Entera Bio

Global Leader in Oral Peptide Therapeutics

Disclaimer

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Entera Highlights

First-in-Class, Oral Peptide Treatments for Severe, Clinical Conditions Where an Oral Format Holds the Potential to Significantly Improve Patient Care

- **N-Tab™: Disruptive oral peptide technology platform**
- **Convenient daily tablets**
- **Oral PTH (1-34) tablets showed clinical benefit across two diseases (Phase 1 and 2, N=255)**
- **5 programs expected to enter clinic (Phase 1 – Phase 3) by 2025:**
  - First daily oral PTH (1-34) for osteoporosis (Phase 3 ready), stress fractures (Phase 2)
  - First daily oral PTH (1-34) peptide replacement therapy for hypoparathyroidism
  - Strategic Partnership with OPKO Health for 2 novel Peptides (SBS and Obesity)
- **Strong IP estate**
- **Cash runway through H1 2025 – Nasdaq: ENTX**

Our Vision

We develop first-in-class, daily tablet protein and peptide replacement therapies, designed for patients to live healthier and injection-free, as they manage their chronic diseases

Our goal is for our small, oral peptide tablets to change treatment outcomes for patients globally

We aspire to continue to validate our platform across a plethora of additional high value therapeutic peptides via our internal efforts and in collaboration with leading protein therapeutic companies

Experienced Leadership Team

Management

Miranda Toledano	Chief Executive Officer	Royalty Pharma, MLV, Compass Therapeutics, TRIGR Therapeutics
Hillel Galitzer, PhD	Chief Operating Officer	The Hebrew University of Jerusalem, Hadasit Bio-Holdings Ltd.
Gregory Burshtein, PhD	EVP, Head of R&D	The Hebrew University of Jerusalem
Rachel B. Wagman, MD	Key Clinical Advisor	Lilly, Amgen, Myovant Sciences, Sumitomo Pharma
Felicia Cosman, MD	Key Clinical Advisor	Columbia University Irving Medical Center
Steven R. Goldstein, MD	Key Clinical Advisor	NAMS
Anke Hoppe, BSc	VP of Clinical Operations	GSK, Syneos Health
Dana Yaacov, CPA	Chief Financial Officer	pwc

Clinical & scientific advisory board

William Fraser, MD	UEA	**Bart Clarke, MD**	Mayo Clinic Care Network
John P. Bilezikian, MD	Columbia University Irving Medical Center	**Sophia Ish-Shalom, MD**	Rambam
Maria Luisa Brandi, MD, PhD	FIRMO	**Socrates Papapoulos, MD**	Leiden University Medical Center
Roger Garceau, MD	NPS Pharma, Shire, sanofi	**Art Santora, MD, PhD**	Merck, NIH, FDA

Entera Oral Peptide Pipeline

Program	Indication	Target	Preclinical	Phase 1	Phase 2	Phase 3	Partner
EB613	Osteoporosis	PTH 1-34					
EB612	Hypoparathyroidism	PTH 1-34					
EB613	Stress Fractures	PTH 1-34					Investigator Sponsored Trial
GLP-2	Short Bowel Syndrome	Long Acting GLP-2					OPKO
OXM	Obesity / Metabolic	GLP-1 & Glucagon Agonist					OPKO

Oral Peptide Delivery Technology Platform

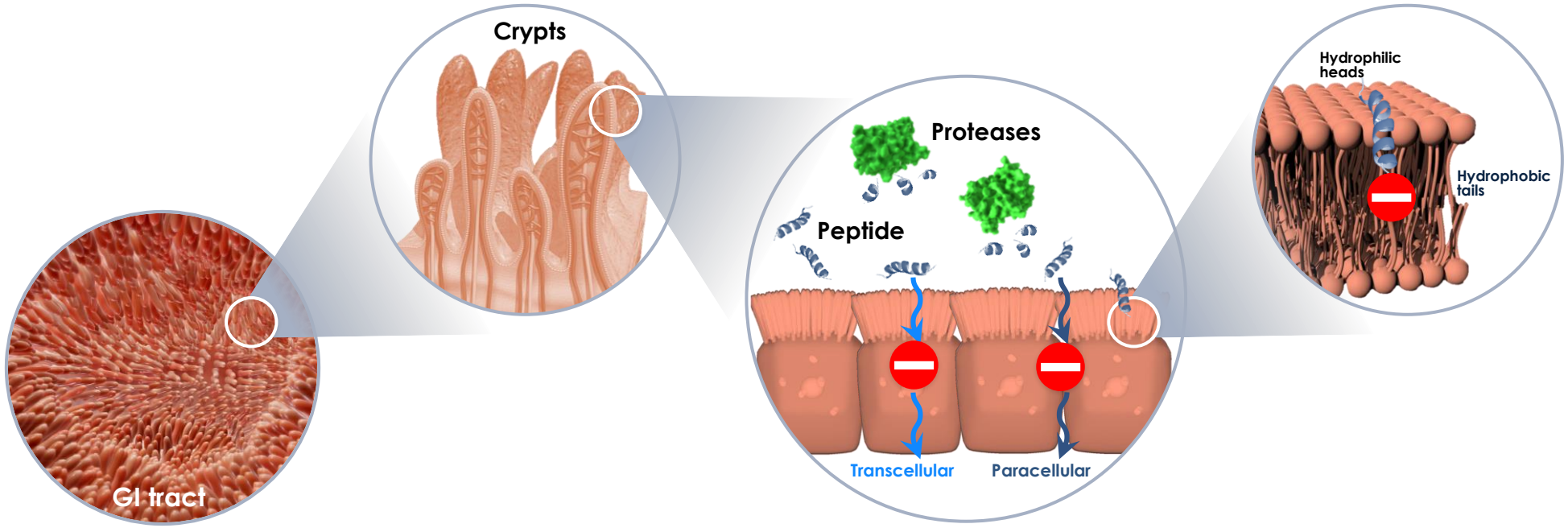
Oral Delivery of Peptide Therapies Designed to Improve the Standard of Care

Oral Bioavailability of Therapeutic Peptides is Negligible

GI system is designed to breakdown proteins and peptides into amino acids

- Pepsin and acid environment (H+ ions) act in stomach
- Trypsin and α-chymotrypsin further degrade protein in intestinal lumen

Peptide drug absorption is limited by polarity (transcellular) and size (paracellular)



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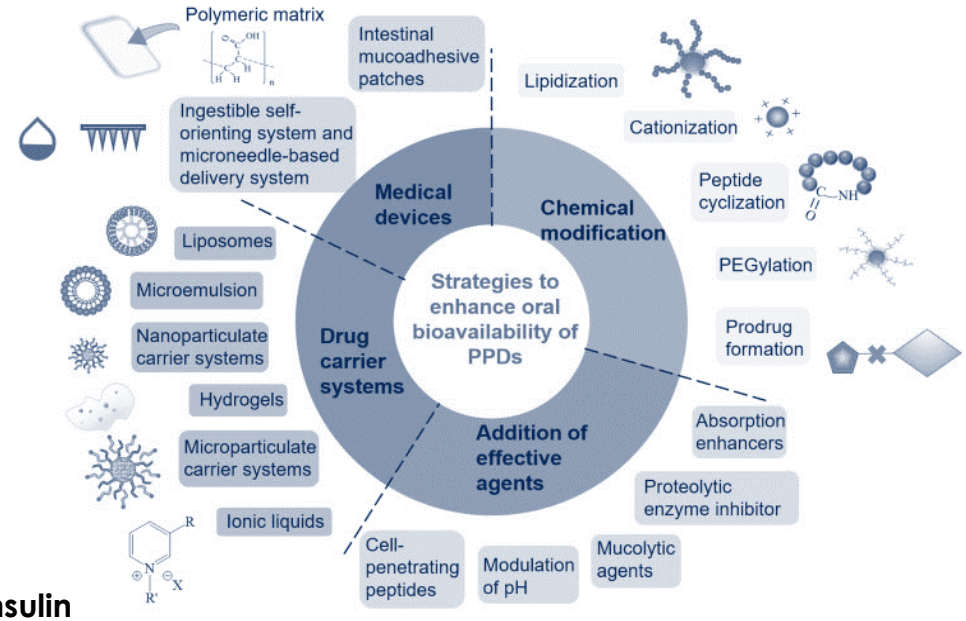
Oral Delivery of Biologic Drugs Has Lagged

Out of >80 approved injectable peptide therapies over the past 100 years since insulin was isolated, 3 hydrophilic peptides are orally available and only 1 (GLP-1) is a peptide >4kDa



Large linear hydrophilic peptides >4 kDa | Small lypophilic peptides | Peptides with local effect in GI tract | Small cyclic peptides ~1kDa

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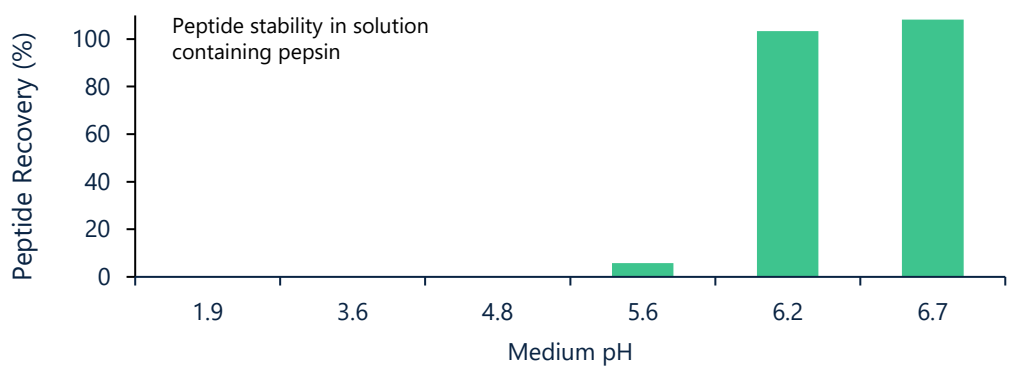
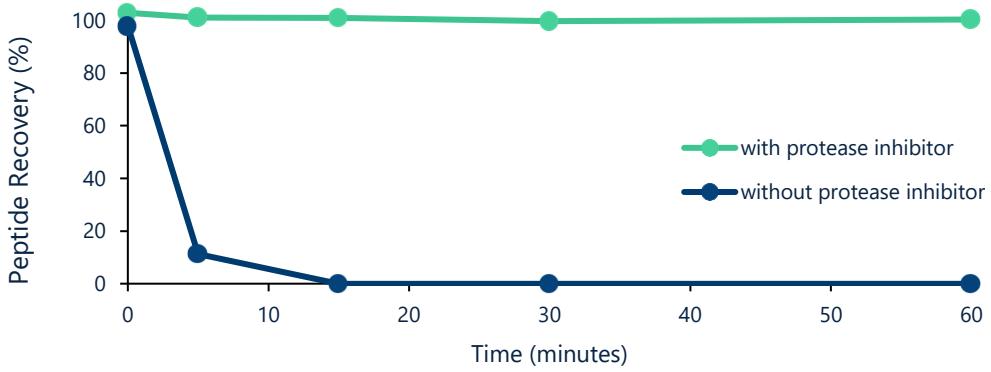
Entera Platform Inhibits Proteolysis in GI Tract and Enables Bioavailability

