Transforming Anabolic Treatments for Osteoporosis:

New Clinical Data Supports a **Single EB613 Tablet [Oral PTH(1-34)]** as the Final Candidate for a Phase 3 Study

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Disclosures

- Gregory Burshtein, Constantin Itin, Hillel Galitzer, Michal Kushnir, Anke Hoppe, and Miranda Toledano – are employees of and own stock/options, Entera Bio Ltd.
- Felicia Cosman – Key clinical advisor and scientific advisory board member, stock options, Entera Bio Ltd.
- Helen Pentikis – Clinical Pharmacology advisor and owns stock/options, Entera Bio Ltd.
- Chana Sternberg and Yoseph Caraco – nothing to disclose

Barriers to Oral Peptide Delivery

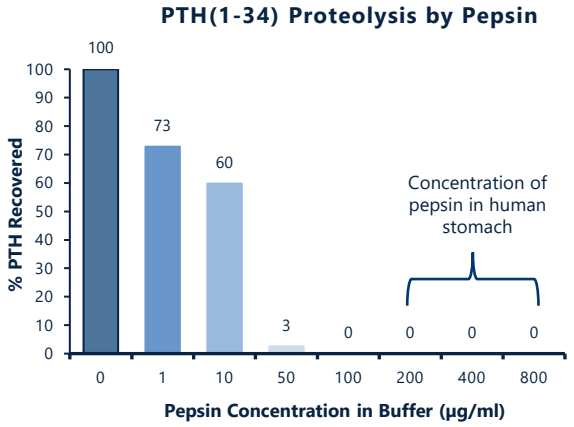
Proteolytic Degradation

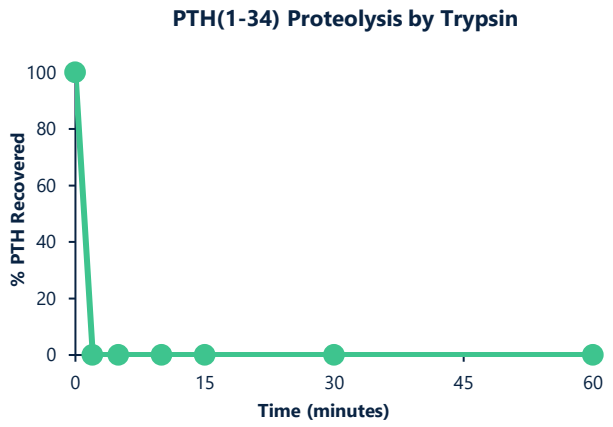
Stomach:

- Pepsin-mediated peptide cleavage
- Acidic pH → protein denaturation

Small Intestine:

- Trypsin & α-chymotrypsin degradation
- Brush-border metabolism





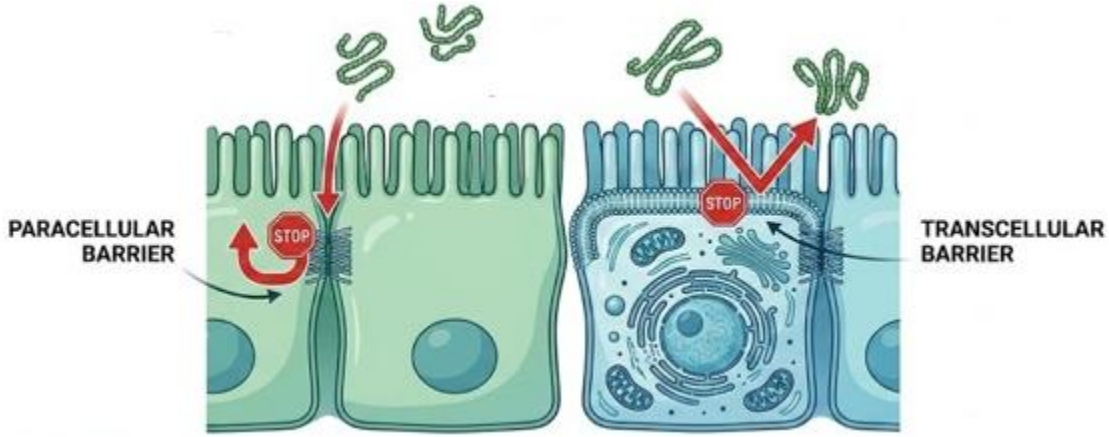
100%

peptide breakdown within few min of luminal exposure

Epithelial Permeability Barrier

Paracellular: Too large for tight junction transport

Transcellular: Too hydrophilic to cross the hydrophobic core of enterocyte barrier



