)
p-value vs. placebo		0.505	0.719
Total Cholesterol			
N	331	334	331
Median % change	-2.02	-12.38	-12.44
(95% CI)	(-3.53,0.00)	(-14.42,-11.11)	(-14.04,-11.30)
P-value vs. placebo		<0.001*	<0.001*
Apolipoprotein A-1			
N	327	330	327
Median % change	1.09	5.99	7.23
(95% CI)	(-0.60,2.08)	(4.88,7.26)	(5.11,8.33)
P-value vs. placebo		<0.001*	<0.001*
Apolipoprotein B100			
N	327	330	327
Median % change	0.00	-13.04	-11.76
(95% CI)	(-1.16,1.67)	(-14.29,-10.84)	(-14.02,-10.39)
P-value vs. placebo		<0.001*	<0.001*
Triglycerides			
N	331	334	331
Median % change	-5.45	2.59	-0.59
(95% CI)	(-10.11,0.00)	(-3.67,7.84)	(-5.13,7.21)
P-value vs. placebo		0.013*	0.033*
Hs-CRP			
N	327	329	327
Median % change	0.00	-15.79	-12.50
95% Confidence Interval	(0.00, 12.00)	(-22.22, 0.00)	(-18.18, 0.00)
P-value vs. placebo		<0.001*	0.001*

All parameters are reported in mg/dL

*P-value significant versus placebo.

6.5.5. Adjudicated Hospital Admission for Cardiovascular Events

The risk of hospital admission for cardiovascular events, a composite endpoint in PEARL that included hospitalization for MI, angina, congestive heart failure, TIA, stroke, arterial peripheral vascular disease, DVT, PE, and RVT, was similar across all treatment groups through 3 years and 5 years (Table 45).

Table 45. Analysis of Time to First Adjudicated Hospital Admission for Cardiovascular Event - PEARL – Full Analysis Set

		Lasofoxifene	
	Placebo N=2852	0.25 mg N=2852	0.5 mg N=2852
3 Years			
Patient-years	8130	8146	8138
Number (%) with event	61 (2.1)	63 (2.2)	76 (2.7)
Incidence rate/1000 patient-years (95% CI)	7.5 (5.7, 9.6)	7.7 (5.9, 9.9)	9.3 (7.4, 11.7)
Hazard ratio (95% CI)		1.03 (0.72, 1.47)	1.24 (0.89, 1.74)
P-value		0.866	0.205
5 Years			
Patient-years	12,612	12,706	12,629
Number (%) with event	114 (4.0)	109 (3.8)	108 (3.8)
Incidence rate/1000 patient-years (95% CI)	9.0 (7.5, 10.9)	8.6 (7.0, 10.4)	8.6 (7.0, 10.3)
Hazard ratio (95% CI)		0.95 (0.73, 1.23)	0.94 (0.72, 1.22)
P-value		0.692	0.631

Through both 3 years and 5 years, results were similar for comparisons of the lasofoxifene dose groups to placebo for hospital admissions for atherosclerotic events and stroke events. There was a statistically significant higher risk of hospitalization for VTE in the lasofoxifene dose groups compared to placebo (3-year lasofoxifene 0.5 mg HR=3.25; 95% CI: [1.06, 9.52]; p=0.029; 5-year lasofoxifene 0.5 mg HR=2.86; 95% CI: [1.21, 6.75]; p=0.012).

6.5.6. QT Interval

There is no evidence of an effect of lasofoxifene on the QT interval.

The effect of lasofoxifene on electrocardiographic QT interval was assessed from (i) the results of a population PK/QTc analysis across 9 Phase 1 and Phase 2 studies, which included single doses of lasofoxifene up to 100 mg and multiple dose administration of lasofoxifene up to 10 mg for 1 year, (ii) analyses of ECG data from the clinical pharmacology studies and the Phase 2/3 clinical program, and (iii) evaluation of adverse events that may be indicative of risk for arrhythmia.

The population PK/QTc analysis found no clinically significant effect of lasofoxifene on QTc at concentrations far in excess of those expected in clinical use. Estimates of the maximal change in QTc that might be expected at the proposed 0.5 mg/day clinical dose of lasofoxifene (based on the maximum expected plasma concentrations and the upper bound of the 95% CI about the slope of the PK/QTc relationship) are nearly 10 times below the 5 msec threshold for potential clinical significance (ICH E14 Guidance), supporting the conclusion of a large therapeutic index for any potential effect of lasofoxifene on the QT interval. Changes in QTc between baseline and end of study were variable in Phase 2/3 Clinical Program studies depending on the correction factor used (Bazett, Fridericia or population-specific) but all supported a lack of effect of lasofoxifene on QTc. Adverse events indicative of cardiac arrhythmia occurred at comparable incidence among treatment groups.

6.6. Hepatic Safety

There have been no reports of hepatic failure or liver necrosis in the Phase 2/3 Clinical Program through 03 December 2007. There were no deaths reported for the Hepatobiliary Disorders SOC. All causality AEs in the Hepatobiliary Disorders SOC occurred in 3.0%, 3.7%, and 4.2% of patients in the placebo, lasofoxifene 0.25 mg, and lasofoxifene 0.5 mg groups, respectively. For all causality SAEs in the Hepatobiliary Disorders SOC, there were 1.5, 1.8, and 1.8 events per 100 patients in the placebo, lasofoxifene 0.25 mg, and lasofoxifene 0.5 mg groups, respectively. One patient (who received placebo) met the criteria for Hy's Law (ALT or AST ≥ 3 x ULN and a concomitant total bilirubin ≥ 1.5 x ULN).

Clinical laboratory tests, including assessments of liver function, were performed annually through 3 years in PEARL. The incidence of elevated ALT and AST was low ($<1.0\%$) across all treatment groups. ALT elevations (≥ 3 x ULN) were reported for 18 (0.7%), 24 (0.9%), and 17 (0.6%) patients in the placebo, lasofoxifene 0.25 mg, and lasofoxifene 0.5 mg groups, respectively. AST elevations (≥ 3 x ULN) were reported for 9 (0.3%), 24 (0.9%), and 16 (0.6%) patients in the placebo, lasofoxifene 0.25 mg, and lasofoxifene 0.5 mg groups, respectively. The difference compared to placebo was statistically significant for the 0.25 mg treatment group only and was not dose-related. Elevated ALT and AST often occurred in association with other risk factors for liver disorders, or resolved while the subject continued to be treated with lasofoxifene. After 3 years, performance of liver function tests was not specified in the protocol; investigators could perform 'for cause' tests and were responsible for notifying Pfizer of any abnormal results. There were no additional cases of ALT or AST ≥ 3 x ULN between 3 years and 5 years in PEARL and no additional patients met the criteria for Hy's Law.

6.7. Serious Gallbladder Events

Lasofloxifene did not significantly increase the incidence of serious gallbladder events, a composite endpoint composed of a number of SAE terms including the overlapping preferred terms cholecystitis and cholelithiasis, compared to placebo through 3 years (HR=0.95; 95% CI: [0.62, 1.47]; p=0.816 for lasofoxifene 0.25 mg; HR=0.97; 95% CI: [0.63, 1.50]; p=0.898 for lasofoxifene 0.5 mg) or through 5 years (HR=1.06; 95% CI: [0.72, 1.56]; p=0.781 for lasofoxifene 0.25 mg; HR=1.18; 95% CI: [0.81, 1.72]; p=0.389 for lasofoxifene 0.5 mg) in the PEARL study.

6.8. Cataracts

Lasofloxifene did not significantly increase the odds of cataract events, a composite of both serious and nonserious adverse events, compared to placebo through 3 years (odds ratio=0.88, 95% CI [0.73, 1.06]; p=0.155 for lasofoxifene 0.25 mg; odds ratio=0.88, 95% CI: [0.73, 1.06]; p=0.158 for lasofoxifene 0.5 mg) or through 5 years (odds ratio=0.88, 95% CI: [0.73, 1.06]; p=0.180 for lasofoxifene 0.25 mg; odds ratio=0.89, 95% CI: [0.73, 1.07]; p=0.206 for lasofoxifene 0.5 mg) in the PEARL study.

6.9. Gynecological Safety

6.9.1. Introduction

The size and scope of gynecological surveillance in the lasofoxifene development program have been extensive due to safety concerns regarding gynecological findings in other SERM development programs and the desire of the applicant to provide the most complete gynecological safety profile for lasofoxifene.

Transvaginal Ultrasounds (TVUs)

Per protocol, TVUs were performed in Phase 2/3 osteoporosis prevention and treatment studies to provide estimates of sonographic endometrial thickness and echotexture. In PEARL, TVUs were performed for 2 separate subgroups of patients:

- TVU-Prevalence (TVU-P) subgroup – patients underwent evaluation at Month 36 only to determine the prevalence of asymptomatic histological findings such as polyps and/or simple hyperplasia.
- TVU-Incidence (TVU-I) subgroup – patients underwent serial evaluations to assess sonographic effects over time.

TVUs were centrally read for consistency and only centrally-read results were used in the analyses of the sonographic endpoints in the TVU-I substudy of PEARL and in all patients in other studies.

In addition to TVUs performed for the subgroups above, TVUs were also performed at some sites in PEARL in accordance with the local standard of care. These TVUs were collected and centrally reviewed retrospectively.

The timing of scheduled TVU assessments is shown by study in [Table 46](#).

Table 46. Per Protocol Transvaginal Ultrasound Assessments - Lasofoxifene Phase 2/3 Studies 218-101/E, 218-102, 218-103, A2181002 (PEARL), A2181003/1004 OPAL, A2181002 (CORAL), A2181037 (JADE)

		Month				
	Screening	3	6	12	24	36
Phase 2 Studies						
218-101/101E	X	X	X	X ^a	X ^a	
218-102	X	-	X	X		
218-103	X	-	X	X ^a		
A2181037 (JADE)	X	-	-	X ^a		
Phase 3 Studies						
A2181002 (PEARL) TVU-I Substudy ^b	X	-	-	X	X	X
A2181002 (PEARL) TVU-P Substudy ^c		-	-	-	-	X
A2181003, A2181004 (OPAL)	X	-	-	-	X ^a	X ^a
A2181030 (CORAL)	X	-	-	-	X ^a	

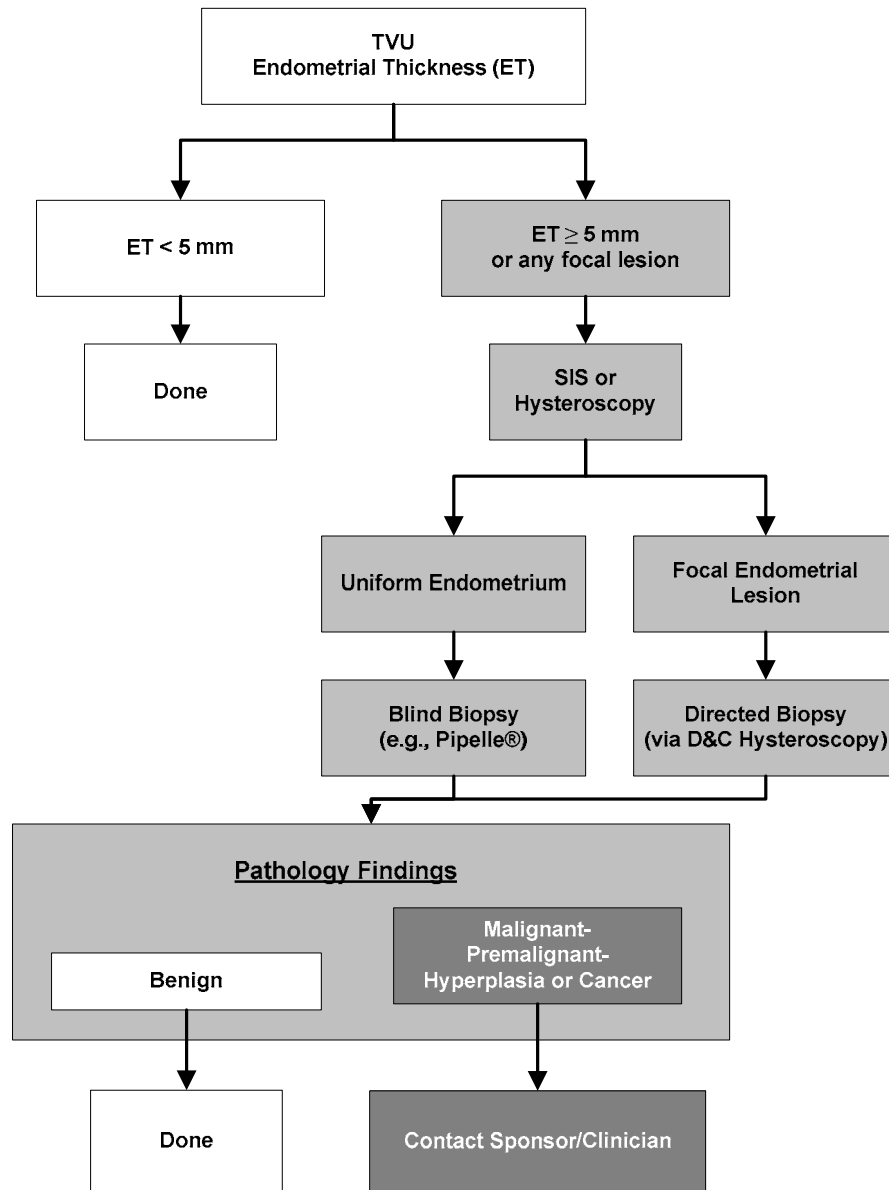
^aEnd of study

^bTVU-I = transvaginal ultrasound incidence

^cTVU-P = transvaginal ultrasound prevalence

Specific TVU findings mandated further evaluation including examination and/or procedures such as saline infusion sonography (SIS), hysteroscopy, polypectomy, and endometrial biopsy as indicated per protocol. This is illustrated in the patient management algorithm for the PEARL TVU-I substudy, which is shown in [Figure 10](#).

Figure 10. A2181002 (PEARL): TVU-I Management Algorithm



In studies other than those listed in [Table 46](#), TVUs could have been performed for cause. General guidance, rather than a specific management algorithm, was provided in the protocols of those studies.

Endometrial Biopsies

End of study biopsies were performed in Studies 218-101E, 218-102, 218-103, and A2181003/A2181004 (OPAL) in all patients with an intact uterus and in Study 218-101, in patients with an endometrial thickness ≥ 5 mm at the end of study (Week 12). In all studies, endometrial biopsies were performed as necessary to follow-up signs or symptoms.

All biopsy specimens from Studies 218-101, 218-101E, 218-102, 218-103, and A2181003/A2181004 (OPAL), as well as Study A2181030 (CORAL) were centrally reviewed by expert pathologists who were blinded to study drug treatments, prior pathology assessments, or colleague assessments. Additionally, biopsies in patients from TVU substudies in PEARL as well as in patients with local pathology reporting malignant/premalignant findings required such central review.

Central review of endometrial biopsies was considered key to obtaining an accurate assessment of endometrial histology. The use of a central reader was based on expert opinion at the time of study design and is consistent with regulatory comments on the advantages of utilizing a central-read process in the assessment of endometrial histology (FDA consult review regarding endometrial polyps in approval package of NDA 20-815 EVISTA [Raloxifene]). This opinion has subsequently been incorporated into the FDA and European Agency for the Evaluation of Medicinal Products (EMA) regulatory guidelines: FDA Guidance: Estrogen and estrogen/progestin drug products to treat vasomotor symptoms and VVA symptoms – recommendations for clinical evaluation (FDA Guidance for Industry, 2003) and Committee for Medicinal Products for Human Use (CHMP) Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women (CHMP Guideline, 2005).

In order to achieve a consensus, central review consisted of a sequential review of the same slide sets by up to 3 expert pathologists who were blinded to study treatment, prior pathology assessments and colleague assessments in order to identify the consensus diagnosis. In cases where local review of endometrial biopsies was performed initially (as for PEARL patients who were not in a TVU sub study), this result served as the first review of this process.

Per protocol, central review of endometrial biopsies performed in A2181037 (JADE), FSD studies, and VVA studies was not required, and there was no report of endometrial hyperplasia or cancer in these studies.

