FABLYN®
(lasofoxifene tartrate)
0.5 mg Tablets

Reproductive Health Drugs
Advisory Committee Meeting

September 8, 2008
Rockville, MD

Pfizer, Inc.

FABLYN Tablets

Proposed Indication

- Treatment of osteoporosis in postmenopausal women at increased risk of fracture

Proposed Dose

- 0.5 mg/day

Agenda

Dr. Steven Cummings Director, SF Coordinating Center Professor, Epidemiology & Medicine (emeritus), UCSF	Treatment of Osteoporosis: Unmet Medical Need
Dr. David Thompson Development Team Leader	Lasofoxifene Program Overview and Efficacy
Dr. Róisín Armstrong Clinical Lead	Lasofoxifene Safety
Dr. Claudia Turner Safety & Risk Management	Lasofoxifene Risk Management
Dr. Steven R. Goldstein Professor of Obstetrics and and Gynecology, NYU	Lasofoxifene Benefit-Risk

Consultants Available to the Committee

- **Steven R. Cummings, MD, FACP**
  Director, SF Coordinating Center
  Professor of Epidemiology &
  Biostatistics and Medicine
  University of California, San Francisco
- **Steven R. Goldstein, MD**
  Professor of Obstetrics and
  Gynecology
  New York University Medical School
- **Charles H. Hennekens, MD, DrPH**
  Sir Richard Doll Professor
  Florida Atlantic University
  Boca Raton, FL
- **Patrick Neven, MD, PhD**
  Professor of Gynecological Oncology
  University Hospitals Leuven, Belgium
- **Robert J. Kurman, MD**
  Professor, Departments of Gynecology,
  Obstetrics, and Pathology
  Johns Hopkins School of Medicine
  Baltimore, MD
- **Susan R. Johnson, MD, MS**
  Professor, Division of Obstetrics
  and Gynecology
  University of Iowa Medical Center
- **Gary G. Koch, PhD**
  Professor of Biostatistics
  University of North Carolina at
  Chapel Hill
- **Thomas Fuerst, PhD**
  Scientific Director, Osteoporosis
  SYNARC, San Francisco, CA

Treatment of Osteoporosis Unmet Medical Need

Steven R. Cummings, MD

Director, SF Coordinating Center

Professor of Medicine and Epidemiology, UC San Francisco (emeritus)

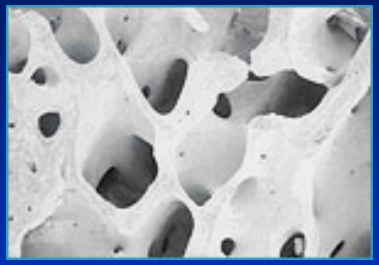
Chair, PEARL Scientific Advisory Committee

Outline

- Definition, prevalence and consequences of osteoporosis
- Risk and consequences of common postmenopausal diseases
- Efficacy and safety of current treatments for osteoporosis

Osteoporosis

A disease characterized by low bone mass and structural deterioration of bone leading to bone fragility and an increased risk of fractures



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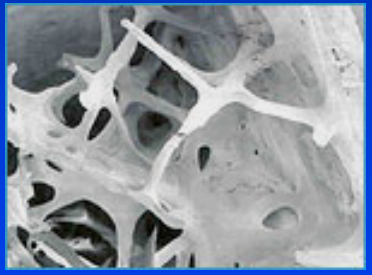


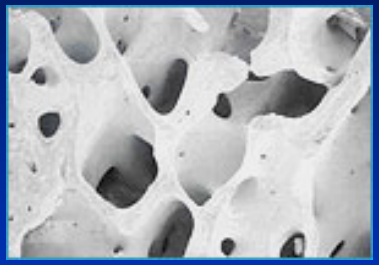
Osteoporosis

From the National Osteoporosis Foundation

Osteoporosis

- Diagnosis of osteoporosis
  - Bone mineral density 'T-score' ≤-2.5
  - Vertebral fracture

- 10 million U.S. women have osteoporosis



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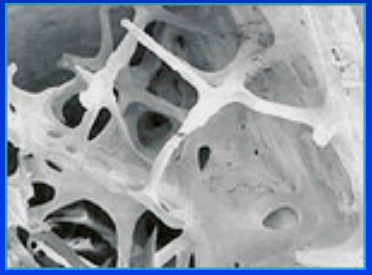


Osteoporosis

From the National Osteoporosis Foundation

Incidence of Fractures in the US

- A 50 year old white woman has a 50% risk of suffering a fracture in her lifetime
- In 2005, 2 million fractures and $19 billion per year were attributed to osteoporosis
  - 500,000 vertebral fractures
  - 1,500,000 non vertebral fractures
- By 2025, 3 million fractures and $25 billion per year

From the National Osteoporosis Foundation

Fractures impair quality of life

Clinical vertebral fractures

- Short-term
  - 3 weeks of bed rest[1]
  - 6 months of limited activity[1]
- Long-term (average 7 years post-fracture)
  - difficulty bending, lifting, dressing, or shopping[2]

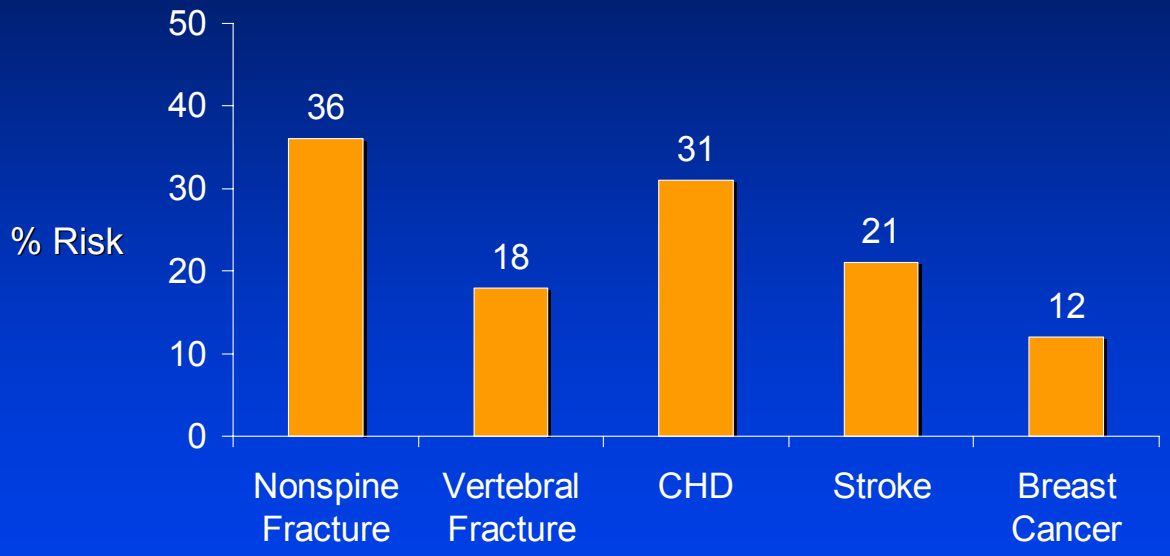
Nonvertebral fractures

- Short-term
  - 2 to 6 months of limited activity[1]
- Long-term (average 7 years post-fracture)
  - difficulty dressing, shopping and doing housework[2]

1. Fink et al. Osteoporos Int 2003;14:69-76
2. Greendale et al. J Am Geriatr Soc 1995;43:955-961

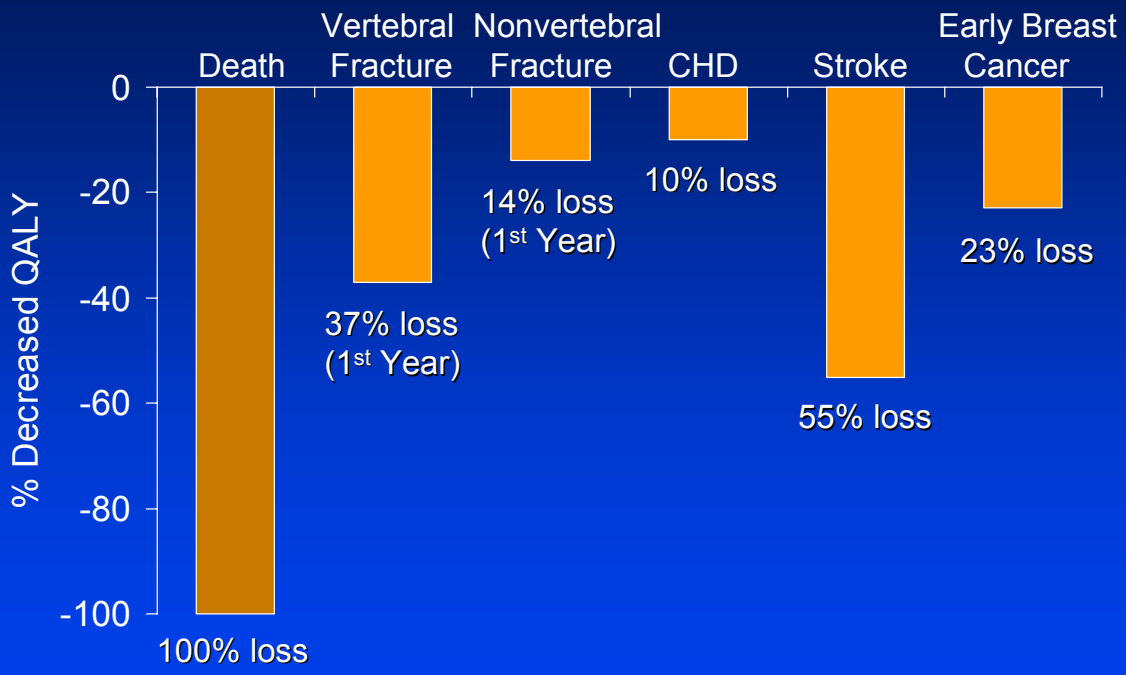
Other important diseases in postmenopausal women

Lifetime Risks of Disease Events in White Postmenopausal Women



Cummings, Arch Intern Med 1989;149:2445-2448
SEER Stat Fact Sheets 2008
Lloyd-Jones, Lancet 1999;353:89-92
Nguyen, JBMR 2007;22:781-788
Seshadri, Lancet Neurol 2007;6:1106-1114

Postmenopausal Diseases Impair Quality of Life[1]



Kanis JA et al. Osteoporos Int 2004; 15:20-26
Oostenbrink JB et al. J Vasc Surg 2001;34:254-62
Kanis JA et al. Osteoporos Int 2005; 16: 15-25
Thompson D et al. Value in Health 2007; 10: 367-76

[1] Based on Quality Adjusted Life Year (QALY) values assessed by EQ5D

The Ideal Treatment for Postmenopausal Women Would:

- Decrease vertebral fractures
- Decrease nonvertebral fractures
- Decrease coronary heart disease
- Decrease stroke
- Decrease breast cancer
- Decrease vulvar and vaginal atrophy (VVA)
- Decrease hot flushes
- Not increase endometrial cancer
- Not increase venous thromboembolism (VTE)

Treatments for osteoporosis

Bisphosphonates: Efficacy

- Decrease in vertebral fractures 50 to 70%
- Decrease in nonvertebral fractures 20 to 35%

Wells GA 2008 Cochrane Database of Systematic Reviews, Issue 1

Bisphosphonates: Adverse Effects

- Gastrointestinal symptoms (alendronate)
- Atrial fibrillation? (zoledronate, alendronate)
- Acute phase reactions (zoledronate)
- Rarely, osteonecrosis of the jaw (ONJ)
- Rarely, femoral shaft fractures?*

Bisphosphonate use has declined ~20%

*Case series reported with long term alendronate

Estrogen Therapy: Efficacy

- Decrease in vertebral fractures 35-40%
- Decrease in nonvertebral fractures 25-35%

Cauley JA et al. JAMA 2003; 290:1729-1738
Jackson RD et al. JBMR 2006; 21: 817-828

Hormone Therapy: Adverse Effects

- Increase in breast cancer*
- Increase in CHD*
- Increase in stroke
- Increase in VTE*
- Increase in dementia (after age 65)

*No significant increase for estrogen therapy alone

Women's Health Initiative Steering Committee JAMA 2004; 291: 1701-1712
Shumaker S et al. JAMA 2004; 291:2947-2958

Raloxifene: Efficacy

- Decrease in vertebral fracture ~35-40%
- No decrease in nonvertebral fracture
- Decrease in invasive breast cancer ~50-70%
- No effect on CHD or stroke

Ettinger, JAMA 1999;282: 637-645
Cummings, JAMA 1999; 281:2189-2197
Barrett-Connor, NEJM 2006; 355:125-137

Raloxifene: Adverse Effects

- Increase in VTE, ~2-3 fold
- No increase in vaginal bleeding
- Increase in endometrial polyps, ~2-fold
- Increase in endometrial biopsies, ~2-fold

Ettinger, JAMA 1999;282: 637-645
Martino, Cur Med Res Opin 2005; 21: 1441-1452

Summary of Current Treatments for Osteoporosis

	BPs	Raloxifene	Hormone therapy
Vertebral fracture	↓	↓	↓
Nonvertebral fracture	↓	0	↓
Breast cancer	0	↓	↑
CHD	0	0	↑
Stroke	0	0	↑

The Ideal Treatment for Postmenopausal Women Would:

- Decrease vertebral fractures
- Decrease nonvertebral fractures
- Decrease coronary heart disease
- Decrease stroke
- Decrease breast cancer
- Decrease VVA
- Decrease hot flushes
- Not increase endometrial cancer
- Not increase venous thromboembolism

The Ideal Treatment for Postmenopausal Women Would:

- Decrease vertebral fractures
- Decrease nonvertebral fractures
- Decrease coronary heart disease
- Decrease stroke
- Decrease breast cancer
- Decrease VVA
- Decrease hot flushes
- Not increase endometrial cancer
- Not increase venous thromboembolism

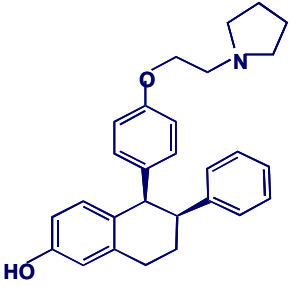
No current treatment meets these needs

Lasofoxifene Program Overview and Efficacy

Dr. David Thompson
Development Team Leader
Pfizer, Inc.

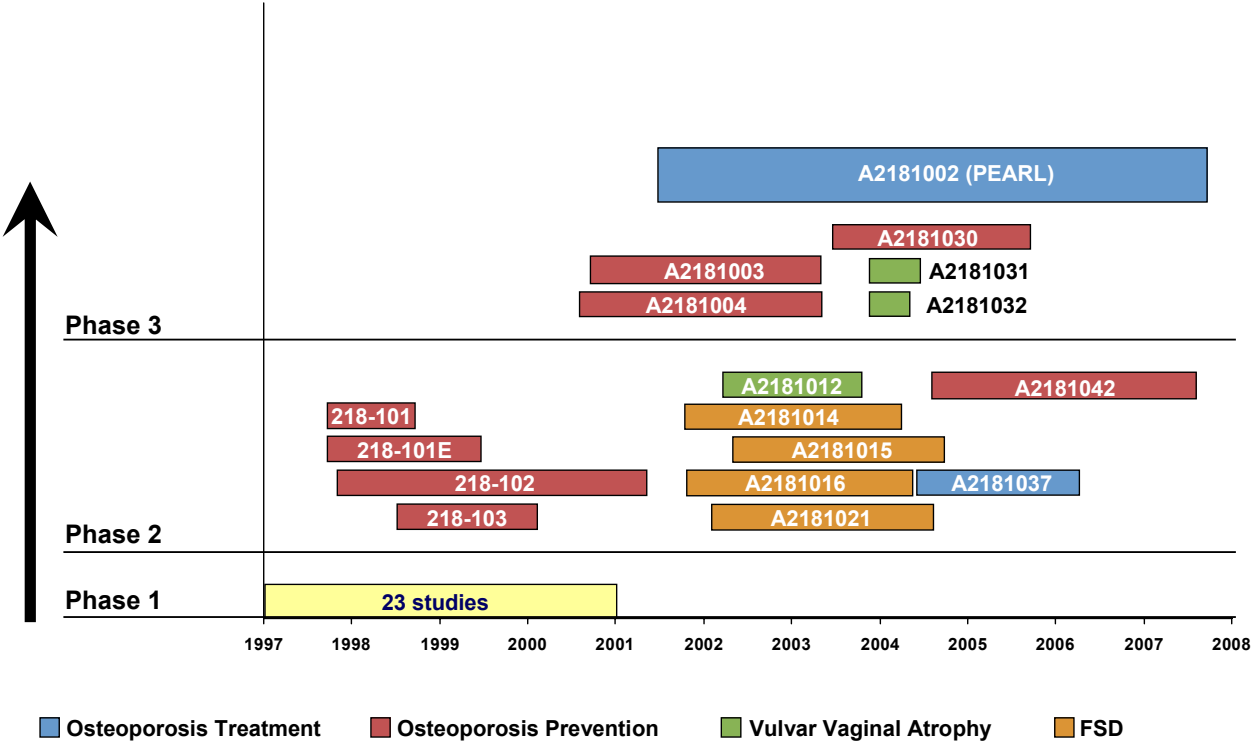
Lasofoxifene

Selective Estrogen Receptor Modulator (SERM)

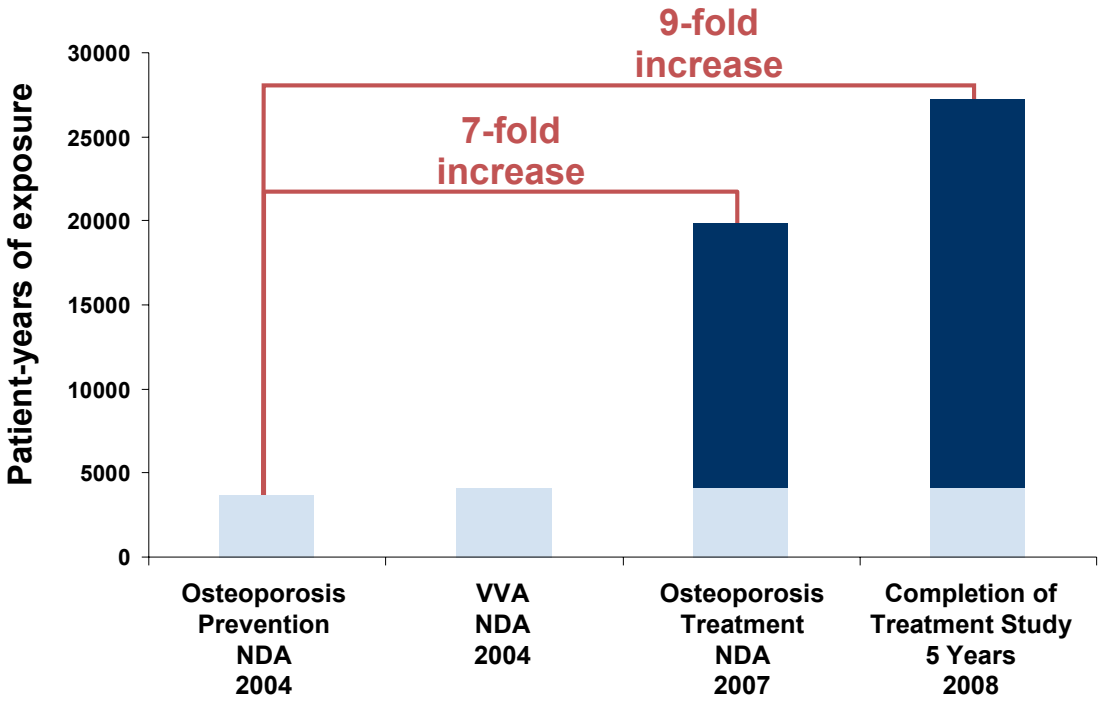


- High affinity ER receptor binding
- Potently initiates ER-mediated gene transcription
- Demonstrated ER-mediated tissue selectivity
- Efficacious in animal models of osteoporosis

