

A PHASE I STUDY TO EVALUATE THE EFFECT OF FOOD AND GASTRIC ACID SUPPRESSION ON THE PHARMACODYNAMIC EFFECT OF A NOVEL ORAL RECOMBINANT SALMON CALCITONIN

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ABSTRACT

INTRODUCTION: Salmon calcitonin (sCT) is a safe and effective antiresorptive for osteoporosis; however utility is limited by its parenteral and intranasal routes of administration. An oral formulation with acceptable bioavailability has the potential to increase patient compliance. We have developed an orally administered recombinant sCT (rsCT) tablet that is in late clinical development.

OBJECTIVES: In this Phase 1 study we examined the influence of food and gastric acid suppression on the pharmacodynamic (PD) effect of orally administered rsCT.

METHODS: In a 3 period crossover design, 24 healthy postmenopausal women were randomly assigned 1:1 to either fasting oral rsCT (200 µg tablet, Period 1) followed by rsCT administered with a high fat morning meal (Period 2) or vice-versa. Twelve (12) additional subjects were assigned to fasting placebo followed by placebo with a high fat meal, or vice-versa. All 36 subjects were assigned to Period 3: omeprazole (OMP) 40mg/day for 5 days plus fasting rsCT on Day 5. Subjects were unaware of treatment assignment (i.e., rsCT or placebo) in Periods 1 and 2; they were housed in a clinical pharmacology unit on days of study drug administration. The primary PD outcome was comparison of the plasma concentration versus time profiles of CTx-1, a marker of bone resorption.

RESULTS: The rsCT fed group demonstrated greater CTx-1 suppression than the rsCT fasted group in the 24 hour period following dosing; the ratio of predose adjusted (for baseline CTx-1) AUC₀₋₂₄ favored the fed state versus the fasted (AUC₀₋₂₄ ratio 128.9% [90%CI; 113.5-146.4]). In fed subjects the CTx-1 response was time-shifted by several hours and had not returned to baseline by 24h. The minimum concentrations of CTx-1 (C_{min}) were not significantly different in the 2 periods. The OMP + rsCT fasted and rsCT fasted (without OMP) groups did not differ with respect to pre-dose adjusted AUCs (ratio 93.3% [90% CI; 81.9-106.3]) or C_{min} of CTx-1. Serum calcium was slightly lower in subjects receiving rsCT, but remained in the normal range. Adverse events (AEs) were mild in nature and appeared to be evenly distributed across treatment groups, however the group with the greatest % of subjects who experienced an AE was the rsCT fasted group.

CONCLUSIONS: The data obtained in this study are consistent with a delayed, and greater, pharmacodynamic effect when oral rsCT is administered with food as compared to the fasting state, and consistent with a shift of the PD effect from the first 12 hours following administration to the second 12 hour period following administration, and possibly longer, since CTx-1 did not return to baseline by 24 hours in the fed state. Use of the proton pump inhibitor omeprazole did not affect the PD response to orally administered rsCT.

INTRODUCTION

Calcitonin has been in use for the treatment of postmenopausal osteoporosis for more than 30 years; however it has had limited use, in part because the currently available routes of administration, parenteral and intranasal, are not conducive to patient compliance. Tarsa Therapeutics, Inc. is developing an oral formulation of calcitonin which has the potential to improve convenience and patient compliance. A multinational Phase 3 efficacy and safety trial of this agent recently completed, and regulatory marketing applications are planned. A Phase 2 trial for prevention of postmenopausal osteoporosis was recently initiated.

Oral delivery of peptide agents has multiple challenges, including limited absorption due to molecular size and potential digestion of the peptide by hydrolyzing GI enzymes.

Tarsa Therapeutics has developed a tablet which employs an enteric coating to prevent digestion in the stomach, and an organic acid to facilitate absorption in the small intestine. All of the excipients are generally recognized as safe (GRAS).

INTRODUCTION (cont.)