Proteolysis Inhibition

Locally Elevated Gastric pH Inactivates Pepsin

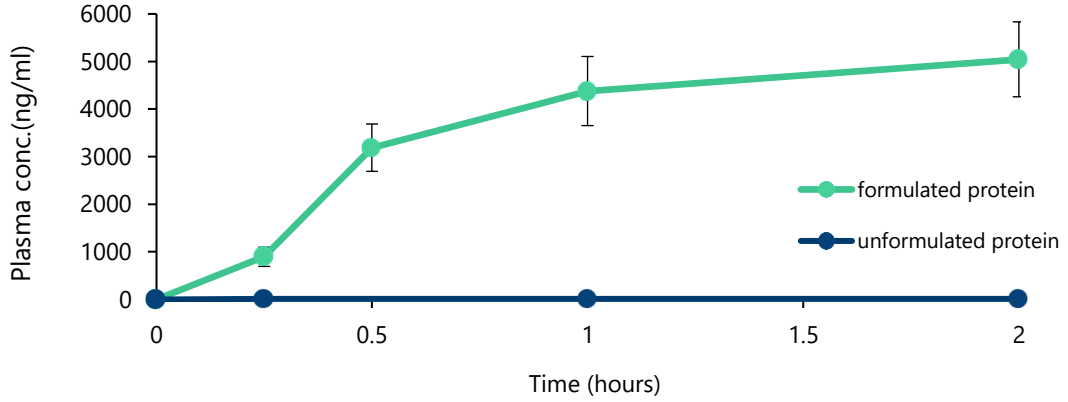


Protease Activity Inhibited

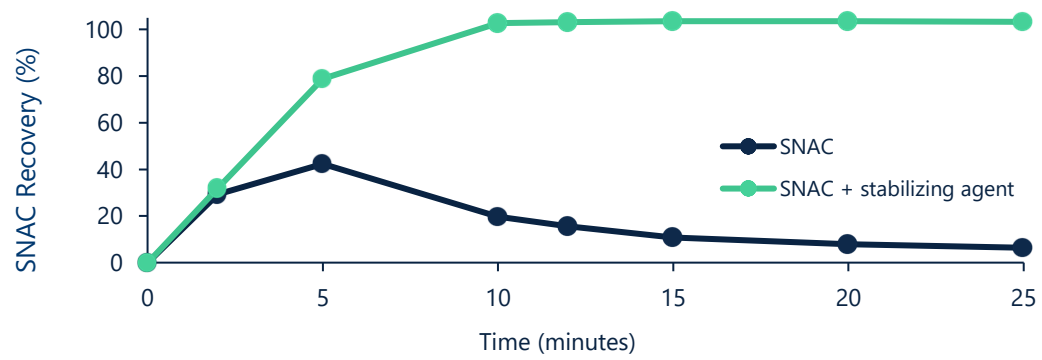


Absorption Enhancement

SNAC Increases Transcellular Absorption via Enterocyte Membrane



SNAC Further Stabilized to Enhance Activity



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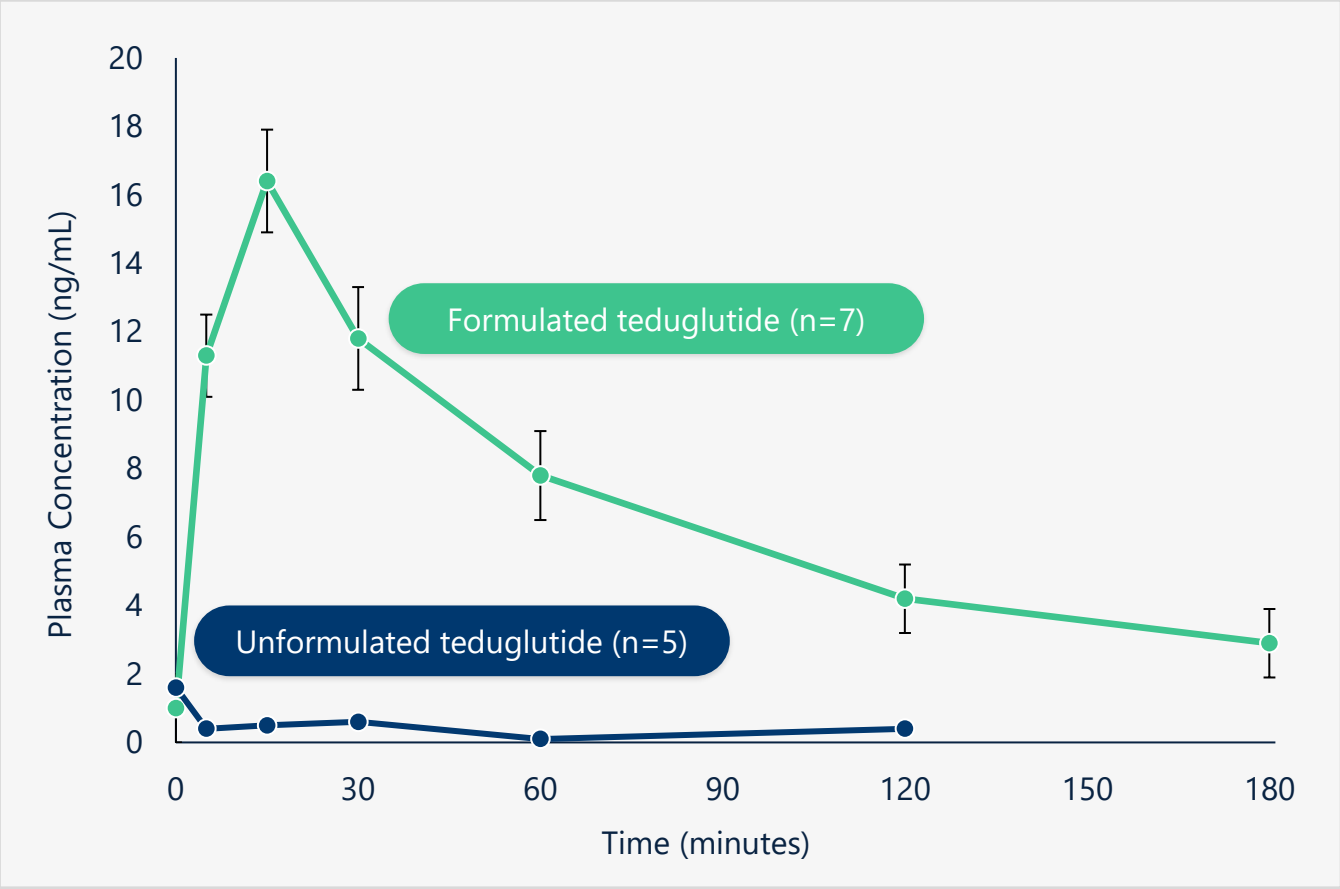
First Oral GLP-2 Analog Tablets for Short Bowel Syndrome (SBS)

Entera was first to publish pre-clinical gastromucosal absorption of oral GLP-2 tablets pre-clinically using the standard of care GLP-2 peptide (Gattex®)



Devastating and potentially life-threatening organ failure condition

Rare disease: 30K patients across the US and EU

50% require lifelong parenteral nutrition (PN)

Treatment with glucagon-like peptide-2 (GLP-2) improves absorption of nutrients and reduce PN

Gattex® (teduglutide), the only approved GLP-2, requires daily SC injections ($622M US sales in 2022)

Once-weekly SC injectables - Zealand (glepaglutide, PDUFA 12/22/24) Vectiv/ Ironwood (apraglutide, Phase 3, acquired $1.1B)

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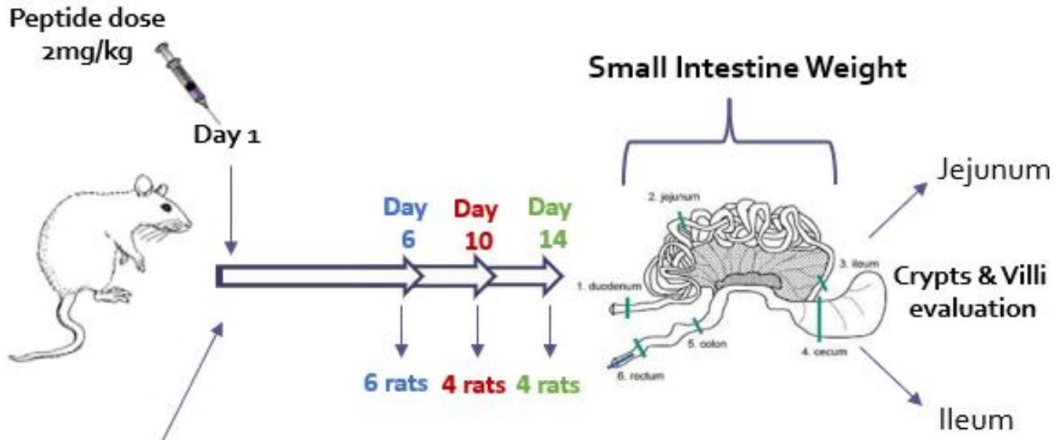
OPKO Long Acting GLP-2 Analog Collaboration with Entera

