

Clinical Development of An Orally Delivered Recombinant PTH Analog

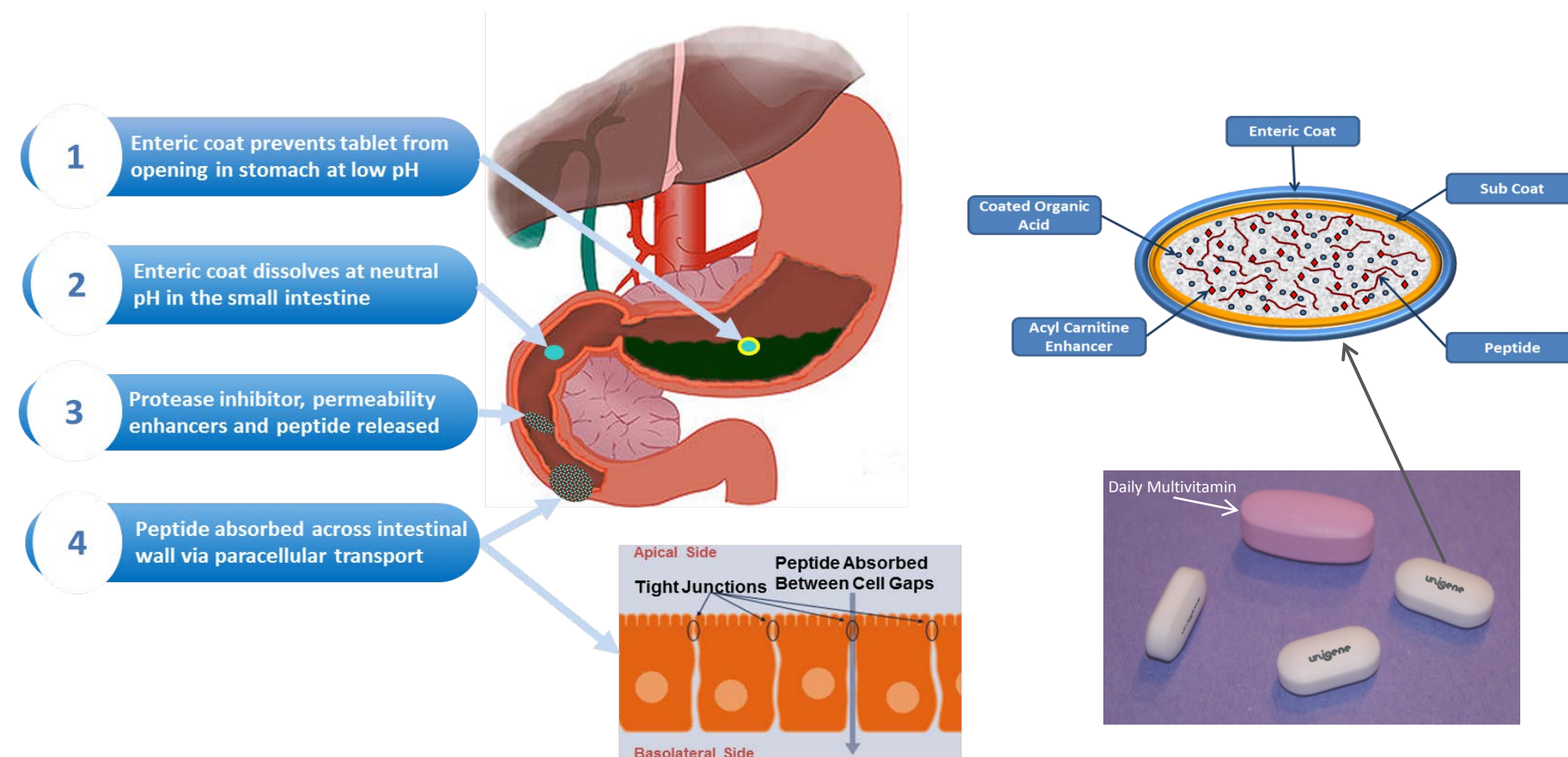
Nozer Mehta¹, Roxanne Tavakkol¹, Kristine Erickson¹, William Stern¹, Tamara James¹, Seymour Fein¹, Sheela Mitta¹, Amy Sturmer¹, Paul Shields¹, Andy Rasums¹, Lorraine Fitzpatrick² ¹Unigene Laboratories, Inc., 81 Fulton Street, Boonton, NJ 07005, ²GlaxoSmithKline, 709 Swedeland Road, King of Prussia, PA

