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Initiating Coverage
Healthcare

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Entera Bio Ltd. (ENTX)
Rating: Buy

Raghuram Selvaraju, Ph.D.
212-916-3966
rselvaraju@hcwresearch.com

Boobalan Pachaiyappan, Ph.D.
646-975-6959
bpachaiyappan@hcwco.com

Transforming Injectable Drugs Into Pills; Initiating at Buy and $10 PT

Stock Data	09/02/2022
Price	$1.40
Exchange	NASDAQ
Price Target	$10.00
52-Week High	$5.24
52-Week Low	$1.31
Enterprise Value (M)	$23
Market Cap (M)	$40
Public Market Float (M)	18.9
Shares Outstanding (M)	28.8
3 Month Avg Volume	33,331
Short Interest (M)	0.04
Balance Sheet Metrics	
Cash (M)	$17.3
Total Debt (M)	$0.0
Total Cash/Share	$0.60
Book Value/Share	$0.60

EPS ($) Diluted			
Full Year - Dec	2021A	2022E	2023E
1Q	(0.43)	(0.13)A	(0.13)
2Q	(0.22)	(0.11)A	(0.17)
3Q	(0.09)	(0.16)	(0.23)
4Q	0.16	(0.15)	(0.27)
FY	(0.47)	(0.55)	(0.80)

Revenue ($M)			
Full Year - Dec	2021A	2022E	2023E
1Q	0.2	0.1A	0.1
2Q	0.1	0.1A	0.1
3Q	0.2	0.1	0.1
4Q	0.2	0.1	0.1
FY	0.6	0.3	0.4

Disruptively reinventing drug delivery in high-value markets. We are initiating coverage of Entera Bio Ltd., an emerging biotechnology company focusing on transformation of injection-administered biologic drugs into oral medications. From our vantage point, Entera Bio's technology platform—in-licensed from Oramed Pharmaceuticals, another company we cover, in exchange for a flat 3% royalty on revenues to Entera—provides an invaluable benefit by protecting molecules that are typically readily digestible in the gastrointestinal (GI) tract from being cleaved by stomach enzymes, facilitating delivery via the oral route. Entera Bio's two most advanced candidates, EB613 and EB612, are both based on parathyroid hormone (PTH)—a peptide naturally produced by the human body that is considered a master regulator of bone and calcium homeostasis—and target osteoporosis and hypoparathyroidism (hypoPT), respectively. Osteoporosis can be considered an aging- and menopause-related disorder, manifesting in reduced bone mineral density (BMD) and increased bone porosity and fragility, which raises fracture risk. Tens of millions are estimated to have osteoporosis in the U.S. alone. Hypoparathyroidism stems from parathyroid gland dysfunction and is a niche disorder, which may afflict over 100K individuals in the U.S. alone. It can cause a wide array of symptoms, including neurological, ocular, renal, respiratory and musculoskeletal problems. In our view, Entera Bio is well-positioned with its focus on these areas, since both represent lucrative target markets that are poorly served by existing treatment options. Our rating is Buy with a 12-month price target of $10 per share.

Osteoporosis patients sorely need oral anabolic intervention. While the osteoporosis market is relatively mature, with multiple available branded and generic agents, none of the oral agents rebuild bone and instead solely inhibit its breakdown. Anabolic agents—e.g., romosozumab, teriparatide and abaloparatide—are able to induce new bone formation and enhance bone density, but are only deliverable via injection and are currently used in under 10% of patients who could benefit. Since osteoporosis constitutes a chronic condition, long-term administration of drugs solely via injection often leads to poor compliance and non-adherence. Entera Bio's EB613—an oral version of historically-injectable teriparatide—could be positioned as the sole anabolic pill for treatment of osteoporosis. We think this agent could reach peak sales of over $2B in the U.S. alone by 2035.

Hypoparathyroidism market appears underserved. We point out that, while the osteoporosis market would probably require the participation of a well-established pharma partner for effective commercial penetration to be achieved, the hypoPT indication is a niche market in which Entera Bio could self-commercialize EB612 using a specialty sales force targeting endocrinologists. We think this is a particularly opportune time to target this indication, since current therapy is solely in the form of calcium and vitamin D supplementation and the only Rx agent previously approved—Natpara, an injectable formulation of the same API that Entera can deliver orally with EB612—has been withdrawn from the U.S. market and may not return. We think EB612 could achieve peak U.S. sales of nearly $350M by 2033.

Clinical data for both lead candidates appears promising and indicative of commercially impactful potential. Positive Phase 2 data (n=161) for EB613 showed robustly statistically significant impact on BMD vs. placebo (p=0.002) with a clear dose-response after six months of treatment in post-menopausal women with low bone mass. Fractures can be particularly devastating in elderly patients. Oral EB613 at the 2.5mg once-daily dose produced a placebo-adjusted increase in BMD at the lumbar spine (3.78%), total hip (1.38%) and femoral neck (2.42%) measurement points at six months, which compares favorably to Forteo (teriparatide), the clearest direct comparator. Forteo only showed an increase in lumbar spine BMD, while failing to increase BMD in either the total hip or femoral neck regions. We think these results bode well for future positioning of EB613 with a product profile that emulates the safety and efficacy of Forteo, but with the added edge of oral delivery. In the case of EB612, the Phase 2a data (n=19) demonstrated significant reduction in calcium usage (42%; p=0.0001), serum phosphate levels (23%; p=0.0003) and urine calcium excretion, all of which are validated measures of therapeutic impact in hypoPT patients. In a second Phase 2a trial, EB612 showed comparable efficacy, safety and tolerability to Natpara, but—again—with the advantage of oral delivery. Thus, we feel that EB612 also appears to have an attractive profile that bodes well for future clinical development. Entera Bio is working on an optimized formulation that would permit twice- or thrice-daily dosing.

Risk-mitigated, capital-efficient and cost-effective clinical development and regulatory pathways. Entera Bio's business strategy is aimed initially at developing oral versions of well-known existing active pharmaceutical ingredients (APIs), which significantly decreases clinical development as well as regulatory risk. The company's lead assets are thus eligible for regulatory review via the 505(b)(2) pathway. For both EB613 and EB612, the clinical development path is clearly defined and both the outcome measures and target patient populations can be readily identified. In the case of EB613, Entera Bio appears poised to capitalize upon a highly intriguing recent development with direct relevance to osteoporosis clinical trial design—the promulgation of a new standard for development of next-generation anti-osteoporosis drugs that uses BMD as a surrogate endpoint for fractures. This has been built on the work of an American Society for Bone and Mineral Research (ASBMR) Foundation for the National Institutes of Health (FNIH) project team. The group, working under the sobriquet of the Strategy to Advance BMD as a Regulatory Endpoint (SABRE), conducted comprehensive analyses and meta-analyses of data from a wide array of clinical studies involving anti-osteoporosis drugs and concluded that BMD decline is well-correlated with increased fracture risk, while impact on BMD decline parameters directly decreases the likelihood of fractures. We expect the FDA to formally authorize the qualification package prepared by the FNIH during 1H23. Entera Bio has integrated this into its pivotal trial plan for EB613. The Phase 3 program would constitute a single placebo-controlled, double-blinded, 2:1 randomized trial comprising 600 patients, with the primary endpoint being fracture risk reduction based on total hip BMD surrogate threshold effects (STEs). In our view, the fact that this is a placebo-controlled study constitutes a risk-mitigating factor, while use of treatment-related BMD change as a surrogate endpoint should enable faster execution and eliminate the risk of insufficient fracture incidence for adequate statistical powering. Since EB613's active ingredient is teriparatide, first launched in the U.S. in late 2002 with a lengthy record of effectiveness in treating osteoporosis, we think the pivotal trial looks risk-mitigated.

Multiple strategic options to optimize equity value. In our view, Entera Bio could readily pursue a bifurcated strategy—out-licensing or partnering EB613 to maximize its commercial value and ensure global market penetration, while focusing on self-developing and self-commercializing EB612, since the commercial infrastructure required to launch that product would be much less capital-intensive. EB613 and EB612 could reach the U.S. market within less than a year of one another, with EB613-generated revenues providing a cushion and EB612-related revenues largely falling to the bottom-line. If Entera Bio—with or without a partner aboard—were to obtain regulatory approval in the U.S. for both EB613 and EB612, we believe the company could prove attractive to strategic acquirers. Ascendis Pharma A/S, which reported highly favorable data with its TransCon PTH candidate in the hypoPT indication earlier this year, currently trades at a roughly $5B market cap and > $4.5B enterprise value, while Entera Bio has a sub-$50M market cap and sub-$35M enterprise value. Ascendis Pharma has yet to obtain regulatory approval for its candidate, while Entera Bio could enter Phase 3 next year with EB612. We also note that—even though Ascendis Pharma has set a high bar with its pivotal data for TransCon PTH—the Ascendis molecule is still only administrable via injection. Accordingly, as long as EB612 shows a relatively solid efficacy profile (i.e., analogous to the withdrawn Rx drug Natpara, which was originally approved in 2015 and taken off the market in 2019 due to potential contamination issues from rubber particulates originating from the septum of the NATPARA cartridge) in pivotal testing, we believe that its oral delivery should facilitate commercial uptake even in the presence of TransCon PTH.

Valuation and risks. We have assessed Entera Bio using a discounted cash flow (DCF)-based valuation methodology, Employing a 15% discount rate, 3% terminal rate of decline and 50% and 30% probabilities of regulatory approval for EB613 and EB612 respectively, we obtain a $465M enterprise value. We assume that EB613 and EB612 could both be launched in 2026, with potential generic erosion starting in 2036 for EB613 and in 2034 for EB612. In our view, the probabilities of approval that we have applied should be considered conservative, since EB613 and EB612 are both based on PTH and are oral versions of well-known existing drugs. We also note that EB613 and EB612 have already shown safety and tolerability as well as comparable efficacy to the injectable agents on which they are based in mid-stage clinical studies. Lastly, Entera Bio is not seeking to reposition these candidates in new indications, but is focusing on the diseases that injectable PTH is already used to treat. These all represent powerful risk-mitigating factors, in our view. Our assessment yields a price objective of $10 per share, assuming 47.7M shares outstanding as of mid-2023. Risks include, but are not limited to: (1) failure to advance EB613 or EB612 through clinical development in a timely manner; (2) adverse results from pivotal studies with EB613 or EB612; (3) inability to secure a partner to optimize the commercial value of EB613; (4) failure to obtain regulatory approval for EB613 or EB612; (5) slower-than-anticipated commercial uptake for EB613 or EB612 due to higher-than-expected levels of competition or other factors; and (6) possible near-term dilution risk.

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I. Company Overview

Company Highlights

Snapshot

- Sector: Healthcare
- Classification: Biotech
- Founded in 2009
- Headquarters: Jerusalem, Israel
- Employees: 16

Financial Highlights

- June 2018: Announced initial public offering of 1.4 million shares of its common stock ($8 per share; gross proceeds ~$11.2 million)
- Shares trade on Nasdaq (ticker: ENTX)
- December 2019: $14.3 million private placement completed (~6.04 million shares; $2.37 per share)
- Cash and cash equivalents: $17.3 million as of June 30, 2022 (runway to last till mid-2023)

Top 3 shareholders

- Knoll Capital Management – 8.6%
- RA Capital Management – 8.2%
- Centillion Fund – 3.9%

Focus

- Entera Bio is a late-stage biotech focused on developing oral biologicals using its proprietary platform licensed from Oramed Pharmaceuticals
- Entera's flagship asset—EB613, an oral formulation of the parathyroid hormone 1-34 (PTH)—is being evaluated in osteoporosis and osteopenia patients (Phase 3-ready)
- In addition, Entera's oral PTH (EB612) candidate demonstrated benefits in hypoparathyroidism (hypoPT) patients in Phase 2a/b studies (second-generation formulation development in progress)
- In the next 12-24 months, the clinical advancement of EB613 and EB612 that inform their trajectory towards market entry shall be critical drivers of stock performance; other assets represent potential upside optionality

Platform

- Entera Bio's platform enables oral delivery of biologic drugs that are currently administered parenterally (i.e., via subcutaneous injection)
- A typical drug formulation is comprised of a biologic molecule, a protease inhibitor and an absorption enhancer

EB613

- EB613 is designed to increase bone mass and strength in osteoporosis patients
- When tested in Phase 2 (n=161), EB613 (2.5mg QD) showed dose-dependent increases in BMD of the lower spine, total hip and femoral neck, with efficacy comparable to FDA-approved FORTEO (teriparatide, originally launched by Eli Lilly & Co.)
- A Phase 3 program is slated to start in mid-2023, using a placebo-controlled design that has been discussed with the FDA

EB612

- Oral EB612 is designed to replace the abnormally low PTH levels observed in hypoPT patients
- EB612 reduced calcium intake and serum phosphate and raised urine calcium reabsorption in two Phase 2a trials, suggesting efficacy
- Importantly, the Phase 2a results are on par with subcutaneously injectable Natpara (recombinant human parathyroid hormone—Takeda/Shire); twice-daily formulation in development

Other Assets

- Entera is also developing oral drugs for non-union fractures (proof-of-concept clinical program under assessment), short bowel syndrome and growth hormone deficiency (both preclinical)
- A strategic R&D collaboration with Amgen is being pursued in the inflammatory diseases space

Company Pipeline

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

Note: The FDA awarded Orphan Drug Designation to Entera Bio's hypoparathyroidism program; end-of-Phase 2 (EOP2) meeting with the FDA to discuss pivotal trial parameters for EB613 program completed in January 2022; items in the purple box are included in our valuation assessment. Our probability of approval (POA) values are as follows: osteoporosis: 50%; hypoparathyroidism: 30%; Entera expects to seek approval for EB613 and EB612 from the FDA via the 505(b)(2) pathway.

Source: Entera Bio, Ltd.

Catalyst Calendar

Agent	Indication	Details	Timing	Impact on Stock
EB613	Osteoporosis	FDA Type C meeting to discuss Phase 3 trial protocol	2H22	Medium
	Osteoporosis	**Formal FDA validation of key surrogate endpoint (bone mineral density)**	**1H23**	**High**
	Osteoporosis	**Identification of development and commercialization partner for EB613**	**Mid-2023**	**High**
	Osteoporosis	Phase 3 study initiation	Mid-2023	Medium
	Osteoporosis	**Phase 3 top-line results**	**1H25**	**High**
	Osteoporosis	New Drug Application (NDA) filing	2H25	Medium
	Osteoporosis	**EB613 U.S. approval and launch**	**Mid- to late 2026**	**High**
EB612	Hypoparathyroidism	PK data with novel EB612 multi-dosing formulation	1H23	Medium
	Hypoparathyroidism	Phase 2/3 study initiation	2H23	Low
	Hypoparathyroidism	**Phase 2/3 study top-line data**	**1H25**	**High**
	Hypoparathyroidism	NDA filing	1H26	Medium
	Hypoparathyroidism	**EB612 U.S. approval and launch (self-commercialization)**	**2H26 / 1H27**	**High**
EB613	Non-union fractures	Phase 1/2 study start	1H23	Low

Note: Our POA values are: EB613 (osteoporosis): 50%; EB612 (hypoparathyroidism): 30%; Entera Bio expects to seek approval for EB613 and EB612 from the FDA under the 505(b)(2) regulatory pathway.

Source: H.C Wainwright & Co. estimates; Entera Bio, Ltd.

II. Investment Thesis

1. A Dark Horse in Oral Delivery of Biologic Agents

Program	Indication	Scientific Rationale	Current Stage	# of Patients	Comments
EB613	Osteoporosis	Oral delivery of PTH[1-34]	Phase 3-ready	~8M (U.S.) ~32M (EU)	First oral anabolic bone-building therapy for osteoporosis patients; in Phase 2, EB613 showed bone mineral density improvements at the spine, femoral neck and hip; end-of-Phase 2 (EOP2) meeting held; Phase 3 start in mid-2023
EB612	Hypoparathyroidism (hypoPT)	Oral delivery of PTH[1-34]	Phase 2a completed	~60K to 115K (U.S.) ~257K (EU)	First oral therapy; produced positive findings in two Phase 2a trials conducted in Israel; additional multi-dose formulation and development activities ongoing
PTH[1-34]	Non-union fractures	Oral delivery of PTH[1-34]	Preclinical	7M+ (U.S.)	Current treatments are surgical operation-based; oral PTH[1-34] could claim first-in-class status for this indication
GLP-2	Short bowel syndrome (SBS)	Oral glucagon-like peptide-2 (GLP-2)	Preclinical	15K (U.S.) 13K (EU)	Orphan indication; GATTEX (generic name: teduglutide) is the only drug currently approved to treat SBS
hGH	Growth hormone deficiency (GHD)	Oral growth hormone (GH)	Preclinical	6K (U.S.) 243K (EU)	*In vivo* proof-of-concept (POC) testing in progress

Entera Bio is an oral biologics pure-play dedicated to advancing standard-of-care (SOC) therapy in a plethora of indications, with its most compelling near-term market opportunity focused on treatment of osteoporosis and hypoparathyroidism (hypoPT). At the nucleus of Entera's value proposition is the patented oral biologics delivery platform acquired from Oramed Pharmaceuticals that facilitates the delivery of peptides, proteins and other large molecules often delivered via injection. We believe such delivery should rapidly increase patient compliance and market adoption over injectable formulations.

Entera's outlook rests mainly on the performance of its oral delivery platform, which is significantly de-risked in the clinic (data from both Entera's pipeline candidates and Oramed's late-stage assets). Our valuation accounts only for the osteoporosis (POA 50%) and hypoPT (POA 30%) indications, while clinical catalysts with other assets and the Amgen collaboration could represent significant upside to our thesis. Given multiple near- and medium-term catalysts, we believe the current share price (a ~70% decline from its 52-week high vs. a ~38% decline in the benchmark XBI index relative to its 52-week peak) constitutes an attractive entry point.

Source: Entera Bio Ltd.

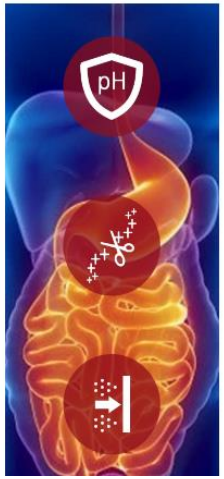
Entera's Platform Targets the Achilles' Heel of Oral Biologics Delivery

Human Digestive System is Harsh to Biologics

Harsh pH
Stomach acidity cleaves and shreds protein

Protease attack
Proteases attack and break down proteins

Absorption barrier
Therapeutic proteins fail to be absorbed via the intestinal wall (barrier)



Entera's Technology Delivers Intact Oral Biologics Without Concerns of Degradation or Absorption

pH shield
Sensitive enteric coating protects capsule contents before entering small intestine

Protease protection
Protease inhibitors protect the active agent

Absorption enhancement
Assists the permeation of proteins/peptides across intestinal membrane and into bloodstream

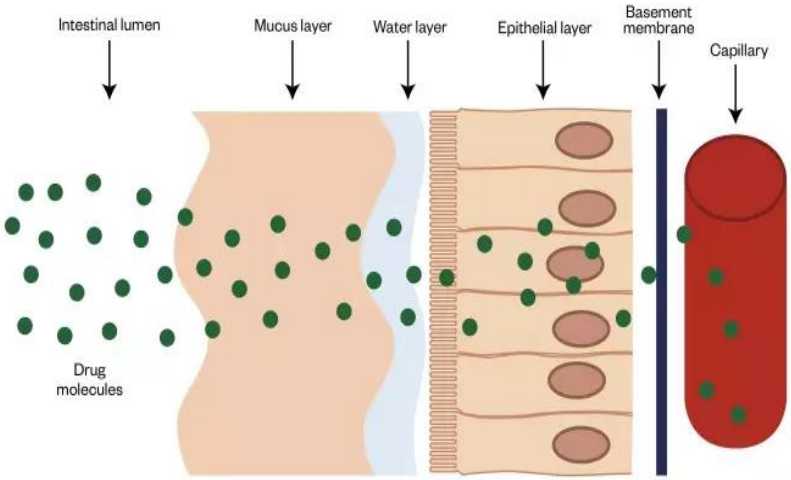
While injectable drugs often display a faster onset of action, which may translate to quicker relief, attributes such as patient inconvenience, complex manufacturing procedures and high pricing limit their adoption. Accordingly, the medical community prefers oral drugs, though such a route has been mainly limited to delivering payload involving small molecules. In addition, oral biologics are often difficult to formulate, given the harsh pH conditions in the stomach that rapidly degrade the integrity of biologics and intestine barriers that limit the absorption and translocation of large molecules. Importantly, oral biologics typically have exhibited very low bioavailability (<1%), often leading to variability and dosing complications.