~0%

typical oral bioavailability for unformulated peptides

Burshtein et al. Int. J. Pharm.: X. 2021

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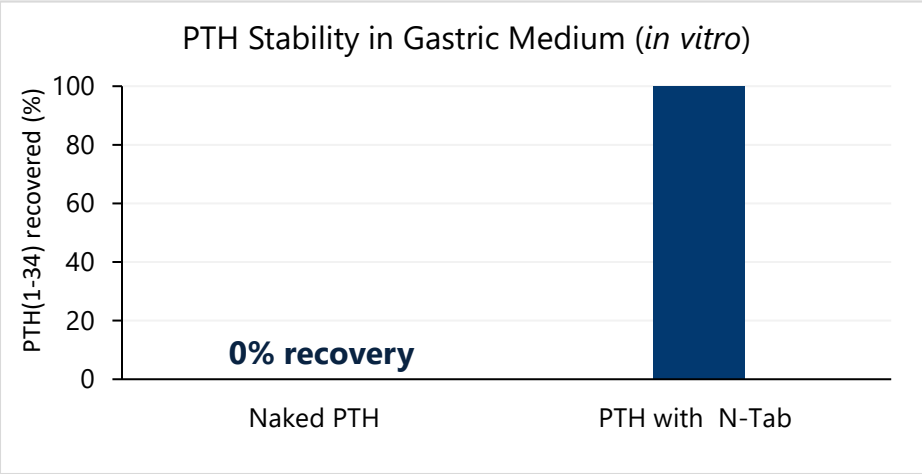
Two Synergistic Mechanisms of the Entera N-Tab® Platform

1 Proteolysis Inhibition

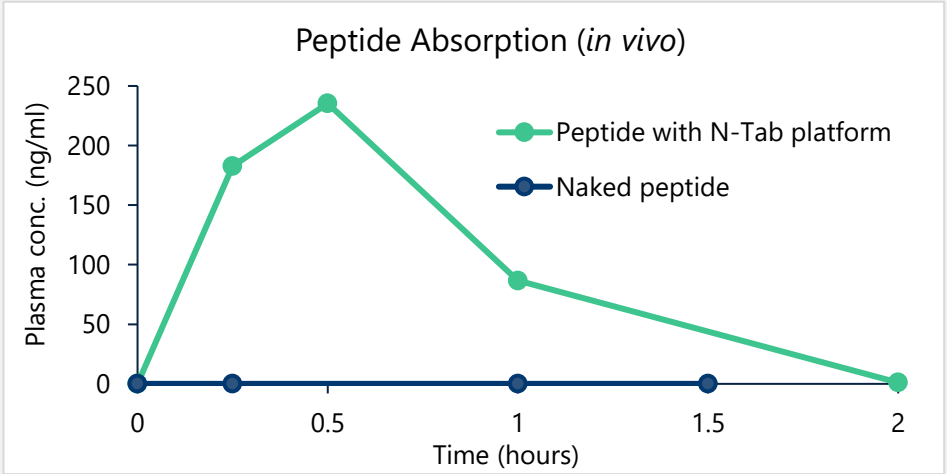
Protease Activity is Blocked.
Peptide Survives.



The naked peptide is completely degraded in the stomach within 5 minutes. N-Tab platform locally stabilizes the peptide

2 Permeability Enhancement

Membrane Fluidity Transiently Increased.
Drug Absorbed Systemically.