Abstract

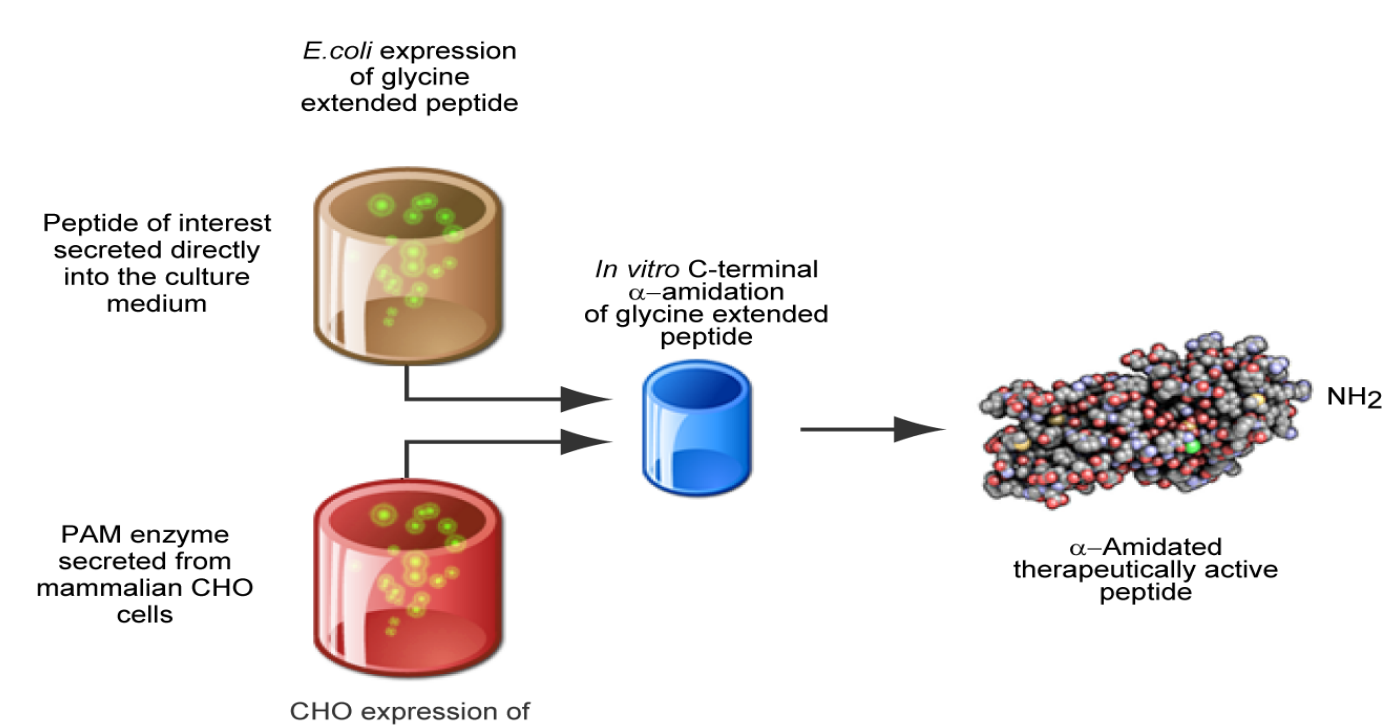
An oral tablet formulation of a recombinant human PTH analog has been developed and initially optimized in a dog model. The rhPTH analog was produced by recombinant expression in *E. coli*. An initial rising dose pharmacokinetic (PK) study in postmenopausal women examined PTH levels following administration of tablets containing 2, 4, 6 and 8 mg of the rhPTH analog. A linear dose-dependent response was seen at the three higher doses. A second two-period replicate dose PK study was then carried out to evaluate the safety as well as the inter- and intra-subject variability of two dosing regimens in an open label study in postmenopausal women. Blood samples were collected over a 6 hour period following dosing and rhPTH analog levels were quantified using a specific sandwich ELISA. The C_{max} values with both the 6 mg and 2x4 mg tablets were in the 200 to 300 pg/mL range, and hence achieved or exceeded blood levels that have been shown to be anabolic with an existing injectable formulation. The PK profiles were consistent with the requirement for bone anabolic activity, with an elimination $t_{1/2}$ of 13-21 minutes. Both the inter- and intra-subject variability was deemed to be more desirable with the 6 mg dose. There were no clinically significant changes in serum calcium, phosphate, magnesium or endogenous PTH activity and no serious adverse events were reported. A phase 2 study has been initiated in postmenopausal osteoporotic women to further evaluate the safety and efficacy of the oral rhPTH analog formulation. This 24-week double blind, randomized, repeat dose parallel group study will evaluate the oral rhPTH analog formulation or a placebo tablet. The study also includes an open label active comparator Forsteo[®] arm. The study will measure the change in bone mineral density at the lumbar spine, compared to baseline, in the three arms of the study. Serum markers of bone formation and resorption will also be measured as a secondary endpoint.