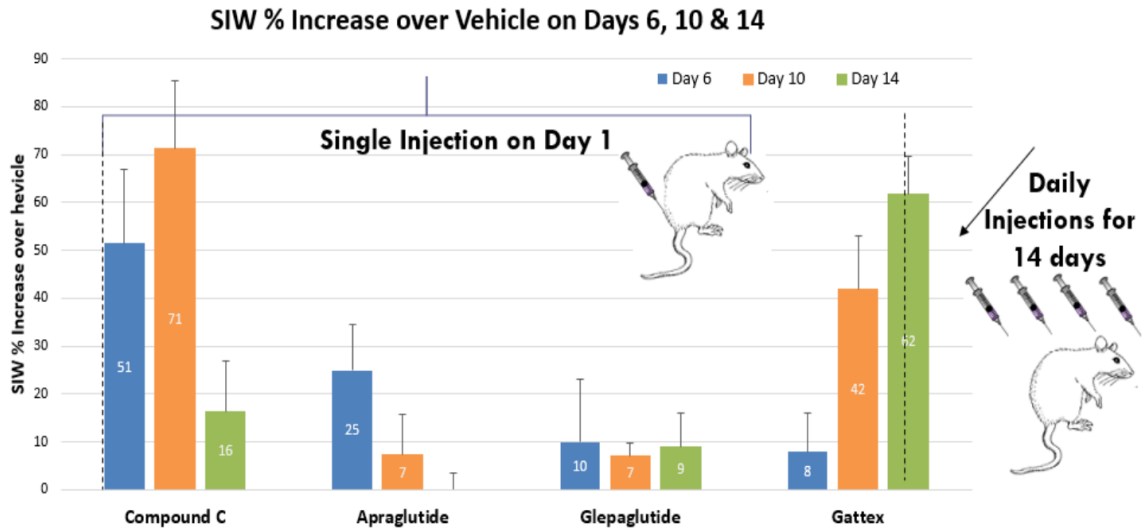
OPKO's proprietary long-acting GLP-2 analog has demonstrated PK/PD effect as a once weekly injectable



GATTEX animals received 2.5mg/kg daily injection (14 days)

Compound C (OPKO-Entera), Apraglutide and Glepaglutide received a single 2 mg/kg injection

Increase in small intestine weight (SIW) measured as PD effect



Pharmacological data for oral GLP-2 tablets using Entera's platform is expected in H1 2024

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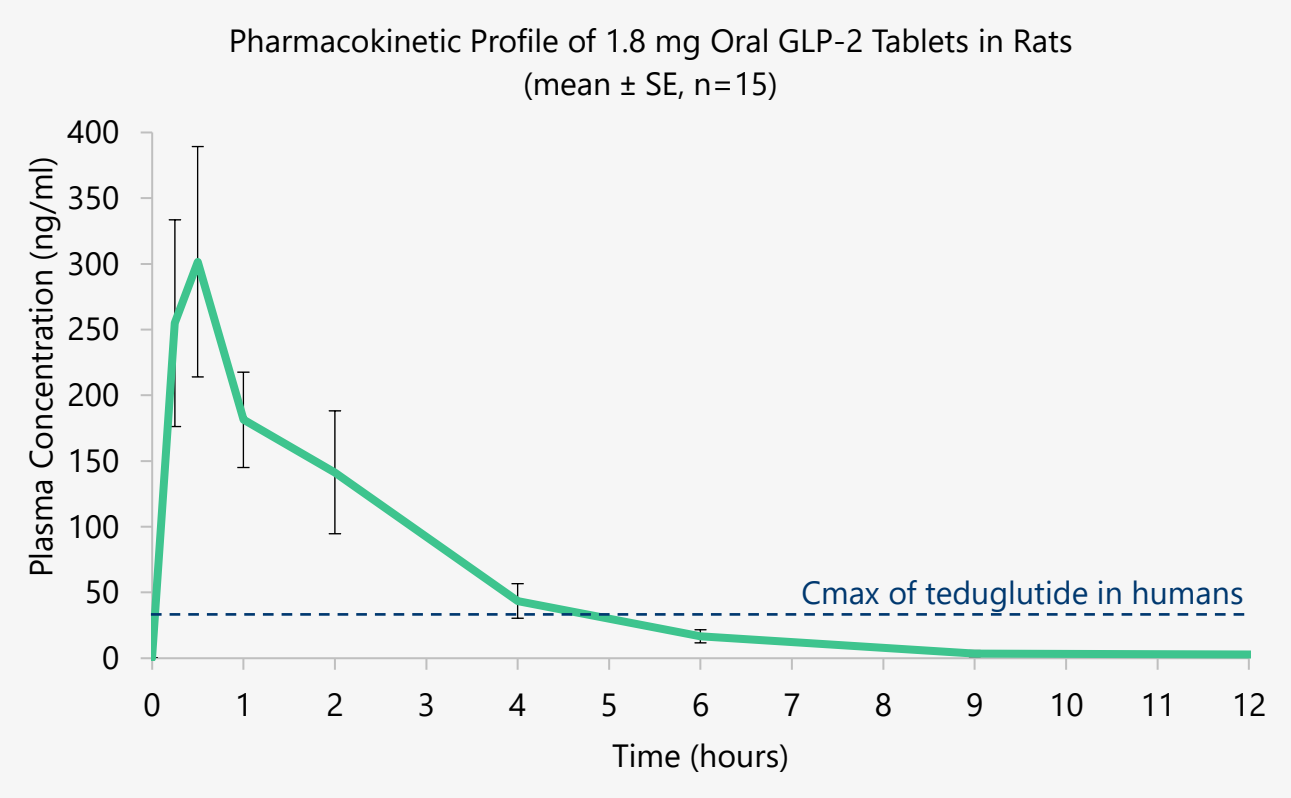
OPKO/Entera: Oral Long Acting GLP-2 Tablet POC PK Data

Proof-of-concept single dose pharmacokinetic study in rodents showed robust systemic absorption of OPKO's long acting GLP-2 analog using Entera's N-Tab™ oral peptide delivery technology



- The plasma half-life of OPKO's GLP-2 peptide following IV injection was found to be about 6 times longer than the half-life reported for teduglutide in the same animal model

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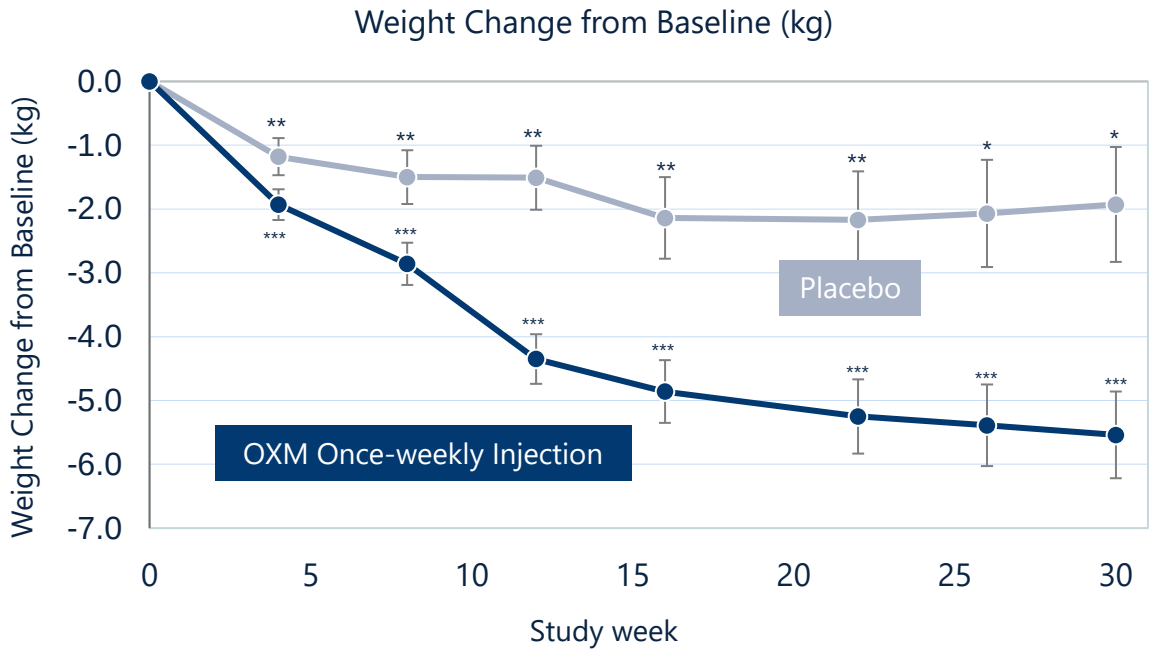
First Oral GLP-1/Glucagon Agonist for Obesity / Metabolic Disorders

OXM Phase 2B Results



Parameter	OXM (N=45)	Placebo (N=28)
Triglycerides (mg/dL)	-40.5 (12.52) (p=00019)	-9.7 (16.34)m(p=0.5554)
Total Cholesterol (mg/dL)	-13.9 (4.79) (p=0.0080)	-2.4 (6.23) (p=0.7066)

- Oxyntomodulin (OXM) is a next generation GLP-1/glucagon dual agonist
- >1 billion people suffer from obesity globally; market is estimated to grow to $100B by 2030
- Phase 1 SAD/MAD with ~100 obese and diabetic patients
- Phase 2/2b studies (N>430 patients) with once-weekly injectable OXM:
  - Significant weight loss
  - Decreased plasma triglyceride levels with potential cardioprotective effects

Entera's oral peptide platform combined with OPKO's proprietary long-acting OXM analog is in development; PK data for oral OXM tablets expected in mid-2024

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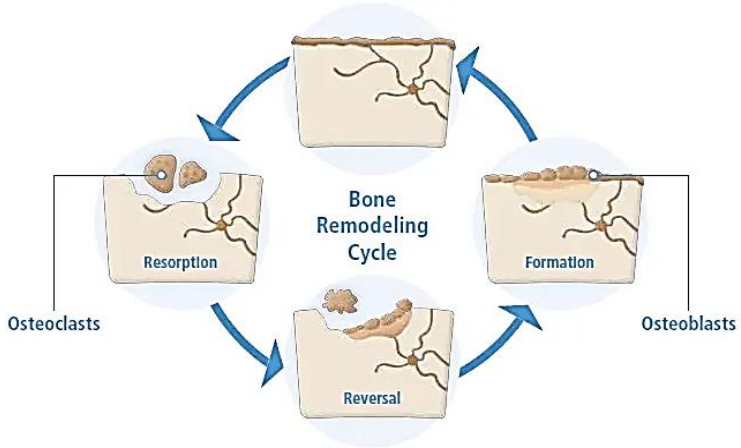
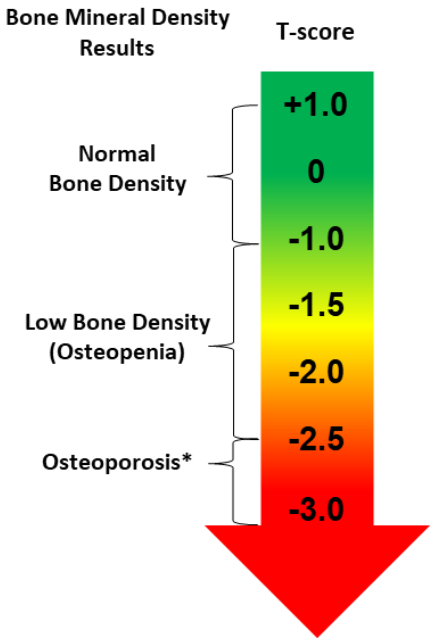
EB613 Oral PTH (1-34)