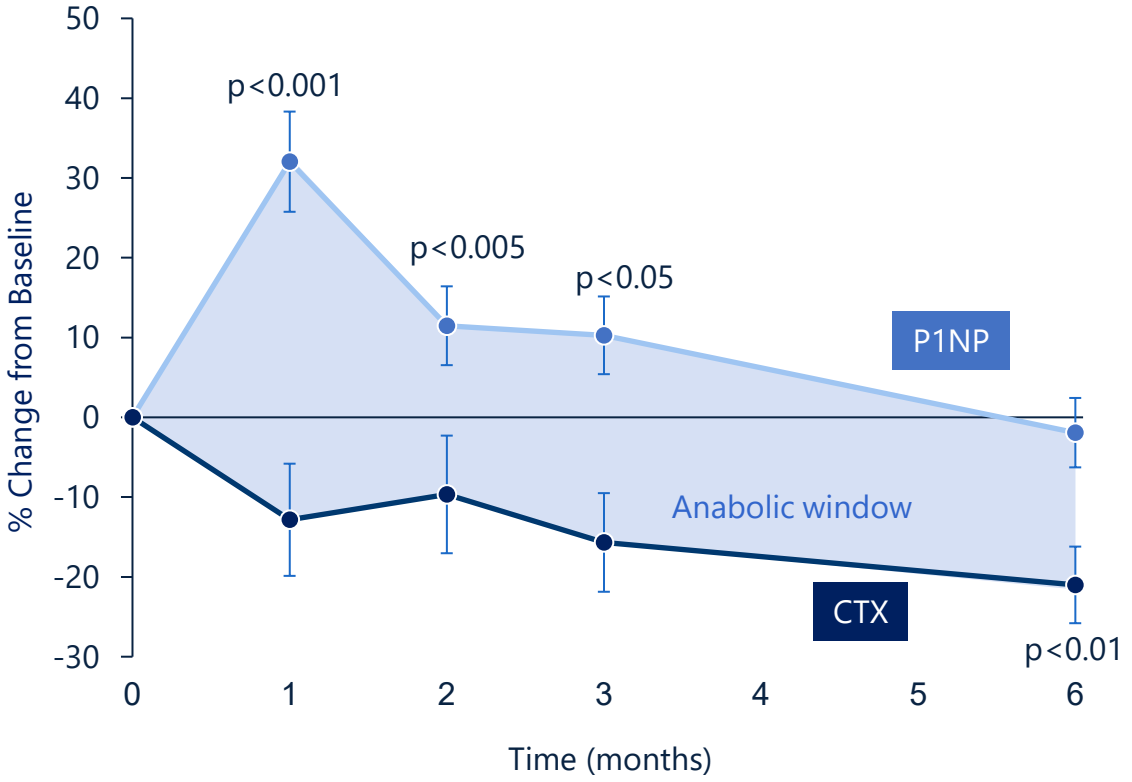
The N-Tab platform transiently increases enterocytes membrane fluidity, enabling transcellular permeation of the peptide through gastric wall

EB613, First Once Daily Anabolic Tablet Treatment for Osteoporosis

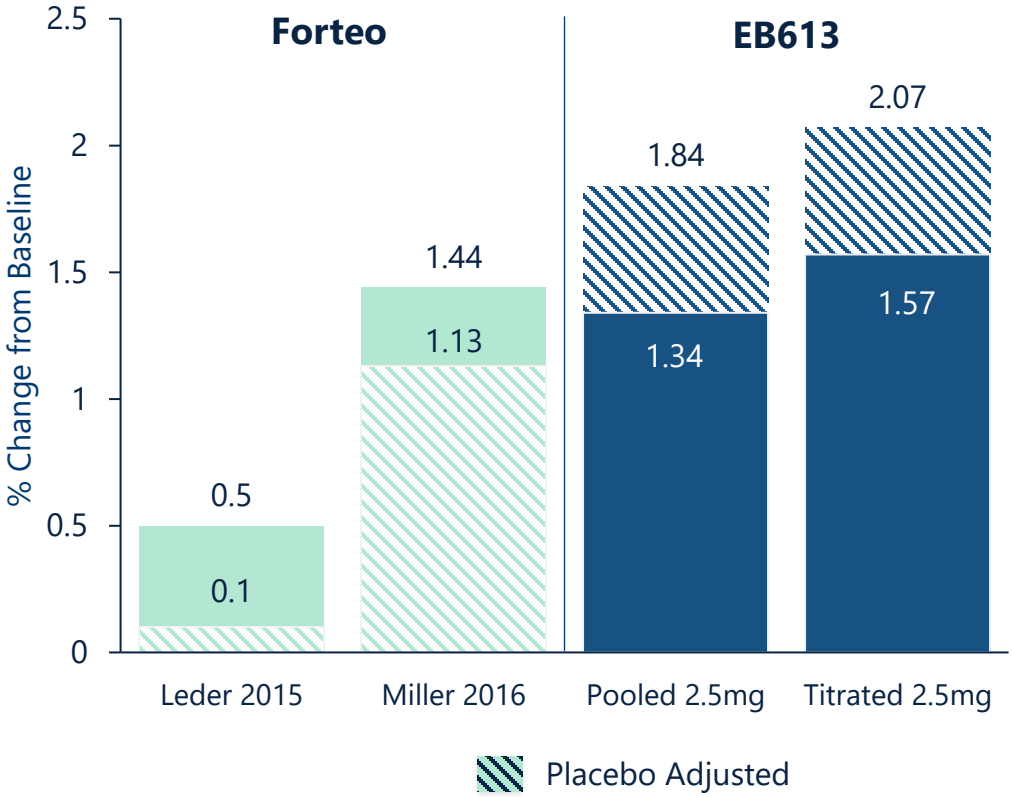
- First PTH anabolic tablet treatment for osteoporosis utilizing Entera's N-Tab® oral peptide platform
- EB613 tablets were tested in three comparative phase 1 studies
- Oral EB613 shows rapid absorption (Tmax ~20 min) and a brief elimination phase, leading to shorter systemic exposure relative to Forteo® injection
- EB613 was also evaluated in three phase 2 studies