Background

Unigene's Proprietary Oral Peptide Delivery Technology



Unigene's Proprietary Recombinant Peptide Manufacturing Technology



1. Oral Tablet Optimization and Phase I Trial Design for rhPTH Analog

Tablet Optimization

- Identified a coated citric acid as compatible excipient with peptide affording room temperature stability
 - Peptide bonds are labile in the presence of organic acid, reducing stability of tablet
- Simplified manufacturing process by preparing standard non-bilayer tablets
- Demonstrated tablet with appropriate hardness, friability and stability could be prepared by direct compression of dry blended peptide, coated citric acid and other excipients
- Optimized thickness and type of subcoat and enteric coat
- Demonstrated >6 month room temperature stability of rhPTH analog tablet
- Filed broad patent application on improved technology that will provide protection up to 2028

2. Results from Phase I Studies

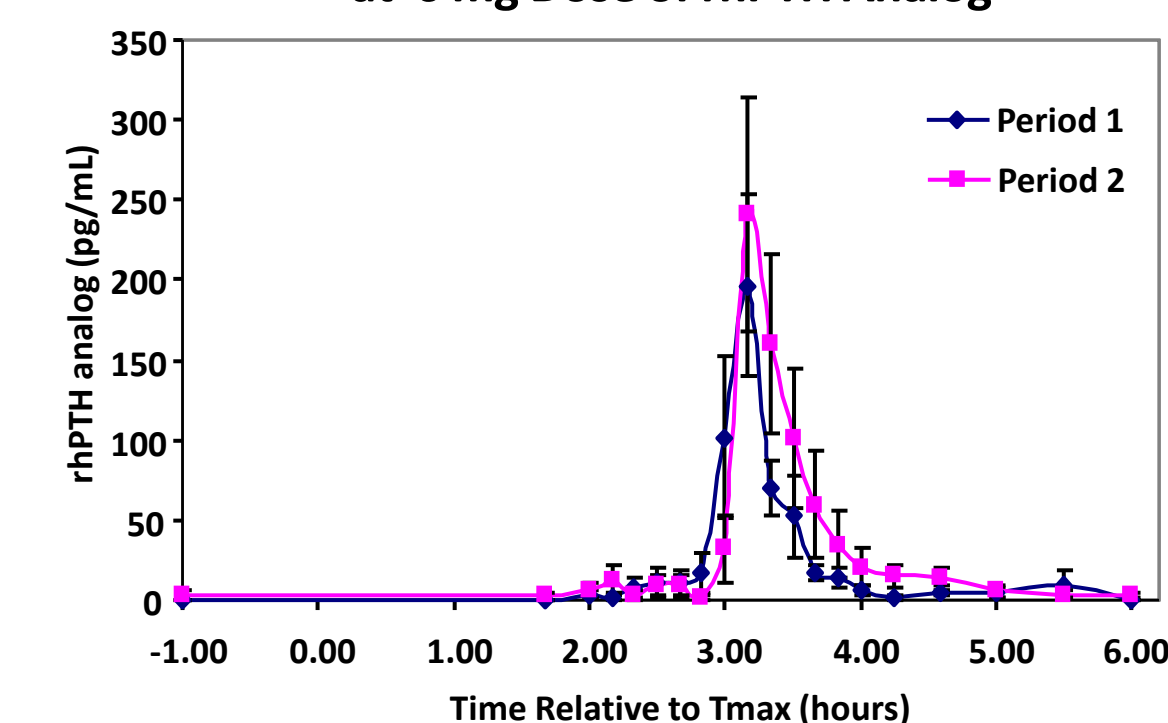
Phase I Objectives

- Two-period replicate dose study to determine inter- and intra-subject variability
- Measure rhPTH analog plasma levels with a sandwich ELISA that measures only the intact molecule
- Determine whether blood levels and PK profile are adequate for bone anabolic effect
- Determine safety of orally administered rhPTH analog

