



Entera Bio

Global Leader in Oral Peptide Therapeutics



Disclaimer

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Entera Highlights

- **First-in-Class Oral Peptide and Protein Replacement Therapies**
- **Proprietary N-Tab™ Platform Stabilizes Peptide in GI Tract and Facilitates Systemic Absorption**
- **Tablet Format Designed to Unlock Patient Acceptance and Drive Superior Health Outcomes**
- **Programs across GYN/Endocrinology, GI and Metabolic Diseases (Validated Peptide Targets)**
- **EB613 is the first daily PTH (1-34) osteoanabolic tablet treatment in development to address treatment chasm in ~40% of 200 million osteoporosis patients globally (Phase 3, planned H1 2025)**
- **Additional Programs:**
 - **EB612: first oral PTH (1-34) peptide replacement therapy for hypoparathyroidism (Phase 1)**
 - **GLP-2 and GLP-1/Glucagon oral tablet programs with OPKO Health for SBS and Obesity (pre-clinical)**
- **Cash runway through Q3 2025 – Nasdaq: ENTX**



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

N-Tab™ Proprietary Platform



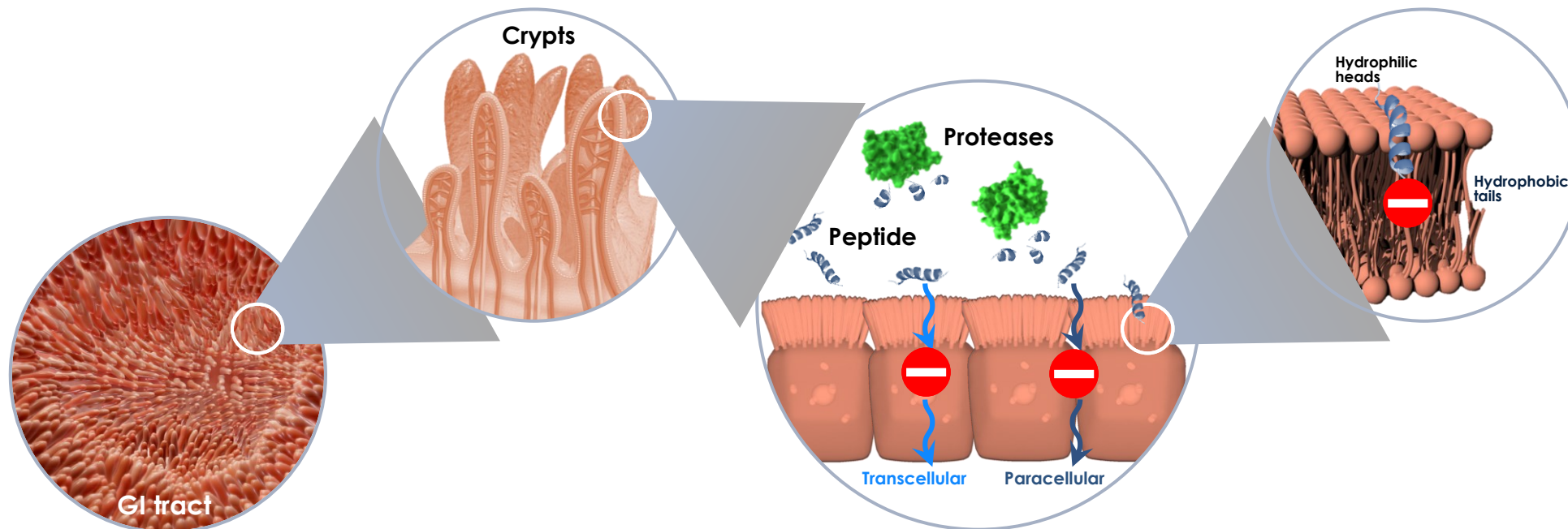


Oral Bioavailability of Therapeutic Peptides is Negligible

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

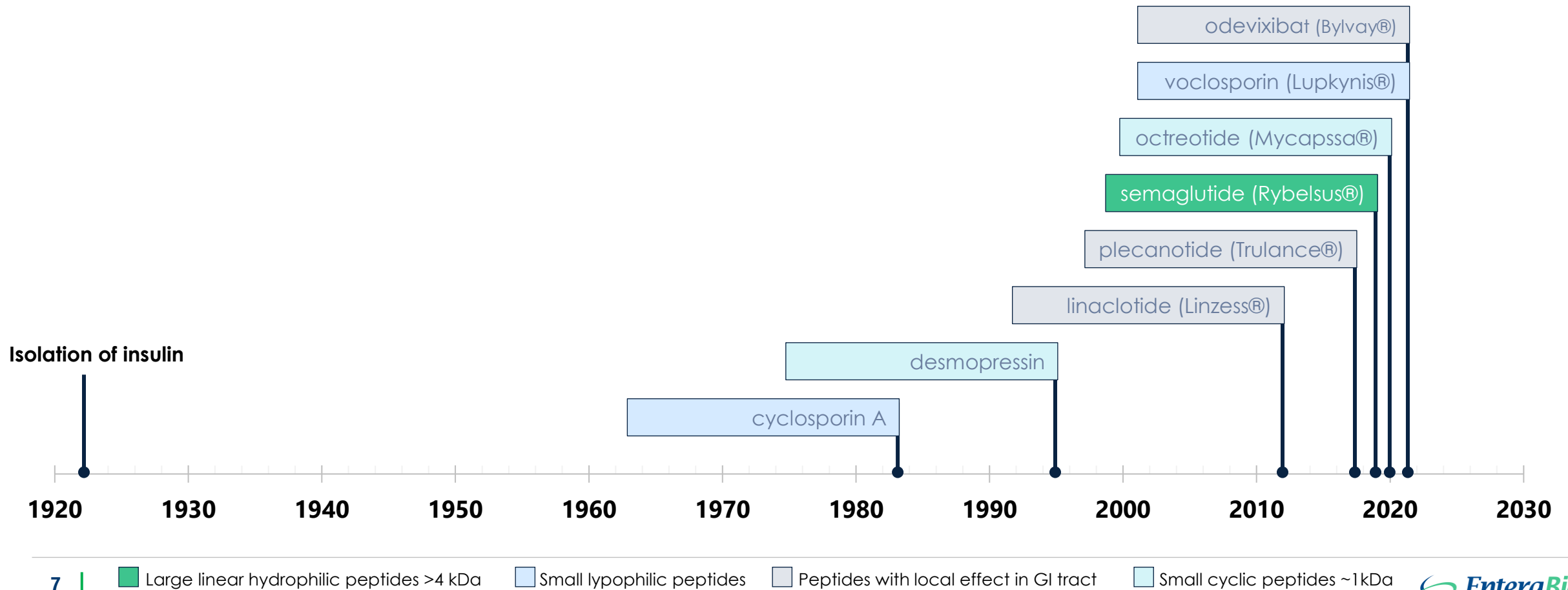
Peptide drug absorption is limited by polarity (transcellular) and size (paracellular)





Oral Delivery of Peptide Drugs Has Lagged

Out of >80 approved injectable peptide therapies, there is only one approved oral peptide >4kDa (GLP-1, Rybelsus®)

