Entera Bio

Corporate Presentation

March 2023

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Important factors that could cause actual results to differ materially from those reflected in Entera’s forward-looking statements include, among others: changes in the interpretation of clinical data; results of our clinical trials; the FDA’s interpretation and review of our results from and analysis of our clinical trials; unexpected changes in our ongoing and planned preclinical development and clinical trials, the timing of and our ability to make regulatory filings and obtain and maintain regulatory approvals for our product candidates; the potential disruption and delay of manufacturing supply chains; loss of available workforce resources, either by Entera or its collaboration and laboratory partners; impacts to research and development or clinical activities that Entera is contractually obligated to provide, such as those pursuant to Entera’s agreement with Amgen; overall regulatory timelines; the size and growth of the potential markets for our product candidates; the scope, progress and costs of developing Entera’s product candidates; Entera’s reliance on third parties to conduct its clinical trials; Entera’s expectations regarding licensing, business transactions and strategic collaborations; Entera’s operation as a development stage company with limited operating history; Entera’s ability to continue as a going concern absent access to sources of liquidity; Entera’s ability to obtain and maintain regulatory approval for any of its product candidates; Entera’s ability to comply with Nasdaq’s minimum listing standards and other matters related to compliance with the requirements of being a public company in the United States; Entera’s intellectual property position and its ability to protect its intellectual property; and other factors that are described in the “Cautionary Statements Regarding Forward-Looking Statements,” “Risk Factors” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations” sections of Entera’s most recent Annual Report on Form 10-K filed with the SEC, as well as the company’s subsequently filed Quarterly Reports on Form 10-Q and Current Reports on Form 8-K. There can be no assurance that the actual results or developments anticipated by Entera will be realized or, even if substantially realized, that they will have the expected consequences to, or effects on, Entera. Therefore, no assurance can be given that the outcomes stated or implied in such forward-looking statements and estimates will be achieved. Entera cautions investors not to rely on the forward-looking statements Entera makes in this presentation. The information in this presentation is provided only as of the date of this presentation, and Entera undertakes no obligation, to update or revise publicly any forward-looking statements, whether as a result of new information, future events or otherwise, except to the extent required by law.

Entera Bio: Leader in Oral Protein Therapies

- **First-in-class, daily mini tablets of protein and peptide replacement therapies** designed for patients to live well as they manage their chronic diseases
- Underserved conditions where **oral administration can significantly shift treatment outcomes**, versus standard of care injectable proteins
- **Proprietary platform** simultaneously inhibits proteolytic (enzymatic) degradation in the GI tract (stability) and facilitates therapeutically relevant absorption into the plasma (bioavailability)
- **Our proprietary oral daily hPTH*(1-34) teriparatide mini tablets** have been administered to a total of 225 subjects (153 patients) with **demonstrated PK and clinical benefit across two distinct diseases (osteoporosis and hypoparathyroidism)**
- **Strategic partnership** with Amgen (2018) and undisclosed MTAs to diversify pipeline and revenue streams
- **2022 core management changes; foundational year for the Company**

*Parathyroid hormone (PTH) is an 84-amino acid hormone and the primary regulator of calcium and phosphate metabolism in bone and kidney. The synthetic analog of PTH, hPTH (1-34) peptide, Forteo® (teriparatide injection) has been approved in the US and EU (Forsteo®) for the treatment of osteoporosis since 2002/2003.

Brief Historical Overview of Our Lead Programs: 2022 Was a Foundational Year for Entera

EB613*: Potentially the First Daily Oral PTH Mini Tablets, OsteoAnabolic Treatment for Osteoporosis - FDA Discussions on Track for Phase 3 Initiation (H2 2023E)

- **June 2021: Phase 2 study met biomarker/PD (P1NP, CTX) and 6-month BMD** endpoints** in post-menopausal women with osteoporosis (ASBMR 2021)
- **January 2022: End of Ph2 Minutes** – FDA suggests placebo-controlled rather than the NI H2H vs. Forteo®
- **June 2022 - October 2022: Type C Meeting - FDA concurrence that a *placebo-controlled Ph3* study with TH BMD as primary endpoint could support an NDA under the 505B(2) pathway**
- **February 8th 2023: Entera Submits Type D Meeting – Ph3 protocol review expected March 2023**
- **EB613 is the first program permitted by FDA to conduct a *single-placebo* controlled registrational study with a BMD (NOT fracture) endpoint to potentially secure an NDA (Phase 3 initiation H2 2023E)**

EB612*: Potentially First Daily Oral Mini Tablet PTH Replacement Therapy for the Treatment of Hypoparathyroidism – New Tablets PK Read-Out (H2 2023E)

- Pilot 4-month Phase 2 results presented (ASBMR 2015) and published (JBMR 2021)
- **Phase 1 PK data from a novel mini tablet formulation (H2'2023E)**

*EB612 and EB613 are **hPTH(1-34) teriparatide Tablets** BMD = Bone Mineral Density; ** TH = Total Hip

Experienced Leadership Team

Miranda Toledano, MBA Chief Executive Officer	Director at Entera since 2018 (CEO since 2022); 23 years of C-level leadership, principal investment and wall street/ transactional experience in the biotech sector; Previously co-founder, COO/CFO TRIGR (Acquired by Compass Therapeutics (Nasdaq: CMPX); Head of HC Investment Banking at MLV/FBR (Acquired B Riley); VP Investment Team at Royalty Pharma (Nasdaq: RPRX)
Art Santora, MD, PhD Chief Medical Officer	35 years of endocrinology/ special care and pharmaceutical experience; 28 years at Merck (lead clinical physician for Fosamax®); Medical Officer at the US FDA in the Division responsible for osteoporosis and other diseases of bone and calcium metabolism
Dana Yaacov, CPA, MBA Chief Financial Officer	15 years of finance management and accounting experience; Previously served as Senior Manager at PwC Israel overseeing audits of public and private companies. She is an expert in financial planning, operations management, external and internal audit for public multinational companies under US GAAP, IFRS and PCAOB standards
Hillel Galitzer, PhD, MBA Chief Operating Officer	21 years of biotech , early R&D, supply chain and operating experience. Previously, served as analyst and the chief operating officer for Hadasit Bio Holdings Ltd., a publicly traded company on the Tel Aviv Stock Exchange (TASE: HDST) and co-founder and former chief operating officer of Optivasive Inc.
Anke Hoppe, BSc VP of Clinical Operations	30 years of clinical operations experience in major international pharmaceutical and biopharmaceutical companies and various clinical research organizations. Her experience ranges from serving as clinical research associate (Sanofi for 9 years) to project management lead at several of the leading CROs and Vertex Pharmaceuticals
Gregory Burshtein, PhD VP of R&D	20 years experience in pharmaceutical and biopharmaceutical research focusing on advanced oral drug delivery, protein based oral drug delivery and oral delivery of biologic molecules

Clinical & Scientific Advisory Board

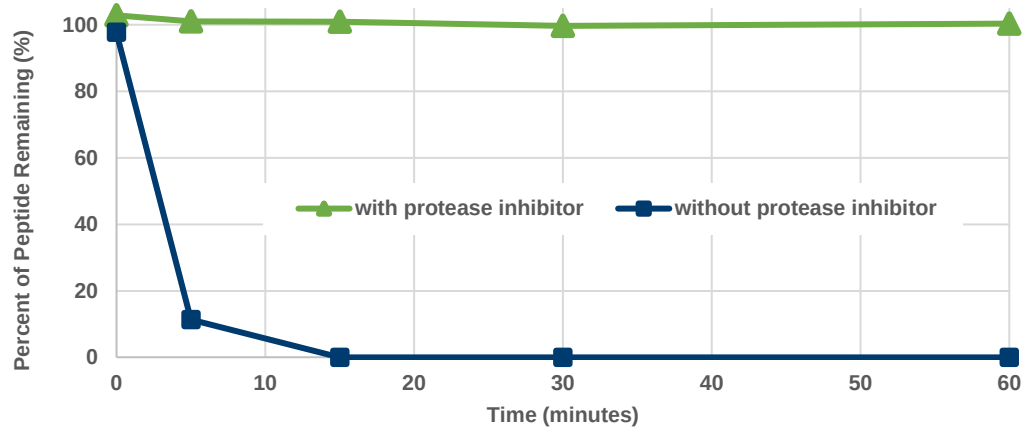
Professor John P. Bilezikian	Vice-Chair, Department of Medicine for International Research and Education; Chief, Emeritus, of the Division of Endocrinology; Director, Emeritus, of the Metabolic Bone Diseases Program at Columbia University Medical Center
Professor Maria Luisa Brandi	Professor of Endocrinology, FIRMO Foundation, Italy
Professor Bart Clarke	Professor of Medicine and Consultant, Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Mayo Clinic
Professor Felicia Cosman	Professor of Medicine, Emerita, Columbia University College of Physicians and Surgeons, Division of Endocrinology; Co-Editor in Chief of the journal Osteoporosis International
Professor William Fraser	Professor of Medicine at Norwich Medical School at the University of East Anglia and Consultant in Metabolic Medicine at the Norfolk and Norwich University Hospital, UK
Dr. Roger Garceau	Former Chief Medical Officer and EVP at NPS Pharmaceuticals and Shire plc (Natpara®); Sanofi/Pharmacia
Professor Sophia Ish-Shalom	Vice President of the Israeli Foundation for Osteoporosis and Bone Diseases (IFOB) , Endocrine Clinic Elisha Hospital prior Head of Bone and Mineral Metabolism Unit, Rambam Health Care Campus , Israel
Professor Socrates Papapoulos	Emeritus Professor in Diseases of Bone & Mineral Metabolism, Advisor Center for Bone Quality, Leiden University Medical Center, The Netherlands

