



Clinical Development of an Oral Formulation of Recombinant Salmon Calcitonin

Nozer Mehta
Unigene Laboratories

The Peptide Conference 2010

unigene

Introduction to Unigene

- Founded in 1980
- R & D Facility in Fairfield, New Jersey, Opened in 1983
- cGMP Manufacturing Facility in Boonton, New Jersey Completed in 1995
- Public Offering in 1987
- Corporate Headquarters in Boonton, New Jersey
- Initial Business Model Performing Contract Research for Major Pharmaceutical Companies
- Peptide Manufacturing and Drug Delivery Technologies



Strategic Partnerships and Licenses



Fortical® Nasal Spray

- Fortical® Calcitonin-Salmon (rDNA origin) Nasal Spray Received Marketing Approval by the FDA on August 12, 2005
- Currently Marketed by Upsher-Smith Laboratories
- Fortical sales for year ending Dec 31 2009 were \$50.8 Million
- Fortical Rx share Dec 2009 was 43%



Platform Technologies and Therapeutic Programs

Unigene Dual Business Model

Peptide Technology Platforms

- **Secrapep™**
 - r-DNA Peptide Manufacturing
- **Enteripep™**
 - Solid Dosage Oral Peptide Delivery
- **Nasapep™**
 - Nasal Peptide Delivery

Broad Patent portfolio covering Platform technologies for Recombinant and Oral/Nasal Delivery

Therapeutic Product Programs

- **Oral PTH Analog**
- **Oral Calcitonin**
 - Osteoporosis
 - Osteoarthritis
 - Rheumatoid Arthritis
- **Site Directed Bone Growth**
- **Diabetes & Obesity**
- **Novel Peptides**

Each therapeutic product is covered by the platform patents and/or individual patents on the products

Enteripep[®] :An Innovative Solution For Oral Peptide Delivery

Challenges for Oral Peptide Delivery

- Low absorption through the GI tract
 - Molecules with molecular mass greater than 300 (more than 2-3 amino acids) have limited bioavailability
 - Hydrophilic nature of peptides inhibits absorption
 - Mucus layer of GI tract binds charged molecules such as peptides, inhibiting absorption
- Degradation of peptide in the stomach by gastric acid and pepsin



Oral Peptide Delivery with Enteripep[®]

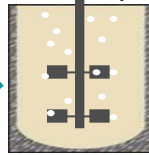
- Enteric coating permits passage through the stomach into the small intestine
- Organic acid inhibits proteases
- Absorption enhancer facilitates the uptake of the peptide by a paracellular transport mechanism
- Absolute bioavailability ranging from 1% to greater than 20% depending upon the peptide

Secrapep™: A Robust and Scalable Peptide Manufacturing Technology

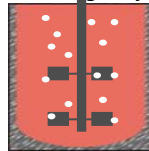
Secrapep™ Recombinant Peptide Manufacturing

Product of Interest is Secreted Directly into the Culture Medium

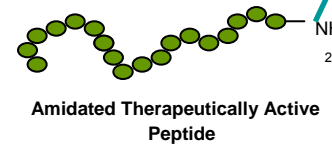
E. coli Expression of Glycine Extended Peptide



CHO Expression of α -Amidating Enzyme

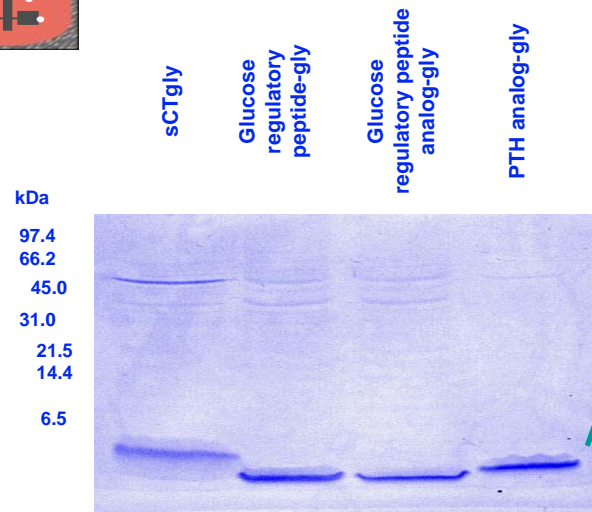


In-vitro Amidation of peptide



In-vitro Amidation

- Required for peptides that need C-terminal amide for activity
- Can enhance bioavailability for non-amidated peptides