Lasofoxifene Clinical Development Program
15,000 Patients in 40 Clinical Trials



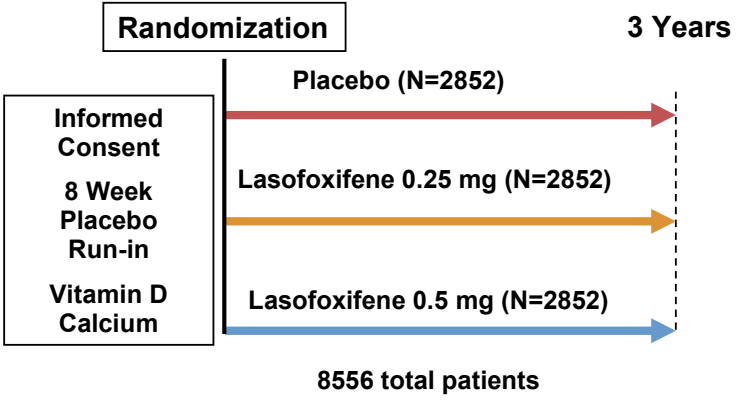
Patient-Years of Lasofoxifene Exposure in the Clinical Development Program



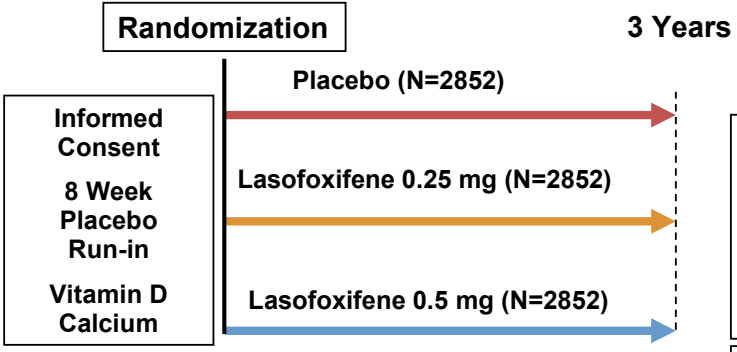
Treatment of Osteoporosis Trial

- **PEARL (Postmenopausal Evaluation And Risk Reduction with Lasofoxifene)**
- **Prospective, double-blind, randomized, placebo-controlled, multi-national study**
- **Intent-to-Treat Design and Analysis**
  - Off Drug In Study (ODIS)
- **Eligibility**
  - Women 60-80 years, at least 5 yrs postmenopausal
  - BMD of femoral neck or lumbar spine (LS) T-score ≤ -2.5 and T-score ≥ -4.5 below mean for young adults
  - < 4 vertebral fractures at baseline

PEARL Study Design – May 2001



PEARL Study Design – May 2001



Primary Endpoint

Vertebral (radiographic) fractures

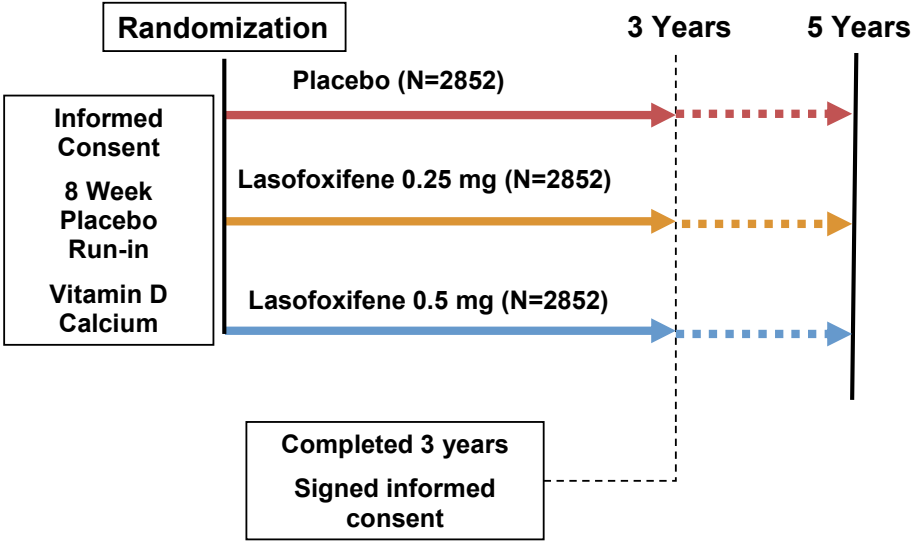
Key Secondary Endpoints

Multiple vertebral fractures
Clinical vertebral fractures

Other Secondary Endpoints

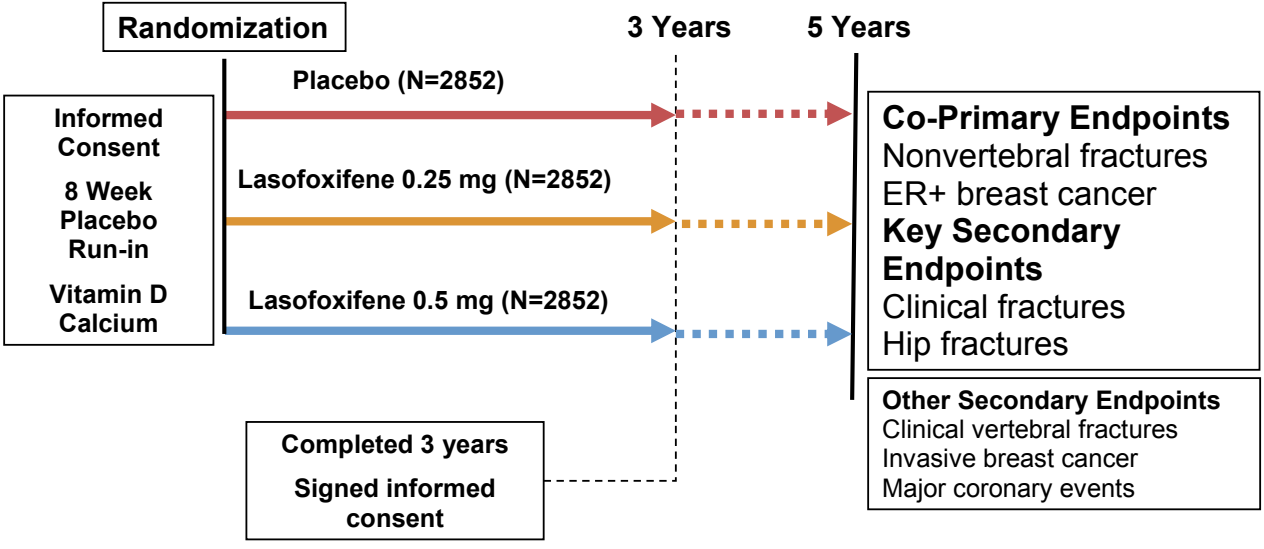
Clinical fractures
Nonvertebral fractures
Hip fractures
BMD
Bone markers
ER+ breast cancer
Major coronary events
Lipids
Vaginal pH and maturation index

PEARL Study Extension – April 2004



PEARL Study Extension – April 2004

To obtain long-term efficacy and safety data



PEARL: External Endpoint Adjudication and Central Reading of X-rays and Biopsies

- **Endpoint adjudication committees (blinded):**
  - Breast cancer
  - Cardiovascular
  - Gynecologic
- **Central reading (blinded):**
  - X-rays of all fractures, mammographic breast density (substudy), endometrial thickness (TVU-I substudy) (Synarc)
  - Endometrial histology, including polyps (TVU-P, TVU-I) (Expert GYN Pathology Panel)

PEARL: Baseline Characteristics

	Placebo N=2852	Lasofoxifene 0.25 mg N=2852	Lasofoxifene 0.5 mg N=2852
Age – years Mean (SD)	67.5 (5.2)	67.5 (5.2)	67.3 (5.2)
Years post menopause Mean (SD)	19.5 (7.2)	19.5 (7.2)	19.4 (7.1)
Body mass index (m/kg^2) Mean (SD)	25.4 (3.8)	25.2 (3.8)	25.4 (3.7)
LS-BMD T-score Mean (SD)	-3.0 (0.7)	-3.0 (0.7)	-3.0 (0.7)
Femoral neck BMD T-score Mean (SD)	-2.2 (0.7)	-2.3 (0.7)	-2.2 (0.7)
Prevalent fracture (%)	803 (28)	807 (28)	808 (28)
Gail score (≥1.66%)	45.5%	44.8%	44.8%

PEARL: Results

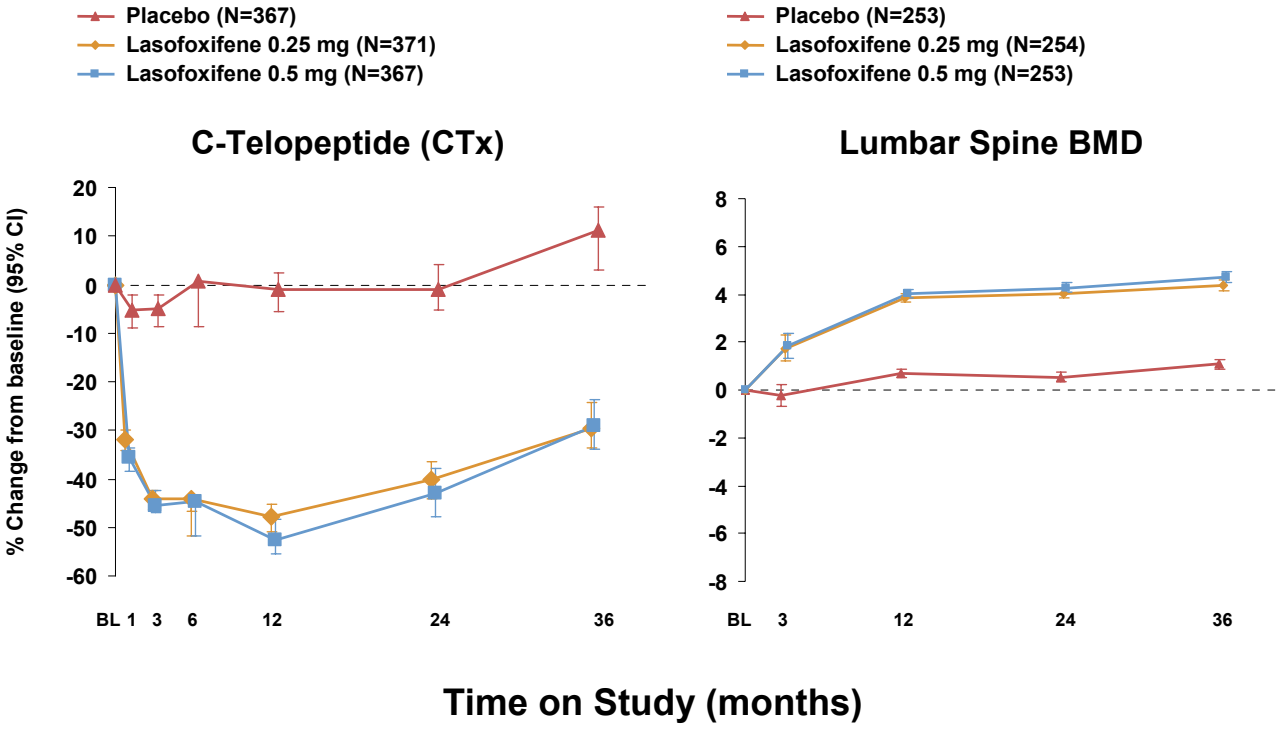
Efficacy – 3 Years

- **Bone**
  - BMD
  - Biomarkers
  - Fractures (except for major nonvertebral – 5 years)
- **Vaginal Atrophy**
  - Vaginal pH
  - Maturation index

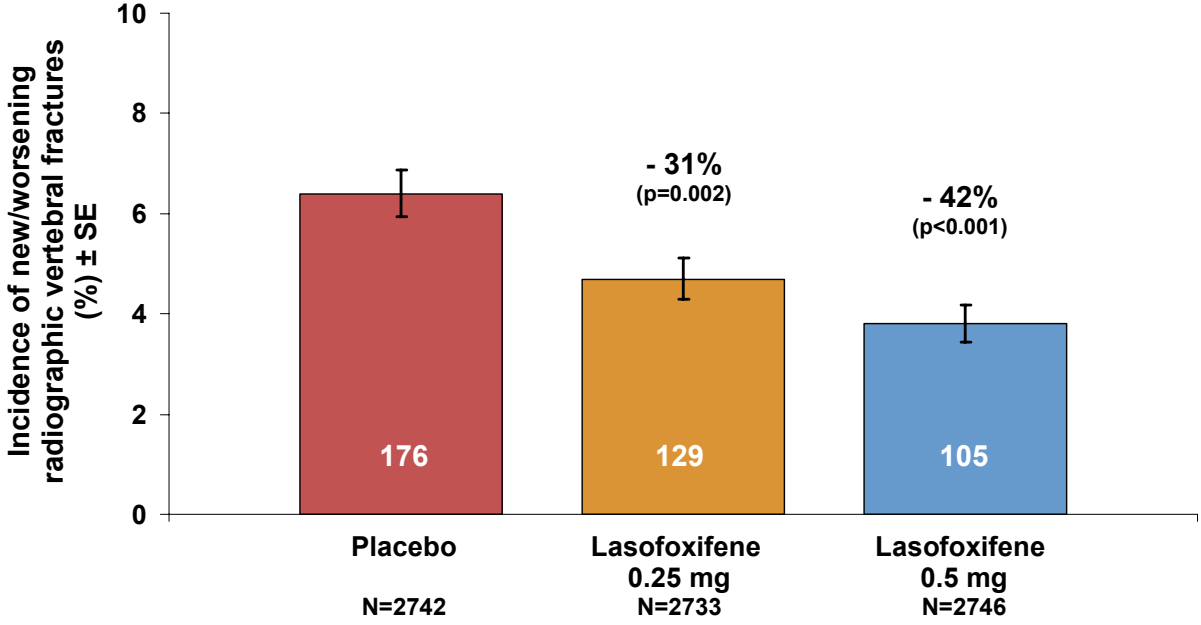
Safety – 5 Years

Seeking approval for the treatment of osteoporosis in postmenopausal women with lasofoxifene 0.5 mg

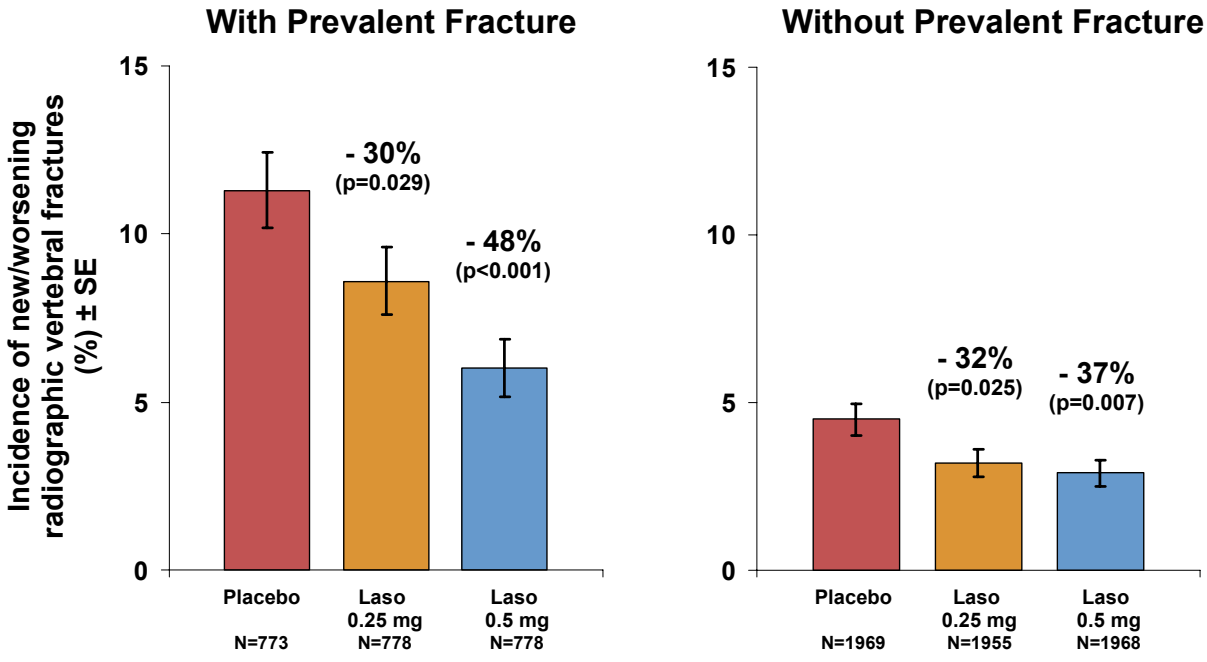
Changes in Bone Turnover and Bone Mass through 3 Years in PEARL



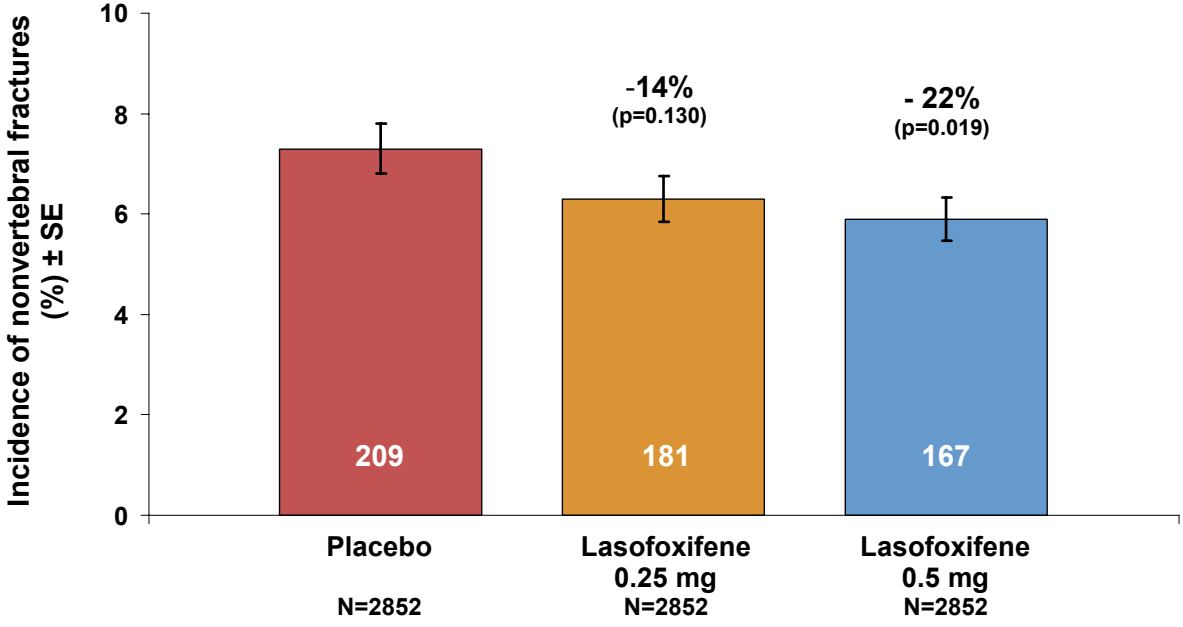
Radiographic Vertebral Fractures through 3 Years



