

# Nighttime Dosing With An Oral Calcitonin Tablet Significantly Reduces Plasma CTx-1

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## Abstract

The rate of bone resorption in humans follows a diurnal variation, with the highest level of resorption occurring after midnight. Therefore, we wished to determine whether the administration of an enteric-coated tablet containing recombinant salmon calcitonin (rsCT) following the evening meal would result in a robust decrease in CTx-1 levels during the night. Since previous studies indicated that the Tmax of oral rsCT was approximately 3 hours after dosing, we determined in a placebo-controlled study in normal postmenopausal women the effect of administering a single 200 µg tablet of rsCT approximately 4 hours following the evening meal on the concentration of plasma CTx-1. In a second phase of this study, an open-label comparison was made between a single dose of the 200 µg rsCT tablet and a single dose of commercially available nasal spray calcitonin (200 IU) both given in the evening at bedtime, approximately 2 hours following the evening meal. Subjects remained fasting for twelve hours after dosing and following the final blood draw subjects were given a meal. Drinking water was allowed *ad lib*. Blood samples were obtained for CTx-1 determinations at the following times: pre-dose, 2, 4, 6, 8, 10, and 12 hours after dosing. Subjects who were given placebo tablets showed the expected variation in CTx-1 levels, with the highest levels between 2 AM and 6 AM. Subjects receiving either regimen of the oral tablet dose, or the nasal spray calcitonin showed a highly significant mean decrease in CTx-1 throughout the 12 hour observation period, compared to placebo. The results demonstrate that the oral rsCT tablet formulation dosed in the evening hours at variable times following the evening meal can achieve a robust reduction in bone resorption during the hours where the rate of bone turnover is at its peak. The goal of this clinical program is to develop an oral tablet formulation of rsCT that will provide a safe and efficacious anti-resorptive therapy for the treatment of postmenopausal osteoporosis.