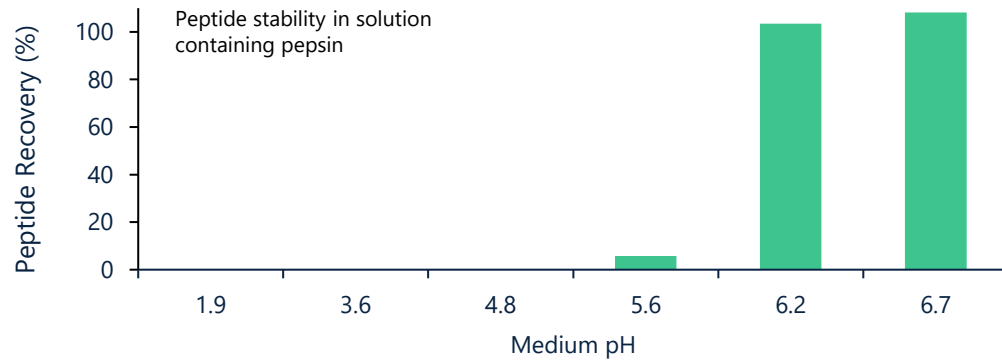




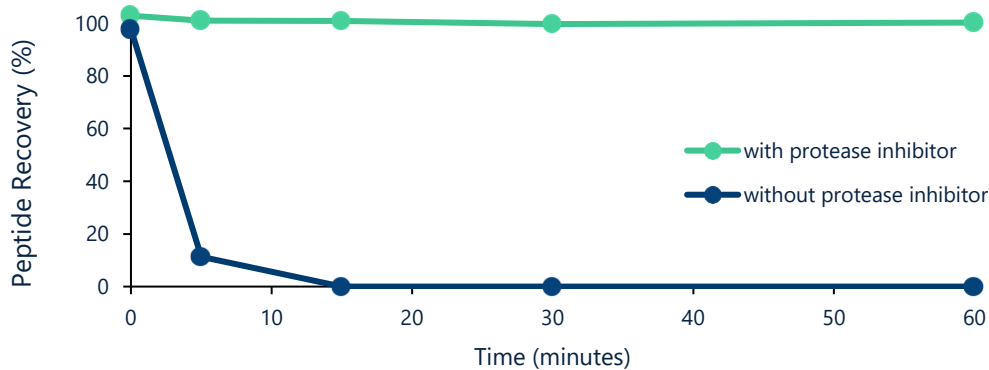
N-Tab™ Platform Inhibits Proteolysis in GI Tract and Enables Bioavailability

↓ Proteolysis Inhibition

Locally Elevated Gastric pH Inactivates Pepsin

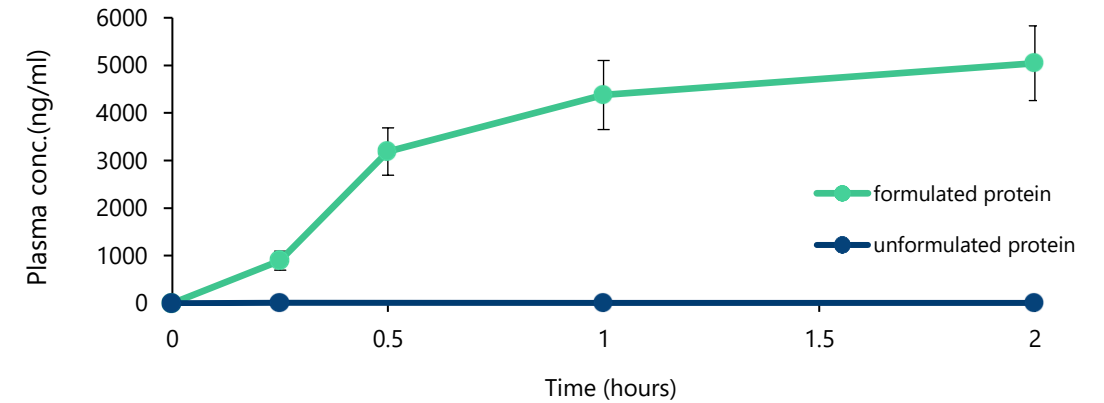


Protease Activity Inhibited

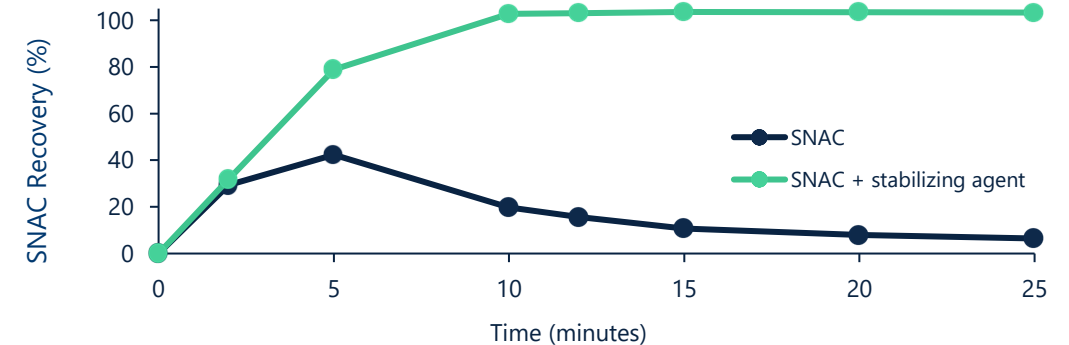


↑ Absorption Enhancement

SNAC Increases Transcellular Absorption via Enterocyte Membrane



SNAC Further Stabilized to Enhance Activity



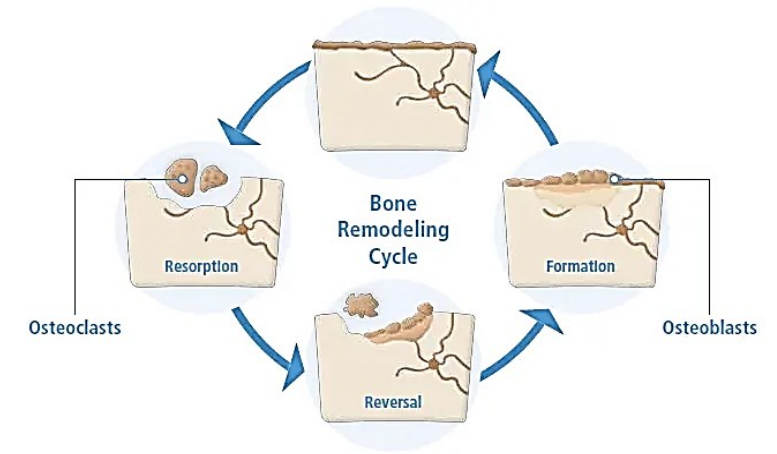
EB613 Oral PTH (1-34)

First Once Daily Osteoanabolic Tablet Treatment in development for Post-Menopausal Women at High Risk of Osteoporotic Fracture

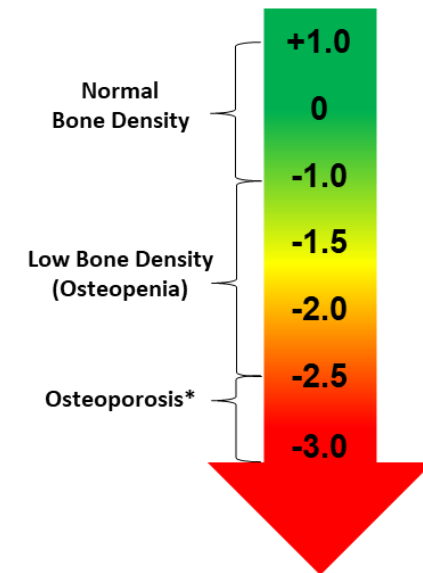


Osteoporosis

- **Dysregulated Bone Remodeling and Increased Osteoclast Activity**
 - ↑ resorption (CTX biomarker), ↓ formation (P1NP biomarker)
- Osteoporosis is a chronic, debilitating and often lethal disease
- **Diagnosed and Managed via Bone Mineral Density (BMD) T- Score**
 - Standard bone density test is used to measure bone mineral content and density
 - Non-invasive X-rays, dual-energy X-ray absorptiometry (DXA) scan to determine bone density of the hip, femur or spine
 - T-Score stages severity of low bone mass and osteoporosis