Entera's proprietary technology—acquired from Oramed—is designed to address absorption and degradation challenges that limit the development and evolution of oral biologics. By formulating biologics with a synthetic intestinal permeation enhancer (e.g., salcaprozate sodium or SNAC) and a trypsin inhibitor that resists enzymatic degradation in the gastrointestinal (GI) tract, Entera believes traditional challenges that mar clinical development could be minimized (or even eliminated). In our view, Entera's proprietary platform is a game-changing technology that could transform injectably delivered biologics (novel or repurposed molecules) into oral formulations, thereby maximizing compliance and adoption.

Source: Oramed Pharmaceuticals, Inc.; Entera Bio Ltd.

An Oral Biologics Delivery Platform That Resists Enzymatic Degradation and Facilitates Intestinal Permeation Could be Transformational, in Our View

Physiological Barriers Hinder Absorption of Biologics



Given that physiological barriers preclude macromolecules' absorption, enhancers (such as SNAC) could be deployed to overcome intrinsic resistance.

Intestinal Enzymes Degrade Biologics Thereby Compromising Their Integrity

Enzyme	Specificity	pH Optimum
Trypsin	Lys, Arg	7.5–8.5
Chymotrypsin	Tyr, Phe, Trp	7.8–8.0
Carboxypeptidase A	Aromatic or branched sidechains	7–9
Carboxypeptidase B	Arg, Lys, also Val, Ile, Asn Gly, Gln	9.0
Elastase I	Ala-Ala, Ala-Gly	8.5
Elastase II	Medium to large hydrophobic residues	8.5

Entera's formulation uses a trypsin inhibitor to prevent degradation from GI enzymes. Such molecules also protect biologics' integrity while simultaneously increasing their bioavailability.

Effective delivery of oral biologics to the site of action continues to be a formidable task for drug developers, despite significant scientific advancements. Notably, the presence of natural physiological barriers in the GI tract—e.g., intestinal epithelium that hinders the passage of hydrophilic macromolecules—precludes the entry of xenobiotics. Furthermore, stomach acid and GI enzymes (e.g., trypsin, chymotrypsin, carboxypeptidases and elastases) activate pH-induced proteolysis mechanisms to cleave biologics into peptides and amino acids, thus destroying the integrity of the drug.

Entera's oral biological formulation comprises: (1) an active protein; (2) an absorption-enhancing carrier that facilitates transcellular absorption without compromising the integrity of physiological barriers; and (3) a protease inhibitor that resists GI enzymes. While choosing a permeation enhancer or trypsin inhibitor could be easy, identifying an optimal formulation without compromising efficacy could be arduous, in our view. Accordingly, Entera considers a protein molecule's size, physicochemical properties, mechanism of action (MoA) with GI constituents and the opportunity to create a schedule that supports multiple dosing per day prior to incepting specific pipeline programs. In addition, given that the platform could deliver protein molecules up to 150kDa (though management indicated that the optimal payload is 50kDa), opportunities abound to target both mass market and rare disease indications, in our view.

Source: Oramed Pharmaceuticals, Inc.; Entera Bio Ltd.

A Deep Dive Into Entera's Oral Biologics Platform Technology

Protein	Permeation Enhancer	Trypsin Inhibitor
Entera's proprietary platform technology facilitates the development of oral formulations for peptides, proteins and other molecules. Though the initial focus is on oral PTH formulation, we expect the company to rapidly expand the utility of the drug to include other biomolecules that could target both mass market and rare disease (i.e., orphan) indications.	The permeation enhancer used in Entera's oral formulation is salcaprozate sodium (SNAC), a synthetic molecule known to facilitate transcellular permeation by increasing the membrane fluidity of cells lining the GI tract. We note that a weak association between SNAC and the protein or peptide molecule of interest preserves the chemical integrity of the API.	Soybean trypsin inhibitor used in Entera's oral formulation is well-known for its protective effects against intestinal enzymes (proteases pepsin, chymotrypsin, and trypsin)

Entera's proprietary platform is disruptive as it facilitates oral delivery of biologics currently delivered via injections. From our vantage point, such oral biologics should increase compliance while simultaneously lowering cost. Given the fact that the APIs that form the basis for the company's disclosed pipeline candidates are significantly de-risked due to extensive human clinical and real-world experience, Entera Bio could leverage the FDA's 505(b)(2) pathway and the European Medicines Agency (EMA) mixed application process to obtain market authorization for its products. The regulatory route in the U.S. and Europe would be more straightforward and higher-probability than that used for *de novo* applications.

Source: Entera Bio Ltd.

Entera's Platform is Positioned to Drive the Next Wave of Innovation in Oral Biologics Delivery

We believe Entera is well-positioned to advance its mission—to develop oral versions of biologic agents that are currently delivered via injection. Our enthusiasm for the company stems from the platform's unique design, solid clinical data in two indications (osteoporosis and hypoparathyroidism) and Entera Bio's demonstrated ability to forge a partnership with an industry leader (Amgen). Despite being effective, injectable drugs are inconvenient to most patients (elderly individuals, in particular), resulting in poor compliance. By formulating known FDA-approved biologic drugs with a synthetic permeation enhancer and a protease inhibitor, Entera has shown that the traditional challenges (e.g., bioavailability and degradation) associated with oral biologics development could be circumvented. Such attributes should broadly facilitate the development of oral formulations of peptides, proteins and antibodies, without compromising cost, convenience and quality, in our view.

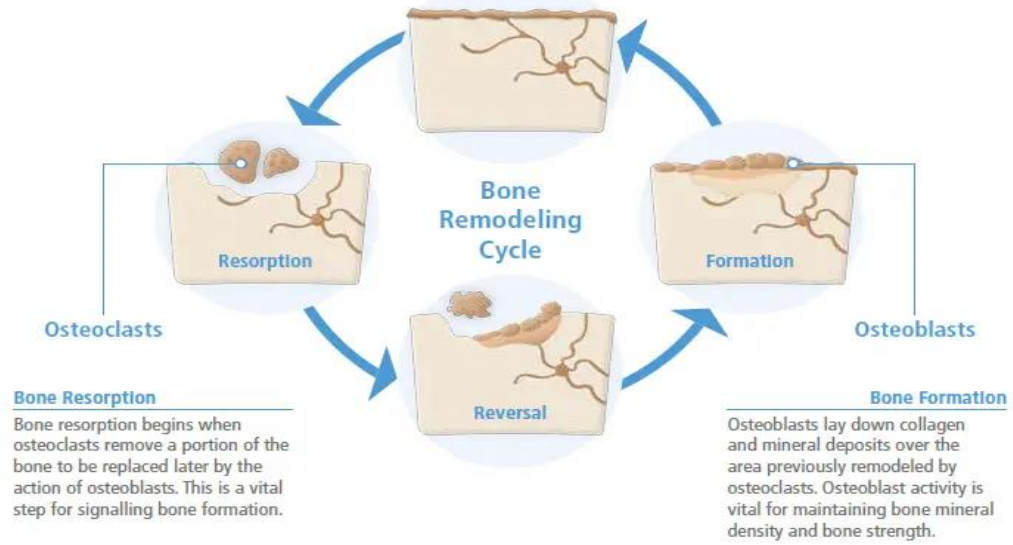
In order to demonstrate clinical proof-of-concept (POC) of its proprietary platform, Entera has appropriately chosen both a mass-market indication (i.e., osteoporosis) as well as a rare disease (hypoPT) condition where unmet needs are severe. The connecting link in both these indications is the human parathyroid hormone (PTH), which is known to regulate calcium homeostasis, among other functions. Entera's EB613, a key fragment of the full-length hormone, improved bone mineral density in the lumbar spine, femoral neck and total hip regions, demonstrating efficacy in osteoporosis (Phase 2 data). Separately, EB612 demonstrated a significant reduction in calcium intake while simultaneously decreasing serum phosphate and urine calcium levels in hypoPT patients (Phase 2a and Phase 2b data), supporting continued advancement.

Entera's oral biologics platform is not fully de-risked as the company is yet to garner its first FDA approval. However, we are optimistic about the technology, given its safety and efficacy record (a total of more than 260 healthy volunteers and patients have received multiple doses of various formulations of oral PTH (1-34) in clinical trials). In addition, Entera is making strides to diversify its pipeline (e.g., Amgen collaboration and the company's internal GLP-2 program), though visibility remains limited at this juncture. From our perspective, Entera is an industry leader in the development of oral versions of biologic agents, though competitors are adopting alternative approaches to achievement of the same aim (e.g., a drug-agnostic oral delivery platform in the form of an ingestible capsule is currently in Phase 1 testing).

Source: Entera Bio Ltd.

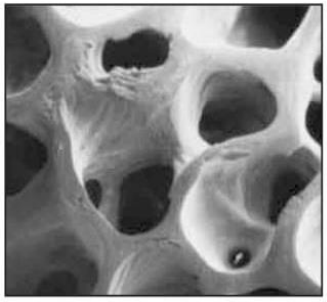
2. Turning the Tide in Osteoporosis Treatment With Oral EB613

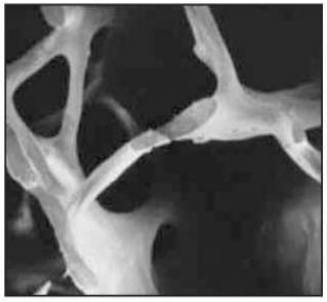
Bone Remodeling Cycle



The balance between bone resorption (osteoclast activity) and new bone formation (osteoblast activity) drives healthy bone remodeling. However, such balance is skewed in osteoporosis, resulting in more bone resorption and less bone formation. Over time, this causes bone loss, fragility and heightened fracture risk.

Normal Bone vs. Osteoporotic Bone





As can be observed (left) from the scanning electron micrographs, a clear pattern of inter-connected plates seen in normal bones is missing in osteoporotic bone, implying bone loss.

Osteoporosis is a chronic skeletal disease characterized by excessive bone loss and deterioration of bone tissue microarchitecture, eventually leading to bone fragility and fracture. The disease is caused by imbalances in bone remodeling, resulting in decreased new bone formation.

Nearly eight million women have osteoporosis in the U.S., though it is more common among the elder (50 years+). Physicians use a combination of techniques to diagnose osteoporosis, the primary method being the bone mineral density test. In this test, X-rays are used to measure the content and packing of calcium and bone minerals in the bone segment (commonly tested areas are the spine, hip and forearm). A T-score of -1 and above signifies healthy bones, whereas a score between -1 and -2.5 denotes osteopenia (low bone density), and -2.5 or below denotes osteoporosis (bone loss).

The goals of osteoporosis therapy are: (1) to prevent fractures by improving bone strength and reducing the risk of falling and injury; (2) to relieve symptoms of fractures and skeletal deformity; and (3) to maintain normal physical function and improve quality of life (QoL).

Source: International Osteoporosis Foundation; U.S. National Library of Medicine; Sozen et al, European Journal of Rheumatology (2017).

World Health Organization (WHO) Definitions of Osteoporosis

Classification	Bone Mineral Density	T Score*
Normal	Within 1 SD of the mean level for a young adult reference population	−1.0 and above
Low bone mass (Osteopenia)	Between 1 and 2.5 SD below that of the mean level for a young adult reference population	Between −1.0 and −2.5
Osteoporosis	2.5 or more below that of the mean level for a young adult reference population	At or below −2.5
Severe or established osteoporosis	2.5 or more below that of the mean level for a young adult reference population **with fractures**	At or below −2.5 or -3.0 with one or more prior fragility fractures

Osteoporosis is a global public health problem with a higher incidence rate in Caucasians, women and older people. When left diagnosed or treated, secondary health problems, including death, could occur, given the silent nature of the disease. In real-world settings, osteoporosis is diagnosed by measuring bone mineral density (BMD) using dual X-ray absorptiometry (DXA). Per WHO, a T-score of -1 and above signifies healthy bones, whereas a score between -1 and 2.5 denotes osteopenia (low bone density), and -2.5 or below denotes osteoporosis (bone loss).

Given the severity of osteoporosis and its concomitant secondary effects, the United States Preventive Services Task Force (USPSTF) recommended that all women aged 65 years and above and younger women whose fracture risk is equal to or greater than that of a typical 65-year-old Caucasian woman test for osteoporosis.

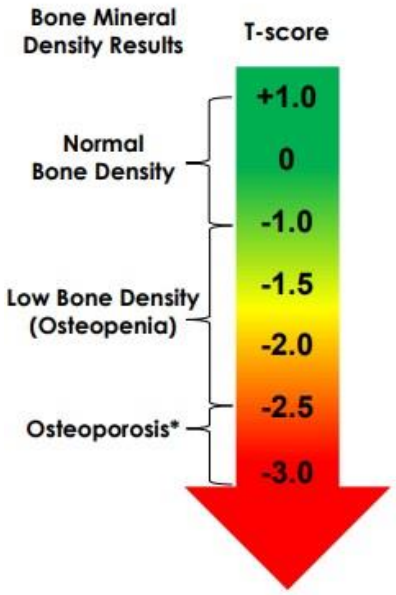
Osteoporosis is treated using anti-resorptive agents (1L agents; e.g., bisphosphonates) and/or anabolic agents (2L agents; e.g., teriparatide). Despite multiple FDA approvals in the space, the prevalence of osteoporosis is growing, highlighting standard-of-case (SOC) deficiencies (detailed later in this report) and the need for improved therapies. Importantly, teriparatide (FORTEO) treatment is usually limited to one to two years, given the apparent lack of efficacy beyond this time frame.

*Note: *The difference between the patient's BMD and mean BMD of young females aged in the range of 20–29 years (divided by the standard deviation (SD) of the reference population) yields the T-score.*

Source: Kanis, on behalf of the World Health Organization Scientific Group. Technical Report (2007); Sozen et al, European Journal of Rheumatology (2017).

T-Score BMD Classifications and Patient Fracture History Drive Therapy Selection

T-Score Scale



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%	Bisphosphonates; limited Anabolic penetration
Very High Risk Osteoporosis *(T-scores ≤ -3.0 or ≤ -2.5 with prior fragility fractures)*	10%	23%	Bisphosphonates / Anabolic therapies

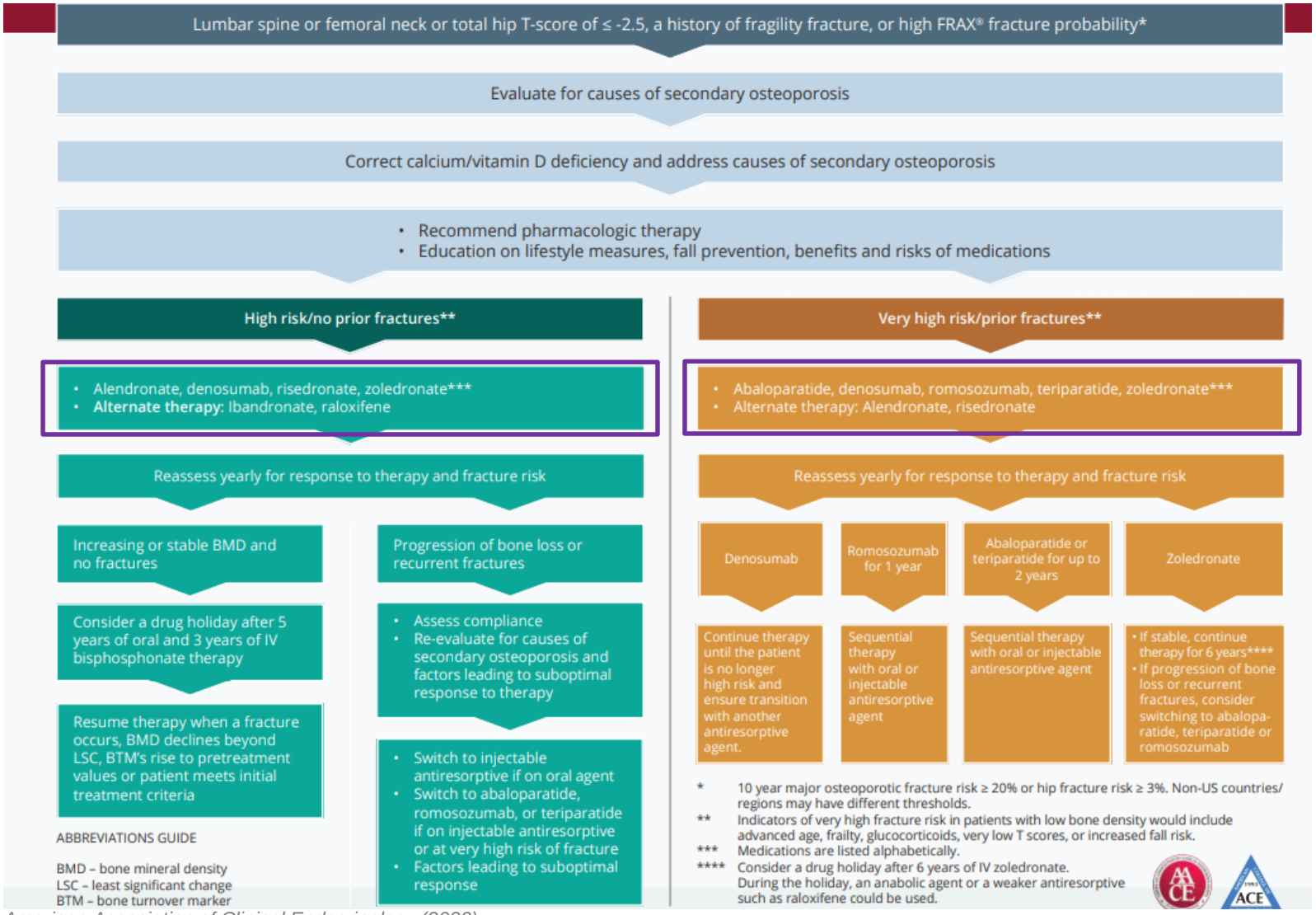
HCPs indicated most of their osteoporosis patients are:

Post-menopausal women (~70%)
Or older men (~15%)

Injections deter many patients from employing PTH to treat osteoporosis, which has been a significant factor in creating a treatment void when it comes to high-risk patients. An orally deliverable formulation of PTH with adequate bioavailability and similar impact on BMD with analogous safety vs. existing injectable versions may address this unmet clinical need and significantly impact the lives of large numbers of patients.

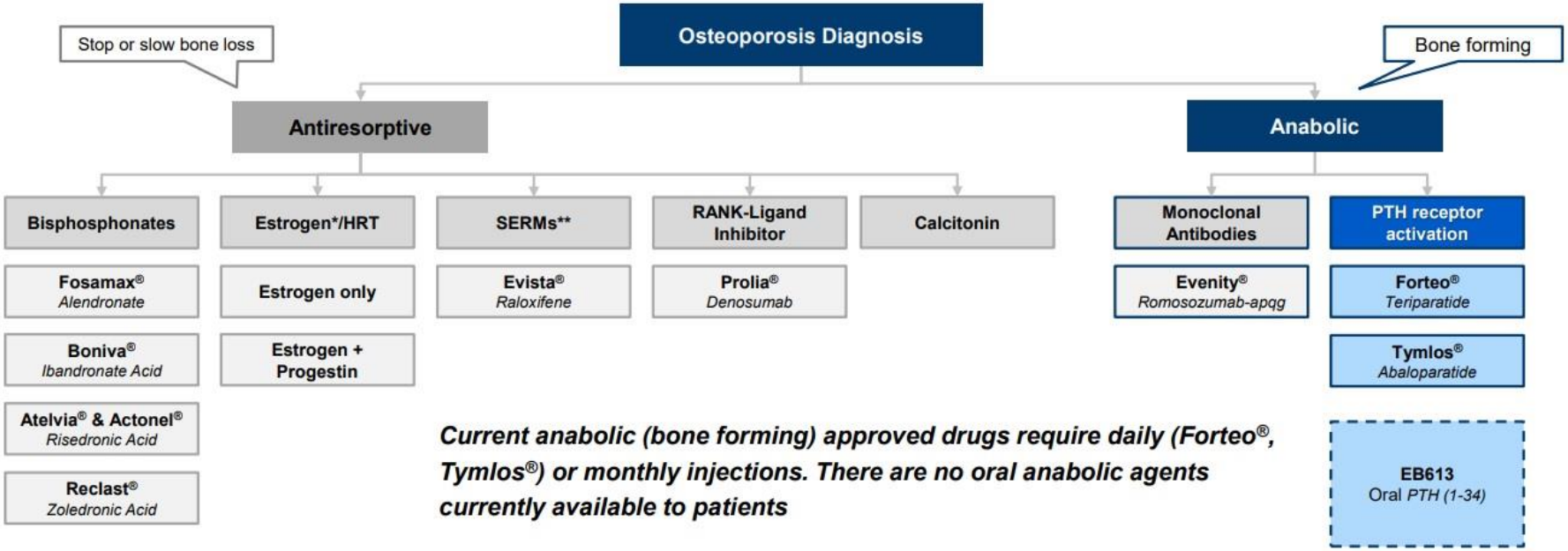
Source: American Association of Clinical Endocrinology (AACE) Guidelines; Triangle Insights Primary Research, April 2022.