Entera Proprietary Oral Delivery Platform

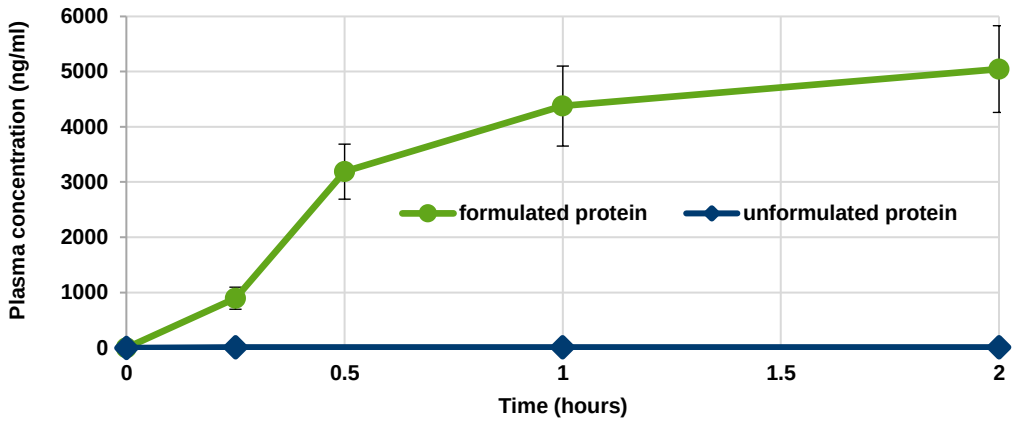
Synergistic Activity of Proteolysis Inhibition and Permeability Enhancement

- **Oral delivery of most therapeutic proteins is challenging due to poor absorption into the blood stream, enzymatic degradation within the gastrointestinal tract, and variable drug exposure; therefore, patients are required to take SC, IM, or IV injectables**

Stability of 4kd Peptide in Presence of Trypsin



Absorption Enhancer Dramatically Increases Systemic Plasma Levels of 65kd Protein



Entera's Proprietary Technology Synergistically Protects & Transports Large Molecules

1. Prevents the degradation of the therapeutic protein in the GI tract; maintains the integrity of the protein (stability)
2. Enhances peptide absorption by increasing transcellular transport (bioavailability)
3. The result is a simple, small (6mm) daily tablet form

Note: SNAC (Salcaprozate sodium) increases gastric epithelial membrane fluidity without affecting tight junctions, thereby allowing transcellular passage into systemic circulation of the protein API. SNAC is a component of Novo Nordisk's Rybelsus® which has been approved by the FDA and EMA.

Internal Pipeline Focused On Oral Mini Tablets of Approved Injectable Proteins

Partnership Agreements Include Novel Undisclosed Targets

Program	Target	Preclinical	Phase 1	Phase 2	Phase 3	Partner
EB613	Osteoporosis	**PTH 1-34**				
EB612	Hypoparathyroidism *(Orphan Disease)*	**PTH 1-34** (2nd generation)				
EB613	Non-Union Fractures	**PTH 1-34**				
GLP-2	Short Bowel Syndrome					
hGH	GH deficiency					
Undisclosed	Anti-inflammatory					AMGEN
Undisclosed	Various					Multiple

EB613 (oral PTH (1-34), teriparatide)
First Daily Oral Osteoanabolic Mini Tablets for the Treatment of Osteoporosis

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EB613: First Daily Oral PTH Daily Mini Tablets for Osteoporosis

Indication

Osteoporosis: Skeletal disease characterized by low bone mass, micro-architectural deterioration of bone tissue and increased bone fragility leading to an increased susceptibility to fractures; **13 million estimated post-menopausal women diagnosed with osteoporosis and only an estimated 3 million of these are treated, in the United States alone (Less than 10% of those on therapy are on osteoanabolic injectables)**

Molecule/ Drug Product

- EB613 is the first oral daily mini tablet formulation of synthetic PTH (1-34), teriparatide, a peptide consisting of the first 34 amino acids of PTH
- Teriparatide [hPTH(1-34)] daily subcutaneous SC injection (Forteo®) is an osteoanabolic treatment that has been shown to reduce the risk of vertebral fractures by 65% to 80%; EB613 has the same sequence as Lilly's Forteo® which has been approved since 2002, is the leading anabolic (bone forming) treatment of osteoporosis and generated peak sales of $1.7bn prior to genericization
- **Despite being recommended in the guidelines, highly efficacious approved anabolic agents (Forteo®, Tymlos®, Evenity®) have minimal penetration - Injections deter many osteoporotic patients from either starting or continuing the drug, contributing to the treatment gap in high-risk patients**
- **Entera Bio is developing oral hPTH(1-34) formulation (EBP05 / EB613) as the first potential osteoanabolic agent to treat osteoporosis**

Key Efficacy Profile

- Phase 2 study met primary endpoint and showed a statistically significant increase of P1NP*, a key marker of bone formation at 3 months
- At 6 months of treatment with EB613, the increase in lumbar spine BMD was similar in magnitude to that previously reported with SC Forteo® injections; Increases in total hip and femoral neck BMD with EB613 were greater than those previously reported with SC Forteo® injections

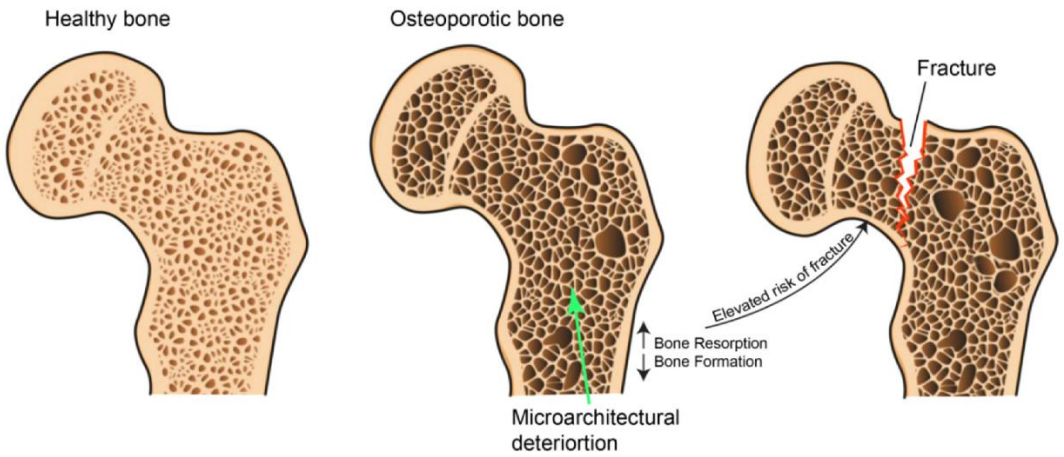
Key Safety Profile

Phase 3 safety profile consistent with Forteo® injections and differentiated from oral bisphosphonates; The most common adverse events were headache, nausea, presyncope and dizziness

*P1NP: pro-peptide of type 1 collagen

Osteoporosis Results From An Imbalance In The Bone Remodeling Cycle That Occurs When Bone Resorption Outpaces Bone Formation