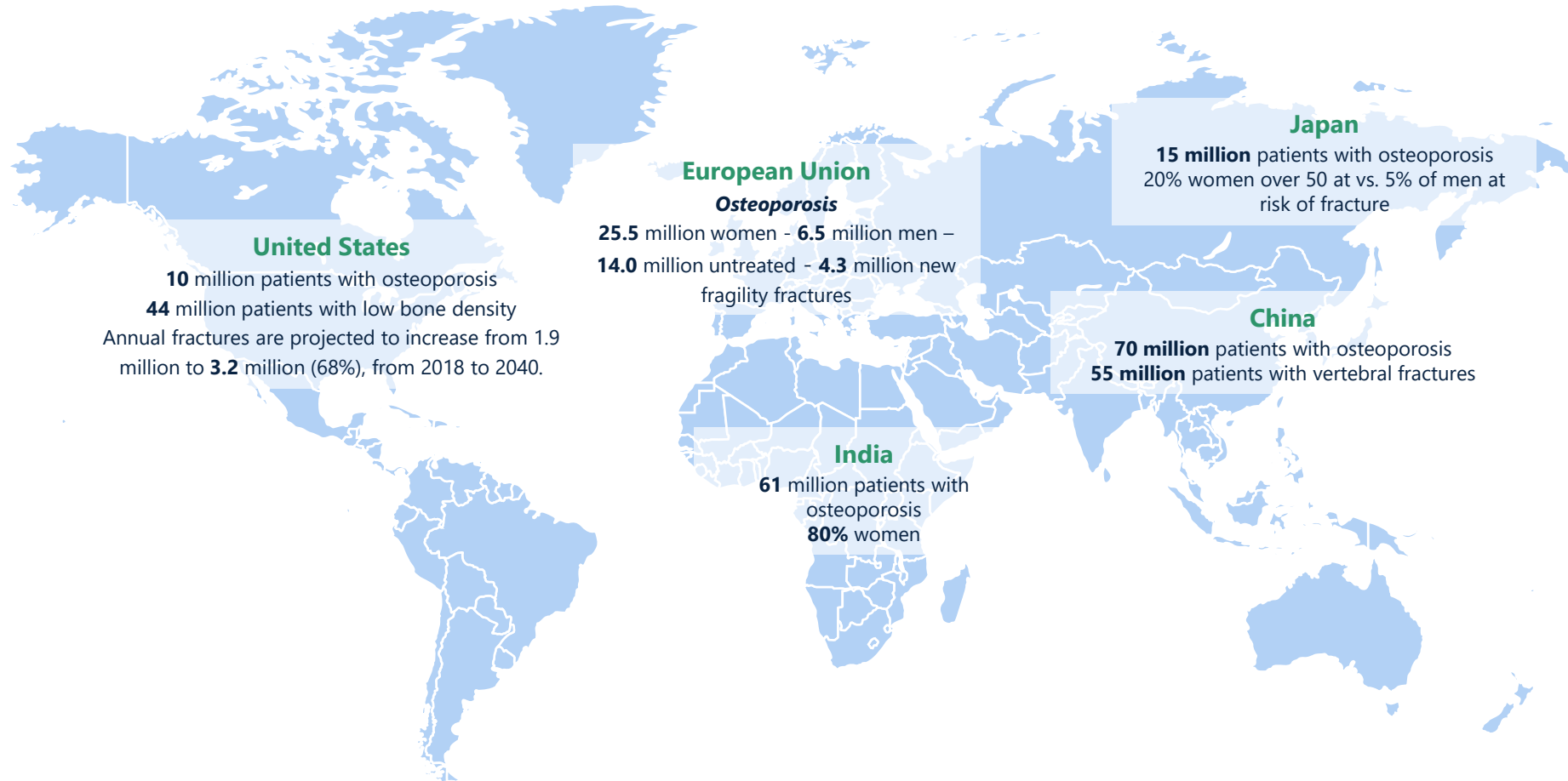
Bone Mineral Density Results T-score





Globally, Osteoporosis Afflicts ~200 million Women

More than Heart Attack, Stroke, and Breast Cancer Combined



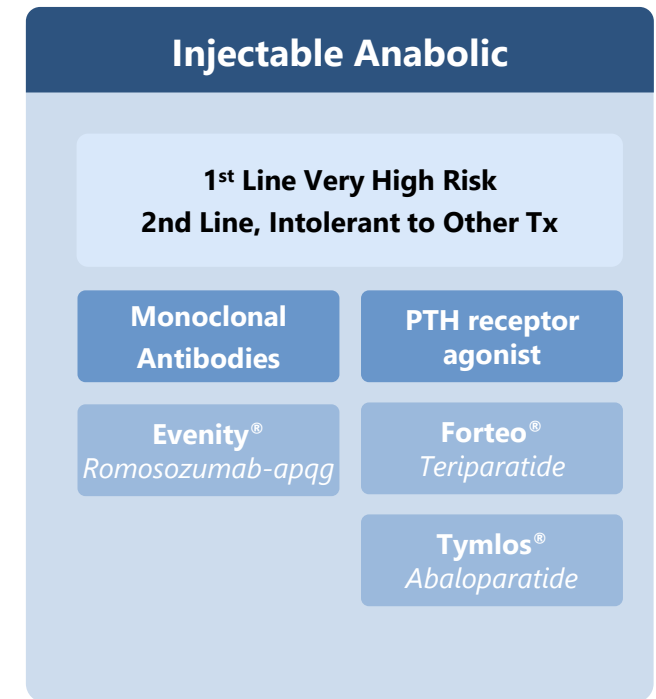
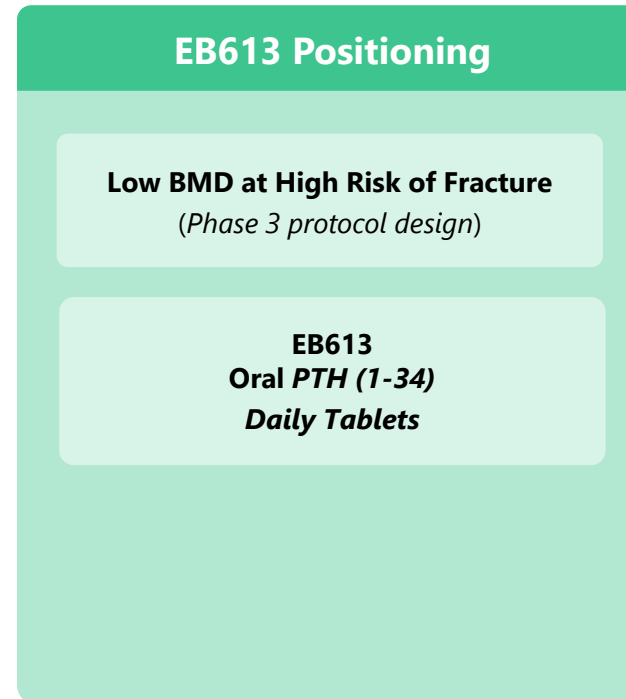
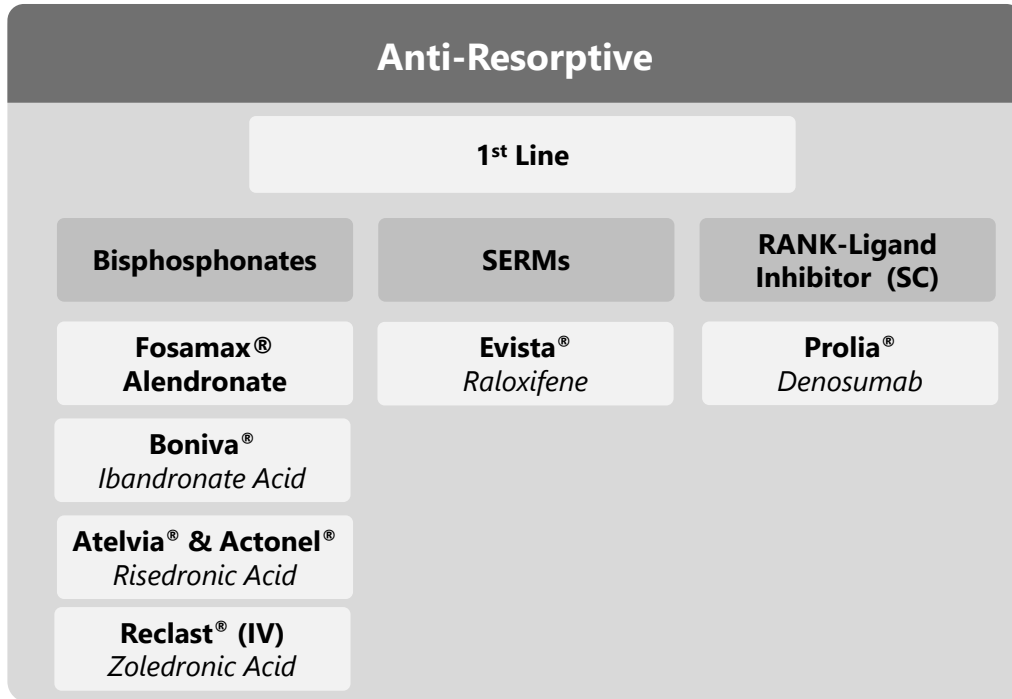
~**50%** of women over the age of 50 will experience an osteoporosis-related fracture