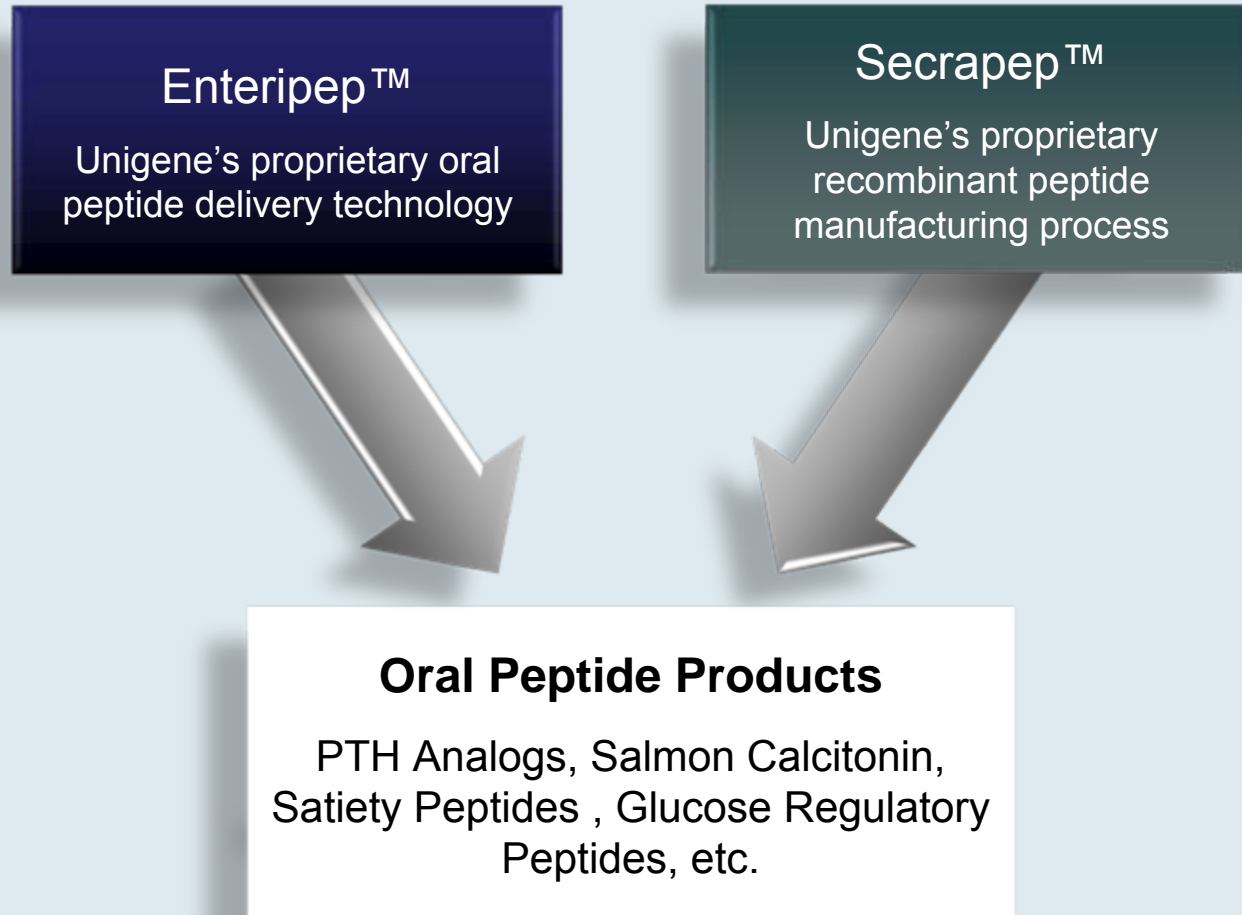


SDS PAGE of Crude Medium

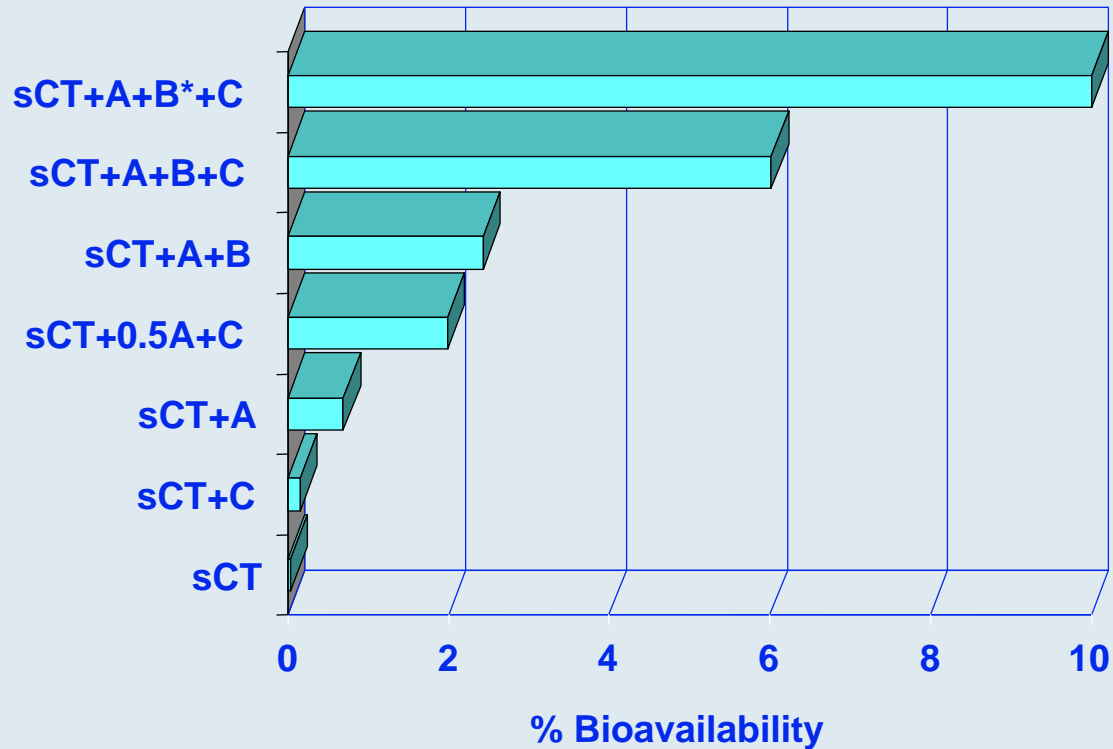
- Enriched Starting Material
- Extracellular yields of 400 to 1300 mg/L
- Reduced purification steps

unigene

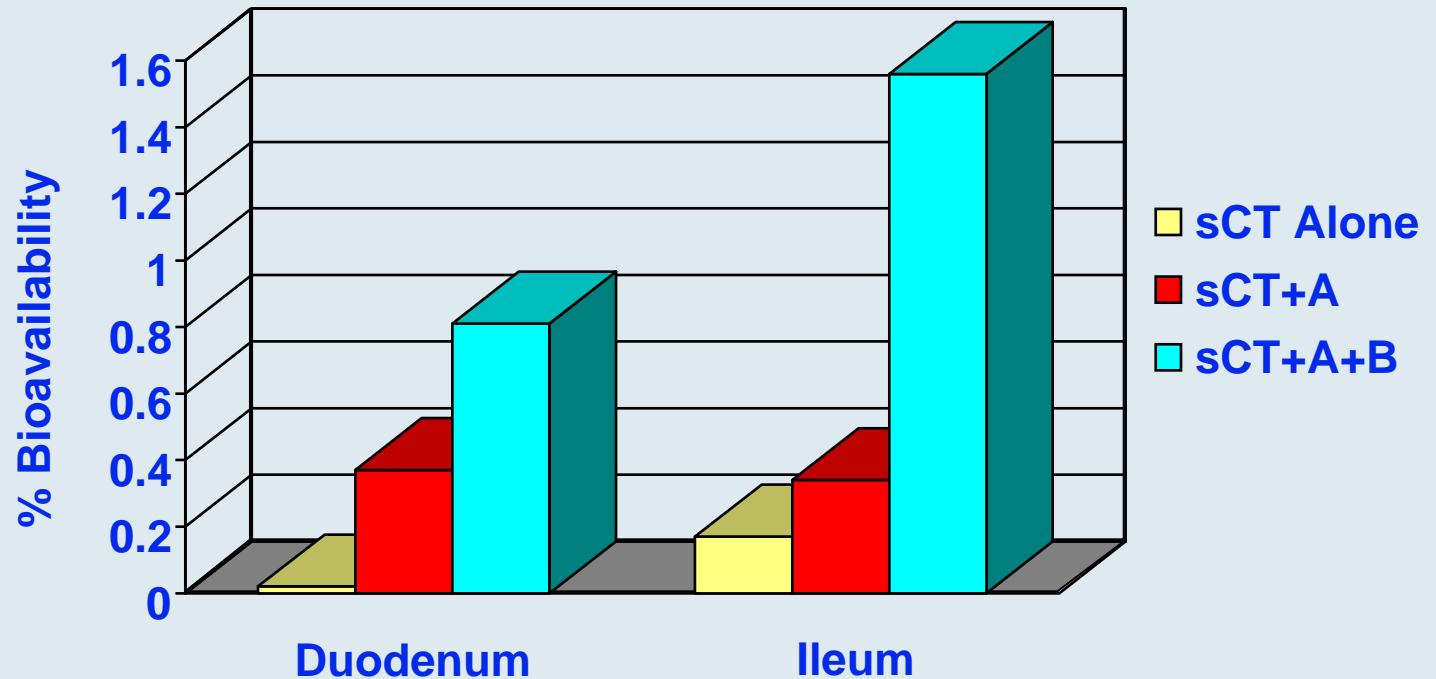
Combination of Technology Platforms Enables Peptide Drugs With Large Markets and Chronic Usage