Bone Density Healthy vs. Osteoporotic

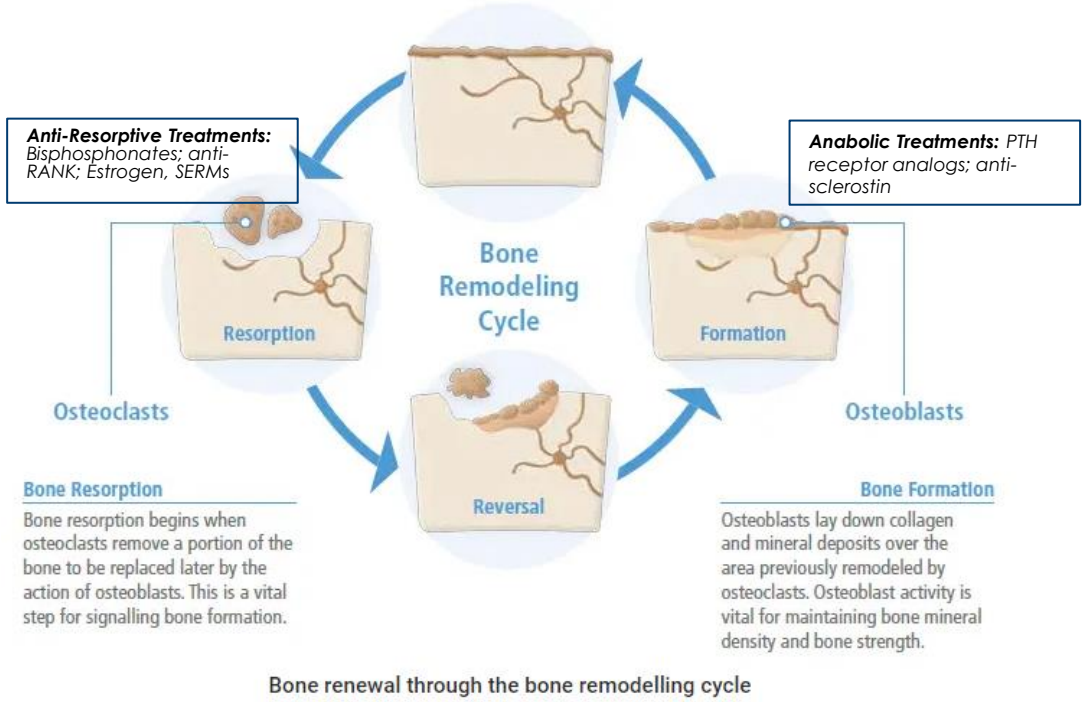


Osteoporosis is a disease associated with low bone mass and enhanced skeletal fragility and is most commonly caused by:

1. Menopause in women
2. Aging in both women and men
3. Glucocorticoid steroid use (greater than 3 months)

Osteoporosis and the Bone Remodeling Cycle

The Bone Remodeling Cycle can be separated into two distinct processes: **Resorption (osteoclasts) and Formation (osteoblasts)**



Bone renewal through the bone remodelling cycle

Sources: International Osteoporosis foundation accessed March 2022; Salamanna, F. et al.

Current Osteoporosis Pharmacologic Treatment Is Segmented Into: Anti-Resorptive & Anabolic Options

Osteoporosis Diagnosis

Stop or slow bone loss

Bone forming

Antiresorptive

Bisphosphonates	Estrogen*/HRT	SERMs**	RANK-Ligand Inhibitor	Calcitonin
Fosamax® *Alendronate*	**Estrogen only**	**Evista®** *Raloxifene*	**Prolia®** *Denosumab*	
Boniva® *Ibandronate Acid*	**Estrogen + Progestin**			
Atelvia® & Actonel® *Risedronic Acid*				
Reclast® *Zoledronic Acid*				

Anabolic

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

Current anabolic (bone forming) approved drugs require daily (Forteo®, Tymlos®) or monthly (Evenity®) injections. There are no oral anabolic agents currently available to patients

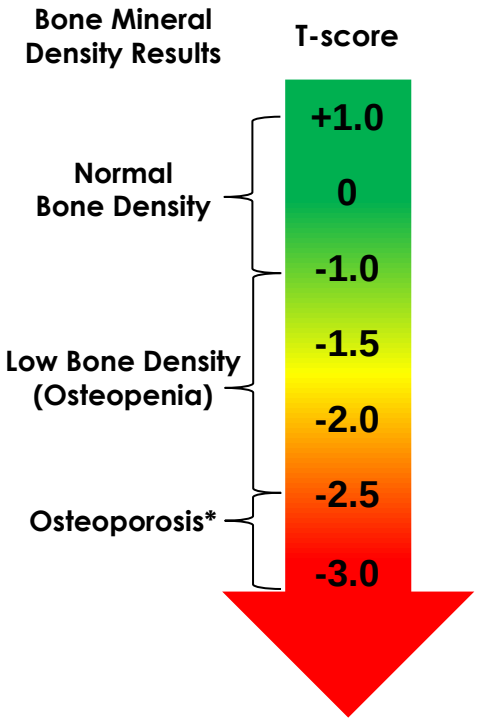
EB613
Oral *PTH (1-34) Daily Tablets*

Notes: * Estrogen products are indicated for prevention of osteoporosis as a secondary benefit when used to control menopausal symptoms. Not a 1st line treatment due to adverse reactions, **SERMs – Selective estrogen receptor modulators

Sources: Osteoporosis, accessed March 2022, retrieved from: hopkinsmedicine.org; DerSarkissian, C. Osteoporosis: Diagnosis and Treatment. 2021, Retrieved from: webmd.com; Frost & Sullivan, EnteraBio Initiation of Coverage, 2019;.

Healthcare Providers Typically Use T-score BMD Classifications, Patient Fracture History and Preference To Drive Therapy Selection

T-Score Scale



- ***Injections deter many patients from using extremely effective PTH therapy, contributing to a treatment gap in high-risk patients***
- ***An oral PTH analogue tablet formulation with adequate bioavailability, similar safety and effects on BMD may displace current injectable anabolics and serve to significantly increase care to high-risk osteoporosis patients (est. 40% of pop)***

Low BMD Category	Percent of Patients with low BMD		Initial Typical Treatment Recommendation
	Internists	Endocrinologists	
Osteopenia	55%	27%	Vitamin D and Calcium Supplements
High Risk Osteoporosis *(T-scores between -2.5 and -3.0 without a history of fractures)*	35%	43%	Mostly Anti-Resorptives (Bisphosphonates, Prolia); limited Anabolic penetration
Very High Risk Osteoporosis *(T-scores ≤ -3.0 or ≤ -2.5 with prior fragility fractures)*	10%	23%	Start with Anabolic therapies (1-2 years) then transition to Anti-Resorptives

Source: Triangle Insights Primary Research Apr. 2022;, Low BMD Category based on AACE guidelines (Camacho 2020, Endo Practice)

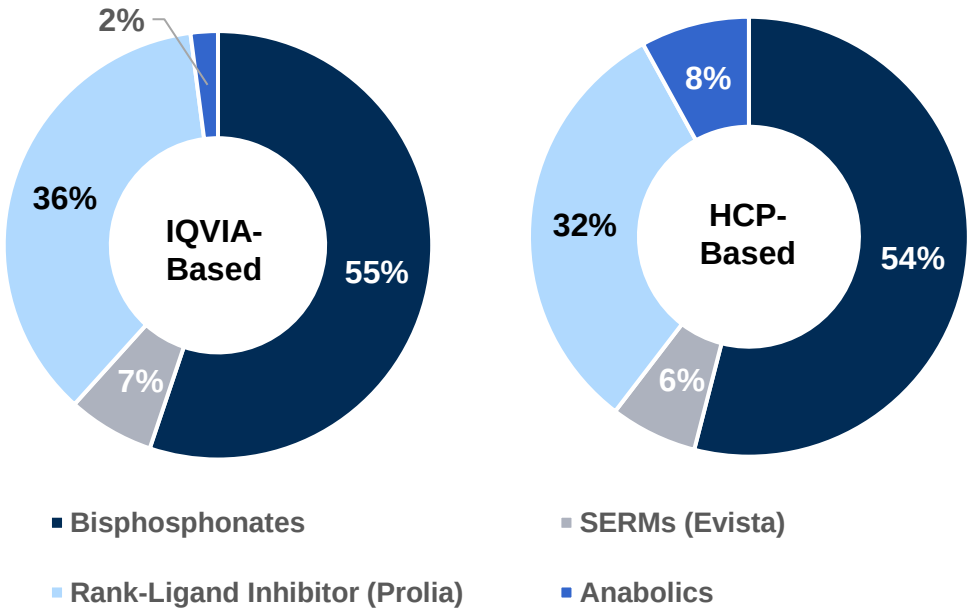
Anabolic Treated Patients Comprise Less Than 10% of Currently Treated Osteoporosis Patients

Estimated Treated Population by Class of Osteoporosis Medication

Population Treated by Class of Osteoporosis Medication (2021)