Pelvic Prolapse Evaluation

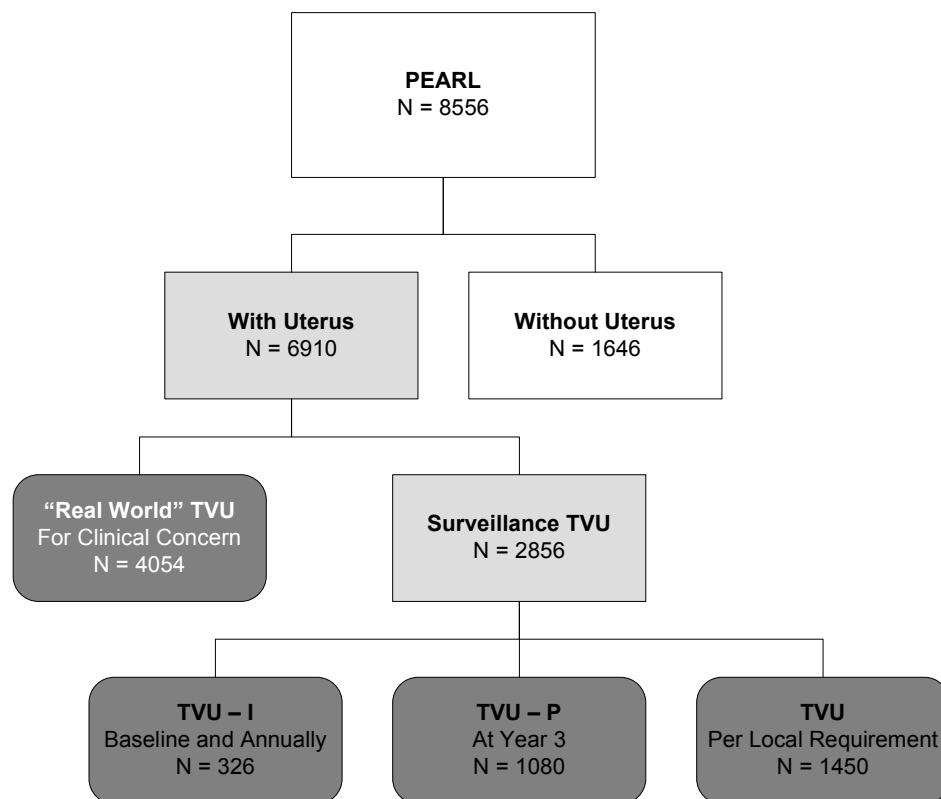
A comprehensive, standardized and validated evaluation of anatomical pelvic prolapse (prolapse score) was implemented in Phase 2 Study 218-102 and Phase 3 Studies A2181002 (PEARL), and A2181003/A2181004 (OPAL) due to its being an endpoint of potential concern for any new SERM.

“Real World” TVU Surveillance PEARL

In PEARL, patients could have had TVUs mandated either because of participation in the TVU-I or TVU-P substudy or if required by a local authority (e.g., local institutional review board, country regulatory authority, or to accord with local standard of care at the investigative site). In other patients with a uterus (N=4,054) TVUs would have been performed only as required for patient management (e.g, investigative follow-up triggered by clinical signs or symptoms, such as vaginal bleeding). Although a greater number of such tests might have been performed for these patients than would be expected in a community

health setting (due to their participation in a clinical trial), these patients have been categorized as “real world” patients for the purposes of assessing the frequency of gynecological events, as their outcomes more closely approximate what would likely occur with the marketed use of lasofoxifene than other subgroups in PEARL. The number of patients who had TVUs in TVU-I and TVU-P in PEARL is shown by subgroup in [Figure 11](#).

Figure 11. Gynecological Surveillance by TVU - PEARL



TVU = transvaginal ultrasound; I = incidence; P = prevalence

Numbers of patients in the “Real World” and “TVU per Local Requirement” represent patients who could have had a TVU.

One patient who had a pre-study partial hysterectomy is counted both in ‘TVU-P’ and in ‘without uterus’.

6.9.2. Endometrial Cancer

Phase 2/3 Clinical Program

There is no evidence of an increased risk of endometrial cancer associated with the use of lasofoxifene.

A cross-program analysis of time to first endometrial cancer was conducted as of 03 December 2007. The analysis included all patients with a uterus in studies of at least 1 year in duration. For PEARL, the occurrence and date of onset of endometrial cancer was adjudicated by the gynecological endpoint committee. For other studies, the occurrence and date of onset of endometrial cancer was obtained from the serious adverse event database using a list of predefined event terms.

Results of the analysis summarized in Table 47 show no difference in the incidence of endometrial cancer among patients who received lasofoxifene compared to those who received placebo (HR=0.84; 95% CI: [0.24, 2.86]; p=0.774).

Table 47. Analysis of Incidence of Endometrial Cancer in Lasofoxifene Phase 2/3 Studies of at Least 1 Year in Duration

	Placebo	Lasofoxifene		
		0.25 mg	0.5 mg	Pooled
Number of patients	3421	3291	3136	7268
Total years	11,600	11,523	11,237	23,813
Number (%) with event	4 (0.1)	4 (0.1)	2 (0.1)	7 (0.1)*
Incidence rate/1000 patient-years	0.3	0.3	0.2	0.3
95% CI	(0.1, 0.9)	(0.1, 0.9)	(0.0, 0.6)	(0.1, 0.6)
Hazard Ratio				0.84
95% CI				(0.24, 2.86)
P-value				0.774

*Total includes 1 patient who received lasofoxifene 0.025 mg

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

No new cases of endometrial cancer have been reported since the cutoff date for the cross-program analysis.

In the lasofoxifene clinical development program there have been 2 cases of uterine sarcoma, both of which occurred in lasofoxifene-treated patients (0.025 mg and 0.25 mg) in Female Sexual Dysfunction Study A2181015. Endometrial adenocarcinoma and uterine sarcoma are generally classified separately as they are considered to arise via different mechanisms (Amant et al, 2005)

The two uterine sarcoma cases observed in the lasofoxifene development program to date both presented symptomatically within 4-6 months of randomization, thus rendering an association with study drug unlikely as these events were likely pre-existing given the expected growth rate of these tumors (Cotran 1999; Fingert, 1993). The calculated incidence rate of uterine sarcoma across the clinical development program, even including these 2 events that are unlikely to have been associated with lasofoxifene treatment, is ~8 per 100,000 subject-years (2/24,680 subject-years).

The data above stand in contrast with the sarcoma data for tamoxifen, where an increased incidence of uterine sarcoma, reported to be between 17 and 27 per 100,000 subject-years (Wickerham, 2002; Lavie, 2008) has been observed. Additionally, the median duration of

exposure to treatment with tamoxifen-related cases was 6 years (Kloos, 2002), versus the 4-6 months observed with lasofoxifene.

PEARL

There was also no evidence of an increased risk of endometrial cancer with lasofoxifene treatment based on the pooled dose analysis through 3 years or through 5 years in PEARL (Table 48).

Table 48. Analysis of Incidence of Endometrial Cancer – PEARL – Full Analysis Set Excluding Patients with Pre-Treatment Hysterectomy

		Lasofoxifene		
	Placebo	0.25 mg	0.5 mg	Pooled
3 Years				
Number of patients	2309	2300	2301	4601
Total years	6633	6587	6635	13,222
Incidence rate/1000 patient-years	0.3	0.3	0.2	0.2
Number (%)with event	2 (0.1)	2 (0.1)	1 (<0.1)	3 (0.1)
Hazard Ratio				0.75
95% CI				(0.13, 4.50)
P-value				0.755
5 Years				
Number of patients	2309	2298	2302	4600
Total years	10,325	10,283	10,337	20,620
Number (%)with event	3 (0.1)	2 (0.1)	2 (0.1)	4 (0.1)
Incidence rate/1000 patient-years	0.3	0.2	0.2	0.2
Hazard Ratio				0.67
95% CI				(0.15, 2.97)
P-value				0.592

A difference in endometrial cancer incidence between the tamoxifen and placebo was evident within 3 years in the 5-year National Surgical Adjuvant Breast and Bowel Project (NSABP P-1) trial, (Fisher, 1998). In contrast, no evidence of increased endometrial cancer risk was shown with raloxifene in the MORE 4-year study (RR 0.8; 95% CI: [0.2, 2.7]) reported in Cummings et al, 1999). Lasofoxifene exposure in the 5-year PEARL dataset is twice that of tamoxifen in the NSABP P-1 trial (2,227 patients with a uterus \geq 50 years of age) and exceeds the raloxifene exposure in the MORE study as shown in Table 49. If lasofoxifene increased the risk of endometrial cancer in a manner similar to tamoxifen, the effect would be expected to manifest during a 5-year study.

Table 49. Lasofoxifene Exposure in PEARL versus Raloxifene in MORE and Tamoxifen in NSABP P-1

	Number of Patients	Patient-Years
All Randomized Patients		
A2181002 (PEARL 5-year analysis)	8556	34,692
A2181002 (PEARL 3-year analysis)	8556	23,639
Raloxifene (MORE Trial 4-year study) ^b	7705	25,703
Tamoxifen (NSABP P-1 Trial 5-year study) ^c	7998	30,997
Patients on Active Treatment With a Uterus		
A2181002 (PEARL 5-year analysis)	4601	18,460
A2181002 (PEARL 3-year analysis)	4601	12,637
Raloxifene (MORE Trial 4-year study) ^b	3960	13,068*
Tamoxifen (NSABP P-1 Trial 5-year study) ^c	2227	8853*

*Estimated assuming that women with a uterus had the same mean follow-up time as the study population as a whole.

^bGrady, 2004

^cFisher, 1998 ≥50 years of age

Results from 2-year rat and mouse carcinogenicity studies, 2-year ovariectomized (OVX) monkey and 1-year OVX rat studies provide further evidence that lasofoxifene is not associated with an increased risk of endometrial cancer or hyperplasia.

6.9.3. Endometrial Hyperplasia

Endometrial hyperplasia is regarded as a precursor of endometrial cancer (Kurman, 1985; FDA Guidance for Industry, 2003). The incidence of centrally-confirmed endometrial hyperplasia in the lasofoxifene clinical development program was low, and there is no evidence of an increased risk of endometrial hyperplasia associated with the use of lasofoxifene.

In PEARL, all suspected cases of endometrial hyperplasia were required to provide biopsy specimen/slides for central histopathology review. Results of this review together with available medical records were submitted to the gynecological endpoint classification committee (GECC) for adjudication resulting in the case being confirmed or not confirmed as endometrial hyperplasia. In cases where no tissue was available for central review, results of the local pathology report were used in lieu of a central report as the basis for GECC adjudication. For studies outside of PEARL, all suspected cases of endometrial hyperplasia were submitted for central histopathology review.

A cross-program analysis of time to endometrial hyperplasia, including all adjudicated events from PEARL and serious adverse events of the preferred term “endometrial hyperplasia” from all other studies which did not employ adjudication, was performed as of 3 December 2007.

Based on the cross-program analysis shown in Table 50, there was no evidence of an increased risk of endometrial hyperplasia associated with the use of lasofoxifene.

Table 50. Analysis of Time to First Endometrial Hyperplasia – Lasofoxifene Phase 2/3 Clinical Program - Full Analysis Set Excluding Patients with Pre-treatment Hysterectomy

	Placebo	Lasofoxifene		
		0.25 mg	0.5 mg	Pooled
N	3844	3685	3518	8347
Total years	11,772	11,731	11,398	24,399
Number (%) with event	0 (0.0)	2 (0.1)	2 (0.1)	4 (<0.05)
Incidence rate/1000 patient-years (95% CI)	0.0 (0.0, 0.3)	0.2 (0.0, 0.6)	0.2 (0.0, 0.6)	0.2 (0.0, 0.4)
Hazard ratio (95% CI)				Inf (0.00, Inf)
P-value				0.993

Subsequent to the data cutoff for the cross-program analysis (03 December 2007), there were 2 more centrally-confirmed cases of endometrial hyperplasia, both reported in PEARL. Thus, there have been 6 cases of endometrial hyperplasia in subjects treated with lasofoxifene and none in subjects who received placebo as of 16 April 2008. Five cases occurred in PEARL: 3 in the lasofoxifene 0.25 mg treatment group and 2 in the lasofoxifene 0.5 mg treatment group. Of the 5 events, 2 were confirmed based on protocol-specified centrally-read pathology report. The remaining 3 cases were confirmed on the basis of locally-read pathology reports of specimens, since specimens were unavailable for central pathology review (e.g., sample destroyed). The sixth case occurred in a subject receiving lasofoxifene 0.5 mg in Study A2181003.

The 5 cases in PEARL through 5 years correspond to an absolute annual incidence rate in lasofoxifene-treated subjects of 0.24 per 1000 patient-years (95% CI: 0.1, 0.6). FDA guidance specifies that the incidence of endometrial hyperplasia should be statistically less than 1% after one year of treatment with the upper limit of a two-sided 95% confidence interval not exceeding 4% to establish endometrial safety in agents indicated for the treatment of menopausal symptoms (FDA Guidance for Industry, 2003).

The reported incidence rate, therefore, does not suggest an increased risk for endometrial cancer. Additionally, in the PEPI trial, a difference in endometrial hyperplasia incidence between unopposed estrogen and placebo groups was evident within 1 year (Writing Group for the PEPI Trial, 1996). In the unopposed estrogen group the incidence of any hyperplasia was 62% compared with 1.6% for the placebo group.

6.9.4. Endometrial Effects of Lasofoxifene

Lasofoxifene is not associated with an increased risk of endometrial cancer or hyperplasia. Lasofoxifene does, however, have endometrial effects characterized by ~1.5 mm mean increase in endometrial thickness and atrophic cystic changes which result in an increased incidence of cystic echotexture. These benign findings are described in more detail in the following sections.

6.9.4.1. Endometrial Cystic Changes

The incidence of cystic echotexture was increased in lasofoxifene-treated patients compared to placebo, but there was no evidence of a dose response or treatment duration effect. The effect is variable and appears to be reversible upon discontinuation of treatment.

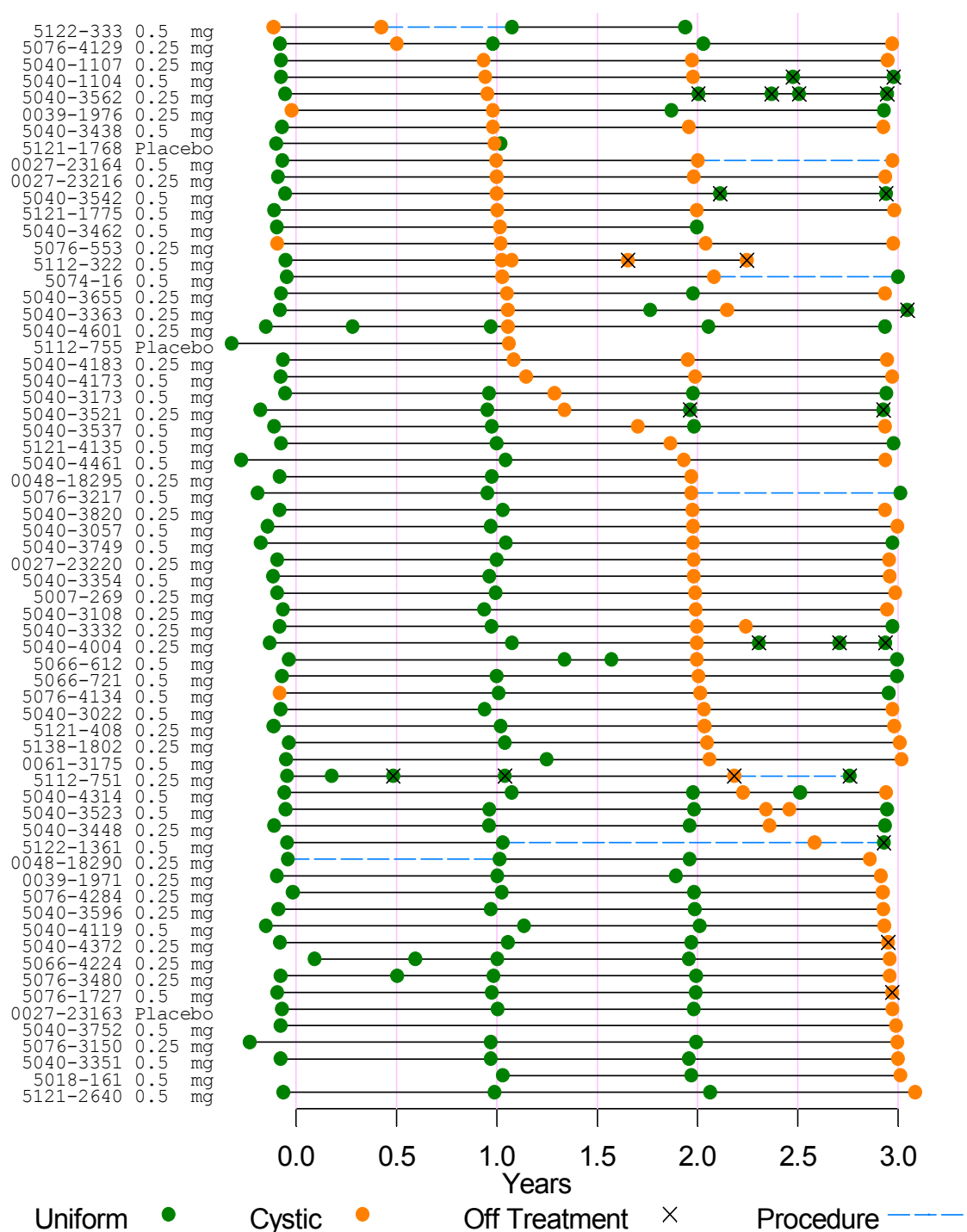
The echotexture of the endometrium was assessed by TVU at baseline and at 1, 2, and 3 years for patients in the TVU-I substudy of PEARL. Echotexture was classified as heterogeneous (cystic echotexture) if there were at least one hypoechogenic area, indicative of a cystic area greater than 1 mm in diameter. There was a higher incidence of cystic echotexture among lasofoxifene-treated patients compared to placebo (Table 51).

