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Company Overview

Entera Bio Ltd. (NASDAQ:ENTX) is a product-focused biotechnology company, founded in 2009 by Dr. Phillip Schwartz. The platform developed by Entera Bio allows for the oral administration of pharmaceutically active large molecules and biologics that would otherwise need to be injected. Entera Bio is conducting clinical trials for two candidate drugs that are designed to treat three different indications: hypoparathyroidism, osteoporosis, and non-union fractures. Entera Bio's proprietary technologies act synergistically to both drive absorption of large molecules via the gastrointestinal tract and protect these same large molecule/biologic drugs from rapid degradation.

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Entera Bio developed a delivery platform for replacing injections with pills; the Company has two drugs in clinical phases; market potential for their platform is significant; Entera Bio recently entered into a $270 million license agreement with Amgen; price target is set at $17.6

Stock Exchange: NASDAQ

Symbol: ENTX

Sector: Health Care

Sub-sector: Biotechnology (Holdings)

Stock Target Price: $17.6

As of June 30, 2019:

Closing Price: $3.1

Market Cap: $35.2 million

# of Shares: 11.46 million

Stock Performance (52-Week Change): -53%

Average Vol (3 month): 8.5K

Lead Analysts:
Dr. Tiran Rothman
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Highlights

The Company's main focus is applying its technology to develop an **oral formulation of human parathyroid hormone (1-34), or PTH**, which has been approved in the U.S. in injectable form for over a decade. Their lead oral PTH product candidates are EB613 for the treatment of osteoporosis and EB612 for the treatment of hypoparathyroidism.

Entera Bio's platform technology enables oral therapies based on molecules that would otherwise undergo gastric degradation and have limited or no bioavailability. By transforming injectable drugs to oral drugs, the treatment becomes more 'user friendly' which may lead to higher patient and physician acceptance. Furthermore, as an oral drug, various treatment regimens become possible, enabling personalized care.

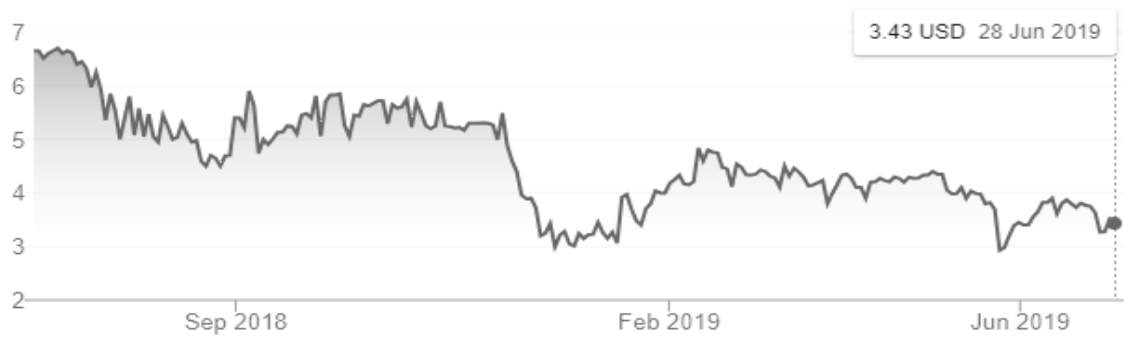
On January 31, 2019, Entera Bio announced a positive outcome of a pre-IND meeting held with the FDA. The meeting mainly focused on the 505(b)(2) regulatory pathway and the use of bone mineral density (BMD) instead of fracture incidence as the primary endpoint to support a new drug application (NDA). **The 505(b)(2) pathway is estimated to save 2-3 years of development and potentially more than $100 million USD in development costs. Furthermore, the oral PTH clinical development program will include one or two pivotal phase 3 studies, conducted with approximately 600 - 800 osteoporosis patients instead of 3,000 patients, as typical in fracture studies.**

Entera's platform technology has recently been utilized by Amgen and on December 11th 2018, Entera Bio announced a research collaboration and license agreement with Amgen in the area of inflammatory disease and other serious illnesses totaling up to $270 million in milestone payments as well as a mid-single digit royalty on commercial sales.

We view Entera Bio as a great investment opportunity: the Amgen agreement and the regulatory path transformation will positively and significantly affect time-to-market and investor exposure to the Company's platform of large molecule delivery.

We value Entera Bio at $201.6M; with a price target in the range of $18.1 to $17.1 and at a mean of $17.6 per share.

Stock overview YTD (Source: NASDAQ website)



Executive Summary

Investment Thesis – Delivery Platform for Large Molecules

Entera Bio LTD. is a clinical-stage biopharmaceutical company with a platform that enables the delivery of molecules that are currently administered by injection. The company is also focusing on development and commercialization of orally delivered large molecules and biologics for unmet medical needs.

In recent years, the development of peptides and proteins for drug design purposes has become the primary avenue for therapeutic development because the mechanism of action of biological drugs is better understood more effective as medication due to the fact that they better mimic the natural regulatory pathways in the human body. Worldwide, there are currently around 500 peptide/protein-based medications in clinical trials. A handful of peptide/protein medications are already commanding revenues in the billions[1].

Currently, biologics are generally delivered by intravenous or subcutaneous injection, which may be effective but not desired by patients, particularly for chronic conditions. Furthermore, proteins and peptides have low bioavailability when taken orally and are subject to acid and enzymatic degradation (by the stomach), further reducing the therapeutic exposure to these agents[2]. Entera Bio offers a unique solution to these problems. Their oral platform combines both the protection from gastric degradation as well as enhances absorption.

By transforming injectable drugs to orally delivered ones, the treatment burden on patients is lowered and this may lead to higher patient and physician acceptance. In addition, oral drug delivery provides significantly more flexibility, both in size of dose and number of doses per day than injectable drugs, which are frequently administered only once per day by preset injection pens. Moreover, oral tablets are generally superior to injections in terms of shelf life, supply chain convenience, and other distribution and logistics related aspects.

The Company's main focus for its internal pipeline is to apply its technology to develop an oral formulation of human parathyroid hormone (1-34), or PTH. Injectable PTH has been approved in the U.S. and EU for more than 15 year for the treatment of osteoporosis and currently generates revenue in excess of $1.6 billion/year. Entera Bio's lead oral PTH product candidates are EB613 for the treatment of osteoporosis and EB612 for the treatment of hypoparathyroidism as can be seen in the Figure 1.

- ***EB613 for Osteoporosis***: Entera Bio is set to perform a phase 2a dose ranging study in patients. The company aims to use the 505(b)(2) regulatory pathway, which is less expensive and a much faster route to approval.
- ***EB612 for Hypoparathyroidism***: Entera Bio successfully completed a phase 2a clinical trial for hypoparathyroidism. A pharmacokinetic/pharmacodynamic (PK/PD) cross over study of EB612 versus Natpara (*orphan drug designation*) will be reported later this year with the next planned step for clinical development being a phase 2b/3 pivotal study.