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



Osteoporosis Treatment Chasm

Anabolic Agents are More Effective in High Risk Patients; Injectable Format Limits Patient Acceptance



- ~3 million patients are estimated to be treated in the U.S. with osteoporosis therapy
 - ~40% are recommended to take anabolic treatment per guidelines/ disease severity
 - ~10% of patients are estimated to be on an injectable anabolic agent
- **EB613 is positioned as the first oral anabolic treatment to support earlier intervention in post-menopausal women with high risk osteoporosis**

EB613 Phase 2 Results

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





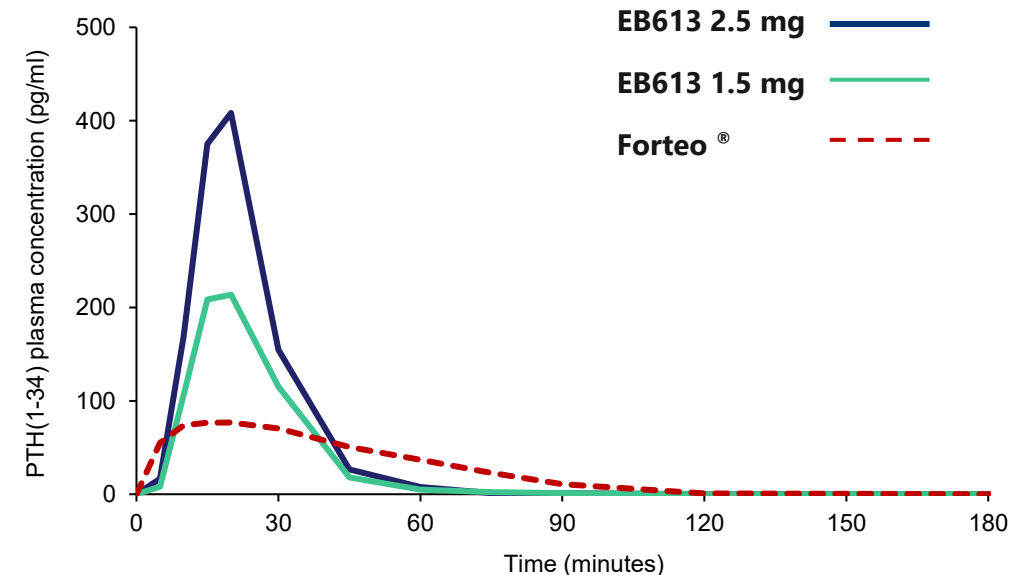
EB613 Oral PTH(1-34) Pharmacokinetics (PK)

EB613 consistently demonstrates rapid increases in PTH(1-34) plasma levels and robust bioavailability in Phase 1 and 2 studies

- Short absorption phase with T_{max} similar to that observed with SC injection, Forteo® (≤20 minutes)
- Rapid elimination (T_{1/2} of ~10 minutes) results in shorter duration of systemic exposure as compared to SC injection, Forteo® which has potential safety benefit
- Dose proportional increase in C_{max} and AUC with EBP05 1.5mg and 2.5mg doses

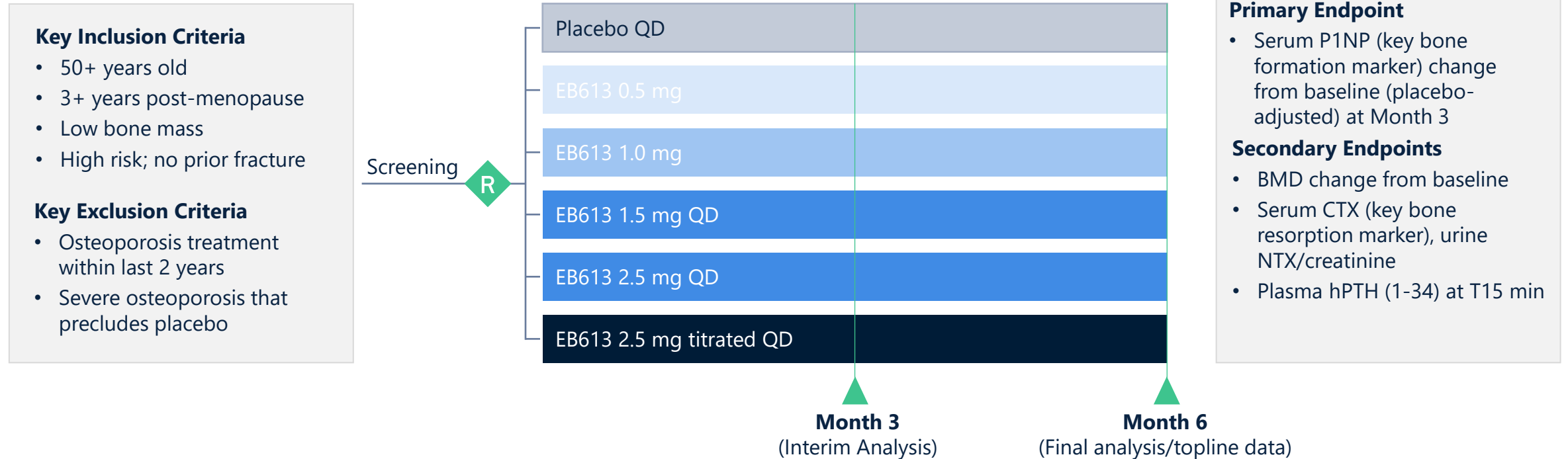
PK parameters Measured Following Administration of 2.5 mg and 1.5 mg EB613 tablets, and Forteo® SC injection (0.02 mg)

Treatment	C _{max} (pg/ml; mean, SE)	AUC _{last} (pg/ml*min; mean, SE)	T _{max} (min, median, range)	T _{last} (min, median, range)
EBP05 1.5 mg	270 (109)	4590 (2200)	15 (10-20)	20 (10-90)
EBP05 2.5 mg	488 (122)	7590 (2000)	15 (10-20)	30 (20-90)
Forteo® 0.02 mg	89.3 (10.5)	4080 (466)	20 (5-45)	75 (30-120)