Table 51. Endometrial Morphology at End-of-Study –PEARL – TVU-I

	Placebo N=108	Lasofoxifene	
		0.25 mg N=102	0.5 mg N=98
Echotexture			
Homogeneous	106 (98.1)	79 (77.5)	78 (79.6)
Heterogeneous	2 (1.9)	23 (22.5)	20 (20.4)

Figure 12 shows on-study cystic echotexture for lasofoxifene- and placebo-treated patients, ordered chronologically by first on-treatment cystic finding. There is an approximately equal distribution of first observation of cystic change across the 3 annual visits. Almost half of the lasofoxifene patients with cystic echotexture did not have this observation at a subsequent visit following continued treatment, suggesting spontaneous on-treatment regression. Furthermore, reversibility of these changes was observed in patients who stopped treatment, and occurred in placebo patients i.e. in the absence of active therapy.

Figure 12. All Patients with On-Study Cystic Echotexture - PEARL -TVU-I Subgroup



No apparent dose response (0.017 to 10 mg) or treatment duration (3 to 24 months) effect is shown by the results for the individual Phase 2 Prevention studies in [Table 52](#).

Table 52. Heterogeneous Endometrial Echotexture at End-of-Study (All Patients without Polyps Confirmed by Histology) – Studies 218-101/E, 218-102, and 218-103

	Number (%) of Patients							
	3 Months		6 Months		12 Months		24 Months	
218-101/E								
Lasofloxifene 0.4 mg	33	2 (6.1)	40	2 (5.0)	37	5 (13.5)	-	-
Lasofloxifene 2.5 mg	27	1 (3.7)	30	1 (3.3)	26	0	-	-
Lasofloxifene 10.0 mg	25	2 (8.0)	27	1 (3.7)	28	2 (7.1)	-	-
218-102								
Lasofloxifene 0.25 mg	-	-	47	2 (4.3)	42	4 (9.5)	34	3 (8.8)
Lasofloxifene 1.0 mg	-	-	40	2 (5.0)	38	3 (7.9)	34	3 (8.8)
218-103								
Lasofloxifene 0.017 mg	-	-	44	2 (4.5)	41	1 (2.4)	-	-
Lasofloxifene 0.05 mg	-	-	47	3 (6.4)	43	5 (11.6)	-	-
Lasofloxifene 0.15 mg	-	-	41	2 (4.9)	35	5 (14.3)	-	-
Lasofloxifene 0.5 mg	-	-	50	4 (8.0)	49	5 (10.2)	-	-

N = number of patients; SD = standard deviation

The sonographic endometrial changes are a result of the increased cystic nature of the endometrium manifesting as benign cystic atrophy seen on biopsy as described in Section 6.9.4.3.

6.9.4.2. Endometrial Thickness

Lasofloxifene use is associated with a small, nonprogressive increase (~1.5 mm mean change from baseline) in the thickness of the endometrial lining. This effect, demonstrated to be reversible upon discontinuation of treatment in some patients, is associated with cystic echotexture on ultrasound and is consistent with benign cystic atrophy on biopsy. The increase in endometrial thickness is not associated with endometrial hyperplasia.

The change in sonographic endometrial thickness from baseline to the end of study (3 years in PEARL) by dose was assessed for patients without a hysterectomy prior to the first intake of study drug. Measurements were obtained from centrally-read TVUs (see Section 6.9.1). These results are shown in Table 53.

Table 53. Endometrial Thickness (mm) - Analysis of Change from Baseline to End-of-Study – PEARL – TVU-I

Study	N	Mean Baseline	LS Mean Change	LS Mean Change vs. Placebo (95% CI)	P-value vs. Placebo
A2181002 (PEARL) - TVU-I – Month 36					
Lasofloxifene 0.25 mg	86	2.55	1.18	1.89 (1.29, 2.49)	0.001*
Lasofloxifene 0.5 mg	75	2.35	1.44	2.15 (1.53, 2.77)	<0.001*
Placebo	85	2.59	-0.71	-	-

*P-value significant versus placebo.

Endometrial thickness results from the increased cystic nature of the endometrium manifesting as benign cystic atrophy seen on biopsy as described in Section 6.9.4.3.

Based on a review of endometrial thickness results from all Phase 2/3 studies in which endometrial thickness was measured (101/E, 102, 103, 1002 (TVU-I and retrospective), 1003, 1004, 1030, 1037), the increase in endometrial thickness from baseline was evident at 3 months, the earliest timepoint examined. Within each treatment group, there was no apparent effect of duration.

Lasofoxifene is also associated with an increased incidence of patients with an endometrial thickness ≥ 8 mm (endometrial thickness outliers), as shown in Table 54.

Table 54. Incidence of Endometrial Thickness Outliers –PEARL – TVU-I

	Placebo	Lasofoxifene	
		0.25 mg	0.5 mg
A2181002 (PEARL) - TVU-I – Month 36			
Number of patients with measurement	107	100	95
Number (%) of patients ≥8 mm	0	19 (19.0)	17 (17.9)
95% CI	(0.0, 2.7)	(11.8, 28.0)	(10.7, 27.1)
P-value	-	0.001 [†]	0.001 [*]

*P-value significant vs. placebo.

For patients identified as endometrial thickness outliers, endometrial thickness often regressed to < 8 mm with continued study treatment and without undergoing a procedure. Figure 13 through Figure 16 highlight the variability in individual endometrial thickness over time for patients identified as endometrial thickness outliers in PEARL – TVU-I. TVU-I is the main population with the most data for the lasofoxifene 0.5 mg dose in the Phase 2/3 development program for which serial TVUs were performed and hence, which was used to assess endometrial thickness effects over time. These results suggest that the increase in endometrial thickness may resolve spontaneously on treatment and is reversible following cessation of treatment. Further, these results indicate that endometrial thickening is associated with cystic change, a benign finding.

Figure 13. Endometrial Thickness and Echotexture for Lasofoxifene Patients with Maximum On-Study Endometrial Thickness ≥ 8 mm by the Year 1 Visit and no Endometrial Thickness Measurement Subsequent to a Polypectomy or D&C - PEARL

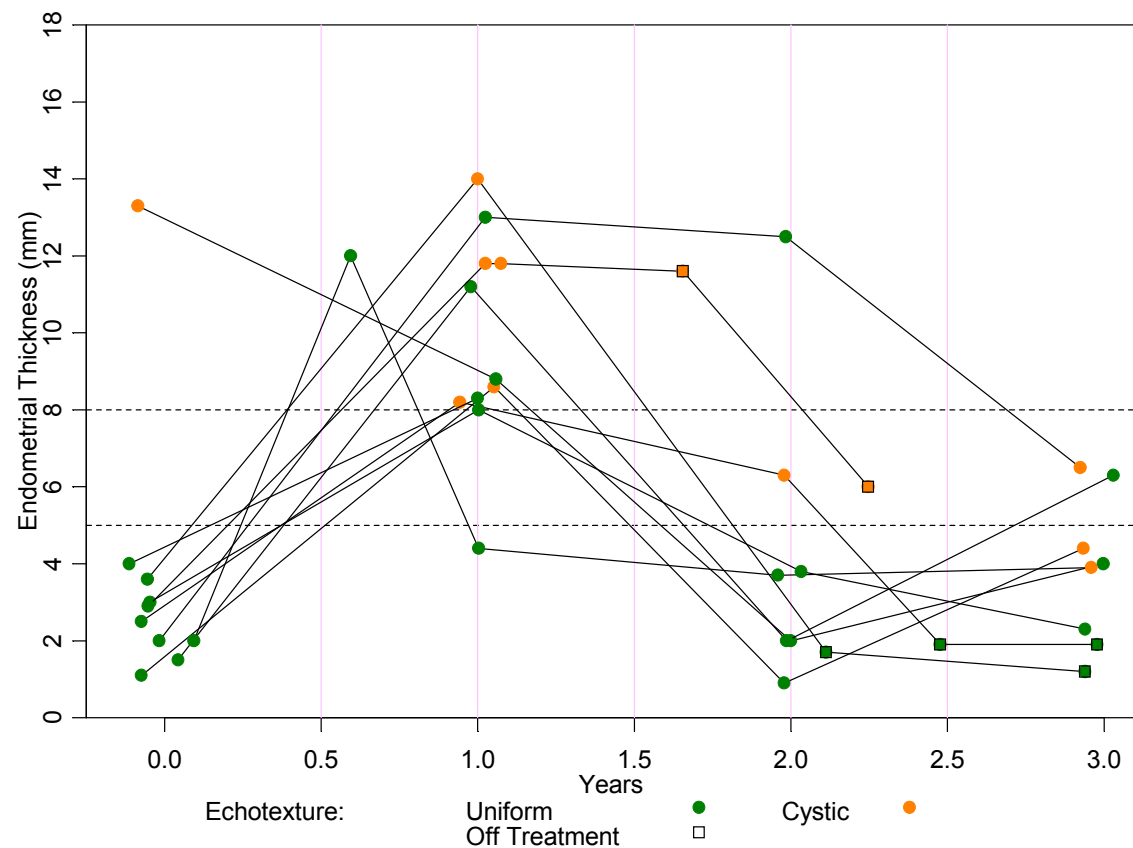


Figure 14. Endometrial Thickness and Echotexture for Lasofoxifene Patients with Maximum On-Study Endometrial Thickness ≥ 8 mm after the Year 1 Visit and by the Year 2 Visit and no Endometrial Thickness Measurement Subsequent to a Polypectomy or D&C - PEARL

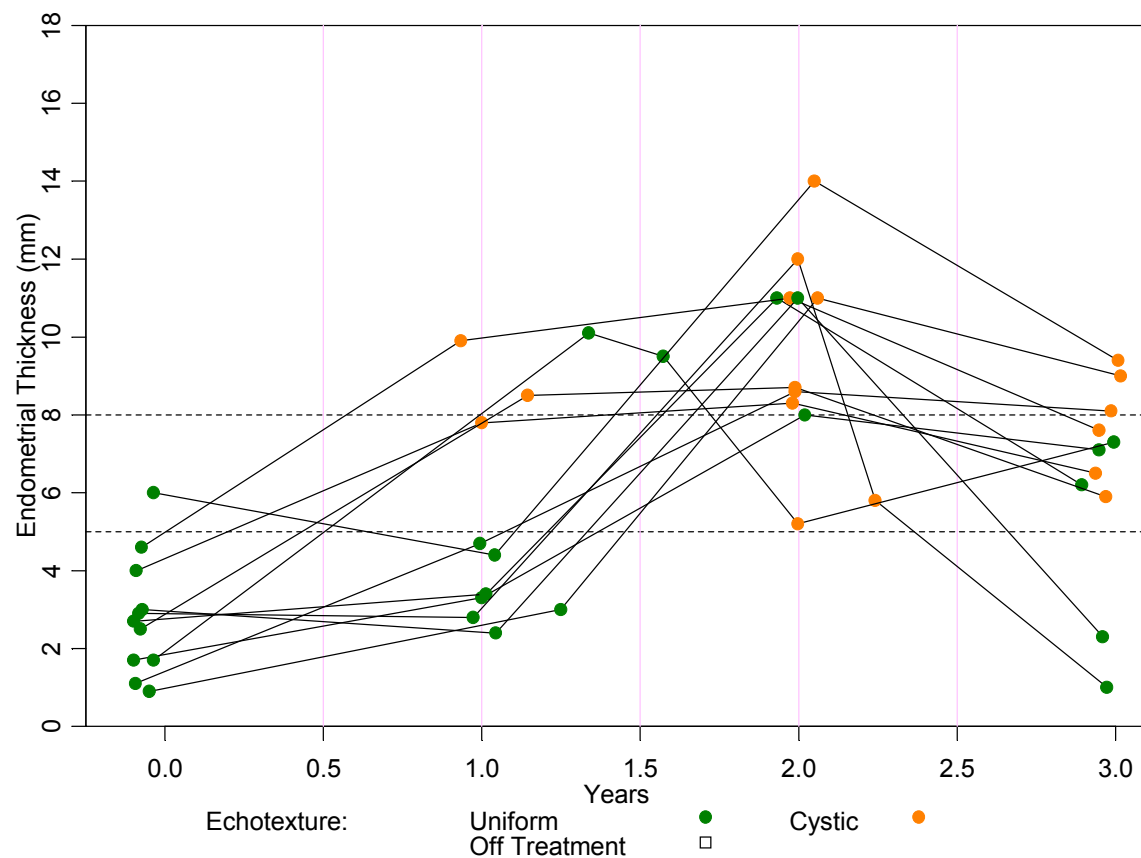


Figure 15. Endometrial Thickness and Echotexture for Lasofoxifene Patients with Maximum On-Study Endometrial Thickness ≥ 8 mm after the Year 2 Visit and no Endometrial Thickness Measurement Subsequent to a Polypectomy or D&C - PEARL

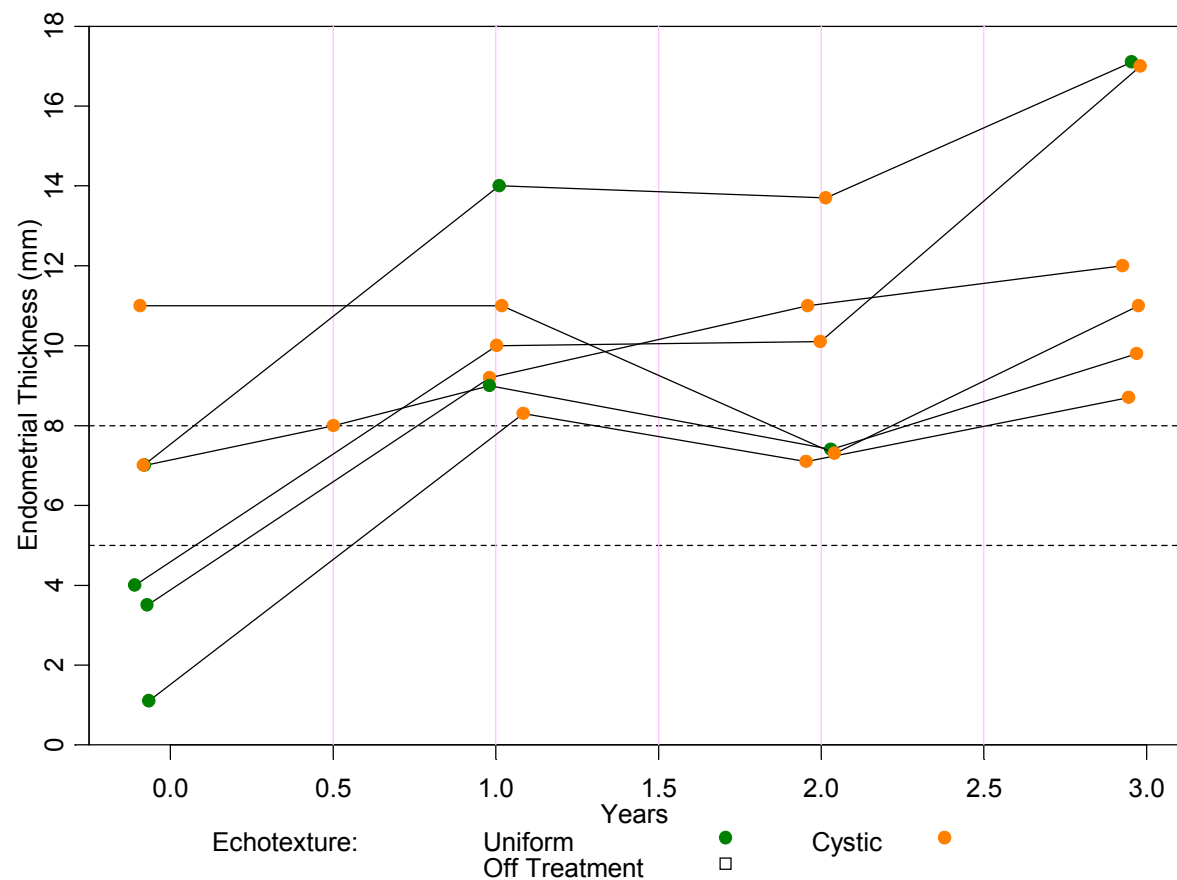
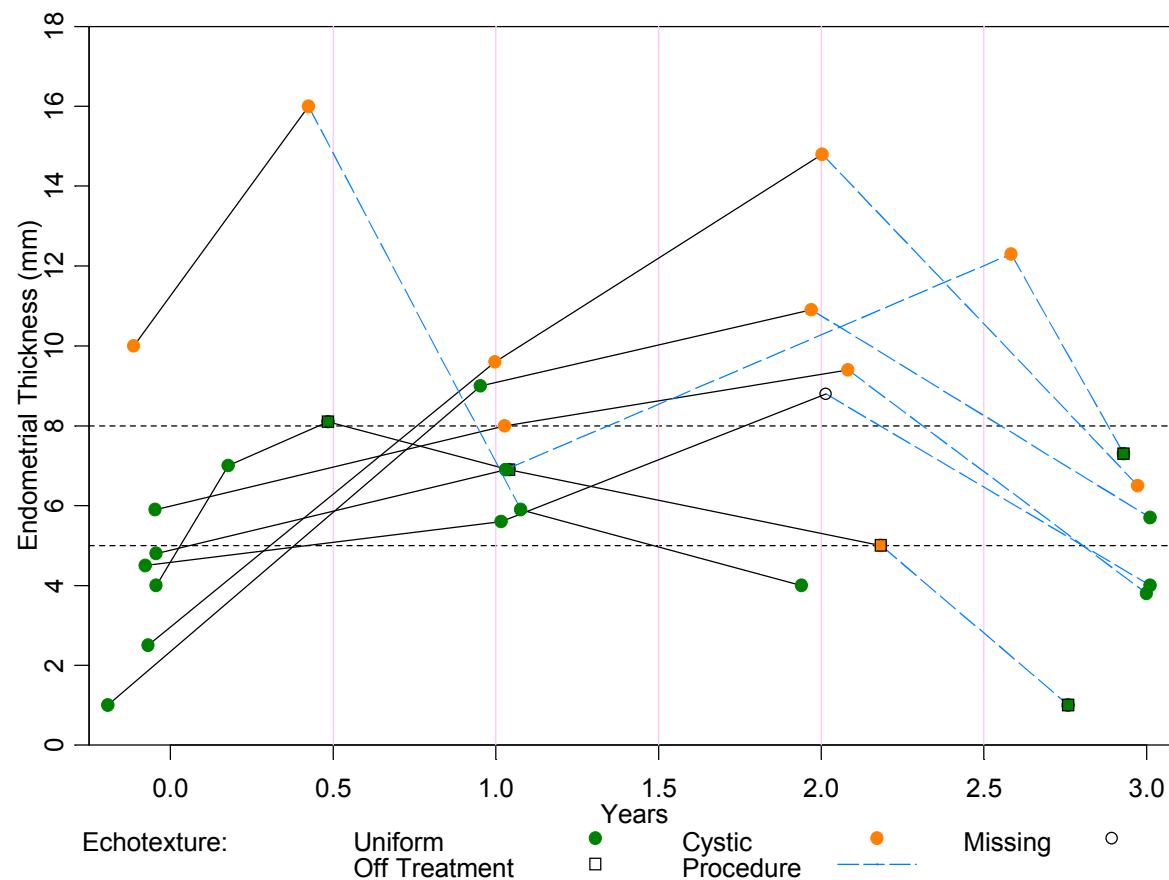


Figure 16. Endometrial Thickness and Echotexture for Lasofoxifene Patients with Maximum On-Study Endometrial Thickness ≥ 8 mm and an Endometrial Thickness Measurement Subsequent to a Polypectomy or D&C - PEARL



6.9.4.3. Benign Cystic Atrophy

The incidence of histological changes other than endometrial cancer and endometrial hyperplasia was summarized for women across studies in which central review of biopsies was required (218-101, 218-101E, 218-102, 218-103, A2181002 (PEARL), A2181003/A2181004 (OPAL), and A2181030 (CORAL)).