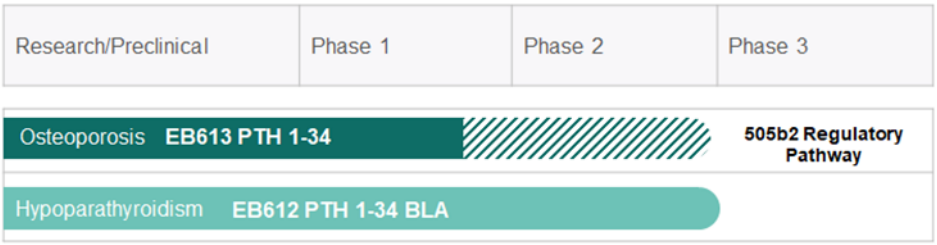


Figure 1: Entera Bio LTD. Lead candidates (Source: Investors presentation 2019)

[1] https://www.sciencedaily.com/releases/2018/02/180221122406.htm
[2] http://www.pmlive.com/pharma_intelligence/oral_biologics_delivery_still_elusive_908436

On December 11th 2018, Entera Bio announced a research collaboration and license agreement with Amgen in the area of inflammatory disease and other serious illnesses. Entera Bio will use its proprietary drug delivery platform to develop oral formulations for one preclinical large molecule program that Amgen has already selected. Amgen also has an option to select up to two additional programs to include in the collaboration.[3] Entera Bio will be eligible to receive up to $270 million in milestone payments, for the development of three different molecules.

Entera Bio's clinical development and promising results along with the Amgen agreement emphasize the potential commercial opportunities that exist for the company. Entera Bio's orally delivered PTH hormone may substitute the current injectable hormone, providing a combination of efficacy, tolerability, and convenience as can be seen in the table below. Furthermore, the company could be the first oral bone-building therapy for osteoporosis and the first to receive orphan designation in both the US & EU for hypoparathyroidism. Alongside this, Entera Bio's long-term pipeline is set to develop solutions for indications that presently lack treatment and to license the use of its technology to numerous other companies.

Parameter	Oral PTH (Tablet)	SC-PTH (Injection)
Product cost	Lower than Injection	Cost of goods due to the injectors, Ultra-sterile processing
Transportation Logistics	None	Complicated, Cold chain
Patient compliance	High	Most patients won't continue the treatment over time
Doctor preference	High	Lower
Shelf life	Longer	Several months-years
Dosage	Flexible: Single or multiple daily doses	Injection –once a day
Reimbursement*	√	√

Pharmaceutical formulation and treatment process attributes, such as dose frequency and route of administration, can have an impact on quality of life, treatment adherence, and disease outcome. Given the choice, most patients would prefer to take a drug orally instead of getting an injection.

We view Entera Bio as a great investment opportunity: the Amgen agreement and the regulatory path transformation, will positively and significantly affect time-to-market and investor exposure to the company's platform of large molecule delivery.

[3] https://investors.enterabio.com/news-releases/news-release-details/entera-bio-and-amgen-enter-strategic-research-collaboration

* Osteoporosis increases the risk of fractures, which leads to major consequences for the individual and society. Fracture treatment can cost up to $150K per patient, thus reimbursement of new drug will be highly supported. Worldwide, osteoporosis causes more than 8.9 million fractures annually, resulting in an osteoporotic fracture every 3 seconds.

Upcoming Potential Catalysts

Program	Indication	Event	Significance	Timeline
EB613: PTH (1-34)	Osteoporosis **505(b)(2)**	IND submission	Medium	H2 - 2019
		Initiation of phase 2a trial- dose ranging study	High	Mid-2019
		Dose ranging study- bone marker data	High	Q1-2020
		Dose ranging study- bone mineral density (BMD) data	High	2020
		Pivotal phase 3, multicenter study BMD endpoint study comparing Oral PTH with Forteo®	Medium	H2-2020
		Expected commencement of sales by partner	High	H1-2023
EB612: PTH (1-34)	Hypoparathyroidism **Orphan Drug**	PK/PD study head to head with Natpara in hypoparathyroid patients	Medium	Achieved
		Submit IND Multi National Study	Medium	H2-2019
		Dose ranging study	Medium	H1-2020
		Phase 2b/3 clinical trial	High	H1-2021
		Expected commencement of sales	High	2023

Upside scenarios	Downside scenarios
Success in reaching the pivotal trial endpoints will significantly affect the company's value	Failure to reach pivotal trial endpoints will significantly affect Entera Bio's value
Successfully expanding drug delivery technology to other product candidates	The company won't be able to raise additional funds to support its long term growth strategy
Additional licensing agreements with additional pharmaceutical companies	The company may not be successful in its efforts to use and expand its drug delivery technology to other product candidates

Valuation Methodology

R&D company valuations are challenging due to a non-cash valuation with a long time-to-market in most cases. Methods typically used for company valuations, such as asset valuation or multiplier methods, are incompatible with the valuation of R&D companies. In such companies, the current status of business cannot be analyzed by the capital in the balance sheet, and in most cases cannot be compared to similar companies due to their uniqueness, in both technological and financial aspects.

As part of a discounted cash flow (DCF), the accepted method used in financial valuations, there are several modifications to an R&D company's valuation. In general, there are three primary methods within the DCF method:

1. **Real Options** - valuation method designated for pre-clinical and early-stage clinical programs/companies where the assessment is binary during the initial phases, and based upon scientific-regulatory assessment only (binomial model with certain adjustments).
2. **Pipeline assessment** - valuation method used for programs/companies prior to the market stage. The company's value is the total discounted cash flow plus unallocated costs and assessment of future technological basis. The assessment of the future technological basis is established based on the company's ability to "produce" new clinical and pre-clinical projects and their feed rate potential.
3. **DCF valuation** - similar to companies not operating in the life sciences field, this method applies to companies with products that have a positive cash flow from operations.

Entera Bio's valuation was conducted under the "Pipeline assessment" method, suitable for the developmental stages of the company's products. The company's valuation is calculated by examining the company as a holding company vis-à-vis existing projects, with risk-adjusted net present value (rNPV) capitalization to the net present value, including weighting of several scenarios. These primarily include analysis of the company's income, evaluated in accordance with scientific/technological assessment, based on various sources and estimates relating to the market scope, the degree of projected market success, and regulatory risk.

The weighted average of company revenue in the pharmaceutical and medical equipment market is based on the following data:

- Total Market - market potential for the product/product line
- Market Share – the company's ability to penetrate the market during the forecast period
- Peak Sales - peak sales of the company/product during the forecast period
- Annual Cost of Treatment – estimated annual cost per patient, based on updated market studies
- Success Rate - chances for success of clinical trials and transition to the next phase in the examined sub-field

Valuation of Entera Bio's "technological basis" is, in fact, a valuation of the company's "residual value". This valuation was conducted using the Feed Rate methodology that is common in the field of life sciences, rather than using the conventional terminal value, normally used by non- life-science companies.

Valuation Summary

Equity Value

Non-operational assets/liabilities and unallocated costs

As of December 31, 2018, Entera Bio has non-operational assets (cash) of approximately $11.5M with an estimated monthly burn rate of $1.4M. The company has no loans.

The equity valuation elements are presented in the table below:

Pipeline Analysis		rNPV ($K)
EB 612	Hypoparathyroidism	10,256
EB 613	Osteoporosis	25,867
Amgen partnership		59,620
Total rNPV Pipeline		**95,744**
Unallocated Costs		-21,859
Terminal Technology Value		**123,173**
Enterprise Value		**197,057**
Total Non-Operational Assets/Liabilities		**4,521**
Equity Value		**201,578**

Based on the above data we value Entera Bio at $201.6M.

Sensitivity Analysis

The table below presents Entera Bio's equity value in relation to the capitalization rate. We set a range of 0.5% change from our CAPM model (see Appendix B). Entera Bio has 11.46M shares.