Effect of Various Additives on sCT Bioavailability in Rats Following Intra-Duodenal Administration



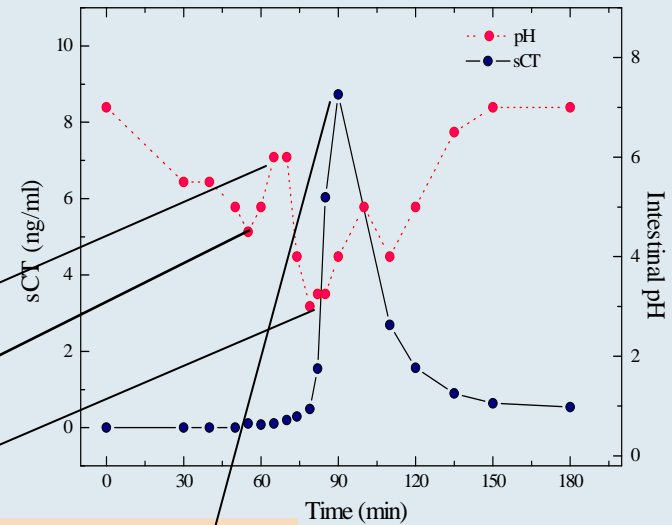
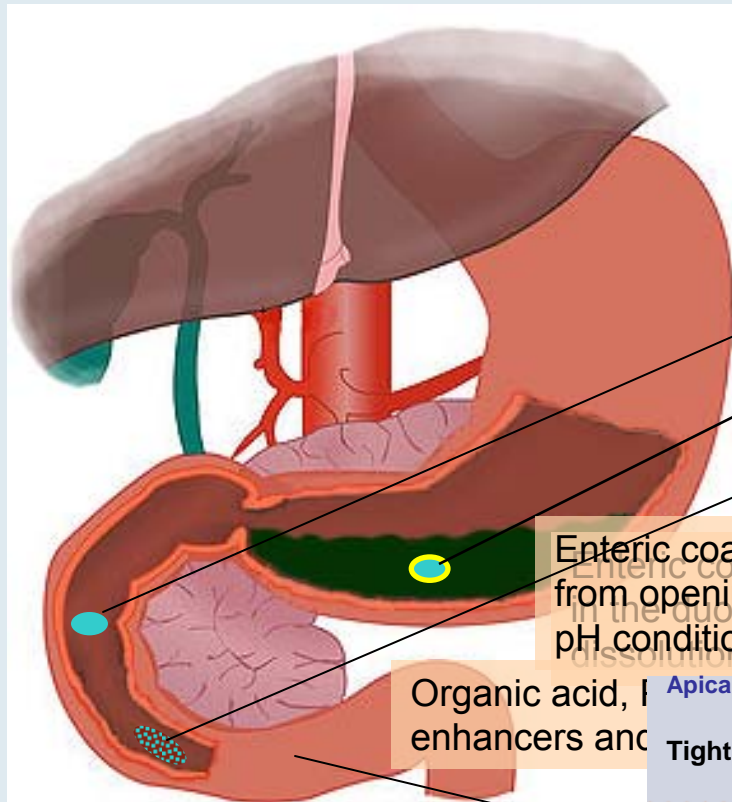
Effect of Additives on Bioavailability of sCT Administered through Intestinal Ports in Dogs