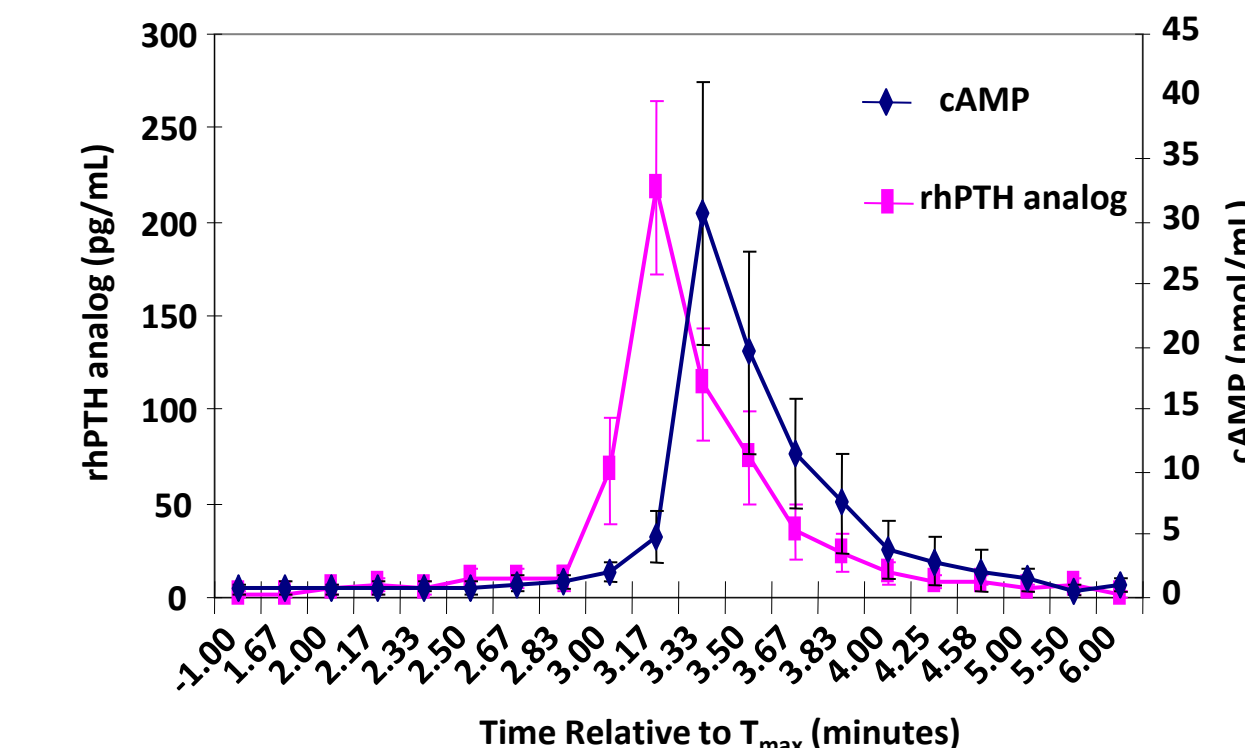
PK Results: Phase I Study

Dose	Period	C_{max} pg/mL
6 mg	Period 1	197
6 mg	Period 2	241
2 x 4 mg	Period 1	361
2 x 4 mg	Period 2	163