Postmenopausal Osteoporosis Treatment Algorithm



Source: American Association of Clinical Endocrinology (2020).

Osteoporosis Pharmacological Treatment Segmentation



Note: *Estrogen products are indicated for prevention of osteoporosis as a secondary benefit when used to control menopausal symptoms and are not considered front-line therapy due to adverse reactions; **SERMS – selective estrogen receptor modulators.

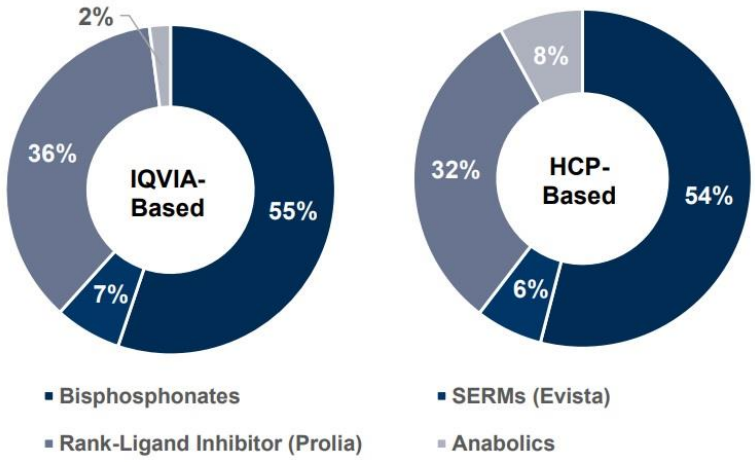
Source: Johns Hopkins School of Medicine; WebMD; Frost & Sullivan.

Osteoporosis Treated Population Segmentation by Medication Class

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

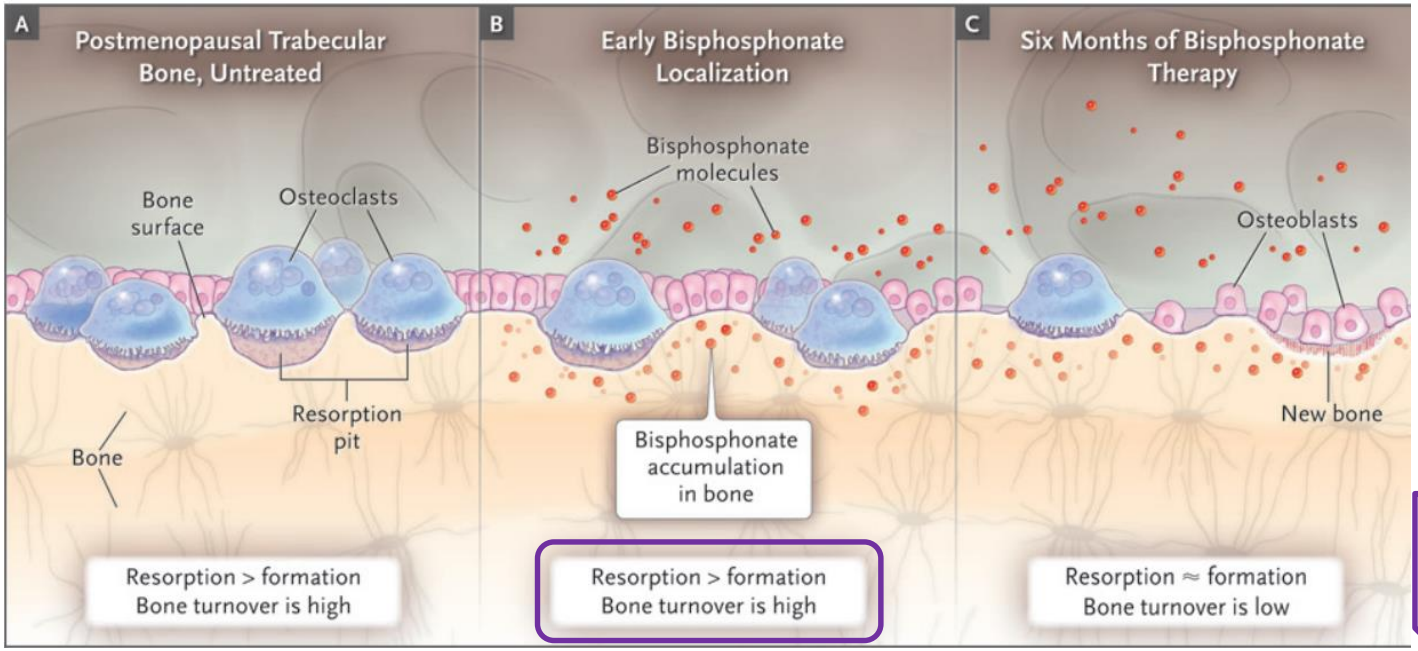


As shown above, the percentage of treated patients suffering from osteoporosis who are typically on anabolics represents <10% of the total treated population. Since anabolic agents are the only therapies that rebuild bone, rather than merely slowing bone loss, we believe that a more convenient, safe and effective anabolic product could penetrate market segments that are currently going unaddressed by the existing anabolic agents—all of which are solely administrable via injection. We believe available data shows that anabolic solutions should be used more broadly.

Note: Bisphosphonate class comprises Fosamax, Boniva, Atelvia, Reclast and generic versions of listed products that are off-patent; SERMS include both Evista and generic raloxifene; RANK ligand blockers include Prolia (denosumab); anabolics include Evenity (romosozumab), generic teriparatide and Tymlos (abaloparatide).

Source: IQVIA prescription data; TIG Primary Research, April 2022.

Oral Bisphosphonate Therapy Uptake Appears Limited by Poor Adherence Driven by Perception that Treatment Benefits Are Negligible



Bone Resorptive Biomarkers
CTX
NTX
ICTP
PYR

Bone Formation Biomarkers
P1NP
CPICP
OC
BSAP

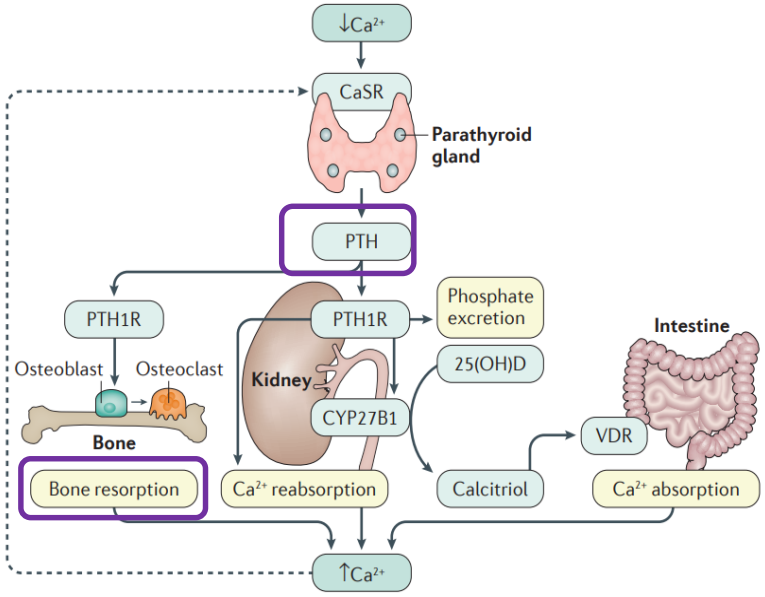
Of the several bone markers, CTX and P1NP gained prominence in osteoporosis conditions.

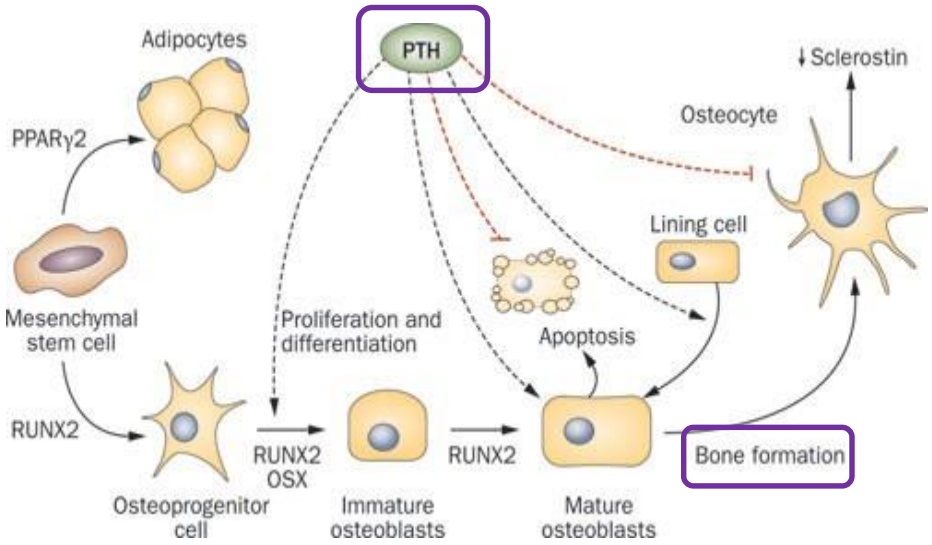
Given the fact that osteoporosis increases the risk of fracture (due to very low bone density), which could lead to mobility loss, it was believed that agents that slow down bone loss and accelerate bone formation could provide therapeutic benefit. A notable group of molecules that reduces bone desorption is the bisphosphonate class—this comprises synthetic compounds with a high affinity for the calcium hydroxyapatite of the bone. Drugs approved in the space (including alendronate, ibandronate, risedronate and zoledronic acid) had been shown to increase bone mineral density by 5 – 7% (spine) and 1.65 – 5% (femoral neck) after three years of treatment (in addition to reducing fracture risk), suggesting lower bone turnover.

However, a key sticking point limiting oral bisphosphonate (BP) therapy is low adherence, commonly observed in postmenopausal osteoporosis patients. The poor compliance is driven by severe side effects (femoral fractures and bone loss), a lack of motivation and the patient's inability to perceive meaningful improvement. Per World Osteoporosis Foundation, bisphosphonates therapy adherence varies between 43% and 59%, suggesting opportunities for new interventions. This shines a positive light on parathyroid hormone (PTH), given its positive impact on bone resorption and bone-building (anabolic effects).

Source: Favus, New England Journal of Medicine (2010); World Osteoporosis Foundation.

Parathyroid Hormone Orchestrates Mineral Homeostasis and Appears to Provide More Osteoporotic Benefits vs. Antiresorptive Molecules





PTH plays a central role in the regulation of calcium and phosphate homeostasis. When calcium is sensed to be at low levels, PTH is secreted to maintain the balance in bone, kidneys and intestine.

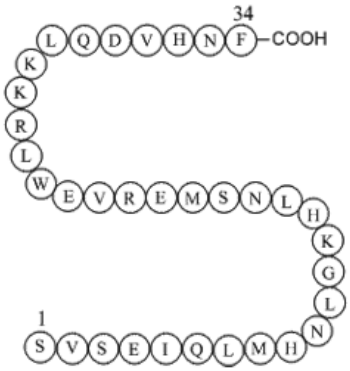
PTH induces RUNX2 expression in osteoblasts, increases osteoblast numbers, prolongs osteoblast survival and inhibits sclerostin production (an inhibitor of bone formation). Such attributes stimulate new bone formation and increase bone mineral density, preferentially through stimulation of osteoblastic activity (not reduction in osteoclastic activity).

The defining characteristic of osteoporosis is abnormally low bone mineral density (T-score of -2.5 or below). Evidence suggests that parathyroid hormone (secreted by the parathyroid gland) acts on its cognate receptor and triggers a complex mechanism resulting in bone resorption, calcium resorption and reabsorption from renal tubules. Importantly, given PTH's anabolic role in new bone formation, it is envisaged as a potential treatment method in osteoporosis patients who exhibit poor adherence to antiresorptive therapy.

Source: Kraenzlin & Meier, Nature Reviews Endocrinology (2011); Mannstadt et al., Nature Reviews Disease Primers (2017).

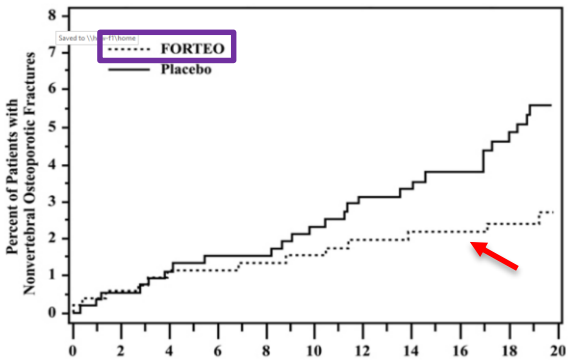
FORTEO Is Effective in Osteoporosis—Subcutaneous Delivery Constitutes a Drawback

FORTEO (Teriparatide)



FORTEO (PTH[1-34]) is a synthetic PTH indicated for use in adult osteoporosis patients who failed bisphosphonates.

FORTEO Reduces Fractures



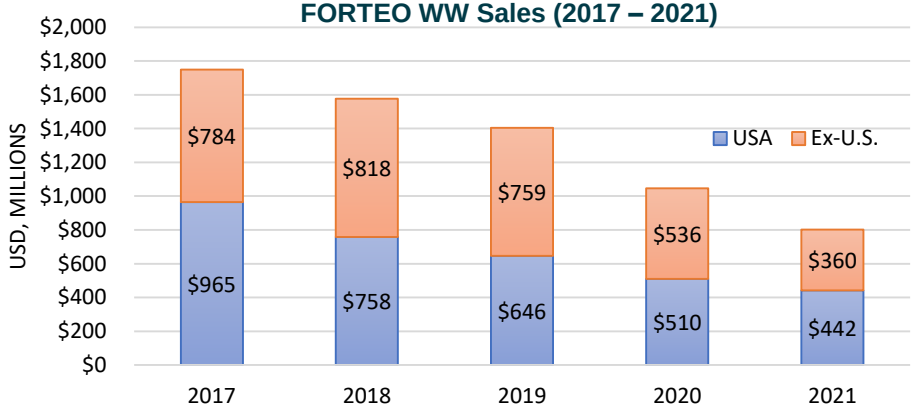
FORTEO-treated patients demonstrated a significant reduction in new non-vertebral fractures (vs. placebo), demonstrating efficacy.

FORTEO Increases Bone Mineral Density

Item	FORTEO (n=541)	Placebo (n=544)
Lumbar spine	9.7	1.1
Femoral neck	2.8	-0.7
Total hip	2.6	-1.0
Trochanter	3.5	-0.2
Intertrochanter	2.6	-1.3
Ward's triangle	4.2	-0.8
Total body	0.6	-0.5

Importantly, FORTEO-treated patients displayed an increase in bone mineral density, suggesting anabolic effects (new bone formation).

FORTEO WW Sales (2017 – 2021)



FORTEO utilizes a validated molecular mechanism that reduces fracture risk and increases bone formation in osteoporosis patients (anabolic effects). While we acknowledge the significant drawbacks associated with FORTEO usage (including discomfort, local irritation and the opportunity to induce antibodies) and its declining sales (mainly due to biosimilar competition), teriparatide has not totally lost its luster. In this context, we believe that a cost-effective, patient-friendly oral formulation of PTH that is scalable and stable could provide transformative benefits to the osteoporosis community. This spotlights Entera Bio's EB613, a once-daily oral formulation of PTH[1-34] that has shown clear safety, tolerability and bioavailability in Phase 2 studies.

Source: Forteo package insert; Entera Bio Ltd.

Entera Bio Could Rely on the FDA's Risk-Mitigated 505(b)(2) Pathway to Rapidly Advance EB613 to Market Entry, in Our View

Company	Agent	API MW (g/mol)	Bioavailability
Entera Bio	PTH (1-34)	4118	1.5%
Novartis/Emisphere (Eligen - CNAC)	PTH (1-34)	4118	0.2 - 0.5%
Enteris Biopharma - Unigen (Peptelligence)	PTH (1-31)	3719	0.52%
Multiple manufacturers	Desmopressin	1069	0.16%
Chiasma (TPE)	Octreotide	1019 (Cyclic peptide)	0.67%
Proxima Concepts (AXCESS)	Insulin	5733	0.7%

Among the oral PTH agents in development, EB613 demonstrated better bioavailability vs. others, suggesting competitive differentiation.

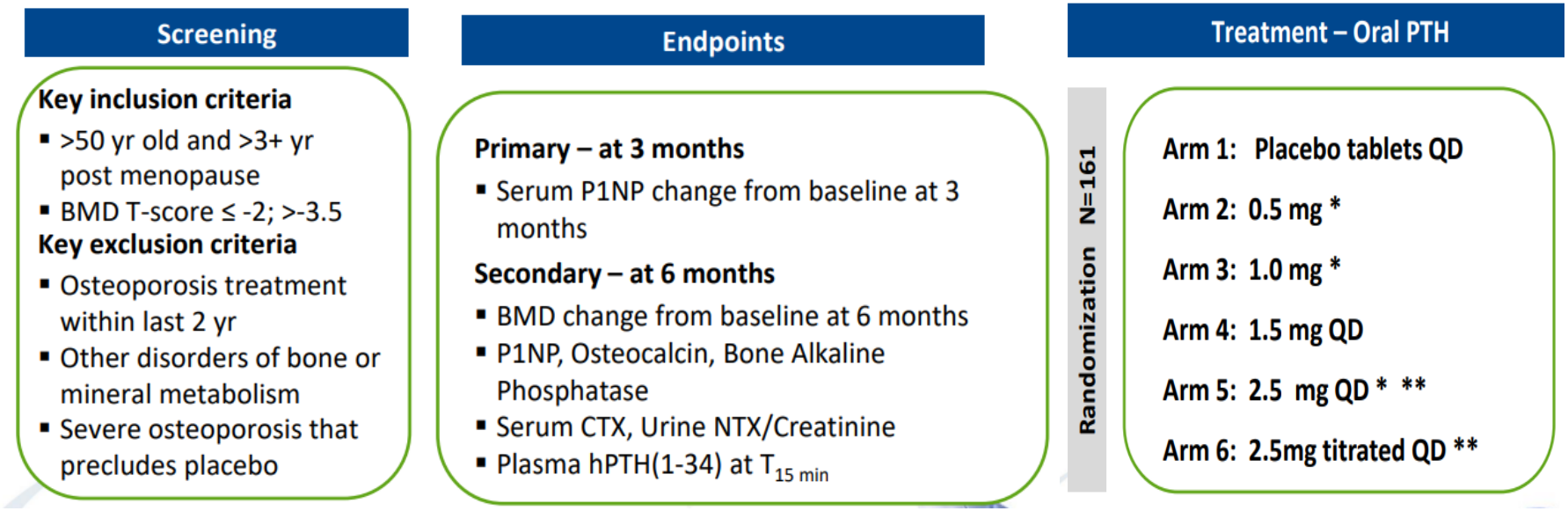
Entera's EB613 (an oral formulation of PTH[1-34]) is designed to deliver active teriparatide in a patient-friendly manner. In our view, this should be a welcome relief to the osteoporosis community, given the poor adherence (~50 – 75%) observed in 1L treatment involving bisphosphonates and the well-known fear of needles associated with FORTEO (administered via once-daily subcutaneous injection). Notably, a third-party market research study (sponsored by Entera Bio) suggested that clinicians favored oral solutions over injectables because of their advantages for patients.

In our view, EB613 clinical development boasts the following advantages: (1) since the efficacy and safety of FORTEO are already demonstrated in the clinic, the EB613 program is significantly de-risked (bioequivalence has already been established in Phase 2 head-to-head studies); (2) the FDA agreed that bone mineral density and biomarkers (P1NP and CTX) are important clinical endpoints, which obviates the need for expensive vertebral and non-vertebral fracture studies (several million-dollar savings); and (3) regulatory approval can be sought under the risk-mitigated 505(b)(2) pathway.

The 505(b)(2) pathway—created via the Hatch-Waxman Amendments legislation of 1984—provides a less expensive alternative route to approval while preserving product differentiation and competitive positioning. In our view, Entera Bio could leverage the 505(b)(2) pathway to rapidly, cost-effectively advance its programs while simultaneously diversifying its portfolio beyond osteoporosis and hypoparathyroidism.

Source: Entera Bio Ltd.