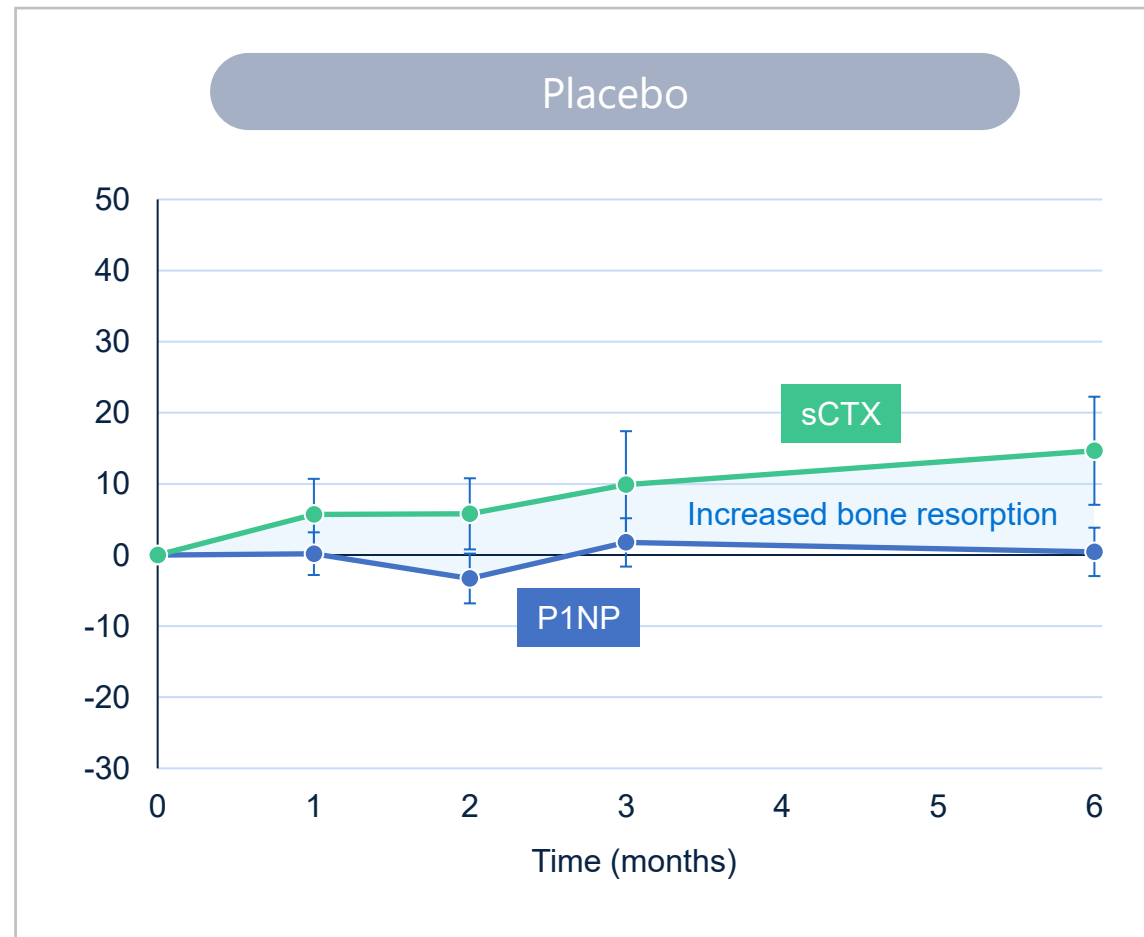
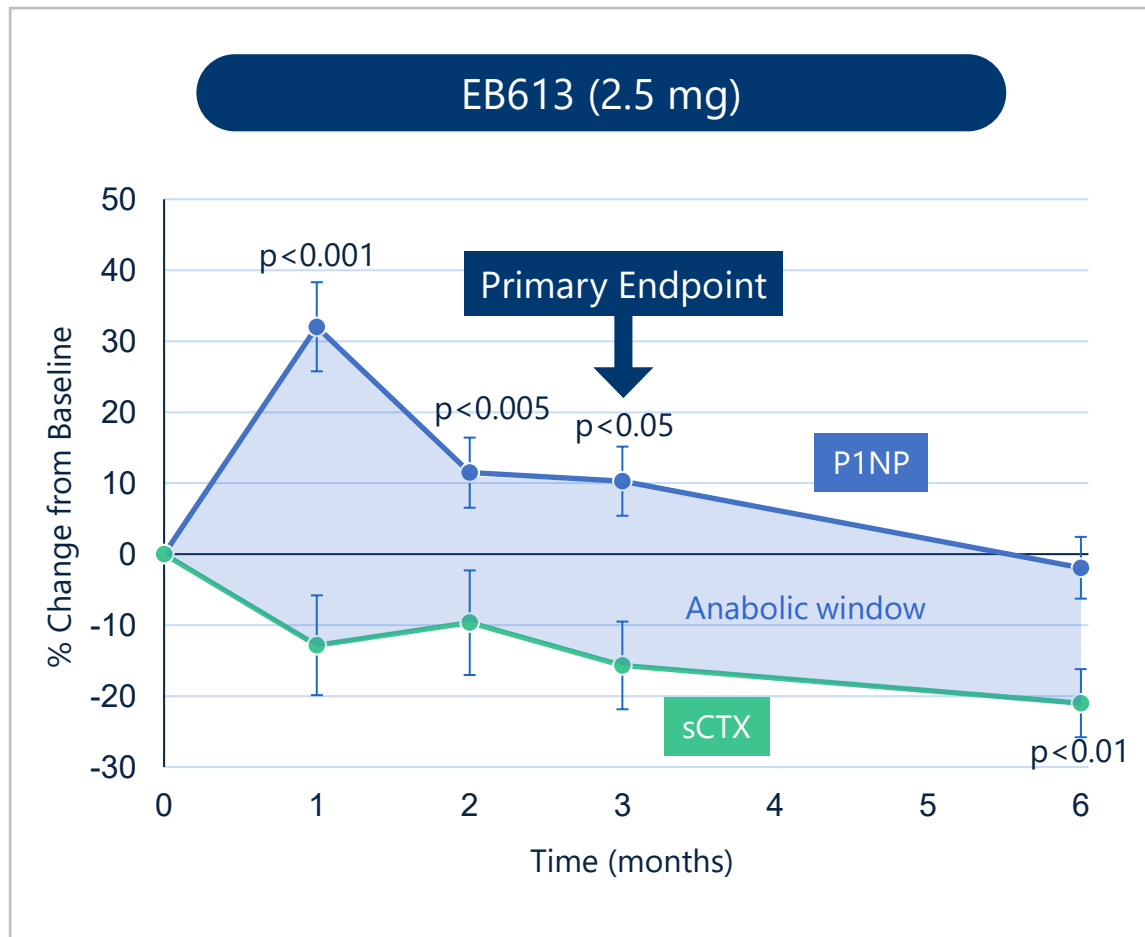
EB613 Phase 2 Clinical Study Design



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



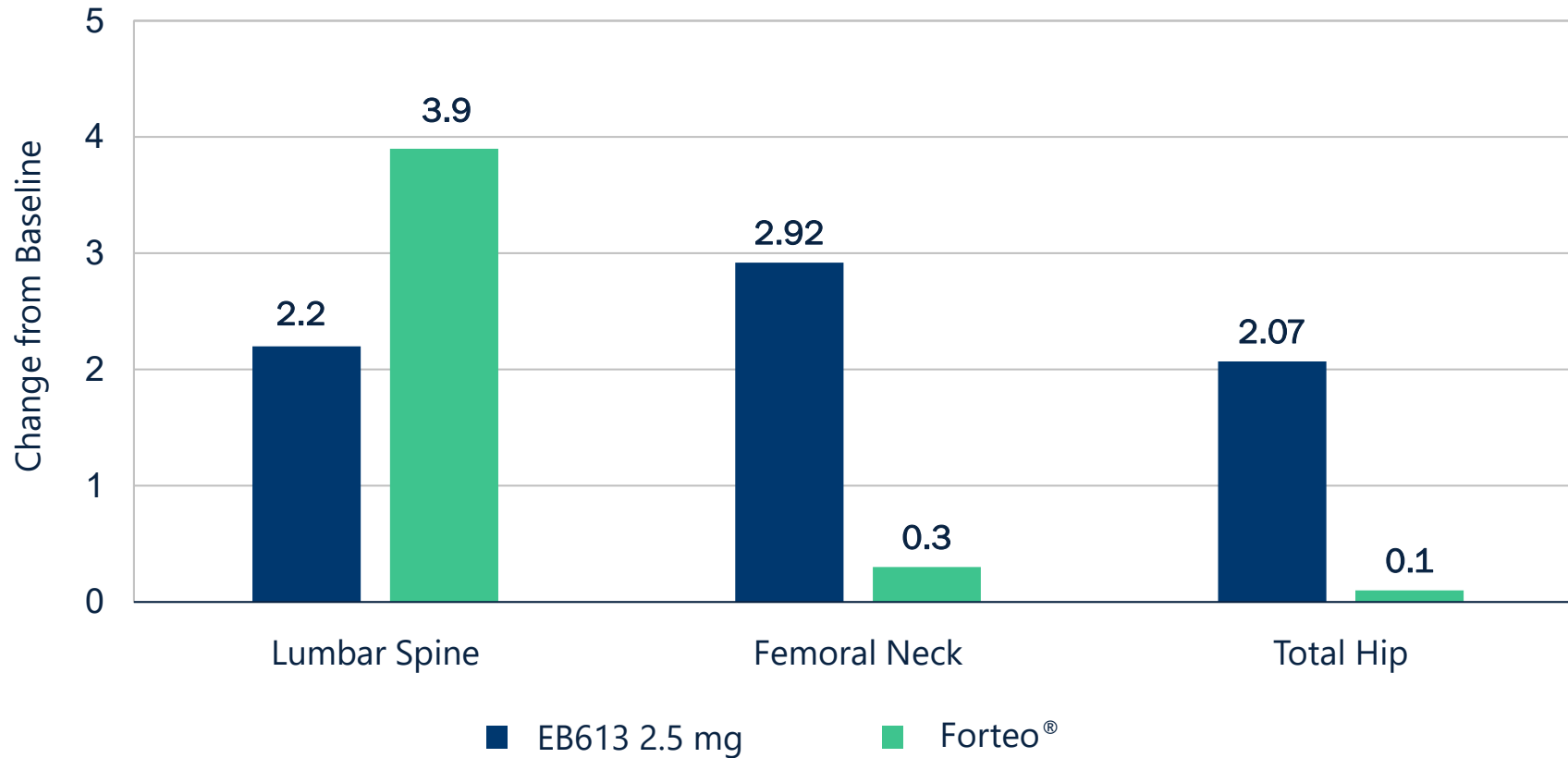
Phase 2: Biochemical Markers of Bone Turnover Showed EB613 Distinct Profile of Increased Bone Formation (P1NP) and Reduced Bone Resorption (CTX)