EB613 Phase 2 Study in 161 Postmenopausal Women with Osteoporosis or Low BMD

6-month, placebo-controlled blinded study with 2.5 mg daily oral multi-tablet arm



EB613 2.5 mg induces bone formation (P1NP) while reducing resorption (CTX)



EB613 2.5 mg produced comparable total hip BMD increases to Forteo®

Forteo® data based on Leder BZ et al. JCEM (2015) N=39, and Miller et al. JAMA (2016) N= 754
EB613 data based on Tripto-Shkolnik L et al. JBMR (2024), 2.5 mg N=21, Titrated 2.5 mg N=14

Study Objective

- The current study was designed to assess a single oral PTH(1-34) EB613 tablet developed in order to simplify administration for patients
- PK and PD profiles of single EB613 tablet was compared to similar doses of the multi-tablet formulation used in the phase 2 study

Multi-tablet 2.5 mg dose of EB613

Single 2.5 mg EB613 tablet

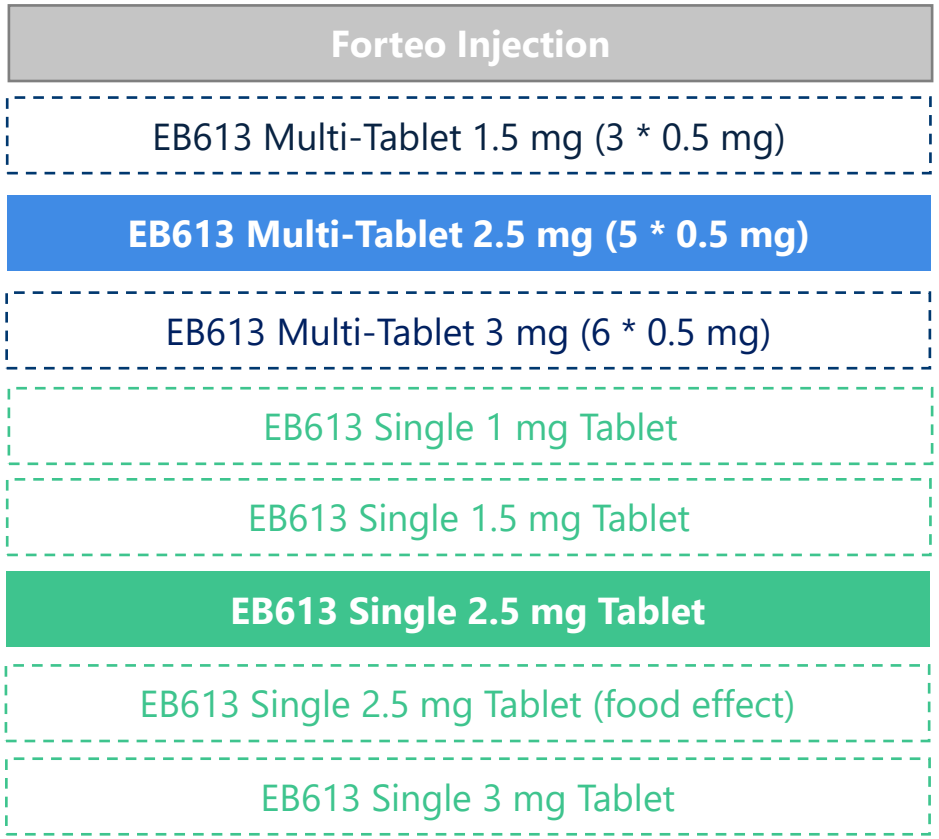
Phase 1 Study Overview: Bridging Study of Simplified Single Oral Tablet EB613