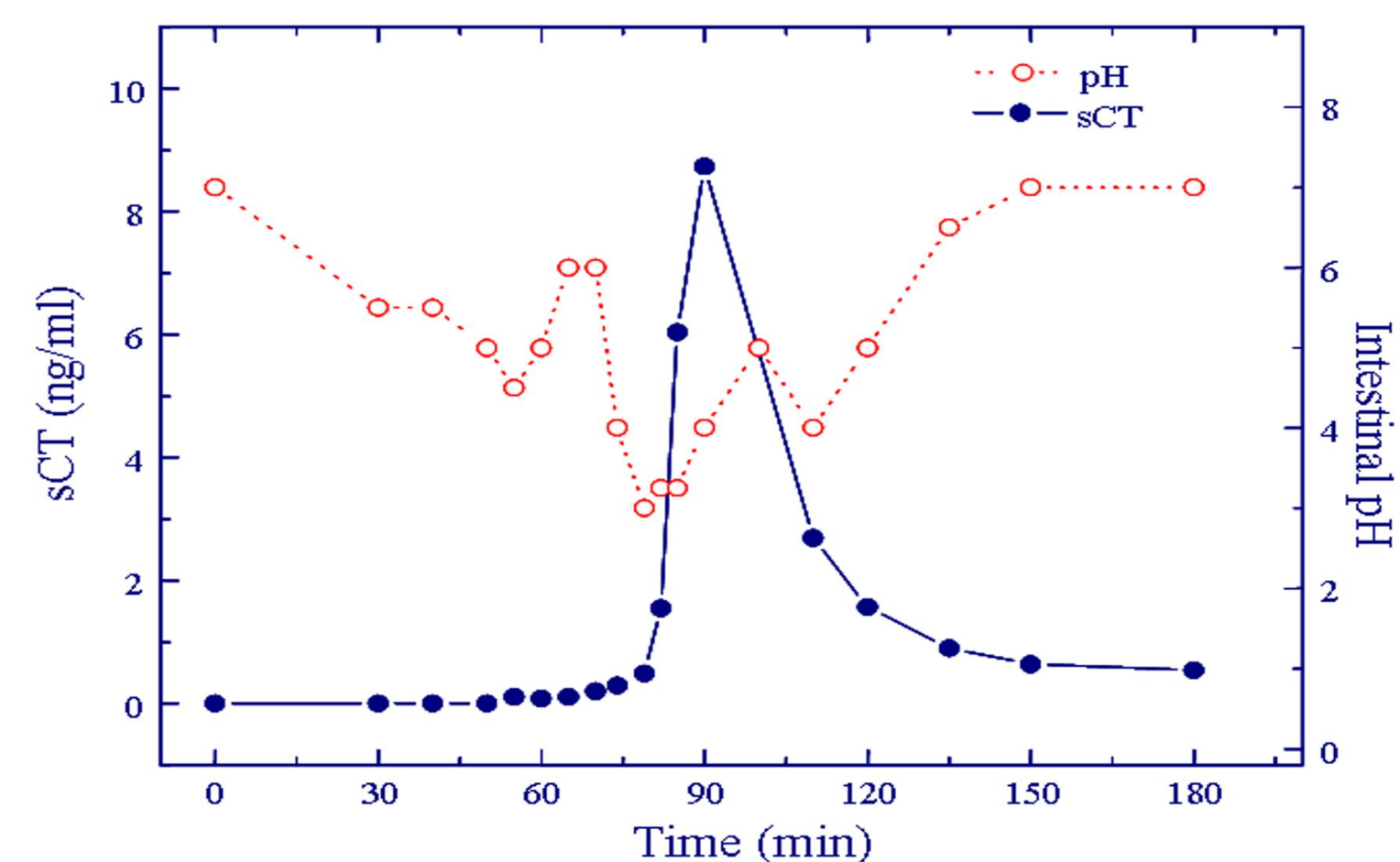
## Introduction

- Oral delivery of peptide drugs has the potential to significantly increase patient acceptance and compliance for chronic use compared to other routes of administration
- A salmon calcitonin (sCT) tablet is being developed through a 505(b)(2) regulatory pathway for the treatment of postmenopausal osteoporosis
- A Phase I Exploratory Study and a Phase II Dose Selection Study have been completed
- Since it is well known that bone resorption in humans follows a diurnal variation, a nighttime dosing study was conducted to determine the efficacy of oral sCT during the night, when bone resorption is at its highest level
- The effect of food on the bioavailability of sCT in the oral formulation was also evaluated in this study by dosing at 2 or 4 hours following consumption of an evening meal
- The reduction in CTx-1 following dosing with the enteric-coated sCT tablet was compared to nasal spray sCT and to placebo
- The sCT used in these studies was produced by a robust and scalable "Direct Expression" recombinant technology that reduces the cost-of-goods for the peptide

