

The Evista® brand of raloxifene is indicated for use by women experiencing decreases in estrogen levels after oophorectomy or menopause which lead to increases in bone resorption and bone loss. Bone is initially lost rapidly because the compensatory increase in bone formation is inadequate to offset resorptive losses. This imbalance between resorption and formation is related to loss of estrogen, and may also involve age-related impairment of osteoblasts or their precursors. Raloxifene reduces resorption of bone and decreases overall bone turnover. These effects on bone are manifested as reductions in the serum and urine levels of bone turnover markers and increases in bone mineral density (BMD)<sup>1</sup>.

Raloxifene is a poorly soluble yet well absorbed BCS Class 2 drug (approximately 60% of the Evista® oral dose is absorbed) having an absolute bioavailability in humans of approximately 2%. The Evista® drug utilizes a combination of small particle sizes and surfactant to optimize drug solubilization to maximize the extent of absorption. Using this technology, drug loads of 60 mg are required to provide an efficacious dose in the Evista® product.

SCOLR Pharma's goal is to utilize its patented and proprietary CDT® technology to produce a raloxifene formulation that more efficiently delivers the drug allowing a dose of raloxifene to be used that is substantially lower than 50 mg and is also bioequivalent to Evista®. SCOLR Pharma's results on its trial formulations demonstrate very positive progress toward that goal.

In its most recent clinical trial, SCOLR Pharma demonstrated that application of its CDT® technology with granulated, unmodified drug yielded dose proportionality between two dosage levels of raloxifene. **Table 2** shows basic pharmacokinetic parameters observed in the trial.

**Table 2.** Mean Pharmacokinetic parameters of raloxifene in normal, healthy, non-smoking, post-menopausal or surgically sterile female subjects.

N=34-32	Geometric Mean (%CV)			
	Raloxifene CDT® Tablets (A)	Raloxifene CDT® Tablets (B)	Raloxifene CDT® Tablets (A) *Enhanced	Evista® 60 mg Tablets (D)
AUC <sub>0-inf</sub> (pg·hr/mL) (vs. Evista)	9976.99 (37.53) (61.1%)	12909.36 (50.87) (75.8%)	12794.92 (38.33) (79.1%)	15941.26 (40.66) (100.0%)
C <sub>max</sub> (pg/mL) (vs. Evista)	180.06 (45.11) (56.0%)	256.83 (51.27) (81.3%)	273.72 (42.53) (85.4%)	317.98 (56.48) (100.0%)
90% Confidence Interval (AUC <sub>0-inf</sub> )	55.9% - 66.8%	69.2% - 83.0%	72.3% - 86.6%	

Using the (A) CDT® formulation as a test product, the results indicated that a non-optimized \*Enhanced CDT® formulation increased the relative bioavailability of raloxifene by approximately 30%. When compared to Evista® 60 mg Tablets, the bioavailability of raloxifene was increased 20%, from 60% to 80% when the \*Enhanced (A) CDT® formulation was administered. The non-optimized test formulation containing less than 50 mg of drug achieved a 96% relative bioavailability compared to Evista®.

<sup>1</sup> Eli Lilly, Evista® product insert.

Figure 1 shows the time-dependent change in blood levels of raloxifene comparing the \*Enhanced CDT® formulation A with its dose matched control. The results demonstrate the dramatic increase in AUC as a consequence of bioavailability enhancement. As compared to formulation (A), the enhanced values represent an increase in AUC by ~30% and an increase in Cmax by over 50%.

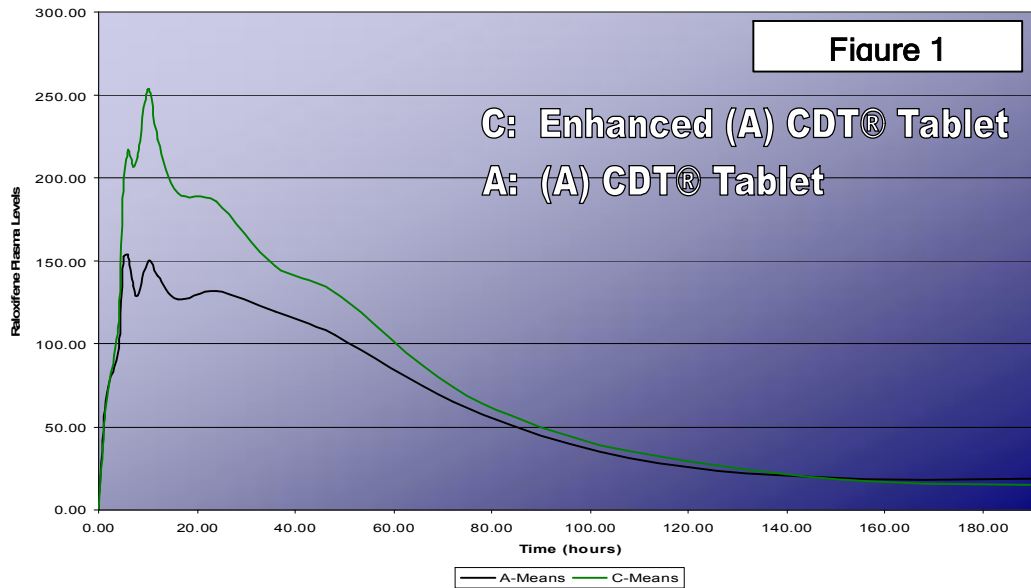


Figure 2 shows the time-dependent comparison of raloxifene blood levels between the \*Enhanced CDT® formulation A containing under 50 mg of raloxifene and Evista® as a control.



In addition, the non-optimized application of the enhanced CDT® technology appeared to moderately reduce the interpatient variability of the drug suggesting a potential for a more profound reduction in drug variability in an optimized formulation.

SCOLR Pharma is very encouraged by these results and believes their technology is scalable and will provide the ability to achieve our goal of producing a raloxifene formulation containing substantially less than 50 mg of drug that is also bioequivalent to Evista®.