	IQVIA-Based	HCP Primary-Based
Total Osteoporosis Treated Population	**~3.16M**	**~3.23M**
Bisphosphonate Patients	~1.74M *(~55%)*	~1.74M *(~54%)*
SERMs Patients	~206K *(~7%)*	~206K *(~6%)*
Rank-Ligand Inhibitor Patients	~1.14M *(~36%)*	~1.02M *(~32%)*
Anabolic Patients	~65K *(~2%)*	~260K *(~8%)*

Share of Osteoporosis Treated Population by Medication Class



Bisphosphonates include Fosamax®, Boniva®, Atelvia®, Reclast®, and generic versions of listed products;
SERMs include Evista® and generic raloxifene;
Rank-Ligand Inhibitors include Prolia®;
Anabolics include Evenity®, Forteo®, generic teriparatide, and Tymlos®

Source: IQVIA prescription data (note the capture rate of IQVIA may be low due to injectable administration of anabolic drugs on the market); HCP = Prescriber survey conducted by TIG Primary Research Apr. 2022

EB613 Poised To Create A Paradigm Shift In The Treatment of Osteoporosis To Be The First Daily Tablet Anabolic Therapy

Key Product Needs	Forteo® (Lilly)	Tymlos® (Radius)	Evenity® (Amgen)	Prolia® (Amgen)	Bisphosphonates (generics)	Entera EB613
Treats Osteoporosis	✓	✓	✓	✓	✓	✓
Rebuilds Bone	✓	✓	✓			✓
Oral Dosing					✓	✓
No Refrigeration		✓			✓	✓
Self-Administered	✓	✓			✓*	✓

Current Anabolic drugs, including PTH (1-34) (teriparatide) injections - Forteo® or PTH Injectable Generics, Tymlos® and Evenity® **effectively increase the rate of bone formation** but require **daily or monthly injections**

EB613 is positioned to be the first potential oral daily tablet osteoanabolic treatment for osteoporosis

Source: Triangle Insights Primary Research Apr. 2022

*Zoledronic acid is administered by intravenous administration

EB613 Positioning

- EB613, as a first in class daily oral tablet PTH treatment, seeks to offer a viable anabolic (bone forming) therapeutic option to lower the risk of fracture for many more high risk osteoporotic patients
- *PTH receptor activation is a validated mechanism of action for treating osteoporosis, as evidenced by the approvals of Forteo® (2002) and Tymlos® (2017)*
- Based on third party research, approximately 40% of the estimated 3.2 million treated patients in the US are reluctant to take daily injections even as their BMD scores decline and only turn to currently injectable anabolic drugs when their disease becomes very severe (with multiple fractures)
- Successful Conclusion of FDA Type C Meeting; 24 month Total Hip BMD established as primary endpoint in placebo-controlled design relying on 505(B)2
- No requirement for fracture endpoint or an active control in the proposed pivotal study
- Based on recent third-party market research and published Guidelines (AACE 2020, NAMS) healthcare providers would support the use of anabolics earlier in the treatment paradigm - yet hampered to date due to difficulty of administration (injectables) and very high price

EB613 Phase 2 Results

A Six-Month Study of Oral PTH in Postmenopausal Women with Low Bone Mass – 6 Month Bone Mineral Density (BMD) Results

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EB613 Phase 2 Clinical Trial Design

- **6-Month, Randomized Dose-Ranging Placebo-Controlled Study in Post-Menopausal Women with Osteoporosis**
- **Conducted at 4 sites in Israel between June 2019 and May 2021; Final enrollment = 161 patients**

Screening

Key inclusion criteria

- 50+ years old and 3+ years post menopause
- Low bone mass

Key exclusion criteria

- Osteoporosis treatment within last 2 years
- Known medical predisposition
- Severe osteoporosis that precludes placebo

Randomization N=160 (target)

Treatment*

Arm 1: Placebo tablets QD

Arm 2: 0.5 mg *

Arm 3: 1.0 mg *

Arm 4: 1.5 mg QD

Arm 5: 2.5 mg QD * **

Arm 6: 2.5mg titrated QD **

Endpoints

Primary – at 3 months

- Serum P1NP placebo adjusted change from baseline at 3 months

Secondary – at 6 months

- BMD change from baseline at 6 months
- P1NP, Osteocalcin, Bone Alkaline Phosphatase
- Serum CTX, Urine NTX/Creatinine
- Plasma hPTH (1-34) at $T_{15\ min}$

Data

3 M **Partial** & Final interim analysis of primary endpoint**

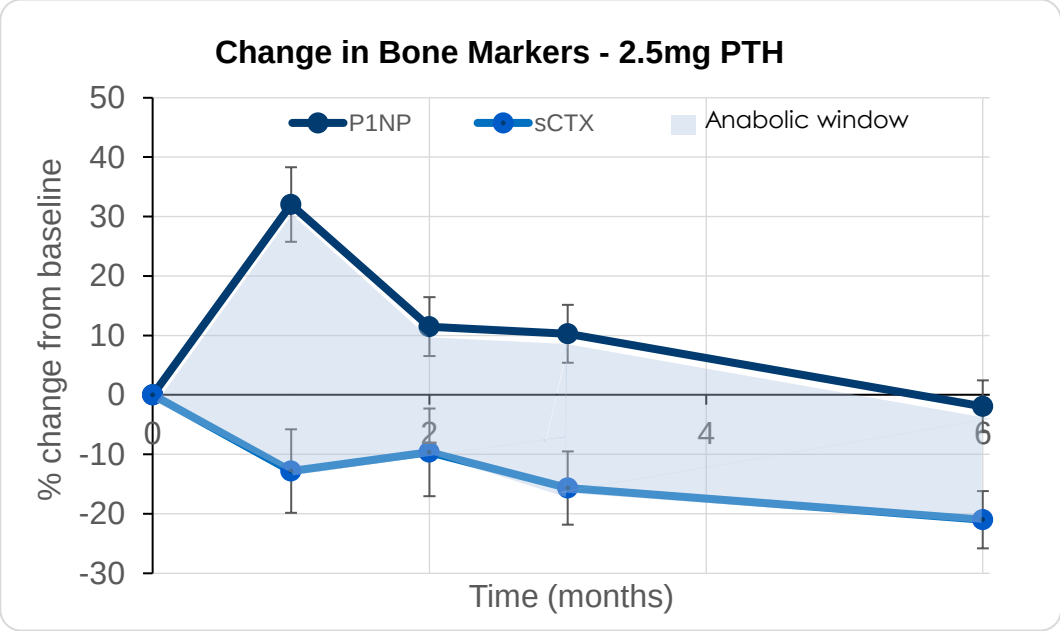
6 M **Final analysis / Topline data – All endpoints**

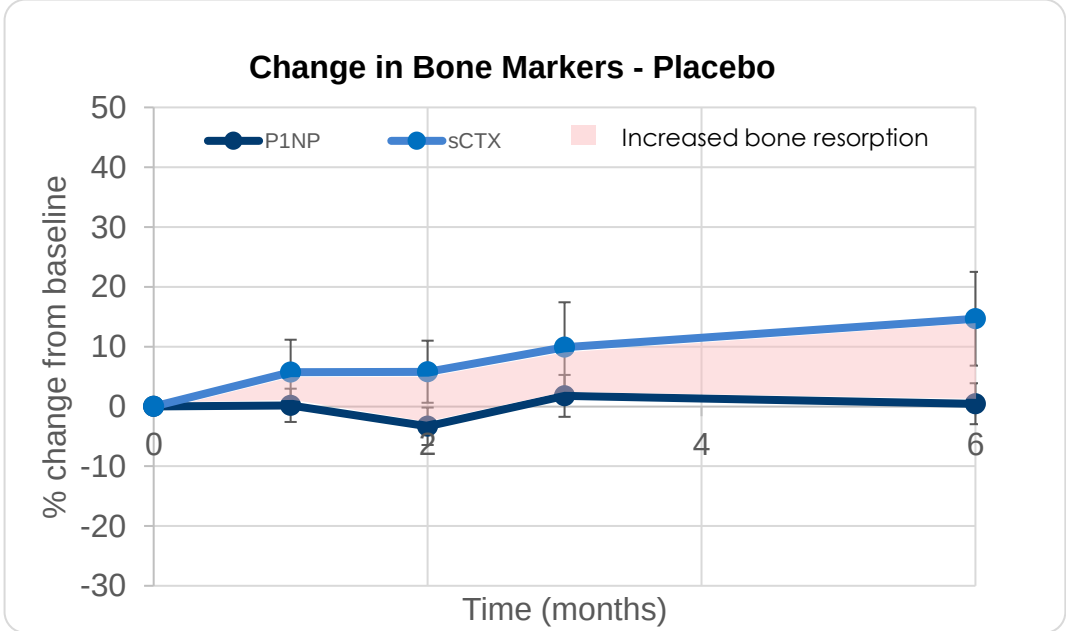
* Following an interim analysis, a 2.5mg arm was added and recruitment to the 0.5mg & 1.0 mg arms was stopped

** Following AEs typical of orthostasis additional subjects in the 2.5mg group received 1.5mg for 1 month, 2.0mg for the next month and 2.5mg during months 3 to 6 (Titrated).