**Table 1:** Components of Solid Dosage Oral Tablet Formulation

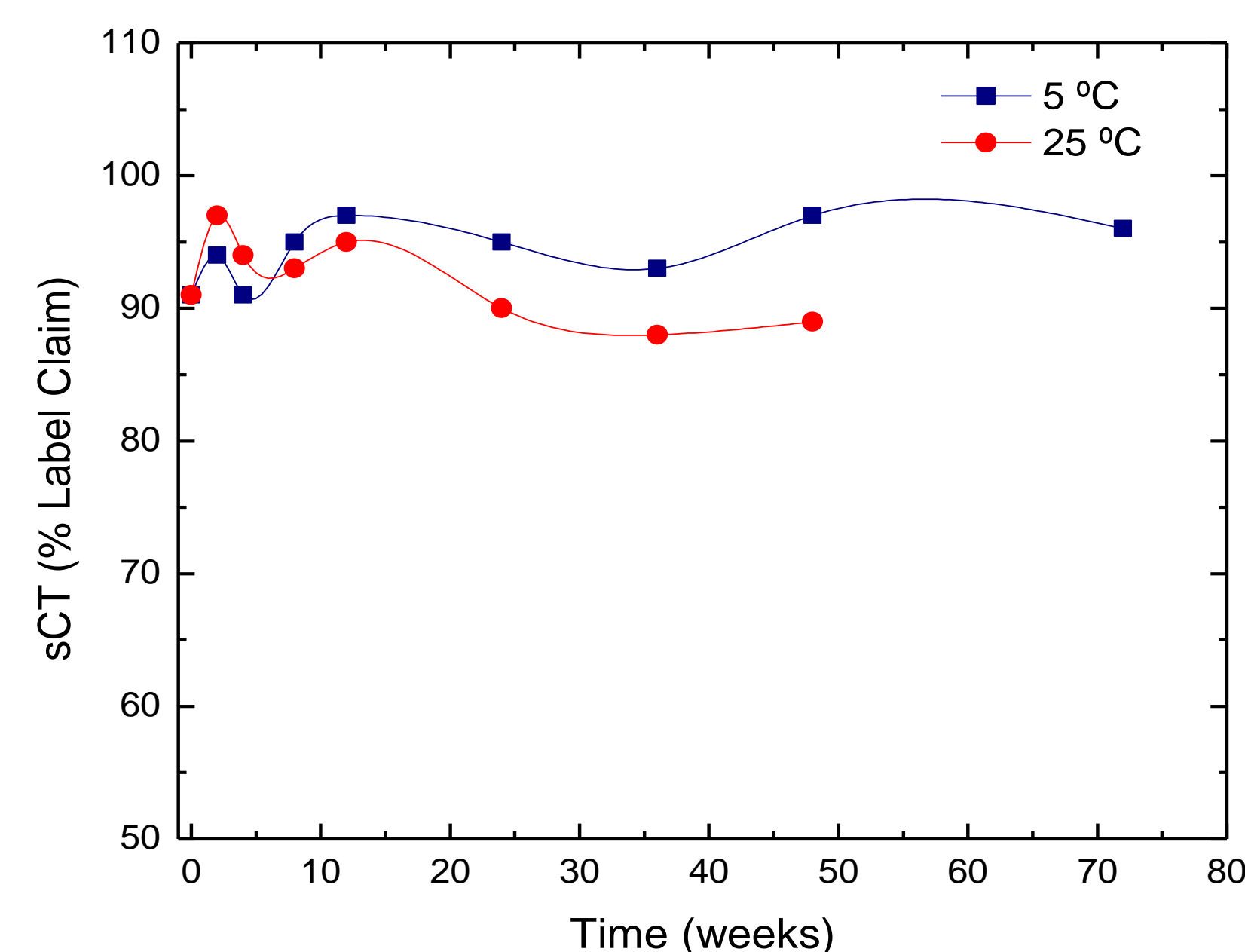
EXCIPIENT	FUNCTION
Salmon Calcitonin	Peptide
Coated Citric Acid	Protease Inhibitor
Lauroylcarnitine	Absorption Enhancer (Optional)
Nonionic Polymer	Subcoat
Eudragit L30D-55	Enteric Coat

**Figure 2:** Pharmacokinetic and pH Profiles of an Orally-Administered Enteric-Coated rsCT Capsule Tethered to a Heidelberg Capsule



**MECHANISM OF ORAL DELIVERY TECHNOLOGY:** The PK and pH profiles of an orally-administered, enteric-coated sCT capsule tethered to a Heidelberg capsule (to measure pH by radio telemetry) are shown