Components of Unigene's Oral Delivery Formulation

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

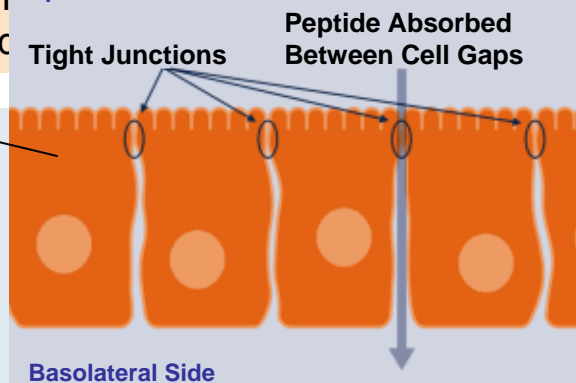
Enteripep™ Oral Delivery Methodology



Enteric coat dissolves at neutral pH in the duodenum exposing pH to dissolution

Organic acid, I enhancers and

Apical Side

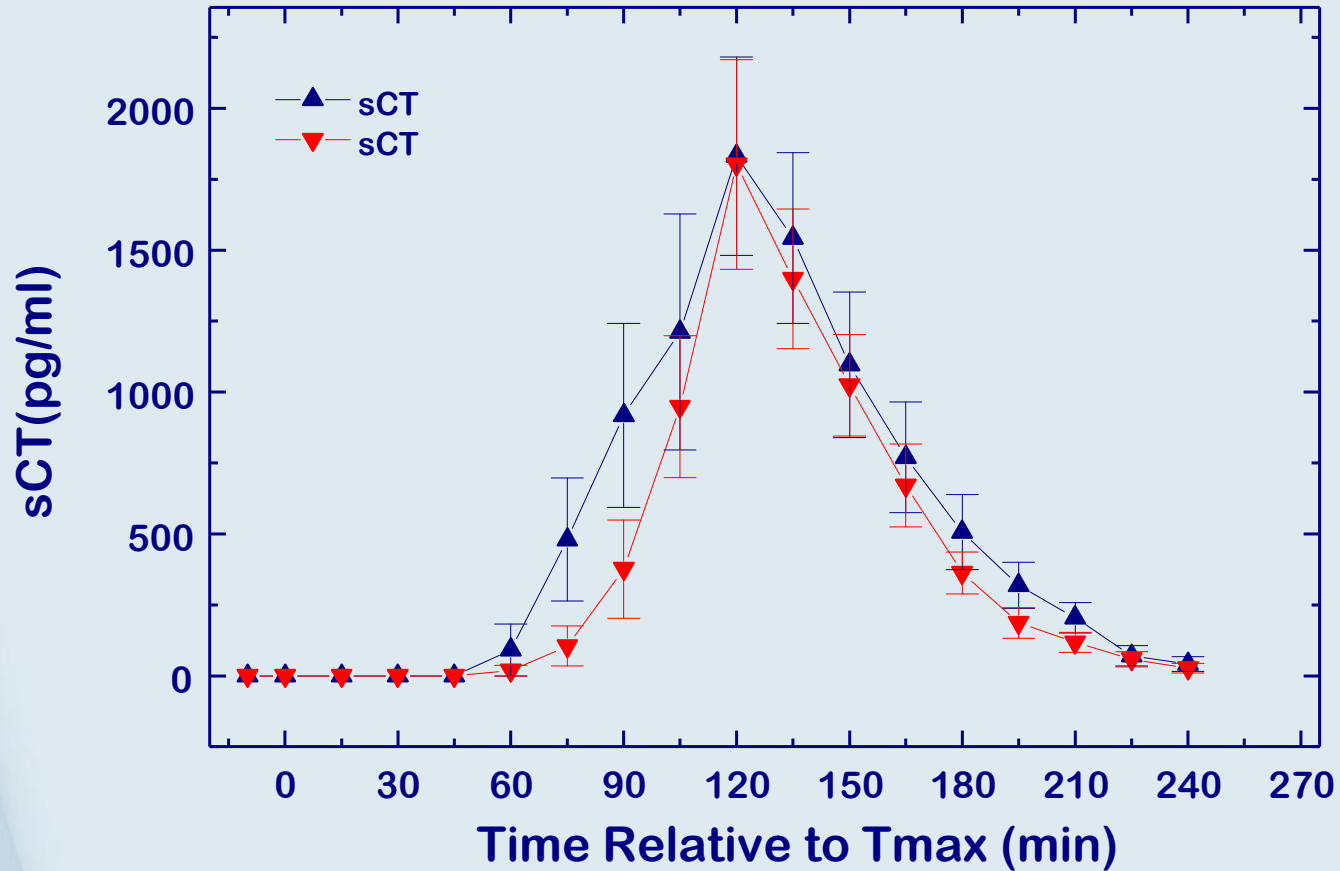


Basolateral Side

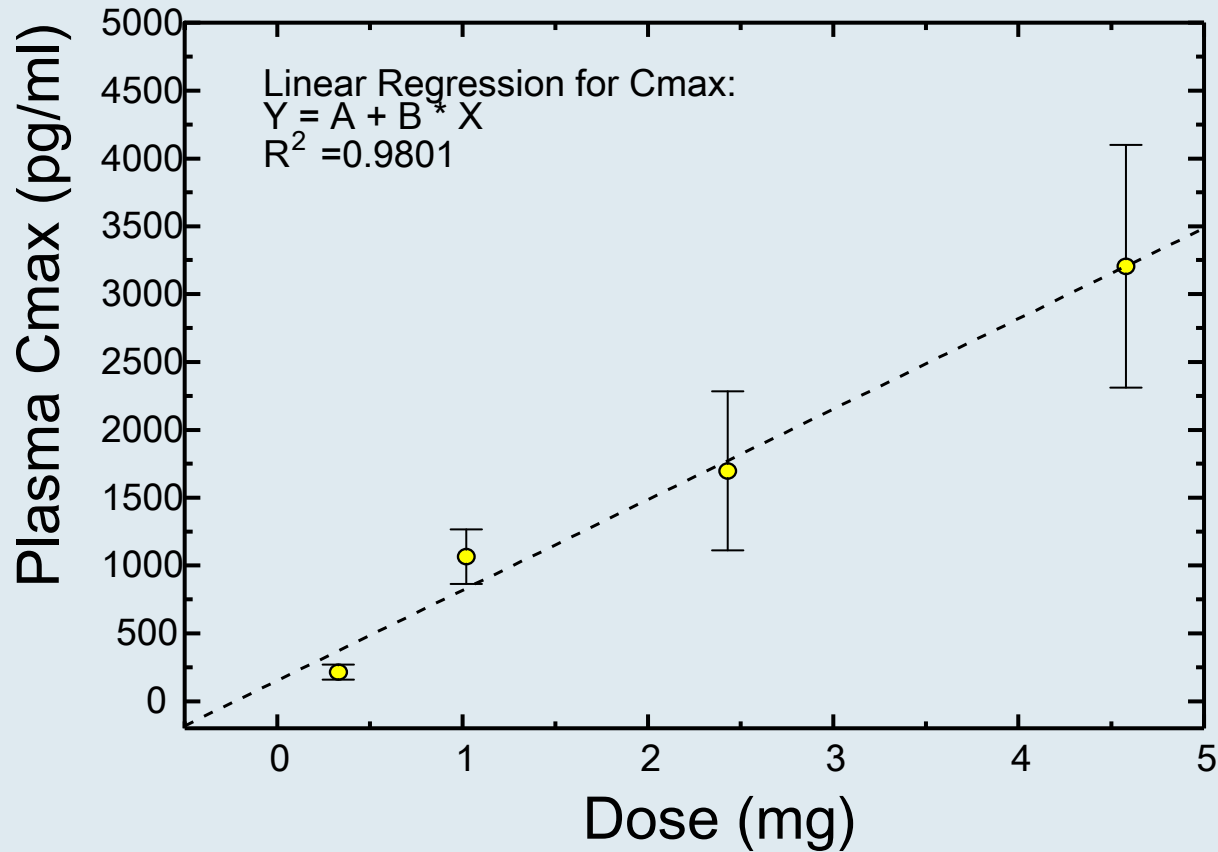
Oral Delivery of Salmon Calcitonin in a Dog Model

- Two Studies were carried out with enteric coated capsules
- Each study was carried out in a group of 8 dogs
- Each capsule contained 1 mg of calcitonin
- The individual T_{max} value of each dog has been normalized to a common T_{max}

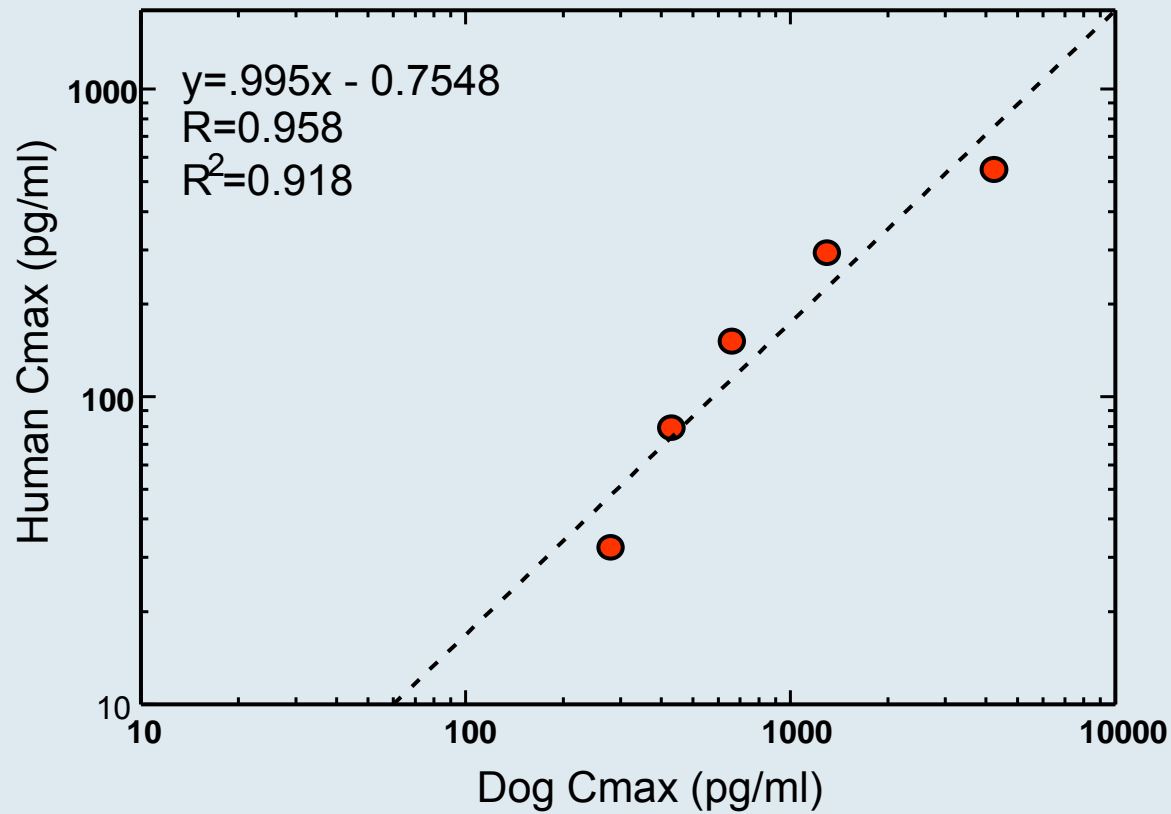
Mean PK Profile After Oral Delivery of sCT