We wished to evaluate the effect of oral administration concomitant with a high fat meal compared to fasting, and of a proton pump inhibitor on the pharmacodynamic effect of oral rsCT. Currently approved oral bisphosphonates require a restrictive dosing regimen and are contraindicated for patients with GERD. An oral calcitonin that has a more convenient dosing regimen and that could be administered to patients with GERD taking a proton pump inhibitor or H2 blocker may provide an attractive option to osteoporosis patients.

OBJECTIVES

- To evaluate the effect of food on the pharmacodynamics (PD) of oral recombinant salmon calcitonin (oral rsCT).
- To evaluate the effect of gastric acid suppression by omeprazole on the PD of oral rsCT; and
- To evaluate the safety and tolerability of oral rsCT when administered in the fasted and fed states, and following gastric acid suppression by omeprazole.

Figure 1. Trial Design

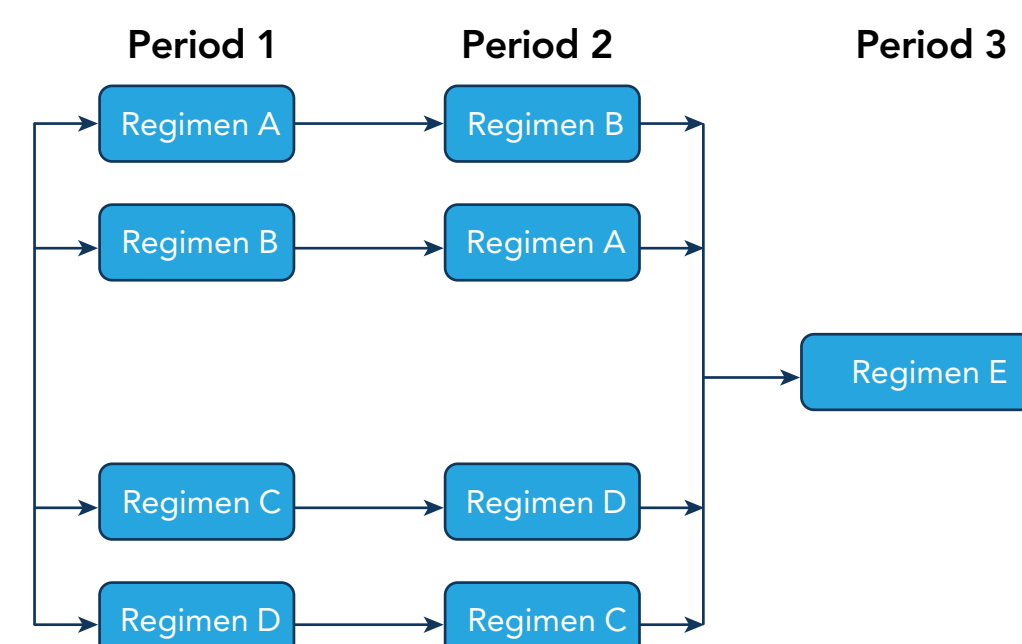


Table 1. Regimens

Regimen	Description	Fed/Fasted
Period 1 and 2		
A	Single Dose Oral rsCT 200 µg	Fasted
B	Single Dose Oral rsCT 200 µg	Fed
C	Single Dose Placebo	Fasted
D	Single Dose Placebo	Fed
Period 3		
E	Omeprazole 40mg/day x 5 days + Single Dose Oral rsCT 200 µg on Day 5	Fasted

METHODS

- Major Inclusion Criteria
 - Healthy postmenopausal women 45-70 years of age
 - BMI 18-35 kg/m²
 - Fasting CTx-1 > 50th percentile for age
- Major Exclusion Criteria
 - Recent peptic ulcer disease or GERD
 - Any prior use of osteoporosis meds
- 36 subjects were to be randomized to one of four treatment sequences such that all subjects received rsCT in the presence of omeprazole in the final period (Fig 1, Table 1):
 - ABE (n = 12)
 - BAE (n = 12)
 - CDE (n = 6)
 - DCE (n = 6)

METHODS (cont.)