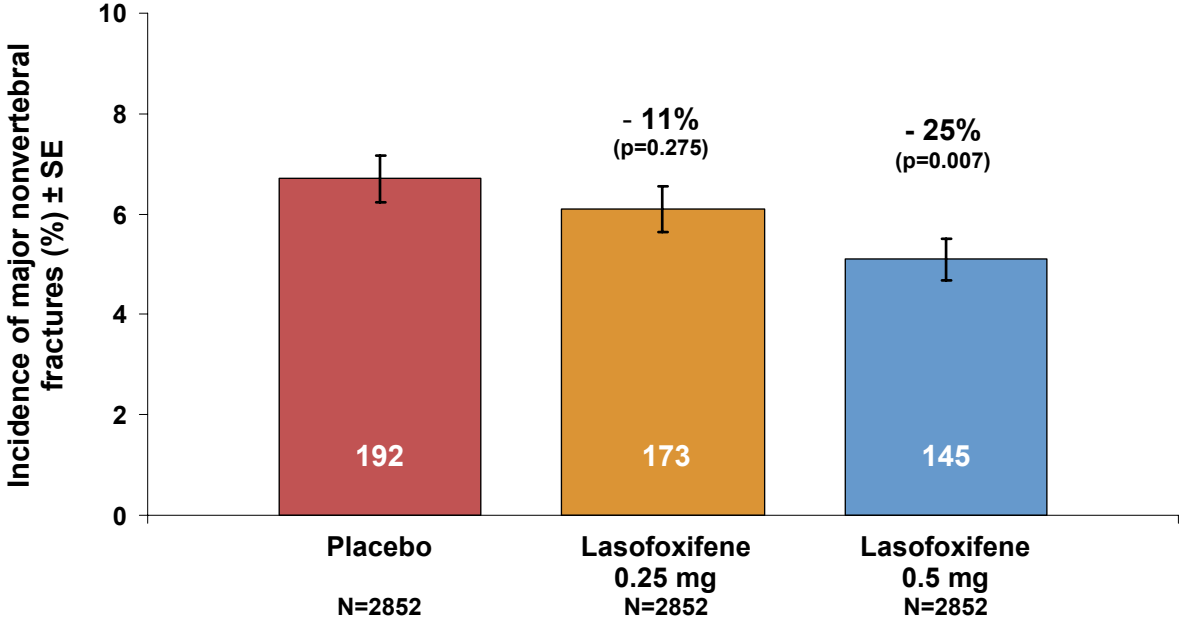
Radiographic Vertebral Fractures in Subgroups through 3 Years



Nonvertebral Fractures through 3 Years

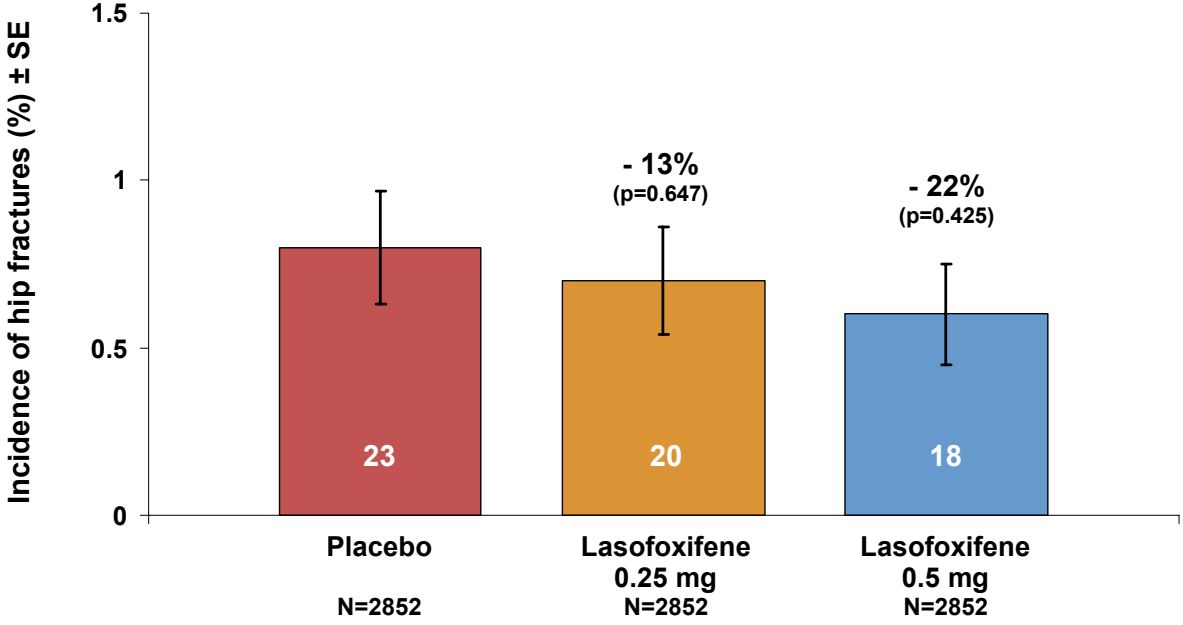


Major Nonvertebral Fractures through 5 Years

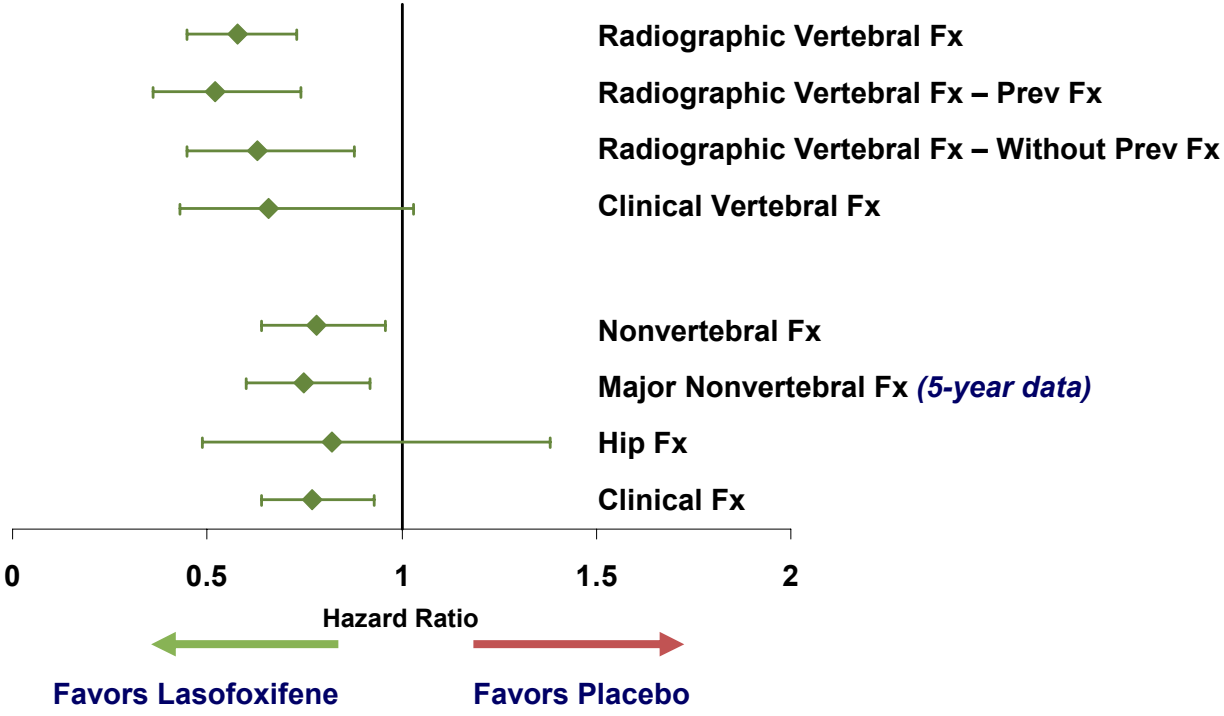


Major nonvertebral fractures include Hip, Pelvis, Femur, Lower Leg, Humerus, Forearm, Wrist, and Rib

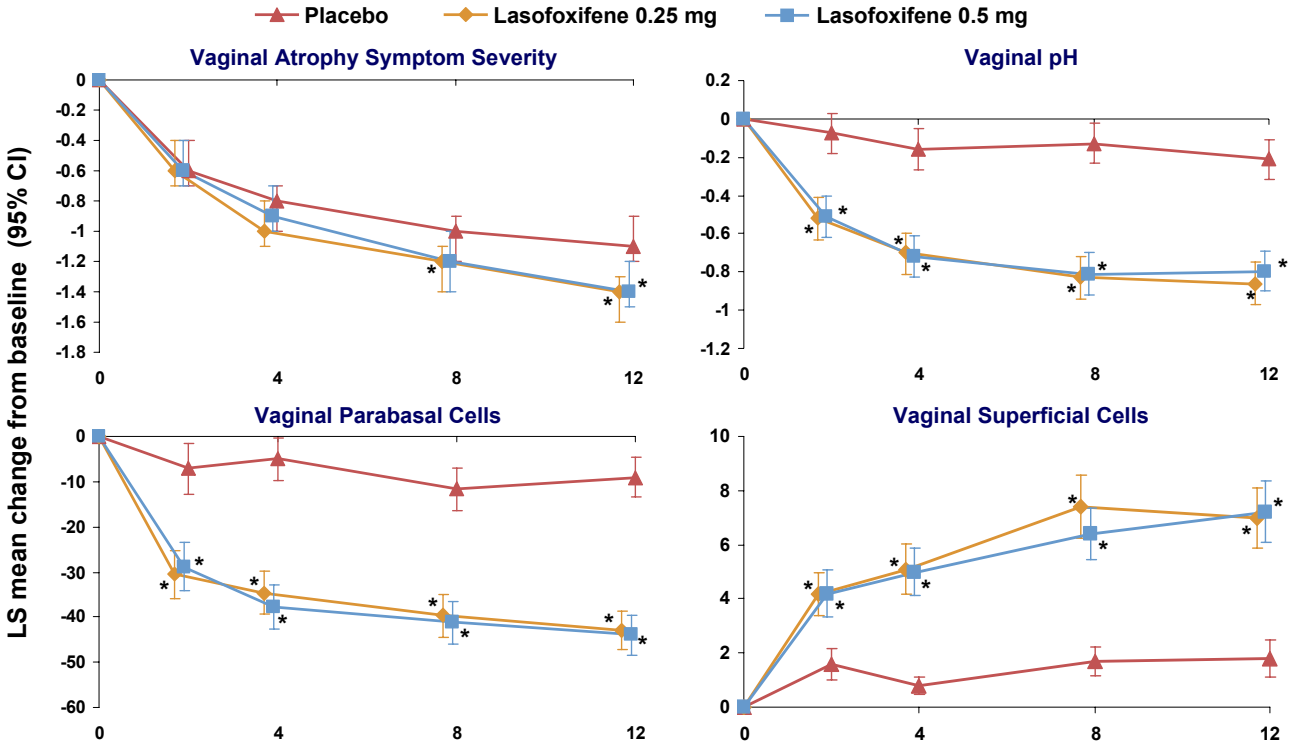
Hip Fractures through 3 Years



Summary – Effects of Lasofoxifene 0.5 mg on Bone at 3 Years

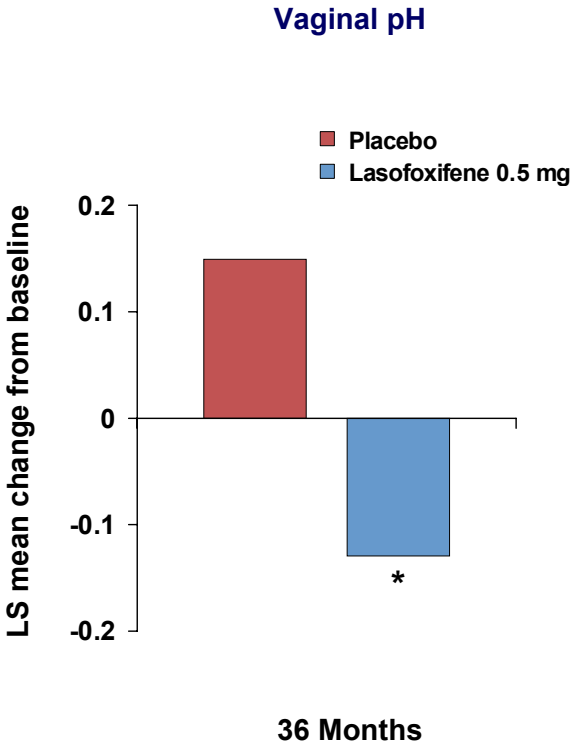


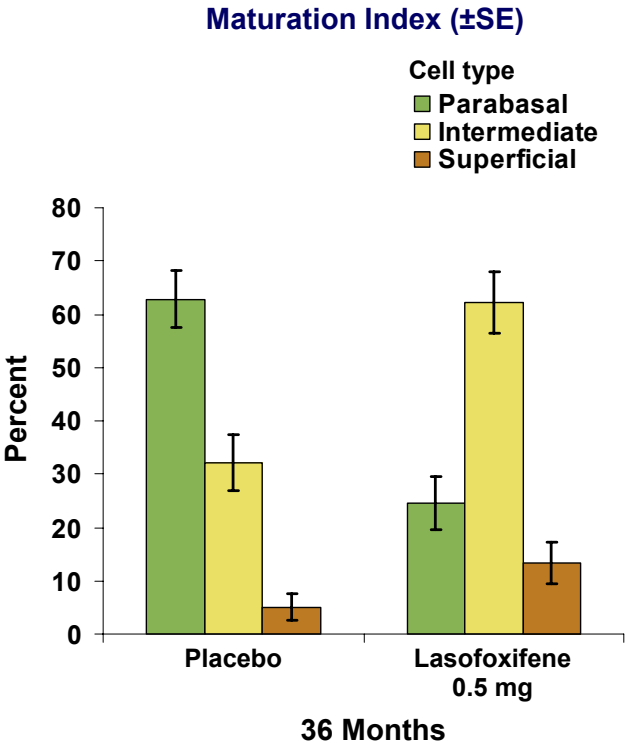
Vaginal Effects of Lasofoxifene in PM Women with Symptoms of VVA (A2181031)



* p-value significant vs. placebo

Vaginal Effects in Postmenopausal Women with Osteoporosis (PEARL)





* p-value significant vs. placebo

Vaginal Benefits of Lasofoxifene

VVA Efficacy Established in Phase 3 Trials

- Induces differentiation leading to a shift in the maturation index
- Superficial and intermediate cells contain glycogen
- Glycogen acts as substrate for lactobacillus
- Production of lactic acid
- Decrease in vaginal pH
- Leading to self-reported improvement in vaginal health

Efficacy of Lasofoxifene 0.5 mg – Conclusions

- Significantly reduced vertebral fractures
- Significantly reduced nonvertebral fractures
- Significantly reduced signs of VVA
- Lasofoxifene is a new therapeutic option for the treatment of osteoporosis in postmenopausal women

Lasofoxifene Safety

Dr. Róisín A. Armstrong
Clinical Lead
Pfizer, Inc.

Overview

- **General Safety**
  - Adverse events
  - Treatment discontinuations
  - Serious adverse events
  - Mortality
  - Events of special interest for SERMs
- **Gynecological Safety**

Adverse Events in the Lasofoxifene Phase 2/3 Clinical Program

	Number (%) of Patients			
		Lasofoxifene		
	Placebo	0.25 mg	0.5 mg	Pooled*
	N=4701	N=4547	N=4308	N=10,257
Muscle spasm	356 (7.6)	676 (14.9)	673 (15.6)	1498 (14.6)
Hot flush	309 (6.6)	690 (15.2)	631 (14.6)	1615 (15.7)
Vaginal discharge	134 (2.9)	296 (6.5)	265 (6.2)	673 (6.6)

* Includes other doses in addition to lasofoxifene 0.25 mg and lasofoxifene 0.5 mg

Treatment Discontinuations in the Lasofoxifene Phase 2/3 Clinical Program

	Number (%) of Patients			
		Lasofoxifene		
	Placebo N=4701	0.25 mg N=4547	0.5 mg N=4308	Pooled* N=10,257
Any Reason	1237 (26.3)	1251 (27.5)	1152 (26.7)	2734 (26.7)
Any adverse event	443 (9.4)	515 (11.3)	464 (10.8)	1132 (11.0)
Hot flush	35 (0.7)	79 (1.7)	74 (1.7)	190 (1.9)
Muscle spasm	17 (0.4)	32 (0.7)	40 (0.9)	77 (0.8)
DVT	6 (0.1)	30 (0.7)	18 (0.4)	51 (0.5)

* Includes other doses in addition to lasofoxifene 0.25 mg and lasofoxifene 0.5 mg

Serious Adverse Events in the Lasofoxifene Phase 2/3 Clinical Program

	Events (%)			
		Lasofoxifene		
	Placebo	0.25 mg	0.5 mg	Pooled*
	N=4701	N=4549	N=4308	N=10,257
DVT	11 (0.2)	33 (0.7)	22 (0.5)	58 (0.6)
PE	5 (0.1)	18 (0.4)	11 (0.3)	31 (0.3)
Uterine polyp	13 (0.3)	36 (0.8)	28 (0.6)	64 (0.6)
Endometrial hypertrophy†	4 (0.1)	23 (0.5)	24 (0.6)	47 (0.5)
Uterine prolapse	7 (0.1)	16 (0.4)	14 (0.3)	30 (0.3)

* Includes other doses in addition to lasofoxifene 0.25 mg and lasofoxifene 0.5 mg

† Endometrial hypertrophy events based on investigator reporting of endometrial thickness findings

Mortality through 5 Years in PEARL

Deaths = 228
N = 8556
Patient-years = 38,551

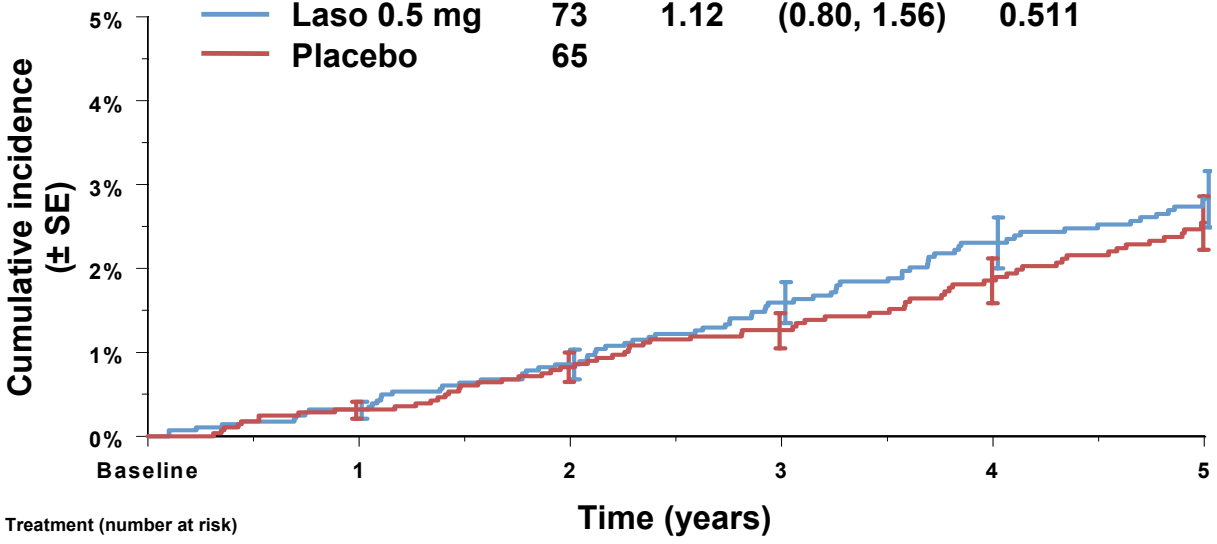
Placebo
IR 5.1/1000 P-Y
(95% CI 3.9, 6.5)

Lasofoxifene Pooled
IR 6.3/1000 P-Y
(95% CI 5.4, 7.4)

Difference
IR 1.2/1000 P-Y
(95% CI -0.4, 2.9)