Most patients in each treatment group at risk for a biopsy did not have a centrally-read biopsy. Of those who did, most had a finding of atrophic/inactive endometrium, the incidence of which was higher among lasofoxifene-treated patients compared to placebo (20.3%, 24.6%, and 25.8% in the placebo, lasofoxifene 0.25 mg, and lasofoxifene 0.5 mg treatment groups). Although occurring with lower incidence than atrophic endometrium, the incidence of weakly/marginal proliferative histology was higher among lasofoxifene-treated patients compared to placebo (0.2%, 2.3%, and 2.0% in the placebo, lasofoxifene 0.25 mg, and lasofoxifene 0.5 mg treatment groups). Weakly marginal proliferative histology is considered a benign finding with morbidity similar to atrophic changes (Fugere, 2000; Neven, 2004).

The incidences of histological changes other than endometrial cancer and endometrial hyperplasia in the subset of women with a centrally-read biopsy are shown in [Table 55](#).

Table 55. Benign Histological Changes – Lasofoxifene Phase 2/3 Clinical Studies - Patients at Risk for Centrally-Read Biopsy

	Number (%) of Patients		
	Placebo	Lasofoxifene	
		0.25 mg	0.5 mg
Number of patients	1101	1047	894
Total years at risk	2925	2887	2594
No centrally-read biopsy ^a	719 (65.3)	614 (58.6)	512 (57.2)
No sample obtained ^b /identified grossly	11 (1.0)	12 (1.1)	10 (1.1)
No interpretable endometrium present	142 (12.9)	134 (12.8)	119 (13.3)
Atrophic/inactive endometrium - physiologic	224 (20.3)	258 (24.6)	231 (25.8)
Secretory endometrium - progestational	0	2 (0.1)	0
Proliferative endometrium			
Weakly/marginal	3 (0.2)	25 (2.3)	18 (2.0)
Cyclic	1 (<0.1)	0	1 (0.1)

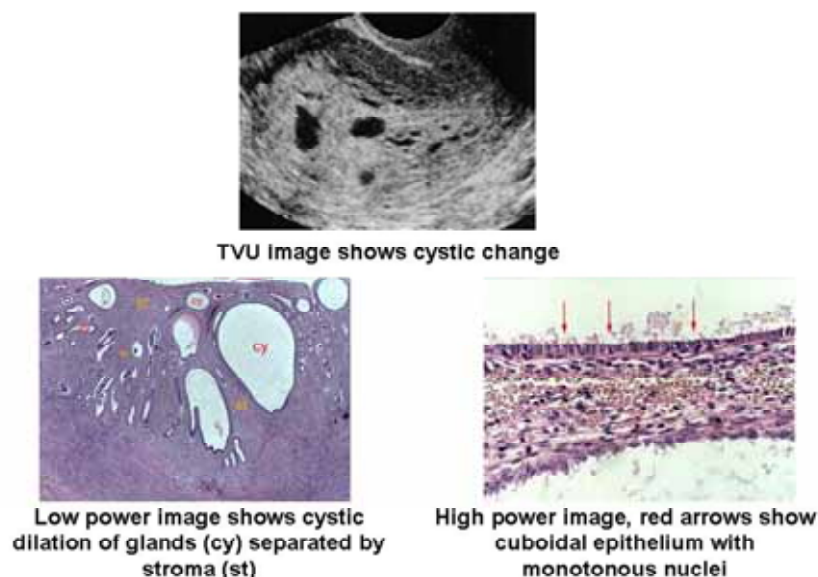
Includes all studies with per-protocol centrally-read biopsies: 218-101, 218-101E, 218-102, 218-103, A2181002 (TVU-I and TVU-P, only), A2181003, A2181004, A2181030.

^aRequirements for central reading of biopsies varied among studies.

^bBiopsy performed but no tissue was obtained.

External gynecological experts have reviewed histology and sonogram findings from the lasofoxifene clinical development program and concluded that the benign cystic atrophy findings observed on histology are consistent with cystic echotexture. Sonographic changes and benign cystic atrophy on histology are shown together in [Figure 17](#).

Figure 17. Benign Endometrial Effects of Lasofoxifene – Cystic Changes and Benign Cystic Atrophy



The benign nature of the sonographic changes is substantiated by biopsy findings that were collected from 47 patients who had on-treatment cystic change (24, 22, and 1 in the 0.25 mg lasofoxifene, 0.5 mg lasofoxifene, and placebo treatment groups, respectively). In all cases, the central histology reading was benign. Given the correlation of endometrial thickness and cystic echotexture findings of benign cystic atrophy on biopsy, it is likely that the histology findings will show similar on-treatment spontaneous regression to that observed for cystic echotexture and endometrial thickness.

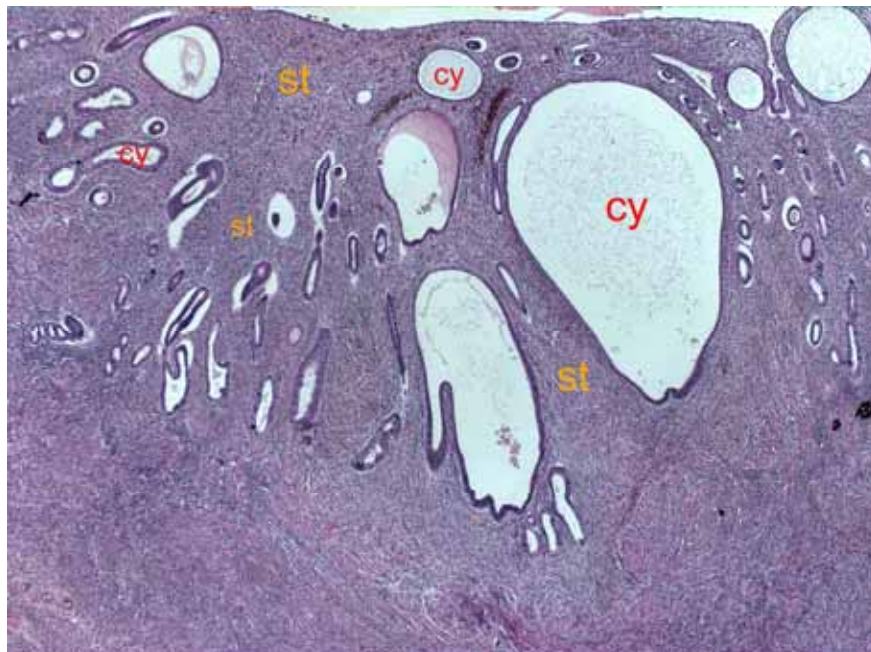
Although biopsies were diagnosed correctly by local review in the majority of cases, the pattern of cystic change observed with lasofoxifene may have resulted in the incorrect diagnosis of endometrial hyperplasia in a small number of cases. Of the greater than 1400 endometrial biopsies that were read by local pathologists over the course of the lasofoxifene development program, 45 cases of suspected endometrial hyperplasia were forwarded for central review. Forty of the 45 cases were determined not to show evidence of endometrial hyperplasia based on central review, and the local diagnosis of endometrial hyperplasia was overturned. Thus, there was less than 3% incongruence between local and central pathology reports. Risk management efforts will be directed at minimizing this incongruence.

In order to understand the pattern of some local pathologists incorrectly reporting endometrial hyperplasia, one of the external expert pathologists was asked to select micrographs of lasofoxifene-treated patients that compared true hyperplasia with incorrectly diagnosed hyperplasia. The histological appearance of incorrectly diagnosed hyperplasia was noted as consistent with benign cystic atrophy. Benign cystic atrophy is a recognized

characteristic of postmenopausal endometrial histology that may be confused with simple hyperplasia (Clement, 2003, Cano and Hermenegildo, 2000).

Low-powered views of micrographs of a patient with benign cystic atrophy and a patient with endometrial hyperplasia are shown in [Figure 18](#); high-powered views are shown in [Figure 19](#). The patient with benign cystic atrophy (left image in both figures) is typical of patients who were locally diagnosed with endometrial hyperplasia but not found to have endometrial hyperplasia following central review. The micrograph on the right is an example of one from a patient with centrally-confirmed endometrial hyperplasia.

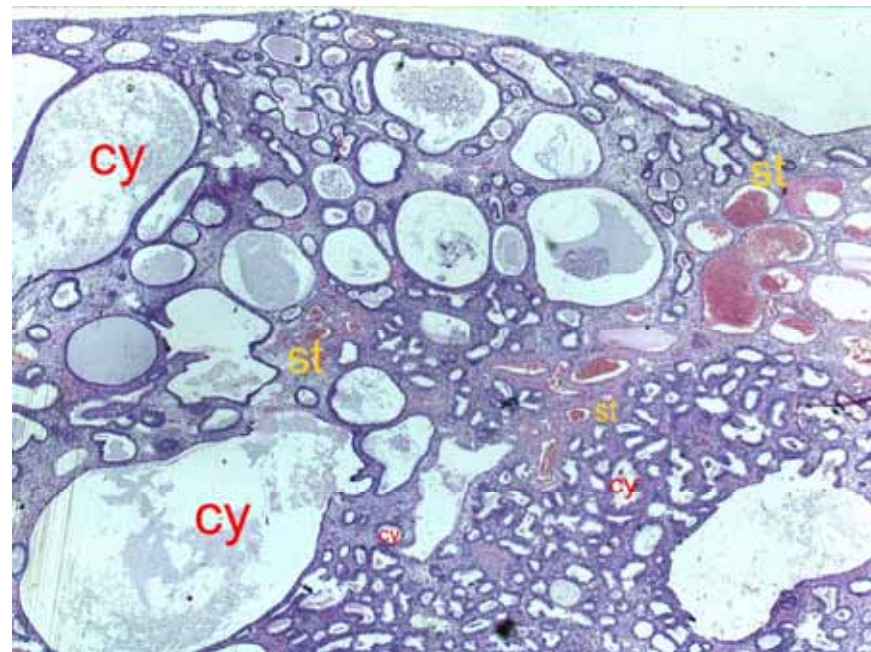
Figure 18. Comparison of Benign Cystic Atrophy and Endometrial Hyperplasia – Low Power Photomicrographs (25x original magnification)



Benign Cystic Atrophy

Patient 5039-86 on lasofoxifene 0.5 mg.

Areas of cystic dilation of glands (cy) separated by stroma (st).

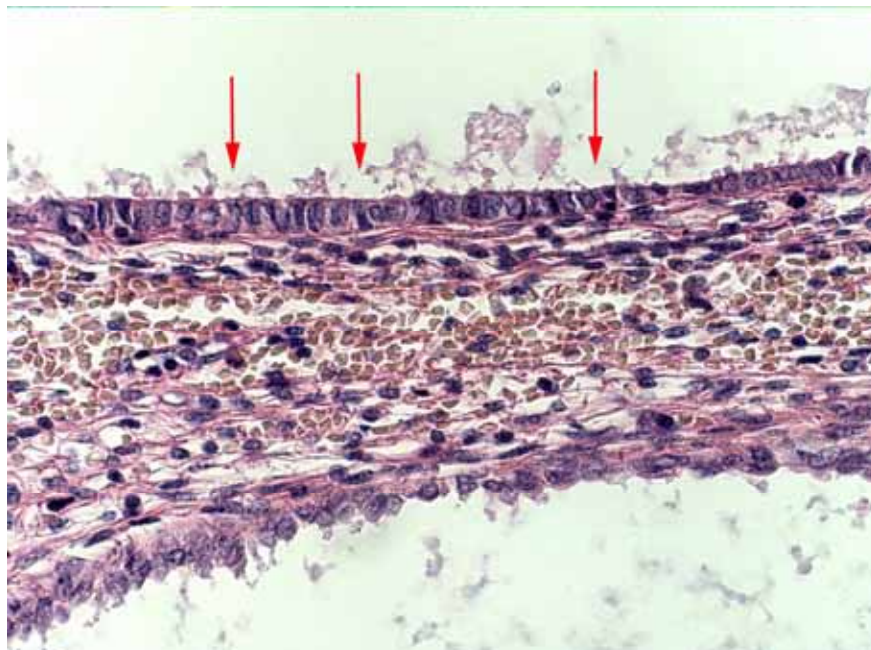


Endometrial Hyperplasia

Patient 5048-3712 -86 on lasofoxifene 0.5 mg.

In addition to sharing stromal and cystic gland features with atrophic endometrium, hyperplasia also shows foci of crowded glands.

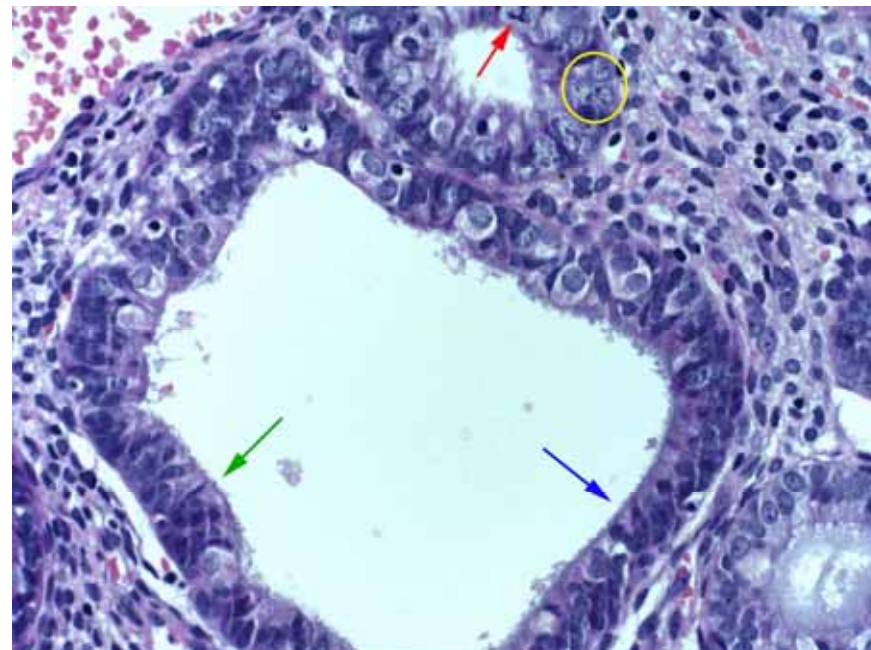
Figure 19. Comparison of Benign Cystic Atrophy and Endometrial Hyperplasia – High Power Photomicrographs (400x original magnification)



Benign Cystic Atrophy

Patient 5039-86 on lasofoxifene 0.5 mg.

Red arrows point to cuboidal epithelium with monotonous nuclei.



Endometrial Hyperplasia

Patient 5048-3712 on lasofoxifene 0.5 mg.

Green arrow – epithelial stratification.

Blue arrow – nuclear overlap.

Red arrow – epithelial mitosis.

Yellow circle – nuclear atypia.

6.9.4.4. Mechanism of Benign Cystic Change

Data from nonclinical studies in mice, rats and primates confirm the benign nature of the endometrial thickness findings with lasofoxifene.