Recombinant salmon calcitonin was available in a 200 µg dosage strength tablet for oral administration. Matching placebo tablets were also administered. Placebo tablets were identical to the active tablets in appearance, and contained identical excipients, but no rsCT.

Omeprazole was available in a 40 mg dosage strength capsule for oral administration.

After an overnight fast of ≥10 hours, on the morning of Day 1 Period 1, subjects were randomized to receive either placebo fed/fasted or rsCT fed/fasted in Periods 1 and 2 with the order of fed/fasted being period balanced.

For dosing in a fed state, subjects were administered a high-fat breakfast 30 minutes prior to administration of study medication following an overnight fast of at least 10 hours. Study subjects were required to eat this meal in 30 minutes or less; the study medication was administered 30 minutes after start of the meal. The high-fat breakfast derived approximately 150 calories from protein, 250 calories from carbohydrate, and 500-600 calories from fat. It included the following: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, and 8 ounces of whole milk.

For Period 3, subjects reported to the clinic daily in the morning of Days 1 to 4 for observed dosing with omeprazole 40 mg. Subjects were admitted to the clinical pharmacology unit on the evening of Day 4. On Day 5, following an overnight fast of 10 hours, subjects were administered the 5th dose of omeprazole 40 mg with 240 mL (8 fluid ounces) of room temperature water. One hour after taking omeprazole 40 mg, while subjects were still fasting, a single dose of rsCT 200 µg was administered with 240 mL (8 fluid ounces) of room temperature water.