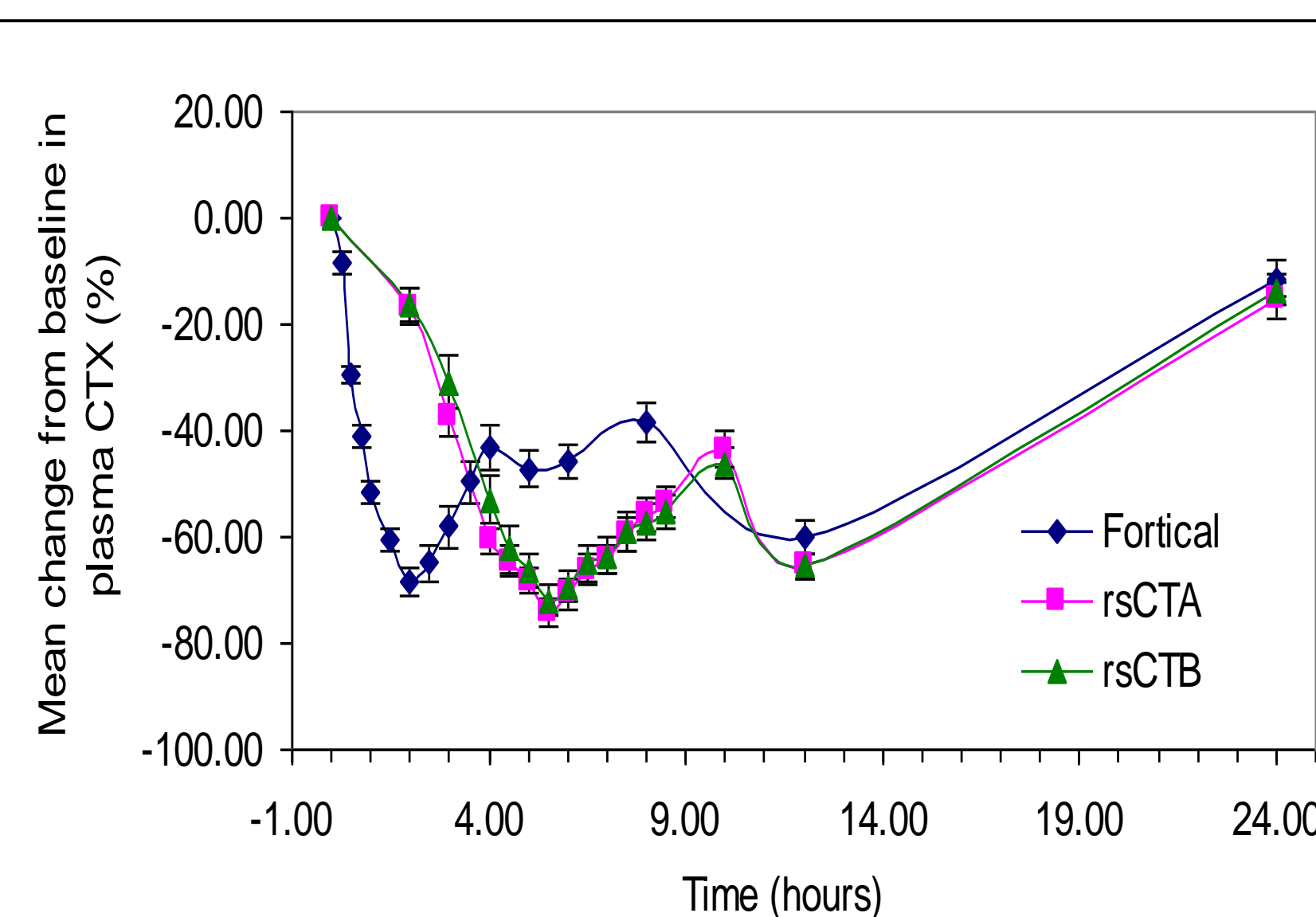
**Figure 3:** Stability Data from Oral sCT Tablet