Oral Dosing in Dogs: Demonstration of Linearity with Respect to Dose



Correlation of Dog and Human Plasma sCT Levels



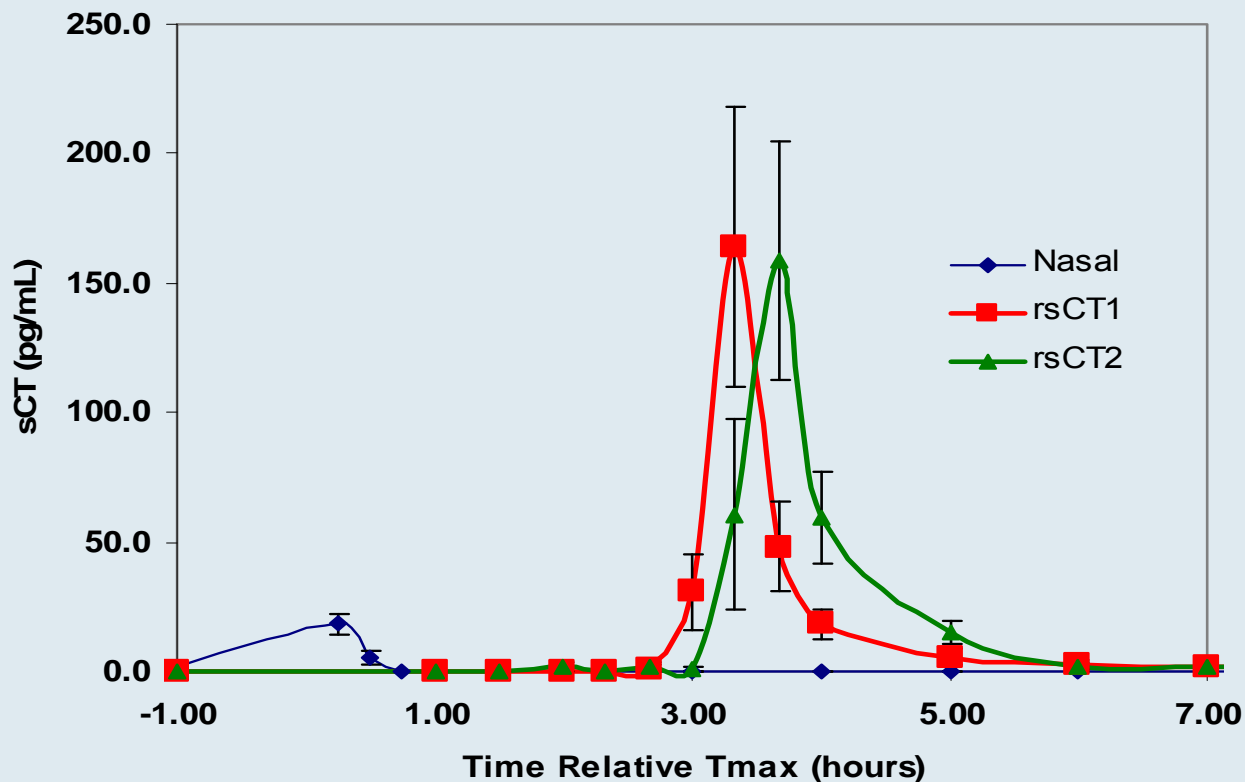
Unigene's 505(b)(2) Oral sCT Program

- Exploratory study to select formulation and determine PK and PD parameters
- Dose selection study to pick oral dose that is equivalent to nasal sCT
- Nighttime dosing study
- Pivotal study to determine comparable efficacy of oral and nasal formulations.
- The approved indication will be identical to Miacalcin: Indicated for the treatment of postmenopausal osteoporosis in women greater than 5 years postmenopause with low bone mass relative to healthy premenopausal women.