First Oral Osteoanabolic Mini Tablets for High-Risk Post-Menopausal Women with No Prior Fracture

Osteoporosis

- **Dysregulated bone remodeling and increased osteoclast activity**
  - ↑ resorption (CTX biomarker), ↓ formation (P1NP biomarker)
- **Osteoporotic fractures result in pain, permanent disability, loss of independence, reduced quality of life and often death**
- **Primarily women**
  - 1 in 3 women will suffer a fracture after the age of 50
  - More common than heart attack, breast cancer and stroke combined
- **Diagnosed and managed via bone mineral density (BMD) T- Score**
  - High Risk Osteoporosis *(T-scores between -2.5 and -3.0 without a history of fractures) ~40% of patients*
  - Rapid bone loss is found to be a predictor of post-fracture mortality risk in both women and men
  - ~9 million fractures each year worldwide and predicted to increase 2-4 fold with aging population





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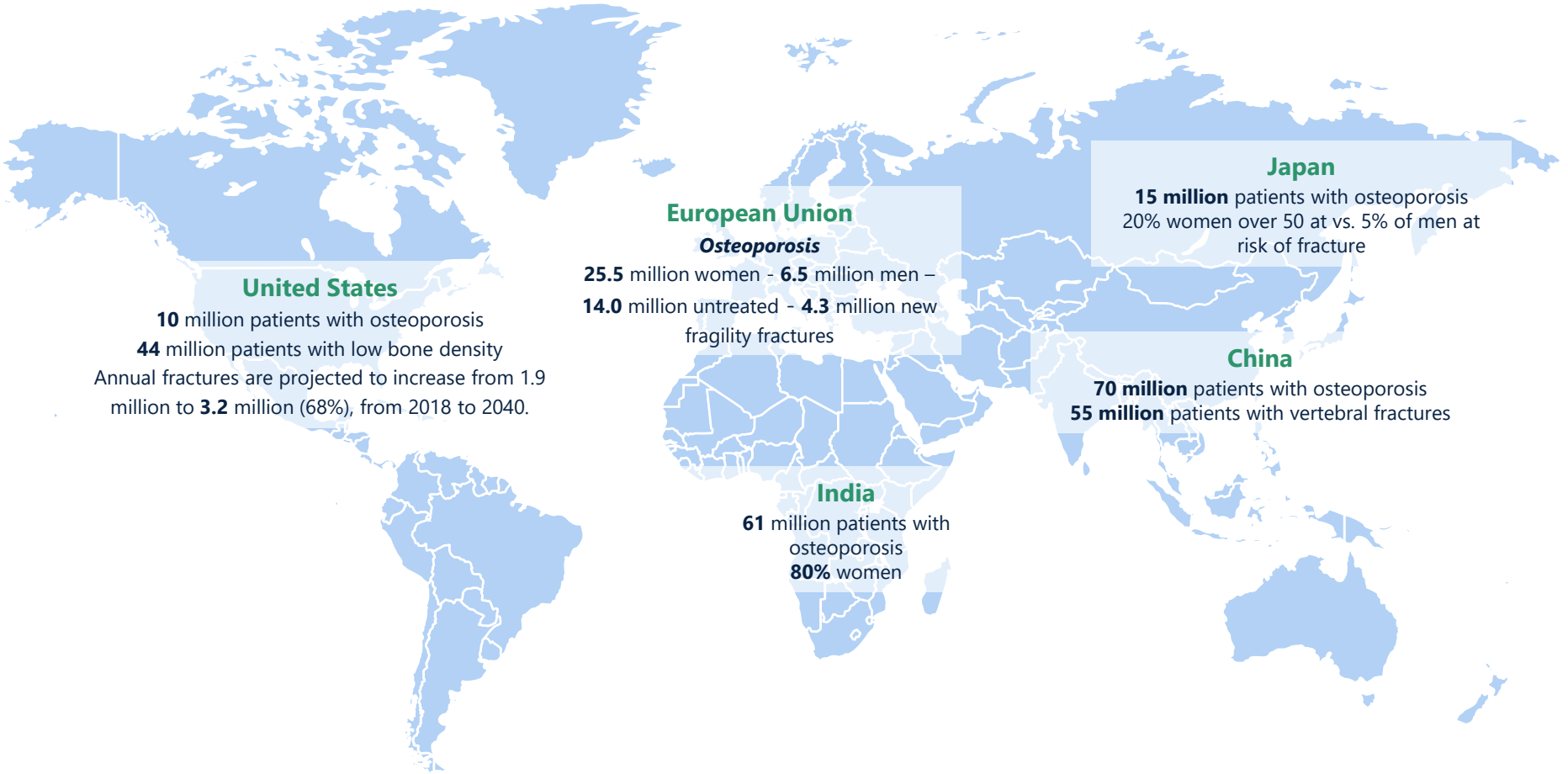
Globally, Osteoporosis Afflicts ~200 million Women

More than Heart Attack, Stroke, and Breast Cancer Combined



~50% of women over the age of 50 will experience an osteoporosis-related fracture

~1 billion women globally will enter menopause in the coming years

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Current Osteoporosis Treatment Paradigm and EB613 Opportunity

Oral Agents are Preferred, Anabolic Agents are More Effective

Anti-Resorptive

1st Line

Bisphosphonates	SERMs	RANK-Ligand Inhibitor (IV)
Fosamax® *Alendronate*	**Evista®** *Raloxifene*	**Prolia®** *Denosumab*
Boniva® *Ibandronate Acid*		
Atelvia® & Actonel® *Risedronic Acid*		
Reclast® (IV) *Zoledronic Acid*		

Oral Anabolic

High Risk no Prior Fracture
(Phase 3 protocol design)

EB613
Oral *PTH (1-34)*
Daily Mini Tablets

Injectable Anabolic

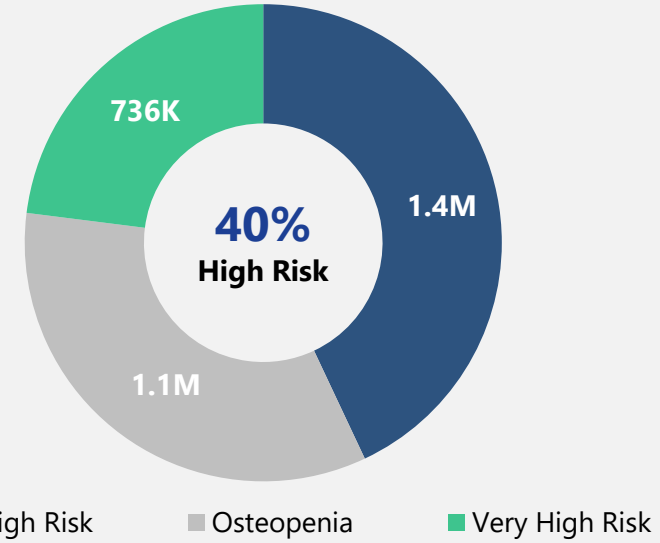
1st Line Very High Risk
2nd Line, bisphosphonate intolerant

Monoclonal Antibodies	PTH receptor agonist
Evenity® *Romosozumab-apqg*	**Forteo®** *Teriparatide*
	Tymlos® *Abaloparatide*

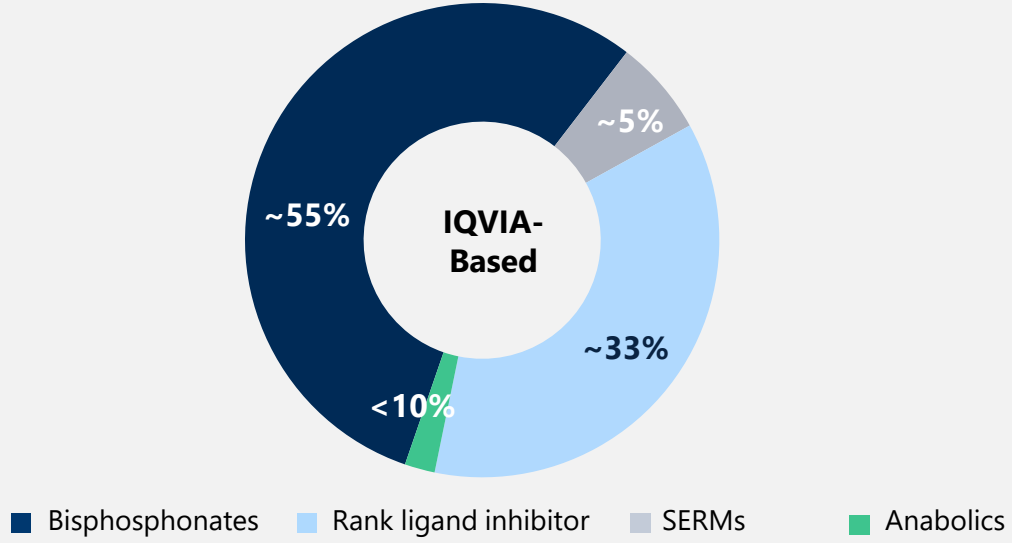
- Treatment gap exists due to poor patient acceptance of injectable anabolic drugs
- Genericization of PTH injectables has not increased Rx
- **No new osteoporosis therapy has been approved since 2019**

Despite the Guidelines and Their Efficacy: Anabolics Remain Underused

EB613's target patient population comprises **40%** of **currently treated patients with low BMD**



Despite the guidelines, less than **10%** of **currently treated patients are on anabolics**



Anabolics are Recommended as 1st Line Tx in Very High Risk and 2nd Line Tx in High-Risk Pts

- More efficient increase in bone density
- Reduce fracture risk vs bisphosphonates
- Improved bone formation stimulation and microarchitecture

Barriers to Anabolic Use:

- Acceptance - Compliance **with weekly or monthly injections**
- **Pain & Cost**

EB613 Potential Best in Class without Disadvantages of Injections

EB613 Phase 2 Results

A Six-Month Study of Oral PTH in Post-Menopausal Women with Osteoporosis / Low Bone Mass