Sensitivity Analysis - Capitalization Rate vs. Equity Value

Cap. rate	Price Target ($)
17.5%	18.7
18.0%	**18.1**
18.5%	**17.6**
19.0%	**17.1**
19.5%	16.6

We estimate Entera Bio's price target to be in the range of $18.1 to $17.1 and at a mean of $17.6.

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Company Overview

Entera Bio Ltd. is a clinical-stage biopharmaceutical company focusing on developing solutions for oral delivery of large molecules and biologics. Oral administration offers increased patient comfort, compliance, and cost effectiveness, and is therefore the preferred method of drug administration. Entera Bio's oral delivery platform may be applied to an array of drugs.

Entera Bio was founded in 2009 and commenced operations the following year. The Company's principal executive offices are located in Kiryat Hadassah, Jerusalem, Israel. Entera Bio Inc., a wholly-owned subsidiary of Entera Bio, was incorporated on January 8, 2018 under the laws of the State of Delaware. The registered office of Entera Bio Inc. is located at 1209 Orange St., Wilmington New Castle, Delaware 19801. Below are the main shareholders as of December 31, 2019:

Name	Number and Percentage of Ordinary Shares	
	Number	Percent
5% or Greater Shareholders (other than directors and executive officers)		
D.N.A Biomedical Solutions Ltd.	3,978,780	34.7
Centillion Fund	2,192,060	17.5
Capital Point Ltd.	1,151,806	9.9
Menachem Ehud Raphael	661,180	5.7
Pontifax Management 4 GP (2015) Ltd.	853,450	7.3

*Source: 20-F, 2018

The company's main focus is applying its technology to develop an oral formulation of human parathyroid hormone (1-34), or PTH, which has been approved in the U.S. in injectable form. PTH is critical in maintaining mineral balance in the body (magnesium, phosphorus and calcium), while its main function is to increase calcium levels when they are too low[4]. Their lead oral PTH candidates are EB613 for the treatment of osteoporosis and EB612 for the treatment of hypoparathyroidism. The company has strategically chosen to develop tablets comprising biological substances that today are given as injections, with a proven therapeutic and side effect profile, and are thus well positioned to 'go to market'.

The company received positive feedback from the FDA regarding the use of the 505(b)(2) regulatory pathway to develop their osteoporosis treatment, and additional positive feedback regarding the use of bone mineral density (BMD) rather than fracture incidence as a primary endpoint in their phase 3 clinical trial. This feedback is testimony of the shorter and more efficient development process that the company will need to implement as well as of the market potential.

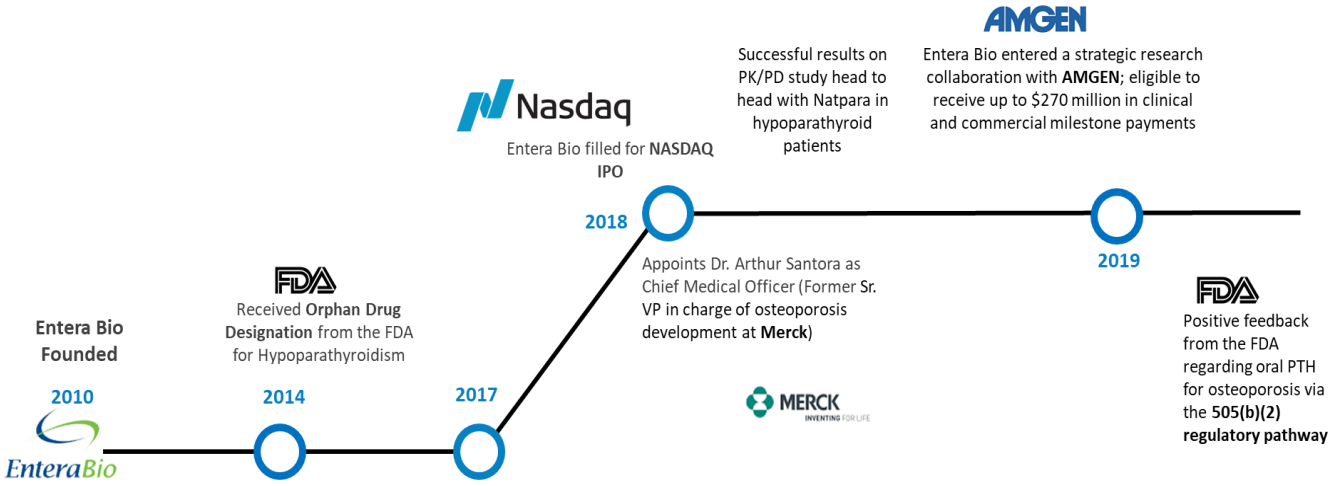
Entera bio holds orphan drug designation for the hypoparathyroidism indication from the FDA (US) and EMA (Europe) as of April 2014 and June 2016, respectively, potentially accelerating market penetration for this product. For the most part, rare-disease treatments are considered an attractive market because the relatively small patient population is an incentive for insurance companies to reimburse orphan diseases.

The advent of an orally ingestible alternative will only further these, already lucrative, monetization possibilities. The company finished the treatment periods and is in the process of completing the data collection and analysis of its phase 2 clinical trial for hypoparathyroidism.

An additional indication in the osteoporosis product's pipeline addresses non-union fractures. The current treatment for these fractures is only operative and there are no medications available to accelerate bone healing. The idea of

[4] https://selfhacked.com/blog/parathyroid-hormone-pth/

offering PTH (1-34) which is a bone building hormone will help to reduce the amount of non-unions occurring each year and can help in the bone healing process for people who suffer from non-union[5].



With the completion of the dose finding study, EB613 will be an exceptionally attractive asset for large pharmaceutical companies. Entera Bio can choose to sell/ co-develop it, eliminating the need for more capital, or Entera Bio can continue development via the 505(b)(2) pathway with relatively small amounts of capital and a rapid data read out. Entera bio is continuing with the development of EB612 for hypoparathyroidism and plans to bring it to market.

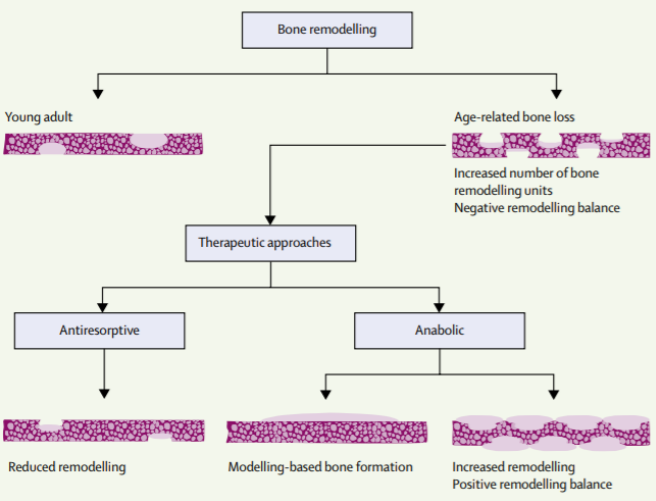
Entera Bio has positioned itself as a category leader in transforming injectable drugs into orally delivered ones. Furthermore, the Company has the potential to be the first oral bone-building therapy for osteoporosis and the first to obtain orphan designation in both the US & EU, granting 7 years of market exclusivity for hypoparathyroidism.