Entera's Phase 2 Trial Included Key Characteristics to Obtain Proof-of-Concept Data in Osteoporosis Patients

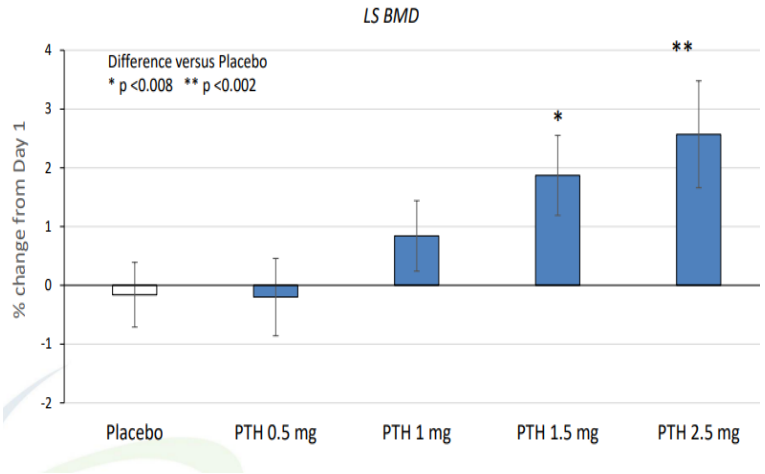


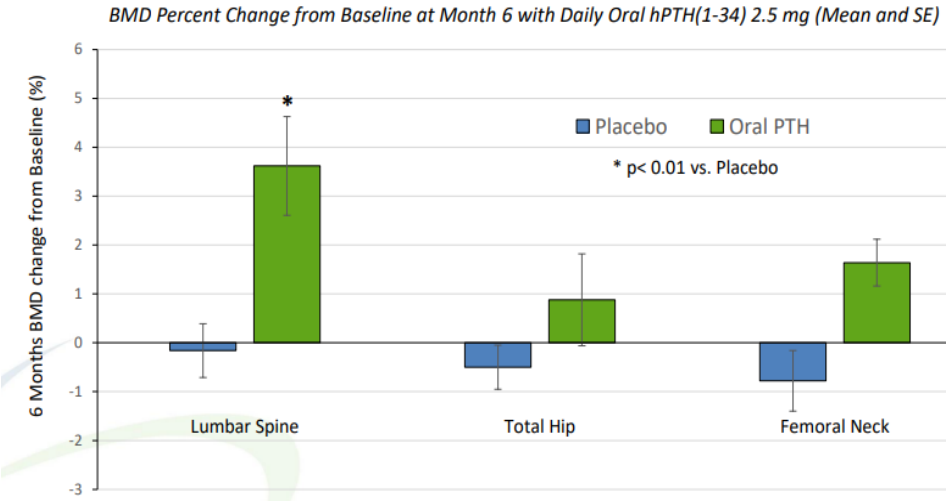
In July 2019, Entera Bio launched a dose-ranging, placebo-controlled Phase 2 trial of EB613 involving postmenopausal female subjects (n=160) with osteoporosis or low BMD (NCT04003467). The trial was conducted in four leading medical centers in Israel and was designed to obtain POC information in clinical settings and inform dose selection for pivotal Phase 3 studies.

The study's primary endpoint was a change in P1NP at three months, though Entera investigated sCTX in the secondary analysis (see above for a complete list of endpoints). We note that serum P1NP is a validated biomarker in the osteoporosis indication, given its past utility in the FORTEO and EVENITY (romosozumab) drug approvals. Furthermore, Entera evaluated BMD improvements, given the well-established association between high bone mineral density and low fracture incidence.

Source: Entera Bio Ltd.

EB613 Treatment Demonstrated Significant Increase in Bone Mineral Density Thereby Providing Validation to Entera's Scientific Hypothesis





In Phase 2 assessment, EB613 (QD) treatment for six months demonstrated a linear and statistically significant dose-response as evidenced by gains in BMD (vs. placebo) at the lumbar spine region, demonstrating efficacy.

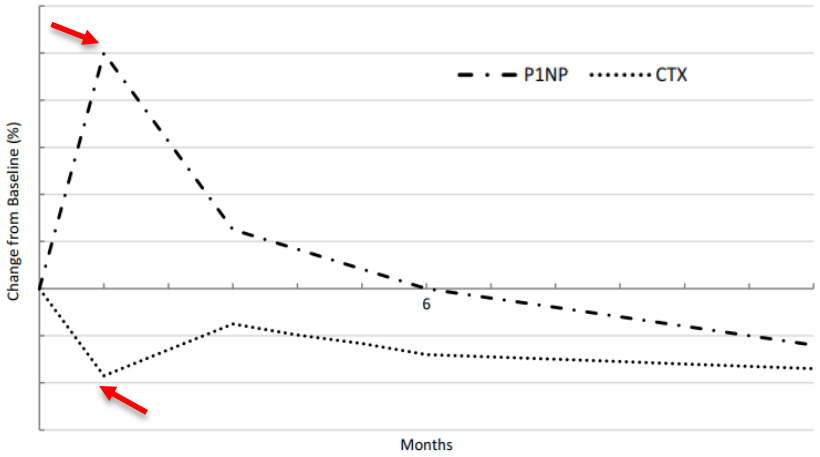
A similar trend in the total hip and femoral neck regions was also statistically significant. Importantly, oral 2.5mg EB613 produced a placebo-adjusted increase in BMD at the lumbar spine (3.78%), total hip (1.38%), and femoral neck (2.42%) measurement points at six months, suggesting benefits for fracture-risk osteoporosis patients.

From our vantage point, the solid improvements in BMD using multiple measurements provide strong validation for Entera's oral biologics delivery technology. In addition, we note that FORTEO treatment produced a similar increase in lumbar spine BMD (Δ=3.9%), though it failed to increase BMD in the femoral neck and total hip regions, underscoring opportunities for EB613 differentiation. Furthermore, EB613's safety profile was consistent with that of FORTEO without any drug-related severe adverse events (SAEs).

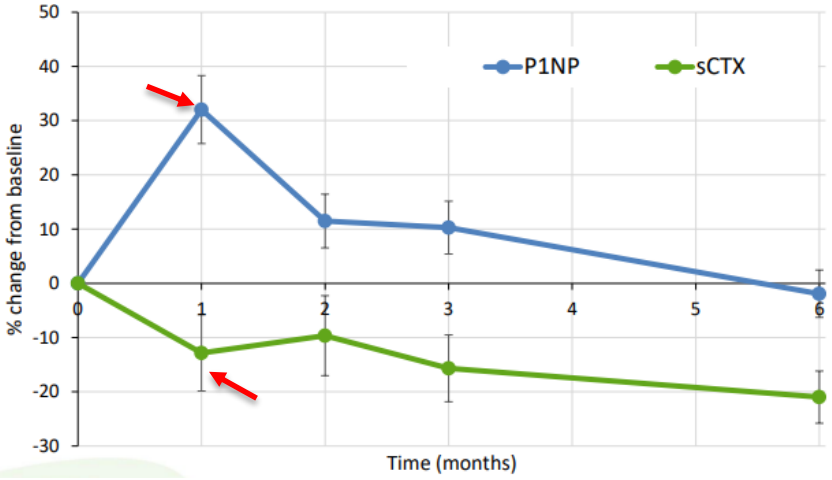
Source: Entera Bio Ltd.

EB613 Treatment Positively Influenced Bone Turnover Markers P1NP and sCTX, Suggesting Dual Mechanisms of Action

Evenity Biomarker Data



EB613 Biomarker Data



In pivotal studies, Evenity treatment triggered a spike in P1NP levels, causing maximum bone formation effects at Month 1. Such effects descended below baseline after six months, suggesting its anabolic effects are limited. Alternatively, sCTX (bone resorption biomarker) decreased within a month and remained suppressed through Month 12.

Comparison to Evenity suggests a similar trend for EB613 (see above graph), i.e., the bone formation marker P1NP showed a rapid increase that peaked at Month 1, returning to baseline by Month 6. In contrast, CTX (bone resorption marker) decreased at Month 1 and continued to Month 6, suggesting the dual effect of EB613 on bone remodeling.

The rapid increase to peak P1NP levels (a bone formation biomarker) and subsequent descent below baseline suggests that the bone formation effects of both Evernity and EB613 are transient. In addition, sCTX (a bone resorption marker) is suppressed with both agents, with the greatest decrease during the first month of therapy. Overall, the biomarker data of EB613 (similar to Evenity) suggest dual functions (bone formation and suppression of bone resorption). With added oral convenience, such characteristics should delineate EB613's market positioning, in our view.

Source: Entera Bio Ltd.

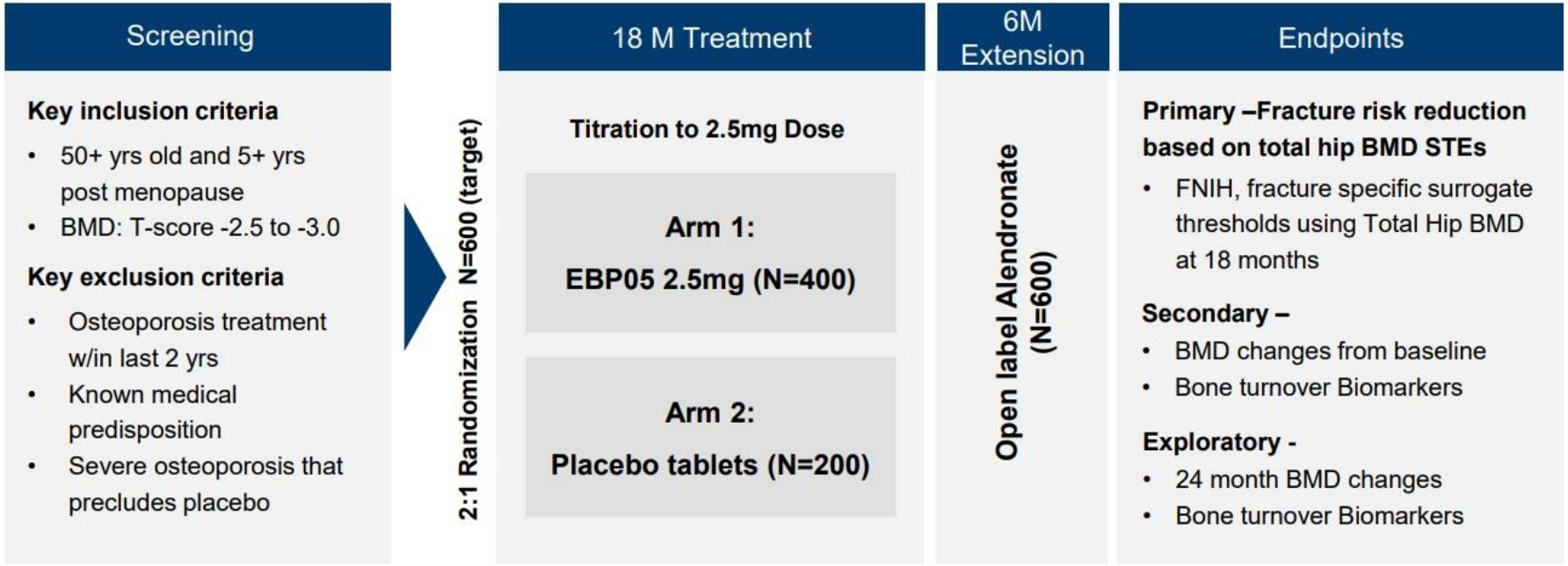
EB613 Safety Profile Appears Favorable and Comparable to Forteo

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's adverse event (AE) profile to date has proven similar to that of Forteo (teriparatide). Entera's candidate has not been associated with serum calcium increases or hypercalcemia-related safety issues. Over 90% of treated subjects tolerated the 2.5mg dose well, after titration (1.5mg for one month, 2mg for the subsequent month and 2.5mg administered during months 3 to 6). AEs commonly attributed to vasodilation seen with subcutaneously-delivered PTH were observed (headache, nausea, presyncope—namely, the sensation of being about to faint—and dizziness). There were no serious AEs. In our view, continued demonstration of such a safety profile in larger studies should bode well.

Source: Entera Bio Ltd.

EB613 Osteoporosis Pivotal Phase 3 Trial Design



In our view, Entera Bio has intelligently and pragmatically incorporated the evolution of thinking around surrogate endpoints in osteoporosis drug development to design a pivotal program for EB613 that appears risk-mitigated and regulatorily appropriate. The above trial design comprises a global, placebo-controlled, double-blinded 18-month longitudinal study slated to enroll a total of 600 patients (2:1 randomization). There is a six-month extension stage that would involve open-label treatment with alendronate (a bisphosphonate drug). Per the American Society for Bone and Mineral Research (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 treatment-related change in BMD as a surrogate endpoint for fractures in studies of novel anti-osteoporosis drugs, Entera Bio has defined the primary endpoint using fracture risk reduction based on total hip BMD surrogate threshold effects (STEs). After 18 months, the final analysis and top-line data would comprise both primary and secondary endpoints, while the 24-month time point following completion of the extension stage would involve release of data on exploratory endpoints post-extension period completion.

Source: Entera Bio Ltd.

Correlation Between Bone Mineral Density Parameters and Fracture Risk Hazard Ratio

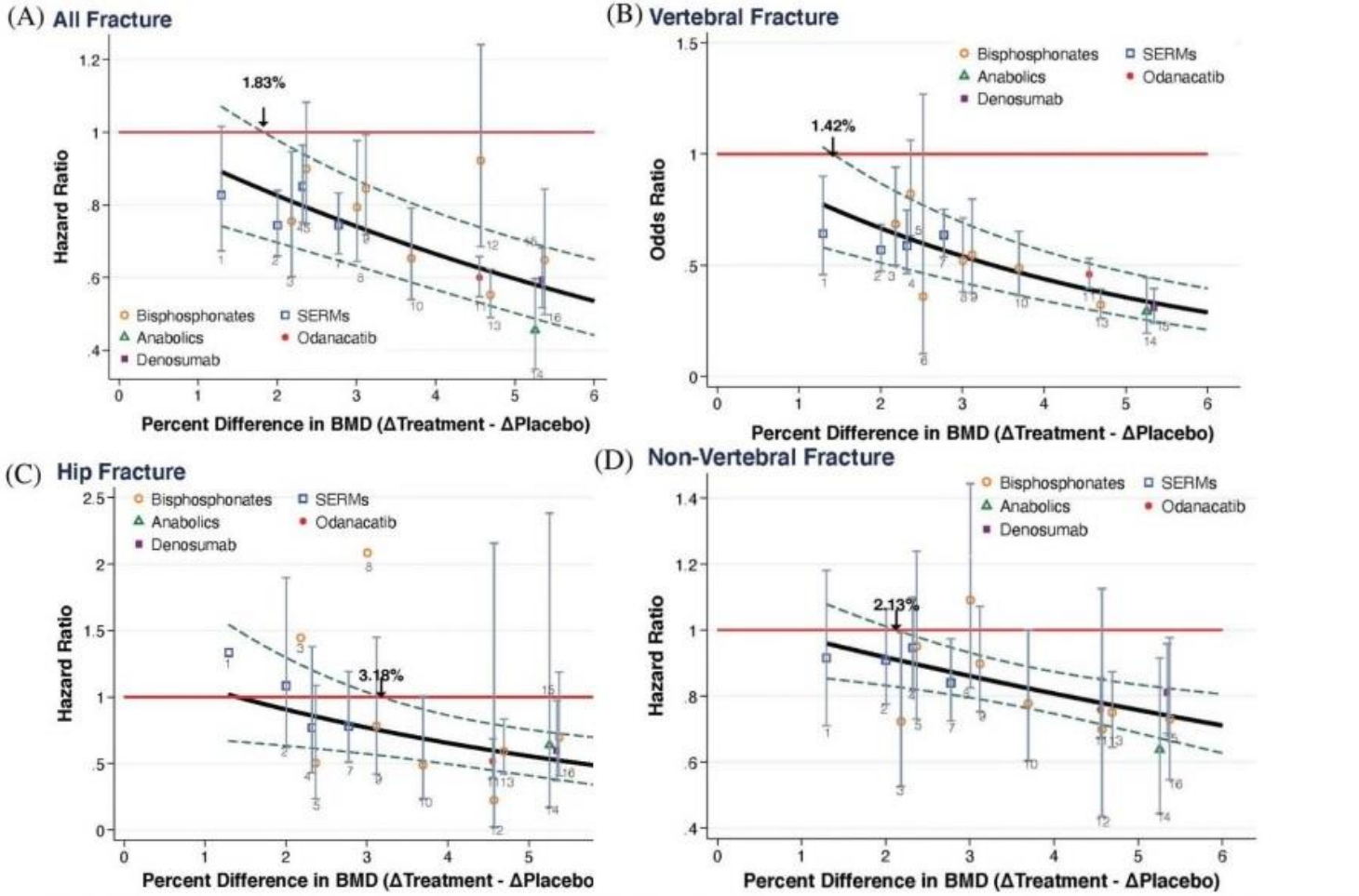


Fig 1. Relationship between difference in the change in total hip BMD between active and placebo groups at 24 months and the hazard or odds ratio of all, vertebral, hip and nonvertebral fractures. The red horizontal line is the ratio of 1 (no treatment effect) and the STE is the point where the upper 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

Source: Eastell et al., Journal of Bone and Mineral Research (2021).

EB613 Pivotal Trial Design Rationale

- The FNIH collected data from over 50 randomized trials in osteoporosis and individual data from over 170,000 patients.
- A meta-regression of 38 placebo-controlled trials comprising 19 therapeutic agents and meta-regression analyses of 91,779 individual patient data records from 23 randomized, placebo-controlled trials was conducted by FNIH

The FNIH concluded that total hip (TH) BMD—rather than lumbar spine and femoral neck BMD—was the best predictor of fracture risk reduction at all sites (vertebral, non-vertebral and hip). Placebo-adjusted TH BMD STEs are as follows:

- 1.42%: vertebral fractures
- 1.83%: all fractures
- 2.13%: non-vertebral fractures
- 3.18%: hip fractures

Message from the president of the ASBMR on June 23, 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.

Entera's proposed Phase 3 trial design aims to evaluate the percentage change in BMD measured at the hip for the EB613 treatment arm vs. the placebo arm. The change shall be tested to assess which of the BMD STEs are surpassed, starting with vertebral fractures and followed by all fractures and non-vertebral fractures. We believe that this is congruent with the SABRE project team's qualification plan, which is aimed at establishing BMD as the key surrogate endpoint for fractures. The fact that EB613 is oral teriparatide, has shown impact at least equivalent to Forteo—with indications of superiority on multiple aspects—and is being benchmarked vs. placebo in the pivotal trial bodes well, in our view, for the ultimate outcome of the study and appears to mitigate risk on multiple levels. We await final FDA authorization of the full qualification package for the surrogate BMD endpoint, which we expect to occur in 1H23. FNIH submission of the qualification package is slated for end-2022.

Source: Entera Bio Ltd.

EB613 is Poised to Become the First Oral Anabolic Drug, Despite a Crowded Osteoporosis Treatment Landscape

Selected Osteoporosis Drugs

Product	Company	Generic Name	Route	MoA	Launch Year	Patent Expiry	2021 WW Sales ($MM)
Prolia	Amgen	denosumab	Injection	Receptor activator of nuclear factor kappa-B (RANK) ligand antibody	6/1/2010	2/19/2025	3,248
Evenity	Amgen	romosozumab	Injection	Sclerostin antibody	3/4/2019	4/9/2031	530
Viviant	Pfizer	bazedoxifene	Injection	Selective oestrogen receptor regulator (SERM)	10/13/2010	4/6/2015	443
Caltrate	GSK	calcium carbonate	Oral	Voltage-dependent L-type calcium channel alpha-1C ligand	6/30/2009	NA	475
Evenity	Astellas Pharma	romosozumab	Injection	Sclerostin antibody	3/4/2019	2026 (composition-of-matter)	259
Forteo	Eli Lilly	teriparatide recombinant human	Injection	Parathyroid hormone regulator	12/20/2002	12/8/2018	802
Prolia	Daiichi Sankyo	denosumab	Injection	Receptor activator of nuclear factor kappa-B (RANK) ligand antibody	6/11/2013	NA	338
Calcitriol	Sino Biopharmaceutical	calcitriol	Oral	Vitamin D3 receptor agonist	12/31/2004	NA	176
Tymlos	Radius Health	abaloparatide	Injection	Parathyroid hormone regulator	5/31/2017	12/4/2030	219
Evenity	UCB	romosozumab	Injection	Sclerostin antibody	3/4/2019	4/9/2031	12
Teribone	Asahi Kasei	teriparatide acetate	Injection	Parathyroid hormone regulator	11/25/2011	9/17/2020	231
Premarin	Pfizer	estrogens, conjugated		Oestrogen receptor agonist	5/8/1942	NA	270

Though multiple drugs are approved for osteoporosis treatment, none of the bone-building (anabolic) drugs are delivered orally, limiting their market adoption. From our vantage point, EB613 could address this limitation, as it is the only oral anabolic osteoporosis drug in development that demonstrated robust Phase 2 data. In addition, EB613's dual MoA should bode well with physicians and needle-averse osteoporosis patients.