Cumulative Mortality for Lasofoxifene 0.5 mg through 5 Years in PEARL

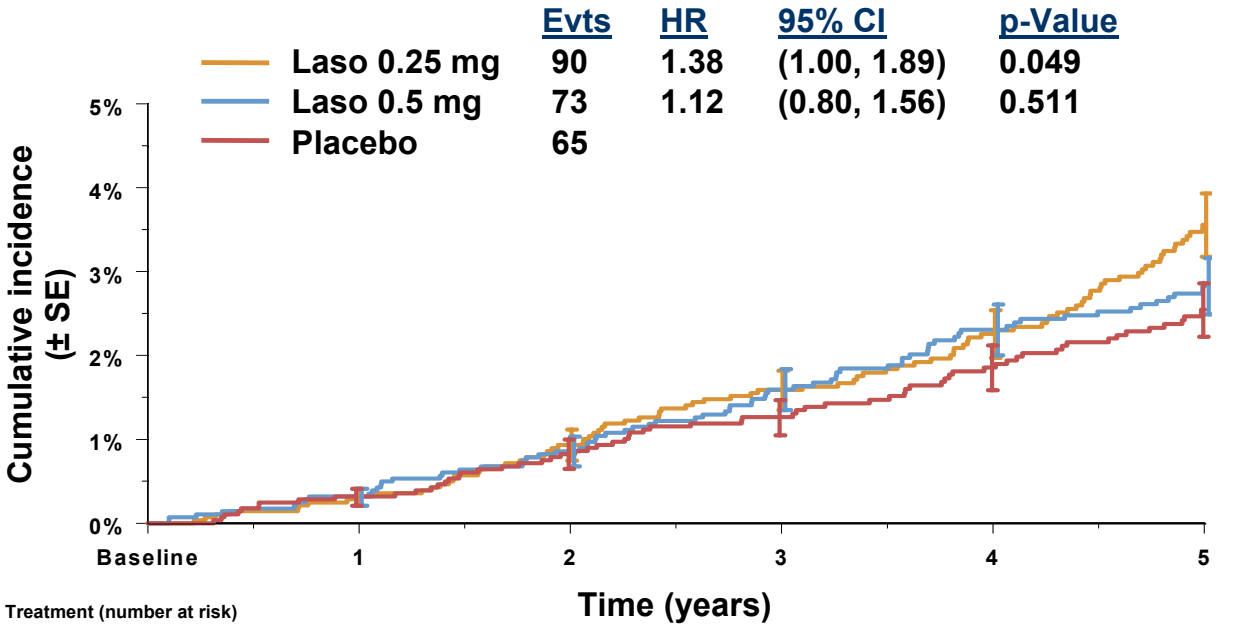
	Evts	HR	95% CI	p-Value
Laso 0.5 mg	73	1.12	(0.80, 1.56)	0.511
Placebo	65			



Treatment (number at risk)

Laso 0.5 mg	2852	2804	2739	2668	2306	2232
Placebo	2852	2799	2738	2664	2303	2227

Cumulative Mortality for Lasofoxifene 0.25 mg and 0.5 mg through 5 Years in PEARL



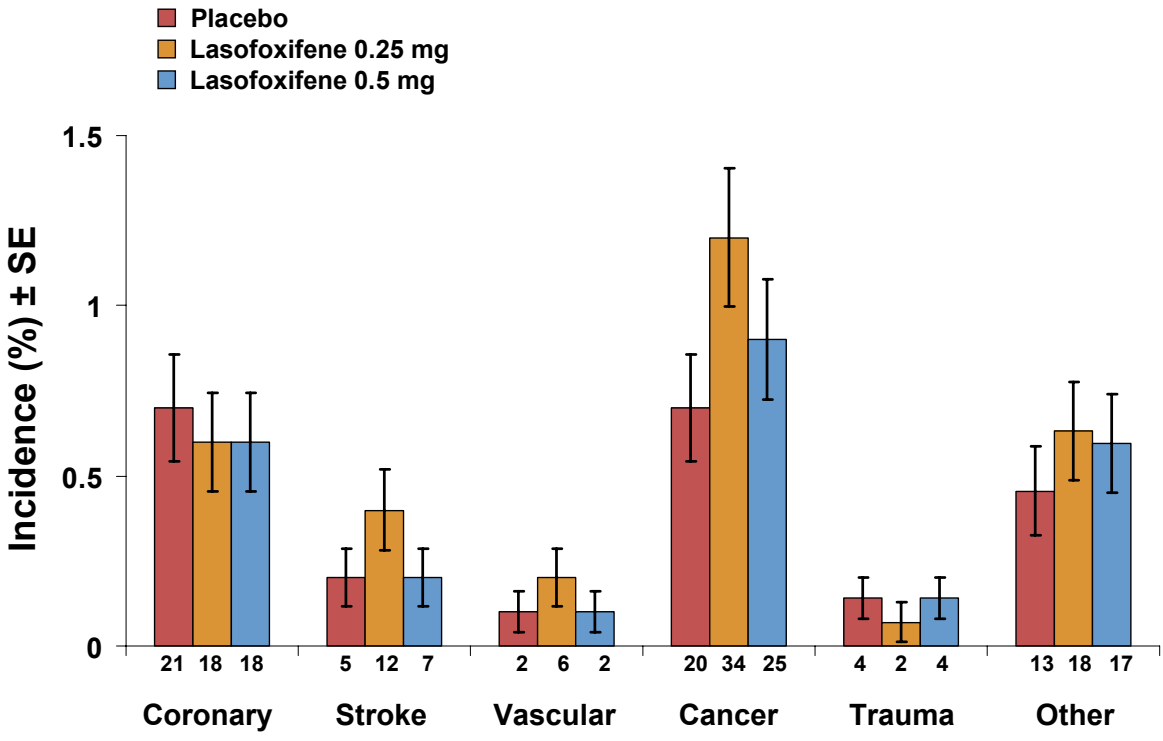
Treatment (number at risk)						
Laso 0.25 mg	2852	2794	2746	2681	2329	2227
Laso 0.5 mg	2852	2804	2739	2668	2306	2232
Placebo	2852	2799	2738	2664	2303	2227

Exploratory Analyses of Mortality in PEARL

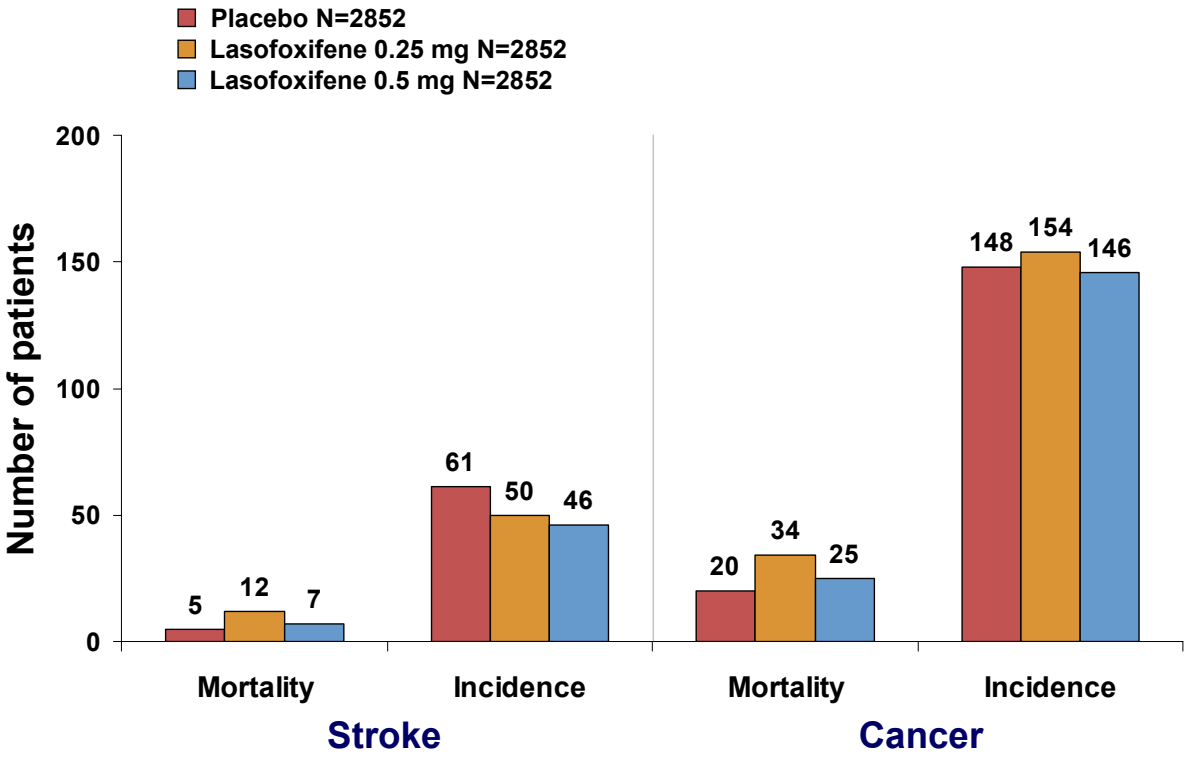
Potential explanations for apparent difference for lasofoxifene 0.25 mg compared to placebo were explored

- Person: Baseline characteristics
- Place: Geographic regions
- Time: Follow-up

Adjudicated Cause of Death through 5 Years in PEARL



Stroke and Cancer through 5 Years in PEARL



Adjudicated Cancer Deaths by Anatomical Site through 5 Years in PEARL: Lasofoxifene 0.5 mg

	Placebo N=20	Lasofoxifene 0.5 mg N=25
Bile Duct/ Gallbladder	2	2
Bladder	0	1
Brain	1	1
Colorectal[a]	2	3
Esophageal	0	0
Gastric	1	0
Leukemia / Lymphoma	2	2
Liver	0	1
Lung	2	7
Melanoma	1	1
Mesothelioma	0	1
Other[b]	5	0
Pancreatic	4	2
Renal	0	1
Thyroid	0	1
Unknown	0	2

[a] Colorectal includes colon, rectal, and bowel
[b] Other includes oral, abdominal, endometrial/ovarian

Adjudicated Cancer Deaths by Anatomical Site through 5 Years in PEARL: Lasofoxifene 0.25 mg

	Placebo N=20	Lasofoxifene 0.25 mg N=34
Bile Duct/ Gallbladder	2	1
Brain	1	4
Colorectal[a]	2	5
Esophageal	0	3
Gastric	1	4
Leukemia / Lymphoma	2	3
Leiomyosarcoma	0	1
Lung	2	4
Melanoma	1	2
Other[b]	5	0
Pancreatic	4	3
Peritoneal	0	1
Renal	0	1
Unknown	0	2

[a] Colorectal includes colon, rectal, and bowel
[b] Other includes oral, abdominal, endometrial/ovarian

Lasofoxifene Mortality in All Other 16 Phase 2/3 Trials

- **4923 patient-years**
- **Doses ranging from 17 μg to 10 mg/day**
- **9 deaths**
  - 0.025 mg
    - Other trauma (MVA)
  - 0.25 mg
    - Sudden death (CV disease and sleep apnea)
    - Other trauma (MVA)
    - Other (bronchopneumonia)
    - Other (respiratory exacerbation)
  - 0.5 mg
    - Suicide (drug overdose)
    - Sudden death (CV disease)
    - Sudden death (suspected arrhythmia)
  - 2.5 mg
    - Sudden death (drowning)

Mortality in all Phase 2/3 Trials including PEARL

Deaths = 237
N = 14,960
Patient-years = 45,396

Placebo
IR 4.4/1000 P-Y
(95% CI 3.4, 5.6)

Lasofoxifene Pooled*
IR 5.6/1000 P-Y
(95% CI 4.8, 6.5)

Difference
IR 1.2/1000 P-Y
(95% CI -0.2, 2.6)

* Doses from 17μg to 10 mg

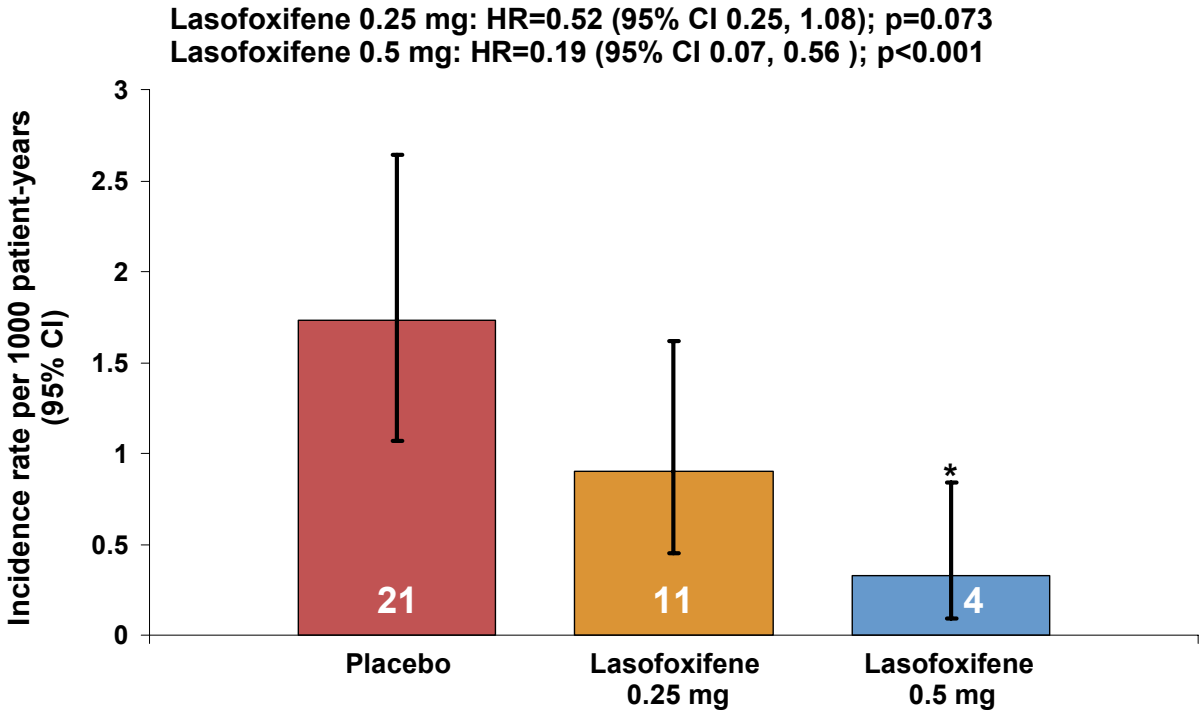
Lasofoxifene Mortality Conclusions

- **Chance likely**
  - No statistically significant increase overall, or on lasofoxifene 0.5 mg
  - 95% confidence intervals include no difference overall and on lasofoxifene 0.5 mg
- **Causality unlikely**
  - No consistent pattern of mortality
  - Increases in stroke or cancer mortality not reflected in overall incidence of events
  - No biologically plausible mechanism
  - No biologically plausible dose response relationship
- **Independently-monitored prospective long-term safety cohort study**

Events of Special Interest for SERMs

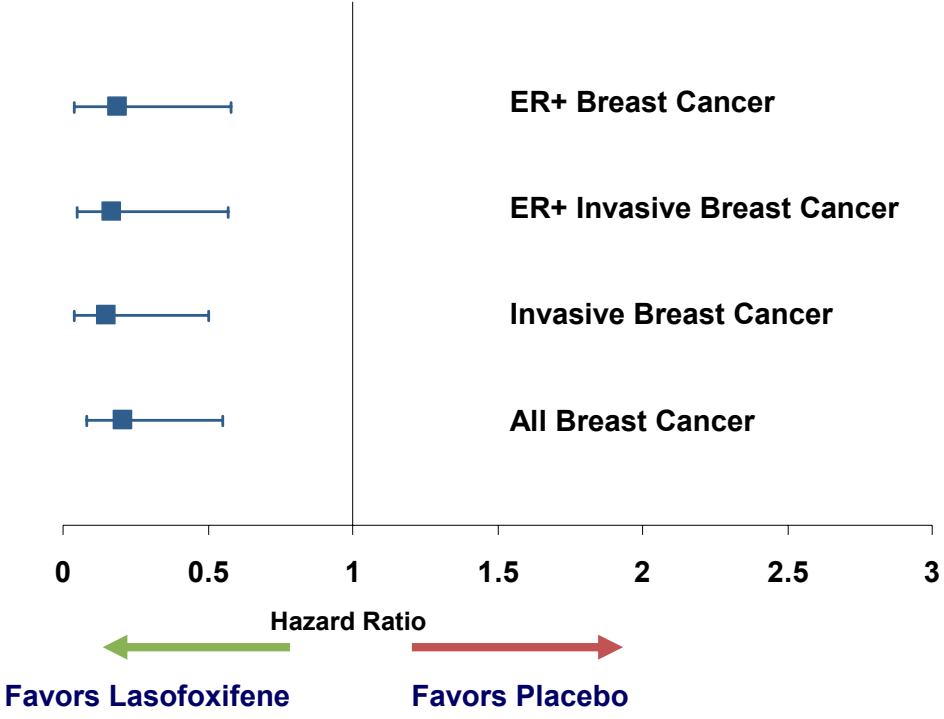
- Breast Cancer
- Venous Thromboembolic Events
- Stroke
- Markers of Cardiovascular Risk
- Coronary Events