[5] https://www.enterabio.com/pipeline/bone-healing

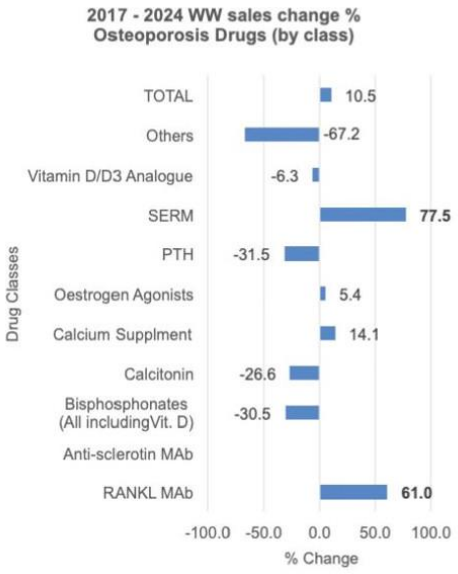
Market, Standard of Care, and Unmet Needs

The Unmet Needs of the Osteoporosis Market

Osteoporosis is a bone disorder that increases a person's risk of fracture due to low bone mineral density (BMD), impaired bone microarchitecture/mineralization, and/or decreased bone strength. This asymptomatic condition often remains undiagnosed until it manifests as a low-trauma fracture of the hip, spine, proximal humerus, pelvis, and/or wrist, which frequently leads to hospitalization[6]. The goal of pharmacological therapy is to reduce the risk of fractures. The currently offered medications to treat osteoporosis are categorized as either antiresorptive (bisphosphonates, estrogen agonist/ antagonist, estrogens, calcitonin, and Denosumab) or anabolic (teriparatide). Antiresorptive medications primarily decrease the rate of bone resorption while anabolic medications increase bone formation more than bone resorption[7].

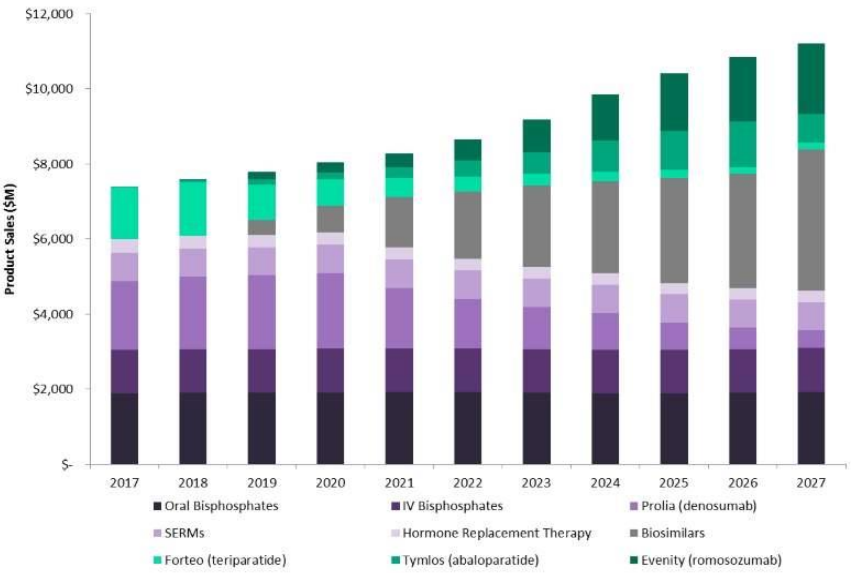


The aging of the global population is causing an increase in the prevalence of age-related chronic diseases, including osteoporosis. Clinical development in osteoporosis represents an excellent opportunity to bring new and more affordable medications to patients. Despite the wide availability of several classes of approved osteoporosis medications, and even after documented osteoporotic fractures occur, initiation of treatment rates has been observed to be quite low, ranging from 5% to 30%. According to the International Osteoporosis Foundation, "the cost of osteoporosis is 37 billion euros per year in the EU, and $19 billion USD per year in the US." Costs are projected to rise dramatically alongside osteoporosis prevalence in the coming year[8].



[6] Osteoporosis: A Review of Treatment Options,2018
[7] Osteoporosis. Juliet E Compston, Michael R McClung, William D Leslie. Lancet 2019; ; 393: 364–76
[8] https://www.americanpharmaceuticalreview.com/Featured-Articles/357057-Osteoporosis-Addressing-the-Unmet-Need/

For many years the only anabolic therapy on the market has been Forteo®, which due to its high price and resistance of patients to injections, has been restricted to the later lines of therapy and more severely-affected patients. However, the diversification of the anabolic offering is likely to increase competition within this space, driving down high prices and potentially bolstering the use of these therapies up the treatment paradigm. Forteo® lost its exclusivity at the end of 2018, followed by Prolia® (Denosumab) with patent expiration in the U.S. in February 2025 and in Europe in June 2022 (except for France, Italy, Spain and the U.K., which expire in 2025).



The osteoporosis treatment market is expected to experience exponential growth in emerging treatments, such as RANKL mono clonal antibodies (Mab), anti-sclerotin Mab and biosimilar[9].

The challenge in the delivery of large biological molecules

Entera Bio develops orally delivered large molecules and biologics to address under attended clinical demand. Entera Bio's oral delivery platform can be applied to an array of molecular and therapeutic substances such as peptides and proteins that are currently given as injections or are being developed as injections. Peptides and proteins have great potential as therapeutics compared with the typical small-molecule drugs that currently make up the majority of the pharmaceutical market, as they are highly selective and present an opportunity for therapeutic intervention that closely mimics natural pathways.[10] [11] Peptides can be designed to address a broad range of physiological and pathological targets, offering multiple advantages in fields such as oncology, immunology, infectious disease and endocrinology. There is also a great deal of interest in the development of systems allowing for the oral delivery of peptide and protein therapeutics, as oral delivery has many advantages over injection such as ease of administration, improved patient compliance, is less prone to contaminations, and is usually less expensive[12]. All of the above increase the therapeutic value of the drug[13], as well as its economic value in the market

Unfortunately, oral bioavailability of peptides and proteins (biologics) is limited by degradation in the gastrointestinal (GI) tract, as well as their inability to cross the epithelial barrier. Protein and peptide biological therapeutics have high molecular weights, low lipophilicity and charged functional groups that hamper their absorption.[14] These characteristics lead to the exceptionally low bioavailability of most orally administered peptides (<0.2%) and short half-lives (<30 min).[15]

[9] https://www.americanpharmaceuticalreview.com/Featured-Articles/357057-Osteoporosis-Addressing-the-Unmet-Need/
[10] Craik, D. J. et al., Chem. Biol. Drug. Des. (2013). 136–147.
[11] https://www.sciencedirect.com/science/article/pii/S0968089617310222?via%3Dihub
[12] https://www.doctors.net.uk/_datastore/ecme/mod1227/Drug_dosage_Table1.pdf
[13] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2792531/
[14] Aungst B, et al. . J. Control. Release. (1996) 41(1), 19–31.
[15] Borchardt T, et al., Adv. Drug Deliv. Rev. (1997) 235–256.; Bruno, B.et al., Therapy Delivery. (2013) 4(11), 1443–1467.

Intravenous (IV), intramuscular (IM), subcutaneous (SC), intrarectal, transdermal and pulmonary delivery routes of therapeutics overcome the issue of absorption through the GI. However, these administration routes are limited by other factors including systemic proteases, rapid metabolism, opsonization, conformational changes, dissociation of subunit proteins, non-covalent complexation with blood products, and destruction of labile side-groups[16], which can lead to the elimination of the drug's biological activity. In addition, the use of injections on a daily basis during long-term treatment has obvious drawbacks in contrast to the oral route which offers the advantages of self-administration with a high degree of patient acceptability.