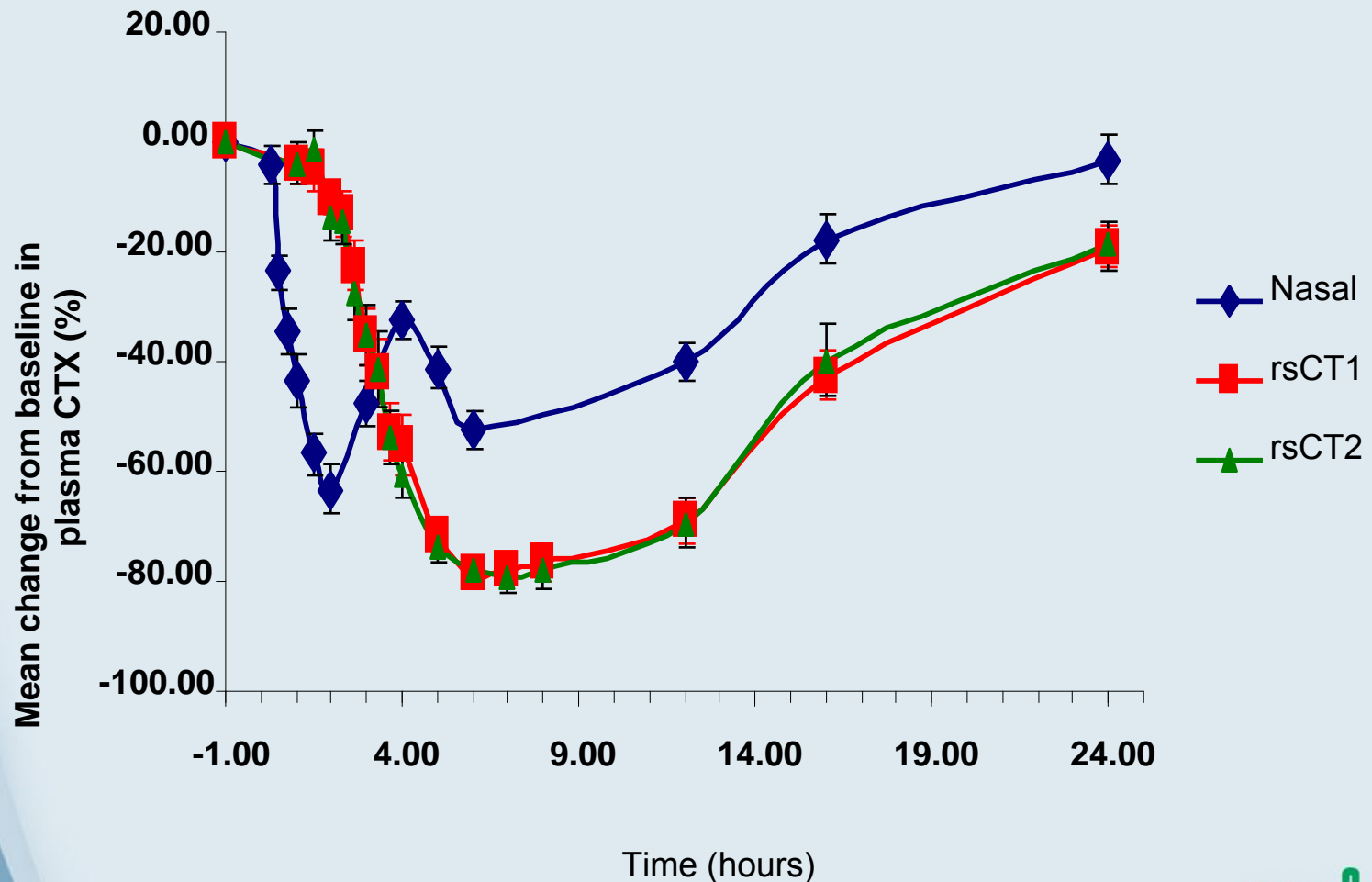
Phase I sCT Exploratory Study with “Monolayer” Formulation

- *Design:* Single Dose, Open, Crossover Design Study
- *Subjects:* 18 Postmenopausal Women
- *Study Medication Doses:* 500 µg +LLC Tablet (rsCT1), 1500 µg – LLC Tablet (rsCT2), 200 IU Fortical[®] Nasal Spray
- *Assessments:*
 - PD Measurements (CTX-1) up to 24 hours Post Dosing
 - PK Measurements up to 24 hours Post Dosing

sCT PK Profiles Following Oral Administration of sCT to Postmenopausal Women



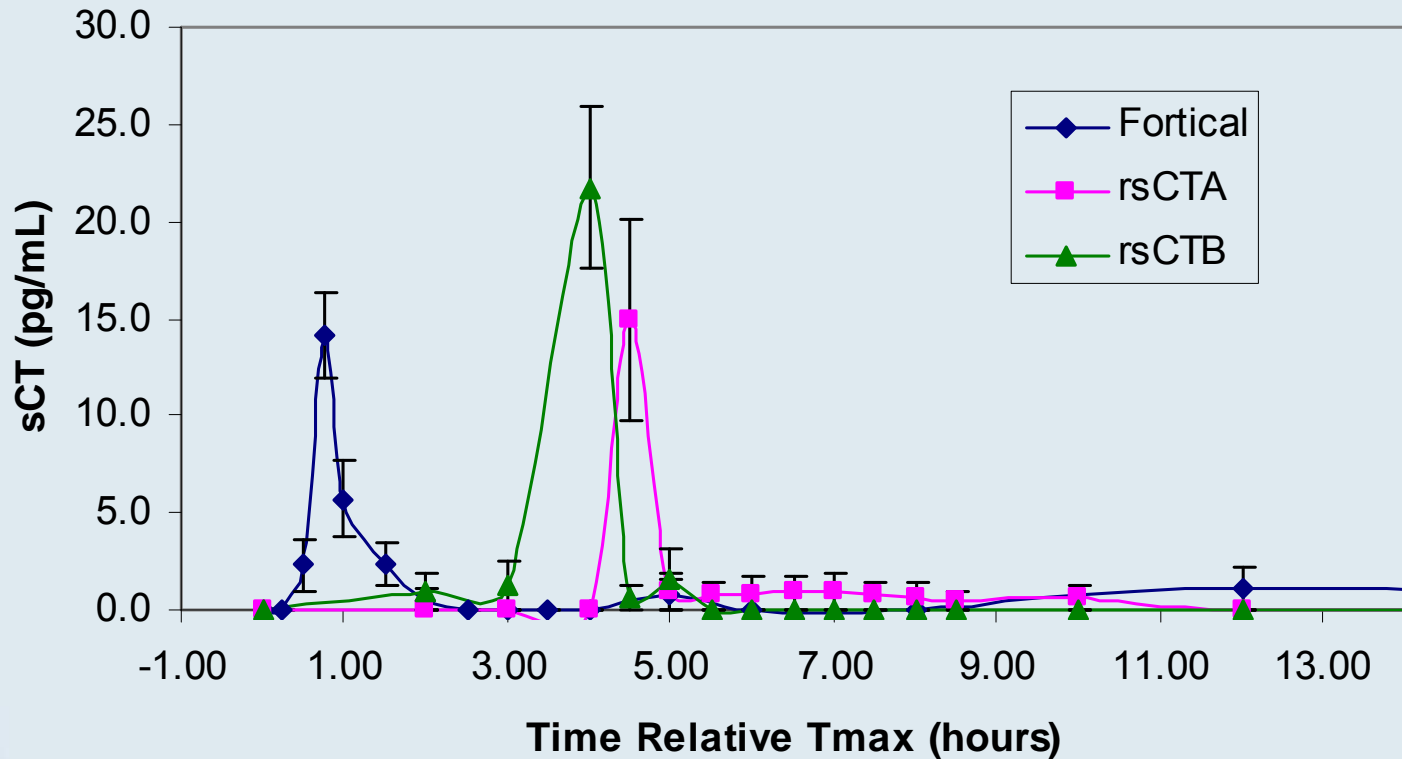
Percent Change in CTX-1 Following Oral Administration of sCT to Postmenopausal Women