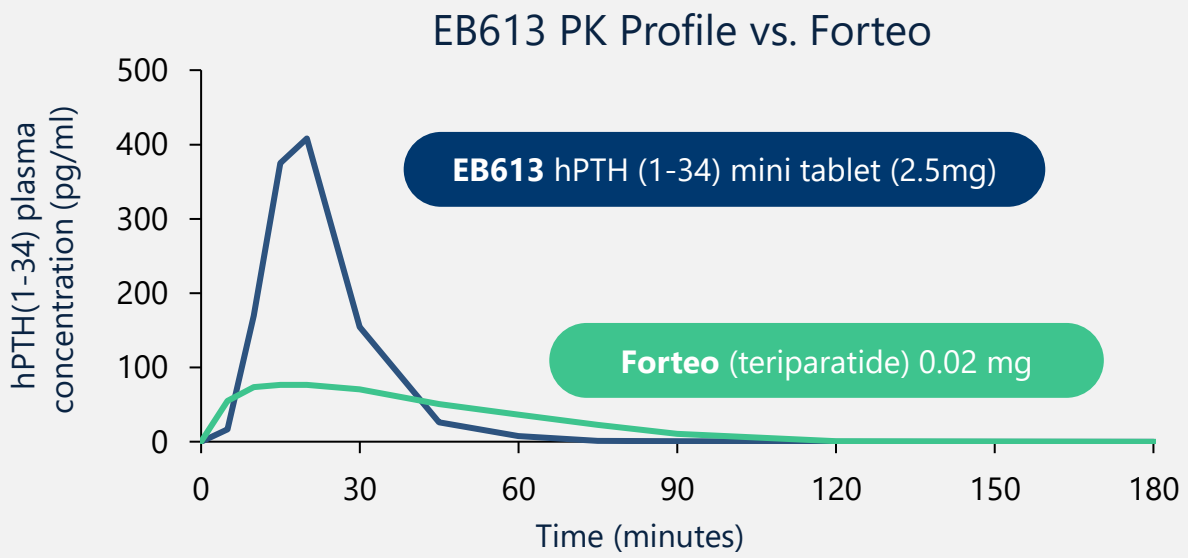
Parathyroid Hormone (PTH) Receptor (PTH1R) Agonists

- PTH (1-34) (teriparatide) is a peptide with the first 34 amino acids of human PTH (1-84)
- Brief “pulses” (30 to 60 minutes) of high concentrations stimulate bone formation
- Longer PTH pulses may stimulate both bone formation and bone resorption (Forteo®)
- Continuous infusions of PTH stimulate bone resorption without bone formation (catabolic effect)

EB613 consistently shows an increased Cmax and shorter duration of systemic exposure optimizing the anabolic effect

EB613 Human Experience:

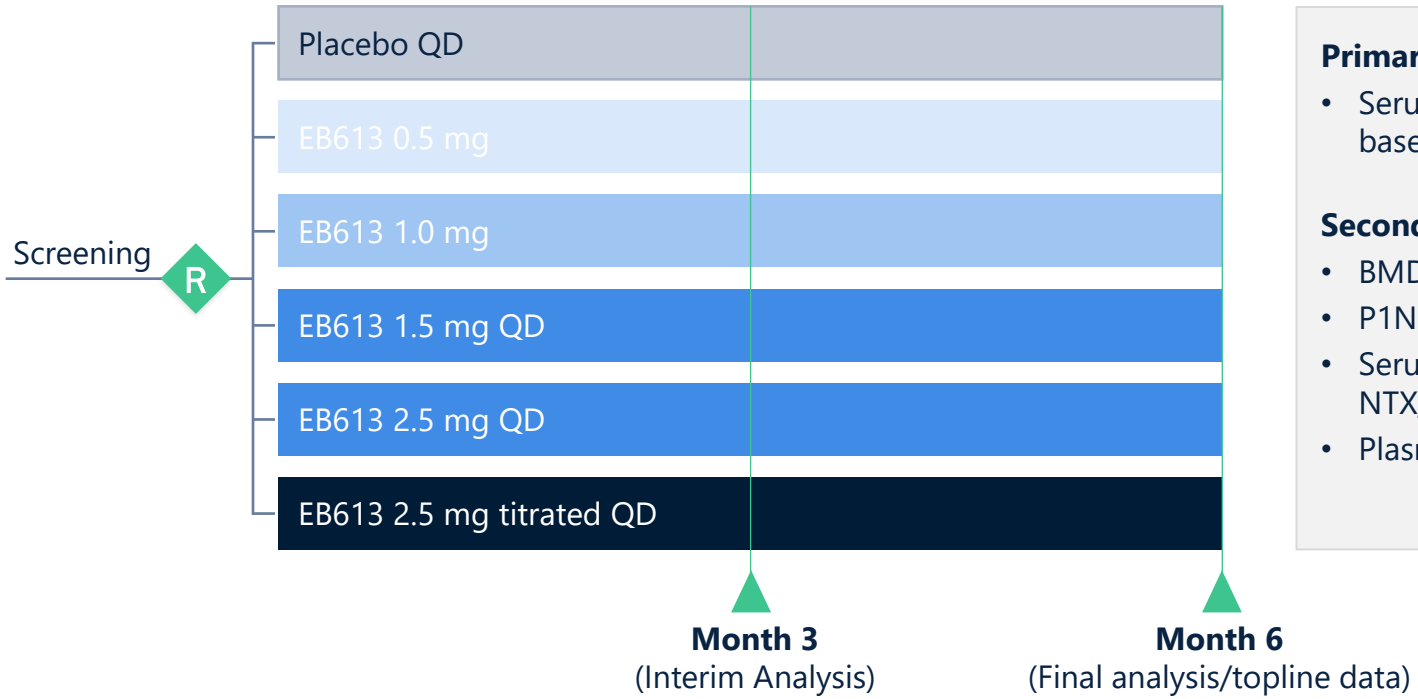
- Two Phase 1 SAD studies (N=25)
- Phase 2 six month placebo controlled study (N=118)



EB613 Phase 2 Clinical Study Design

Key Inclusion Criteria
- 50+ years old
- 3+ years post-menopause
- Low bone mass
- High risk; no prior fracture

Key Exclusion Criteria
- Osteoporosis treatment within last 2 years
- Severe osteoporosis that precludes placebo

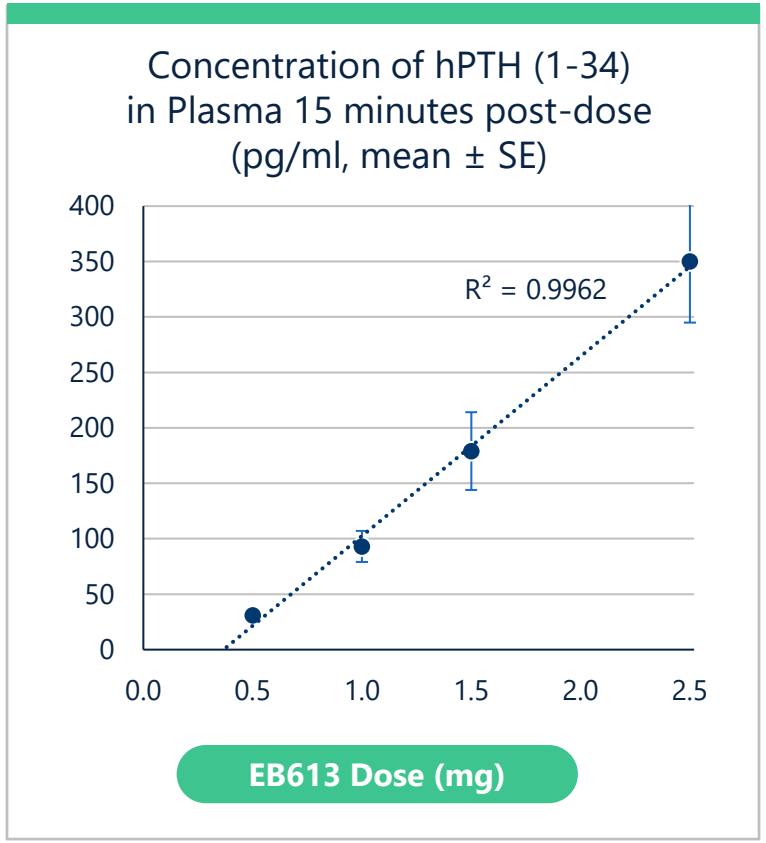


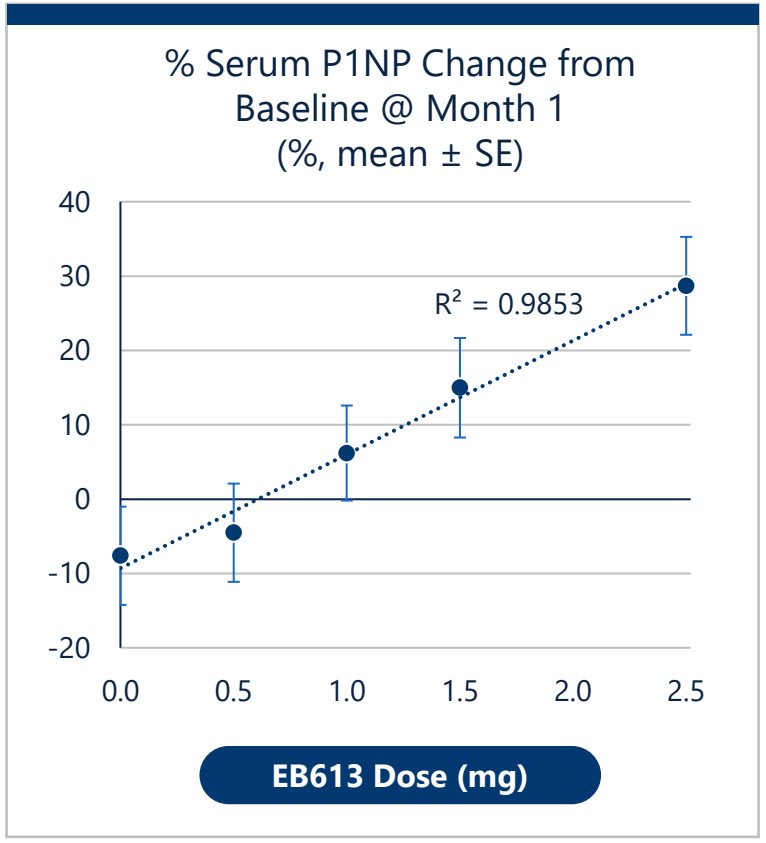
Primary Endpoint
- Serum P1NP change from baseline (placebo-adjusted)