Methods to improve the bioavailability of protein therapeutics through oral administration can be broadly classified into categories of structural modifications, enzyme inhibitors, absorption enhancers, and carrier systems.

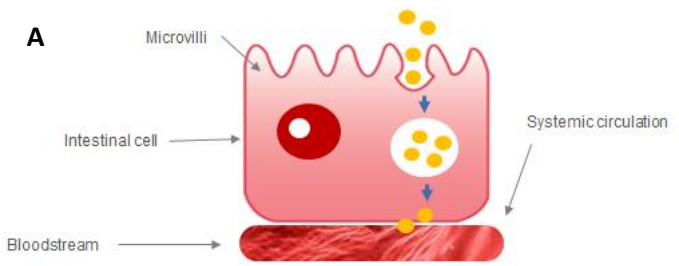
- **Structural modifications,** including cyclization, PEGylation, fusing therapeutic proteins to vitamin B12, protein lipidization, stapled peptides, substitution of natural L-amino acids with d-amino acids and pro-drugs strategies[17]
- **Enzyme inhibitors** such as soybean trypsin inhibitor and Aprotinin (Trasylol)
- **Absorption enhancers,** including chitosan, medium-chain fatty acids, lectins, certain toxins, cell-penetrating peptides (CPPs) and surfactants
- **Carrier systems**, including hydrophilic mucoadhesive polymers, thiomers, polymer matrices, nano-emulsions, hydrogels, liposomes, and nanoparticles (NPs)

Despite current advancements and the fact that oral delivery remains the mainstay for the administration of small molecules, it cannot be reliably used to deliver proteins and peptides, owing to poor transport across the intestinal membrane and poor absorption into systemic circulation (Figure 2B).

Several approaches including nanoparticles, mucoadhesive modifications, intestinal patches, hydrogels, peptide modifications and permeation enhancers have been developed to enhance the oral delivery of biologics. Furthermore, devices that physically disrupt the intestinal barrier to facilitate biologic transport have also been developed[18].

Entera Bio's platform for oral delivery of biological macromolecules:

Entera Bio's platform technology consists of an oral tablet that facilitates effective oral administration and absorption of intact proteins through the gastrointestinal (GI) tract. The technology is based on co-administration of a therapeutic protein along with two functional components. The first is a proprietary "cocktail" of ***protease inhibitors and chemical entities*** that protect the therapeutic proteins from gastric degradation by enzymes and acids in the stomach and intestine. Each "cocktail" is customized for the drug molecule candidate. The second is an ***absorption enhancer*** that enables transcellular transport of large molecules through the intestinal wall.



[16] Torchilin, V. et al., Therap. Deliv. (2009) 5(2–3),1443–1467.
[17] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4908063/
[18] Non-invasive delivery strategies for biologics, Review 2019

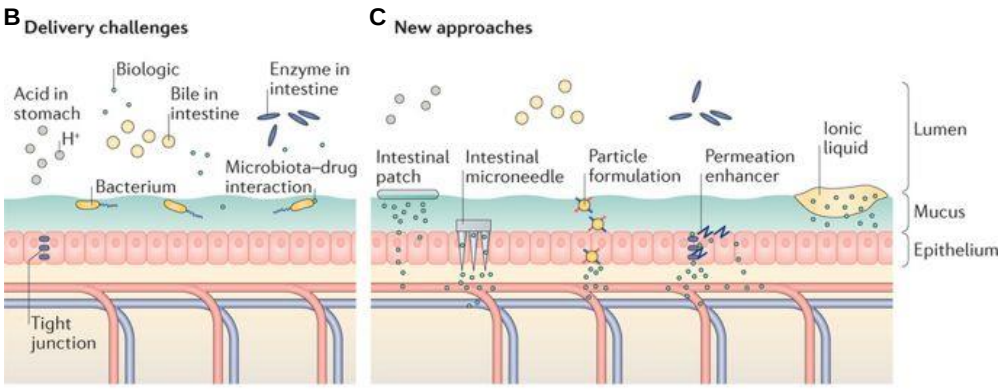


Figure 2: (A) Transport of drug through the cell (Entera Bio investor presentation, 2019) (B) Delivery barriers and micro environmental challenges that limit biologic absorption via the oral route. (C) Approaches to overcome these barriers and micro environmental challenges[18].

Preclinical data in animals supports oral delivery and has shown success in various biological molecules of different sizes, from small molecules (1.6kD) to larger compounds (22kD) and perhaps even higher. PK/PD profiles seem favorable for either single or multiple daily oral doses, administered based on optimal therapeutic requirements and individualized titration.

The first two products in the company's pipeline are based on a formulation of synthetic parathyroid hormone PTH (1-34), an important hormone in bone remodeling and serum calcium regulation. The drug is identical to a portion of the human parathyroid hormone (PTH), consisting of the (N-terminus) 34 amino acids, which is the bioactive portion of the hormone. It is an effective anabolic (bone building) agent used in the treatment of some forms of osteoporosis[19]. Its intermittent use activates osteoblasts more than osteoclasts, which leads to an overall increase in bone mass.

The main superiority of Entera Bio over currently available drugs is the precision of oral delivery, meaning that the amount of drug absorbed is consistent between patients and administrations.

Market Overview

Entera Bio's primary innovation is its development of an oral delivery technology for large peptides, proteins and other large molecules. The company answers a long-term critical market need as a **provider of oral solutions for injectable medications** that can quickly reach the market. After having received positive feedback from the FDA regarding the use of the 505(b)(2) regulatory pathway, the company is currently focused on the development of EB613 for the treatment of osteoporosis .

Entera Bio has witnessed an emerging interest within various healthcare market segments for administration of injectable drug solutions through novel oral means that are considerably more consumer friendly, and consequently more profitable. The medical world has experienced prolific growth in the number of experiments taking place to discover oral solutions to drugs that had only been effective when administered intravenously or intramuscularly.[20] Oral administration has many inherent advantages over injections including self-administration, and suitability for those sensitive to injections. Consequently, the treatment tends to be more receptive among patients. The market

[19] Saag KG, et al., The New England Journal of Medicine (2007) 20, 357
[20] DNA Biomedical Solutions. Financial Report for 2016. (2017).

potential for orally ingestible alternatives is lucrative. A table of recent activity among leading market players is detailed in the table below.

Investor (Country)	Investee (Country)	Amount	Product	Date
Johnson & Johnson (US)	Protagonist Therapeutics (US)	$50 million	Inflammatory Bowel Disease injectables in pill form.	June 2017[21]
Hefei (Sinopharm) (CN)	Oramed (IL)	$50 million	Orally ingestible insulin	Nov 2015[22]
Google Ventures, Novartis, AstraZeneca and many others (US)	Rani Therapeutics (US)	$70 million	General platform, including; TNF-alpha inhibitors, interleukin antibodies, insulin and GLP-1.	Feb 2016[23]
25 major financial institutions (US)	Chiasma (US)	$26.4 million (at 30.8.17)	Oral therapies for acromegaly (Phase III).	Via Nasdaq in 2017[24]

Comparing conventional pharmaceutical drugs to biologics, the latter feature robust therapeutic efficacy, high selectivity, and limited side effects. The oral route of administration is the undisputed ultimate goal of any drug therapy[25].

