

Results of the ORACAL Trial: A Phase 3 Randomized Trial of the Safety and Efficacy of Orally Administered Recombinant Salmon Calcitonin Tablets

BACKGROUND: An oral preparation of recombinant salmon calcitonin (oral rsCT) has previously been shown to be orally bioavailable, safe, and to suppress CTx in short term use.

METHODS: In this Phase 3, multinational, three-armed, double-blind, double-dummy study, women were randomized 4:3:2 to receive daily 200 µg oral rsCT tablets plus nasal placebo, oral placebo and 200 IU commercially available synthetic nasal salmon calcitonin (nasal ssCT), or placebo-placebo for 48 weeks. All doses were administered at bedtime. Calcium and vitamin D (1000mg/800IU) were provided to subjects for daily use. Major inclusion criteria included vitamin D replete postmenopausal women age ≥ 45 years, with a bone mineral density (BMD) T score ≤ -2.5 at the lumbar spine (LS), femoral neck or total hip, or ≤ 2.0 with a prior vertebral fracture. Replicate DXA scans were obtained at baseline, weeks 24 and 48, and read centrally. The primary efficacy variable was the % change in LS-BMD over 48 weeks in the modified intent-to-treat (mITT) population. Biomarkers of bone resorption (CTx, NTx) and formation (P1NP) were also assessed. **RESULTS:** 565 subjects were enrolled in 6 countries; 411 were in the mITT population and contributed efficacy data, 549 contributed safety data. The mean age was 66.5y and mean LS T score -2.84. The mean % increase in LS BMD was:

	N	% Increase LS BMD (SD)	Change From Baseline
Oral rsCT	189	1.53 (3.17)	p < 0.001
Nasal ssCT	140	0.76 (2.91)	p = 0.014
Placebo	82	0.47 (3.21)	p = ns

Although powered to show non-inferiority, oral rsCT was superior to nasal ssCT (delta 0.77% [95% CI: 0.09, 1.45], p=0.026). Conclusions for the per-protocol population were similar (delta 1.05% [95% CI: 0.32, 1.78], p=.005). Consistent with the change in BMD, fasting CTx at the exit visit decreased by 29.9%, 11.4% and 11.8% in the oral, nasal, and placebo arms (oral rsCT vs. nasal ssCT: p < 0.001). Tolerability was similar among the groups; the most common adverse events (AEs) in each group were GI; few serious AEs occurred. Most AEs were mild or moderate in severity. Few fractures occurred. **CONCLUSIONS:** After 48 weeks of treatment subjects receiving oral rsCT tablets had an improvement in LS-BMD which was superior to that of subjects receiving nasal ssCT. The efficacy data (i.e., bone turnover markers and BMD) were robust and internally consistent. The safety and tolerability profiles were similar. Oral rsCT has potential to provide an additional oral treatment option for postmenopausal women with osteoporosis.