Source: EvaluatePharma.

EB613 Profile Benchmarks Favorably Against Existing Osteoporosis Drugs, Highlighting Commercial Potential

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

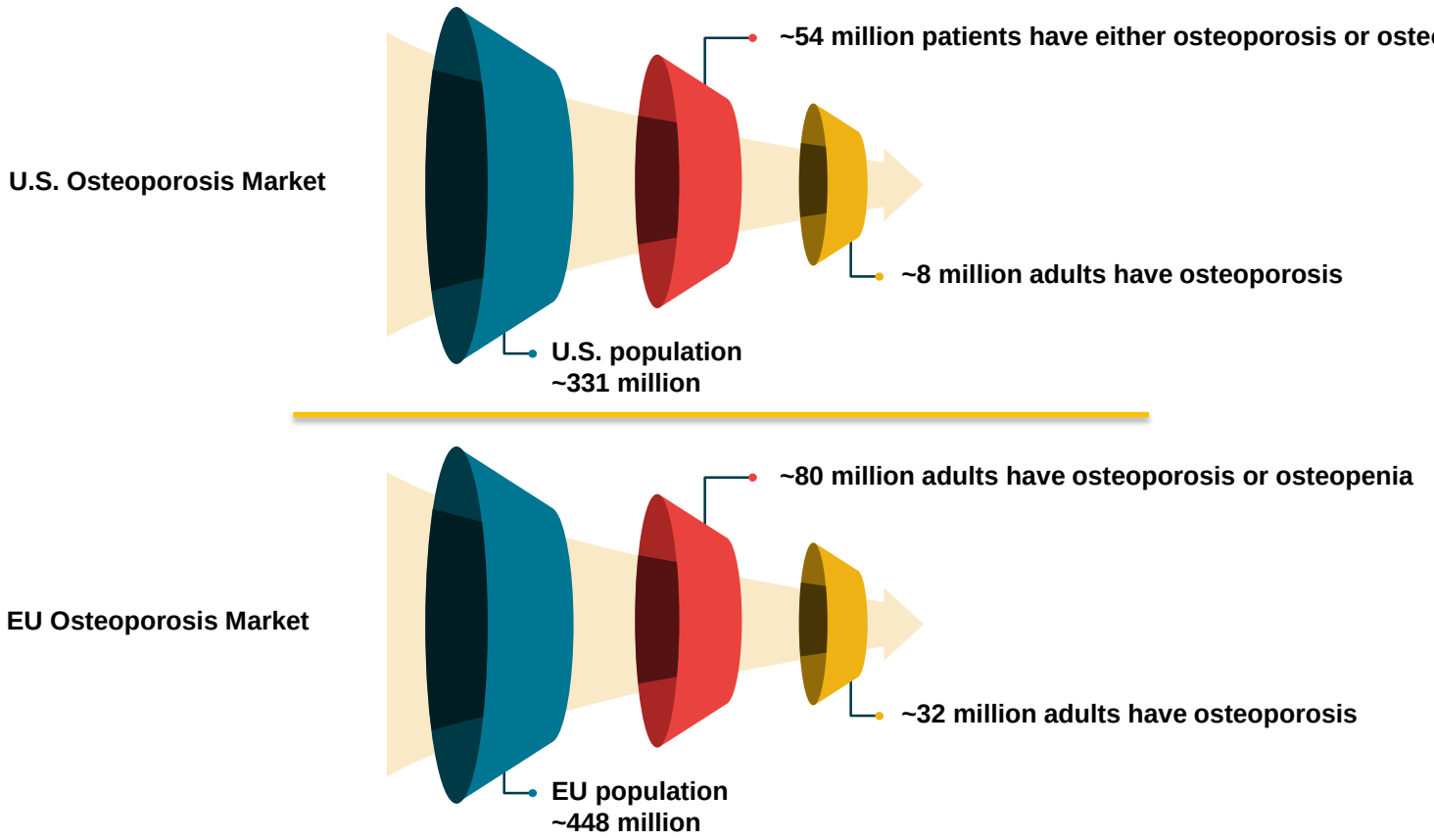
Product Metrics **						Target
Peak WW Sales	$1.9 B	$175 M	$2.6 B	$350 M	$300M	↗
Annual Treatment Price	~$35K +	~$20K +	$3-5K	~$21K	generics	Flexible
% of Market	~1%	<1%	3-4%	<1%	>90%	Growth

Though the osteoporosis treatment landscape appears crowded, we believe there are significant opportunities for new entrants, given the inefficiencies associated with approved agents. We draw investors' attention to the fact that patients show poor compliance with oral bisphosphonates as well as FORTEO and TYMLOS (delivered via injection). There have been no new orally-bioavailable drugs for treatment of osteoporosis introduced for over a decade.

We consider EB613 solidly differentiated vs. FORTEO: (1) oral convenience; (2) statistically significant impact in femoral neck or total hip BMD in most clinical studies (this was not the case with FORTEO); (3) lower clinical development cost with a faster path to market as it involves the risk-mitigated 505(b)(2) pathway; and (4) strong IP, with protection up to 2035. From our vantage point, the potential for EB613 to be introduced as the first oral anabolic PTH treatment appears highly attractive.

Source: Entera Bio Ltd.

U.S. Market Segmentation of Osteopenia and Osteoporosis



Market estimates suggest ~54 million U.S. patients have osteoporosis (bone loss) or osteopenia (low bone mineral density). In the EU region, we estimate this population to be ~80 million. Since Entera Bio is a small firm that operates under lean principles, we expect the company to forge partnerships with more established pharmaceutical entities for EB613 commercialization. Entera may elect to initiate pivotal clinical development of EB613 with a partner on board—preferably an entity with global reach that can optimize the value of the asset in multiple markets.

Source: H.C. Wainwright & Co. estimates.

We Believe EB613 Could Capture Significant Market Share From FORTEO and TYMLOS

Osteoporosis is a skeletal disorder affecting over 8M American women above 50 years of age. Despite the approval of anti-resorptive (bisphosphonates, denosumab, calcitonin and raloxifene) and bone-forming agents (teriparatide and abaloparatide), patients often exhibit poor compliance, limiting the market penetration of these drugs. Entera's strategy is to develop an oral biologic that retains the bone-building characteristics of the natural human PTH while simultaneously eliminating patient aversion to painful injections. If successful in the clinic, EB613 could take significant market share from FORTEO (originally developed and launched by Eli Lilly & Co.) and its biosimilar (developed by Pfenex, Inc.), in our view.

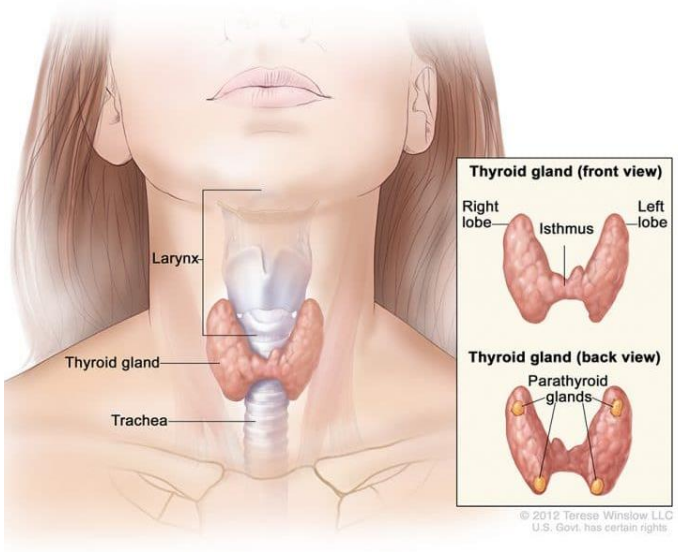
Entera's flagship oral human parathyroid hormone (1-34) stands to benefit from the multimodal MoA of PTH. In the present context, low PTH levels could increase osteoporosis risk, causing approximately 1.5 million disease-triggered fractures in elderly patients annually. When tested in the clinic, FORTEO increased bone mineral density and reduced fracture incidence, demonstrating efficacy. Oral EB613 (pharmacologically equivalent to FORTEO) retained comparable efficacy in Phase 2 studies, supporting continued advancement. Since Entera will be pursuing the risk-mitigated 505(b)(2) pathway, the company does not have to conduct the expensive bone fracture study, as it can rely on findings from the FORTEO clinical data package. The agreed-upon primary endpoint for EB613's Phase 3 program is BMD improvements, which, in our opinion, the agent would comfortably meet, given the solid effects observed on the lumbar spine, femur and total neck regions in Phase 2 studies.

In our view, Entera's osteoporosis program is differentiated from approved therapies (e.g., FORTEO and TYMLOS) and agents in development (e.g., a candidate called RT-102, which is currently in Phase 1 development). FORTEO and TYMLOS are both delivered subcutaneously, creating long-term discomfort and local irritation. Though RT-102 is an oral formulation (like EB613), the agent's efficacy profile remains to be established in the clinic. If approved, EB613's once-a-day oral formulation might take significant market share from FORTEO and TYMLOS and facilitate the possibility for new patients to avoid injectable biologics altogether. We also note that the osteoporosis target market clearly appears amply large enough to support multiple orally bioavailable biologic agents. The possibility for EB613 to reach the market as the first oral anabolic PTH-based drug could prove a powerful advantage from a commercial perspective.

Source: Entera Bio Ltd.

3. Pushing the Boundaries of Hypoparathyroidism Treatment With Oral EB612

Hypoparathyroidism



Hypoparathyroidism is a rare endocrine disorder that arises due to PTH deficiency. The hallmarks of the disease are hypocalcemia (low calcium levels), hyperphosphatemia (high phosphate levels) and hypercalciuria (high calcium in the urine).

Hypoparathyroidism (hypoPT) is a disease characterized by the body's inability to produce adequate circulating parathyroid hormone (PTH), which is a key signaling molecule produced by the parathyroid glands in the neck that regulates calcium homeostasis. Low PTH levels trigger a slew of mechanisms resulting in calcium imbalance in many body parts, including the bones, heart, kidneys, brain and nerves.

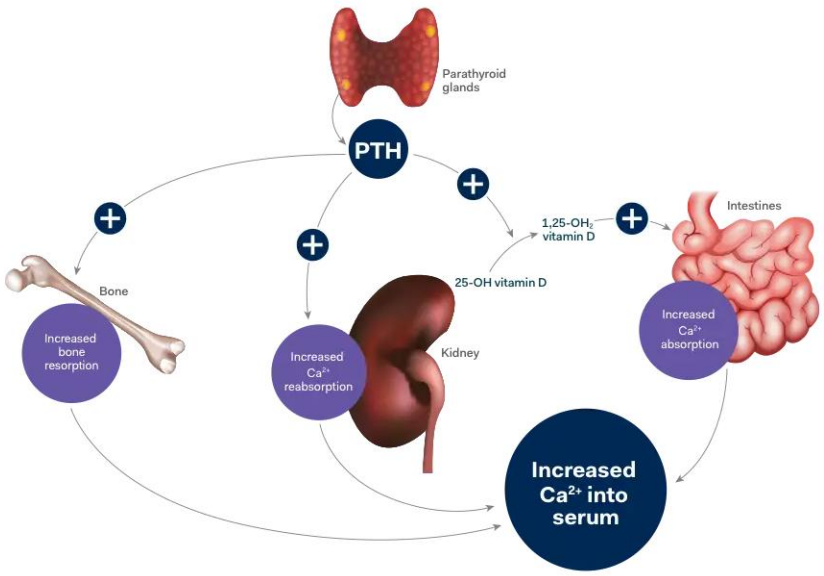
Though hypoPT is caused by many factors, including genetic, idiopathic and autoimmune deficiencies, epidemiological studies suggest that accidental thyroid removal or injury remains the critical causative factor. HypoPT is usually diagnosed and confirmed by lab tests, which typically involve analysis of serum calcium levels, intact PTH, phosphates, estimated glomerular filtration rate (eGFR), 25-O vitamin D and urine. Low bone turnover and reduced vitamin D concentration signify hypoPT.

HypoPT patients are often treated with oral calcium supplements and/or active Vitamin D or its analogs (e.g., calcitriol). However, dose titration is challenging in many patients, often resulting in poor efficacy and compliance. Importantly, since these agents fail to address the root cause of the disease, physicians find it challenging to control low bone turnover and renal complications. Accordingly, a hormone replacement therapy (HRT) that replenishes endogenous PTH levels is considered beneficial for hypoPT management.

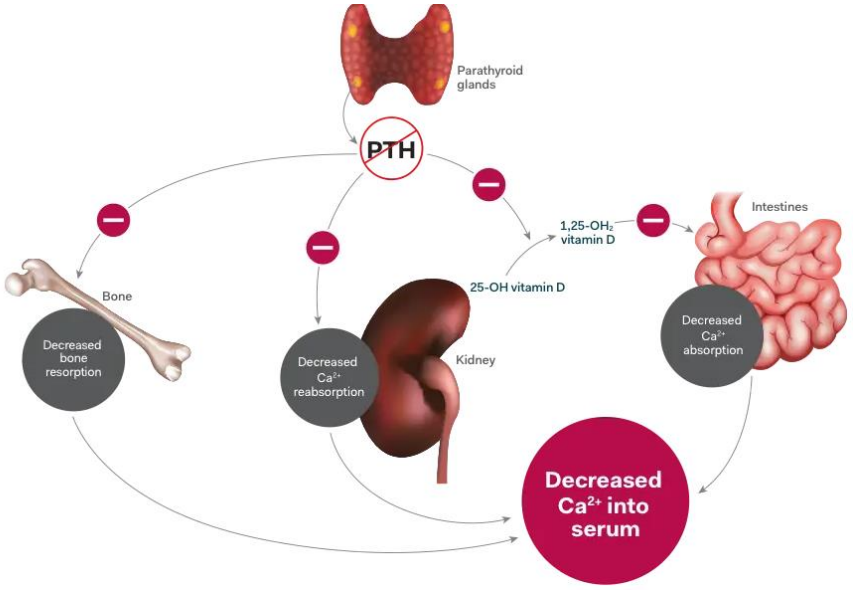
Source: Parathyroid UK.

Abnormal Regulation of Calcium Homeostasis Drives Hypoparathyroidism

Normal PTH Function



Abnormal PTH Function



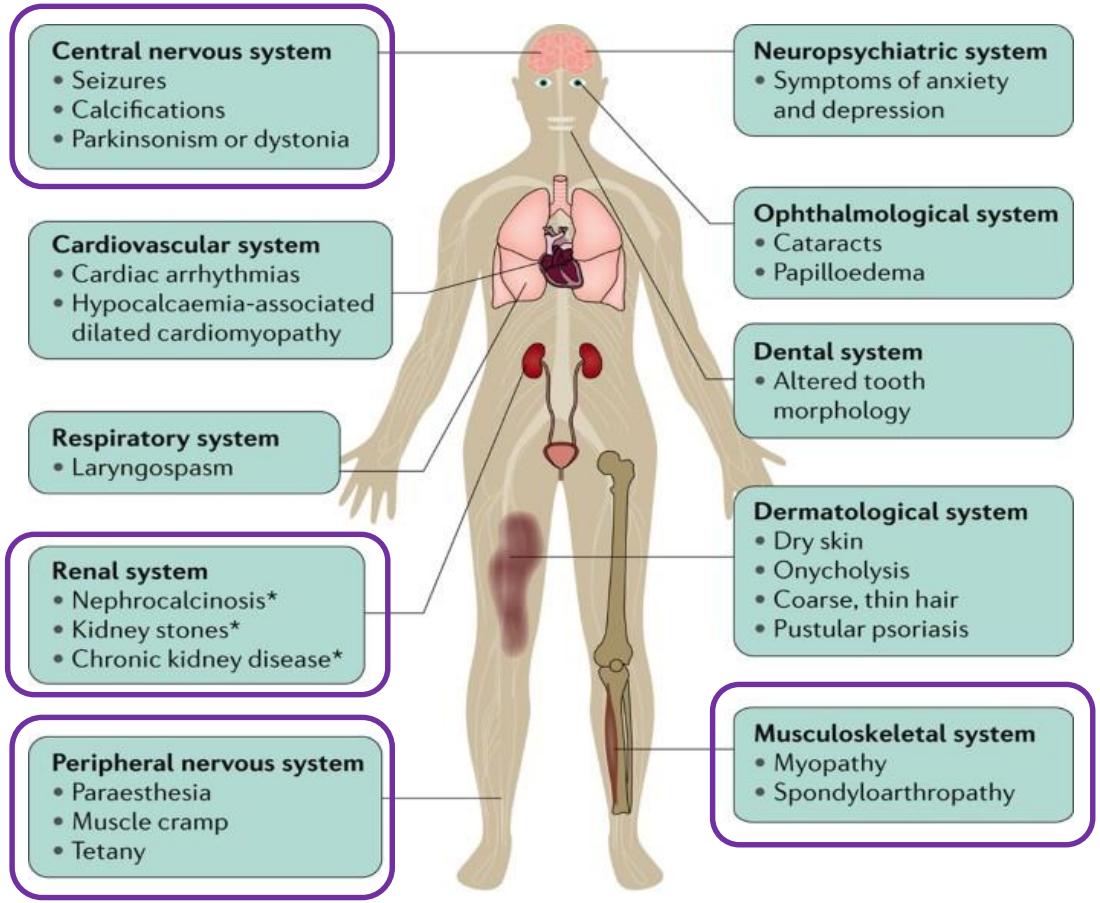
Parathyroid hormone (secreted by the parathyroid glands located in the neck) is the central signaling molecule that regulates active vitamin D synthesis and minerals (calcium, phosphate and magnesium) in bones, the kidneys and the intestines.

Hypoparathyroidism is a rare endocrine disorder borne out of deficiencies in PTH levels. Accordingly, hypoPT develops hypocalcemia and hyperphosphatemia, requiring intervention.

The defining theme of hypoparathyroidism is the presence of inappropriately low levels of circulating PTH, which triggers a slew of mechanisms resulting in decreased bone turnover, decreased renal reabsorption of calcium and decreased intestinal calcium absorption. Accordingly, PTH replacement is envisaged as a potential adjunct treatment to correct calcium imbalances, given that calcium and active vitamin-D supplements do not adequately address the root cause of the disease.

Source: www.natpara.com (accessed February 22, 2022).

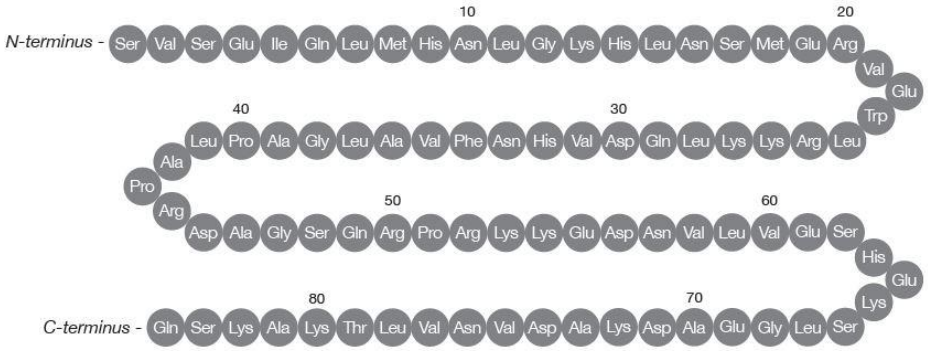
HypoPT Manifests in Multiple Clinical Symptoms That are Often Cumbersome to Both Patients and Treating Physicians



Most hypoPT patients experience neuromuscular irritability due to hypocalcemia, with accompanying tingling, muscle cramps and seizures (sometimes). Since hypoPT is a disorder of PTH, hypoPT patients experience long-term complications, including nephrocalcinosis (calcium deposition in the kidney), kidney stones and brain calcification.

Source: Mannstadt et al., Nature Reviews Disease Primers (2017).

The Curious Case of Natpara



Natpara remains the first and only FDA-approved PTH therapy for managing hypoPT in patients where SOC is ineffective. When tested in the clinic, Natpara produced sustained serum calcium concentration for up to 24h, demonstrating therapeutic benefits.

WARNING: POTENTIAL RISK OF OSTEOSARCOMA

See full prescribing Information for complete boxed warning.