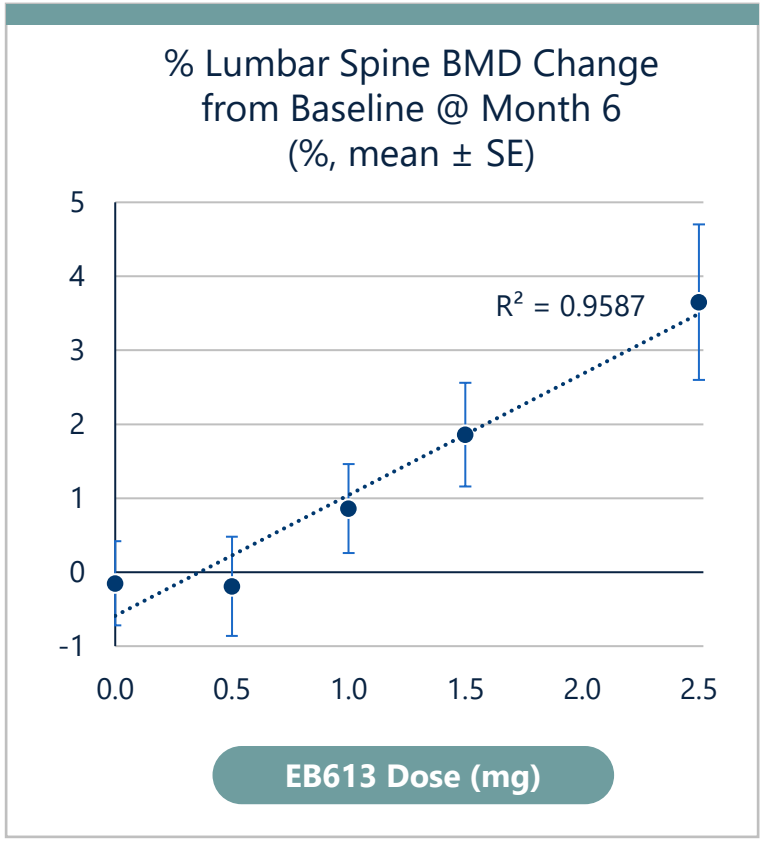
Secondary Endpoints
- BMD change from baseline
- P1NP, osteocalcin, bone ALP
- Serum CTX, urine NTX/creatinine
- Plasma hPTH (1-34) at T15 min

- 6-month, randomized, dose-ranging, placebo-controlled study in post-menopausal women with osteoporosis
- Conducted at 4 sites; Final enrollment = 161 patients (118 active, 43 placebo)

EB613 Showed Linear Dose Response Across PTH Exposure, P1NP Biomarker, and BMD







EB613 produced a statistically significant BMD dose response in lumbar spine BMD ($p<0.0001$), femoral neck BMD ($p<0.002$), and total hip BMD ($p<0.008$)

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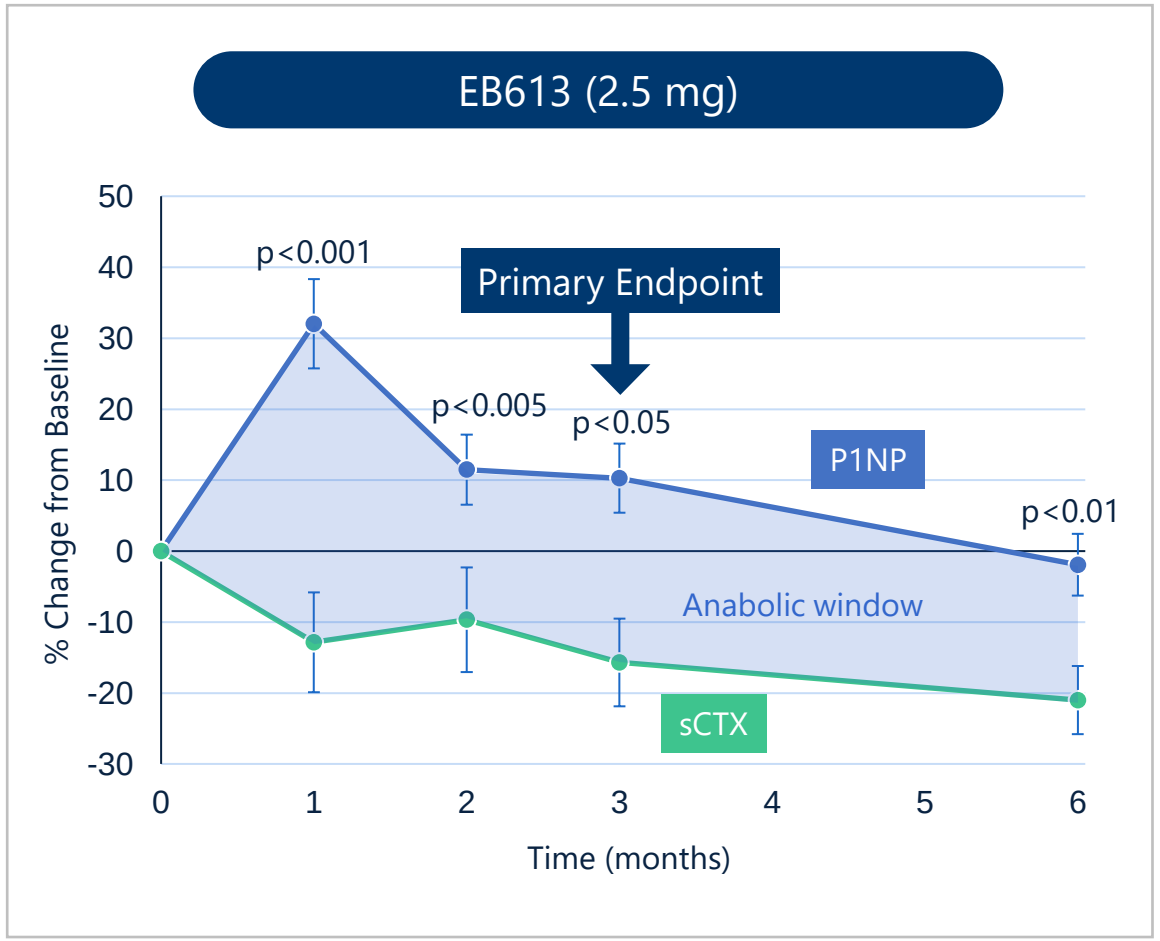
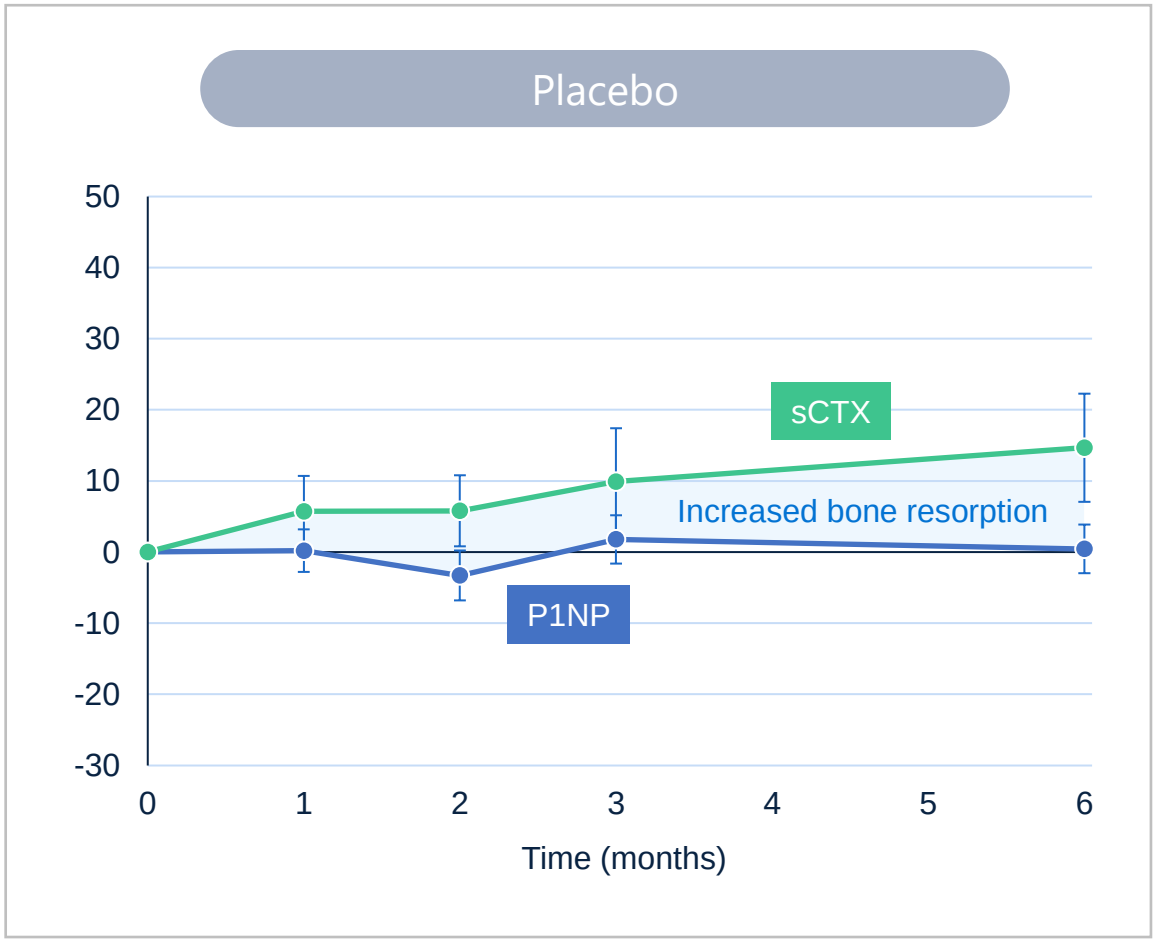
EB613 Demonstrated a Sustained Anabolic Window Resulting from a Dual MOA of Bone Formation and Anti-Resorptive Properties