Study Design

Crossover, adaptive design

Study in 15 healthy volunteers, 18 - 35 years of age

All subjects were administered single tablet and multi-tablet oral EB613 and SC Forteo



Endpoints

PK
Plasma PTH(1-34) levels

PD
Serum calcium
Endogenous PTH(1-84)

Safety
Adverse events
Labs

Administration Experience
Questionnaire

- Tablets were administered in the morning after an overnight fast
- Plasma levels of PTH(1-34) were measured by validated LC-MS/MS method

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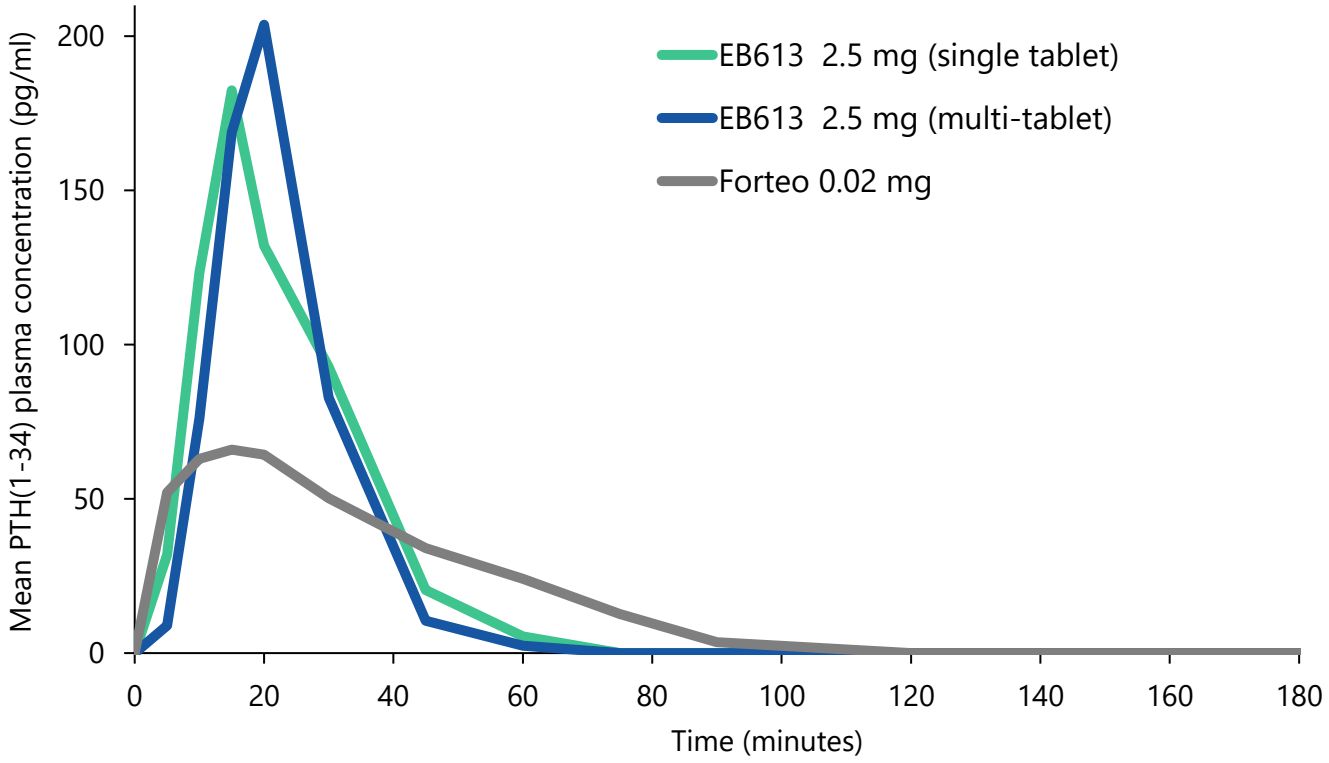
Single Tablet EB613 Showed Similar PK Profile to Multi-Tablet EB613