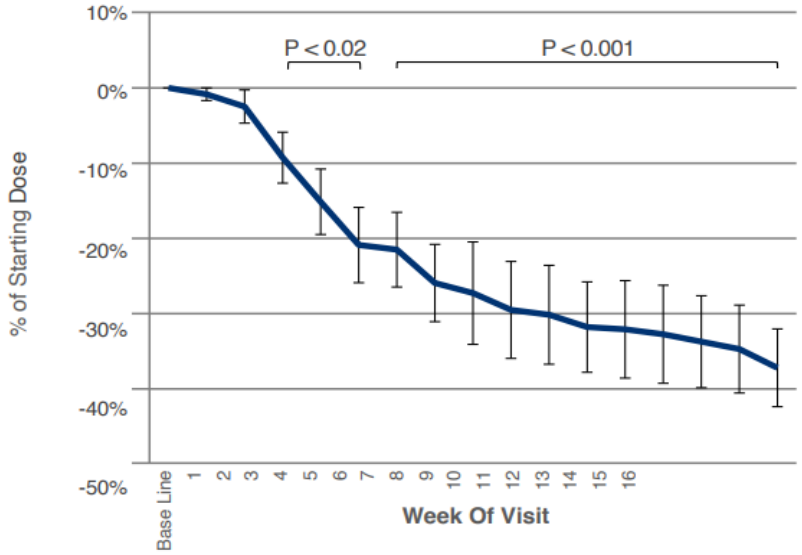
- **In male and female rats, parathyroid hormone caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. A risk to humans could not be excluded (5.1, 13.1)**
- **Because of the potential risk of osteosarcoma, prescribe NATPARA only to patients who cannot be well-controlled on calcium and active forms of vitamin D and for whom the potential benefits are considered to outweigh the potential risk. (1, 5.1)**
- **Avoid use of NATPARA in patients who are at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, patients with hereditary disorders predisposing to osteosarcoma or patients with a history of prior external beam or implant radiation therapy involving the skeleton) (5.1)**
- **NATPARA is available only through a restricted program called the NATPARA REMS Program (5.2)**

Natpara—originally developed by NPS Pharmaceuticals, later acquired by Shire (now Takeda)—is the recombination version of full-length human PTH shown to control hypocalcemia in adult hypoPT patients. The FDA approved the subcutaneous formulation of Natpara in 2015. However, its availability was regulated under the Risk Evaluation and Mitigation Strategy (REMS) Program to lower the potential risk of osteosarcoma (see the above black box warning).

In 2019, Takeda issued a mass recall of all doses of Natpara owing to manufacturing issues (specifically, the presence of rubber particulates). Takeda received a second Complete Response Letter (CRL) from the FDA in March 2022 as it attempted to relaunch the drug. Currently, the timeline for Natpara's return is unclear. Natpara's manufacturing issues and its restricted access through the REMS program may have significantly impacted its commercial outlook, in our view. This situation may have opened an opportunity for Entera Bio's EB612—an oral drug that mimics natural PTH produced by the body.

Source: www.natpara.com; FDA-authorized package insert.

In a Phase 2a Open-Label Study, Oral EB612 Demonstrated Efficacy Supporting its Continued Advancement



Attribute	Description
Stage	Phase 2a, open-label trial
Regimen	0.75mg QD EB612 (16 weeks)
Participants	19 subjects (15 subjects completed the study)
Objectives	Evaluation of safety, tolerability and preliminary efficacy in hypoPT patients
Key findings	42% reduction (p=0.001) from baseline in exogenous calcium dose; median serum phosphate levels decreased (23%; p=0.0003)

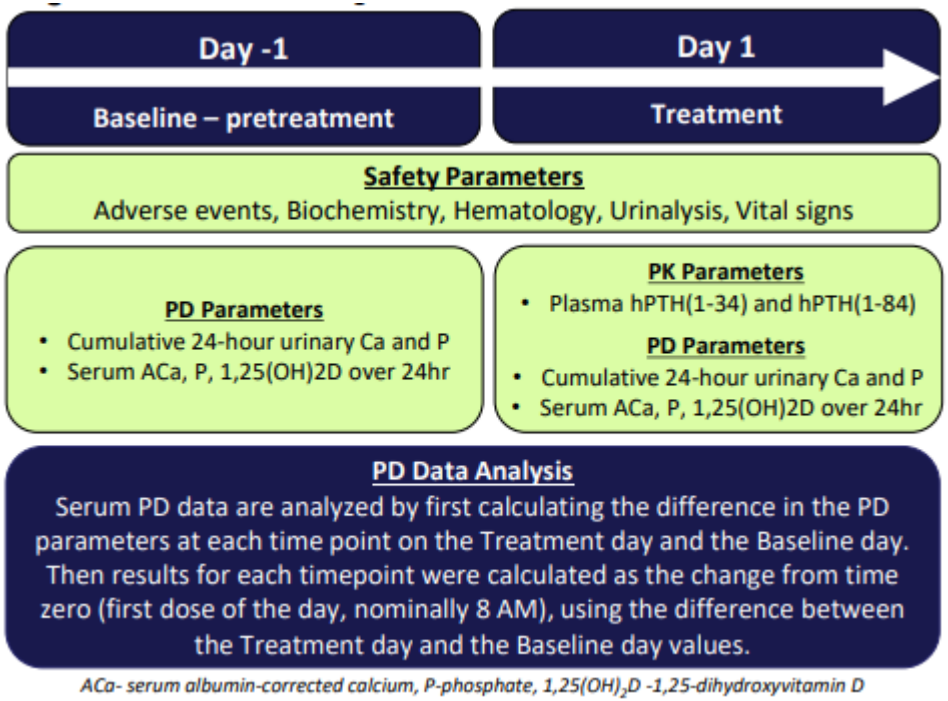
In 2015, Entera launched a Phase 2a open-label study to evaluate the suitability of EB612 in hypoPT patients whose disease characteristics were not controlled using SOC alone. In brief, the study enrolled 19 hypoPT patients, of which 15 were per protocol. The trial was conducted in Israel and was designed to obtain preliminary POC information in clinical settings and inform dose selection for subsequent studies.

The study's primary endpoint was a reduction in calcium supplement intake. As shown above, EB612 treatment demonstrated a significant reduction in calcium usage (42%; p=0.0001), decrease in serum phosphate levels (23%; p=0.0003; data not shown) and decrease in urine calcium excretion, suggesting potential therapeutic benefits to hypoPT patients.

From our vantage point, the Phase 2a findings with EB612 provided preliminary POC data in hypoPT patients while also supporting continued clinical development. While we acknowledge sample size limitations, shorter study duration (four weeks vs. Natpara's six weeks study) and the absence of a control arm, in our view the findings validate the suitability of Entera's oral biologics delivery platform for hypoPT patients.

Source: Ish-Shalom et al., Journal of Bone and Mineral Research (2021).

Entera's Second Phase 2 PK/PD Study Was Designed to Compare Safety, Efficacy and Tolerability Against Natpara



ACa- serum albumin-corrected calcium, P-phosphate, 1,25(OH)$_2$D -1,25-dihydroxyvitamin D

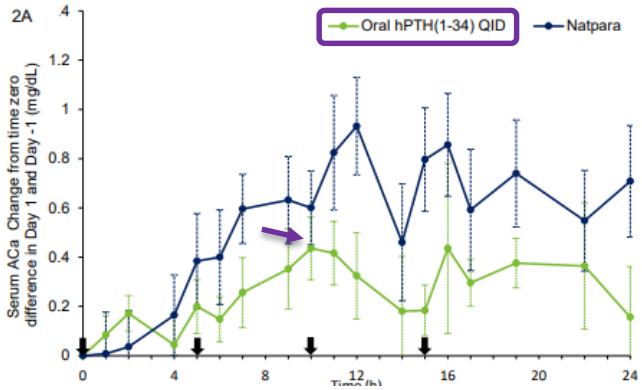
Treatment	Time of Dose			
	8:00	13:00	18:00	23:00
SC Natpara® 100 µg	7*	-	-	-
Oral hPTH(1-34) TID 0.75 mg	8	-	8	7*
Oral hPTH(1-34) BID 2.25 mg	8	-	8	-
Oral hPTH(1-34) TID 2.25 mg	8	-	8	8
Oral hPTH(1-34) QID 2.25 mg	8	8	8	7*

Number of Patients	Age *Mean (range) - yr*	Male / Female	Serum ACa *Mean (range) - mg/dL*	Serum Phosphate *Mean (range) - mg P/dL*	Serum 1,25(OH)$_2$D *Mean (range) - ng/L*
16	**46** (18-63)	**4 / 12**	**7.9** (6.6-10.2)	**4.8** (3.6-6.5)	**33.7** (7.5-73.5)

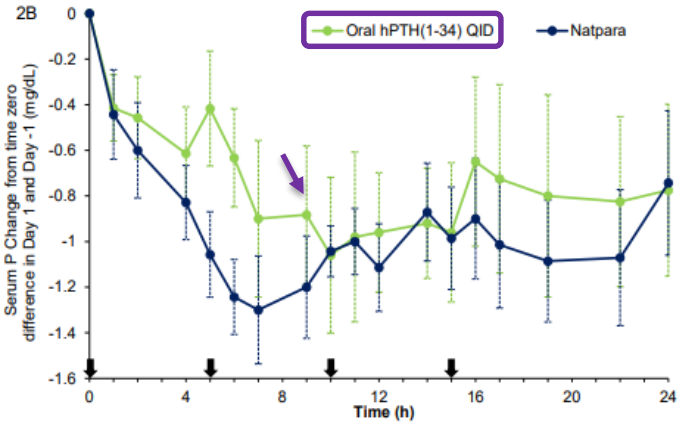
Following successful completion of the open-label Phase 2a study, which yielded positive data as shown earlier, Entera launched a two-part Phase 2 pharmacokinetic and pharmacodynamic (PK/PD) study to validate the target product profile of EB612 against the active comparator Natpara.

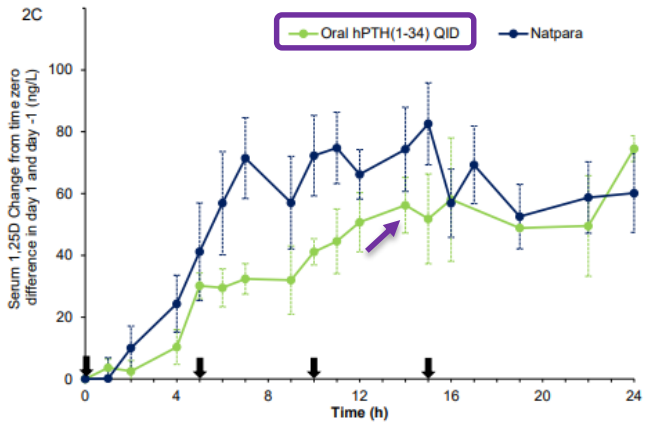
Source: Caraco et al., ASMBR (2019); Entera Bio Ltd.

EB612 Demonstrated Efficacy Across the Board, With an Efficacy Profile Similar to FDA-Approved Natpara



Treatment	N	Serum ACa $\Delta AUEC_{0-24}$ (h*mmol/L)	Serum P $\Delta AUEC_{0-24}$ (h*mg/dL)	Serum 1,25(OH)$_2$D $\Delta AUEC_{0-24}$ (h*ng/L)
Natpara®	7	**3.2** ± 0.9	**-23** ± 4	**1290** ± 207
TID 0.75mg	5	**-0.3** ± 0.8	**4.2** ± 6	**116** ± 148
BID 2.25mg	7	**0.9** ± 0.7	**-11** ± 5	**393** ± 60
TID 2.25mg	8	**-0.1** ± 1.0	**-12** ± 2	**692** ± 112
QID 2.25mg	4	**1.9** ± 0.9	**-19** ± 7	**962** ± 134





Treatment with EB612 (2.25mg QD for one day) increased serum albumin-corrected calcium and active vitamin-D while decreasing serum phosphate and urinary calcium excretion. The initial efficacy profile compares favorably to Natpara, warranting a large Phase 2b/3 study under controlled conditions, in our view. Importantly, Entera is evaluating additional EB612 formulations—i.e., twice-daily (BID) or thrice-daily (TID) in lieu of once-daily (QD) used in two Phase 2 studies). A PK study is slated to start in 1H23, with a possible Phase 2b/3 study initiation in 2H23.

Source: Caraco et al., ASMBR (2019); Entera Bio Ltd.

A Closer Look at the HypoPT Competitive Landscape Suggests Oral EB612 is Well-Differentiated From its Peers

Sponsor	Drug	Route	Rationale	Current Status	Comments
Takeda	Natpara	Injectable	Synthetic PTH[1-84]	Approved	Product recalled in the U.S. due to manufacturing issues
Ascendis Pharma	TransCon PTH	Injectable	Extended-release PTH [1-34]	NDA submitted to FDA	Produced solid Phase 3 data; NDA filing anticipated in 3Q22 with potential U.S. approval in 2023
BridgeBio Pharma	Encaleret	Oral	Calcium-sensing receptor antagonist	Phase 3 ready	Full Phase 2 data anticipated in 1H22; interim findings revealed normalized blood and urine calcium
Entera Bio	EB612	Oral	Oral PTH[1-34]	Phase 2 completed; additional formulation activities ongoing	Oral EB612 produced positive results in two Phase 2 studies, demonstrating drug efficacy
Amolyt Pharma	AZP-3601	Injectable	Long-acting PTH analog	Phase 2-ready	Phase 1 data suggest dose-dependent increase in serum calcium levels
Chugai Pharmaceutical Co.	PC0371	Oral	Parathyroid hormone 1 receptor (PTH1R) agonist	Phase 1	PC0371 treatment increased bone turnover and restores calcium levels; being developed ex-U.S.
Aeterna Zentaris	AEZS-150	Injectable	Delayed clearance formulation of parathyroid hormone fusion polypeptide	Preclinical	Technology licensed from The University of Sheffield, UK

While oral calcium supplements and vitamin D analogs are crucial in managing hypoPT, they do not sufficiently compensate for low endogenous PTH levels. In addition, though Natpara (Takeda) demonstrated promise in correcting calcium deficiencies and was approved for use in 2015, the product was recalled in 2019 due to manufacturing issues and currently remains off the market. These situations indicate that SOC remains inadequate for hypoPT patients.

Of the six candidates being developed for hypoPT patients, Ascendis Pharma's TransCon PTH leads the race with promising Phase 3 data (see next slide). To some investors, it might appear Entera is restarting its EB612 program by focusing on a new multi-dose oral formulation (BID vs. QD used in two previous Phase 2 studies). However, we do not anticipate significant setbacks in the clinical development, as the agent has already demonstrated safety and efficacy in hypoPT patients.

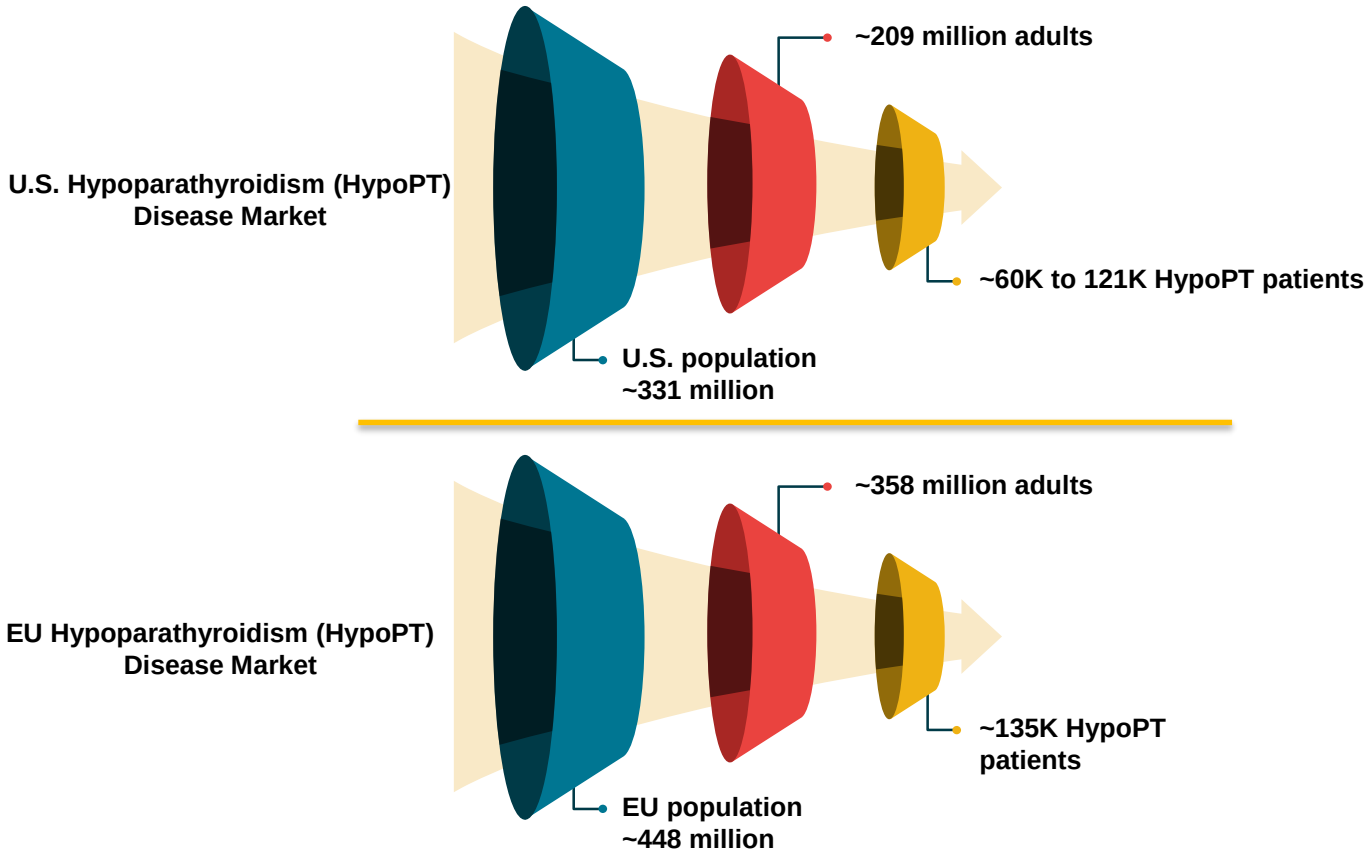
Source: Biomedtracker; H.C. Wainwright & Co. equity research.

We Predict a Three-Horse Race in HypoPT Treatment; Route of Administration and Clinical Data Strength Shall Determine the Ultimate Winner

	TransCon PTH	Encaleret	EB612
Sponsor	Ascendis Pharma	BridgeBio	Entera Bio
Modality	Hormone	Small molecule	Short version of the natural hormone
Indication (Stage)	Hypoparathyroidism (hypoPT)	Autosomal Dominant Hypocalcemia type 1 (ADH1), a rare form of hypoPT	HypoPT
MoA	Long-acting PTH delivered using TransCon technology	Calcium-sensing receptor antagonist	PTH delivered using company's proprietary oral biologics platform technology
Route (regimen)	Subcutaneous injection (QD) for 26 weeks	Oral (QD) for 24 weeks	Oral (QD) for 16 weeks; new oral formulation could involve twice-daily (BID) regimens
Status	NDA stage	Phase 3	Phase 2A & Phase 2B complete; new formulation will be tested in healthy volunteers in 2H22 with a possible Phase 2B/3 pivotal study initiation in 2023
Top-line clinical data	In the Phase 3 PaTHway trial, TransCon PTH-treated patients showed a response rate of 78.7% vs. 4.8% for placebo control (p<0.0001) after 26 weeks Statistically significant decreases in patient-reported, disease-specific physical (p=0.0038) and cognitive symptoms (p=0.0055), disease impact (p=0.0046) and daily life (p=0.0061)	In a Phase 2 trial at 24 weeks of encaleret treatment, 92% (12/13) of participants achieved normal trough blood calcium levels in the absence of extra-dietary calcium supplements and active vitamin D; 77% (10/13) of subjects had normal urinary calcium excretion	In a Phase 2a trial (open-label), EB612 achieved a 42% reduction (p=0.001) from baseline in exogenous median calcium dose; in addition, median serum phosphate levels decreased by 23% (p=0.0003). In a second Phase 2 study, EB612 produced similar biological effects to those observed with Natpara administered at 100µg QD (highest approved dose)
Next Steps	NDA submitted to FDA in 3Q22 and MAA filing slated for 4Q22 U.S. approval decision in 2023	Phase 3 initiation in 2H22	Initiate human PK assessment using new EB612 formulation in 1H23; possible Phase 2b/3 study initiation in 2H23
Unique value proposition	Once-daily hormonal therapy via injection; robust Phase 3 data	Oral formulation with customizable-dosing option (BID or TID); Phase 2 data comparable to Natpara	Once-daily oral formulation; solid Phase 2 data; novel MoA

Source: Company reports; H.C. Wainwright & Co.