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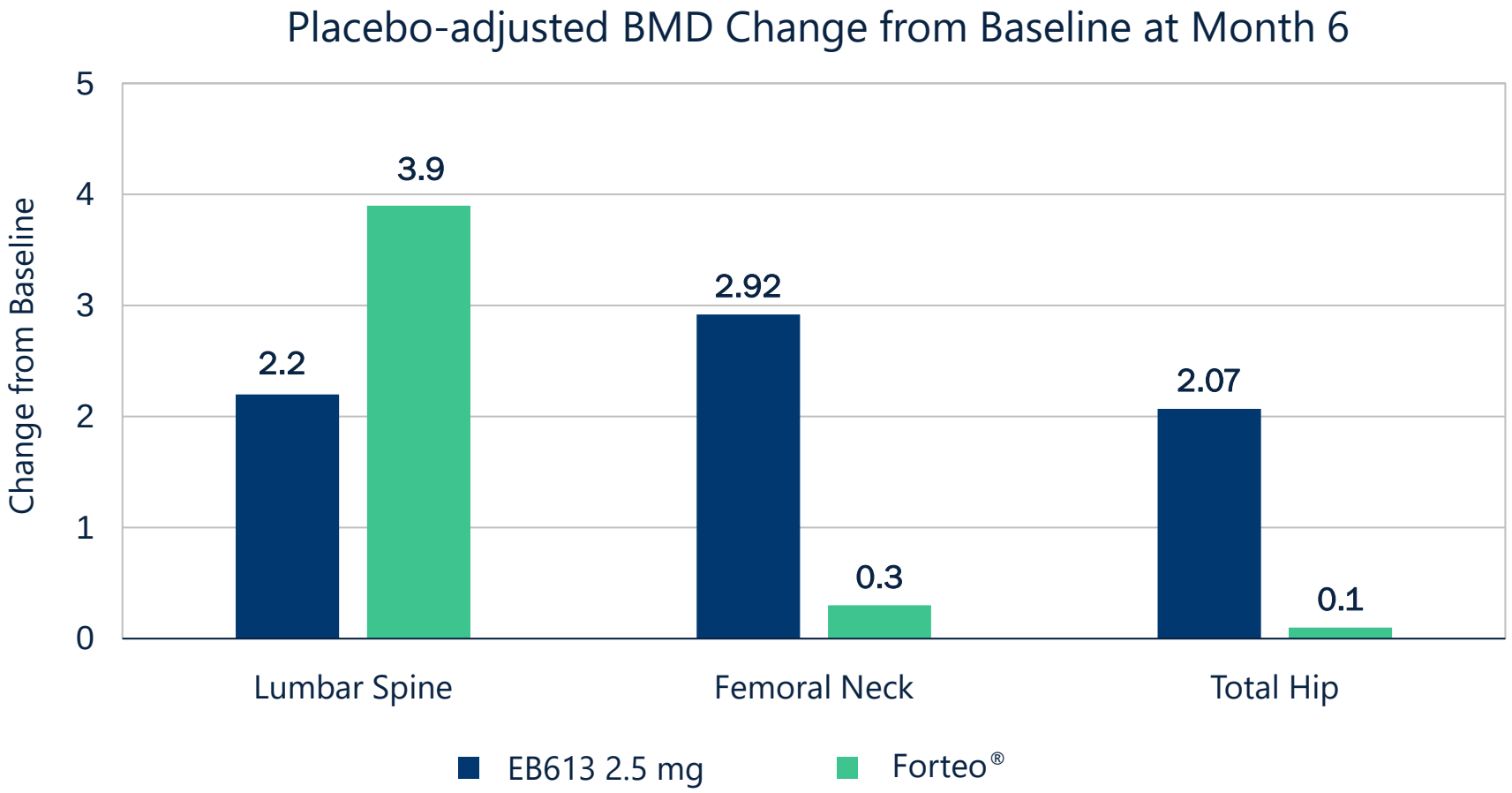
EB613 Increased BMD at All Major Skeletal Sites



Faster onset and greater increases of hip and femoral neck BMD vs. Forteo® at month 6

Patients on placebo had decreases in BMD score across all skeletal sites

- Forteo® data based on 20µg injection - Leder BZ et.al. JCEM (2015)
- EB613 data based on titrated 2.5mg tablets– Tripto-Shkolnik L et.al. JBMR (2024)

EB613 Safety Profile Consistent with PTH Targeted Injectables

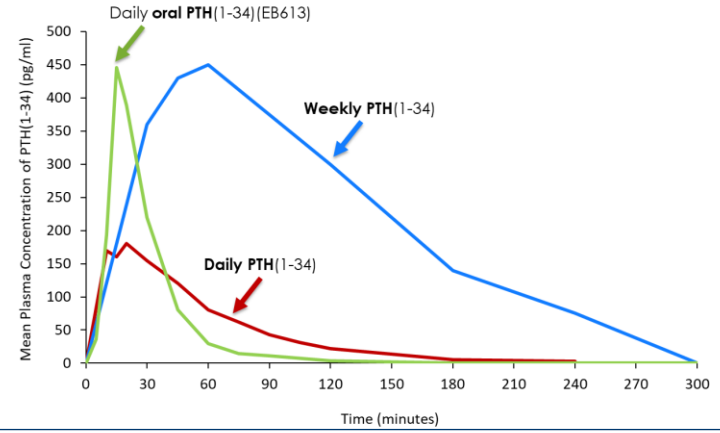
Most Common Treatment Emergent AE (≥5% of participants)	EB613 Treated (N=118) n (%)
Headache	21 (17.8)
Nausea	18 (15.3)
Diziness	13 (11.0)
Nasopharyngitis	7 (5.9)
Back pain	7 (5.9)
Palpitation	6 (5.1)
Dyspepsia	6 (5.1)
Presyncope	6 (5.1)

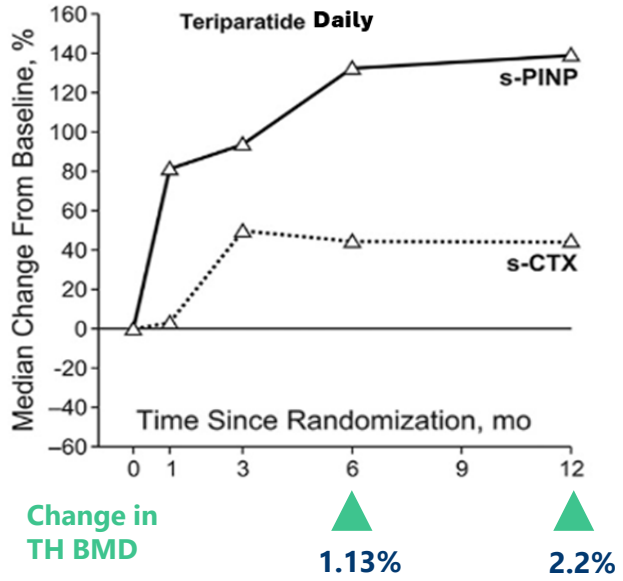
- Adverse event profile - similar to AE profile reported with Forteo® and typical of orthostatic hypotension
- EB613 was not associated with serum calcium increases or hypercalcemia adverse events
- 2.5 mg dose with titration (1.5mg for 1 month, 2.0mg for the next month and 2.5mg during months 3 to 6) well tolerated
- AEs commonly attributed to vasodilatation with subcutaneous injectable PTH were observed (headache, nausea, presyncope and dizziness)
- No serious AEs related to EB613

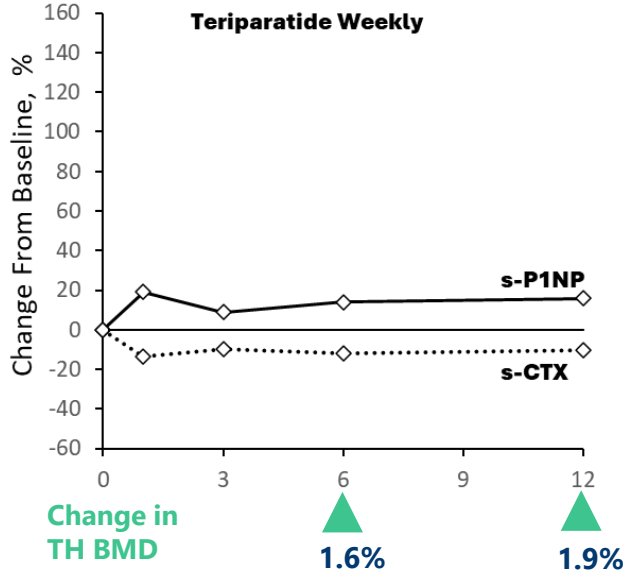
Change in Pharmacokinetics Profile of PTH (1-34) Results in Different Effect on Bone Markers

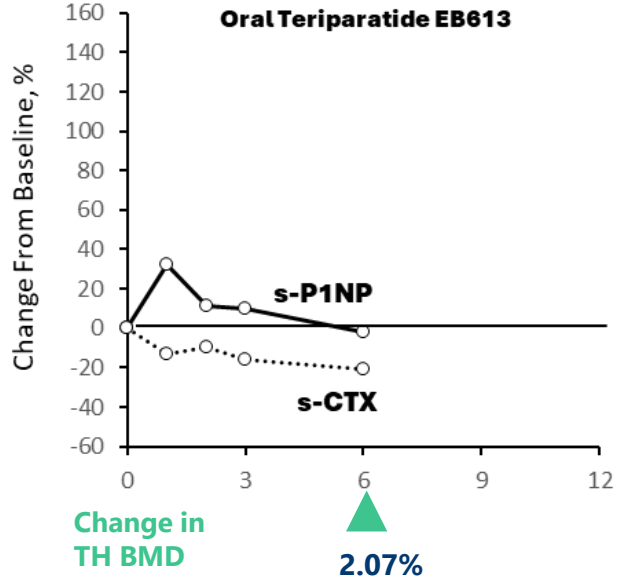
Different pharmacokinetic profiles and dose regimens of teriparatide result in:

- Different profile of bone turn over markers
- Persistent “anabolic window”
- Similar effect on bone mineral density and fracture outcomes









Bone markers and placebo adjusted BMD data for Daily Teriparatide, is extracted from Paul D. Miller et all, JAMA, 2016.
Data for once-weekly Teriparatide injection is extracted from Tower and TWICE studies (Sugimoto et al. 2019 and Toshitaka Nakamura et al. 2012).

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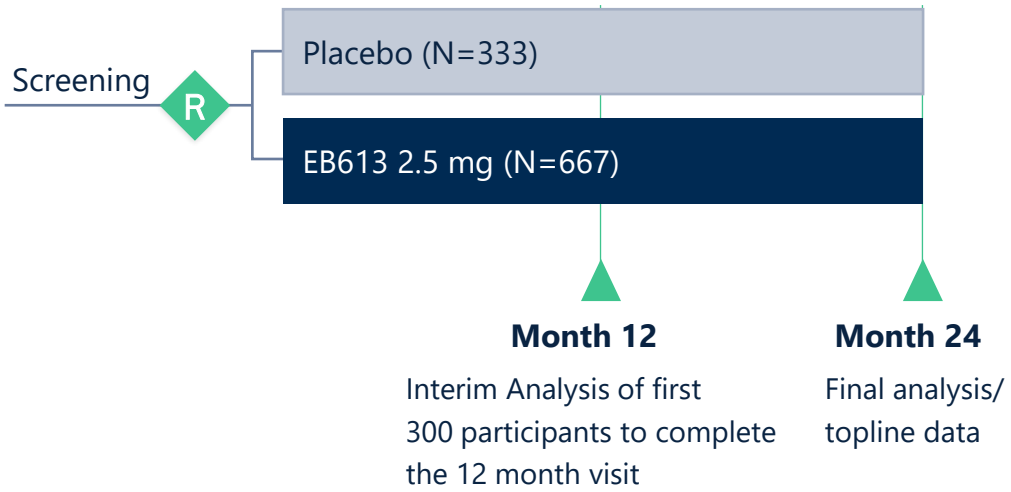
EB613 Phase 3 Study

A Single Global Phase 3 24-Month Double-Blind Placebo-Controlled Registrational Study

EB613 Phase 3 Clinical Study Design

Key Inclusion Criteria
- 50-80 years old
- 5+ years post-menopause
- BMD T-score ≤ -2.5
- No prior fracture

Key Exclusion Criteria
- Subjects with very low BMD; if < 75 years old, BMD T-score ≤ -3.5; if ≥ 75 years old, BMD T-score ≤ -3.0
- Osteoporosis treatment within last 2 years



Primary Endpoint
- Mean change from BL in total hip (TH) BMD at month 24

Secondary Endpoints
- Change in total hip BMD vs. STEs associated with fracture reduction
- TH, lumbar spine (LS), and femoral neck (FN) BMD changes from BL at month 6, 12, 18, and 24
- LS and FN BMD changes from baseline at month 24

Exploratory Endpoints
- Bone Turnover Biomarkers

- 24-month, double-blind, placebo-controlled registrational study in post-menopausal women w/ osteoporosis
- Designed with FDA Concurrence (Pursuant to Type C and Type D Meeting)

* STE = Surrogate Treatement Effects; 24-month STEs are those reported by FNIH-ASBMR-SABRE (Eastell 2022).