Pharmaceutical researchers have spent decades trying to figure out how to deliver injectable drugs by means other than injections, pills being the most attractive option. So far, all attempts to replace injectables have been unsuccessful. Some companies are still trying to develop a new technology to overcome this problem:

- A team of investigators from Harvard-affiliated Brigham and Women's Hospital, MIT, and Novo Nordisk has pioneered a new approach that brings closer to the clinic an oral formulation of insulin that can be swallowed rather than injected. The size of a pea, the Self-Orienting Millimeter scale Applicator (SOMA) houses a needle made of insulin and its injection is controlled by a spring held in place by a sugar disc. The sugar disc allows the humidity in the stomach to serve as the trigger of the micro-injection, and the solid insulin needle enables delivery of a sufficient dose of the drug. Its size and material makeup are similar to previously approved FDA ingestible devices[26].
- Shire and Rani Therapeutics have partnered to investigate the use of oral Rani Pill technology as the carrier system for clotting factor VIII in hemophilia A patients (2017). Hemophilia A patients are now treated mainly by factor replacement therapy, in which patients are injected with concentrates of clotting factor VIII. But this method of delivery entails significant safety and compliance challenges. The Rani Pill allows the drug that's inside to navigate through the stomach without being degraded by the gastrointestinal tract secretions. Once in the small intestine, the carrier system undergoes a transformation that enables it to adhere to the intestine's wall and inject the drug[27].

The distribution of the administration method of current marketed pharmaceutical products is shown in Figure 3. Overall, the oral delivery route (62.02%) makes the largest contribution to pharmaceutical products, followed by injection (22.43%), cutaneous (8.70%), mucosal (5.22%), inhalation (1.21%) and others (0.42%) (Figure 3a). The results reveal that oral delivery remains the most appealing route due to high patient compliance and ease of

[21] https://www.businessinsider.com.au/protagonists-oral-peptides-pill-versions-of-blockbuster-drugs-2017-6?r=US&IR=T.
[22] http://www.reuters.com/article/oramed-china-idUSL8N13O0AO20151130.
[23] http://www.biospace.com/News/bay-area-startup-rani-therapeutics-tops-70-million/409783.
[24] NASDAQ Website. (2017)
[25] https://www.portalinstruments.com/blog/biologics-advanced-drugs-that-deserve-advanced-delivery/
[26] https://news.harvard.edu/gazette/story/2019/02/microneedle-pill-takes-the-sting-out-of-insulin/
[27] https://hemophilianewstoday.com/2017/12/11/shire-and-rani-therapeutics-enter-into-collaboration-to-evaluate-use-of-the-rani-pill-technology-for-the-oral-delivery-of-factor-therapy/

administration. Generic drug companies are more likely to develop traditional administration routes such as oral delivery compared to innovative drug companies that develop different types of administration (Figure 3b)[28].

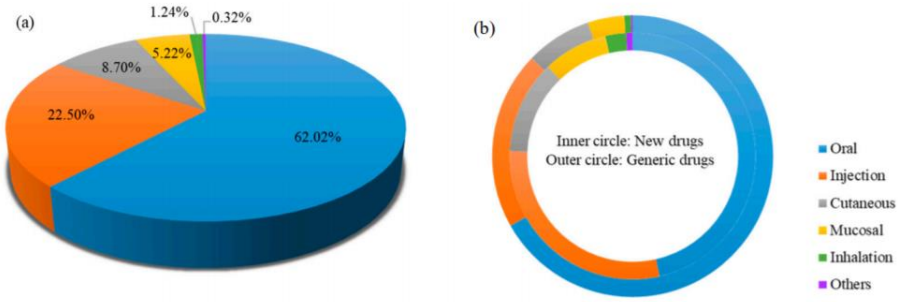
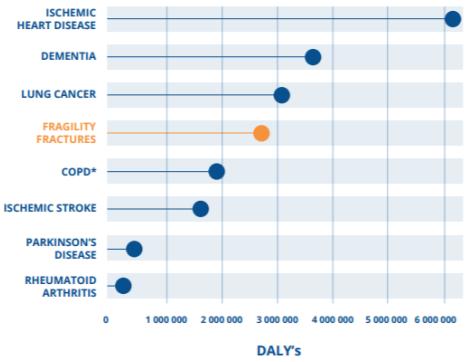


Figure 3: (a) The overall distribution of administration route of FDA-approved pharmaceutical products. (b) The distribution of administration route segmented to new vs generic drugs. The inner circle represents drugs while the outer circle represents generic drugs. As can be seen the major trend is to develop oral drugs.

Osteoporosis Drugs Market

Market Size

According to the National Osteoporosis Foundation (NOF), 10 million people in the U.S. already have osteoporosis, and another approximately 43 million have low bone mass placing them at increased risk for osteoporosis. It is also estimated that 200 million women worldwide suffer from Osteoporosis[29]. Although osteoporosis mainly affects women, men are also at risk for the disease. In fact, half of women and a quarter of men over the age of 50 will break a bone due to osteoporosis. Worldwide, osteoporosis causes more than 8.9 million fractures annually, resulting in an osteoporotic fracture every 3 seconds. According to the NOF, Fragility fractures are the 4th most burdensome chronic disease.



The Osteoporosis Drugs Market was valued at $10.85 billion in 2019, and is set to grow to $14.3 billion by 2022[30] (2019-2022). Some treatments are available, and many are under development by pharmaceutical companies. The principal driver of this market size is the increasing geriatric patient population.

	EU6	France	Germany	Italy	Spain	Sweden	UK
Estimated **number of individuals aged 50+ with osteoporosis** in 2015	20 million	3.8 million	5.3 million	4 million	2.8 million	500 000	3.5 million
Prevalence of osteoporosis among men (♂) and women (♀) aged 50+ in 2015	N.A.	♂ 6.9 % ♀ 22.7 %	♂ 6.7 % ♀ 22.5 %	♂ 7.0 % ♀ 23.1 %	♂ 6.8 % ♀ 22.5 %	♂ 6.9 % ♀ 22.5 %	♂ 6.8 % ♀ 21.8 %

Figure 4: Key statistics for Six European Countries[29]

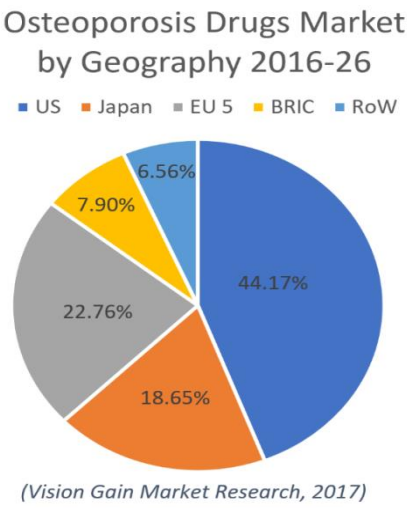
Recently, experts have cited increased incidence rates among women who contract the condition during menopause. Moreover, the geriatric correlation is also significant among females: 67% of 90-year-old women; 40% of 80-year-old women; 20% of 70-year-old women; and 10% of 60-year-old women suffer from the disease. In

[28] A Comprehensive Map of FDA-Approved Pharmaceutical Products, pharmaceutics 2018
[29] https://www.iofbonehealth.org/facts-statistics
[30] https://www.marketresearchfuture.com/reports/osteoporosis-drugs-market-2479

addition, 33% of women over age 50 will experience at least a single osteoporotic fracture.[31] Whilst relative incidence among males is lower, real growth in the number of patients in general, and the male share in particular, is driving the market. This increase can be partially attributed to lifestyle factors that are statistically more prevalent among men and which are known to deteriorate bone health. Such factors include alcohol abuse, a sedentary lifestyle, and tobacco use. Alcohol abuse has a particularly significant correlation with osteoporosis patients, and is perhaps the most influential growth factor for the number of male patients.[32] Recorded incidence among men for medical conditions is generally lower due to a known trend whereby men are far less likely to seek medical assistance than women. Recent awareness programs to address this issue will see higher reporting rates among men and will increase their incidence numbers in both real terms and relative to the number of female patients.