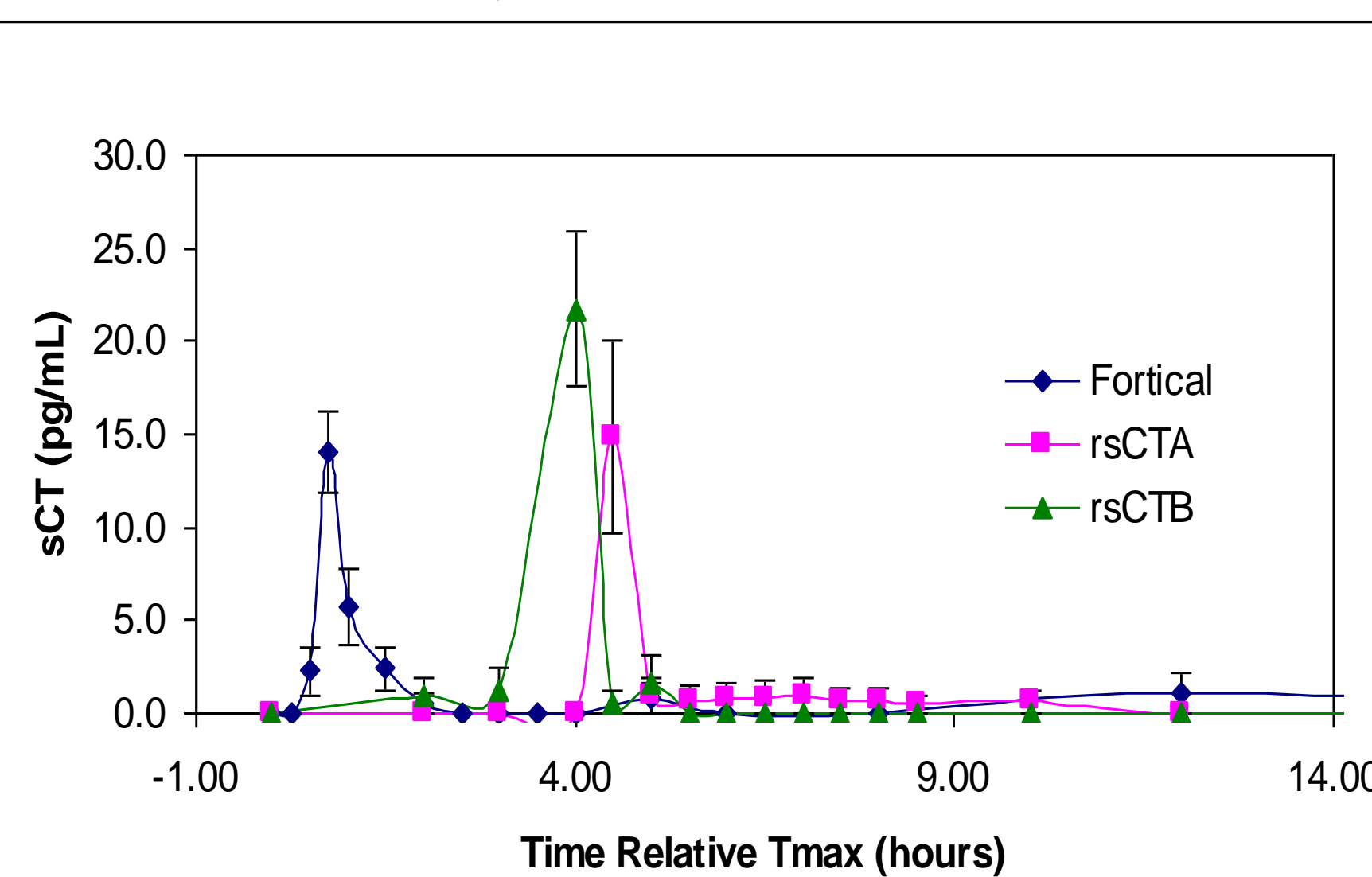
## DESIGN OF PHASE II rsCT DOSE SELECTION STUDY WITH TABLET FORMULATION

- **Design:** Single Dose, Open-Label, Crossover Design Study
- **Subjects:** 24 Postmenopausal Women
- **Study Medication Doses:** 150 µg Tablet (rsCT A), 200 µg Tablet (rsCT B), 200 IU Fortical® nasal spray
- **Assessments:**
  - PK Measurements Up to 24 hours Post-dosing
  - PD Measurements (CTx-1) Up to 24 hours Post-dosing
  - Routine Biochemistry and Hematology, Physical Exams, Vital Signs and Adverse Events

