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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

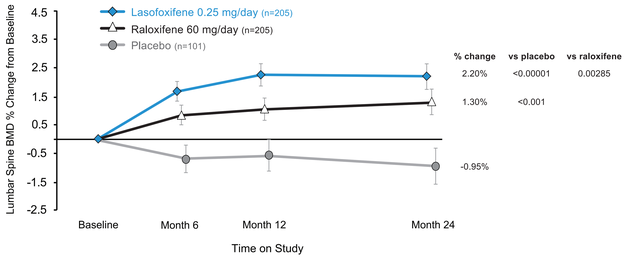
Lumbar Spine Bone Mineral Density (FIGURE 1)

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).

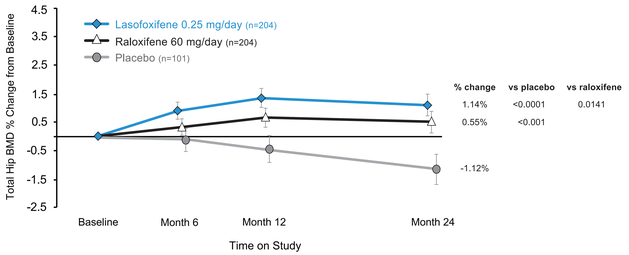
Figure 1.
Lumbar Spine BMD: Least Squares Means and 95% CIs by Treatment over Time - Full Analysis Set (LOCF)



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.

REFERENCES

1. Ke HZ, Foley GL, Simmons HA, et al. Long-term treatment of lasofoxifene preserves bone mass and bone strength and does not adversely affect the uterus in ovariectomized rats. *Endocrinology* 2004;145:1996-2005.
2. Ke HZ, Qi H, Crawford DT, et al. Lasofoxifene (CP-336,156), a selective estrogen receptor modulator, prevents bone loss induced by aging and orchidectomy in the adult rat. *Endocrinology* 2000;141:1338-1344.
3. LaCroix AZ, Powles T, Osborne CK, et al. Breast cancer incidence in the randomized PEARL trial of lasofoxifene in postmenopausal osteoporotic women. *J Natl Cancer Inst* 2010;102:1706-1715.
4. McClung MR, Siris E, Cummings S, et al. Prevention of bone loss in postmenopausal women treated with lasofoxifene compared with raloxifene. *Menopause* 2006;13:377-386.
5. Cummings SR, Ensrud K, Delmas P, et al. Lasofoxifene in postmenopausal women with osteoporosis. *N Engl J Med* 2010;362:686-696.
6. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA* 1999;282:637-645.
7. Silverman SL, Christiansen C, Genant HK, et al. Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo-, and active-controlled clinical trial. *J Bone Miner Res* 2008;23:1923-1934.