EB613 Predictive Profile Of Bone Turnover Biomarkers (PD)

- **Primary Endpoint:** Statistically significant increases in P1NP (key anabolic marker) at Month 1 ($p<0.001$), Month 2 ($p<0.005$) and Month 3 ($p<0.05$), respectively for the 2.5 mg EB613 dose group
- Statistically significant decrease in Serum CTX (marker of resorption) of 21% from baseline to Month 6 ($p<0.01$)
- **EB613 demonstrated a sustained "Anabolic Window" (P1NP increases while CTX decreases)**
- **In contrast, Placebo shows increase in bone resorption (CTX increases while P1NP remains unchanged)**



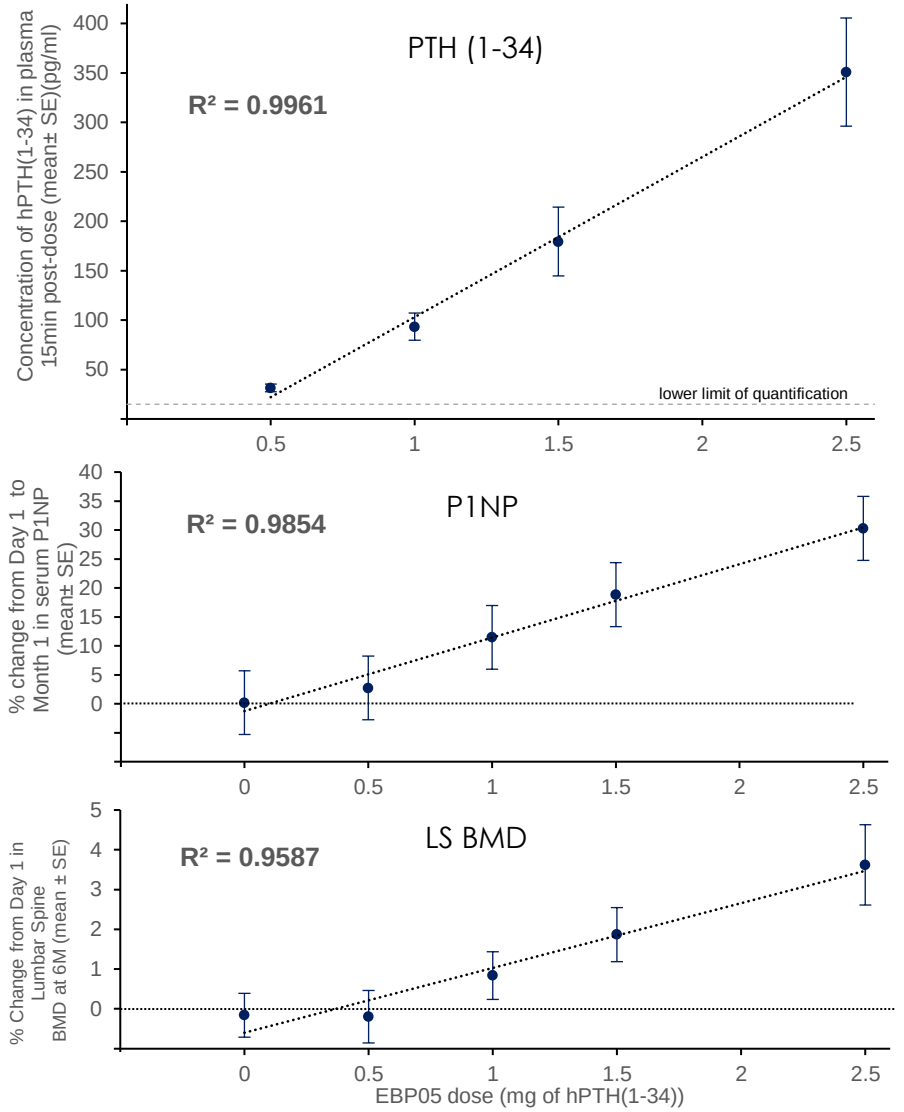


EB613 Significant Dose Response – PTH (1-34) PK, P1NP Marker & BMDs

EB613 (a.k.a. EBP05, hPTH(1-34) min-tablets) showed a linear dose response across PTH exposure, P1NP biomarker and BMD Measurements

- Dose proportional effect (R^2 = 0.959) on Lumbar Spine BMD in postmenopausal women with osteoporosis or low BMD following 6 months of treatment
- At the 1-month time point, where the maximal increase in P1NP was observed, a correlation (R^2 = 0.985) was shown between EB613 dose and mean change in serum P1NP
- A correlation (R^2 = 0.996) was also found between the dose of EB613 and mean hPTH(1-34) plasma levels 15 minutes following drug administration

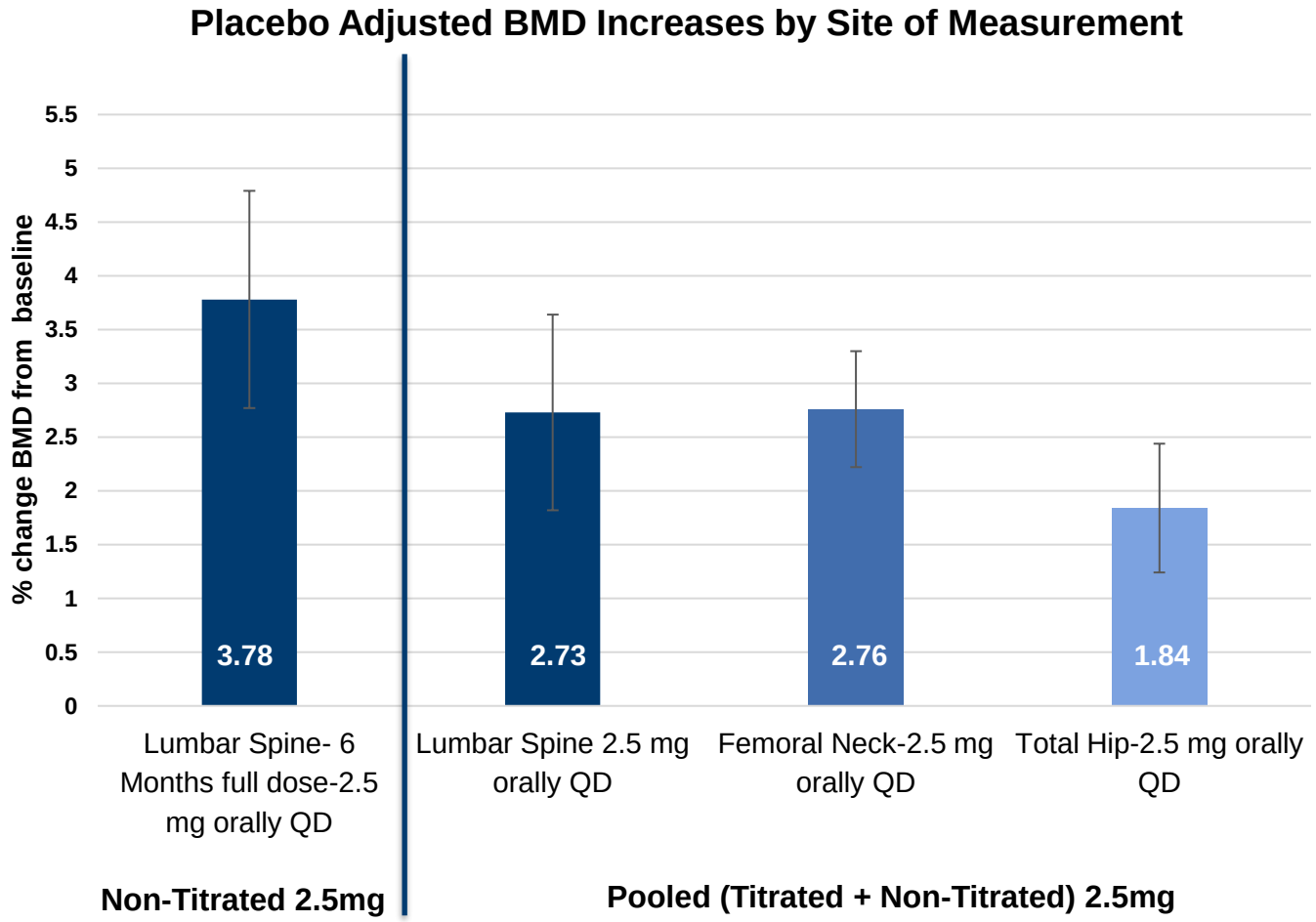
EB613 produced a statistically significant BMD dose response* in lumbar spine BMD (p<0.0001), femoral neck BMD (p<0.002) and total hip BMD (p<0.008)