ER+ Breast Cancer through 5 Years in PEARL

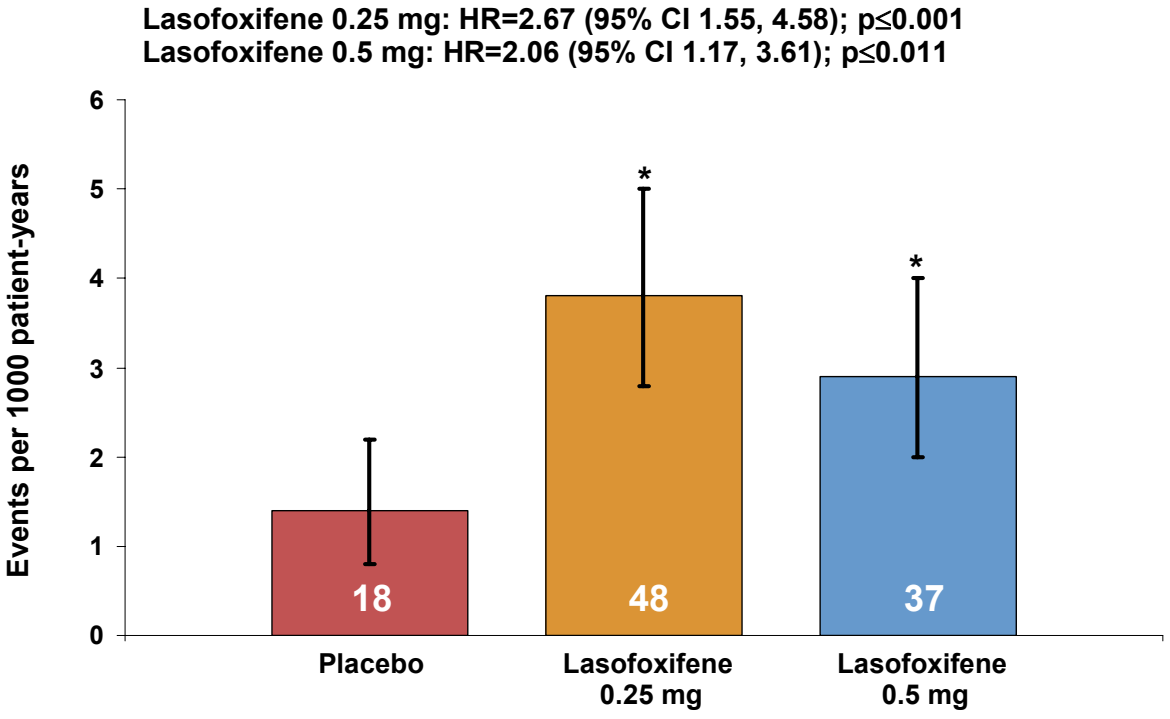


* p-value significant vs. placebo

Effects of Lasofoxifene 0.5 mg on Breast Cancer through 5 Years in PEARL

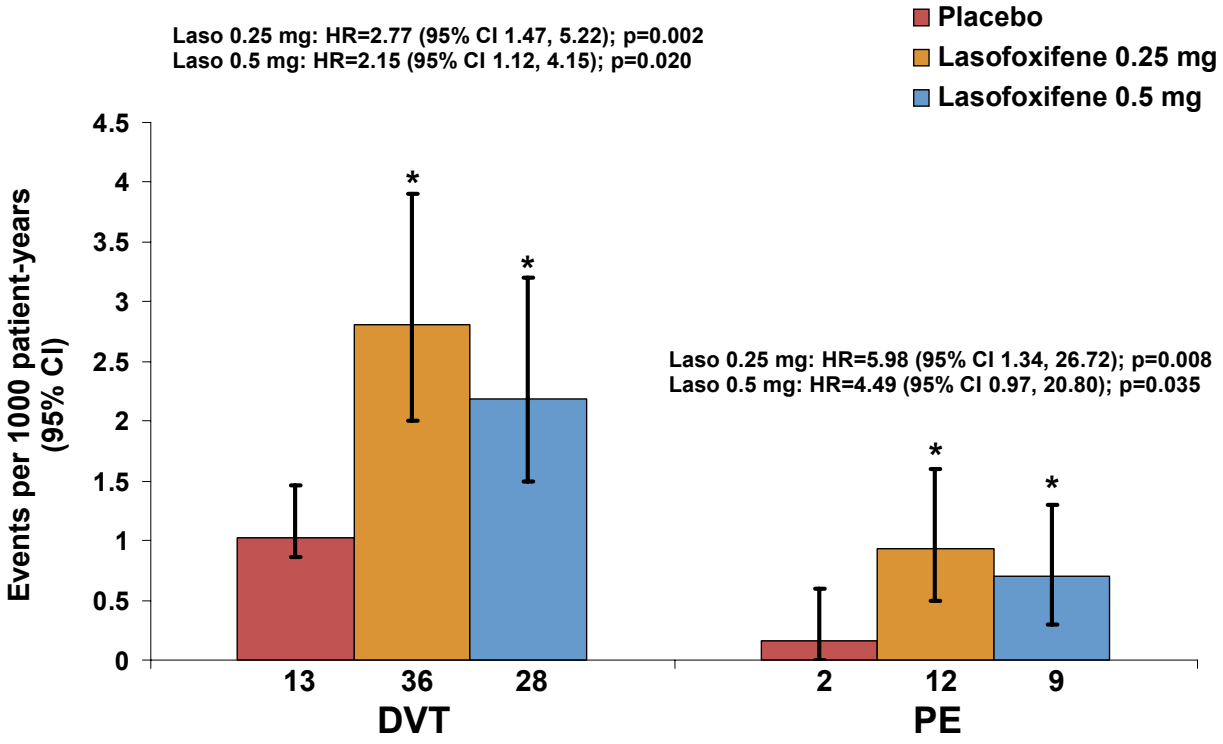


Venous Thromboembolic Events through 5 Years in PEARL



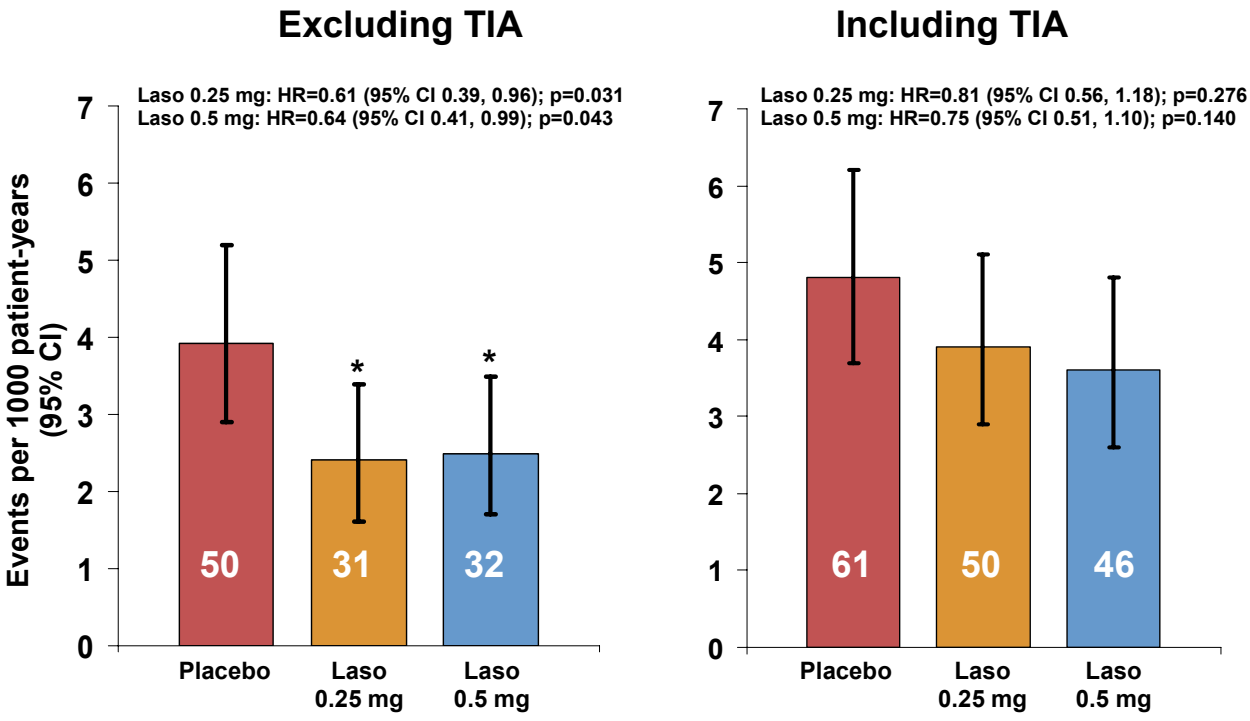
* p-value significant vs. placebo

Deep Vein Thrombosis and Pulmonary Embolism through 5 Years in PEARL



* p-value significant vs. placebo

Stroke through 5 Years in PEARL



* p-value significant vs. placebo

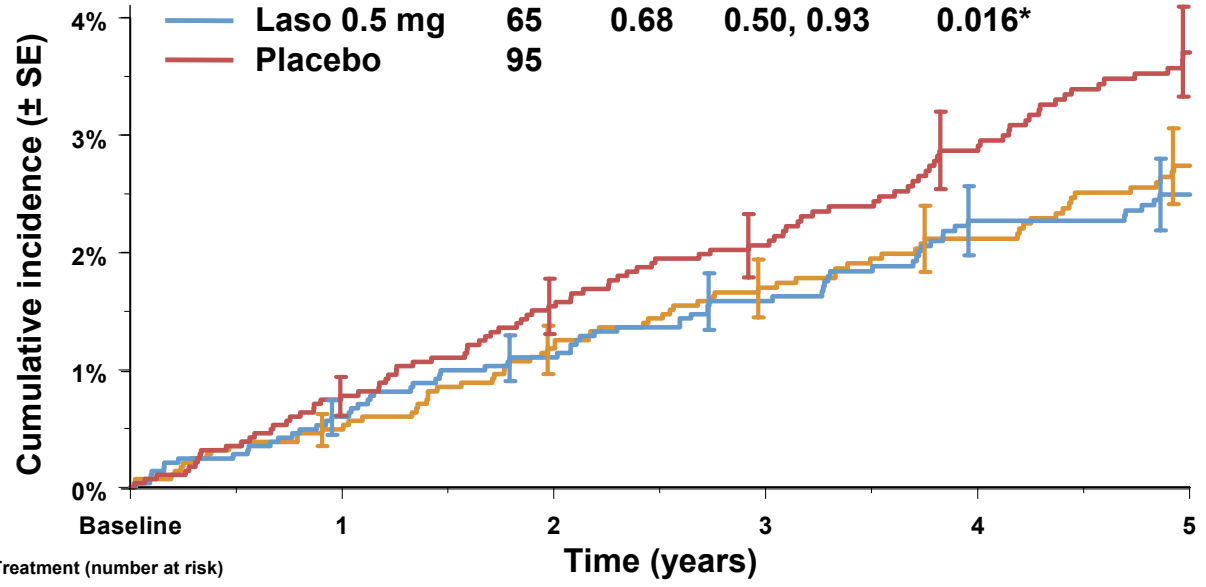
Sub Study of Markers Of Cardiovascular Risk at 3 Years in PEARL

Median % Change from Baseline	Placebo	Lasofoxifene	
		0.25 mg	0.5 mg
Patients randomized	337	341	336
Total cholesterol	-2.0	-12.4*	-12.4*
LDL cholesterol	-1.0	-17.2*	-16.8*
HDL cholesterol	1.6	1.3	2.0
Triglycerides	-5.5	2.6*	-0.6*
hs-CRP	0.0	-15.8*	-12.5*

* p-value significant vs. placebo

Cumulative Incidence of Major Coronary Events through 5 Years in PEARL

	Evts	HR	95% CI	p-Value
Laso 0.25 mg	73	0.76	0.56, 1.03	0.077
Laso 0.5 mg	65	0.68	0.50, 0.93	0.016*
Placebo	95			



Treatment (number at risk)						
Laso 0.25 mg	2852	2783	2721	2647	2298	2189
Laso 0.5 mg	2852	2793	2711	2632	2268	2193
Placebo	2852	2782	2704	2619	2252	2196

* p-value significant vs. placebo

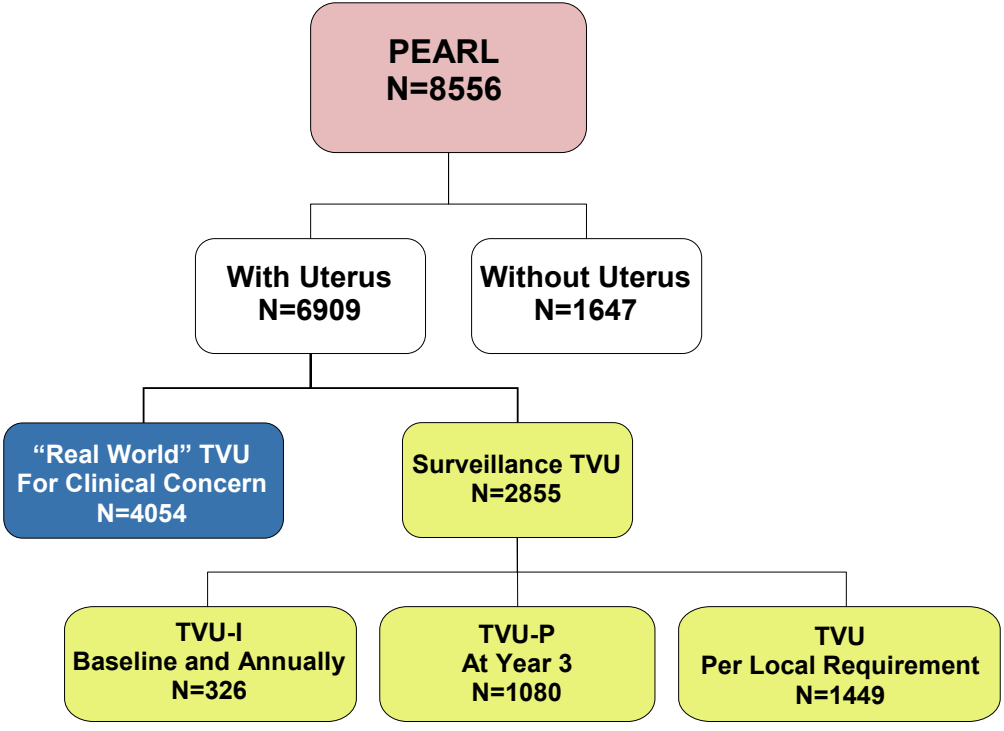
General Safety of Lasofoxifene 0.5 mg – Conclusions

- **Most common AEs:**
  - Hot flush, muscle spasms and vaginal discharge
- **Most common SAEs:**
  - VTEs and gynecological events that would contribute to increased diagnostic uterine procedures
- **No significant difference in mortality**
- **Significantly decreased risk of breast cancer**
- **Significantly decreased risk of stroke**
- **Significantly decreased risk of major coronary events**
  - Decreased markers of cardiovascular risk

Gynecological Safety

- Endometrial Surveillance
- Central Biopsy Review
- Gynecological Outcomes

Endometrial Surveillance



Central Biopsy Review

- **Central reading of endometrial biopsies**
  - TVU substudies
  - Local pathology reporting malignant/premalignant findings
- **Central pathology review process**
  - Same slide set sequentially reviewed by up to 3 experts
    - Drs Terence Colgan, Robert Kurman, Michael Hendrickson
  - Blinded to treatment, prior pathology and colleague assessments
- **Consistent with regulatory guidance**

Gynecological Outcomes

- **Endometrial cancer and hyperplasia**
- **Benign endometrial effects**
  - Sonographic findings
  - Endometrial polyps
- **Vaginal bleeding**
- **Diagnostic uterine procedures**
- **Pelvic organ prolapse**

Endometrial Cancer through 5 Years in PEARL

	Placebo	Lasofoxifene		
		0.25 mg	0.5 mg	Combined Doses
Patients at Risk	2309	2298	2302	4600
Total Years at Risk	10,325	10,283	10,337	20,620
Events (%)	3 (0.1)	2 (0.1)	2 (0.1)	4 (0.1)
Events / 1000 patient-years	0.29	0.19	0.19	0.19
Hazard Ratio vs. Placebo				0.67
95% CI				0.15, 2.97
p-value				0.592

Phase 2/3 Clinical Program: pooled HR=0.84 (95% CI 0.24, 2.86; p=0.774)

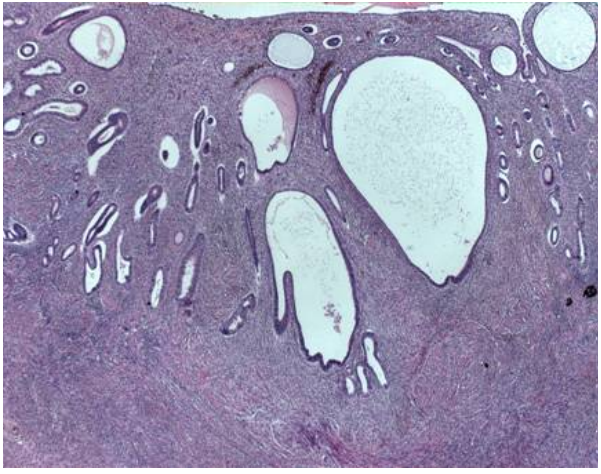
Endometrial Hyperplasia through 5 Years in PEARL

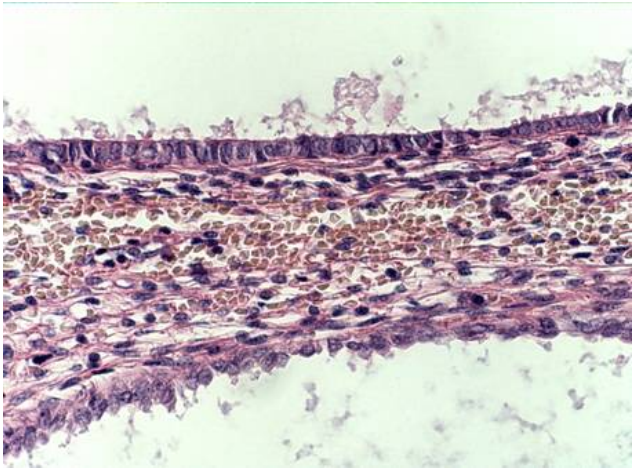
- **5 cases**
  - Two by central pathology read
  - Three by default, no tissue submitted
- **Absolute incidence rate: 0.24 events/1000 patient-years**

Endometrial Hyperplasia: Local vs. Central Pathology Reads

- **Central review was critical for accurate diagnosis**
- **>1400 endometrial biopsies in clinical program**
- **<3% (40 biopsies) with discrepant diagnoses**
  - Local reports of endometrial hyperplasia centrally determined to be benign cystic atrophy

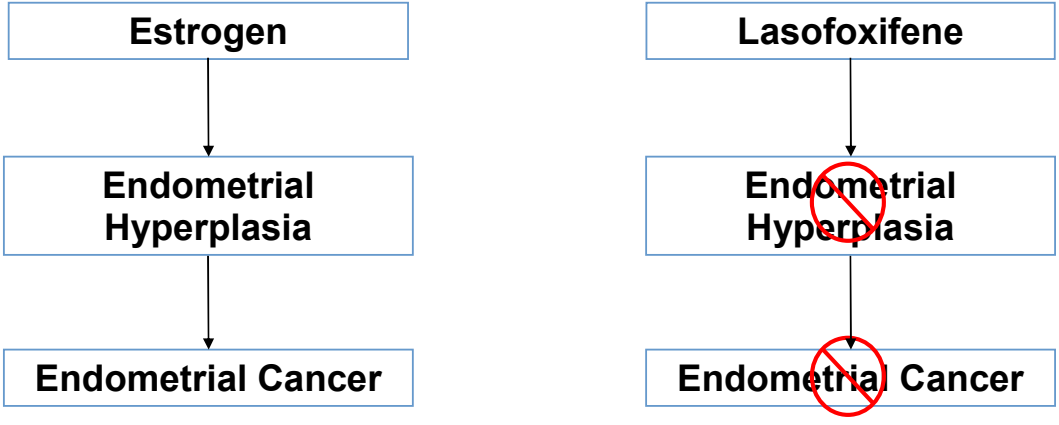
Misdiagnosis of Endometrial Hyperplasia: Lasofoxifene 0.5 mg





- Local Diagnosis: endometrial hyperplasia
- Central Diagnosis: No evidence of endometrial hyperplasia

Estrogen Versus Lasofoxifene



Endometrial Effects of Lasofoxifene

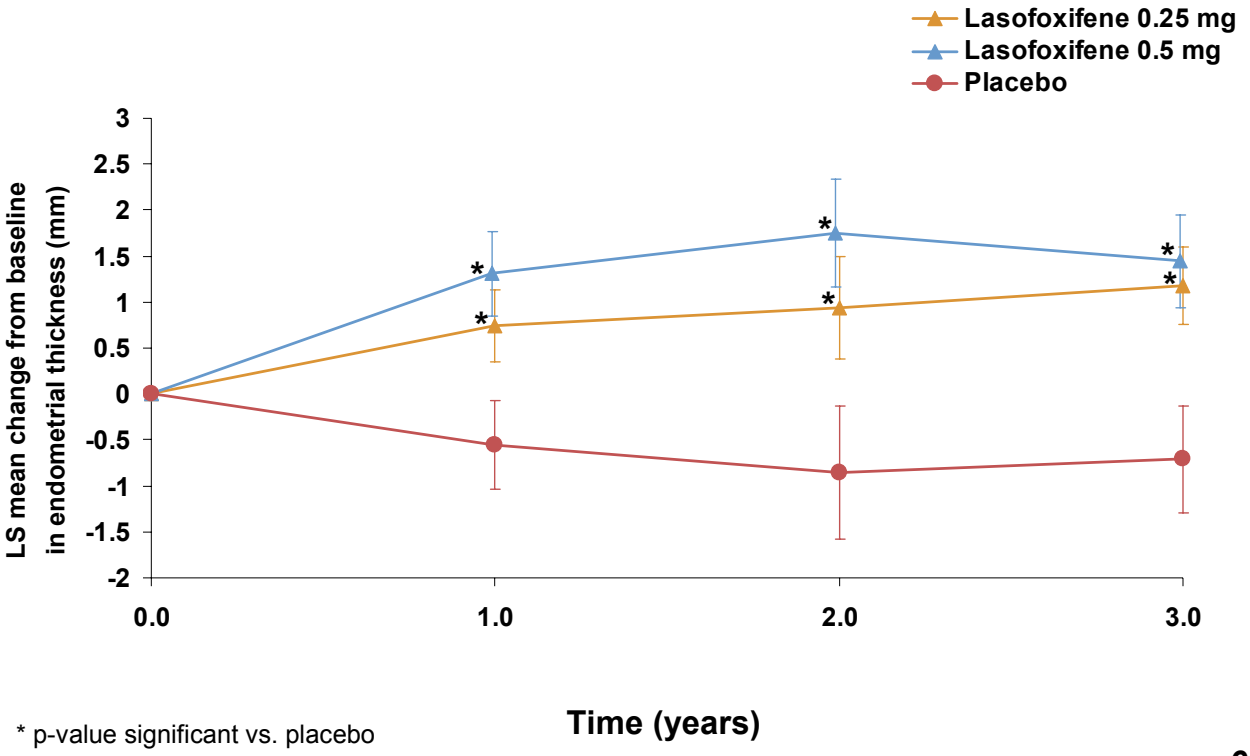
- Benign cystic atrophy
- Increased cystic echotexture
- Increased endometrial thickness

Sonographic Endometrial Cystic Echotexture at 3 Years: TVU-I Substudy

	Echotexture Number (%) of Patients		
		Lasofoxifene	
	Placebo N=108	0.25 mg N=102	0.5 mg N=98
Uniform	106 (98.1)	79 (77.5)	78 (79.6)
Cystic	2 (1.9)	23 (22.5)*	20 (20.4)*