In intact immature and aged rats, lasofoxifene did not increase uterine weight; rather, it caused a small but significant increase in uterine wet weight and epithelial cell heights in ovariectomized (OVX) rats, without any indication of cell proliferation as measured by BrdU labeling. Increased wet uterine weight without an increase in dry uterine weight in OVX rat studies < 8 weeks in duration suggest that the weight increase with lasofoxifene was due to increased tissue hydration.

Studies have shown that primates are relevant models to investigate estrogen and SERM effects on the endometrium and that these effects are predictive of outcomes in humans (Cline et al, 2001). Results from studies in OVX monkey suggest that lasofoxifene does not induce endometrial proliferation but does cause a slight increase in endometrial thickness due to benign cystic change. In a 24-month OVX primate study, lasofoxifene did not cause a significant increase in uterine weight but did cause a numerical but nonstatistically significant increase in endometrial thickness that was due to benign endometrial cystic change as evidenced by histology findings. Additionally, in this primate study, there was no sign of endometrial cell proliferation based on glandular pseudostratification, mitotic bodies, or increases in glandular area.

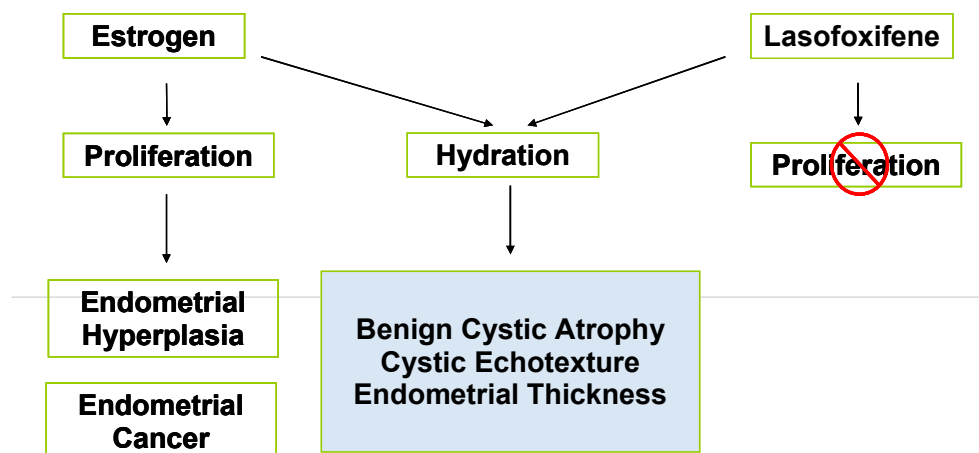
Thus, both clinical and nonclinical studies have shown evidence of benign endometrial effects of lasofoxifene that are likely related to the increased hydration observed in animal models but no evidence of increased endometrial cell proliferation or hyperplasia.

Further analysis of the molecular response in the OVX rat uterus indicated that lasofoxifene treatment results in the upregulation of several gene pathways that are associated with epithelial fluid channel regulation and increase in transudation of fluid from blood vessels into the endometrial glandular lumen. The uterus gene expression data were indicative of activation of biological pathways leading to uterine hydration. These data suggest the following mechanism: lasofoxifene treatment increases vascular permeability leading to uterine imbibition which results in benign accumulation of fluid in both the glands and the stroma of the endometrium. The accumulation of glandular luminal fluid may result in the benign cystic architecture described in endometrium (2-year monkey study). Uterine hydration is also supported by gene expression changes indicating activation of process in response to osmotic stress. While uterine hydration was induced by all agents studied (estradiol, tamoxifen, raloxifene, and lasofoxifene), the magnitude of response was greater with lasofoxifene than with raloxifene.

These results, in conjunction with the absence of malignant or premalignant findings in clinical and nonclinical studies, suggest that the endometrial thickness and benign cystic atrophy associated with lasofoxifene administration represents a benign finding and may be due to tissue hydration.

The mechanism of lasofoxifene's benign effects on the endometrium is depicted in the following figure in contrast to the effects of estrogen.

Figure 20. Endometrial Effects of Lasofoxifene and Estrogen



6.9.4.5. Endometrial Polyps

Endometrial polyps occur fairly commonly in postmenopausal women (Sherman et al, 2002). They are generally asymptomatic and often remain undetected. When detected, the typical medical practice is to remove them as a precaution against endometrial cancer, even though there is minimal literature suggesting that the presence of a suspected endometrial polyp predisposes women to endometrial cancer. In endometrial polyps which have been biopsied, only approximately 3% demonstrate malignancy (Antunes et al, 2007). Thus the majority of polyps remain asymptomatic, undetected, and do not provide a meaningful contribution to morbidity in postmenopausal women. Because the incidence of endometrial polyps has been correlated with the frequency of surveillance (Martino et al, 2005), routine screening for polyps is not recommended in general practice.

The incidence of centrally confirmed polyps was evaluated in a subset of patients who had no prior on-study transvaginal ultrasound (TVU) surveillance (TVU-P; n=1080). At 3 years, the incidence of polyps was 3.1%, 8.8%, and 5.5% in the placebo, lasofoxifene 0.25 mg, and lasofoxifene 0.5 mg treatment groups, respectively. The incidence rate per 1000 patient-years in patients treated with lasofoxifene 0.25 mg was significantly increased compared to placebo. The comparison of lasofoxifene 0.5 mg with placebo was not significant.

Since the TVU-P subgroup represents a unique subset of patients who were required to have no prior TVU or gynecologic diagnostic follow-up through the first 36 months of study treatment, an analysis was also performed on the incidence of polyps in all patients with a uterus at baseline, independent of prior TVU history. In this population, at 5 years, the incidence of polyps was 0.8%, 2.2%, and 1.5% in the placebo, lasofoxifene 0.25 mg, and lasofoxifene 0.5 mg treatment groups, respectively. Endometrial polyps were significantly increased in both lasofoxifene treatment groups compared to the placebo group: the odds ratio for lasofoxifene

0.25 mg was 2.89 (95% CI: [1.68, 4.96]; p=0.001) and for lasofoxifene 0.5 mg was 1.91 (95% CI: [0.07, 3.39]; p=0.025). All centrally confirmed polyps were benign.

Table 56. Analysis of Incidence of Adjudicated Endometrial Polyps – PEARL

	Placebo	Lasofoxifene	
		0.25 mg	0.5 mg
A2181002 (PEARL) – TVU-P			
Number of patients	360	354	366
Years	1631	1539	1604
Number (%) with event	12 (3.3)	31 (8.8)	20 (5.5)
Incidence rate/1000 patient-years (95% CI)	7.4	20.1 (13.7, 28.6)	12.5 (7.6, 19.3)
Odds ratio (95% CI)		2.78 (1.41, 5.51)	1.68 (0.81, 3.48)
P-value		0.003*	0.163
Frequency of polyp biopsy findings			
Atrophic features	11 (3.1)	31 (8.8)	20 (5.5)
Proliferative features	1 (0.3)	0	0
A2181002 (PEARL) – FAS excluding pretreatment hysterectomy (5 years)			
Number of patients	2,309	2,298	2,302
Years	9,344	9,105	9,252
Number (%) with event	18 (0.8)	51 (2.2)	34 (1.5)
Incidence rate/1000 patient-years (95% CI)	1.9 (1.1, 3.0)	5.6 (4.2, 7.4)	3.7 (2.5, 5.1)
Odds ratio (95% CI)		2.89 (1.68, 4.96)	1.91 (1.07, 3.39)
P-value		0.001*	0.025*
Frequency of polyp biopsy findings			
Atrophic features	17 (0.7)	50 (2.2)	31 (1.3)
Proliferative features	1 (0.0)	1 (0.0)	2 (0.1)
Complex hyperplasia	0	0	1 (0.0)

FAS=full analysis set; TVU-P= 3-year transvaginal ultrasound group

*P-value significant vs. placebo ≤0.05

Less than 0.1% of polyps in lasofoxifene-treated patients were proliferative, but it should be noted that proliferative activity in endometrial polyps is not uncommon in postmenopausal women and is not regarded as being clinically significant (McCluggage, 2006).

Based on an analysis performed at 3 years for the Full Analysis Set, most polyps were asymptomatic consistent with literature as noted above; 88% of all patients with centrally-read endometrial polyps did not have vaginal bleeding.

In the large 8-year raloxifene MORE/CORE study (Martino et al, 2005), polyps were seen approximately twice as frequently in raloxifene- versus placebo-treated patients. There was an absolute 8-fold increase in polyps when women underwent scheduled surveillance, as compared to the ‘real-world’ portion of the study, where patients were managed by local standards of care alone. The raloxifene clinical trial data are consistent with literature reports in demonstrating that most endometrial polyps remain asymptomatic and undetected and do not contribute to morbidity.

The results from PEARL are consistent with the results observed with raloxifene showing a small excess relative to placebo and a higher absolute incidence rate in patients with surveillance compared with those managed by local standards of care.

6.9.5. Vaginal Bleeding

Lasofoxifene was associated with a small increase in vaginal bleeding relative to placebo in PEARL but not in other Phase 2/3 studies in the clinical development program. Based on the results of PEARL through 3 years and through 5 years, lasofoxifene is associated with an excess incidence of 3 patients with vaginal bleeding per 1000 patient-years compared to placebo.

A time-to-event analysis for vaginal bleeding was performed using MedDRA preferred term adverse events related to spotting, bleeding, or menstrual flow per vagina, or a subset of the preferred term genital hemorrhage. The overall incidence of vaginal bleeding was low ($\leq 2.6\%$ in all treatment groups), but occurred approximately twice as frequently in lasofoxifene-treated patients compared to placebo-treated patients (Table 57). This incidence was comparable to that reported for raloxifene in MORE (Grady, 2004). Events accumulated steadily over time. Among the 136 patients who reported vaginal bleeding through 5 years, 84% reported only a single episode.

Table 57. Analysis of Time to Vaginal Bleeding (Spontaneously Reported) –PEARL - FAS

	Placebo N=2,852	Lasofoxifene	
		0.25 mg 2,852	0.5 mg 2,852
3 Years			
Years	8173	8158	8148
Number (%) with event	26 (0.9)	48 (1.7)	57 (2.0)
Incidence rate/1000 patient-years (95% CI)	3.2 (2.1, 4.7)	5.9 (4.3, 7.8)	7.0 (5.3, 9.1)
Hazard ratio (95% CI)		1.85 (1.15, 2.98)	2.19 (1.38, 3.48)
P-value		0.011*	0.001*
5 Years			
Years	12,722	12,721	12,654
Number (%) with event	37 (1.3)	62 (2.2)	74 (2.6)
Incidence rate/1000 patient-years (95% CI)	2.9 (2.1, 4.0)	4.9 (3.7, 6.2)	5.8 (4.6, 7.3)
Hazard ratio (95% CI)		1.68 (1.12, 2.52)	2.01 (1.35, 2.98)
P-value		0.012*	0.001*

*P-value significant vs. placebo.

This finding was not associated with any excess in endometrial hyperplasia or cancer. While patients with vaginal bleeding received additional protocol specified gynecologic procedures, the number of patients discontinuing study or treatment as a result of these events was low. In addition, the number of these patients with associated SAEs was also low.

Post menopausal vaginal bleeding is generally associated with a variety of benign conditions. The primary diagnosis of concern in the presence of this symptom is endometrial cancer. In the absence of endometrial cancer or its precursor (endometrial hyperplasia), no major sequelae occur since patients with vaginal bleeding generally do not require inpatient evaluation and when treatment is indicated, it is limited in scope.

6.9.6. Pelvic Prolapse/Urinary Incontinence

Lasofloxifene does not appear to be associated with an increased incidence of pelvic prolapse/urinary incontinence.

Pelvic floor relaxation is common among postmenopausal women, with clinical manifestations ranging from urinary incontinence to total vault prolapse and can represent a serious medical problem due to the necessity for surgical intervention. SERMs have been reported to have differing effects on pelvic organ prolapse and urinary incontinence (Cox and Helvering, 2006), providing further evidence of the diverse pharmacology that exists across this class of compounds. The clinical development programs of levormeloxifene and idoxifene were terminated following an increase in spontaneously reported adverse events associated with pelvic organ prolapse and urinary incontinence. In contrast, tamoxifen was not associated with adverse events related to pelvic organ prolapse or urinary incontinence in clinical trials for breast cancer prevention or treatment. For raloxifene, postmenopausal women reported fewer surgeries for pelvic organ prolapse and no increase in incidence of urinary incontinence in post hoc analyses of clinical trial safety data.

A comprehensive assessment of endpoints associated with pelvic organ prolapse/urinary incontinence was a central component of the lasofloxifene clinical development program. This assessment included a validated rating scale for anatomical prolapse, the modified Halfway measure, employed in the Phase 3 osteoporosis prevention Studies A2181003/A2181004 (OPAL), the Phase 2 osteoporosis treatment study A2181037 (JADE), and most extensively in the annual assessment of all patients in PEARL.

Additionally, in PEARL, adjudicated surgery for pelvic organ prolapse and/or urinary incontinence was a prospectively defined safety endpoint. The assessment of surgery as an endpoint for pelvic organ prolapse and/or urinary incontinence is consistent with the primary safety analysis performed for raloxifene (Goldstein et al, 2001), which was a post hoc blinded assessment by the sponsor of surgeries performed for pelvic floor relaxation, using data from studies not designed to assess this endpoint. In contrast, all potential cases of surgery for pelvic organ prolapse and/or urinary incontinence were reviewed and adjudicated by an independent and external expert committee in PEARL in accordance with the committee's charter. All hysterectomies, regardless of indication for surgery, as well as any other surgeries performed for pelvic prolapse and/or incontinence have been considered for adjudication. Subset analyses of surgeries for any prolapse, as well as surgeries for any incontinence were included for completeness. The adjudicated surgery data from PEARL, which was conducted in an older postmenopausal population (mean age 67 years) at higher risk for pelvic organ prolapse and in a large number of patients, thus provides a further endpoint by which to comprehensively assess any potential treatment effect of lasofloxifene on pelvic floor relaxation.

No statistically significant change from baseline was noted in either uterine prolapse score or total prolapse score at 1, 2, or 3 years in PEARL. Representative results for uterine prolapse and cystocele, 2 representative anatomical compartments, are shown graphically in [Figure 21](#) and [Figure 22](#).