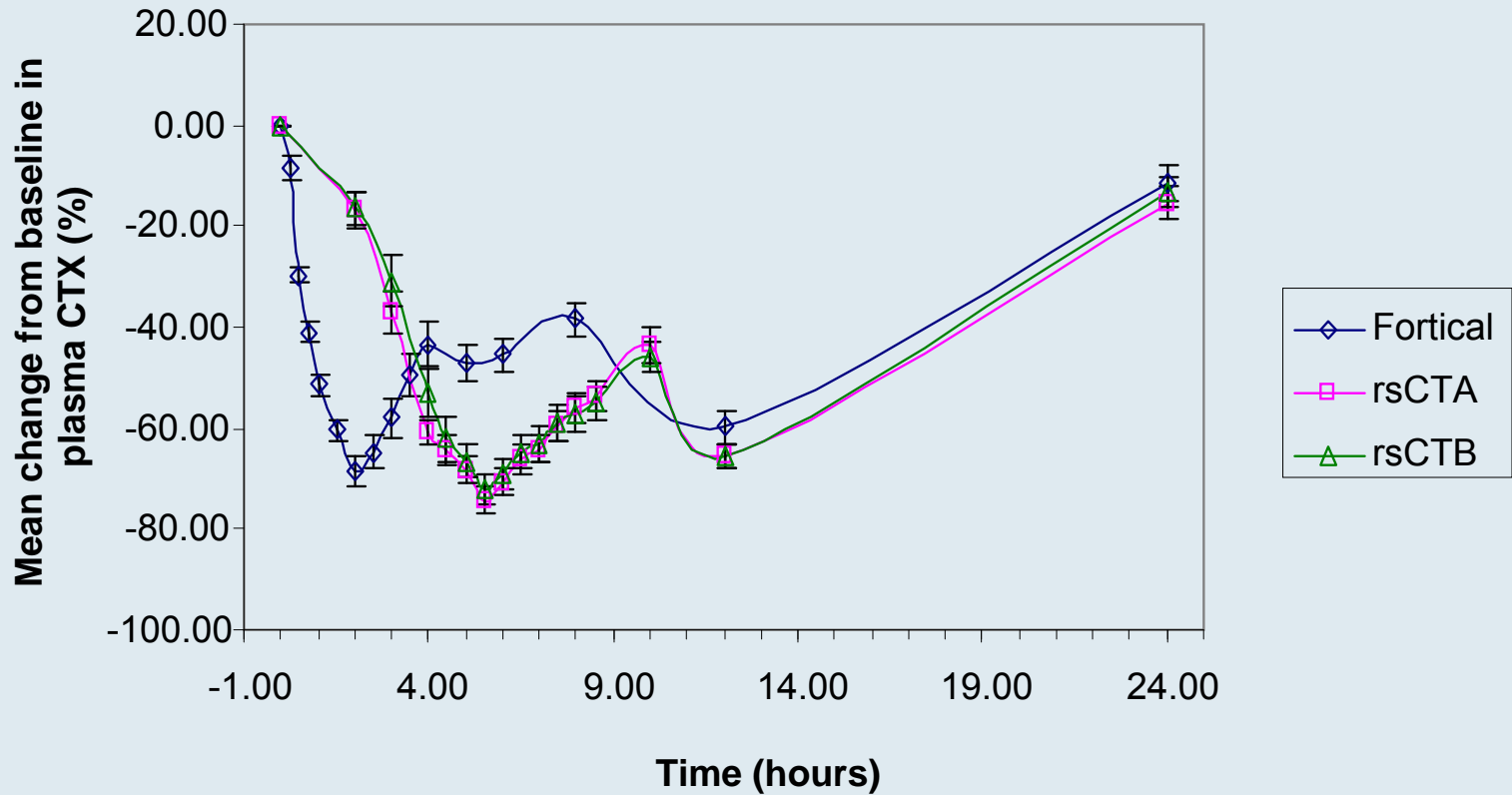
Phase II Oral sCT Dose Selection Study: Tablet Formulation Without LLC

- *Design:* Single Dose, Open, Crossover Design Study
- *Subjects:* 24 Post Menopausal Women
- *Study Medication Doses:* 150 µg Tablet (rsCTA), 200 µg Tablet (rsCTB), 200 IU Fortical[®] Nasal Spray
- *Assessments:*
 - PD Measurements (CTX-1) Up To 24 hours Post Dosing
 - PK Measurements Up To 24 hours Post Dosing