EB613 Increased BMD at All Major Skeletal Sites

Placebo-adjusted BMD Change of EB613 from Baseline to Month 6 as Compared with Published Forteo® Data



Faster onset and greater increases of hip and femoral neck BMD vs. Forteo® in similar patient population open label study at month 6



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)
Dizziness	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

EB613 Phase 3 Study Design

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





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

Challenges Related to Osteoporosis Drug Development

- Fractures are the regulatory endpoint for all osteoporosis trials
- Ethical concern for high fracture risk patients to be potentially randomized to placebo (ECs/IRBs)
- Evaluation of moderate risk patients would require large studies to evaluate treatment effectiveness

Dearth in Osteoporosis Drug Development

- No new osteoporosis therapy has been approved since 2019

The use of treatment related change in bone mineral density (BMD) as a surrogate endpoint for fractures in future trials of new anti-osteoporosis drugs is now undergoing review at the FDA

- **FDA qualification of the proposed BMD endpoint is expected by January 2025 – critical path for EB613 Phase 3 initiation**



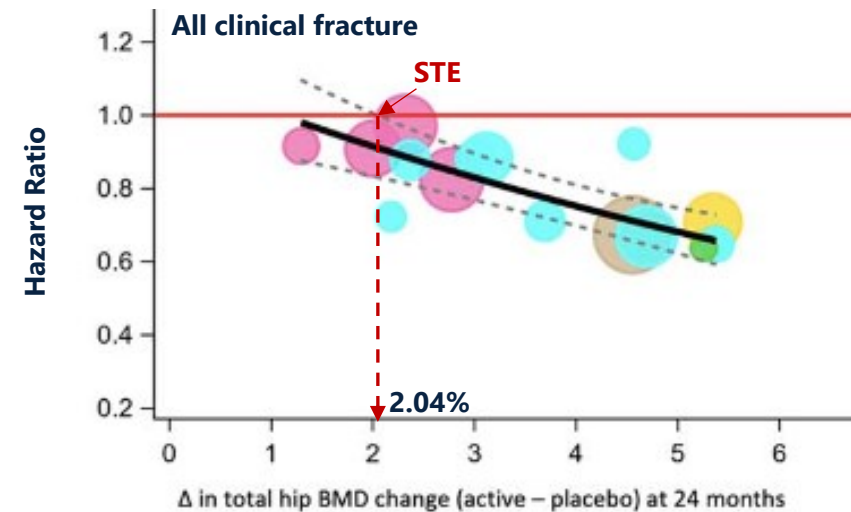
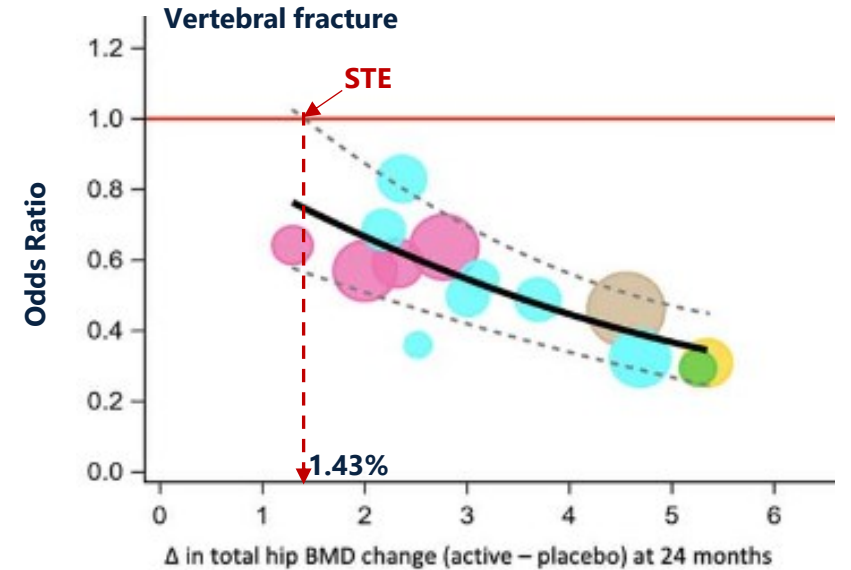
Published Surrogate Threshold Effects (STE) Across Fracture Categories

- The FNIH collected data from over 50 randomized trials and individual data from over 170,000 patients
- STEs depict the treatment difference in total hip BMD (active – placebo) at 24 months that are significantly associated with fracture risk reduction

Fracture Category **Surrogate Threshold Effect (STE)***

Vertebral	1.43%
All clinical (non-vertebral + clinical vertebral)	2.04%
Non-vertebral	2.13%
Hip	3.07%

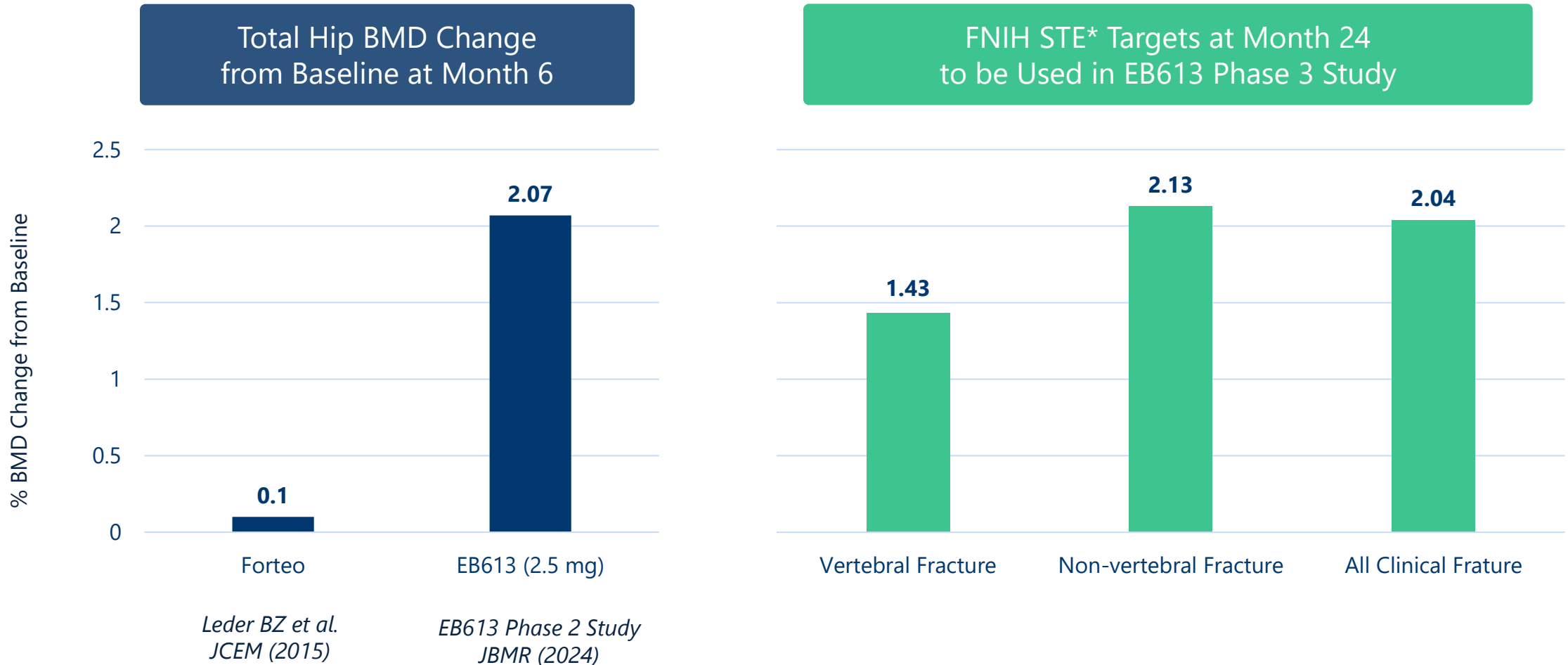
*24-month Interval for BMD changes (active – placebo)