Similar T_{max} , C_{max} , and total systemic exposure (AUC) were observed for EB613 formulations

AUC of EB613 2.5 mg is comparable to Forteo SC, but duration of exposure is slightly shorter

Treatment	**C_{max}** (CV%) (mean; pg/ml)	**T_{max}** (Max-Min) (median; minutes)	**AUC_{last}** (CV%) (mean; min*pg/ml)
Forteo 0.02 mg	75 (38)	15 (5-30)	2939 (42)
EB613 2.5 mg (**multi-tablets**)	233 (108)	15 (10-20)	3566 (123)
EB613 2.5 mg (**single tablet**)	235 (110)	15 (10-30)	3601 (108)

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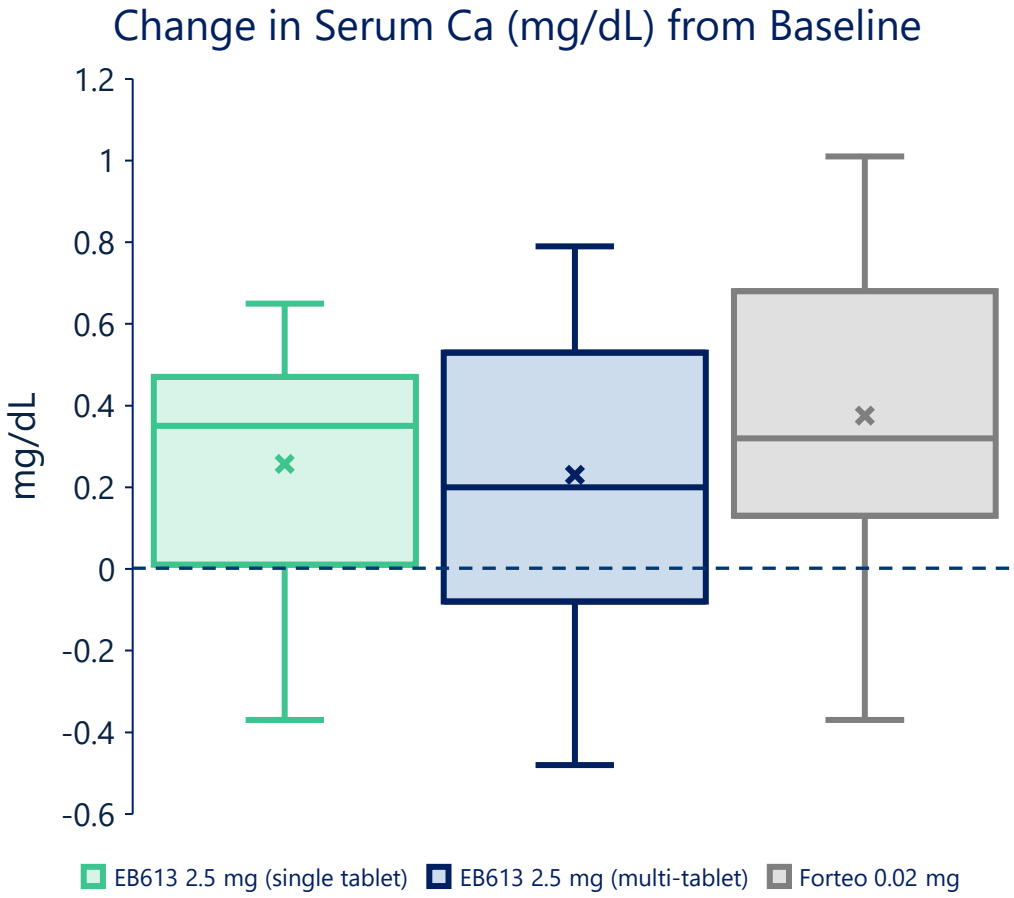
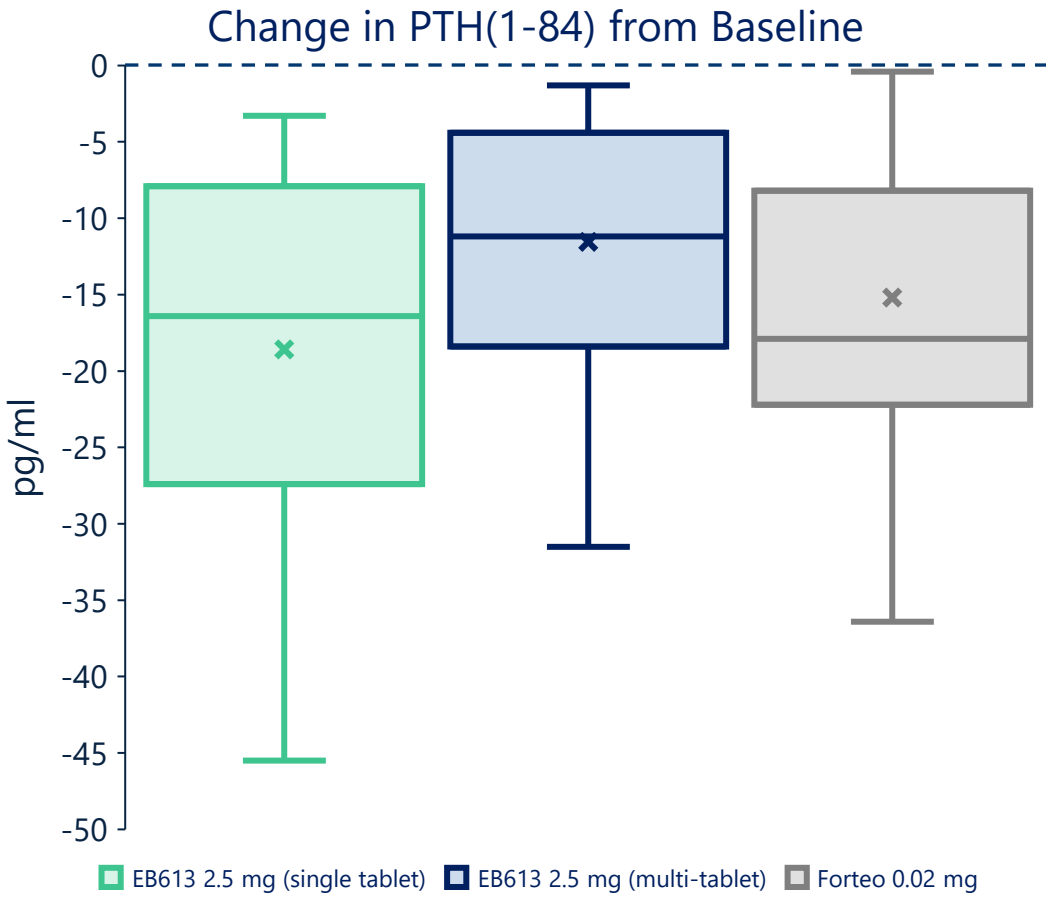
Effects on Serum Ca and PTH(1-84) of Single Tablet EB613 vs Multi-Tablet EB613 and Forteo





Serum Ca and PTH(1-84) were measured 3 hours following EB613 dose and 4 hours following Forteo. The box represents the interquartile range (25th–75th percentile), with the line inside the box indicating the median. The mean is shown as an **x**. The whiskers extend to the minimum and maximum values within the typical range.

EB613 Safety Profile is Consistent with Forteo

- No drug related serious AEs
- All other AEs were mild and resolved with no action taken

Administration Experience

- Participants were requested to complete an administration experience questionnaire following the dosing on each treatment visit
- 14 of 15 participants preferred the single tablet to the multiple tablet dosing
- **All subjects preferred a daily oral tablet over a daily injection**

Summary

- Single EB613 tablet showed similar PK profile to multi-tablet EB613 treatment tested in phase 2 study
- Comparable calcemic effects and consistent suppression of endogenous PTH were shown for both oral EB613 treatments and for Forteo
- Safety profile of EB613 is consistent with Forteo
- This phase 1 bridging study supports advancement of EB613 single tablet into phase 3

Conclusion

A single daily oral PTH tablet (EB613) could make anabolic treatment far more acceptable to many patients and health care providers and make substantial impact toward reducing the treatment gap in patients with osteoporosis

Thank You