Geographic Segmentation

Globally America is the largest market for osteoporosis drugs, due to high prevalence of osteoporosis in the region. According to a report by the National Osteoporosis Foundation in 2016, around 54 million adults in the U.S. suffer from osteoporosis or have low bone density[33]. Europe is the second-largest market for osteoporosis drugs. The developed regions are expected to hold their market leadership in the near future but to lose market share due to the rise of the Asia Pacific region which is expected to be the fastest growing region in the osteoporosis drug market. The Asia pacific region will be led by China and India. China's demand for osteoporosis drugs has grown at a fast pace in the past few years. Geographical analysis of the Chinese osteoporosis drug market shows that there is huge growth potential for the osteoporosis drug market in many cities including Shanghai, Beijing, Guangzhou, and Hangzhou. To gain a competitive advantage, market players should develop cost-competitive drugs with easy dosage patterns, which promote bone building effectively. Large numbers of patients are unable to comply with the strict dosage schedule of traditional osteoporosis drugs. According to recent publications China's demand for osteoporosis drugs will continue to grow at 9% through 2027[34] [35]. Africa is expected to be a laggard in the global osteoporosis market[36].



(Vision Gain Market Research, 2017)

Market Drivers

- Diminishing role of hormone replacement therapy in osteoporosis treatment leads to higher use of drugs in newer product classes
- Increased screening rates and awareness towards female health
- Chronic use of glucocorticoids and aromatase inhibitors that are increasingly used for breast cancer as well as hormone deprivation therapies used for prostate cancer both known to increase osteoporosis
- New product introductions stimulate market penetration and increase awareness
- Aging patient population boosts demand
- Conditions and medical procedures that may cause bone loss such as cancer, autoimmune disorders, thalassemia, hormonal disorders, modern lifestyle etc.
- In the US, osteoporosis treatment is invariably and generously reimbursed because it is considered medically critical

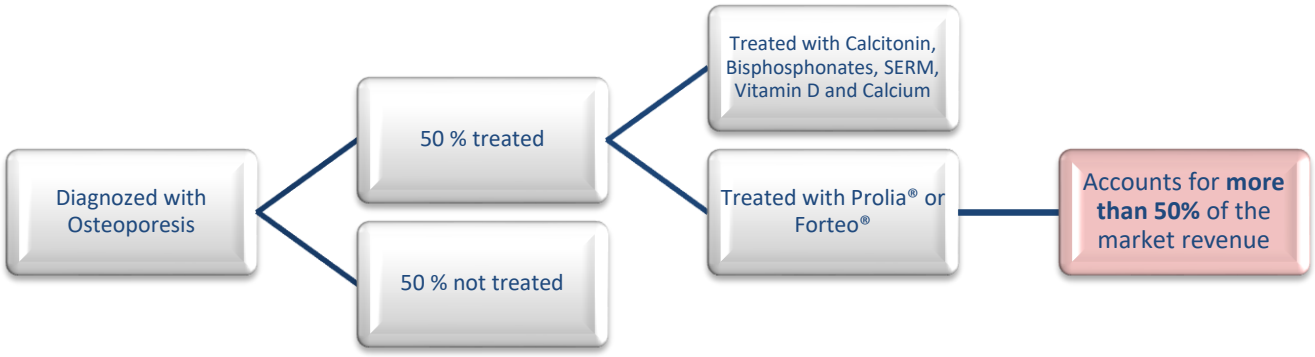
[31] https://www.iofbonehealth.org/facts-statistics#category-19.
[32] Grandview Market Research. Osteoporosis Drugs Market Analysis By Product (Branded, Bisphosphonates, Parathyroid Hormone Therapy, Calcitonin, Selective Estrogen Inhibitors Modulator (SERM), Rank Ligand Inhibitors, Generics), And Segment Forecasts, 2014 – 2024. (2015).
[33] https://www.coherentmarketinsights.com/press-release/osteoporosis-treatment-market-to-surpass-us-166-bn-threshold-by-2026-1063
[34] http://tmrreport007.pixnet.net/blog/post/110833687
[35] https://www.researchandmarkets.com/reports/3453717/osteoporosis-drugs-companies-in-china
[36] http://www.digitaljournal.com/pr/4085551

- Although out-of-pocket costs for osteoporosis patients are generally low, their variance is high, ranging between $5 and $150 depending on the treatment and the insurer's policy with respect to the treatment.[37]

Market Constraints

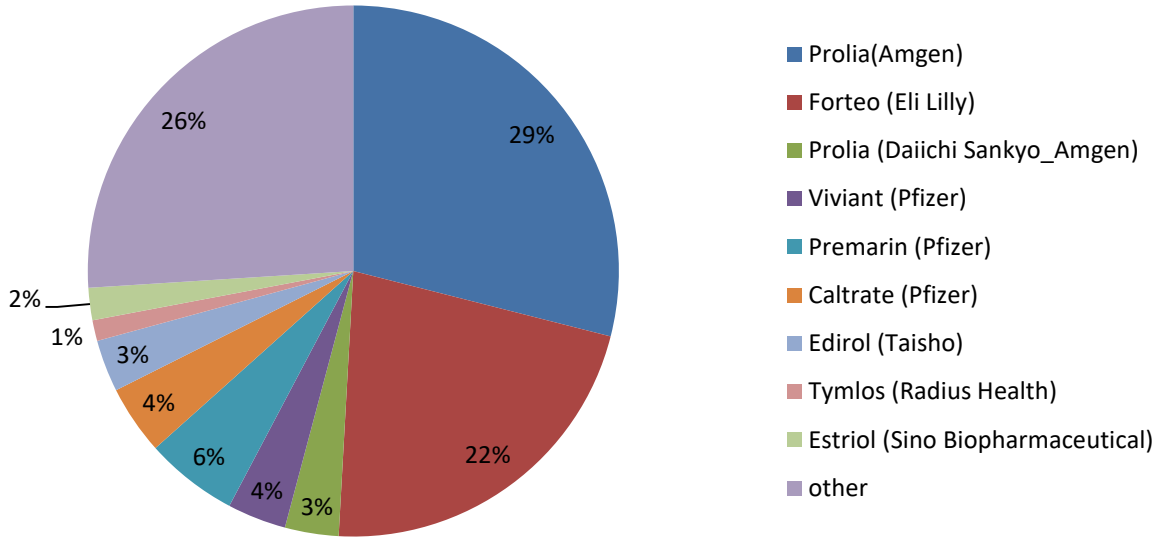
- Side effects and/or intolerance to medication: Bisphosphonates aren't well absorbed in the stomach and can cause upset stomach and heartburn; Forteo® is given by injection but patient's compliance is low.
- High cost of therapy
- Complex drug-taking regimen for the elderly
- Low levels of awareness, treatment and diagnosis due to asymptomatic nature of the condition
- Limited product differentiation as the marketplace becomes increasingly crowded
- Declining reimbursement rates for DEXA scans in the US could lead to fewer diagnoses and thus less patients seeking treatment despite their suffering from the condition.
    - On the other hand, technological development of alternative diagnoses and screening solutions which are reimbursed favorably may sufficiently mitigate this constraint

According to Frost & Sullivan, approximately 50% of osteoporosis patients are not treated at all. More than 50% of the ones that accept treatment receive either Prolia® (Amgen) or Forteo® (Eli Lilly) which currently dominate the market. The approval of EVENITY™ (Amgen) will enlarge Amgen's market share.