**Figure 4:** PD Response following Administration of Nasal and Oral rsCT in Phase II Study



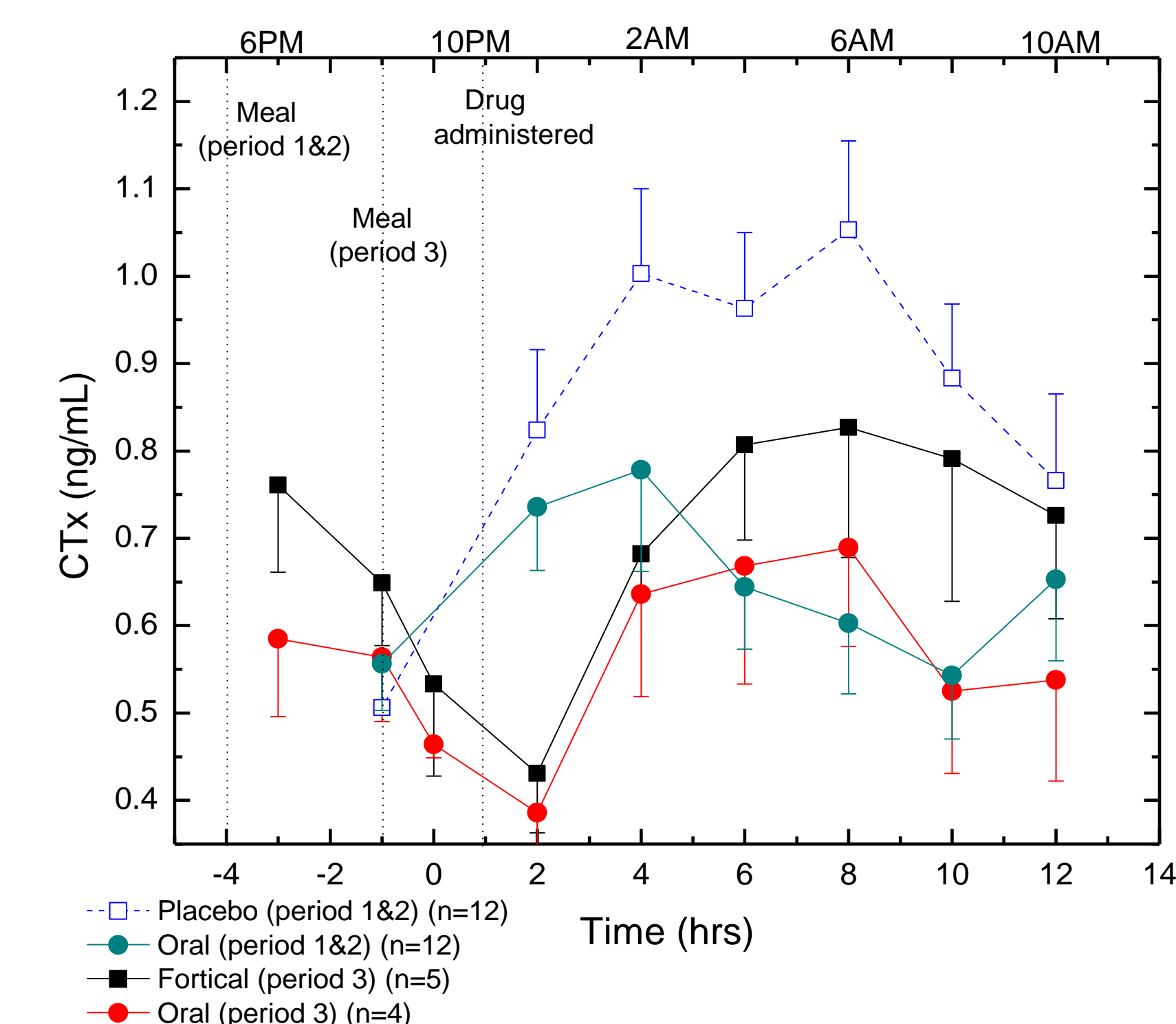
**Figure 5:** PK Response following Administration of Nasal and Oral rsCT in Phase II Study



## DESIGN OF NIGHTTIME DOSING STUDY

- **Design:** Randomized, Open-Label, Placebo-Controlled, Two-Period Crossover Study
- **Subjects:** 24 Normal, Healthy, Postmenopausal Women
- **Study Medication Doses:** 200 µg Recombinant Salmon Calcitonin (rsCT) Tablet, 200 IU Fortical® nasal spray
- **Dosing Schedule:** Subjects will be Dosed either 2 hours or 4 hours following the Evening Meal
- **Assessments:**
  - CTx-1 measurements at pre-doses and 2, 4, 6, 8, 10, and 12 hours Post Dosing
  - Routine Hematology and Biochemistry, Physical Exams, Vital Signs and Adverse Events

**Figure 6:** Post Meal CTx-1 Response to sCT or Placebo Administration



## DESIGN OF PIVOTAL STUDY WITH ORAL sCT TABLET

- **Design:** Double-Blind, Placebo-Controlled, Parallel Design Study
- **Patients:** 520 Postmenopausal Osteoporotic Women
- **Study Medication Doses:** 200 µg Oral sCT Tablet (rsCT B), 200 IU Miacalcin® Nasal Spray
- **Duration:** 48 weeks
- **Assessments:**
  - Primary Endpoint: Lumbar Spine BMD
  - Secondary Endpoints: Serum CTx-1, NTx-1, Serum P1NP
  - Routine Biochemistry and Hematology, Physical Exams, Vital Signs, Immunogenicity and Adverse Events

## Conclusions

- An improved, solid-dosage oral formulation has been developed that affords at least 1 year of room temperature stability and ease of large-scale tablet manufacture on standard equipment
- A Phase II dose selection study has established that a 200 µg oral sCT dose gives a comparable PK and PD profile to the nasal sCT formulation
- A nighttime dosing study demonstrates that the oral sCT tablet is effective in significantly reducing plasma CTx-1 levels at night, when bone resorption is at its highest level
- The nighttime dosing study also demonstrates that the effect of the oral sCT tablet is not impaired by food intake at either 2 hours or 4 hours prior to dosing
- A 12 month pivotal study has been initiated with lumbar spine BMD as the primary endpoint to demonstrate the non-inferiority of the oral sCT tablet to a currently marketed nasal sCT formulation

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