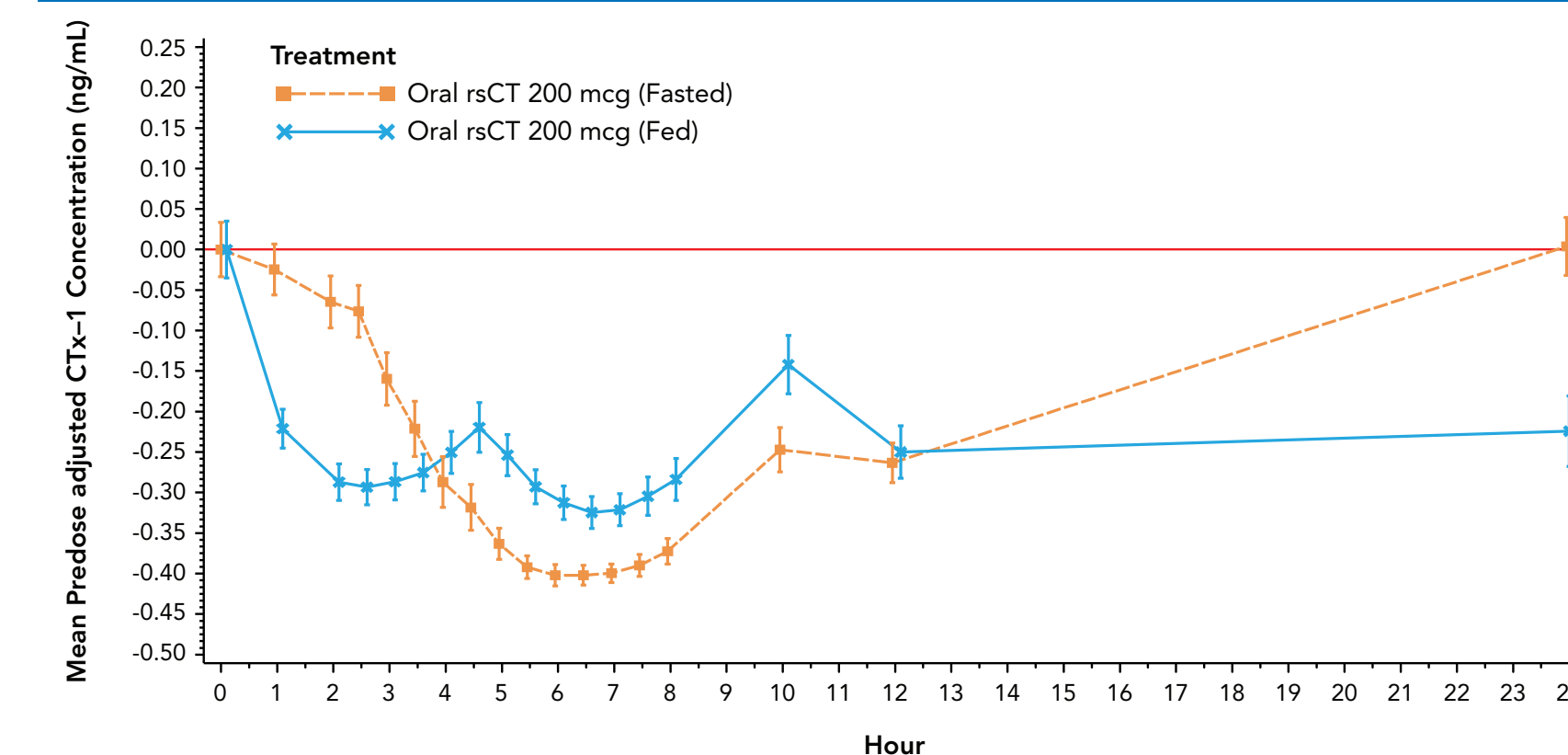
RESULTS

Thirty-seven (37) subjects were randomized to rsCT or placebo (1 subject was enrolled to replace a drop-out); 35 completed Periods 1 and 2 and proceeded to Period 3.

Two (2) subjects withdrew, neither for an adverse event. The average age was 58 years; >97% of subjects were white. Average BMI was 27.1 kg/m².

Fig. 2 shows the change from baseline levels in CTx-1 concentrations in the 24 hour period following administration of rsCT in the fed or fasted state (CTx-1 levels are shown corrected for baseline value, i.e. baseline is set at 0 and subsequent excursions shown). The ratio of the area under the time-concentration curves (AUC) for the fed and fasted CTx in the first 12 hours, when most sampling was done, suggested no difference in the PD effect of oral rsCT according to fed or fasted state, although the fall in CTx-1 was more rapid in the fed subjects (ratio of geometric least squares mean [GLM] 99.8 ; 95% [90%CI: 90.6, 110.1]). After 12 hours, only a single sample was obtained, at 24h, but mean CTx-1 did not return to baseline in the fed subjects, and the ratio of AUCs favored the fed state with respect to PD effect (ratio 128.9 [113.5, 146.4]).