U.S. Hypoparathyroidism Market Segmentation



Market estimates suggest that there are over 80K hypoPT patients in the U.S. and 135K in the EU. Though Entera Bio is a small firm that operates under lean principles, we expect the company to self-commercialize EB613 using a targeted sales force, given the fact that this indication involves a concentrated prescriber base and is classified as an orphan disease. From our vantage point, EB613 could prove particularly lucrative for Entera as revenues generated by this product could fall to the bottom line while royalty-based revenue from a partnership on EB612 alone could easily drive profitability. We also believe success with both EB612 and EB613 may make Entera an attractive acquisition target.

Source: H.C. Wainwright & Co. estimates.

We Predict an Attractive Niche Opportunity for EB612 in Hypoparathyroidism

The hallmark of hypoparathyroidism (hypoPT) is low levels of PTH, resulting in abnormal mineral homeostasis (diagnosed using blood and urine tests). Thus, the treatment goal is to bring the minerals' levels to an acceptable range, though this has not been satisfactorily achievable using supplementation with oral calcium or vitamin D and/or its analogs. The only FDA-approved in the space—Natpara (Takeda), daily life-long injections—has been recalled due to fears of particulates from the covering or septum; it currently remains unclear when Natpara will return to the market. In our view, hypoPT patients are caught between the devil and the deep blue sea as effective agents are not accessible to alleviate their disease burden.

Entera Bio is developing oral EB612 as a 1L hormone therapy targeting patients with different levels of disease severity. Importantly, when tested in two Phase 2 studies, a combination regimen involving EB612 and SOC resulted in a statistically significant decline in supplemental calcium usage and a lowered serum phosphate. From our vantage point, EB612 could be an effective and convenient treatment option, given the needle fears of several patients that limit compliance. Entera is working on an improved formulation that must show safety in healthy volunteers (a new PK study is slated to start in 1H23) to support entry into a single Phase 2b/3 pivotal study.

Given the uncertainty around Natpara, we recognize at least two competitors for EB612, namely TransCon PTH (Ascendis Pharma) and encaleret (BridgeBio).TransCon PTH is a sustained-release prodrug that provides stable PTH for 24 hours/day. In Phase 3, TransCon PTH demonstrated a response rate of ~79% (vs. only 4.8% for placebo; p-value <0.0001) while simultaneously reducing calcium usage and eliminating active vitamin D intake. In our view, TransCon PTH—despite being a once-a-day injection—has set a very high efficacy threshold for follow-on entrants such as Entera Bio's EB612 and BridgeBio's encaleret (Phase 3 ready). In our view, however, patients prefer oral formulations (vs. once-daily life-long injections), provided that the efficacy magnitude is not enormously dissimilar. We do not think Entera needs to directly match TransCon PTH's efficacy in order to be commercially viable, as the convenience advantage of oral delivery should facilitate market adoption.

Source: Entera Bio Ltd.

4. Multiple Additional Programs May Drive Considerable Optionality

Program	Indication	Scientific Rationale	Current Status	# of U.S. Patients	Comments
PTH[1-34]	Non-union fractures	Oral PTH[1-34] to accelerate bone healing in non-union fractures	Preclinical	Over 300K per year	Possible POC clinical program to be conducted near-term; no pharmacological treatment has ever been approved in this indication
GLP-2	Short bowel syndrome (SBS)	Oral analog of glucagon-like peptide-2 (GLP-2)	Preclinical	10K to 20K patients	GATTEX (generic name: teduglutide), the only drug approved to treat SBS, garnered global sales of $676 million in 2021
hGH	Growth hormone deficiency	Hormone replacement therapy	Preclinical	4K to 6K children; Over 50K adults	*In vivo* POC testing to be completed

Entera's flagship oral human parathyroid hormone (1-34) stands to benefit from the multimodal MoA of PTH, with optionality in treating non-union fractures. We note that nearly 5 – 10% of all fractures do not heal promptly, underscoring challenges presented to patients and treating orthopedic surgeons. Although Entera is currently focused on its core osteoporosis and hypoPT programs, the company could conduct a proof-of-concept study in order to demonstrate the applicability of EB613 in non-union fractures as well.

Separately, on February 8, 2021, Entera Bio officially announced its intention to develop an oral analog of glucagon-like peptide-2 (GLP-2) to treat short bowel syndrome (SBS). We inform investors that SBS is characterized by the body's inability to absorb sufficient nutrients from the food due to the small intestine size. GATTEX (injectable GLP-2 analog; Takeda) is the only FDA-approved drug to treat SBS in children and patients, though SBS patients prefer an oral drug over the injectable version, in our view. Per management, POC animal testing is in progress.

Although initial preclinical evidence is emerging, we believe that investors shall likely view the above-mentioned preclinical assets as speculative call options at this juncture due to the absence of human POC data. Accordingly, we have not included these assets in our valuation model. We note that both preclinical and clinical success with any of these programs could drive meaningful upside to our assumptions.

Source: Entera Bio Ltd.

5. Collaboration With Amgen Provides a Proxy for Platform Validation

Initial Terms	Deal Value	Sales-Related Royalty
• Technology access fee of $725K • Entera Bio will be responsible for preclinical development activities at Amgen's expense • Amgen will handle all the clinical development, manufacturing and commercialization responsibilities for any of the resulting programs	Up to ~$270 million in total potential milestones	Tiered royalties up to mid-single digits, should Amgen decide to continue to advance the programs through regulatory approval and commercialization

In 2018, Entera Bio entered into a research collaboration agreement with Amgen—a leader in discovering and developing biological drugs—to advance the development of oral biologics for treating inflammatory diseases and other serious illnesses. The collaboration details are shown above (potential deal value: up to $270 million in milestones alone).

In our view, the Amgen collaboration legitimizes and further validates Entera's oral biological drug discovery platform, though investors will be keenly looking for specific value inflection points in the near term as the program was originally announced three years ago. Furthermore, given that Amgen's collaboration involves a non-PTH agent as an API, a successful outcome could position Entera Bio to attract additional partnerships, in our view.

Entera Bio's research collaboration agreement with Amgen opens doors to non-dilutive financing options that may be favorable to the company's shareholders, in our view. Investors should note that we do not include any contributions from this partnership in our valuation assessment; future inflection points may therefore drive upside to our assumptions.

Source: Entera Bio Ltd.

6. Broad and Solid Intellectual Property Portfolio

Selected Patents

Patent Number	Item	Title	Projected Expiration Dates
US9186412B2	Platform	Methods and compositions for oral administration of insulin	2029
US10583177B2	Platform	Formulations for oral administration of active agents	2035
AU2014218446B2	EB612	Methods and compositions for oral administration of proteins	2033
IL253802D0	EB613	Treatment of osteoporosis	2036
US20180036234A1	Non-union fractures	Treatment of bone fractures and defects	2035

Entera Bio relies upon a combination of patents, trade secrets, proprietary know-how and continuing technological innovations to advance the utility of its assets. These patents are slated to expire between 2029 and 2036.

From our perspective, Entera Bio's intellectual property (IP) pedigree should allow efficient product positioning and lengthy commercial windows with market exclusivity, while simultaneously maximizing competitive differentiation in pertinent markets.

We would point out that formulation patent protection—particularly in a situation where the route of administration is being meaningfully altered (e.g., from injectable to oral)—typically proves robust and difficult for generics firms to overturn. In addition, we believe that investors should be aware of the fact that Entera Bio benefits from what we consider a highly favorable licensing arrangement with Oramed Pharmaceuticals. In 2011, Entera Bio entered into a patent transfer agreement with Oramed, pursuant to which Oramed assigned to Entera Bio all of its rights, title and interest in the patent rights that Oramed had originally licensed to Entera Bio when Entera Bio was initially organized, subject to a worldwide, royalty-free, exclusive, irrevocable, perpetual and sub-licensable license granted to Oramed under the assigned patent rights to develop, manufacture and commercialize products or otherwise exploit such patent rights in the fields of diabetes and influenza. Entera Bio also agreed not to engage in any activities in the fields of diabetes and influenza. In addition, Entera Bio agreed to pay Oramed royalties equal to 3% of the net revenues generated, directly or indirectly, from exploitation of the assigned patent rights, including the sale, lease or transfer of the assigned patent rights or sales of products or services covered by the assigned patent rights. We have projected EBIT margins that account for Entera Bio's royalty obligations to Oramed, but from our vantage point the royalty due to Oramed is *de minimis*.

Source: Entera Bio, Ltd.

7. An Experienced Leadership Team With Clearly Relevant Expertise

Miranda Toledano
Chief Executive Officer, Director

- Over 20 years of C-level executive, principal investment & banking expertise
- Served as a COO, CFO and Director of TRIGR Therapeutics (acquired by Compass Therapeutics)
- Headed healthcare investment banking at MLV & Co. (subsequently acquired by FBR Capital Markets, now B. Riley FBR)
- Formerly Vice President in Royalty Pharma's investment group

Dana Yaacov-Garbeli, CPA, M.B.A.
Chief Financial Officer

- Previously served as Senior Manager at PwC Israel. Ms. Yaacov-Garbeli is also a partner at A2Z-Finance, which provides financial and accounting services.
- B.A in accounting and business management and M.B.A. in financial management from The College of Management and Academic studies.
- Certified Public Accountant in Israel.

Dr. Hillel Galitzer
Chief Operating Officer

- Dr. Galitzer has over a decade of experience in medical research and molecular biology
- Served as Chief Operating Officer at Hadasit Bio Holdings Ltd., a publicly traded subsidiary of the Hadassah University Hospital
- Ph.D. from the Hebrew University Medical School in Jerusalem, and M.B.A. from Bar-Ilan University in Israel

Dr. Arthur Santora
Chief Medical Officer

- Dr. Santora has over 30 years of experience, a majority of which was obtained at Merck & Co., wherein he led the development of Fosamax and Fosamax Plus D
- He had a brief career at the FDA following his NIH fellowship
- Dr. Santora was awarded an M.D. degree and a Ph.D. in biochemistry from Emory University in Atlanta, GA

Gerald Lieberman
Chairman of the Board

- Mr. Lieberman is an accomplished leader with several years of experience in finance, risk management, human capital development, succession planning and compensation
- Received a B.S. Beta Gamma Sigma with honors in business from the University of Connecticut

Dr. Roger Garceau
Chief Development Officer, Director

- Dr. Garceau has over 30 years of pharma industry experience
- Prior to joining Entera, he served as Chief Medical Officer and Executive Vice President of NPS Pharma (now Takeda)
- Dr. Garceau holds B.S. from Fairfield University in Fairfield (CT) and an M.D. from the University of Massachusetts Medical School

We believe that Entera's management team and board of directors collectively possess an extensive and successful track record of clinical development, marketing and sustained revenue growth. We also believe that the team has the pertinent scientific and financial expertise to advance the company's clinical and preclinical development programs and continue to identify other applications for Entera's technology platform.

Source: Entera Bio, Ltd.

III. Financials

Market Models

EB613 (Osteoporosis) U.S.	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040
U.S. population ('000)	339,509	341,207	342,913	344,628	346,351	348,082	349,823	351,572	353,330	355,096	356,872	358,656	360,450	362,252	364,063
U.S. population growth rate 0.5%	*0.5%*	*0.5%*	*0.5%*	*0.5%*	*0.5%*	*0.5%*	*0.5%*	*0.5%*	*0.5%*	*0.5%*	*0.5%*	*0.5%*	*0.5%*	*0.5%*	*0.5%*
U.S. population 50 or older ('000)	101,853	102,362	102,874	103,388	103,905	104,425	104,947	105,472	105,999	106,529	107,062	107,597	108,135	108,676	109,219
	30.0%	*30.0%*	*30.0%*	*30.0%*	*30.0%*	*30.0%*	*30.0%*	*30.0%*	*30.0%*	*30.0%*	*30.0%*	*30.0%*	*30.0%*	*30.0%*	*30.0%*
Osteoporosis women patients (U.S. population; '000)	8,148	8,189	8,230	8,271	8,312	8,354	8,396	8,438	8,480	8,522	8,565	8,608	8,651	8,694	8,738
Incidence rate 8%	*8.0%*	*8.0%*	*8.0%*	*8.0%*	*8.0%*	*8.0%*	*8.0%*	*8.0%*	*8.0%*	*8.0%*	*8.0%*	*8.0%*	*8.0%*	*8.0%*	*8.0%*
Number of women patients diagnosed ('000)	1,793	1,802	1,811	1,820	1,829	1,838	1,847	1,856	1,866	1,875	1,884	1,894	1,903	1,913	1,922
Treatment rate 22%	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*
Patients treated with EB613	1,434	14,413	34,401	47,310	64,006	82,704	103,436	126,228	141,784	163,117	154,511	142,028	131,319	109,023	82,657
Penetration rate (%)	*0.1%*	*0.8%*	*1.9%*	*2.6%*	*3.5%*	*4.5%*	*5.6%*	*6.8%*	*7.6%*	*8.7%*	*8.2%*	*7.5%*	*6.9%*	*5.7%*	*4.3%*
Annual price of treatment ($)	$10,000	$10,300	$10,609	$10,927	$11,255	$11,593	$11,941	$12,299	$12,668	$13,048	$13,439	$13,842	$14,258	$14,685	$15,126
Annual inflation rate (%)	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*
Sales of EB613 in the U.S. ($MM)	**$14**	**$148**	**$365**	**$517**	**$720**	**$959**	**$1,235**	**$1,552**	**$1,796**	**$2,128**	**$2,077**	**$1,966**	**$1,872**	**$1,601**	**$1,250**

EB612 (Hypoparathyroidism) U.S.	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040
U.S. population ('000)	339,509	341,207	342,913	344,628	346,351	348,082	349,823	351,572	353,330	355,096	356,872	358,656	360,450	362,252	364,063
U.S. population growth rate 0.5%	*0.5%*	*0.5%*	*0.5%*	*0.5%*	*0.5%*	*0.5%*	*0.5%*	*0.5%*	*0.5%*	*0.5%*	*0.5%*	*0.5%*	*0.5%*	*0.5%*	*0.5%*
Hypoparathyroidism prevalence	67,902	68,241	68,583	68,926	69,270	69,616	69,965	70,314	70,666	71,019	71,374	71,731	72,090	72,450	72,813
Incidence rate 0.02%	*0.02%*	*0.02%*	*0.02%*	*0.02%*	*0.02%*	*0.02%*	*0.02%*	*0.02%*	*0.02%*	*0.02%*	*0.02%*	*0.02%*	*0.02%*	*0.02%*	*0.02%*
Patients treated with EB612	54	1,638	3,086	4,756	6,442	9,537	11,544	14,133	12,225	10,085	8,636	7,030	5,263	3,260	2,257
Penetration rate(%)	*0.1%*	*2.4%*	*4.5%*	*6.9%*	*9.3%*	*13.7%*	*16.5%*	*20.1%*	*17.3%*	*14.2%*	*12.1%*	*9.8%*	*7.3%*	*4.5%*	*3.1%*
Annual price of treatment ($)	$20,000	$20,600	$21,218	$21,855	$22,510	$23,185	$23,881	$24,597	$25,335	$26,095	$26,878	$27,685	$28,515	$29,371	$30,252
Annual inflation rate (%)	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*
Sales of EB612 in the U.S. ($MM)	**$1**	**$34**	**$65**	**$104**	**$145**	**$221**	**$276**	**$348**	**$310**	**$263**	**$232**	**$195**	**$150**	**$96**	**$68**

Source: Company reports and H.C. Wainwright & Co. estimates.

Valuation

Entera Bio Ltd. ($MM except amount per share)	Product	Launch Year	Patent Expiry	Peak Sales	Probability To Launch	NPV	Amount Per Share
Product Portfolio							
Osteoporosis	**EB613**	2026	2036	$2,128	50%	**$465**	$10.00
Hypoparathyroidism (hypoPT)	**EB612**	2026	2033	$348	30%		
Projected enterprise value						$465	$10.00

- Using a 15% discount rate and 3% terminal rate of decline, our discounted cash flow (DCF)-based analysis has resulted in an estimated enterprise value of approximately $400 million. We believe that our discount rate assumption is conservative, considering the substantial size and well-established nature of the target markets in both osteoporosis and hypoparathyroidism. Similarly, we believe that our 3% terminal rate of decline is reflective of the status of the company's intellectual property (IP) estate and what we project to be reasonable commercial windows for EB613 and EB612. Investors should note that Entera Bio also has earlier-stage programs that we do not include in our valuation assessment. We have assumed that Entera Bio would self-commercialize both of its lead programs in the U.S. and establish partnerships in order to launch the drug in ex-U.S. territories. However, we conservatively do not factor any ex-U.S. revenues into our current assumptions. In addition, investors should be aware that if Entera Bio were to successfully consummate a licensing transaction on EB613 with a more established company involving attractive economics, the overall franchise could turn out to be significantly larger than we have projected and Entera Bio would not need to fund the late-stage development and commercialization expenses associated with EB613 on its own.
- The company has no outstanding debt. Assuming roughly 47.7 million fully-diluted shares outstanding as of mid-2023, this leads to a 12-month price objective of $10 per share, which excludes the current cash.
- Although we have forecasted some generic erosion starting in 2036 for EB613 and starting in 2034 for EB612, we note that there are multiple layers to Entera Bio's patent estate and EB612 in particular would likely benefit from specific market exclusivity periods in both the U.S. and Europe as a potential orphan drug. Accordingly, our projections with respect to the timing of generic erosion may prove conservative as well.

Source: Company reports and H.C. Wainwright & Co. estimates.

Discounted Cash Flow Analysis

Fiscal Year Ending	12/31/2022	12/31/2023	12/31/2024	12/31/2025	12/31/2026	12/31/2027	12/31/2028	12/31/2029	12/31/2030	12/31/2031	12/31/2032	12/31/2033	12/31/2034	12/31/2035
Revenue ($MM)	**$0.3**	**$0.4**	**$0.7**	**$1.1**	**$7.5**	**$84.3**	**$202.1**	**$289.7**	**$403.7**	**$545.7**	**$700.2**	**$880.5**	**$991.0**	**$1,143.1**
EBIT	**($17)**	**($33)**	**($38)**	**($56)**	**($70)**	**($12)**	**$91**	**$130**	**$182**	**$246**	**$315**	**$396**	**$446**	**$514**
Less: Taxes	$0	$0	$0	$0	$0	$0	($21)	($30)	($42)	($56)	($72)	($91)	($103)	($118)
Debt-Free Earnings	**($17)**	**($33)**	**($38)**	**($56)**	**($70)**	**($12)**	**$70**	**$100**	**$140**	**$189**	**$243**	**$305**	**$343**	**$396**
Less: Capital Expenditures	($0)	($0)	($0)	($0)	($0)	($3)	($6)	($9)	($12)	($16)	($21)	($26)	($30)	($34)
Less: Working Capital Requirements	$0	($0)	($0)	($0)	($0)	($2)	($4)	($3)	($3)	($4)	($5)	($5)	($3)	($5)
Add: Depreciation and Amortization	$0	$0	$0	$0	$0	$2	$4	$6	$8	$11	$14	$18	$20	$23
Total Net Investment	**$0**	**($0)**	**($0)**	**($0)**	**($0)**	**($3)**	**($6)**	**($6)**	**($7)**	**($10)**	**($12)**	**($14)**	**($13)**	**($16)**
Net Debt-Free Cash Flows:	**($17)**	**($33)**	**($38)**	**($56)**	**($70)**	**($15)**	**$64**	**$95**	**$132**	**$179**	**$231**	**$291**	**$330**	**$380**
Discount Period	0.32	1.32	2.32	3.32	4.32	5.32	6.32	7.32	8.32	9.32	10.33	11.33	12.33	13.33
Discount Factor 15.0%	0.96	0.83	0.72	0.63	0.55	0.48	0.41	0.36	0.31	0.27	0.24	0.21	0.18	0.16
PV of Net Debt-Free Cash Flows:	**($16)**	**($28)**	**($27)**	**($35)**	**($38)**	**($7)**	**$27**	**$34**	**$41**	**$49**	**$55**	**$60**	**$59**	**$59**

DCF Assumptions

Discount Rate	15.0%
Tax Rate	23.0%

Growth Rate

Discount Rate	-7.0%	-5.0%	-3.0%	-1.0%	1.0%
11.0%	820	843	872	911	966
13.0%	605	618	635	656	684
15.0%	448	456	465	477	492
17.0%	331	335	341	348	357
19.0%	242	245	248	253	258

Perpetuity Growth Assumptions

2041 Cash Flow (-3.0% Growth Rate)	$216.1
Growth Rate	(0.03)
Terminal Value	**$1,200**
Discount Period	19.33
Discount Factor @ 15.0%	0.07
PV of Terminal Value	**$81**

Distribution of Value

Period Cash Flow	82.7%
Terminal Cash Flow	17.3%
Total	100.0%

Source: Company reports and H.C. Wainwright & Co. estimates.