● Bisphosphonates ● SERMs ● PTH Analog ● Odanacatib ● Denosumab



Proposed Primary Analysis for EB613 Phase 3 Study: Placebo Adjusted % Change in Total Hip BMD Employing SABRE STEs



Proposed Multinational Randomized, Double-Blinded Placebo-Controlled Ph 3

Study Design Overview for EB613 Schema*

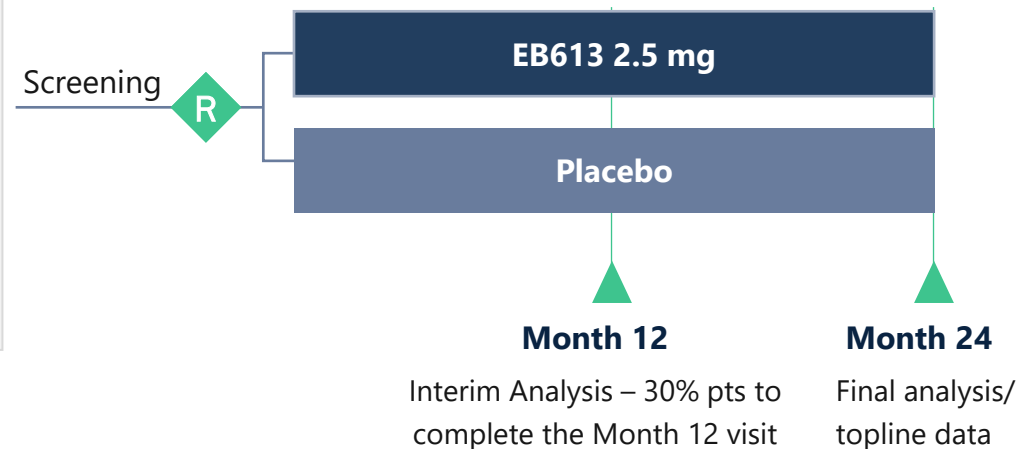


Key Inclusion Criteria

- 50-80 years old
- 5+ years postmenopausal
- BMD T-score \leq -2.5

Key Exclusion Criteria

- Very High risk for fracture
- Specified criteria for past use of agents affecting bone metabolism



Primary Efficacy Endpoint

- Treatment change in total hip BMD at Month 24 significantly associated with fracture risk reduction

Secondary Efficacy Endpoints

- Treatment change in LS, FN, TH BMD at Month 6,12,18, 24
- Substudies planned to evaluate bone quality and histomorphometry (bone biopsy) and changes in bone turnover markers

Safety Endpoints include

- Treatment-emergent AEs, changes in vital signs, and clinical labs
- Fracture outcomes at Months 12 & 24

- **24-month, double-blind, placebo-controlled registrational study in postmenopausal women with osteoporosis at high risk of fracture**

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 -300K in the US, EU, and Japan
- PTH replacement therapy aimed to displace standard of care (calcium and vitamin D supplements) which results in severe long term co-morbidities (cardiovascular, renal, neurologic, and skeletal)

Competitive Landscape

- Natpara[®] (PTH(1-84)) 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 FDA Approved (August 13 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)
- Long acting once weekly injectable PTH peptide prodrug (MBX2109, Ph2 Avail[™] topline data Q3 2025E), oral small molecule PTHR1 (SEP786, Septerna)



EB612: Oral PTH (1-34) Daily Tablets for Hypoparathyroidism

Study Design

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

Population: N=19 with hypoPT \geq 1 year, taking \geq 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

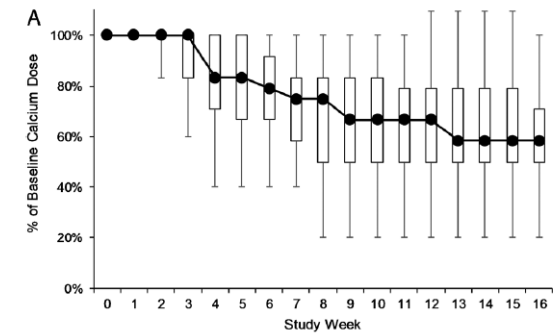
Efficacy:

- 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 1 Study Results Of EB612, A First-in-Class Oral PTH(1-34) Analog For The Treatment Of Hypoparathyroidism (June 2024, ENDO2024 Poster)

- Study tested a new generation of N-Tab™ with PTH(1-34) dosed twice a day (BID) in healthy volunteers (n=15)
- Significant systemic exposure was reported following both administrations of EB612 tablets with PD effects (serum levels of calcium (albumin corrected), phosphate, and 1,25(OH)₂-Vitamin D, endogenous PTH)

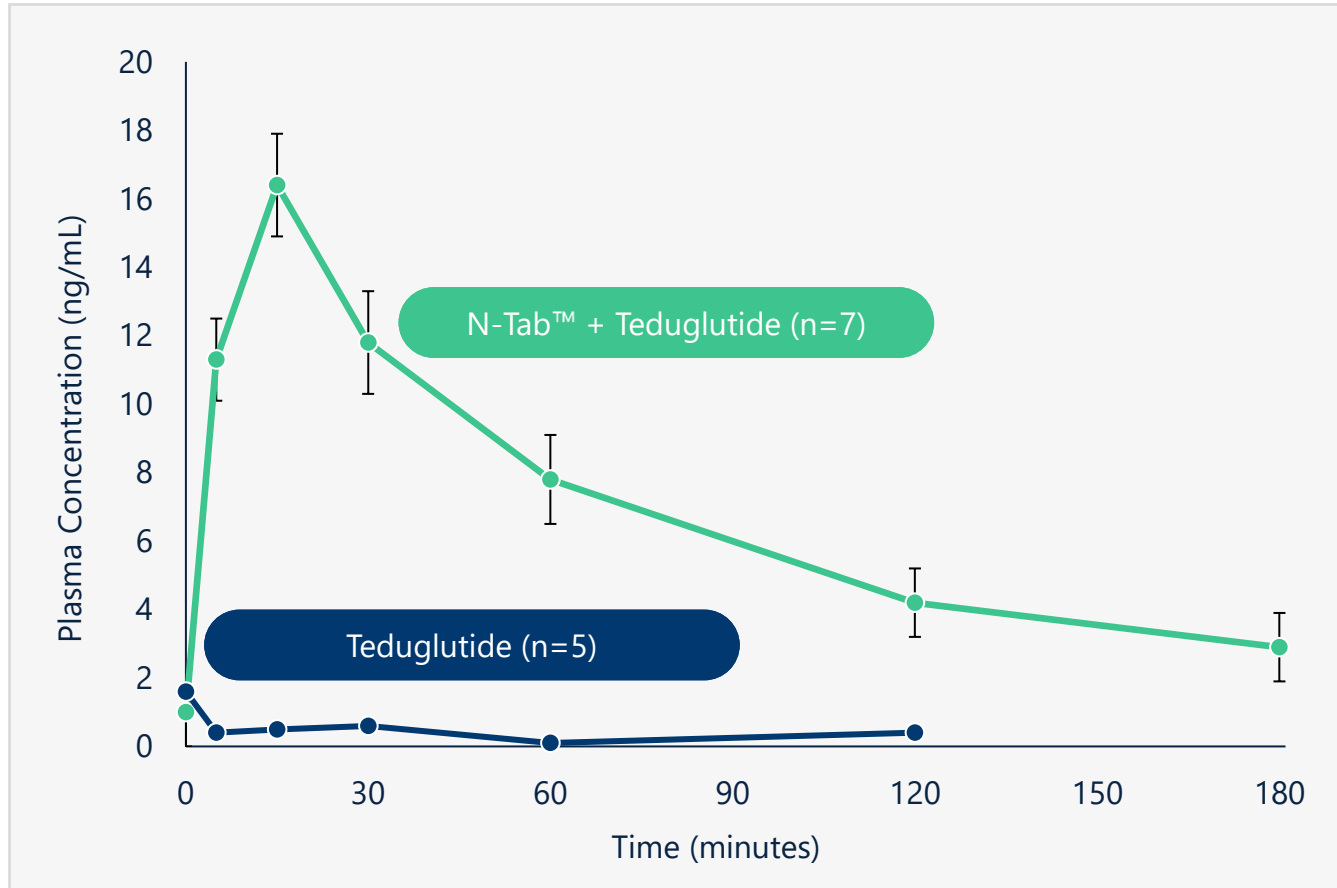
GLP2 GLP1/Glucagon





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

Entera published pre-clinical data on gastromucosal absorption of oral GLP-2 tablets 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