Figure 21. Uterine Prolapse Scores at Baseline and 3 Years –PEARL

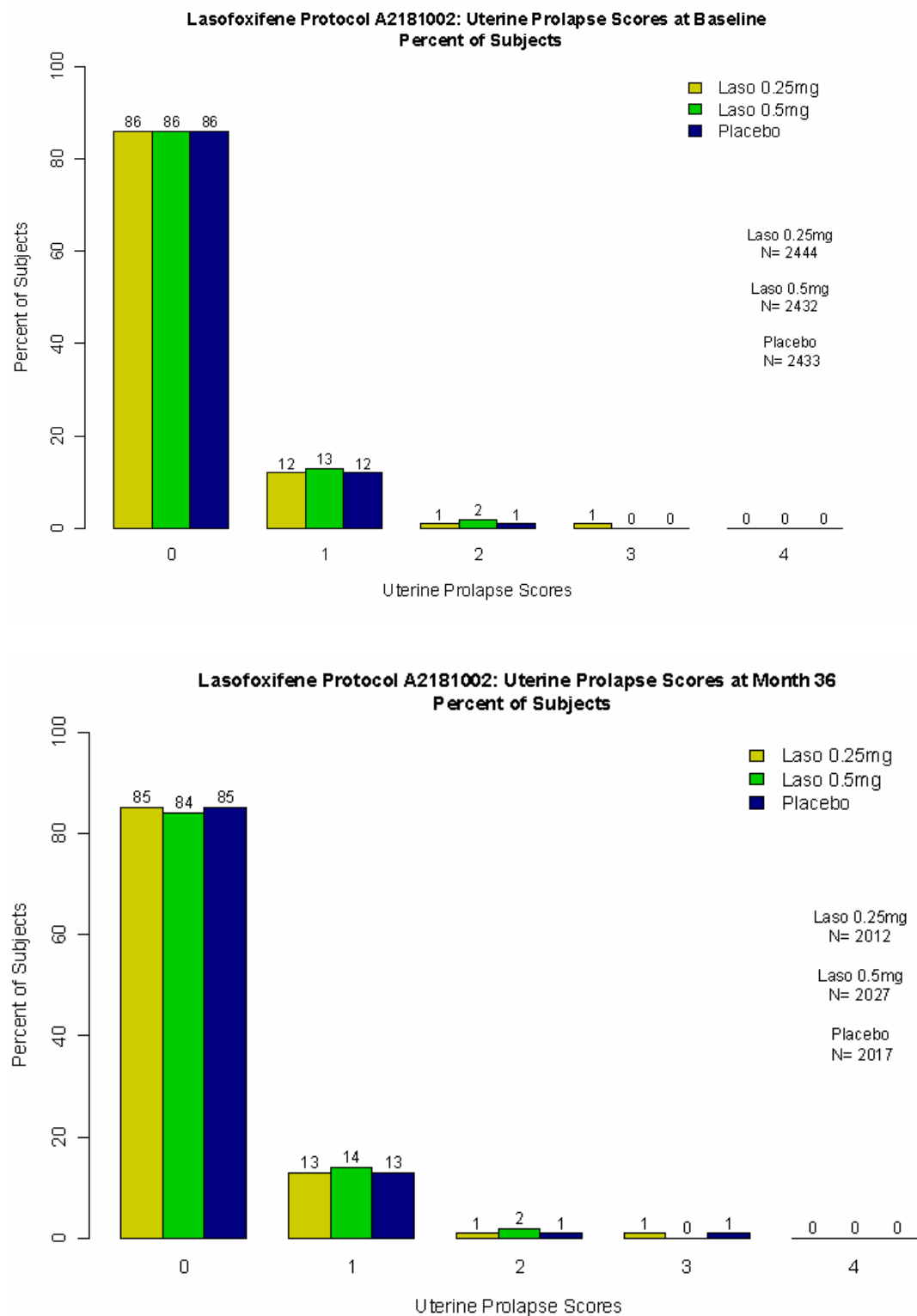
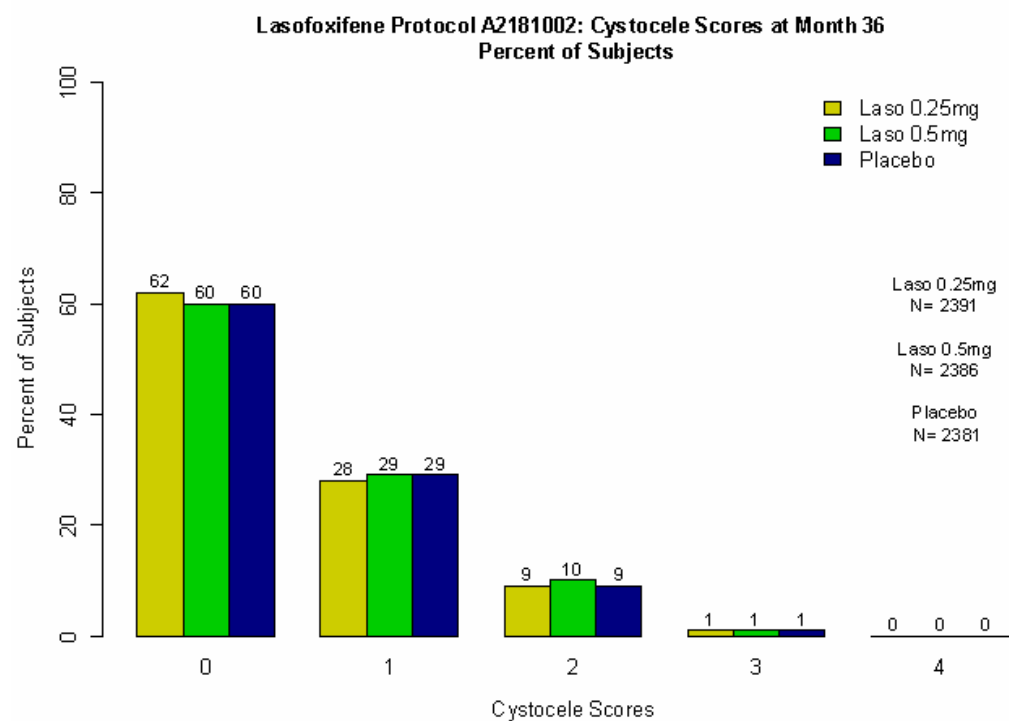
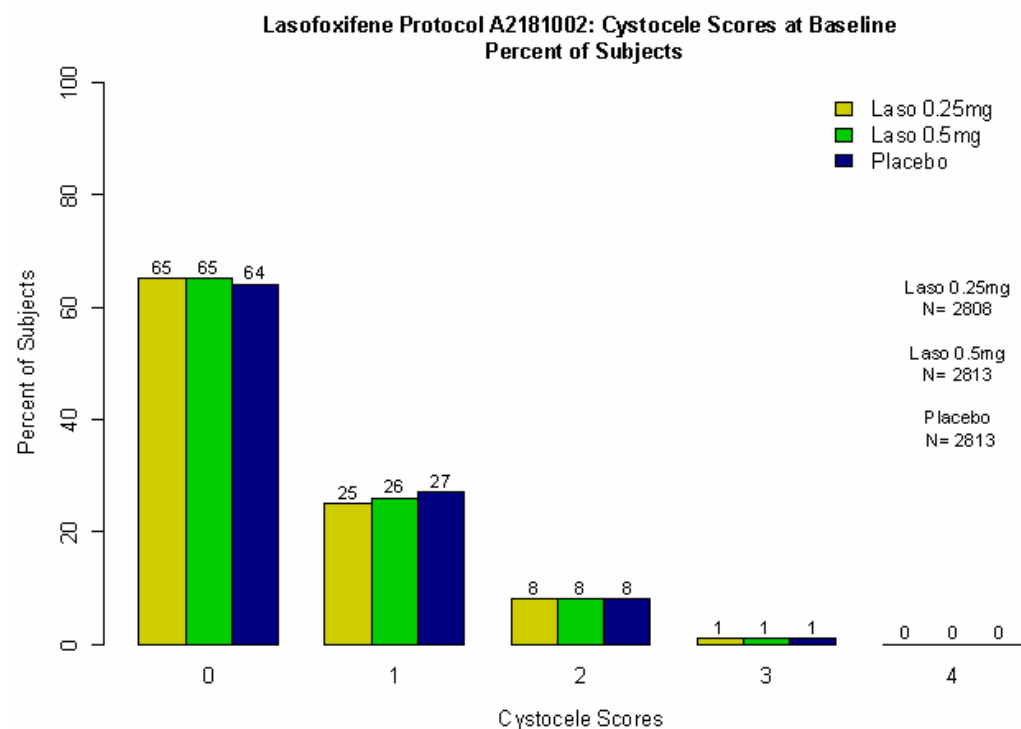


Figure 22. Uterine Cystocele Scores at Baseline and 3 Years –PEARL



The risk of surgery for pelvic organ prolapse or urinary incontinence was not significantly increased in patients assigned to lasofoxifene 0.5 mg compared to placebo, as summarized in Table 58. The hazard ratio was 1.27 (95% CI: [0.0.73, 2.22]; p=0.401) through 3 years and 1.31 (95% CI: [0.85, 2.04]; p=0.224) through 5 years. For the 0.25 mg lasofoxifene group, the HR was 1.59 (95% CI: [0.0.93, 2.71]; p=0.086) through 3 years and 1.57 (95% CI: [1.03, 2.40]; p=0.036) through 5 years.

Table 58. Analysis of Time to Treatment-Emergent Surgery for Either Pelvic Organ Prolapse or Urinary Incontinence - PEARL - Full Analysis Set

		Lasofoxifene	
	Placebo N=2852	0.25 mg N=2852	0.5 mg N=2852
3 Years			
Number (%) with event	22 (0.8)	35 (1.2)	28 (1.0)
Incidence rate/1000 patient-years (95% CI)	2.7 (1.7, 4.1)	4.3 (3.0, 6.0)	3.4 (2.3, 4.9)
Hazard ratio (95% CI)		1.59 (0.93, 2.71)	1.27 (0.73, 2.22)
P-value		0.086	0.401
5 Years			
Number (%) with event	35 (1.2)	55 (1.9)	46 (1.6)
Incidence rate/1000 patient-years (95% CI)	2.8 (1.9, 3.8)	4.3 (3.3, 5.6)	3.6 (2.6, 4.8)
Hazard ratio (95% CI)		1.57 (1.03, 2.40)	1.31 (0.85, 2.04)
P-value		0.036*	0.224

*P-value significant vs. placebo.

Separate analyses of time to first surgery for pelvic organ prolapse and time to first surgery for urinary incontinence showed similar results.

Based on the results of an exploratory analysis of data from PEARL, there was no discernible difference in baseline risk factors (BMI, parity, or years postmenopausal) for women with pelvic organ prolapse compared to those without.

6.9.7. Uterine Procedures

Lasofoxifene use is associated with a small increase in diagnostic uterine procedures. Based on the results for patients with no planned TVU surveillance in PEARL, lasofoxifene is associated with an excess incidence of ~10 patients with uterine procedures per 1000 patient-years compared to placebo. Most procedures were performed on an outpatient basis and had low associated morbidity.

Uterine procedures are presented for patients from PEARL who did not undergo scheduled TVU surveillance (excluding patients with pretreatment hysterectomy) throughout the study. These patients most closely approximate a “real world” patient population, although their participation in a clinical trial may have resulted in the performance of a greater number of procedures and thus be an overestimate of the number that would be expected in a community setting.

In patients with no planned TVU, there was a significant increase in the proportion of patients who had at least 1 diagnostic uterine procedure in both lasofoxifene treatment groups compared to placebo both through 3 years and through 5 years (Table 59). This was due to an increase in a number of different diagnostic procedures, most commonly endometrial biopsy.

Table 59. Incidence of Follow-up Uterine Procedures - PEARL - Patients with No Planned TVU (Without Baseline Hysterectomy)

	Number of Events (Event Rate)		
	Placebo N=1354	Lasofoxifene	
		0.25 mg N=1348	0.5 mg N=1352
3 Years			
Number of patients			
Number (%) with ≥ 1 procedure	35 (2.6)	69 (5.1)*	73 (5.4)*
Diagnostic uterine procedures			
Hysteroscopy	8 (2.1)	28 (7.4)*	17 (4.5)
Saline-infused sonohysterogram†	0 (0.0)	2 (0.5)	1 (0.3)
Endometrial biopsy	26 (6.8)	52 (13.8)*	58 (15.2)*
Polypectomy	3 (0.8)	9 (2.4)	10 (2.6)
Dilation and curettage (D&C)	14 (3.7)	33 (8.7)*	30 (7.9)*
Other	4 (1.0)	3 (0.8)	3 (0.8)
5 Years			
Number (%) with ≥ 1 procedure	36 (2.7)	97 (7.2)*	95 (7.0)*
Diagnostic uterine procedures			
Hysteroscopy	10 (1.7)	43 (7.1)*	30 (5.0)*
Saline-infused sonohysterogram*	0 (0.0)	3 (0.5)	1 (0.17)
Endometrial biopsy	31 (5.2)	72 (12.0)*	80 (13.3)*
Polypectomy	2 (0.3)	18 (3.0)*	15 (2.5)*
Dilation and curettage (D&C)	17 (2.8)	58 (9.6)*	42 (7.0)*
Other	1 (0.2)	1 (0.2)	3 (0.5)*

Event Rate = events per 1000 patient-years

Other includes uterine surgery, endometrial cytology, uterine cytology, endometrial ablation, myomectomy, and uterine tumor excision.

Patients may have more than one procedure or more than one type of procedure.

*P-value significant versus placebo.

†P-value not available for saline-infused sonohysterogram.

A review of the reasons for these procedures was conducted using the PEARL 3-year data. Lasofoxifene-treated patients had a higher proportion of diagnostic procedures performed for vaginal bleeding as mandated by the protocol (28 and 31 in the lasofoxifene 0.25 and 0.5 mg dose groups, respectively, compared to 7 events in the placebo group) and for asymptomatic findings (e.g., uterine polyps, endometrial thickness) discovered by unplanned TVU (46 and 37 in the lasofoxifene 0.25 mg and 0.5 mg dose groups, respectively, compared to 22 events in the placebo group).

In the community setting and according to current national and international guidelines, women who experience vaginal bleeding would undergo a diagnostic test, most likely a TVU, rather than a procedure (ACOG, 2006; Goldstein et al, 2001; NHS guidance, 1999; Sign, 2002). Procedures seen in the clinical trial setting do not reflect actual clinical practice where asymptomatic women would not be expected to have TVU; specifically, guidelines for endometrial cancer screening do not recommend periodic TVU.

Through 5 years, 24 (1.0%), 46 (2.0%), and 27 (1.2%) patients in the placebo, lasofoxifene 0.25 mg, and lasofoxifene 0.5 mg treatment groups, respectively underwent an on-study hysterectomy. The primary driver for the observed excess of events observed with lasofoxifene 0.25 mg was surgery for pelvic organ prolapse/urinary incontinence (Section 6.9.6). Otherwise, reasons for hysterectomies were generally comparable across treatment groups.

6.9.8. Beneficial Vaginal Changes

Lasofoxifene significantly improves postmenopausal VVA symptoms by decreasing vaginal pH, increasing vaginal lubrication, and improving the vaginal cell maturation index. Neither tamoxifen nor raloxifene alone have demonstrated any of these beneficial urogenital effects (Marttunen, et al, 2001; Pinkerton, et al, 2003; Vardy et al, 2003; Checa, et al, 2005).

VVA symptoms in postmenopausal women are associated with a decline in endogenous estrogen levels and are characterized by burning, itching, soreness and dyspareunia as a result of the vaginal epithelial atrophy. This is an ongoing, worsening, chronic condition, which, unlike hot flashes, does not resolve with time. The degree of atrophy can be assessed by the reduction of the vaginal maturation index, which demonstrates a lower proportion of superficial and intermediate cells and an increase in parabasal cells in a vaginal smear. In addition the glycogen content of epithelial cells is reduced, and increased vaginal pH, decreased vascularization, loss of elasticity and loss of lubrication also occur.

The VVA Phase 3 clinical program demonstrated that women taking lasofoxifene reported a significant improvement of their most bothersome symptoms, as well as improvements in the vaginal maturation index and pH. The etiology of these clinical benefits of lasofoxifene could be attributed to the following mechanisms of actions:

- Improvement of vaginal epithelial cell maturation:

Lasofoxifene significantly decreased parabasal cells by ~40% and increased intermediate cells (~30%) and superficial cells (~7%) compared to placebo determined by vaginal exfoliate cytology in the 12-week VVA clinical study. The vaginal cytology is known to correlate with the hormonal status during normal menstrual cycles or with administration of hormonal therapy in the postmenopausal woman and reflects the maturation stages of vaginal mucosal epithelium. Lasofoxifene achieves this maturation by inducing differentiation of the basal cells into intermediate and superficial cells.

- Decrease in vaginal pH and increase in vaginal glycogen production.

Lasofoxifene was associated with a statistically significant decrease in vaginal pH compared to placebo. Adjusted mean changes in pH were approximately -0.8 for lasofoxifene treatment groups and 0.2 for placebo treatment. The decrease in vaginal pH is a further indicator that lasofoxifene matures the vaginal epithelial cells. As the parabasal epithelial cells mature into intermediate and superficial cells, the synthesis and accumulation of glycogen within these cells increases similar to the early follicular phase of the menstrual cycle. When the cells desquamate, glycogen is deposited in the vaginal lumen, where

lactobacilli metabolize the glycogen and form lactic acid. It is the production of this acid that lowers the vaginal pH. These changes may contribute to the improvement in vaginal health reported by women in the VVA program.

In the rodent model, cornification of the vaginal epithelium is the hallmark histological change seen in response to estrogen. In preclinical studies, lasofoxifene treatment resulted in a significant dose-dependent increase in glycogen accumulation in the mature superficial epithelial cells of the rat vagina without inducing cornification (Wang et al, 2006). This indicates that the effects of lasofoxifene in the vagina are different from those of estrogen.

- Increase in vaginal discharge and improvement of lubrication by increasing vaginal mucus production and vascularization.

Postmenopausal women in the lasofoxifene program had a higher incidence of adverse events related to vaginal discharge (Table 23). Vaginal discharge results from a combination of cervical and vaginal epithelial mucus production, vascularization, and hydration. The increased discharge was reported in patients with and without a uterus/cervix, implying that the vagina contributes significantly to vaginal lubrication.

In preclinical rat studies, lasofoxifene demonstrated the greatest increase in expression of the mucin5B gene (one of the major gel-forming mucins) in cervix and vaginal samples in comparison to other SERMs. The gene expression responses to lasofoxifene treatment were different in the uterus versus the vagina. The overall vaginal gene expression profile is consistent with the phenotype of mucification in the OVX rat model.

- No increase in vaginal epithelial cell proliferation.

Lasofoxifene induces maturation of basal vaginal epithelial cells to intermediate and superficial epithelial cells without increasing the rate of cell proliferation. This is clearly demonstrated in preclinical studies where lasofoxifene did not cause any increase in the number of BrdU labeled basal/parabasal cells in OVX rats in comparison to a significant increase by estrogen (5-fold) and tamoxifen (3-fold) (Wang et al, 2006). The histological observations in a 24-month primate study also confirmed that >90% of lasofoxifene-treated monkeys had atrophic vaginal epithelium in comparison with 82% of OVX control monkeys. In contrast, only 4% of estrogen-treated monkeys had vaginal epithelial atrophy, and all monkeys showed cornification.

In summary, in postmenopausal women lasofoxifene significantly improves VVA symptoms by decreasing vaginal pH, increasing vaginal lubrication, and improving the vaginal cell maturation index. The OVX rat has been widely used to characterize the tissue-specific effects of SERMs and the nonclinical data presented above support the clinical findings in the vagina and provide a mechanism of action for the efficacy of lasofoxifene in the treatment of VVA. Together, the data demonstrate that lasofoxifene stimulates vaginal epithelial maturation without causing cell proliferation.

6.10. Safety in Other Groups and Situations

There is no evidence to suggest that age or race influence the safety of lasofoxifene. Results from the clinical safety database are consistent with results of the population pharmacokinetic analysis indicating that from age 40 to 80 years daily steady-state AUC increases by approximately 30%, an amount that is not considered clinically meaningful. Although most patients in the clinical development program were white, lasofoxifene pharmacokinetics were similar in white and Japanese postmenopausal women, and the population pharmacokinetic analysis concluded that no discernible differences in pharmacokinetics were observed between races. No dosage adjustments are required based on age or race.