Financial Review and Outlook

Revenue

We do not project any revenue in 2022 or 2023. In our view, Entera Bio may only begin generating revenue upon approval of EB613 in the U.S. for treatment of osteoporosis or approval of EB612 in the U.S. for treatment of hypoparathyroidism, which may occur in 2026 according to our projections.

Operating expenses

We forecast total R&D spending of $8.6 million in 2022, rising to $25 million in 2023. This reflects the expenses associated with conducting at least one pivotal Phase 3 program with EB613 in osteoporosis, as well as ongoing spending associated with the advancement of earlier-stage pipeline programs, including the initiation of a putative Phase 2b/3 program with EB612. Our assumptions also include G&A spending of $8.4 million in 2022 and $8 million in 2023.

Share Count

Entera Bio closed 2Q22 with 28.8 million shares of common stock outstanding. The company also has roughly 5.8 million options and just under a million warrants to purchase common stock outstanding.

Balance Sheet

As of June 30, 2022, Entera Bio had roughly $17.3 million in cash and equivalents on its balance sheet. We expect these resources to be sufficient to fund operations at least into 2Q23.

Gross Margin

In our view, Entera Bio's lead candidates ought to enjoy typical gross margins associated with peptidic drugs, which generally are from 85% to 90%. We have forecast gross margins in the >85% range.

Taxes

Entera Bio is headquartered in Jerusalem, Israel. We therefore project an effective tax rate of 23%, which corresponds to the Israeli statutory federal corporate income tax rate. Investors should note that Entera Bio may qualify for an extended period of treatment as an emerging enterprise, which would enable the application of a much lower effective tax rate for up to 10 years. However, we do not apply this consideration in our forecasts or valuation assessment.

EPS

We project a net loss of $0.55 per share in 2022 and a net loss of $0.80 per share in 2023. In our view, Entera Bio may not generate earnings until 2027.

Cash Flow

We expect Entera Bio to remain cash flow-negative for the foreseeable future, as it continues the clinical development of its lead candidates. The company may only begin to generate positive cash flow from operations in 2027, following the U.S. launch of its lead assets. This is contingent upon continued success in clinical development with EB613 and EB612.

Investment Risks

Financial outlook risk

Entera Bio has never been a profitable company. There is no guarantee that it will ever become profitable, even if its lead candidates are approved. The company may need to raise further capital in the future in order to fund operations.

Competitive landscape risk

Entera Bio is an emerging player in the niche oral biologicals space. Although we find the preclinical and initial clinical data encouraging, this cannot be considered a guarantee of future clinical or commercial success. This is due to the preclinical nature of the data and the current competitive landscape, which includes multiple companies with substantially greater resources than Entera Bio.

Regulatory unpredictability

The regulatory process involves submission of large amounts of clinical and preclinical data, and there is no guarantee that such data sets, even if furnished, would be sufficient for FDA approval. Applications for approval in the EU may require additional studies, including increased numbers of European patients.

Reimbursement risk

The drug pricing environment in the U.S. is subject to constant change and is currently the basis of some controversy. Drug pricing legislation could enforce price limitations on certain drugs, including those that otherwise might be expected to benefit from premium pricing. We do not expect the debate over drug pricing to subside near-term in the U.S. In other countries, reimbursement is subject to tighter controls due to budgetary concerns and single-payer healthcare systems. Accordingly, achieving reasonable pricing may not be possible ex-U.S.

Commercial risk

The company's products, if approved, may not achieve commercial success due to market size, penetration rate, or competition. Further, we cannot have absolute certainty that another agent in development might not be preferred by physicians, to the detriment of Entera Bio's assets. Sales may lead Entera Bio to profitability but may differ materially from our projections or estimates. Entera Bio may need to seize market share from substantially larger, more established companies, which might prove challenging, particularly in the osteoporosis arena.

Intellectual property risk

Entera Bio's patent portfolio consists of several owned and in-licensed patent families (issued, granted or pending in the U.S., Europe and other jurisdictions). Patent protection is slated to expire between 2029 and 2037, without Hatch-Waxman term extensions. Entera Bio relies on patents and trade secrets to protect its products from the competition, which is rife and, in extreme cases, may lead to lawsuits in the pursuit of the protection of IP. There can be no guarantee that Entera Bio, if party to such litigation, would prevail against opponents.

Historical Income Statement and Financial Projections

FY end December 31
$ in thousands, except per share data

	2021A					2022E					
	1QA	2QA	3QA	4QA	2021A	1QA	2QA	3QE	4QE	2022E	2023E
Revenue											
Product revenue	-	-	-	-	-	-	-	-	-	-	-
Research and other	167	121	151	178	617	80	58	70	90	298	400
Total revenue	167	121	151	178	617	80	58	70	90	298	400
Expenses											
Cost of product and service revenue	58	63	65	187	373	54	33	42	54	183	240
Research & development	1,159	1,258	1,729	2,625	6,771	1,690	1,394	2,500	3,000	8,584	25,000
General and administrative	1,309	1,450	1,450	1,481	5,690	2,171	1,880	2,000	2,300	8,351	8,000
Total expenses	2,526	2,771	3,244	4,293	12,834	3,915	3,307	4,542	5,354	17,118	33,240
Gain (loss) from operations	(2,359)	(2,650)	(3,093)	(4,115)	(12,217)	(3,835)	(3,249)	(4,472)	(5,264)	(16,820)	(32,840)
Other income/expense											
Loss from change in fair value of financial liabilities	(7,103)	(2,427)	697	8,833	-	-	-	-	-	-	-
Other income/expense	12	(37)	(20)	16	(29)	44	60	-	-	104	-
Total investment income and other	(7,091)	(2,464)	677	8,849	(29)	44	60	-	-	104	-
Loss before provision for income taxes	(9,450)	(5,114)	(2,416)	4,734	(12,246)	(3,791)	(3,189)	(4,472)	(5,264)	(16,716)	(32,840)
Deferred income tax benefit	(38)	(40)	(45)	182	59	7	4	-	-	11	-
Net loss/income	(9,488)	(5,154)	(2,461)	4,916	(12,187)	(3,784)	(3,185)	(4,472)	(5,264)	(16,705)	(32,840)
Net loss per share (basic)	(0.43)	(0.22)	(0.09)	0.16	(0.47)	(0.13)	(0.11)	(0.16)	(0.15)	(0.55)	(0.80)
Net loss per share (diluted)	(0.43)	(0.22)	(0.09)	0.16	(0.47)	(0.13)	(0.11)	(0.16)	(0.15)	(0.55)	(0.80)
Weighted average number of shares outstanding (basic)	21,890	23,378	28,681	30,586	26,134	28,804	28,808	28,835	34,885	30,333	41,010
Weighted average number of shares outstanding (diluted)	21,890	23,378	28,681	30,586	26,134	28,804	28,808	28,835	34,885	30,333	41,010

Source: Company reports and H.C. Wainwright & Co. estimates.

Historical Balance Sheet and Financial Projections

FY end December 31
$ in thousands, except per share data

	2021A					2022E					
	3/31	6/30	9/30	12/31	12/31/21A	3/31A	6/30A	9/30	12/31	12/31/22E	12/31/23E
Assets											
Current assets:											
Cash and cash equivalents	16,381	26,926	27,395	24,892	24,892	20,109	17,279	13,653	31,849	31,849	3,009
Accounts receivable	15	116	252	183	183	210	225	225	225	225	225
Other assets and prepaid expenses	1,038	863	459	254	254	1,322	922	922	922	922	922
Total current assets	17,434	27,905	28,106	25,329	25,329	21,641	18,426	14,800	32,996	32,996	4,156
Property and equipment	182	168	161	156	156	163	166	166	166	166	166
Deferred income taxes	-	-	-	217	217	250	280	280	280	280	280
Funds in respect of employee rights upon retirement	-	-	-	46	46	46	46	-	-	-	-
Other assets	306	261	244	239	239	212	170	170	170	170	170
Total Assets	18,527	28,939	29,116	25,987	25,987	22,312	19,088	15,416	33,612	33,612	4,772
Liabilities and shareholder equity											
Current liabilities											
Accounts payable	1,884	1,762	2,016	166	166	199	109	109	109	109	109
Accrued expenses	-	-	-	2,801	2,801	1,993	1,411	1,411	1,411	1,411	1,411
Current maturities of lease liabilities	182	184	179	179	179	142	172	172	172	172	172
Other current liabilities	15	8	-	15	15	-	-	-	-	-	-
Total current liabilities	10,616	3,349	2,893	3,161	3,161	2,334	1,692	1,692	1,692	1,692	1,692
Severance pay and employee rights obligations, net	78	88	88	138	138	135	122	122	122	122	122
Lease liabilities, non-current	220	187	153	123	123	98	5	5	5	5	5
Total Liabilities	10,914	3,624	3,134	3,422	3,422	2,567	1,819	1,819	1,819	1,819	1,819
Shareholder's equity											
Additional paid-in capital	80,827	103,089	105,797	104,950	104,950	105,914	106,623	106,623	129,171	129,171	129,171
Accumulated other comprehensive income	41	41	41	41	41	41	41	41	41	41	41
Other reserves	9,128	9,722	10,142	-	-	-	-	-	-	-	-
Deficit accumulated	(82,383)	(87,537)	(89,998)	(82,426)	(82,426)	(86,210)	(89,395)	(93,067)	(97,431)	(97,431)	(126,271)
Total shareholder's equity	7,613	25,315	25,982	22,565	22,565	19,745	17,269	13,597	31,793	31,793	2,953
Total liability and shareholder's equity	18,527	28,939	29,116	25,987	25,987	22,312	19,088	15,416	33,612	33,612	4,772

Source: Company reports and H.C. Wainwright & Co. estimates.

Cash Flow Statement and Financial Projections

FY end December 31
$ in thousands, except per share data

	2021A					2022E					
	1QA	2QA	3QA	4QA	2021A	1QA	2QA	3QE	4QE	2022E	2023E
Cash flows from operating activities											
Net loss	(9,488)	(5,154)	(2,461)	4,916	(12,187)	(3,784)	(3,185)	(4,472)	(5,264)	(16,705)	(32,840)
Adjustments for:											
Stock-based compensation	-	-	-	-	-	964	696	800	900	3,360	4,000
Depreciation & amortization	-	-	-	-	-	16	16	16	16	64	80
Deferred income tax	-	-	-	-	-	(33)	(30)	-	-	(63)	-
Finance income, net	-	-	-	-	-	(39)	(32)	-	-	(71)	-
Change in operating assets & liabilities											
Accounts receivable	-	-	-	-	-	(27)	(15)	-	-	(42)	-
Other current assets	-	-	-	-	-	(1,099)	395	-	-	(704)	-
Accounts payable	-	-	-	-	-	33	(90)	-	-	(57)	-
Contract liabilities	-	-	-	-	-	(15)	-	-	-	(15)	-
Other liabilities	-	-	-	-	-	(808)	(582)	-	-	(1,390)	-
Total change in operating assets & liabilities	7,212	3,037	448	(7,503)	3,194	(1,916)	(292)	-	-	(2,208)	-
Cash flows from operating activities	**(2,276)**	**(2,117)**	**(2,013)**	**(2,587)**	**(8,993)**	**(4,792)**	**(2,827)**	**(3,656)**	**(4,348)**	**(15,623)**	**(28,760)**
Cash flows from investing activities											
Investment in PPE	-	-	(7)	(10)	(17)	(23)	(19)	(20)	(20)	(82)	(80)
Cash flows from investing activities	**-**	**-**	**(7)**	**(10)**	**(17)**	**(23)**	**(19)**	**(20)**	**(20)**	**(82)**	**(80)**
Cash flows from financing activities											
Principal element of lease payments	(45)	(49)	(51)	145	-	-	-	-	-	-	-
Proceeds from exercise of options and warrants	251	3,181	123	21	3,576	-	-	-	-	-	-
Issuance of shares via At-The-Market program	9,858	9,485	2,462	-	21,805	-	-	-	-	-	-
Proceeds from issuance of common stock and warrants	-	-	-	-	-	-	13	-	22,560	22,573	-
Cash flows from financing activities	**10,064**	**12,617**	**2,534**	**166**	**25,381**	**-**	**13**	**-**	**22,560**	**22,573**	**-**
Net increase/ decrease in cash and cash equivalents	**7,788**	**10,500**	**514**	**(2,431)**	**16,371**	**(4,815)**	**(2,833)**	**(3,676)**	**18,192**	**6,868**	**(28,840)**
Cash and cash equivalents, beginning of period	8,593	16,381	26,881	27,395	8,593	24,964	20,149	17,316	13,640	24,964	31,832
Cash and cash equivalents, end of period	16,381	26,881	27,395	24,964	24,964	20,149	17,316	13,640	31,832	31,832	2,992

Source: Company reports and H.C. Wainwright & Co. estimates.

Public Companies Mentioned in this Report

Aeterna Zentaris Inc. (AEZS; Buy; Selvaraju)
Amgen Inc. (AMGN; not rated)
Asahi Kasei Corporation (AHKSY; not rated)
Ascendis Pharma A/S (ASND; not rated)
Astellas Pharma Inc. (OTCMKTS: ALPMY; not rated)
BridgeBio Pharma, Inc. (BBIO; Buy; Selvaraju)
Chugai Pharmaceutical Co., Ltd. (4519.T; not rated)
Daiichi Sankyo Co. (DSNKY; not rated)
Eli Lilly & Co. (LLY; not rated)
GlaxoSmithKline plc (GSK; not rated)
Novartis AG (NVS; not rated)
Oramed Pharmaceuticals Inc. (ORMP; Buy; Selvaraju)
Pfizer (PFE; not rated)
Radius Health (RDUS; Neutral; Tsao)
Sino Biopharmaceutical Limited (OTCMKTS: SBMFF; not rated)
Takeda Pharmaceutical Co. Ltd. (TAK; not rated)
UCB S.A. (UCB.BR; not rated)

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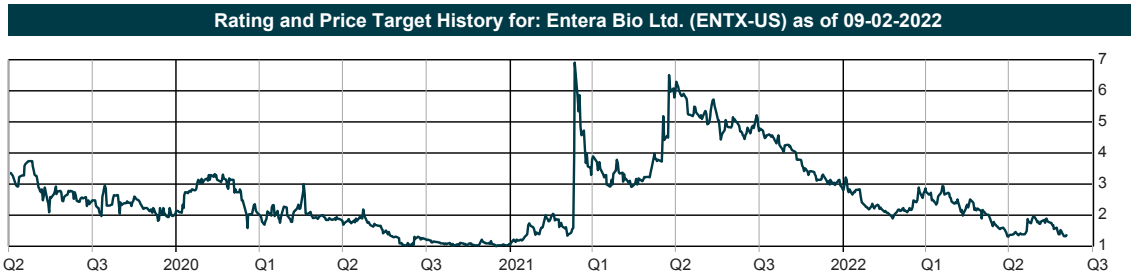
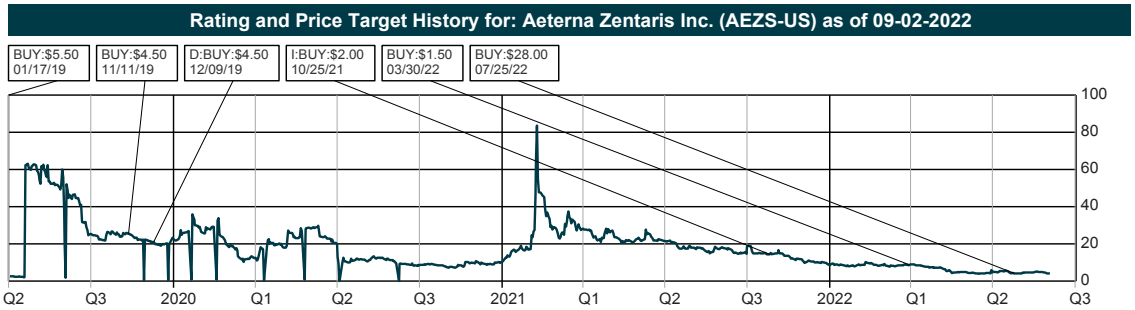
RETURN ASSESSMENT

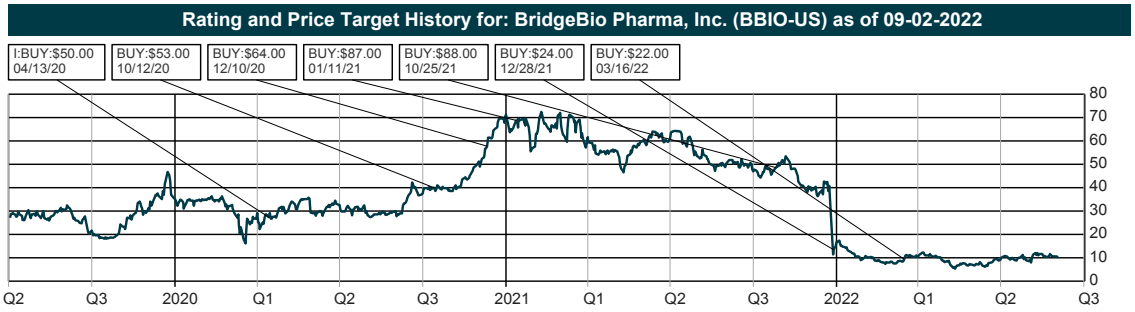
Market Outperform (Buy): The common stock of the company is expected to outperform a passive index comprised of all the common stock of companies within the same sector.

Market Perform (Neutral): The common stock of the company is expected to mimic the performance of a passive index comprised of all the common stock of companies within the same sector.

Market Underperform (Sell): The common stock of the company is expected to underperform a passive index comprised of all the common stock of companies within the same sector.








Rating and Price Target History for: Oramed Pharmaceuticals, Inc. (ORMP-US) as of 09-02-2022
BUY:$20.00 07/22/19
BUY:$16.00 06/22/20
BUY:$17.00 07/13/20
BUY:$32.00 11/29/21
35
30
25
20
15
10
5
0
Q2
Q3
2020
Q1
Q2
Q3
2021
Q1
Q2
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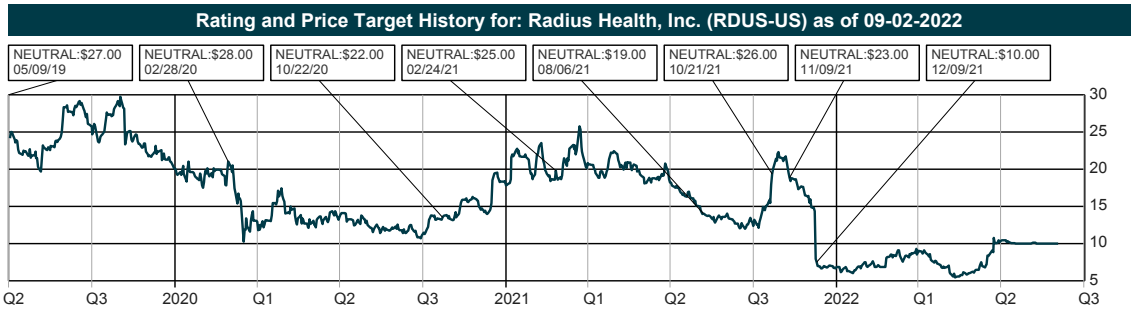
2022
Q1
Q2
Q3


Rating and Price Target History for: Radius Health, Inc. (RDUS-US) as of 09-02-2022
NEUTRAL:$27.00 05/09/19
NEUTRAL:$28.00 02/28/20
NEUTRAL:$22.00 10/22/20
NEUTRAL:$25.00 02/24/21
NEUTRAL:$19.00 08/06/21
NEUTRAL:$26.00 10/21/21
NEUTRAL:$23.00 11/09/21
NEUTRAL:$10.00 12/09/21
30
25
20
15
10
5
Q2
Q3
2020
Q1
Q2
Q3
2021
Q1
Q2
Q3
2022
Q1
Q2
Q3

Related Companies Mentioned in this Report as of Sep/02/2022					
Company	Ticker	H.C. Wainwright Rating	12 Month Price Target	Price	Market Cap
Aeterna Zentaris Inc.	AEZS	Buy	$28.00	$4.35	$21
BridgeBio Pharma, Inc.	BBIO	Buy	$22.00	$10.06	$1491
Oramed Pharmaceuticals, Inc.	ORMP	Buy	$32.00	$8.17	$317
Radius Health, Inc.	RDUS	Neutral	$10.00	$10.08	$465

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Distribution of Ratings Table as of September 2, 2022				
			IB Service/Past 12 Months	
Ratings	Count	Percent	Count	Percent
Buy	568	87.65%	133	23.42%
Neutral	63	9.72%	10	15.87%
Sell	1	0.15%	0	0.00%
Under Review	16	2.47%	1	6.25%

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