Period 1 vs Period 2 Intra-subject Data at 6 mg Dose of rhPTH Analog



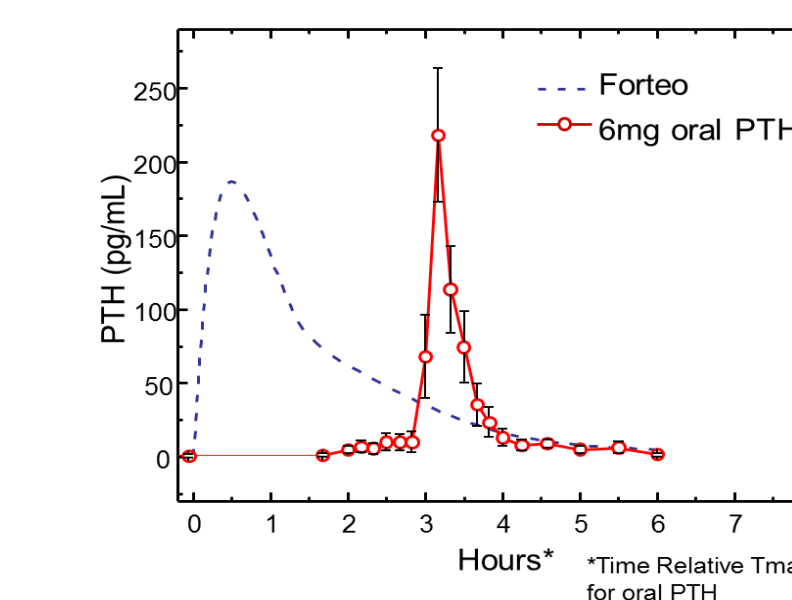
Mean rhPTH Analog and cAMP Levels for All Subjects Given 6 mg Tablets



Safety Results from Phase I Study

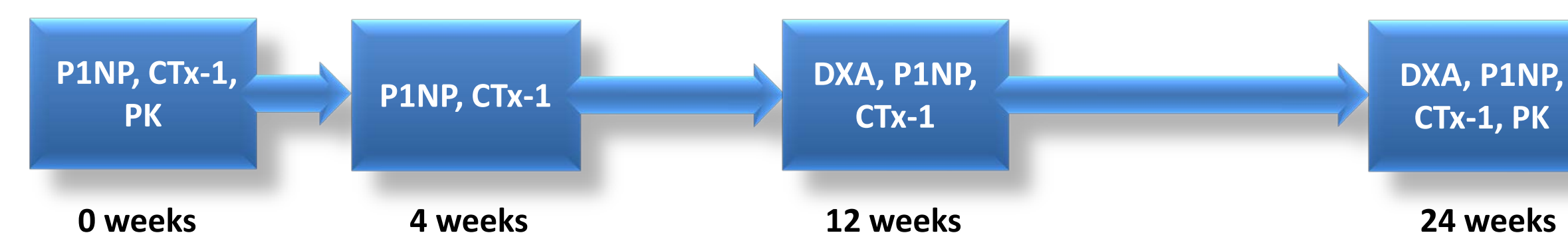
- There were no cardiac events as measured by ECG, Holter monitoring and telemetry at either the 6 mg or 2x4 mg dose
- The sole episode of clinically significant orthostatic hypotension at each dose level was transient
- There were no serious AEs reported during the study, and no clinically significant changes were seen in total Ca, PO_4 , Mg and endogenous PTH

Comparison of PK Profiles of Forsteo[®] vs 6mg Dose of Oral rhPTH Analog



3. Design of Phase II Clinical Trial

- Study design:** Randomized, double blind, repeat dose, parallel group, study of oral rhPTH analog tablets or Placebo tablets with an open arm of the Forsteo[™] injectable formulation
- Primary endpoint:** To characterize percent change from baseline in bone mineral density (BMD) as measured by DXA during screening, 12 and 24 weeks.
- Secondary endpoints:**
 - PINP and CTx-1 (markers for bone turnover)
 - PK profile of rhPTH analog tablets in the study population
- Study Duration:** 6 months
- Population:** 93 postmenopausal osteoporotic women equally divided between the three treatments
- Safety Evaluations:** physical examination, laboratory tests, AEs



Conclusions

- An oral rhPTH analog formulation with acceptable bioavailability, variability and safety has been demonstrated in Phase 1 studies
- The C_{max} value with a 6 mg tablet is higher than that of parenteral teriparatide formulations at 20 µg dose, and the pulsatile PK profile is consistent with the requirement for bone anabolic activity
- Anabolic potential of this oral tablet rhPTH analog formulation is currently being evaluated in a 6 month Phase II study in postmenopausal osteoporotic women where the primary endpoint will be an increase in lumbar spine BMD compared to baseline
- Markers of bone resorption and bone formation, as well as safety parameters, are also being evaluated
- Further successful clinical development of this rhPTH analog formulation will result in a patient friendly oral tablet therapy for the treatment of established osteoporosis