6.11. Long-term Safety

The results of the safety evaluation of lasofoxifene in postmenopausal women in the 5-year PEARL study indicate that lasofoxifene is generally safe and well tolerated, with no evidence of an increased risk of endometrial cancer. In this study, 5,701 women have received lasofoxifene for a total exposure of 23,058 patient-years.

6.12. Clinical Safety Summary of Results

General Safety

- Lasofoxifene does not appear to be associated with an increased mortality risk.
- The overall frequency of all-causality SAEs was similar for all treatment groups.
- A similar percentage of patients across treatment groups experienced all-causality AEs.
 - Most AEs were mild to moderate in severity and did not result in discontinuation.
 - The rate of discontinuations due to AEs (all-causality) was low and similar across all treatment groups.
 - There was a greater incidence of hot flush and muscle spasms in lasofoxifene-treated patients, which accounted for most of the discontinuations due to AEs.
- Lasofoxifene was not associated with a clinically relevant change in hepatic function.
 - No lasofoxifene-treated patients met Hy's law criteria.
- The incidences of gallbladder events and cataracts were not increased in lasofoxifene-treated patients.

Breast Cancer Effects

- Lasofoxifene 0.5 mg reduced the risk of:
 - ER+ breast cancer by 67% through 3 years and by 81% through 5 years.
 - All breast cancer by 65% through 3 years and by 79% through 5 years.
 - ER+ invasive breast cancer by 73% through 3 years and by 83% through 5 years.
 - Invasive breast cancer by 75% through 3 years and by 85% through 5 years.
- No new breast cancer events were reported for lasofoxifene 0.5 mg between 3 and 5 years.

Cardiovascular Safety

- As observed with other SERMs, lasofoxifene increased the risk of VTEs (~ 2-fold).
- The risk of stroke was not increased with lasofoxifene use.
 - The risk of stroke (excluding TIA) was significantly reduced (by 36%) through 5 years
- The risk of a major coronary event was significantly reduced (by 32%) through 5 years compared to placebo.
- Markers of cardiovascular risk (total cholesterol, LDL-cholesterol, and hs-CRP) were significantly reduced at 3 years (the last timepoint assessed) compared to placebo.
- Lasofoxifene was not associated with effects on cardiac function including QTc prolongation.

Gynecological Safety Effects

- There is no evidence of an increased risk for endometrial cancer or hyperplasia associated with the use of lasofoxifene.
- Lasofoxifene has effects on the endometrium including:
 - ~ 1.5 mm mean increase in thickness, which is associated with cystic echotexture on ultrasound and is consistent with benign cystic atrophy on biopsy.
 - Increased incidence in benign atrophic polyps.
 - Increased incidence of vaginal bleeding – in PEARL, lasofoxifene was associated with a ~ 0.3% annual increase in vaginal bleeding, contributing to a ~1.0% annual increase in gynecological procedures.

- Lasofoxifene is not associated with an increased risk of pelvic organ prolapse/urinary incontinence.

7. Proposed Indicated Dose

Lasofoxifene 0.5 mg is the proposed indicated dose for the treatment of osteoporosis in postmenopausal women based on improved efficacy in reducing osteoporotic fractures throughout the skeleton and comparable safety compared to lasofoxifene 0.25 mg.

8. Benefits, Risks and Risk Management

Benefit-Risk Profile

Osteoporosis is a major public health threat for an estimated 44 million Americans (55% of people aged 50 years or older). In the US, 10 million individuals are estimated to already have the disease and almost 34 million more are estimated to have low bone mass placing them at increased risk for osteoporosis (NOF, 2007). Worldwide, osteoporosis affects 200 million people with 75 million of these in Europe, Japan, and the US (International Osteoporosis Foundation [IOF], 2007).

Nonvertebral fractures are an important clinical endpoint since these types of fractures account for most of the disability due osteoporosis (Cummings, 2006; Simonelli et al, 2003), and clinical fractures are considered to be predictive of an increased mortality risk (Trone et al, 2007). Vertebral fractures are associated with loss of height, kyphosis, pain, mobility impairment, and limitations of activities of daily living (Lindsay, R. in Harrison's Online, 2001).

In addition to a growing worldwide elderly population with increased risk of osteoporotic fracture, the number of postmenopausal women currently treated with osteoporosis medicines is low. Thus, despite available therapies, there is a need for additional osteoporosis medications that will address the need of individual patients, help ensure compliance with treatment, and increase our ability to successfully treat this disease.

Lasofoxifene affords a unique benefit among SERMs for the treatment of osteoporosis in postmenopausal women at increased risk of fractures by reducing the incidence of radiographic vertebral and nonvertebral fractures as well as clinical fractures (vertebral and nonvertebral fractures associated with pain and discomfort). The efficacy on nonvertebral and clinical fractures has been observed with bisphosphonates (Black et al, 2007) but not with raloxifene.

Additional benefits of lasofoxifene include increases in BMD, reductions in markers of bone turnover, positive effects on endpoints associated with VVA, and amelioration of serum lipid profiles by reducing LDL-cholesterol and total cholesterol, and a reduction in risk of breast cancer.

Lasofoxifene is unique among SERMs and can be differentiated from bisphosphonates in demonstrating improvements in VVA. Lasofoxifene also has superior effects on BMD, markers

of bone turnover, and serum lipid profiles compared with raloxifene based on published data from raloxifene trials. The effect on reduction in risk of breast cancer is an effect that has also been observed with raloxifene, which was recently approved in the US for the reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and, additionally, reduction in risk of invasive breast cancer in postmenopausal women at high risk of invasive breast cancer.

Lasofoxifene is also unique among SERMs in its clinical pharmacology profile, which suggests that lasofoxifene will be uncomplicated to prescribe and to use in clinical practice: lasofoxifene has linear pharmacokinetics over a wide dose range, and there are no clinically meaningful effects of age, weight, race, mild to moderate hepatic impairment, or mild to moderate renal impairment on lasofoxifene's pharmacokinetics. Additionally, lasofoxifene does not exhibit clinically meaningful pharmacokinetic drug interactions and can be administered without regard to timing of meals. In contrast, the plasma concentration of raloxifene is approximately 150% higher in patients with mild hepatic impairment, and raloxifene is to be used with caution in patients with hepatic impairment.

Lasofoxifene is generally safe and well tolerated. The main general safety risk associated with lasofoxifene use is an increase in VTEs, an effect noted with other SERMs. There is no evidence that lasofoxifene increases the risk of stroke.

With respect to gynecological safety, there is no evidence to suggest that lasofoxifene increases the risk of endometrial cancer or endometrial hyperplasia. The exposure upon which the analysis was based exceeds that used to establish that raloxifene does not increase the risk for endometrial cancer in the MORE Study (Grady et al, 2004).

While all SERMs have uterine effects to varying degrees, lasofoxifene's effects are generally benign. There is no evidence that lasofoxifene use is associated with an increased risk of endometrial cancer. The main risk of lasofoxifene use appears to be a small increase in diagnostic uterine procedures (primarily office endometrial biopsies), as a result of a small increase in vaginal bleeding and investigative follow-up of benign endometrial effects that were detected by unplanned TVU. In the community setting and according to current guidelines, risk minimization activities are likely to limit this risk to women who experience vaginal bleeding. Even women with vaginal bleeding would receive a diagnostic test, most likely a TVU, rather than an invasive procedure per these guidelines.

Although the risk for diagnostic uterine procedures is increased with lasofoxifene, we anticipate that other procedures including breast biopsies and revascularization procedures will be reduced based on the efficacy profile of lasofoxifene.

The benign effects on the endometrium associated with the use of lasofoxifene will require physician education to ensure compliance with present guidelines for gynecologic care, which is an important component of the risk management program for lasofoxifene.

Lasofoxifene's benefit-risk profile is summarized in [Table 60](#).

Table 60. Lasofoxifene 0.5 mg Benefits and Risks

	Number of Patients [Annualized Rate(%)]			
	Placebo	Lasofoxifene 0.5 mg	NNT	NNH
Proposed Indicated Benefits				
Radiographic vertebral fracture	176 (2.14)	105 (1.27)	116	
Nonvertebral fracture	209 (2.44)	167 (1.95)	204	
Clinical fracture	246 (2.88)	193 (2.26)	161	
Additional Benefits				
VVA*	178 (5.97)	213 (7.37)	72	
Major coronary events	95 (0.67)	66 (0.46)	492	
Breast cancer (all types)	24 (0.18)	5 (0.04)	721	
ER+	21 (0.15)	4 (0.03)	806	
Risks				
VTE	18 (0.13)	37 (0.26)		751
DVT	13 (0.09)	28 (0.20)		951
PE	2 (0.01)	9 (0.06)		2037
Diagnostic uterine procedures	36 (0.53)	95 (1.40)		115

NNH=number needed to harm based on 1 year of treatment; NNT=number need to treat based on 1 year of treatment.

*Based on improvement from baseline in the most bothersome symptom in Phase 3 VVA studies; assumes maximal efficacy achieved and maintained after 12 weeks and 50% VVA in osteoporotic patients.

When considering the overall benefit-risk profile for lasofoxifene, a comparison to the benefit-risk profile of raloxifene is relevant.

Similar to raloxifene, lasofoxifene reduces vertebral fracture risk. However, lasofoxifene also reduces nonvertebral fracture risk and clinical fracture risk, effects that have not been observed with raloxifene. Lasofoxifene is superior to raloxifene in improving markers of bone turnover and increasing bone mineral density.

Lasofoxifene has been shown to reduce breast cancer risk in postmenopausal women with osteoporosis, an effect that is also observed with raloxifene. However, lasofoxifene is also effective in improving VVA, an effect that has not been shown with raloxifene.

The non-gynecological safety profile of lasofoxifene is comparable to that of raloxifene based on 3-year data, which indicate that both drugs have an approximately 2-fold risk of VTEs, the majority of which are DVTs, with only rare cases of PE. The gynecological safety profile of lasofoxifene is similar to raloxifene with respect to the absence of elevated risk for endometrial cancer and hyperplasia. Lasofoxifene is, however, associated with a small excess in vaginal bleeding, endometrial thickening and cystic echotexture, all of which contribute to a correspondingly small increase in diagnostic uterine procedures. Raloxifene and tamoxifen have also demonstrated increases in diagnostic uterine procedures.

On balance, these results suggest that lasofoxifene has a unique benefit profile and a favorable risk profile when used for the treatment of osteoporosis in postmenopausal women at increased risk for fractures.

Risk Management Plan

The risks that have been identified and investigated during the lasofoxifene clinical development program are addressed in the proposed prescribing information. In order to further refine the understanding of the lasofoxifene product profile, to optimize patient safety, and to realize the full therapeutic benefit of this product, Pfizer has developed a risk management program to address identified and potential risks associated with lasofoxifene treatment. The activities that will be undertaken to monitor and minimize risk with the use of lasofoxifene are summarized in [Table 61](#).

Table 61. Activities to Monitor and Minimize Risk

	Activities to Minimize Risk		Activities to Assess Risk	
	Package Insert/Patient Information	Web-based Educational Materials for Health-care Providers	Routine Pharmacovigilance	Prospective Cohort Study
Important identified risks				
Venous Thromboembolic Events	√	√	√	√
Diagnostic uterine procedures	√	√	√	√
Important potential risks based on experience with other SERMs and HT				
Endometrial Cancer			√	√
Pelvic Organ Prolapse			√	√
Gallbladder events			√	√
Important missing information				
Adverse event rates with prolonged exposure in a practice setting			√	√

The activities to minimize risk will include:

- Within the Package Insert, specific contraindications, warnings, and recommendations to alert physicians, pharmacists, and patients to the proper prescription and use of FABLYN®.
- Education of health care providers, including web-based education materials, to assist them in (1) understanding the risk factors, risk mitigation and symptoms of VTE, (2) understanding the endometrial changes that occur in postmenopausal women, and (3) ensuring awareness of the currently accepted guidelines for endometrial surveillance.

Assessment of risk will include:

- Routine pharmacovigilance that will include regular monitoring of the Pfizer safety database beginning postapproval using targeted medical event terms to focus on identified and potential risks, statistical analysis of the results obtained, and ongoing product safety and product information reviews;
- A planned 8-year prospective cohort study using medical utilization databases. This study will report on the incidence and hazard ratio for gynecological and non-gynecological outcomes in women treated with lasofoxifene or raloxifene compared to those receiving no osteoporosis treatment in a community setting. Updates on the progress of this study, including incidence of events of interest in the 3 treatment groups, will be provided on a yearly basis, with a full analustic report at the study's conclusion.

In conclusion, FABLYN®, a SERM with a unique benefit-risk profile, has been investigated in a comprehensive clinical development program. It has been shown to be safe and effective in the treatment of osteoporosis in postmenopausal women at increased risk of fracture. With appropriate product labeling and risk management, it is Pfizer's view that the benefits of this product clearly outweigh its risks.

References

1. ACOG Committee on Gynecologic Practice, Opinion No. 336. Tamoxifen and uterine cancer. *Obstet Gynecol* 2006;107(6):1475-8.
2. Amant F, Moerman P, Neven P et al. Endometrial cancer. *Lancet* 2005;366:491-505.
3. Antunes A Jr, Costa-Paiva L, Arthuso M, et al. Endometrial polyps in pre- and postmenopausal women: Factors associated with malignancy. *Maturitas* 2007;57(4):415-21.
4. Approval Package for NDA 20-815/S-003: EVISTA® (raloxifene HCl) for the Treatment of Osteoporosis in Postmenopausal Women (approved 30 September 1999). Food and Drug Administration Web site. Available at: http://www.fda.gov/cder/foi/nda/99/20815S3_Evista.htm. Accessed on 20 August 2007.
5. Barrett-Connor E, Mosca L, Collins P, et al. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med*. 2006;355(2):125-37.
6. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med*. 2007;356(18):1809-22.
7. Cano A, Hermenegildo C. The endometrial effects of SERMs. *Hum Reprod Update* 2000;6(3):244-54.
8. Checa MA, Garrido A, Prat M, et al. A comparison of raloxifene and calcium plus Vitamin D on vaginal atrophy after discontinuation of long-standing postmenopausal hormone therapy in osteoporotic women: a randomized, masked-evaluator, one-year, prospective study. *Maturitas* 2005;52(1):70-7.
9. Clement PB. Miscellaneous primary tumours and metastatic tumours of the uterine cervix. In: Fox H, and Wells M, editors. *Haines and Taylor Obstetrical and Gynaecological Pathology*, 5th ed. London: Churchill Livingstone; 2003. p. 359-90.
10. Cline JM, Soderqvist G, Register JC, et al. Assessment of hormonally active agents in the reproductive tract of female non-human primates. *Toxicol Path* 2001; 29(1): 84-90.
11. Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women. London: European Agency for the Evaluation of Medicinal Products; 2005 13 Oct. Report No: EMEA/CHMP/021/97.
12. Cotran RS, Kumar V, and Collins T, editors. Neoplasia. In: *Robbins Pathologic Basis of Disease*, 6th ed., 1999; Philadelphia: W.B. Saunders Company; 1999. p. 299-305.

13. Cox DA, Helvering, LM. Extracellular matrix integrity: A possible mechanism for differential clinical effects among selective estrogen receptor modulators and estrogens? *Mol Cell Endocrinol* 2006; 247(1/2):53-9.
14. Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: Results from the MORE randomized trial. *JAMA* 1999; 281:2189-2197.
15. Cummings SR, Melton LJ III. Epidemiology and outcomes of osteoporotic fractures. *Lancet* 2002; 359(9319):1761-7.
16. Cummings SR. A 55-year old woman with osteopenia. *JAMA* 2006;296(21):2601-10.
17. Dennison E, Mohamed MA, and Cooper C. Epidemiology of osteoporosis. *Rheum Dis Clin N Amer* 2006;32:617-29.
18. Evista® [package insert]. Indianapolis, IN: Eli Lilly and Company; 2007.
19. Fingert HJ, Campisi J, Pardee AB. Cell proliferation and differentiation. In Holland JF, Frei E III, Bast RC et al, editors. *Cancer Medicine*. 3rd edition, 1993; Philadelphia: Lea and Febiger; 1993. p. 1-14.
20. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer - Report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Nat Cancer Inst* 1998;90(18):1371-88.
21. Food and Drug Administration (FDA) Guidance for Industry. Estrogen and estrogen/progestin drug products to treat vasomotor symptoms and vulvar and vaginal atrophy symptoms – recommendations for clinical evaluation. In: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Jan 2003: 13 pages.
22. FORE 10-year risk calculator accessed at <http://riskcalculator.fore.org/> accessed October, 2007.
23. Fox H and Wells M, editors. Postmenopausal endometrium. In: Haines and Taylor *Obstetrical and Gynaecological Pathology*, 5th edition. London: Churchill Livingstone; 2003. p. 402-3.
24. Fugere P, Scheele WH, Shah A, et al. Uterine effects of raloxifene in comparison with continuous-combined hormone replacement therapy in postmenopausal women. *Am J of Obstet Gynecol* 2000;182(3):568-74.
25. Genant HK, Jergas M, Palermo L, et al. Comparison of a semiquantitative visual and quantitative morphometric assessment of prevalent and incident vertebral fractures in osteoporosis. *J Bone Miner Res* 1996;11(7):984-96.