Phase 2 Study Presented at Late Breaker LB-1116 and Poster FRI-237– ASBMR 2021; A Six-month Phase 2 Study of Oral PTH (EBP05) in Postmenopausal Women with Low Bone Mass – Dose Proportional Absorption and Effect on Lumbar Spine BMD Presented as Poster at ASBMR 2022

*Dose response p values are based on A linear regression analysis of changes in BMD in all study arms

EB613 2.5 mg Dose Positively Impacts Lumbar Spine, Femoral Neck and Total Hip BMD at 6 Months



EB613 Non-Titrated = Patients received EB613 2.5mg tabs daily for **full 6 months of the study**

EB613 Titrated = Patients received EB613 tabs daily as follows: 1.5mg for 1 month, 2.0mg for the next month and 2.5mg from month 3 to 6 **(4 months of 2.5mg dose)**

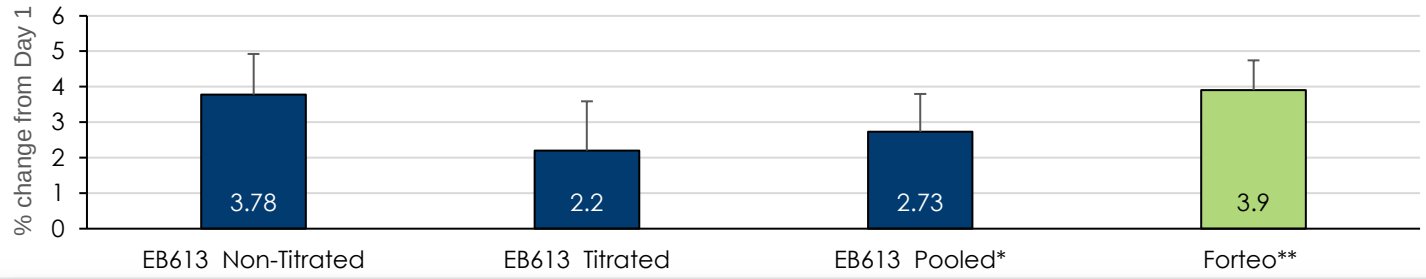
Pooled = Non-Titrated + Titrated Dose Groups

Daily 2.5mg EB613 tabs vs. Placebo produced statistically significant placebo adjusted BMD increases:

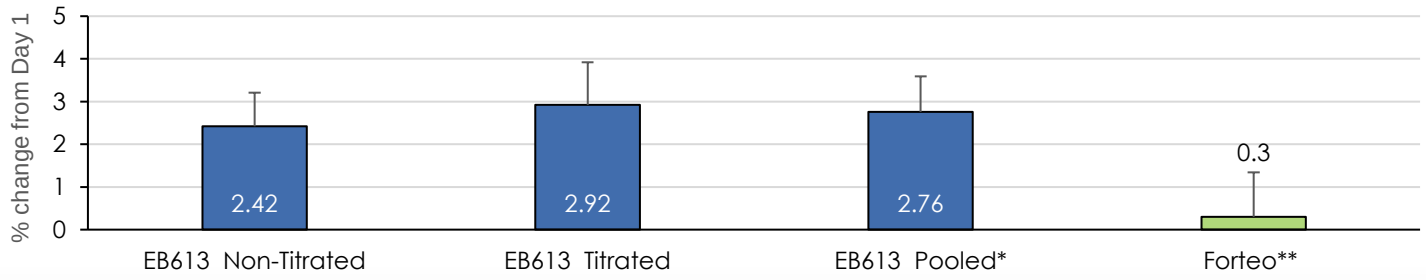
- Lumbar spine ($p<0.002$)
- Femoral neck ($p<0.002$)
- Total hip ($p<0.02$)

EB613: 6 Month Placebo Adjusted BMD by Skeletal Site (2.5mg Dose Groups)

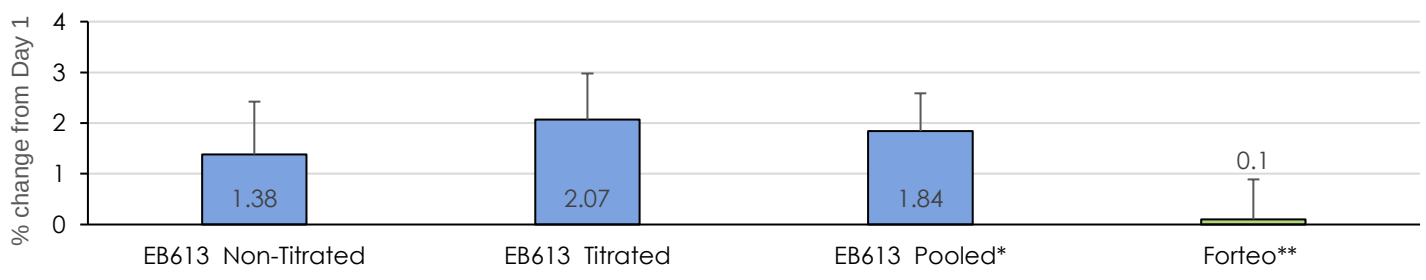
Placebo adjusted Lumbar Spine BMD



Placebo adjusted Femoral Neck BMD



Placebo Adjusted Total Hip BMD



- At full 6 months of treatment with EB613 tabs, the increase in spine BMD was similar in magnitude to that previously reported with SC injection Forteo® [*Cosman, et al.* (2021) *Leder BZ et.al.* (2015)]
- Increases in total hip and femoral neck BMD were greater than those previously reported with SC injection Forteo®

EB613 data first presented at Late Breaker LB-1116 and Poster FRI-237– ASBMR 2021 ; Mean values ±SE of difference between active and placebo presented
*Pooled data includes Titrated & Non-Titrated subjects
** Forteo data based on Leder BZ et.al. JCEM (2015) Placebo and Teriparatide 20ug results for mean and ±SD

EB613 Phase 2 Adverse Event Profile

Adverse event profile similar to that observed with Forteo® and typical of orthostatic hypotension

EB613 not associated with serum calcium increases or hypercalcemia adverse events

Greater than 90% of subjects tolerated the 2.5 mg dose well, after titration (1.5mg for 1 month, 2.0mg for the next month and 2.5mg during months 3 to 6)

AEs commonly attributed to vasodilatation with subcutaneous injectable PTH were observed - headache, nausea, presyncope and dizziness - **There were no serious drug-related AEs**

Subject disposition	Placebo (N=43)		EBP05 0.5 mg orally QD (N=25)		EBP05 1 mg orally QD (N=29)		EBP05 1.5 mg orally QD (N=28)		EBP05 2.5 mg orally QD (N=19)		EBP05 2.5 mg titrated orally QD (N=17)	
	N	%	N	%	N	%	N	%	N	%	N	%
Randomized	43	100	25	100	29	100	28	100	19	100	17	100
Discontinued Before Month 3	3	7	3	12	2	6.9	4	14.3	7	36.8	1	5.9
Discontinued from Study Before Month 6	5	11.6	3	12	3	10.3	6	21.4	9	47.4	1	5.9

EB613 Phase 3 Clinical Trial Design

- Designed with FDA Concurrence (Pursuant to Type C Meeting)
- A Single Global Phase 3, 24-Month Double-Blind, Placebo-Controlled Registrational Study
- Agreement on Total Hip (TH) BMD as Primary Endpoint

Screening

Key inclusion criteria

- 50-90 yrs old
- At least 5 yrs post menopause
- BMD: T-score ≤ -2.5

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 yrs
- Known medical predisposition

2:1 Randomization N=1,000 (target)

24 M Treatment

Titration to 2.5mg Mini Tablets

Arm 1:

EB613 2.5mg, N~667*

Arm 2:

Placebo tablets, N~333*

Endpoints

Primary –

- Mean Change in TH BMD of EB613 daily PTH mini tablets vs. placebo at 24 months

Secondary –

- Change in TH BMD vs. STEs associated with fracture reduction at 24 months**
- TH, LS, FN, BMD changes from baseline at 6,12,18 and 24 months
- LS, FN BMD changes from baseline at 24 months

Exploratory -

- Bone Turnover Biomarkers

Data

12 M Interim analysis – First 300 to complete the 12 month visit

24 M Final analysis / Topline data – Primary & Secondary endpoints

*N=600 with 2:1 randomization agreed to be sufficient to support safety and efficacy for an NDA under 505(b)2 (per FDA guidance at Type C meeting).