ASBMR-Foundation for the National Institutes of Health (FNIH) Strategy to Advance BMD as a Regulatory Endpoint (SABRE)

Issues Related to Osteoporosis Trials

- Fractures are the regulatory endpoint for osteoporosis trials
- Ethical concern for high fracture risk patients (IRBs), large and expensive studies

Result of these issues is a dearth in osteoporosis drug development

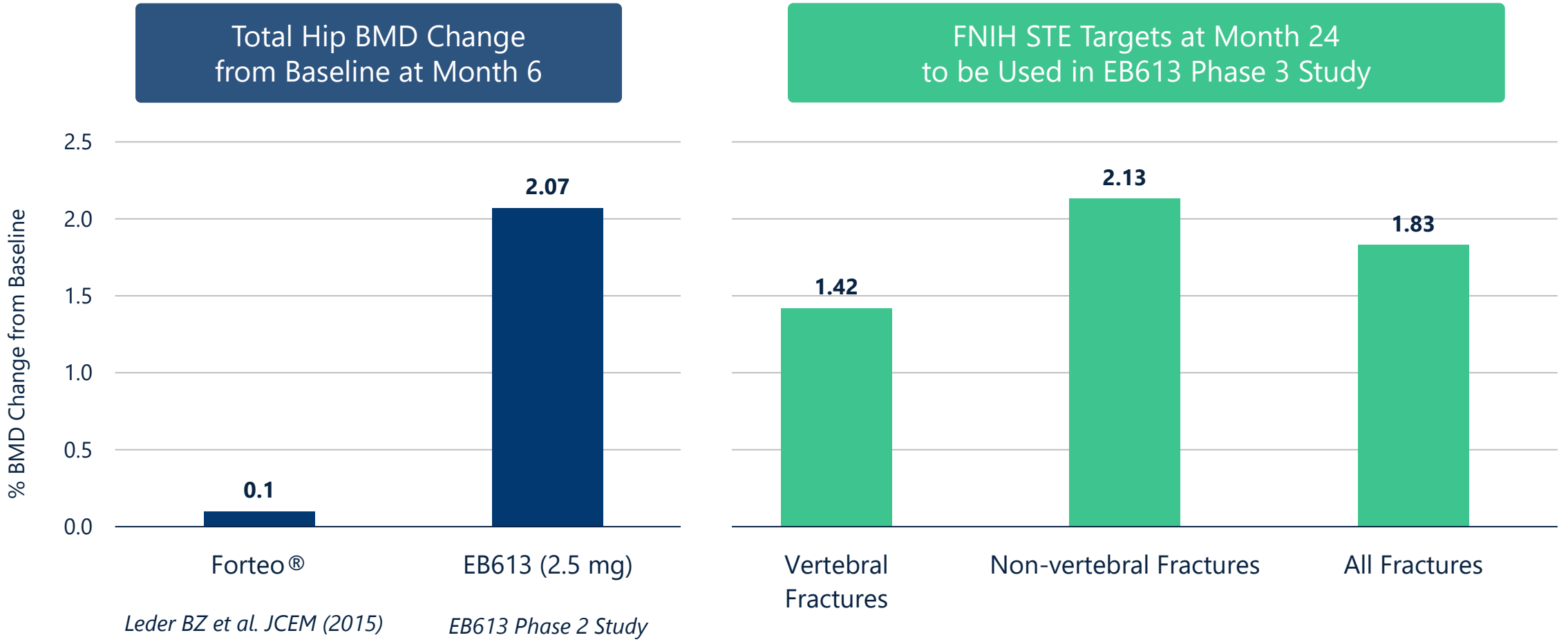
SABRE Proposal to FDA: BMD as Surrogate Endpoint for Fractures (part of 2016 Cures Act)

- TH BMD measurements correlate to fracture outcomes via quantitative surrogate threshold effects (STEs)
- SABRE announced submission of final qualification package to FDA (November 9, 2023)
- **ASBMR-FNIH SABRE qualification expected by January 2025– critical path for EB613 phase 3 initiation**

Placebo adjusted Total Hip BMD STEs:

1.42%	(vertebral fractures)
1.83%	(all fractures)
2.13%	(nonvertebral fractures)
3.18%	(hip fractures)

Proposed Primary End Point for EB613 Phase 3 Study: Placebo adjusted % Change in Total Hip BMD



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EB612 Program

First Daily Oral PTH Replacement Therapy for the Treatment of Hypoparathyroidism

Hypoparathyroidism: PTH Dependent Orphan Indication

Background

- A rare condition in which the parathyroid glands fail to produce sufficient levels of PTH
- Approximately 200K afflicted with hypoparathyroidism in the US, EU, and Japan
- PTH (along with vitamin D and calcitonin) plays a role in regulating the levels of calcium and phosphorus in the blood and in determining bone growth and bone cell activity
- Current standard of care (calcium and vitamin D supplements) creates long term co-morbidities (cardiovascular, renal, neurologic, and skeletal)

Competitive Landscape

- Natpara® (PTH) injection will be permanently phased out globally by end of 2024 (Takeda)
- TransCon PTH, once-daily injectable, long-acting prodrug of parathyroid hormone (PTH(1-34)) developed by Ascendis Pharma resubmitted NDA to FDA (PDUFA August 14 2024); EU Approved (November 20, 2023)
- Eneboparatide, once-daily injectable long-acting parathyroid hormone 1 (PTH1) receptor agonist, developed by Amolyt Pharma (acquired by AstraZeneca for $1BN 2024) Phase 3 (Topline data H1 2025E)

EB612: Potentially First Oral PTH (1-34) Daily Tablets for Hypoparathyroidism, Summary of PK and Pilot Phase 2 Data

Study Design

Phase 2a, open-label, 16 week, multicenter pilot study to evaluate the safety, tolerability and PK (NCT02152228)

Population: N=19 with hypoPT ≥ 1 year, taking ≥1 g/day calcium and 25(OH)D 20 ng/ml

Treatment: first 3 doses of EB612 0.75 mg QID administered at research center; then self administered

Results

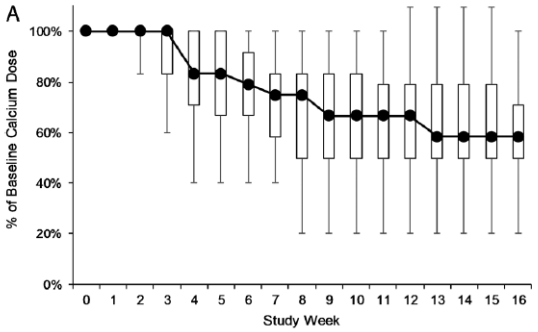
Efficacy:

- 42% reduction (p=0.001) from baseline in median calcium supplement use
- Maintenance of median Ca levels above the lower target level for hypoparathyroidism patients (>7.5 mg/dL) throughout the study
- Rapid decline of 23% (p=0.0003) in median serum phosphate levels 2 hours post first dose maintained for the duration of the study

Safety:

- One subject experienced 4 AEs and left the study after the first day
- One subject experienced an unrelated SAE prior to the administration of the first dose

Oral Calcium Intake
Per Protocol Analysis (N=15)



Phase 2, open-label, 2-period partial crossover study to evaluate the PK and PD (NCT03516773)

Population: N=16 with hypoPT ≥ 1 year, taking supplemental calcium and either alfacalcidol or calcitriol

Treatment: two doses (0.75, and 2.25 mg) and three regimens of EB612 and Natpara® [hPTH(1-84)] 100 µg SC injection QD

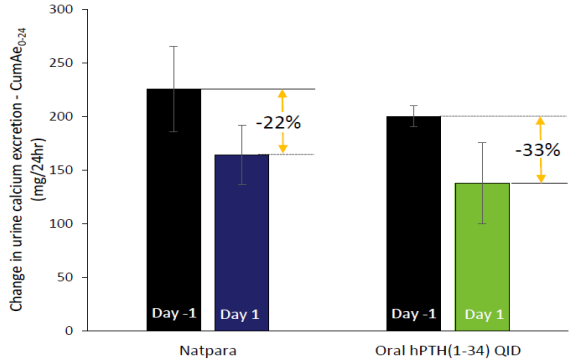
Efficacy:

- EB612 2.25 mg QID for one day is associated with an increase in serum albumin-corrected calcium and 1,25(OH)2D and a decrease in serum phosphate
- Results comparable to those with Natpara® 100 µg QD
- Two, three and four doses/day regimens showed a dose-dependent increase in 1,25(OH)2D
- Less frequent chronic therapy may be an effective treatment option

Safety:

- No hypercalcemia treatment emergent adverse and no treatment-emergent serious adverse events reported

Improved/ Decreased Urinary Ca
Excretion Over a 24-Hour Period



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Key Recent and Near-Term Milestones

EB613

FDA type C & D mtg. (Concurrence on Placebo, unique patient population, BMD Endpoint)

Expect BMD Endpoint Qualification **(Expected by January 2025)**

EB612

Selection of optimal candidate for oral peptide replacement therapy for HypoPT **(H2 2024E)**

EB613

Phase 2 study in young athletes with stress fractured due to intense training **(Update on IST Study Design H2 2024E)**

GLP-2

Pre-IND data from oral GLP-2 **(in vivo PD Data mid-2024E)**

OXM

Pre-IND data from oral OXM **(in vivo PK Data mid-2024E)**

Thank you

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