# PTH1-34 Delivered Orally with Novel Drug Delivery Technology - First in Humans Results

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## Introduction

Current therapies for osteoporosis are based on antiresorptive agents, such as bisphosphonates, estrogen, selective estrogen receptor modulators (SERMs), calcitonins and a monoclonal antibody against receptor activator of Nf kappa B ligand (RANKL).[1]

The only currently available anabolic treatment option for osteoporosis is parathyroid hormone (PTH), which has consistently demonstrated a significant increase in bone formation leading to increased bone mass and substantial reduction in vertebral and non-vertebral fracture risk. PTH is only available as a daily parenteral dosage form. The discomfort and local irritation associated with a daily injectable regimen often leads to low compliance and consequently limits the full therapeutic potential of the drug. An oral form of PTH would very likely improve patient acceptance, and long-term compliance and adherence.[2]

A new oral delivery system of human PTH1-34 is being developed as a more convenient option for the treatment of osteoporosis.

We report herein the results of a First In Human study using Entera's oral PTH1-34.

## Technology

The technology is a novel drug delivery platform that enables the absorption of intact bioactive polypeptides and proteins through the gastrointestinal tract (GIT). It is based on known inactive pharmaceutical ingredients which where found to be safe in extensive human testing. No new chemical entities (NCE) were utilized.

## Objectives

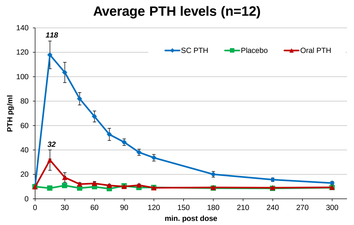
The primary objective of these studies was to assess the safety and tolerability of a new oral PTH1-34 delivery system. Secondary objectives included comparison of a single oral dose of PTH1-34 absorption characteristics and pharmacokinetic (PK) with the human PTH1-34 drug that is in clinical use and administered by s.c. injection. The formulation was also modified throughout the study for additional optimization.

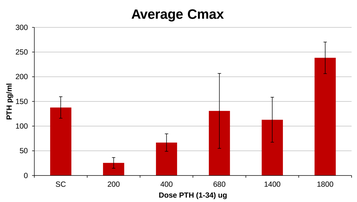
## Methods

A 3 stage Phase I study was conducted at the Hadassah Clinical Research Center under a Hadassah Medical Ctr. IRB. 42 healthy volunteers were included throughout the study receiving various doses and formulations.

## Results

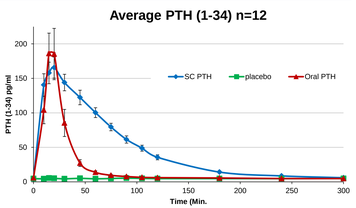
Following preclinical studies showing an 8% bioavailability, the initial dose for the first in human study was restricted to 200ug and resulted in a relatively low Cmax. However, the PK profile was in line with the required 'rapid increase-rapid decrease' which leads to the anabolic effect of PTH.




In the second stage of the study the dose was escalated which at first resulted in an increase in variability. By changing the formulation the variability was reduced to levels similar to the SC injection. Correlation between the dose and plasma PTH 1-34 level was apparent.

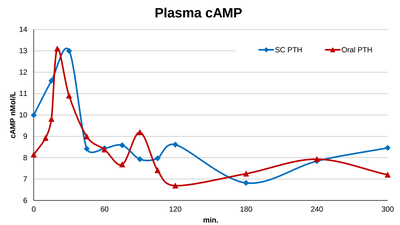
In the final stage 12 volunteers (male & female) were treated with the SC PTH/ placebo/ Oral PTH. Additional time points were added to get a higher resolution of the PK profile. Tmax and Cmax for SC and Oral PTH were similar. The Oral PTH decreases more rapidly resulting in larger error bars for each time point at the peek.




## Results (continued)

cAMP is a known marker of PTH activity. Although usually measured in the urine it is apparent from the analysis of the blood plasma that the increase in circulating PTH led to an increase in circulating cAMP.

This is a significant indication of activity of the orally administered PTH.




## Conclusions

In addition to safety this study presents a strong indication of biologically relevant activity and a suitable pharmacokinetic profile of our novel oral PTH 1-34. Orally administered PTH 1-34 showed a dose-dependent absorption with a PK profile characterized by a rapid Tmax and fast elimination rate which simulate the desired PTH profile required for its anabolic effect.[3,4]

More studies are required, however, our first in human study of oral PTH 1-34 shows that Entera's Oral PTH1-34 can potentially treat osteoporosis patients, showing a PK profile similar to the already approved SC PTH injection.

Oral drug absorption in general, has inherently greater variability in absorption as compared to parenteral administration due to variations between the gastrointestinal tracts' physiology of different individuals. Nevertheless and despite a relatively low number of study participants, our optimized formulation of PTH markedly reduced the oral absorption variability to acceptable levels.

## References

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