**Note: 24-month STEs are those reported by FNIH-ASBMR-SABRE (Eastell 2022).

EB613 Phase 3 Clinical Trial Design Uses ASBMR-FNIH STEs

- **The primary endpoint agreed upon is Mean Change from Baseline in Total Hip BMD of EB613 vs. placebo at 24 months. As a key secondary endpoint, Entera intends to assess this using the pre-defined, published ASBMR- FNIH Surrogate Threshold Effects (STEs, see right panel)**

- STEs are quantitative thresholds depicting the difference in total hip BMD vs. placebo at 24 months that predict a reduction in fracture risk with 95% certainty

- Placebo adjusted Total Hip BMD STEs:
  - 1.42% - vertebral fractures
  - 1.83% - all fractures
  - 2.13% - nonvertebral fractures
  - 3.18% - hip fractures

- Entera's proposed Phase 3 study will evaluate the % change in BMD of EB613 measured at the hip vs. placebo. This change will be tested to see which STEs are surpassed. Beginning with vertebral followed by all fractures and nonvertebral fractures

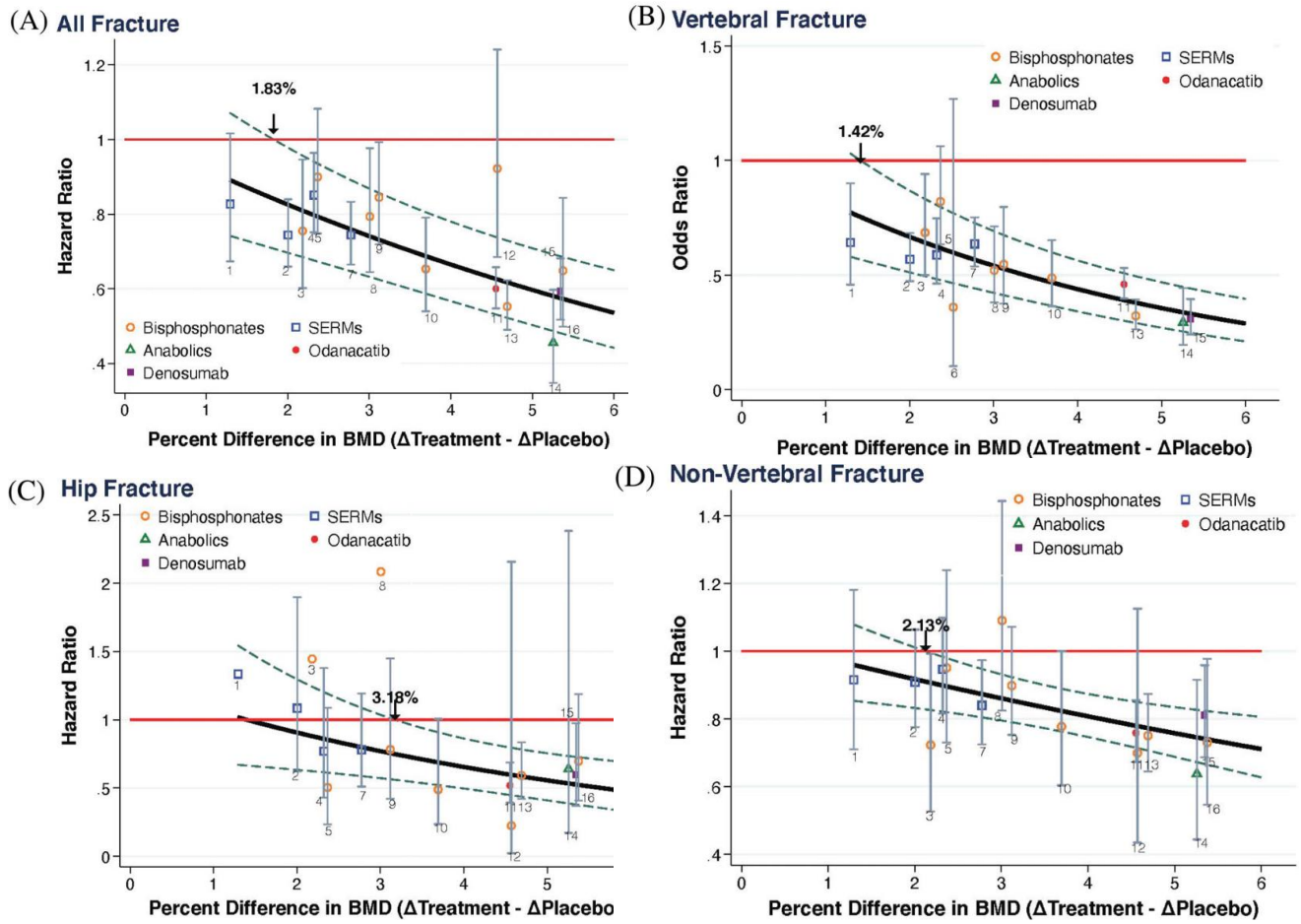


Fig 1. Relationship between difference in the change in total hip BMD between active and placebo groups at 24 months and the hazard or odds ratio of all, vertebral, hip and nonvertebral fractures. The red horizontal line is the ratio of 1 (no treatment effect) and the STE is the point where the upper 95% prediction limits intersects this line; eg, 1.83% for the all fracture outcome. The class of drugs is indicated in the legend. For each trial, the point estimates and 95% confidence intervals for relative risks are given and the numbers 1–16 relate to the studies listed in Table 1.

Eastell et al. J Bone Miner Res. 2022; 37 (1): 29-35

EB612 Oral PTH (1-34) First Daily Oral PTH Mini Tablet Peptide Replacement Therapy for the Treatment of Hypoparathyroidism

EnteraBio

Hypoparathyroidism: PTH Orphan Indication with Sub-Par Clinical Care

Hypoparathyroidism Overview

Hypoparathyroidism (HypoPT) is a rare condition in which the parathyroid glands fail to produce sufficient levels of **Parathyroid hormone (PTH)**

- 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
- HypoPT is characterized by hypocalcemia and hyperphosphatemia
- Clinical management includes frequent high doses of calcium and activated Vitamin D which are associated with severe long-term morbidities:

Cardiovascular Heart failure, blood vessel calcification

Renal Kidney stones, renal failure

Neurologic Cognitive impairment, basal ganglia calcification

Skeletal Reduced bone turnover

Unmet Need and Market Opportunity

How many people are affected by HypoPT?

- Approximately 200K afflicted with hypoparathyroidism in the US, EU and Japan

What is the market opportunity in HypoPT?

- Current standard of care creates long term co-morbidities
- Natpara® (parathyroid hormone) injection was approved in 2015 and will be permanently phased out globally by end of 2024 due to supply issues; Natpara® had sales of $230m in 2018, its 3rd full year of sales, before it was recalled. The recall was connected to a manufacturing issue and not connected to the safety or efficacy of parathyroid hormone
- TransCon PTH, an investigational once-daily Injectable, long-acting prodrug of parathyroid hormone (PTH(1-34)) FDA PDUFA target date of April 30, 2023 and EU MAA submitted (November 14, 2022)

References:
https://rarediseases.org/rare-diseases/hypoparathyroidism
https://www.takeda.com/en-us/newsroom/news-releases/2019/takeda-issues-us-recall-of-natpara-parathyroid-hormone-for-injection-due-to-the-potential-for-rubber-particulate/
TransCon™ PTH Top-Line Phase 3 Data from PaTHway (ascendispharma.com)

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, multicenter pilot study to evaluate the safety, tolerability and PK (NCT02152228)

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

Treatment: first 3 doses of PTH (1-34) 0.75 mg/dose administered at research center; subjects then self administered 4 times/day

Results

Efficacy:

42% reduction (p=0.001) from baseline in median calcium supplement use

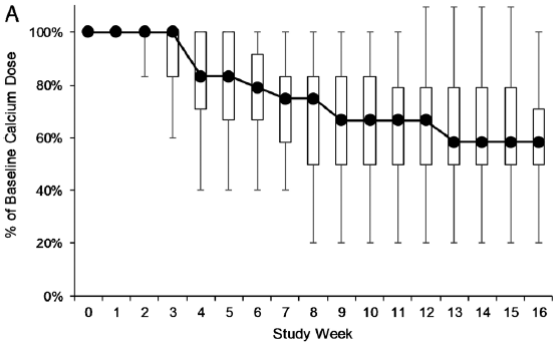
Maintenance of median Ca levels above the lower target level for Hypoparathyroidism patients (>7.5 mg/dL) throughout the study

Rapid decline of 23% (p=0.0003) in median serum phosphate levels 2 hours following the first dose that was maintained for the duration of the study