26. Goldstein RB, Bree RL, Benson CB, et al. Evaluation of the women with postmenopausal bleeding: Society of radiologists in ultrasound-sponsored consensus conference statement. *J Ultrasound Med*. 2001;20(10):1025-36.
27. Goldstein SR, Neven P, Zhou L, et al. Raloxifene effect on frequency of surgery for pelvic floor relaxation. *Obstet Gynecol* 2001;98(1): 91-6.
28. Grady D, Ettinger B, Moscarelli E, et al. Safety and adverse effects associated with raloxifene: Multiple Outcomes of Raloxifene Evaluation. *Obstet Gynecol* 2004;104(4):837-44.
29. IOF (International Osteoporosis Foundation). Available: <http://www.iofbonehealth.org> [Accessed July 30, 2007].
30. Hodgson SF, Watts NB, Bilezikian JP, et al. American Association of Clinical Endocrinologists (AACE) Medical Guidelines for Clinical Practice for the Prevention and Treatment of Postmenopausal Osteoporosis: 2001 Edition, with Selected Updates for 2003. *Endocrine Practice* 2003; 9(6):544-564.
31. Jakob F, Marin F, and Martin-Mola E et al. Characterization of patients with an inadequate clinical outcome from osteoporosis therapy: the Observational Study of Severe Osteoporosis (OSSO) *QJM* 2006;99 (8):531-43)
32. Johnell O, Kanis J. Epidemiology of osteoporotic fractures. *Osteoporos Int* 2005;16 (Suppl 2);S3-S7.
33. Kloos I, Delaloge S, Pautier P, et al. Tamoxifen-related uterine carcinosarcomas occur under/after prolonged treatment: report of five cases and review of the literature. *Int J Gynecol Cancer* 2002; 12(5): 496-500.
34. Kurman R, Kaminski P, Norris H. The behavior of endometrial hyperplasia. A long-term study of "untreated" hyperplasia in 170 patients. *Cancer* 1985;56(2):403-12.
35. Lane NE. Epidemiology, etiology, and diagnosis of osteoporosis. *Am J Obstet Gynecol* 2006; 194 (2) (Suppl): S3-11.
36. Lavié O, Barnett-Griness O, Narod SA, et al. The risk of developing sarcoma after tamoxifen use. *Int J Gynecol Cancer* 2008;18(2):352-6.
37. Levy N et al. Differential regulation of native estrogen receptor regulatory elements by estradiol, tamoxifen, and raloxifene. *Mol Endocrinol Rapid Electronic Pu* first published on October 25, 2007.
38. Lindsay R, Cosman F. Chapter 342 – Osteoporosis in Harrison's Online, 2001. <http://harrisons.accessmedicine.com>

39. Martino S, Disch D, Dowsett SA, et al. Safety assessment of raloxifene over eight years in a clinical trial setting. *Curr Med Res & Opin.* 2005; 21(9):1441-52.
40. Marttunen MB, Cacciatore B, Hietanen P, et al. Prospective study on gynaecological effects of two antioestrogens tamoxifen and toremifene in postmenopausal women. *Br J Cancer* 2001;84(7):897-902.
41. McCluggage W. My approach to the interpretation of endometrial biopsies and curettings. *J Clin Pathol.* 2006;59(8):801-12.
42. McDonnell DP. Mining the complexities of the estrogen signaling pathways for novel therapeutics. *Endocrinology* 2003;144 (10):4237-40.
43. Musa MA, Khan MOF, Cooperwood JS. Medicinal chemistry and emerging strategies applied to the development of selective estrogen receptor modulators (SERMs). *Curr Med Chem* 2007;14(11):1249-61.
44. National Center for Health Statistics (NCHS) Office of Statistics and Programming, National Center for Injury Prevention and Control, CDC. 10 leading causes of death by age group, United States, 2001. Available at: <http://www.chdl.org/Projects/10%20Leading%20Causes%20of%20Death%20by%20Age%20Group%202001.pdf>, accessed 02 October 2007
45. National Osteoporosis Foundation (NOF), 2003. Physician's guide to prevention and treatment of osteoporosis. Available at http://www.nof.org/_vti_bin/shtml.dll/physguide/index.htm. Accessed 30 July, 2007.
46. National Osteoporosis Foundation (NOF), <http://www.nof.org/osteoporosis/diseasefacts.htm>. Accessed 2 November, 2007.
47. Neven P, Quail D, Levrier M, et al. Uterine effects of estrogen plus progestin therapy and raloxifene: Adjudicated results from the EURALOX study. *Obstet Gynecol* 2004; 103(5 Pt 1): 881-91.
48. NHS guidance. Improving outcomes in gynaecological cancers. In: NHS executive guidance on commissioning cancer services: Improving outcomes in gynaecological cancers: the manual. Wetherby: Department of Health; Jul, 1999. Catalogue No. 16149.
49. NIH Consensus Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. *JAMA* 2001;285(6):785-95.
50. Osborne CK, Zhao H, Fuqua SAW. Selective estrogen receptor modulators: structure, function, and clinical use. *J Clin Oncol* 2000; 18(17):3172-86.
51. Papaioannou A, Kennedy CC, Dolovich L, et al. Patient adherence to osteoporosis medications : problems, consequences and management strategies. *Drugs Aging* 2007;24(1):37-55.

52. Pinkerton JV, Shifren JL, La Valleur J, et al. Influence of raloxifene on the efficacy of an estradiol-releasing ring for treating vaginal atrophy in postmenopausal women. *Menopause* 2003;10(1):45-52.
53. Raisz LG. Pathogenesis of osteoporosis: concepts, conflicts, and prospects. *J Clin Invest* 2005, 115 (12): 3318-25.
54. Ridker PM, Rifai N, Rose L, et al. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002; 347 (20):1557-65.
55. Riggs BL, Hartmann LC. Selective estrogen-receptor modulators – mechanisms of action and application to clinical practice. *N Engl J Med* 2003; 348 (7): 618–29.
56. Sherman ME, Mazur MT, and Kurman RJ. Benign Diseases of the Endometrium. In: Kurman, RJ, editor. *Blaustein's Pathology of the Female Genital Tract*. 5th edition. New York: Springer-Verlag;2002. p. 421-466.
57. (SIGN) Scottish Intercollegiate Guidelines Network. Investigation of post-menopausal bleeding. A national clinical guideline: No. 61: Edinburgh, Scotland; 25. Sep 2002: 28 pages.
58. Simonelli C, Chen Y-T, Morancey J, et al. Evaluation and management of osteoporosis following hospitalization for low-impact fractures. *J Gen Intern Med* 2003;18(1):17-22.
59. Trone DW, Kritz-Silverstein D, Muhlen DG, et al. Is radiographic vertebral fracture a risk factor for mortality? *Am J Epidemiol* 2007;166(10):1191-7.
60. US Department of Health and Human Services. Chapter 5: Key Messages. In: *Bone Health and Osteoporosis: A Report of the Surgeon General. Clinical Practice Guideline*. US Dept of Health and Human Services, Public Health Service, Rockville, MD; 2004:p. 88.
61. Vardy MD, Lindsay R, Scotti R, et al. Short-term urogenital effects of raloxifene, tamoxifen and estrogen. *Am J Obstet Gynecol* 2003;189(1):81-8.
62. Wang XN, Simmons HA, Salatto, CT, et al. Lasofoxifene enhances vaginal mucus formation without causing hypertrophy and increases estrogen receptor [beta] and androgen receptor in rats. *Menopause* 2006;13(4): 609-20.
63. Wickerham DL, Fisher B, Wolmark B, et al. Association of tamoxifen and uterine sarcoma [letter]. *J Clin Oncol* 2002;20(11): 22758-60.
64. World Health Organization. Top ten causes of death. Fact Sheet Number 310. February 2007. Available at: <http://www.who.int/mediacentre/factsheets/fs310.pdf>, accessed 02 October 2007.

65. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-33.
66. Writing Group for the PEPI Trial. Judd HL, Mebane-Sims I, Legault C, et al (PEPI Writers Group). Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The postmenopausal estrogen/progestin interventions (PEPI) trial. JAMA 1996; 275 (5) :370-5.

Appendix 1. Phase 2/3 Clinical Studies

Study (Number enrolled) [Duration of treatment] FPFV to LPLV	Study Centers (N) Locations	Study Design	Treatment Groups	Inclusion Criteria	Primary endpoint
Phase 3: Treatment					
A2181002 (PEARL) ^a (8556) [5 years with 3-yr analysis] 20Sep01–18Dec07	113 32 countries world-wide	Randomized, double- blind, placebo- controlled, parallel group, multicenter study	Laso: 0.25 mg/day 0.5 mg/day Placebo	60-80 yr old at least 5 yrs post-menopause lumbar spine or femoral neck T-score ≥ -4.5 and ≤ -2.5	Time to first new or worsening radiographic vertebral fracture
Phase 3: Prevention					
A2181003 (OPAL) (915) [2 years] 12Sep00-16Apr03	40 US, Argentina, Brazil, Canada, France, UK	Prospective, double- blind, randomized, placebo-controlled, parallel group, multicenter study.	Laso: 0.025 mg/day 0.25 mg/day 0.5 mg/day Placebo	40-75 yr old 3-20 yrs post-menopausal lumbar spine T-score ≥ -2.5 and ≤ 0	Percent change from baseline in lumbar spine BMD at 24 months and in LDL-C at 6 months
A2181004 (OPAL) (979) [2 years] 23Aug00-16Apr03	38 US, Argentina, Denmark, Mexico, Norway	Prospective, double- blind, randomized, placebo-controlled, parallel group, multicenter study.	Laso: 0.025 mg/day 0.25 mg/day 0.5 mg/day Placebo	40-75 yr old 3-20 yrs post-menopausal T-score ≥ -2.5 and ≤ 0	Percent change from baseline in lumbar spine BMD at 24 months and in LDL-C at 6 months
A2181030 (CORAL) (540) [2 years] 23May03-5Oct05	32 US	Randomized, double- blind, placebo- and active treatment- controlled, parallel group, multicenter study	Laso: 0.25 mg/day Raloxifene: 60 mg/day Placebo	48-75 yr old and 3 yrs post-menopausal lumbar spine T-score ≥ -2.5 and ≤ 0	(1) Percent change from baseline in lumbar spine BMD at 24 months and (2) percent of BMD responders at 24 months

Appendix 1. Phase 2/3 Clinical Studies

Study (Number enrolled) [Duration of treatment] FPFV to LPLV	Study Centers (N) Locations	Study Design	Treatment Groups	Inclusion Criteria	Primary endpoint
Phase 3: Vulvar and Vaginal Atrophy					
A2181031 (444) [12 weeks] 1Dec03-3Aug04	48 Canada, US	Randomized, double- blind, placebo- controlled, parallel group, multicenter study	Laso: 0.25 mg/day 0.5 mg/day Placebo	50-80 yr old and 3 yrs post-menopausal with vaginal atrophy	Change from baseline to week 12 in: (1) Most bothersome VVA symptom (2) Vaginal pH (3) Percentage of vaginal parabasal cells, (4) Percentage of vaginal superficial cells
A2181032 (445) [12 weeks] 3Dec03-6Jul04	48 Australia, Canada, Denmark, Estonia, Lithuania, Norway, Poland, US	Randomized, double- blind, placebo- controlled, parallel group, multicenter study	Laso: 0.25 mg/day 0.5 mg/day Placebo	50-80 yr old and 3 yrs post-menopausal with vaginal atrophy	Change from baseline to week 12 in: (1) Most bothersome VVA symptom (2) Vaginal pH (3) Percentage of vaginal parabasal cells, (4) Percentage of vaginal superficial cells
Phase 2: Treatment					
A2181037 (JADE) (497) [12 months] 19Jun04-2Mar06	17 Japan, Korea, Taiwan	Randomized, double- blind, placebo- controlled, parallel group, multicenter study	Laso: 0.025 mg/day 0.25 mg/day 0.5 mg/day Placebo	≤80 yr old at least 3 yrs post-menopause lumbar spine T-score ≥-4.5 and ≤-2.5	Percent change from baseline in lumbar spine BMD at 12 months

Appendix 1. Phase 2/3 Clinical Studies

Study (Number enrolled) [Duration of treatment] FPFV to LPLV	Study Centers (N) Locations	Study Design	Treatment Groups	Inclusion Criteria	Primary endpoint
Phase 2: Prevention					
218-101 (321) [3 months] 14Oct97-29Oct98	19 US	Randomized, double-blind, placebo- and active treatment-controlled, parallel group, multicenter study	Laso: 0.4 mg/day 2.5 mg/day 10 mg/day Conj. Est/MPA Placebo	50-68 yr old post-menopausal T-score ≤ 0	Percent change from baseline in urinary NTx and deoxypyridinoline crosslinks at 3 months
218-101E (190) [9 months] 15Oct97-29Jun99	19 US	Randomized, double-blind, placebo- and active treatment-controlled, parallel group, multicenter study.	Laso: 0.4 mg/day 2.5 mg/day 10 mg/day Conj. Est/MPA Placebo	Extension of 218-101	Percent change from baseline in lumbar spine BMD at 12 months
218-102 (410) [2 years] 18Nov98-11May01	26 US	Randomized, double-blind, placebo- and active treatment-controlled, parallel group, multicenter study.	Laso: 0.25 mg/day 1.0 mg/day Raloxifene 60 mg/day Placebo	50-74 yr old post-menopausal Z-score ≥ -2.5 and ≤ 2	Percent change from baseline in lumbar spine BMD at 24 months
218-103 (394) [1 year] 6Jul98-6Jan00	24 US	Randomized, double-blind, placebo-controlled, parallel group, multicenter study	Laso: 0.017 mg/day 0.05 mg/day 0.15 mg/day 0.5 mg/day Placebo	50-74 yr old post-menopausal Z-score ≥ -2.5 and ≤ 2	Percent change from baseline in lumbar spine BMD at 12 months

Appendix 1. Phase 2/3 Clinical Studies

Study (Number enrolled) [Duration of treatment] FPFV to LPLV	Study Centers (N) Locations	Study Design	Treatment Groups	Inclusion Criteria	Primary endpoint
A2181042 (LACE) (51) [2 years] 7Sep04-21Sep07	1 UK	Randomized, double-blind, placebo-controlled, parallel group, single center study.	Laso: 0.25 mg Placebo	>50 yrs and >5 years postmenopause or having had hysterectomy and < 55 yrs with FSH >30 IU/L. BMD T score ≥ -2.5 and ≤ -1	Percentage change in lumbar spine BMD after 2 years
Phase 2: Vulvar and Vaginal atrophy					
A2181012 (387) [24 weeks] 10Jan02-25Nov03	31 US	Randomized, double-blind, placebo-controlled, parallel group, multicenter study	Laso: 0.025 mg/day 0.25 mg/day 0.5 mg/day Placebo	≥ 50 years and postmenopausal with confirmed vaginal atrophy	Change from baseline at 12 weeks in: vaginal parabasal cells vaginal superficial cells vaginal pH subject self-assessments
Phase 2: Female Sexual Dysfunction					
A2181014 ^b (236) [12 months] 8Nov01-25Feb04	45 US, Europe, Canada	Randomized, double-blind, placebo-controlled, parallel group, multicenter study	Laso: 0.25 mg/day 0.5 mg/dau Placebo	≥ 44 years and postmenopausal with Class 2 Female Sexual Arousal Disorder	Change from baseline at 6 months in average weekly number of satisfactory sexual events.
A2181015 (445) [12 months] 13Mar02-14Oct04	74 US, Canada, Australia, Sweden, UK	Randomized, double-blind, placebo-controlled, parallel group, multicenter study	Laso: 0.025 mg/day 0.25 mg/day 0.5 mg/day Placebo	≥ 44 years and postmenopausal with Class 2 Female Sexual Arousal Disorder	Change from baseline at 6 months in average weekly number of satisfactory sexual events.
A2181016 ^b (331) [12 months] 9Nov01-25Mar04	49 US, Europe, Canda	Randomized, double-blind, placebo-controlled, parallel group, multicenter study	Laso: 0.25 mg/day 0.5 mg/dau Placebo	≥ 44 years and postmenopausal with sexual dysfunction/hypoactive desire -Class 1A HSDD	Change from baseline at 6 months in average weekly number of satisfactory sexual event

Appendix 1. Phase 2/3 Clinical Studies

Study (Number enrolled) [Duration of treatment] FPFV to LPLV	Study Centers (N) Locations	Study Design	Treatment Groups	Inclusion Criteria	Primary endpoint
A2181021 (472) [12 months] 16Jan02-16Aug04	72 US, Canada, Europe, Australia	Randomized, double- blind, placebo- controlled, parallel group, multicenter study	Laso: 0.025 mg/day 0.25 mg/day 0.5 mg/day Placebo	≥44 years and postmenopausal, sexually active and diagnosed with Class 1A HSDD	Change from baseline at 6 months in average weekly number of satisfactory sexual events

^a Study A2181002 had a planned analysis at 3 years.

^b Studies A2181014/A2181016 were terminated early due to slow enrollment and to focus recruitment efforts on studies with lower doses of lasofoxifene.