Mean sCT PK Profiles Normalized to a Common Tmax



Mean Change in Baseline Plasma CTX

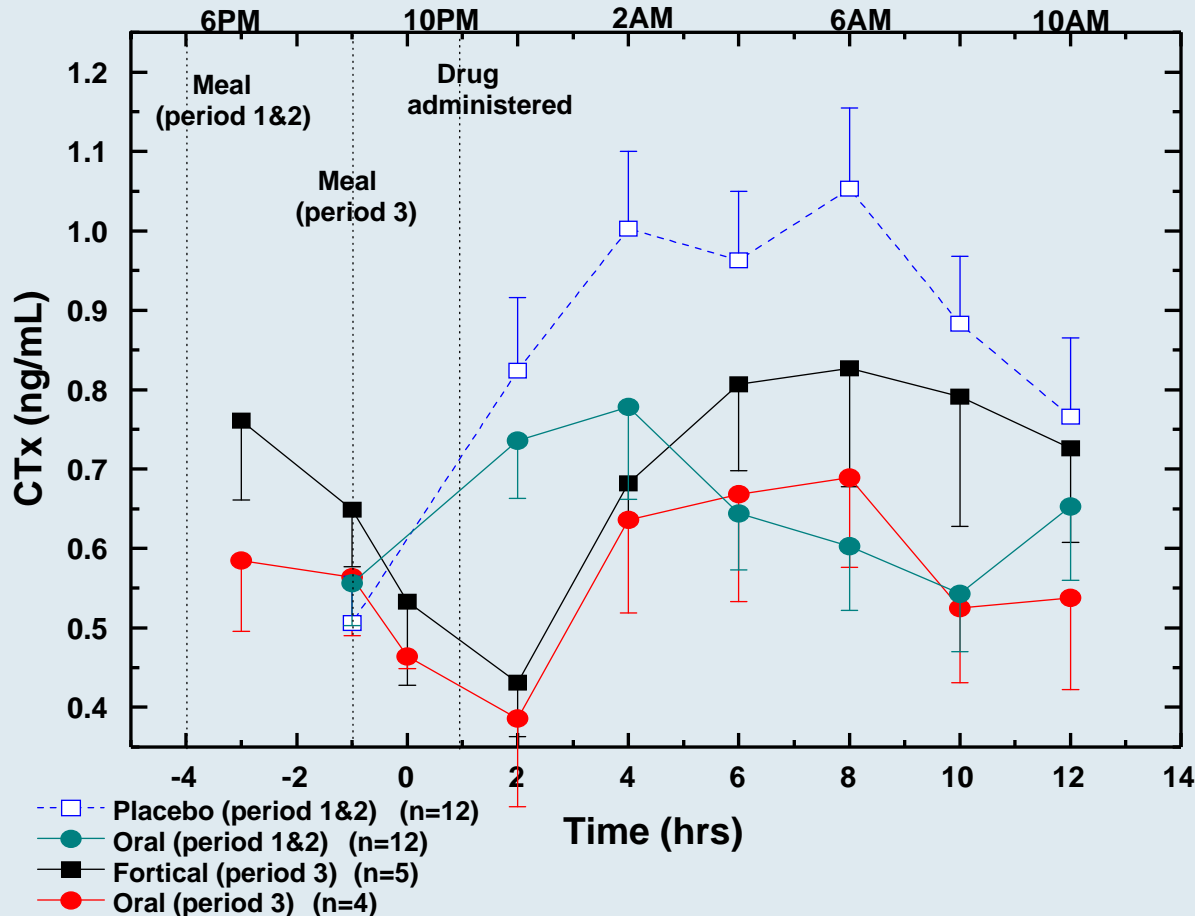


Design Of Nighttime Dosing Study

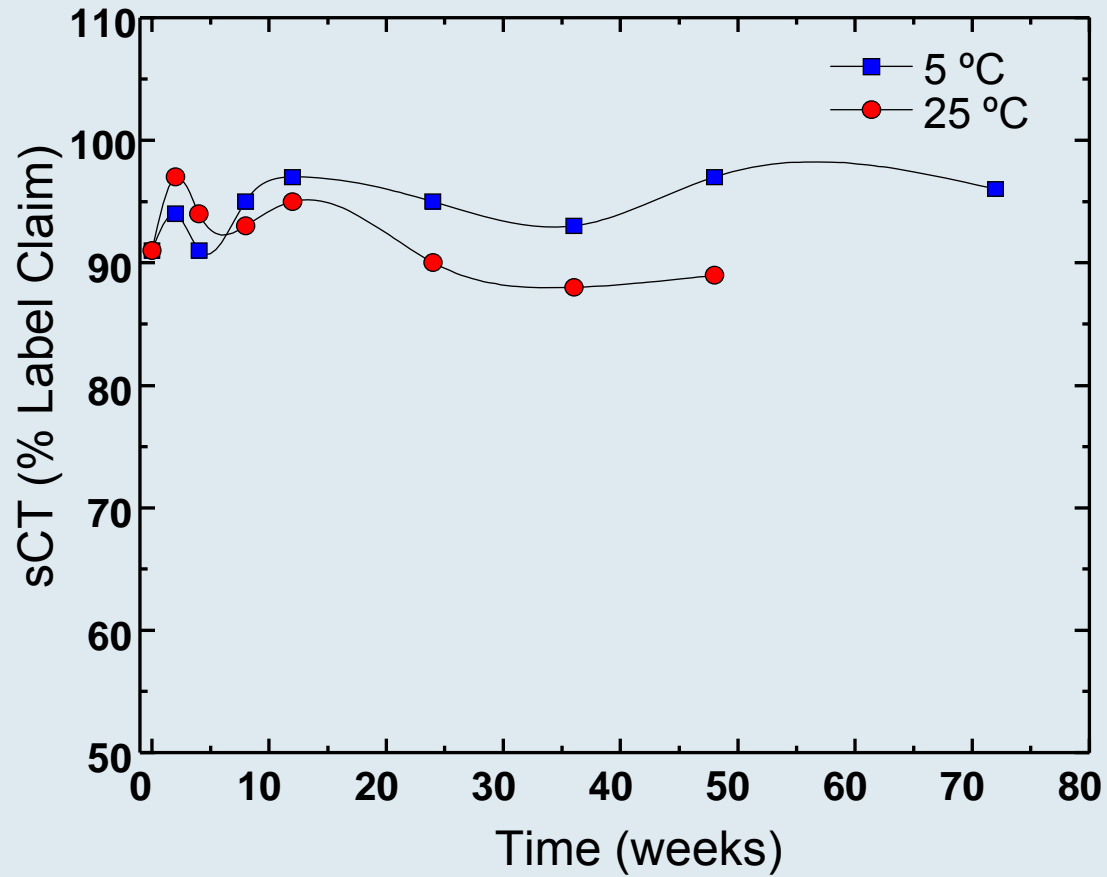
Design: Randomized, Open-Label, Placebo-Controlled, Two-Period Crossover Study

- *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 5 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

Nighttime Dosing of Oral sCT 2 or 5 Hours Following Evening Meal



Tablet Stability



Current Status of Phase III Clinical Program

- FDA has agreed to a 505(b)(2) Submission
- 200 µg dose for Oral sCT Tablets Selected for Pivotal Study
- SPA Submitted and Approval of Study Design Obtained from FDA
 - 48 Week Study with Lumbar Spine BMD as Primary Endpoint
 - Sites in US, EU, and South Africa
 - Double Blind Double Dummy Design
 - Comparator is Miacalcic or Miacalcin Nasal Spray
 - Primary Clinical Endpoint 12 month Vertebral BMD
 - Non-Inferiority Design with Placebo Control
 - 560 Patients Total in 3 Arms
 - Immunogenicity Evaluation at 12 and 48 weeks
- EMEA Formal Scientific Advice obtained October 7, 2008
- Trial has completed enrollment and data will be available in spring of 2011

Advantages of Unigene's Fortical[®] Oral

- Well-Established Safety Record for Salmon Calcitonin
- Low Cost-of-Goods based on Unigene's Recombinant Manufacturing Technology
- High Purity of API and Novel Oral Formulation with Good Bioavailability
- Can Achieve Blood Levels Significantly Greater than Achieved with Miacalcin
- Salmon Calcitonin only Known Osteoporosis Therapy with Analgesic Effect on Acute Vertebral Fractures Demonstrated in Placebo-Controlled Clinical Trials
- May be Used Sequentially following Treatment with an Anabolic Agent such as Forteo[®] to Maintain Bone Mass

Acknowledgements

- **Clinical**
 - James Gilligan
 - Kristine Erickson
 - Sheela Mitta
- **Tablet Manufacturing**
 - William Stern
 - Paul Shields
- **Purification & Amidation**
 - Angelo Consalvo
- **ImmunoAssay Development**
 - Amy Sturmer
 - Ali Bolat
 - Tulin Hakimi
- **Molecular Biology**
 - Vicki Ray
 - Chris Meenan
 - Seth Pennington
 - Nancie Souders

Safe Harbor Statement

Safe Harbor statements under the Private Securities Litigation Reform Act of 1995: This presentation contains forward-looking statements as defined in Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. Such forward-looking statements are based upon Unigene Laboratories, Inc.'s management's current expectations, estimates, beliefs, assumptions, and projections about Unigene's business and industry. Words such as "anticipates," "expects," "intends," "plans," "predicts," "believes," "seeks," "estimates," "may," "will," "should," "would," "potential," "continue," and variations of these words (or negatives of these words) or similar expressions, are intended to identify forward-looking statements. In addition, any statements that refer to expectations, projections, or other characterizations of future events or circumstances, including any underlying assumptions, are forward-looking statements. These forward-looking statements are not guarantees of future performance and are subject to certain risks, uncertainties, and assumptions that are difficult to predict. Therefore, our actual results could differ materially and adversely from those expressed in any forward-looking statements as a result of various risk factors. These risks and uncertainties include the risks associated with the effect of changing economic conditions, trends in the products markets, variations in Unigene's cash flow, market acceptance risks, technical development risks and other risk factors detailed in Unigene's Securities and Exchange Commission filings.