Lasofoxifene 0.25 mg Compared with Raloxifene 60 mg for Effects on Bone Mineral Density and Markers of Bone Turnover: Results from the Phase 3 Comparison of Raloxifene and Lasofoxifene (CORAL) Trial

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INTRODUCTION

- Lasofoxifene is a potent, high affinity, SERM with a long 6-day half-life that may allow for greater receptor activation in bone compared with other SERMs. [1]
- Lasofoxifene has positive estrogen-like effects in the skeleton [2-3] but, unlike estrogen, lasofoxifene acts as an estrogen antagonist in the breast. [4]
- In a Phase 2 study, lasofoxifene 0.25 mg and 1.0 mg were found to be effective in preventing postmenopausal bone loss, and responses in general were greater than that with raloxifene 60 mg. [3]
- In the Phase 3 CORAL clinical trial, reported here, the effects of lasofoxifene and raloxifene on bone mineral density and markers of bone turnover were compared in a larger cohort of postmenopausal women.

STUDY DESIGN

- Multicenter, double-blind, randomized, placebo- and active-controlled Phase 3 study.
- Subjects: women ages 48-75 years, at least 3 years from last menses, with baseline bone mineral density (BMD) lumbar spine (LS) T-score values by DXA between <0.0 and >-2.5.
- Treatment: lasofoxifene 0.25 mg/day, raloxifene 60 mg/day, or matching placebo for 2 years. All were provided a daily supplement of approximately 1000 mg calcium and 400 IU Vitamin D.
- Primary endpoints: effects of active treatments and placebo on LS-BMD (percent change from Baseline and percent of responders at Month 24).
- Secondary endpoints: percent change from Baseline at Month 24 of total hip (TH)-BMD and of biochemical markers of bone turnover.

SUBJECT DEMOGRAPHICS & BASELINE CHARACTERISTICS

540 subjects were enrolled:
- 218 lasofoxifene
- 215 raloxifene
- 107 placebo

Baseline demographics and characteristics were similar across treatment groups.

	Lasofoxifene 0.25 mg/day	Raloxifene 60 mg/day	Placebo
	N=218	N=215	N=107
AGE (YEARS)			
Mean (SD)	62.2 (6.2)	61.8 (6.6)	61.3 (7.1)
[range]	[49-76]	[47-75]	[47-74]
RACE, N (%)			
White	179 (82.1)	173 (80.5)	85 (79.4)
Black	2 (0.9)	2 (0.9)	3 (2.8)
Asian	5 (2.3)	6 (2.8)	2 (1.9)
Hispanic	29 (13.3)	32 (14.9)	17 (15.9)
Other	3 (1.4)	2 (0.9)	0 (0.0)
BODY MASS INDEX			
Mean (SD)	25.9 (3.6)	26.0 (3.4)	26.2 (3.2)
[range]	[15.9 – 32.9]	[17.7 – 32.6]	[20.0 – 32.8]
YEARS POST-MENOPAUSAL			
Mean (SD)	14.1 (7.6)	14.2 (8.2)	13.9 (8.2)
[range]	[3, 41]	[3, 40]	[4, 39]
LUMBAR SPINE BMD			
T Score Mean (SD)	-1.37 (0.66)	-1.31 (0.65)	-1.29 (0.70)
[range]	[-2.5, 0.4]	[-2.6, 0.1]	[-2.5, 0.1]

Table 1.
Subject Demographics and Baseline Characteristics by Treatment Group

RESULTS

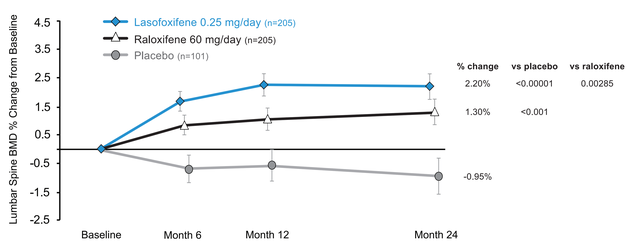
Lumbar Spine Bone Mineral Density (FIGURE 1)

The LS-BMD responses to lasofoxifene 0.25 mg/day and raloxifene were significantly greater than with placebo at Month 24. Superiority of LS-BMD changes with lasofoxifene compared with raloxifene and placebo was observed by Month 6 and sustained over time.

Responder Rates at 24 Months

Logistic regression analysis of the proportion of responders (no decrease from baseline in LS-BMD at a given time point) indicated that the odds of subjects treated with lasofoxifene responding positively were 1.9 times (95% CI: 1.2, 2.9) higher compared with those treated with raloxifene (p-value=0.003) and 7.5 times (95% CI: 4.4, 12.9) higher compared to those treated with placebo (p-value <0.00001).

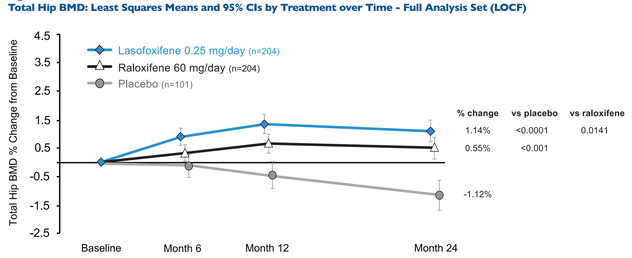
Figure 1.
Lumbar Spine BMD: Least Squares Means and 95% CIs by Treatment over Time - Full Analysis Set (LOCF)



Total Hip Bone Mineral Density (FIGURE 2)

The effects of lasofoxifene at Month 24 were superior to those of raloxifene or placebo in increasing TH-BMD. Raloxifene was also superior to placebo at Month 24. Superiority of lasofoxifene compared with raloxifene and placebo was observed by Month 6 and sustained over time.