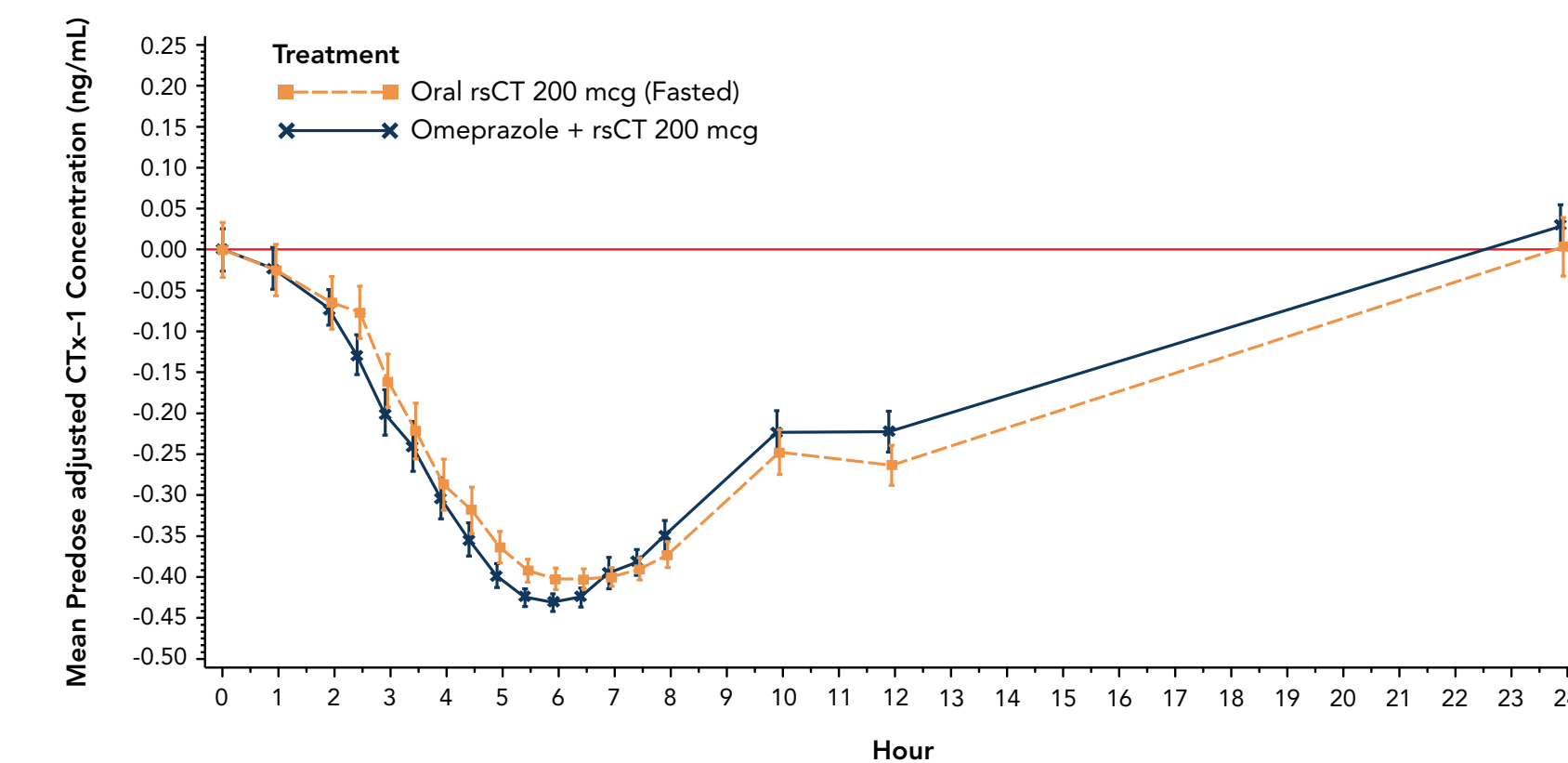
Figure 2. rsCT Fed v. rsCT Fasted



RESULTS (cont.)

Fig 3 shows the change from baseline levels in CTx-1 concentrations in the 24 hour period following administration of rsCT in the fasted state in the presence or absence of omeprazole. The ratio of CTx-1 AUCs did not differ in the 12 hour (OMP vs no OMP 101.3 [91.7, 112.0] or 24 hour [93.3 [81.9, 106.3]) periods. Again only a single sample was obtained after 12h.

Figure 3. Omeprazole + rsCT Fasted vs rsCT Fasted



SAFETY DATA

Table 2 presents an overview of treatment emergent adverse events. The treatment group that had the greatest percentage of subjects who experienced an AE was the rsCT fasted group. A majority of the adverse events were mild in nature and appeared to be evenly distributed across treatment groups. Only one severe AE (radiculopathy) occurred, which was in a placebo recipient. Drug-related AEs (per investigator attribution) occurred more frequently in the rsCT treatment groups compared to placebo. The 2 system organ classes (SOCs) that contained the greatest number of subjects experiencing AEs were the gastrointestinal disorders SOC (n=30) and the nervous system disorders SOC (n=23).