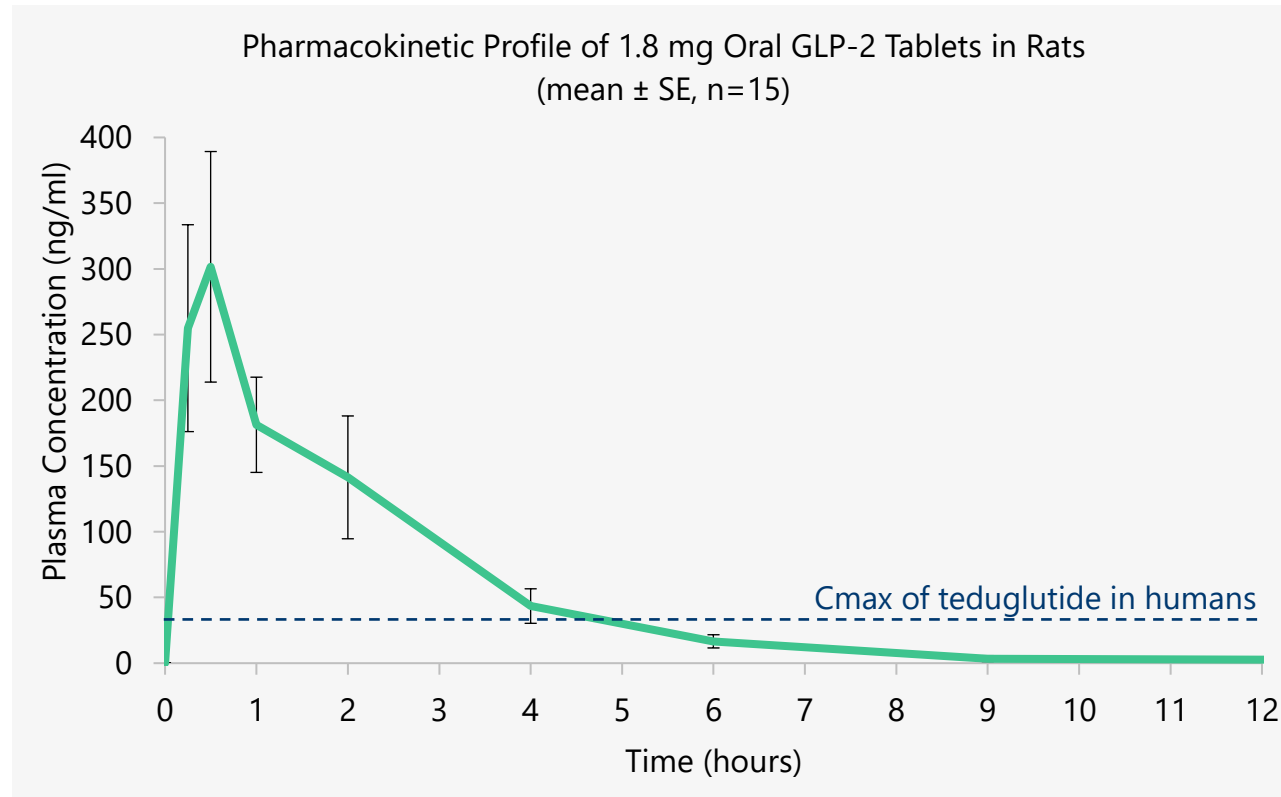
Gattex® (teduglutide), the only approved GLP-2, requires daily SC injections (~\$600M sales in 2023)

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



Entera/Opko: Oral Long Acting GLP-2 Tablet In Vivo PK Data

Proof-of-concept single dose pharmacokinetic study in rodents showed robust systemic absorption of N-Tab™ Oral GLP-2 analog

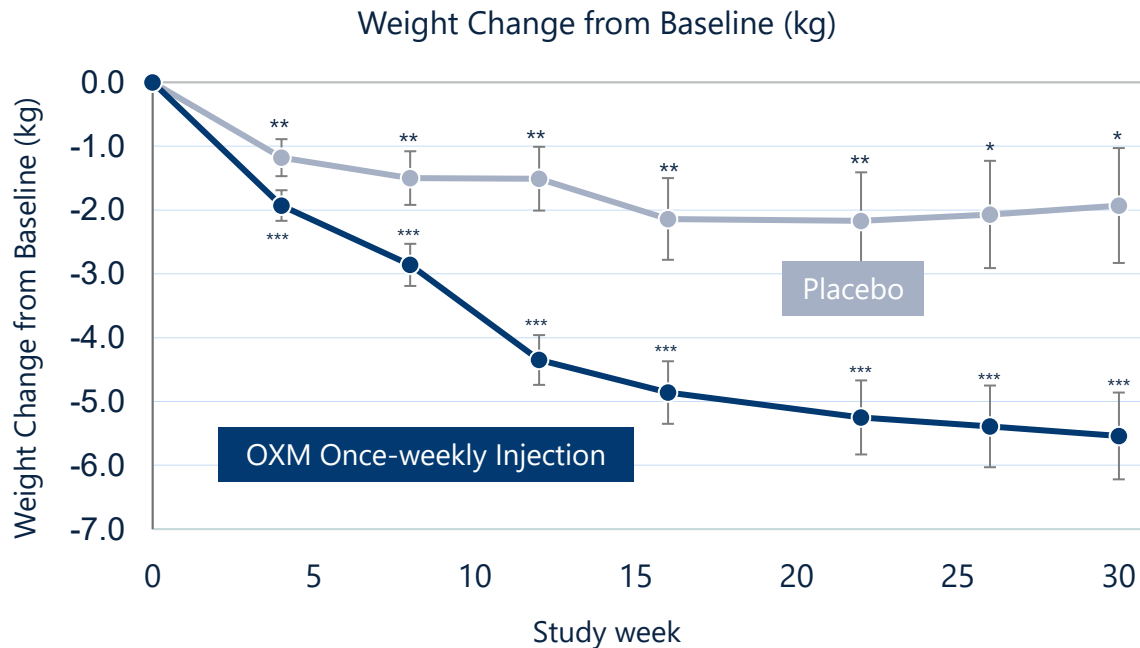


- The plasma half-life of the GLP-2 peptide following IV injection was found to be about 6 times longer than the half-life reported for teduglutide in the same animal model



Entera/Opko: Oral GLP-1/Glucagon Agonist for Obesity / Metabolic Disorders

Injectable OXM Phase 2B Results



Parameter	OXM (N=45)	Placebo (N=28)
Triglycerides (mg/dL)	-40.5 (12.52) (p=0.0019)	-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; No approved OXM agonists; those in development require subcutaneous injections
- >1 billion people suffer from obesity globally; market is estimated to grow to \$100B by 2030
- Phase 2B study with Opko *once-weekly injectable* OXM demonstrated significant weight loss and reduction in HbA1, triglyceride and cholesterol levels in 113 obese and diabetic patients
- N-Tab™ Oral OXM tablets exhibited significant systemic exposure, a favorable PK and robust bioavailability following a single dose in 2 *in vivo* models
- Oral OXM tablets rapidly reduced plasma glucose levels compared with placebo *in vivo*



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
PTH peptide
replacement tablet
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 PK
Data March 2024; PD
Data H2 2024E)**

OXM

Pre-IND data from
oral OXM **(in vivo
PK/Preliminary PD
Data PR
September 2024)**

Thank you

Ms. Miranda Toledano, Chief Executive Officer
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