Figure 2.
Total Hip BMD: Least Squares Means and 95% CIs by Treatment over Time - Full Analysis Set (LOCF)



Markers of Bone Turnover (TABLE 2)

Lasofoxifene was superior to raloxifene and to placebo in reducing markers of bone turnover (C-telopeptide, N-telopeptide, osteocalcin, and bone-specific alkaline phosphatase). Superiority was observed as early as Month 6 and was sustained over time in. Raloxifene was also superior to placebo in all bone markers listed above.

Table 2.
Serum Bone Markers % Change from Baseline at Month 24 – Full Analysis Set (LOCF)

	Lasofoxifene 0.25 mg/day	Raloxifene 60 mg/day	Placebo
	N=204	N=202	N=99-100
C-TELOPEPTIDE			
Median (95% CI)	-40.09 (-47.35, -35.86)	-27.15 (-31.02, -22.09)	-12.07 (-19.34, 1.55)
Median difference vs placebo (95% CI)	-28.01 (-38.18, -17.85)	-15.08 (-25.59, -4.56)	
P-value vs placebo	<0.001*	<0.001*	
Median difference vs raloxifene (95% CI)	-12.94 (-20.15, -5.72)		
P-value vs raloxifene	<0.001*		
N-TELOPEPTIDE			
Median (95% CI)	-14.70 (-20.34, -10.81)	-7.37 (-12.68, -1.85)	-0.38 (-6.63, 5.74)
Median difference vs placebo (95% CI)	-14.32 (-22.83, -5.82)	-6.99 (-16.13, 2.14)	
P-value vs placebo	<0.001*	<0.018*	
Median difference vs raloxifene (95% CI)	-7.33 (-14.89, 0.23)		
P-value vs raloxifene	<0.003*		
OSTEOCALCIN			
Median (95% CI)	-31.88 (-33.93, -28.57)	-21.05 (-24.68, -17.46)	-13.60 (-18.64, -9.64)
Median difference vs placebo (95% CI)	-18.28 (-25.12, -11.44)	-7.46 (-14.68, -0.23)	
P-value vs placebo	<0.001*	<0.001*	
Median difference vs raloxifene (95% CI)	-10.82 (-16.03, -5.61)		
P-value vs raloxifene	<0.001*		
BONE-SPECIFIC ALKALINE PHOSPHATASE			
Median (95% CI)	-22.65 (-25.00, -18.75)	-9.55 (-15.38, -7.14)	0.00 (0.00, 7.14)
Median difference vs placebo (95% CI)	-22.65 (-28.80, -16.50)	-9.55 (-15.80, -3.29)	
P-value vs placebo	<0.001*	<0.001*	
Median difference vs raloxifene (95% CI)	-13.10 (-18.73, -7.48)		
P-value vs raloxifene	<0.001*		

C-telopeptide was measured in pmol/L; N-telopeptide was measured in nmol BCE; osteocalcin and bone specific alkaline phosphatase were measured in µg/L; p-values were based on an analysis of covariance on rank-transformed percent change from baseline with treatment and rank-transformed baseline value as covariates.

*p-value ≤0.05 (2-sided)

Safety and Adverse Events Results

Similar incidence rates of all-causality adverse events (10.1%-10.3%) and discontinuations due to adverse events were observed across treatment groups. A total of 55 subjects reported 88 non-fatal SAEs during the study, and 3 subjects reported non-fatal SAEs post therapy. The incidences of the most frequent (>5%) treatment-emergent and treatment-related adverse events were muscle spasms (15.1%, 6.5%, 2.5%) and hot flashes (10.6%, 5.1%, 8.4%) for lasofoxifene, raloxifene, placebo, respectively.

SUMMARY

- Lasofoxifene 0.25 mg/day was effective and superior to raloxifene in preventing bone loss based on BMD assessments and in reducing bone turnover markers.
- These differences were seen as early as 6 months and persisted out to 24 months.
- Lasofoxifene also had a nearly 2-fold greater likelihood of meeting the definition of response, defined as no loss of BMD from baseline, compared with raloxifene, and a 7.5-fold greater likelihood of response over placebo.

CONCLUSIONS

- The superior effects of lasofoxifene compared to raloxifene noted here are consistent with the results in the smaller Phase 2 study. [3]
- These effects may account for the observed 10% and statistically significant 24% reduction in non-vertebral fractures with the 0.25 mg and 0.5 mg doses of lasofoxifene, respectively, in the 5-year Postmenopausal Evaluation and Risk-Reduction with Lasofoxifene (PEARL) trial [5] whereas neither raloxifene nor bazedoxifene have been shown to reduce non-vertebral fractures. [6,7]
- While comparative fracture trials would be informative, they are unlikely to be conducted due to the duration and size required of such trials.
- In the meantime, indirect evidence from BMD results, bone turnover markers, and responder rates, such as those demonstrated here in the CORAL study, provides insight into clinical responses to different SERMs.

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