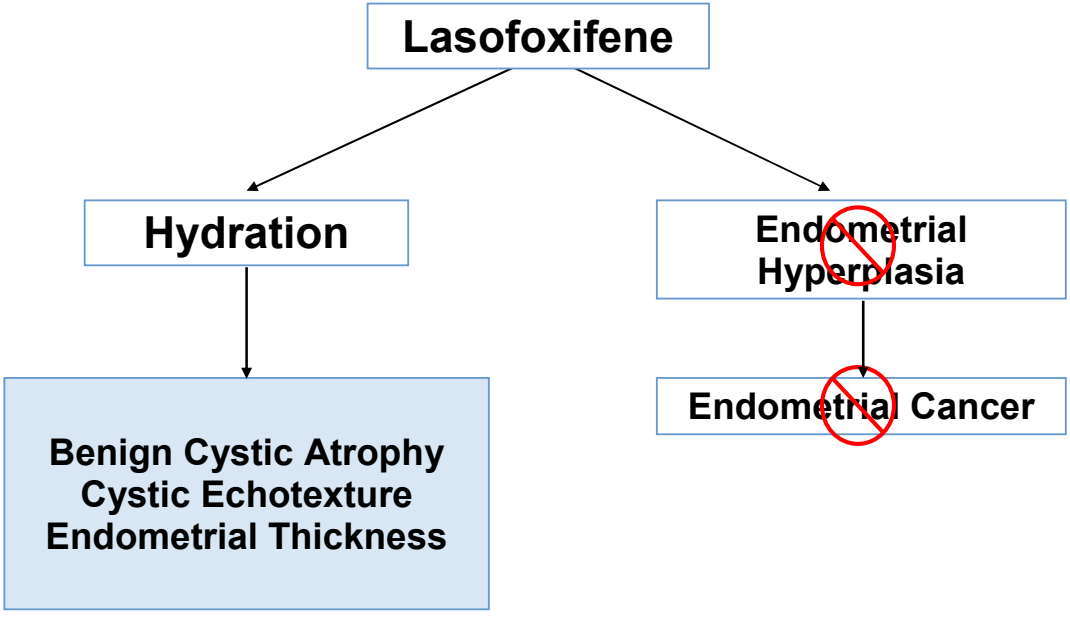
* p-value significant vs. placebo

Endometrial Thickness through 3 Years TVU-I

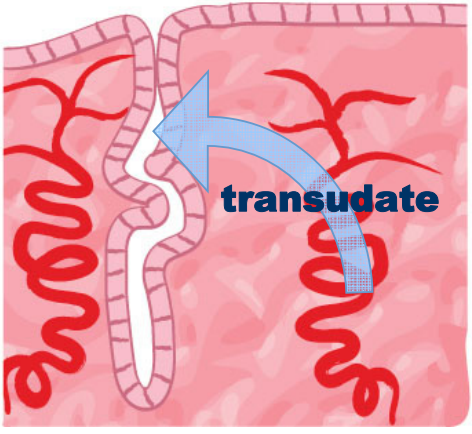


* p-value significant vs. placebo

Benign Endometrial Effects of Lasofoxifene

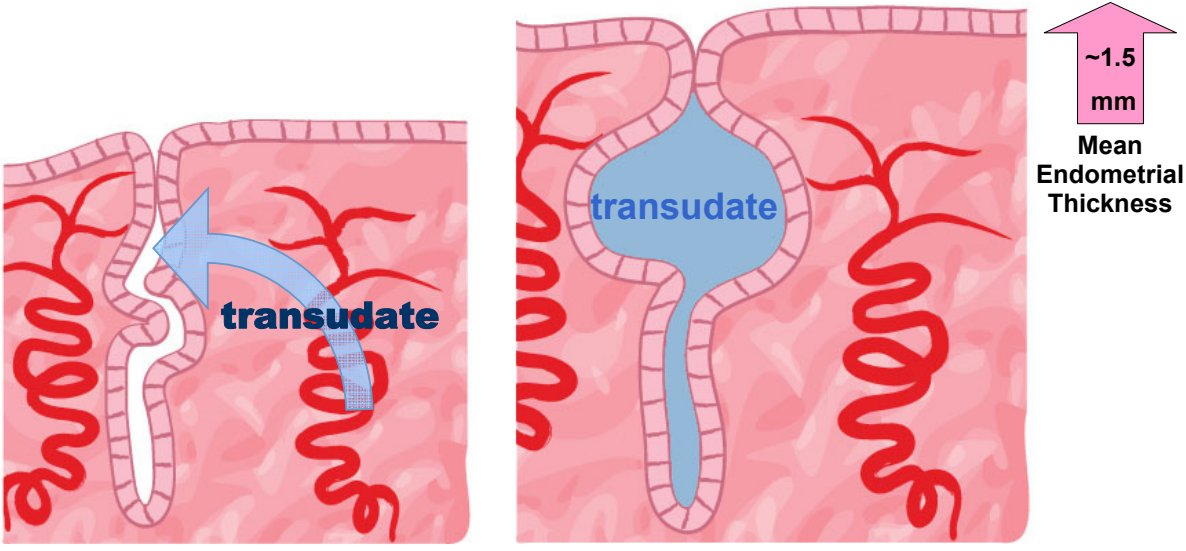


Vascular Permeability Causing Cystic Change



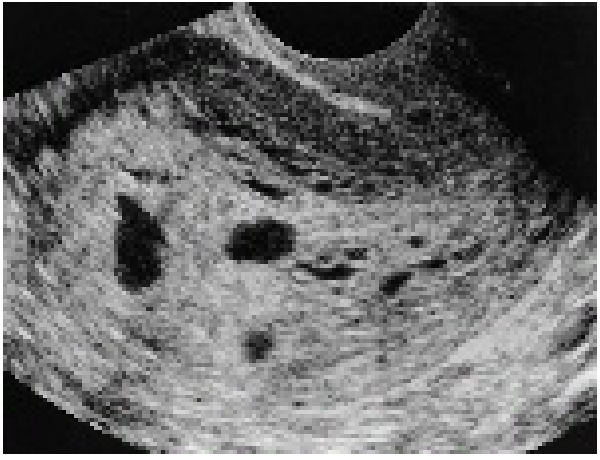
Pre-Treatment → ↑ Vascular Permeability

Vascular Permeability Causing Cystic Change

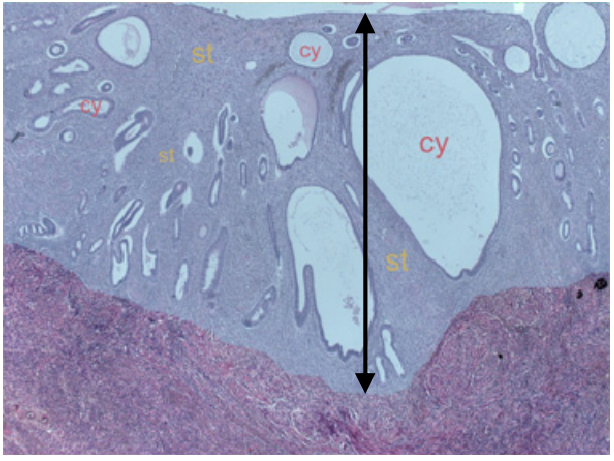


Pre-Treatment → ↑ Vascular Permeability → ↑ Fluid accumulation in glandular lumen → Benign Cystic Atrophy

Benign Endometrial Effects



Cystic Echotexture



Cystic Atrophy
↑ Endometrial Thickness

Endometrial Polyps at 3 Years – TVU-P

- **All lasofoxifene endometrial polyps were atrophic/inactive**

	Placebo	Lasofoxifene	
		0.25 mg	0.5 mg
Patients at risk	360	354	366
Events (%)	12 (3.3)	31 (8.8)	20 (5.5)
Incidence rate/1000 patient-years	7.4	20.1	12.5
Odds ratio		2.78	1.68
95% CI		1.41, 5.51	0.81, 3.48
p-value		0.003*	0.163

* p-value significant vs. placebo

Vaginal Bleeding through 5 Years in PEARL

- **Small excess of vaginal bleeding in lasofoxifene-treated patients: 3 patients/1000 patient-years**

	Placebo	Lasofoxifene	
		0.25 mg	0.5 mg
Patients at risk	2852	2852	2852
Patients (%) with event	37 (1.3)	62 (2.2)	74 (2.6)
Incidence rate per 1000 patient-years	2.9	4.9	5.9
Hazard ratio vs. placebo		1.68	2.01
95% CI		1.12, 2.52	1.35, 2.98
p-value		0.012*	0.001*

* p-value significant vs. placebo

Diagnostic Uterine Procedures through 5 Years in PEARL: "Real World" Patients

- More lasofoxifene-treated patients received at least one diagnostic uterine procedure: 10 patients/1000 patient-years
- Most common procedure was endometrial biopsy

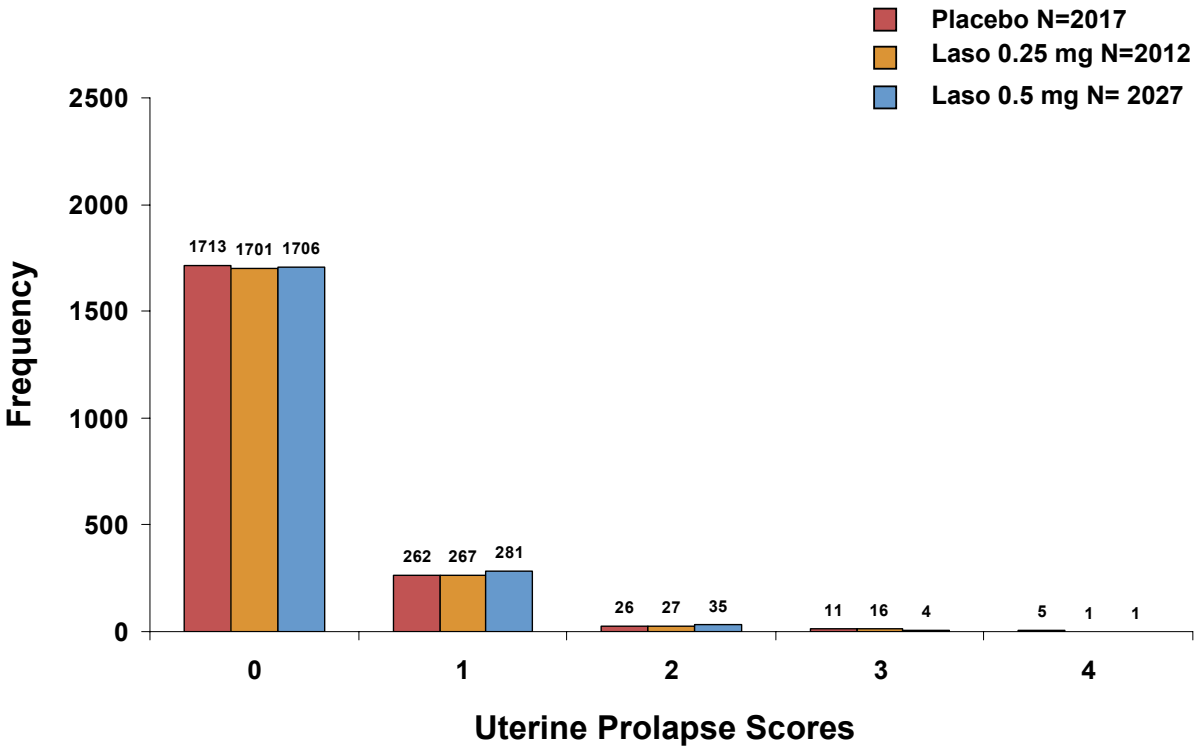
	Placebo	Lasofoxifene	
		0.25 mg	0.5 mg
Patients at risk	1354	1348	1352
Number (%) with ≥ 1 diagnostic procedure	36 (2.7)	97 (7.2)*	95 (7.0)*
95% CI	1.8, 3.6	5.8, 8.7	5.6, 8.5
Incidence rate per 1000 patient-years	6.0	16.1	15.8

* p-value significant vs. placebo

Assessments of Prolapse and Urinary Incontinence in PEARL

- **Validated assessment of anatomical prolapse**
  - Modified Halfway Measure
- **Validated assessment of urinary incontinence**
  - King's Health Questionnaire
- **Surgery for pelvic organ prolapse or urinary incontinence**
  - Adjudicated by GYN Endpoint Committee

Uterine Prolapse Scores at Month 36 in PEARL



King's Health Questionnaire

- **Validated instrument**
- **Assess urinary incontinence symptoms**
- **Administered to all patients in TVU-I substudy**
  - N=326
  - At baseline and years 1, 2, and 3
- **Scores comparable across treatment groups**

Surgery for Pelvic Organ Prolapse or Urinary Incontinence at 5 Years in PEARL

	Placebo	Lasofoxifene	
		0.25 mg	0.5 mg
Patients at risk	2852	2852	2852
Events (%)	35 (1.2)	55 (1.9)	46 (1.6)
Incidence rate per 1000 patient-years	2.8	4.3	3.6
Hazard ratio vs. placebo		1.57	1.31
95% CI		1.03, 2.40	0.85, 2.04
p-value		0.036*	0.224

* p-value significant vs. placebo

Gynecological Safety of Lasofoxifene 0.5 mg – Conclusions

- **No evidence of increased risk of endometrial cancer or endometrial hyperplasia**
- **Endometrial findings:**
  - Benign cystic atrophy
  - Increased cystic echotexture
  - Increased endometrial thickness
- **Excess of vaginal bleeding: 3 patients/1000 patient-years**
- **Excess of diagnostic uterine procedures: 10 patients/1000 patient-years**
- **No consistent signal for pelvic organ prolapse**

Lasofoxifene
Risk Management

Dr. Claudia R. Turner
Safety and Risk Management
Pfizer, Inc.

Overall Risk Management Strategy

- **Education**
  - Label/PIL
  - Programs/Materials
- **Risk Communication**
- **Pharmacovigilance**
  - Routine
  - Enhanced
- **Measurement of Effectiveness**

Risk Identification: Venous Thromboembolism (VTE)

	Placebo		Lasofoxifene 0.5 mg	
	N (%)	IR (per 1000 P-Y)	N (%)	IR (per 1000 P-Y)
VTE	18 (0.6)	1.4 (0.8, 2.2)	37 (1.3)	2.9 (2.0, 4.0)
DVT	13 (0.5)	1.0 (0.5, 1.7)	28 (1.0)	2.2 (1.5, 3.2)
PE	2 (< 0.1)	0.2 (0.0, 0.6)	9 (0.3)	0.7 (0.3, 1.3)

- **Low incidence (~ 1 %)**
  - Primarily driven by DVT
- **Hazard ratio (~ 2-fold) comparable to raloxifene***
- **Raloxifene used for > 10 years with positive benefit-risk profile**

*Grady, et al., 2004

Risk Management: Venous Thromboembolism

- **Label**
  - Risk identification for physicians and patients
  - Ways to mitigate risk
- **Risk Communication to patients**
  - Patient Information Leaflet (PIL)
  - Web-based education
- **Independently – monitored long-term safety cohort study**
- **Measuring effectiveness**
  - Relative frequency to raloxifene 60 mg
  - Relative frequency to non-SERM treated patients

Risk Identification: Increased Diagnostic Uterine Procedures

	Placebo Event Rate/1000 PY N (%)	Lasofoxifene 0.5 mg Event Rate/1000 PY N (%)
Number of patients with ≥1 procedure	36 (2.7)	95 (7.0)
Incidence rate (per 1000 P-Y)	6.0	15.8

- Excess of ~ 10 patients with uterine procedures/1000 P-Y
  - 3/10 due to vaginal bleeding
  - Most common procedure was endometrial biopsy
- Consistent with raloxifene (Martino, et al., 2005)

Risk Management: Diagnostic Uterine Procedures

- **Proposed label**
- **Education**
  - Objectives
    - increase awareness of established surveillance guidelines
    - distinguish between benign cystic endometrium and hyperplasia
  - Delivery:
    - International scientific congresses
    - Presentations in local communities
    - Web-based education
- **Pharmacovigilance**
  - Independently-monitored long-term safety cohort study
- **Risk Communication**
- **Measurement of Effectiveness**
  - Incidence compared to raloxifene 60 mg
  - Web-based testing results

Long-Term Safety Prospective Cohort Study

- **Objective**
  - To detect plausible differences in all SAEs, including relatively rare events such as endometrial cancer, in women treated with lasofoxifene 0.5 mg, raloxifene 60 mg, or SOC
- **Exposure 400,000 P-Y**
  - > 50,000 postmenopausal women for 8 years
  - >10-fold greater exposure than PEARL study
- **Independent oversight**
  - Special Advisory Committee (SAC)
  - Statistical and Data Analysis Center (SDAC)
- **Annual reports issued to regulatory agencies**

Long-Term Safety Prospective Cohort Study: Events of Interest

Identified Risks

- VTE
  - DVT
  - PE
- Diagnostic uterine procedures

Potential Risks (SERM/HRT)

- All cancer (including uterine cancer)
- Pelvic organ prolapse/surgery
- Gallbladder disease/surgery
- Liver abnormalities
- Cataracts
- Major coronary events
- Stroke
- ? All-cause mortality

Risk Management Conclusions

- **Identified Risks: VTE and Diagnostic Uterine Procedures**
- **Potential Risks: Safety events observed with other SERMs**
- **Risk Management**
  - Risk Mitigation (Labeling and Education)
  - Enhanced Pharmacovigilance
    - Long-term safety prospective cohort study
- **Risk Communication**
    - Patients (PIL)
    - Regulators (Annual reports from Cohort Study)
    - Healthcare Providers (education)
- **Measurement of Risk Management Effectiveness**

Lasofoxifene Benefit-Risk

Steven R. Goldstein, MD
Professor of Obstetrics and Gynecology
New York University School of Medicine

Overview

Risks

- Safety profile similar to raloxifene
  - Increase in diagnostic uterine procedures
  - Increase in VTEs

Benefits

- Robust bone activity
- Effective in VVA
- Reduction in breast cancer risk
- Reduction in coronary heart disease

Clinical perspective

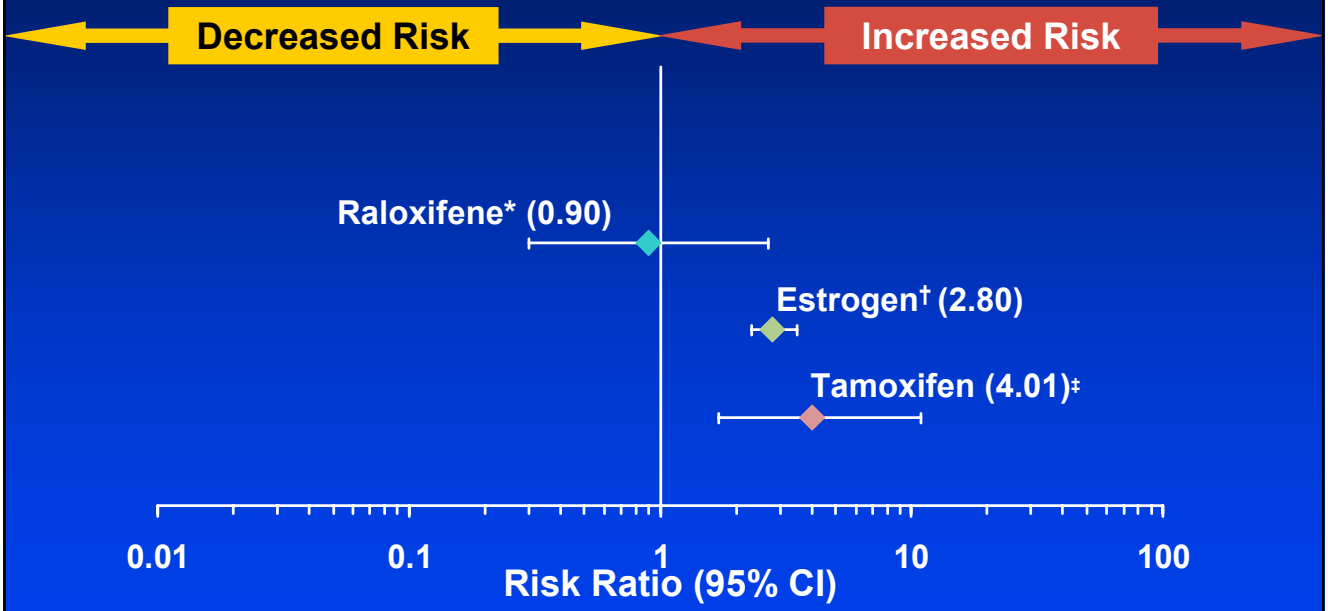
- Benign endometrial effects
- Selecting osteoporosis treatment
- Patient considerations