Safety: One subject experienced 4 AEs and left the study after the first day (withdrew consent), another subject experienced an SAE prior to the administration of the first dose and, hence, unrelated to the drug

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 Ca and either alfacalcidol or calcitriol

Treatment: two doses (0.75 and 2.25) and three regimens of Oral hPTH (1-34) and Natpara® [hPTH(1-84)] 100 µg SC injection QD

Efficacy: Oral hPTH (1-34) 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

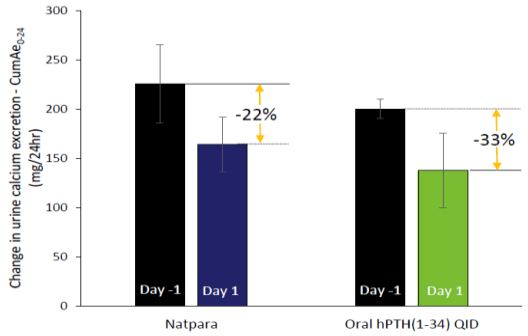
The magnitude of these changes are comparable to Natpara® 100 µg QD

Two, thee and four doses/day regimens showed a dose-dependent increase in 1,25(OH)2D, indicating that the long-term treatment even with the less frequent regimens may be an effective treatment option

Safety: There were no treatment emergent adverse events of hypercalcemia reported and no treatment-emergent Serious Adverse Events

Improved/ Decreased Urinary Ca

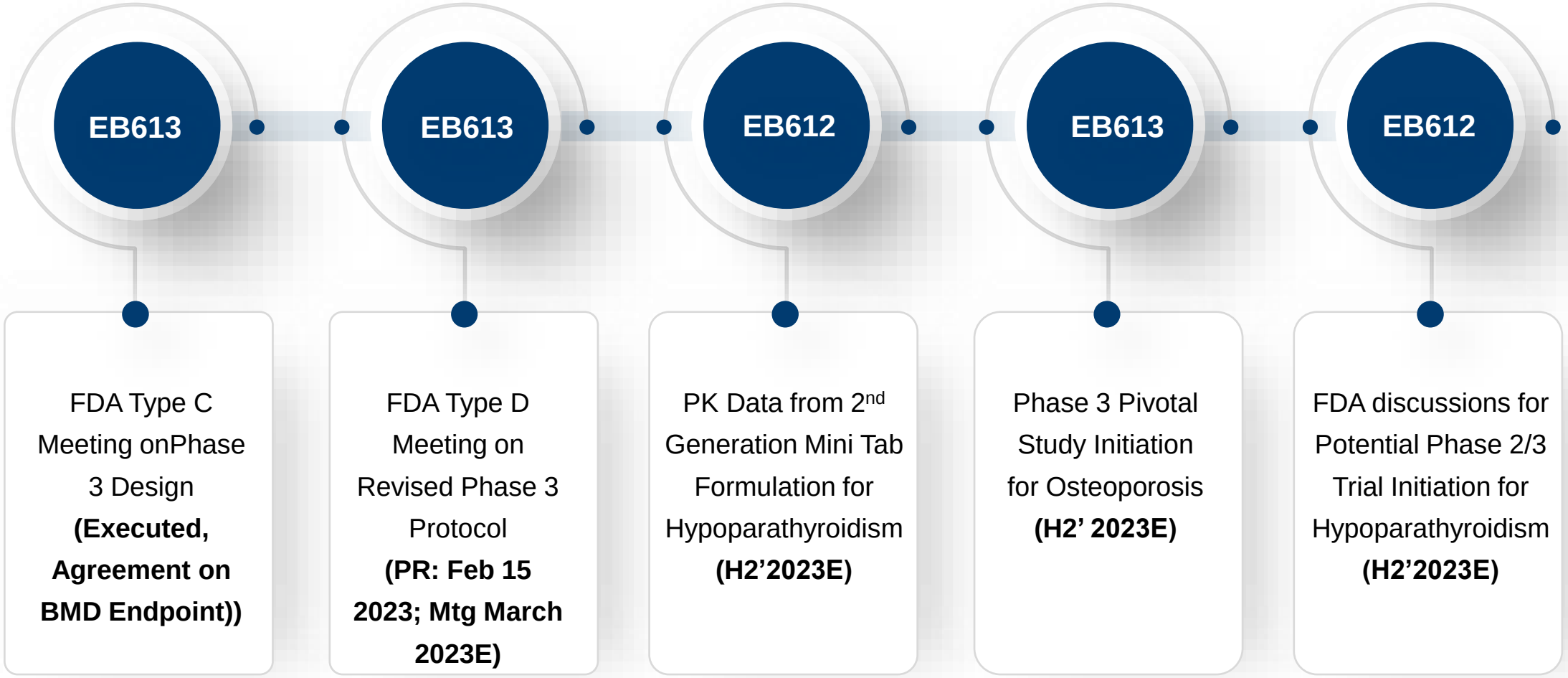
Excretion Over a 24-Hour Period



EB612 Positioning

- EB612 is potentially the first oral PTH (1-34) daily tablet peptide replacement therapy for the treatment of hypoparathyroidism
- Hypoparathyroidism (HypoPT) is a rare condition in which the parathyroid glands fail to produce sufficient levels of Parathyroid hormone (PTH)
- Pilot Phase 2 oral presentation (ASBMR 2015) and peer-reviewed publication in JBMR (March 2021)
  - 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 following the first dose that was maintained for the duration of the study
  - 80% of the subjects had a decrease in urinary calcium levels by the end of the study
- Phase 2 PK-PD study versus Natpara® presented (ASBMR 2019)
- **Novel formulation leveraging our 2nd generation peptide delivery platform PK data is expected in H2'2023**

Key Recent and Near-Term Milestones



Thank You

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ASBMR-FNIH BMD Regulatory Endpoint Backgrounder

- Message from the president of the ASBMR on June 23rd 2022: **The FDA Biomarkers Qualification Program accepted the ASBMR**-Foundation for the National Institutes of Health **(FNIH)** Strategy to Advance BMD as a Regulatory Endpoint (**SABRE**) project team's Qualification Plan **to use the treatment-related change in bone mineral density (BMD) as a surrogate endpoint for fractures in future trials of new anti-osteoporosis drugs**
- The FNIH collected data from over 50 randomized trials and individual data from over 170,000 patients
- The FNIH conducted a meta-regression of 38 placebo-controlled trials of 19 therapeutic agents[1] and a meta-regression analyses of 91,779 individual patient data from 23 randomized placebo-controlled trials[2]
- **The FNIH concluded that total hip (TH) BMD, as opposed to lumbar spine and femoral neck BMD, was found to be the best predictor of fracture risk reduction, at all sites (vertebral, non-vertebral and hip)**
- **FNIH's submission of the Full Qualification Package, for final approval by the FDA, is expected by the end of the year[3]**

ASBMR®
The American Society for Bone and Mineral Research

1. Bouxsein et. al. Journal of Bone and Mineral Research, Vol. 33, 2018, pp 1–11
2. Black et. al. Lancet Diabetes Endocrinol 2020; 8: 672–82
3. FNIH, June 1, 2022 press release https://fnih.org/news/announcements/fda-approves-biomarkers-qualification-plan-first-surrogate-endpoint-anti

ASBMR-FNIH

June 23rd, 2022 message from the president of the ASBMR (American Society for Bone and Mineral research) Dr. Ebeling reported on the FNIH progress and support from the ASBMR[1].

"Dear Colleagues:

I am very happy to announce that the US Food and Drug Administration (FDA) Biomarkers Qualification Program recently accepted the ASBMR-Foundation for the National Institutes of Health (FNIH) Strategy to Advance BMD as a Regulatory Endpoint (SABRE) project team's Qualification Plan to use the treatment-related change in bone mineral density (BMD) as a surrogate endpoint for fractures in future trials of new anti-osteoporosis drugs.

Indeed, this is the first qualification plan accepted by the FDA for a surrogate endpoint under the 21st Century Cures Act, a remarkable achievement for the Project Team. This team, including ASBMR members Dennis Black, Mary Bouxsein and Richard Eastell, now plans to submit a Full Qualification Package based on this approved plan for final approval by the FDA before the end of this year.

The ASBMR is proud to financially support this critical initiative. Achieving FDA approval to utilize BMD as a surrogate endpoint in future osteoporosis drug development trials could provide patients with more options to fight a disease that leads to debilitating fractures that cause disability, loss of independence and even death. It is also likely to attract more researchers to the musculoskeletal field, enabling a new horizon of discoveries to help our patients."

1. https://www.asbmr.org/about/council/presidents-corner-detail/message-from-asbmr-president-peter-ebeling-ao-frac-7