Table 2. Frequency and Severity of Treatment Emergent Adverse Events (TEAEs)

	Placebo Fasted N=13 n (%)	Placebo Fed N=11 n (%)	rsCT Fasted N=24 n (%)	rsCT Fed N=24 n (%)	Omp. + rsCT N=35 n (%)
Any TEAE	5 (38.5)	5 (45.5)	14 (58.3)	11 (45.8)	13 (37.1)
Mild	4 (30.8)	3 (27.3)	10 (41.7)	8 (33.3)	5 (14.3)
Moderate	0 (0.0)	2 (18.2)	4 (16.7)	3 (12.5)	8 (22.9)
Severe	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any study drug-related TEAE	1 (7.7)	2 (18.2)	7 (29.2)	7 (29.2)	10 (28.6)

Those subjects who received rsCT had more GI AEs than those who received placebo, but this effect appeared to be blunted by food and by omeprazole. However, for individual GI AEs the incidence was too small to draw conclusions in this regard. Multiple subjects stated to the investigator they felt nauseated due to the high fat breakfast.

Headache was the most common nervous system AE in each group.

All AEs resolved without sequelae. There were no serious AEs and no deaths.

No clinically significant changes in safety laboratory parameters occurred. However, interestingly the decrements in serum calcium at 24h were larger in the rsCT recipients (fasted -0.21 mg/dL; fed -0.11 mg/dL) than in the placebo recipients (fasted and fed -0.03 mg/dL). All serum calcium values were in the normal range, and the differences were not statistically significant.

SAFETY DATA (cont.)

Table 3. Occurrence of Common GI AEs

System Organ Class Preferred Term	Placebo Fasted N=13 n (%)	Placebo Fed N=11 n (%)	rsCT Fasted N=24 n (%)	rsCT Fed N=24 n (%)	Omp. + rsCT N=35 n (%)
Gastrointestinal Disorders					
Adverse Events	1 (7.7)	2 (18.2)	11 (45.8)	7 (29.2)	9 (25.7)
Nausea	0 (0.0)	0 (0.0)	1 (4.2)	5 (20.8)	4 (11.4)
Abdominal pain	1 (7.7)	1 (9.1)	1 (4.2)	4 (16.7)	2 (5.7)
Abdominal pain upper	0 (0.0)	0 (0.0)	2 (8.3)	1 (4.2)	3 (8.6)
Dyspepsia	0 (0.0)	1 (9.1)	2 (8.3)	0 (0.0)	2 (5.7)
Diarrhea	0 (0.0)	1 (9.1)	0 (0.0)	2 (8.3)	1 (2.9)
Flatulence	0 (0.0)	0 (0.0)	1 (4.2)	1 (4.2)	2 (5.7)
Vomiting	0 (0.0)	0 (0.0)	2 (8.3)	1 (4.2)	1 (2.9)
Abdominal pain lower	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)
Feces discolored	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
GI sounds abnormal	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
GI reflux disease	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
Toothache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)

CONCLUSIONS

CTx-1 is a well established pharmacodynamic surrogate marker to evaluate the antiresorptive effect of certain pharmaceutical agents used for the treatment of osteoporosis.

The interpretation of data in the present study should be considered in light of several factors, including the circadian rhythm indigenous to CTx-1 and the effect of food itself on CTx-1 in the absence of pharmacologic intervention. Food intake stimulates the release of GLP-2, which has been shown to decrease circulating levels of CTx-1.

The data obtained in this study are consistent with a prolonged pharmacodynamic effect when oral rsCT is administered with food as compared to the fasting state, and it is consistent with a shift of the PD effect from the first 12 hours following administration to the second 12 hour period following administration, and possibly longer since CTx-1 did not return to baseline by 24 hours in the fed state. The study design does not allow for conclusive evidence, given that there are no data points between hours 12 and 24 following administration. However, the limited PK data obtained in this study (not shown) are consistent with such an effect, even though the assay employed has a limit of quantitation that is close to the desired therapeutic level of calcitonin.

The study showed no effect on the pharmacodynamic effect of oral rsCT when co-administered with omeprazole. These results support the potential use of oral sCT in patients with GERD taking PPIs or H-2 blockers.

The safety data obtained in this study demonstrated that oral rsCT may be associated with mild GI AEs. Fewer GI AEs were observed overall when rsCT was administered with food, but more nausea occurred. This may be due, in part, to the use of a high fat meal.