Assurance of Uterine Safety

Greater than >2400 women with uteri on lasofoxifene for 5 years

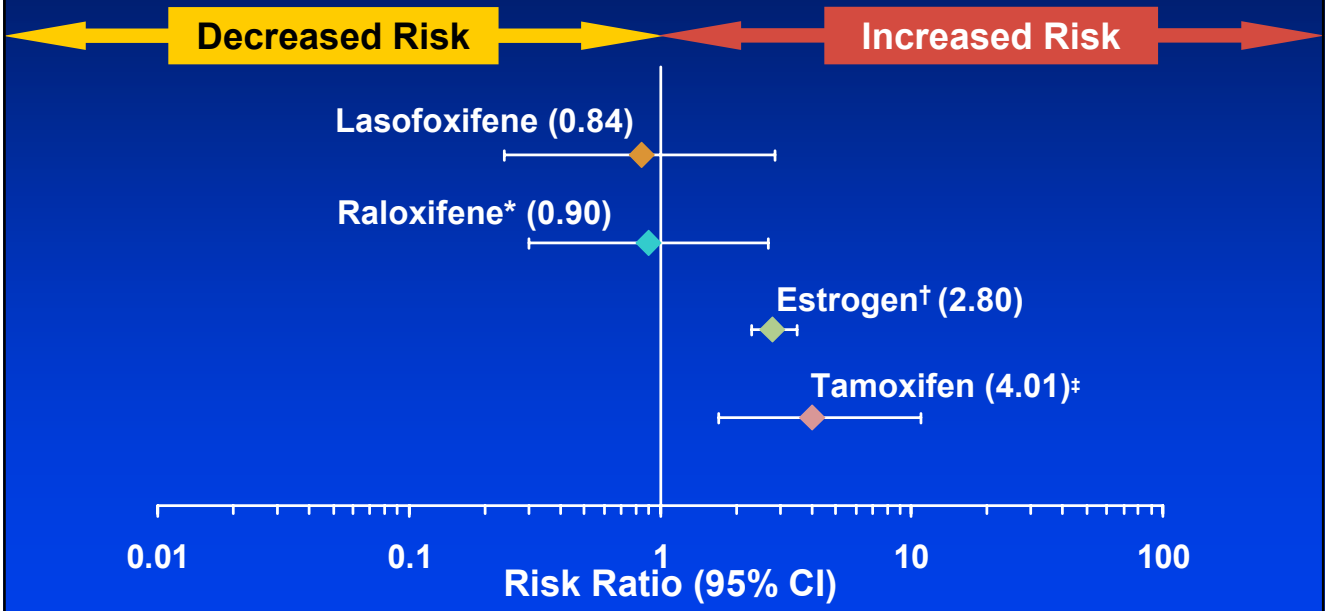
- No signal of endometrial cancer
- No signal of endometrial hyperplasia
- Not like estrogen
- Not like tamoxifen
- Well characterized benign endometrial effects
  - Benign cystic atrophy
  - Benign polyps

Risk of Endometrial Cancer



*Grady et al. Obstet Gynecol 2004; 104 (4) 837-844.
†Grady et al. Obstet Gynecol 1995; 85 (2): 304-13; cohort with 1-5 years use. ‡Fisher, et al. J Natl Cancer Inst 1998. 90(18):1371-88. cohort >50 years

Risk of Endometrial Cancer



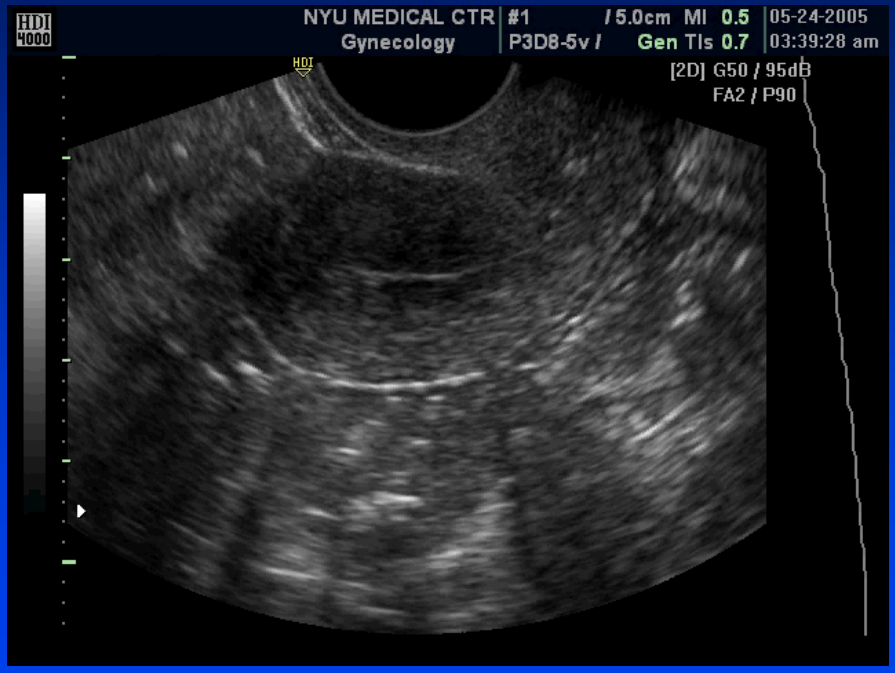
*Grady et al. Obstet Gynecol 2004; 104 (4) 837-844.
†Grady et al. Obstet Gynecol 1995; 85 (2): 304-13; cohort with 1-5 years use. ‡Fisher, et al. J Natl Cancer Inst 1998. 90(18):1371-88. cohort >50 years

Hyperplasia in SERMs

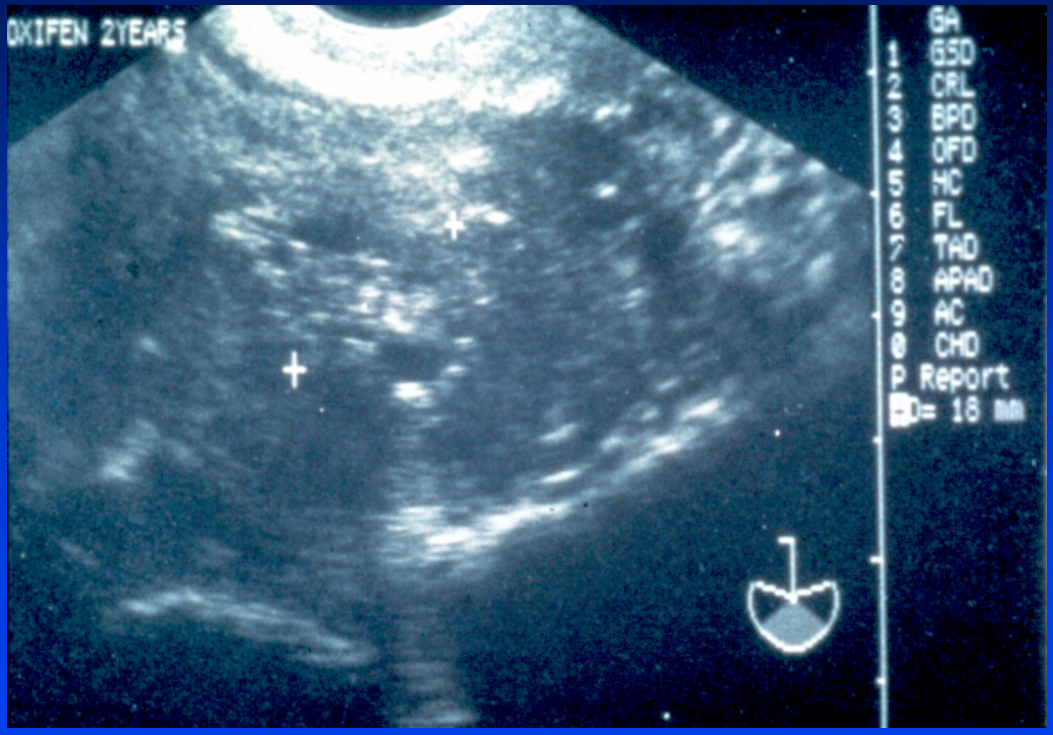
Drug	Hyperplasia (per 1000 PY)
Lasofoxifene	0.24
Raloxifene	0.23
Estrogen	145.75
Tamoxifen	17.96

Cummings, 1999; Chalas, 2005; Kurman, 2000

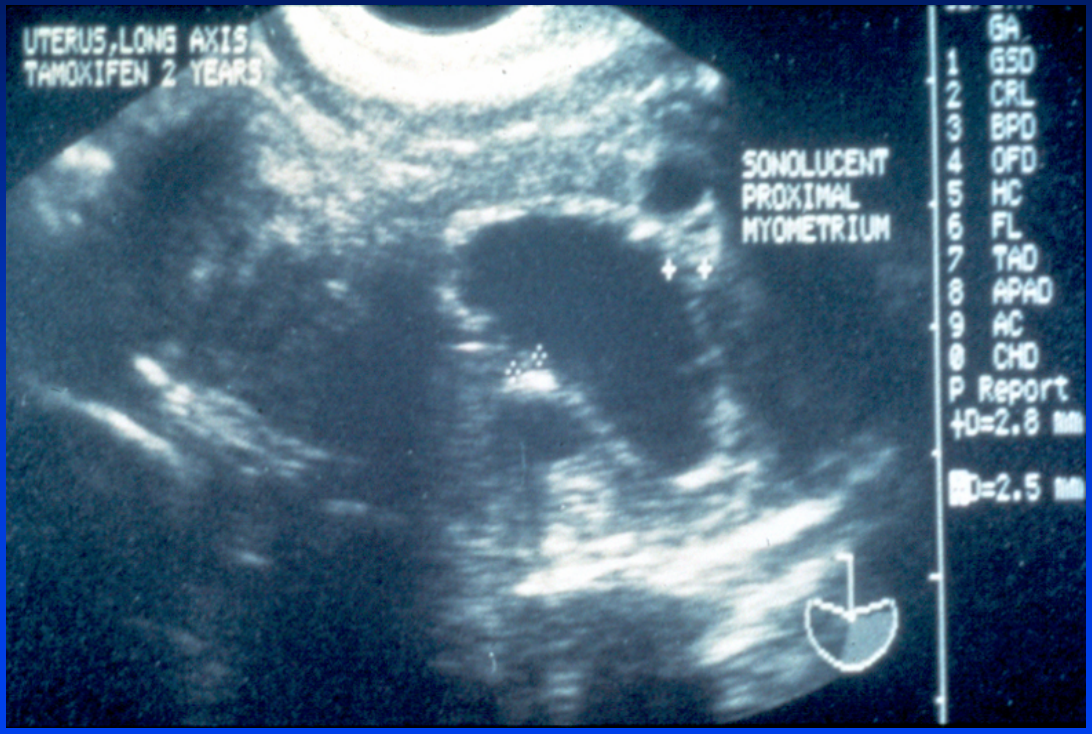
Atrophic Endometrium



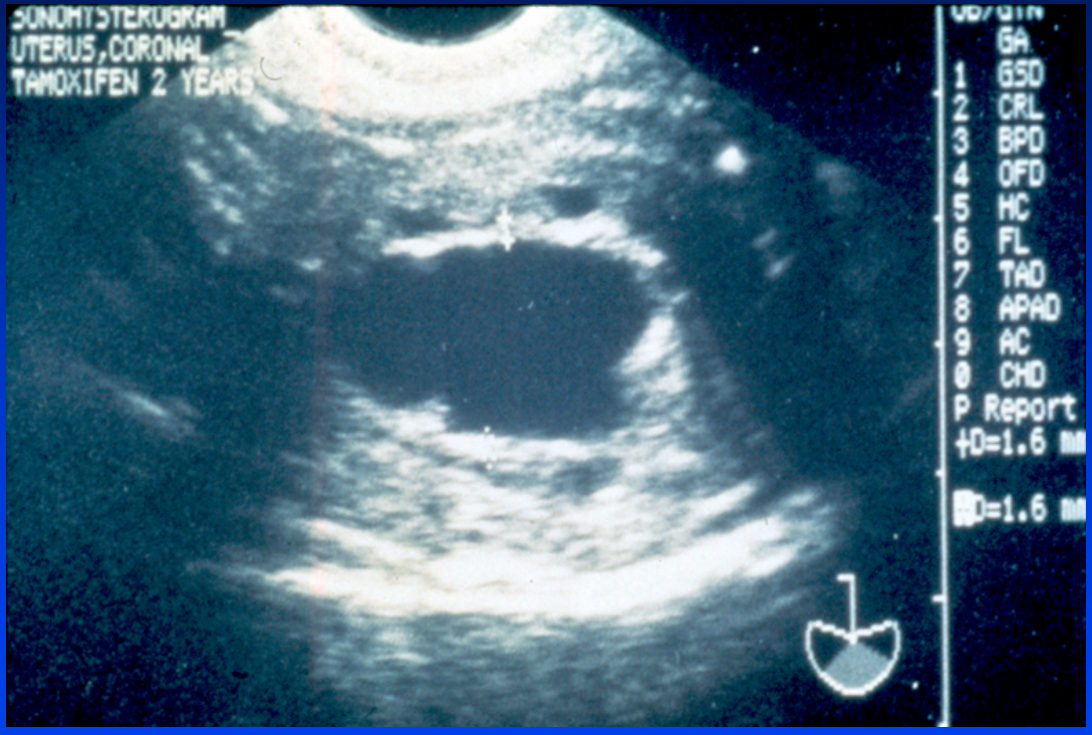
TVU image of benign cystic change



TVU image of benign cystic change



TVU image of benign cystic change



Microcystic Changes

Benign Cystic Atrophy

Low power image shows
cystic dilation of glands (cy)
separated by stroma (st)

Endometrial Polyps at 3 Years – TVU-P

	Placebo	Lasofoxifene	
		0.25 mg	0.5 mg
Patients at Risk	360	354	366
Events (%)	12 (3.3)	31 (8.8)	20 (5.5)
Incidence rate/1000 patient-years	7.4	20.1	12.5
Odds Ratio		2.78	1.68
95% CI		1.41, 5.51	0.81, 3.48
P-value		0.003*	0.163

- All lasofoxifene endometrial polyps were atrophic / inactive
- Similar to raloxifene, OR=1.7†

* p-value significant vs. placebo
† Martino, et al, 2005

Vaginal Bleeding at 5 years in PEARL

- Low incidence of vaginal bleeding (excess 3/1000 P-Y)
- Approximately 2 fold increase (HR 2.01, CI:1.35-2.98)
- Vaginal bleeding mostly associated with benign cystic atrophy

Increased Diagnostic Uterine Procedures in PEARL "Real World" Patients

- Excess of ~ 10 patients with uterine procedures/1000 P-Y
  - 3/10 due to vaginal bleeding
- Raloxifene also increases uterine procedures*

*Martino, et al., 2005

Risk Conclusions

- Gynecological effects of lasofoxifene are benign
  - No increase in endometrial cancer
  - No increase in endometrial hyperplasia
  - Increase in benign cystic atrophy
    - Microcystic changes on TVU interpreted as "endometrial thickness"
  - Small increase in benign endometrial polyps
  - Small increase in vaginal bleeding
  - Small increase in diagnostic uterine procedures
- VTEs similar to raloxifene

Safety profile similar to raloxifene

Benefits

A Clinician's Thoughts About Lasofoxifene

This molecule offers excellent bone efficacy

- Best of SERM class

Impact of vertebral fractures

- Adverse impact on daily activities similar as that seen with hip fractures[1]
- Severe back pain for weeks to months[2]

Lasofoxifene decreases vertebral fractures (42%, $p<0.001$)

Impact of non-vertebral fractures

- Adverse effect on daily living, (e.g. mobility, showering, housework, and driving) [1]

Lasofoxifene decreases non-vertebral fractures (22%, $p<0.019$)

1. Cummings SR, Melton LJ, Lancet 2002;359:1761-67

2. Ross JR, Am J Med 1997; 30s-42s

A Clinician's Thoughts About Lasofoxifene

- Lasofoxifene relieves signs and symptoms of VVA in postmenopausal women
  - Improves symptoms
  - Improves maturation index
  - Decreases vaginal pH

A Clinician's Thoughts About Lasofoxifene

- Reduces risk of major coronary events
- Reduces risk of stroke

A Clinician's Thoughts About Lasofoxifene

- Lasofoxifene (like other SERMs) decreases risk of invasive breast cancer

A Clinician's Thoughts About Lasofoxifene

- No increase endometrial cancer or hyperplasia
- Associated with increase in endometrial glandular cystic atrophy
  - Change is benign
  - Does NOT require intervention
- Associated with a small excess of vaginal bleeding events (3/1000 P-Y)
  - Overwhelming majority of bleeding is associated with endometrial atrophy
- Does result in a small excess (10/1000 P-Y) of diagnostic uterine procedures
  - Potential to reduce the number of procedures with education on current surveillance guidelines

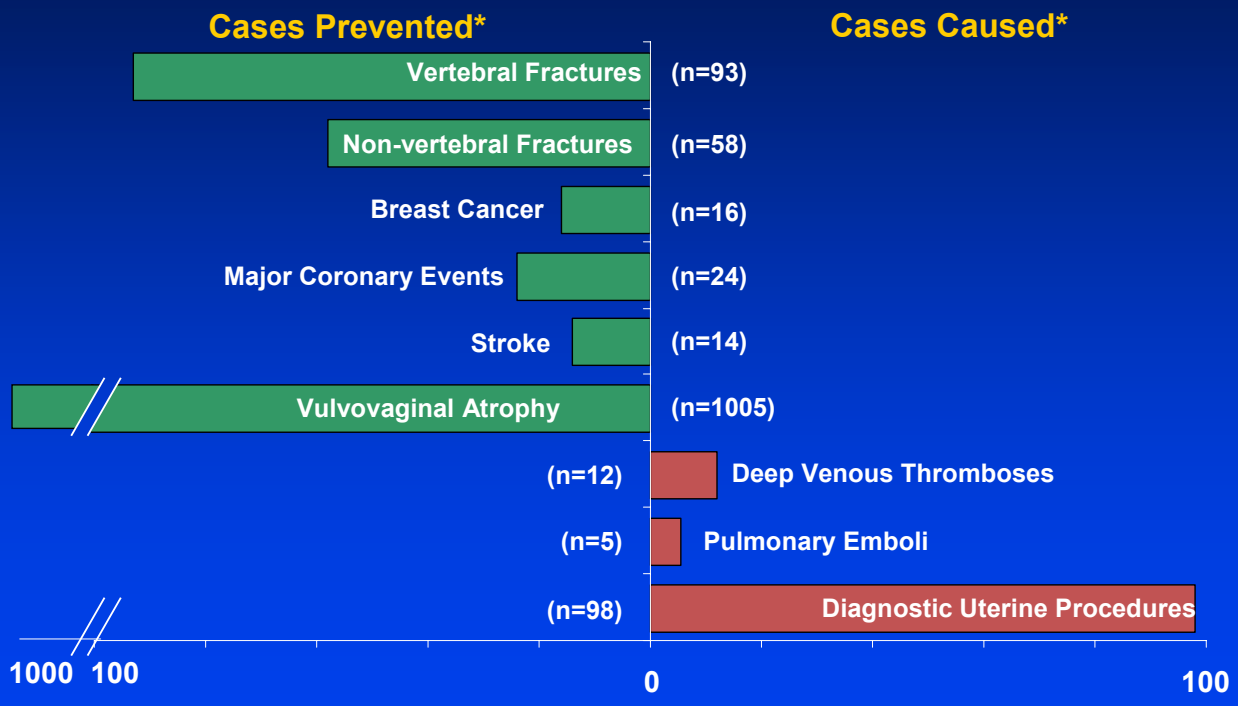
Other Therapeutic Options

Potential bisphosphonate patients include those that:

- Require treatment for low bone density
- Are not susceptible to upper GI disorders
- Factors (real or perceived) that inhibit initiation or may decrease compliance in patients
  - Over suppression of bone turnover
  - Long bone fractures
  - Osteonecrosis of the jaw

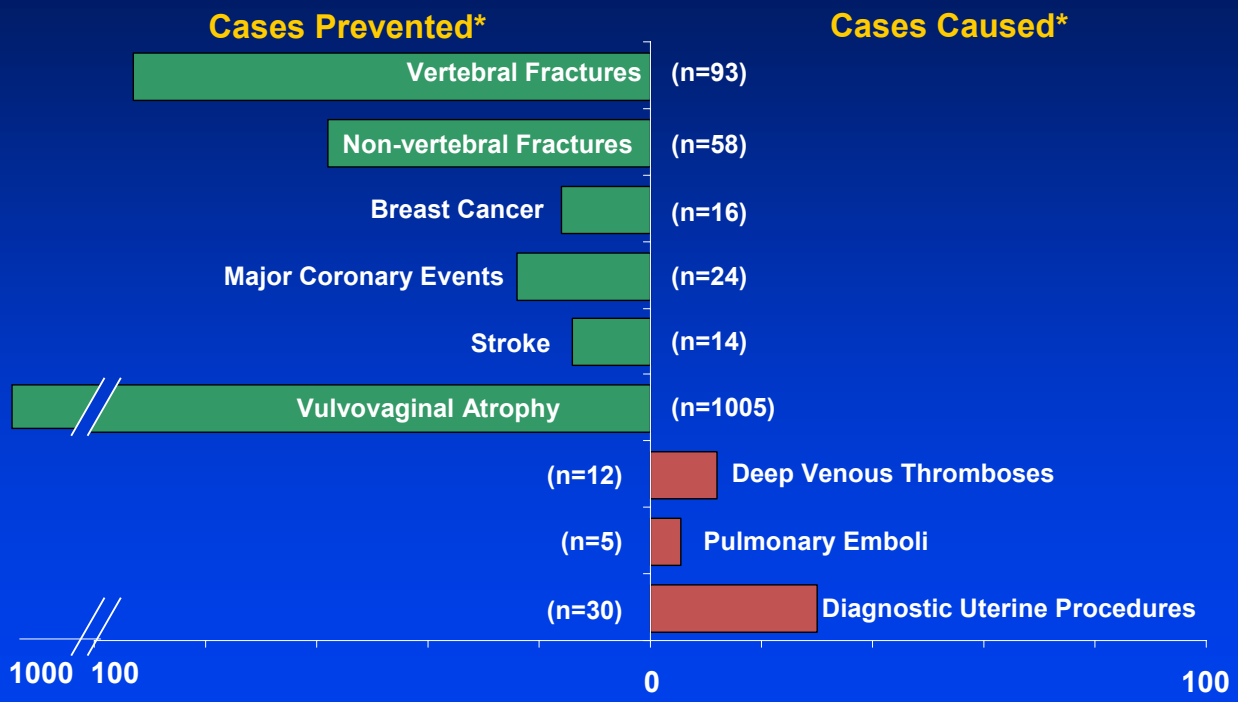
In Summary

Attributable Benefits and Risks of Lasofoxifene 0.5 mg



*per 10,000 patient-years

Attributable Benefits and Risks of Lasofoxifene 0.5 mg



*per 10,000 patient-years

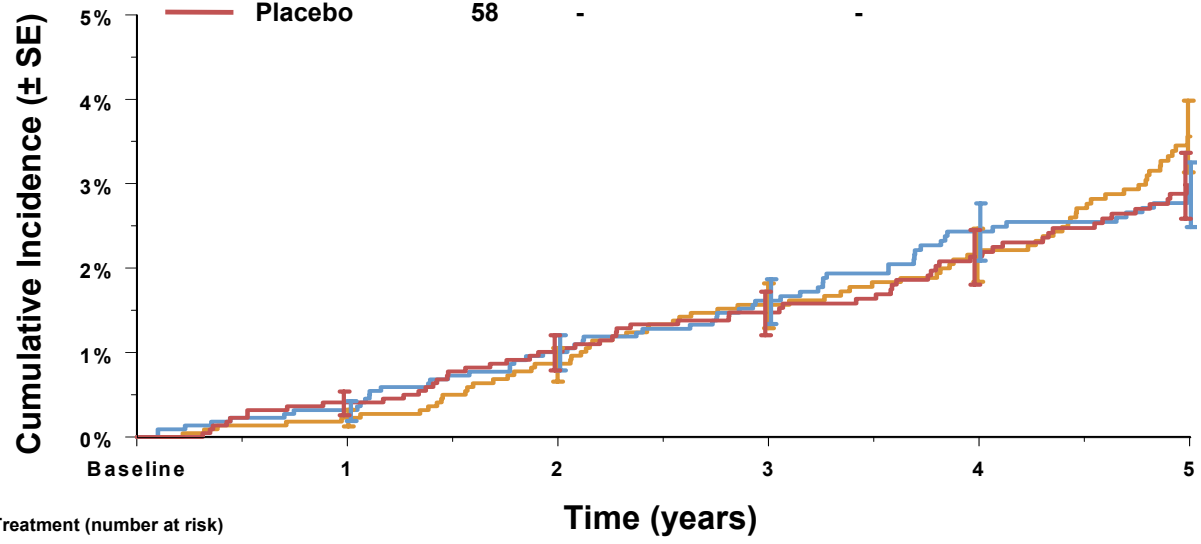
The Ideal Treatment for Postmenopausal Women with Osteoporosis Would:

	Lasofoxifene
Decrease vertebral fractures	✓
Decrease nonvertebral fractures	✓
Decrease coronary heart disease	✓
Decrease stroke	✓
Decrease breast cancer	✓
Decrease VVA	✓
Decrease hot flushes	
Not increase endometrial cancer	✓
Not increase VTE	

Based on its proven efficacy and clearly favorable benefit-risk profile, lasofoxifene is an excellent agent for appropriately selected postmenopausal women with osteoporosis

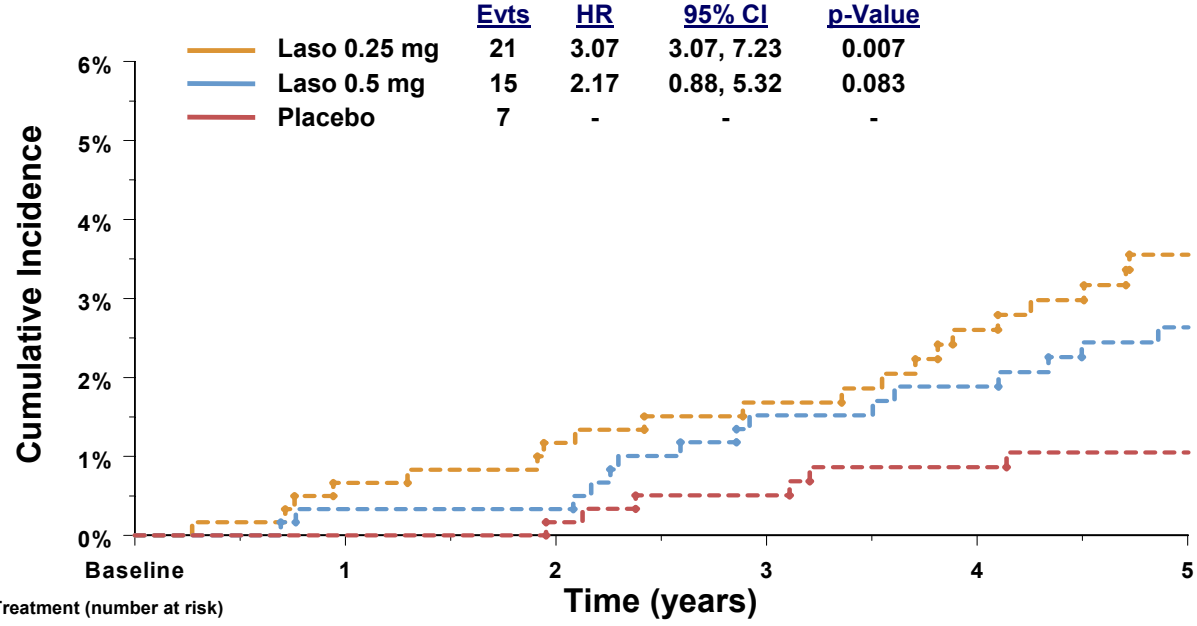
Cumulative Mortality through 5 years in PEARL: Regions 1, 3, 4 and 5 (Excluding Region 2)

	Evts	HR	95% CI	p-Value
Laso 0.25 mg	69	1.17	(0.83, 1.66)	0.372
Laso 0.5 mg	58	0.97	(0.69, 1.43)	0.971
Placebo	58	-		-



Treatment (number at risk)						
Laso 0.25 mg	2240	2194	2160	2105	1804	1727
Laso 0.5 mg	2239	2199	2148	2091	1771	1719
Placebo	2240	2192	2142	2079	1761	1701

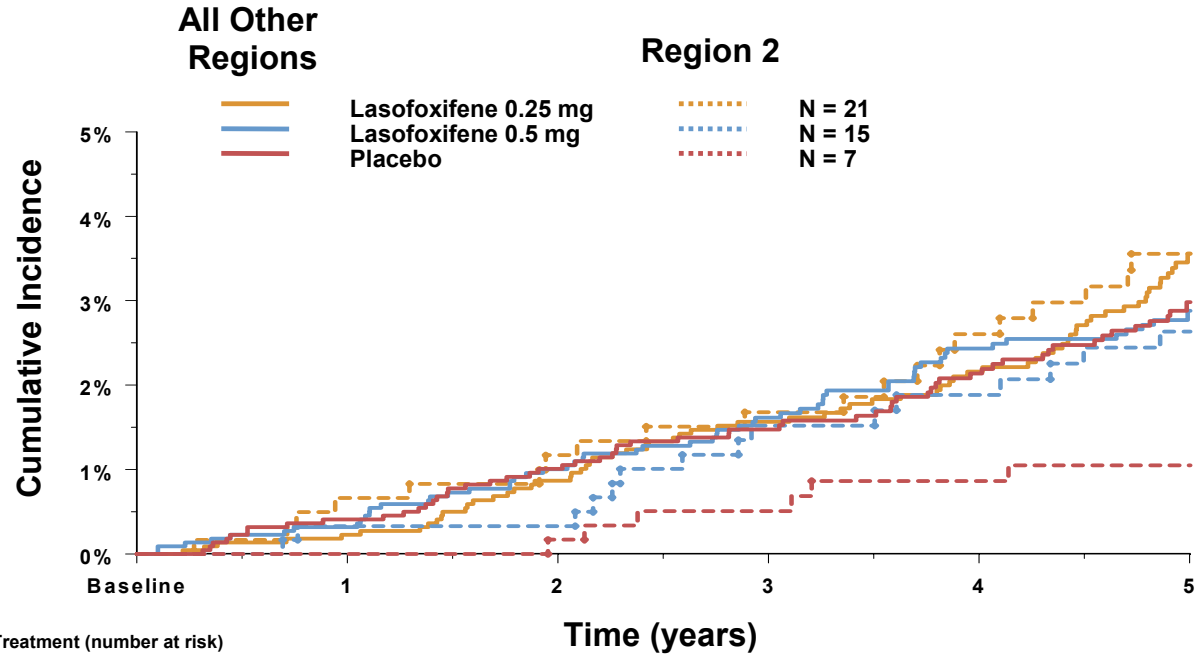
Mortality in PEARL: Region 2



	Evts	HR	95% CI	p-Value
Laso 0.25 mg	21	3.07	3.07, 7.23	0.007
Laso 0.5 mg	15	2.17	0.88, 5.32	0.083
Placebo	7	-	-	-

Treatment (number at risk)						
Laso 0.25 mg	612	600	586	576	525	499
Laso 0.5 mg	613	605	591	577	535	513
Placebo	612	607	596	585	542	526

Cumulative Mortality through 5 years in PEARL: Regions 1,3,4 and 5 Combined vs. Region 2



Treatment (number at risk)						
Laso 0.25 mg	2852	2794	2746	2681	2329	2227
Laso 0.5 mg	2852	2804	2739	2669	2306	2232
Placebo	2852	2799	2738	2664	2303	2227

Mortality in PEARL through 5 Years

	Placebo	Lasofoxifene mg/day	
		0.25	0.5
	N=2852	N=2852	N=2852
Patients with 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

Endometrial Cancer in PEARL (Listing of Cases)

PID	Tx	Age	Days on Tx	Type	Stage	Grade	Vag Bleed	Previous HRT/ERT	ET (mm)
0011 16383	L 0.5 mg	72	1163	mucinous adenocarcinoma	1B	1	YES	NO	7
0026 581	L 0.25 mg	68	1001	mucinous adenocarcinoma	3A	2	YES	NO	10.8
0030 18631	Pbo	76	61	endometrioid adenocarcinoma (w/mucinous foci)	NR	2	YES	NO	NA
5040 451	Pbo	67	1221	endometrioid adenocarcinoma (w/mucinous foci)	1B	1	NO	NO	5.4
5119 1491	L 0.5 mg	70	1022	endometrioid adenocarcinoma	1B	1	YES	YES	11.8
5123 2790	L 0.25 mg	68	907	Serous papillary adenocarcinoma	1A	n/a	YES	NO	ND
5126 15150	Pbo	67	955	endometrioid adenocarcinoma	1B	2	NO	NO	ND

NA = not available; ND = not done

Histological Outcomes - Subjects with TVU ET ≥ 5 mm PEARL TVU–I Sub-study

	Placebo	Lasofoxifene	
		0.25 mg	0.5 mg
	N=116	N=106	N=104
Number of subjects with ET ≥ 5 mm	4	42	35
Frequency of endometrial biopsy findings			
No sample obtained/identified grossly	0	0	1
Subjects with no interpretable endometrium present	1	5	3
Atrophic/inactive endometrium Physiological type	2	25	21
Proliferative endometrium Weakly/marginal	0	3	4
Atrophic Inactive Endometrial Polyp	0	3	6

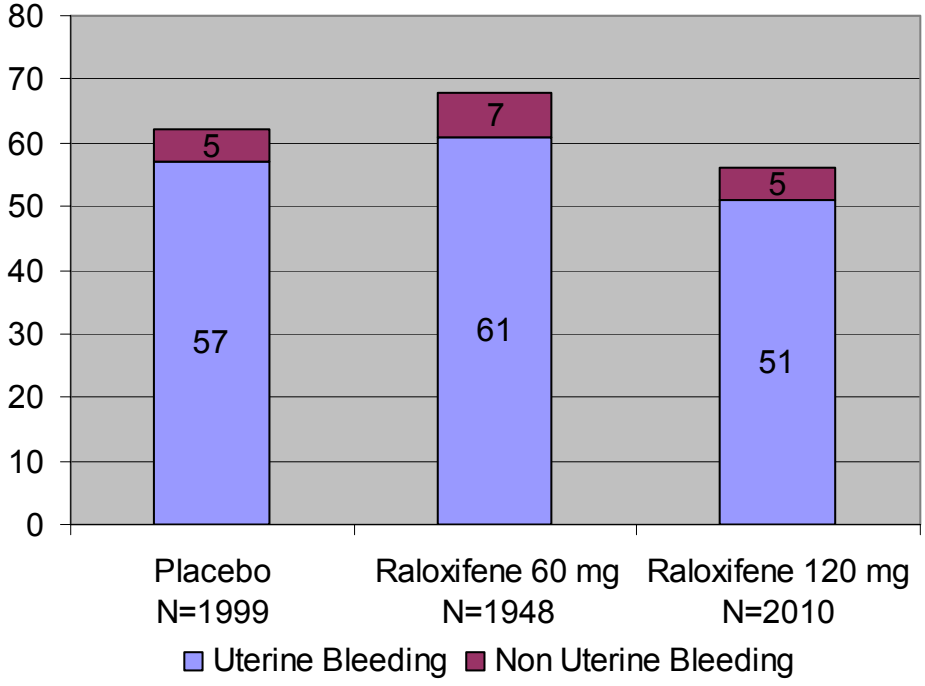
GY102

PE - PEARL and MORE

	Lasofoxifene		Raloxifene	
	Placebo	0.5 mg	Placebo	60 mg
Source (median exposure years)	3-year PEARL (3.10)	3-year PEARL (3.10)	3-year MORE (3.3)*	3-year MORE (3.3)*
Number at risk for event	2852	2852	2576	2557
Number (%) of events	1 (<0.1)	4 (0.1)	3 (0.1)	10 (0.4)
Incidence rate per 1000 Patient years	0.1	0.5	0.3	1.2
Hazard Ratio (95% CI)		4.0 (0.45, 35.73)		3.36 (0.92, 12.2)

*Cummings S, et al. *JAMA*. 1999;281:2189-2197

Incidence of Vaginal Bleeding in MORE



FDA medical review – raloxifene osteoporosis treatment, 1999

GY179

WHI Global Index

- **Includes first occurrence of CHD, stroke, pulmonary embolism, breast cancer, colorectal cancer, hip fracture, or death**
- **Lasofoxifene 0.5 mg:**
  - Incidence of designated events per 100 PY: 1.66
  - HR 0.81; 95% CI 0.68-0.98
- **Lasofoxifene 0.25 mg:**
  - Incidence of designated events per 100 PY: 2.06
  - HR 1.01; 95% CI 0.85-1.20
- **Placebo**
  - Incidence of designated events per 100 PY: 2.03

Death Causality in PEARL by Region 2

43 Total Deaths

	Placebo 7 (1.1%)	Lasofoxifene 0.25 mg 21 (3.4%)	Lasofoxifene 0.5 mg 15 (2.4%)
Coronary	1 (0.2%)	2 (0.3%)	4 (0.7%)
Stroke	1 (0.2%)	4 (0.7%)	2 (0.3%)
Other vascular	0 (0.0%)	2 (0.3%)	1 (0.2%)
Cancer	3 (0.5%)	6 (1.0%)	6 (1.0%)
Trauma	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	2 (0.3%)	6 (1.0%)	2 (0.3%)

Death Causality in PEARL by Region 1, 3, 4, and 5

185 Total Deaths

	Placebo 58 (2.6%)	Lasofoxifene 0.25 mg 69 (3.1%)	Lasofoxifene 0.5 mg 58 (2.6%)
Coronary	20 (0.9%)	16 (0.7%)	14 (0.6%)
Stroke	4 (0.2%)	8 (0.4%)	5 (0.2%)
Other vascular	2 (0.1%)	4 (0.2%)	1 (<0.1%)
Cancer	17 (0.8%)	28 (1.3%)	19 (0.8%)
Trauma	4 (0.2%)	1 (< 0.1%)	3 (0.1%)
Other	11 (0.5%)	12 (0.5%)	15 (0.7%)

Lumbar Spine BMD: CORAL Study at 2 Years

	Placebo	Ral 60 mg	Laso 0.25 mg
Number of Subjects	101	204	205
Mean % Change (vs. BL)	-0.95	1.31*	2.21*
Mean % Change (vs. raloxifene)			0.90*

* p-value for comparison to placebo or raloxifene significant

CORAL (Lasofoxifene vs. Raloxifene)

N = 540 Total

	Placebo 107	Lasofoxifene 0.25 mg 218	Raloxifene 60 mg 215
VTE	0	1 (0.5%)	0
Hot Flushes	9 (8.4%)	23 (10.6%)	11 (5.1%)
Muscle spasm	3 (2.8%)	33 (15.1%)	14 (6.5%)
All Causality SAE	11 (10.3%)	22 (10.1%)	22 (10.2%)

Primary and Alpha Protected Secondary Endpoints

3 Years

Primary

- New/Worsening vertebral (radiographic) fracture

Secondary

- Multiple vertebral fracture
- Clinical vertebral fracture

5 Years

Co-Primary

- Non-vertebral fracture
- ER+ Breast Cancer

Secondary

- Clinical fracture
- Hip fracture