[37] US Department of Health. National Health and Nutrition Examination Survey. (2017).

Osteoporosis: Worldwide Market Share (2018)



Source: Evaluate Pharma

Hypoparathyroidism Drug Market

Market Size

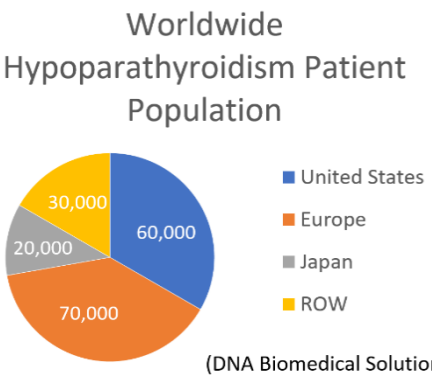
The global hypoparathyroidism treatment market size is expected to be $663.7 million in 2019 with a CAGR of approximately 8% through 2026 (2018-2026)[38].

The hypoparathyroidism drug market is extraordinarily limited, and prior to the technological advent of oral-based solutions, consisted of a single player, Takeda Pharmaceuticals (formerly SHIRE Pharmaceuticals). The PTH injection to treat hypoparathyroidism (hereinafter referred to by its trade name, *Natpara/Natpar*) was developed by NPS (acquired by Shire for $5.2 billion in 2015). On January 8th 2019, Takeda Pharmaceutical Company Ltd. acquired Shire PLC which is one of the biggest pharma deals in history, and the largest-ever international takeover by any Japanese company, at a value of $62 billion[39].

In 2016, Natpara generated revenues of $85.3 million, a significant increase of more than 350% from 2015.[40] Ever since its approval in 2015, Natpara has demonstrated a year-on-year growth of 72.8% through 2017. Despite Natpara's side effects which include possible bone cancer (osteosarcoma) and high blood calcium (hypercalcemia), the US currently accounts for 99 % of the total Natpara sales. In the EU, sales of Natpara reached $109.8 million, in H1-2018. Both the EU and US regions represent substantial revenue growth opportunities. Natpara holds approximately a $2 billion market opportunity[41].

[38] https://www.prnewswire.com/news-releases/hypoparathyroidism-treatment-market-will-reach-at-a-cagr-of-8-from-2018-to-2026-837260191.html
[39] http://fortune.com/2018/05/08/takeda-buys-shire-62-billion-pharma/
[40] Shire Pharmacueticals Plc. Annual Report 2016. (2017).
[41] https://www.prnewswire.com/news-releases/hypoparathyroidism-treatment-market-will-reach-at-a-cagr-of-8-from-2018-to-2026-837260191.html

The prevalence of hypoparathyroidism in the U.S. is estimated at 37 per 100,000, 24 per 100,000 in Denmark[42] and 10.2 per 100,000 in Norway. The total number of individuals diagnosed with chronic hypoparathyroidism is estimated at about 60,000-115,000 in the U.S. The majority of patients are female[43].



(DNA Biomedical Solutions Ltd, 2017)

(There are only a few estimates of the prevalence of hypoparathyroidism in the published literature. Results from a recent study using a large US claims database reported an estimated prevalence of 65,389 insured individuals with chronic hypoparathyroidism in 2008; extrapolation to uninsured individuals gave a prevalence estimate of 78,000[44].)

Market Drivers

- Despite the high costs of rare disease treatment by injection ($100K annually per patient), insurers are usually willing to cover the costs because the patient population is relatively small and the condition can be life-threatening
- Reimbursement policy for an orally ingestible solution would only be more favorable given the lowered risk, and lower practitioner costs due to the safe self-administration of oral alternatives
- Growing prevalence of hypoparathyroidism due to an increase in the number of thoracic surgeries and incidence of cancer
- The demographic drivers of the hypoparathyroidism treatment market include the growing geriatric population and healthcare expenditure across the globe
- Large presence of major players such as Takeda Pharmaceuticals, and Entera Bio, among others, is also expected to drive the growth of the hypoparathyroidism treatment market in the US
- The increasing rate of drug abuse, smoking and alcohol consumption; all of these cause a variety of health problems and imbalance in body hormones
- The development of healthcare infrastructure across the globe coupled with governmental support for hypoparathyroidism treatment is expected to drive the growth of the hypoparathyroidism treatment market

Market Constraints

- Delay in FDA and regulatory approval for drugs might restrain the growth of the market
- Despite *Natpara* receiving landmark approval from the FDA as the first regulated hormone replacement in treating the condition, the FDA warned that once-a-day treatment was far less effective than treatment several times per day (Food and Drug Administration, 2014). The latter preferred dosage will only be easily administered if the substance can be ingested orally. (In the hypoparathyroidism treatment market, Natpara is an approved drug with a **black box** warning notified by the U.S. FDA in January 2015 – enjoying an exclusivity period until 2022[45]).

[42] http://raredisorders.imedpub.com/hypoparathyroidism-review-of-the-literature-2018.pdf
[43] Shire annual report 2016
[44] Monica Therese B. Cating-Cabral, Bart L. Clarke, Epidemiology of Hypoparathyroidism,
[45] https://www.futuremarketinsights.com/reports/hypoparathyroidism-treatment-market

- Orphan drug designation, an accelerated pathway with benefits is a regulatory classification granted to unique FDA approval candidates being developed to address insufficiently met medical needs for diseases affecting a relatively small share of the population (up to 200,000 people in the U.S.). The program is designed to incentivize pharmaceutical firms to develop drugs for rare medical conditions.
- Benefits include: taxation benefits, grants, government R&D subsidies, higher prices, barriers to entry for production of generic drugs, and most importantly, seven years of market exclusivity (even if the patent period ends, the company can continue operating monopolistically).

Company's Products

Intellectual property:

As of December 31, 2018, Entera Bio's patents claimed compositions comprising a protein, an absorption enhancer, and a protease inhibitor as well as methods for oral administration of a protein with enzymatic activity. Their patents have been issued in the U.S., Australia, Japan, China, Israel, Canada, New Zealand and Russia. Related patent applications are pending in the U.S., the European Union, Hong Kong, Brazil, China and India. The company's patents for hypoparathyroidism and osteoporosis, once issued, would expire in 2036.[46]

The company's global patent portfolio included the following:

- Patent applications have been filed to specifically cover PTH (1-34). Such patents have already been granted in the U.S., Australia, Israel, Russia and Japan. Applications in the remaining jurisdictions are pending.
- Two patent applications and one Patent Cooperation Treaty (PCT) application (international filing) may cover certain oral administration technologies
- Three patent applications filed in various jurisdictions, that if issued as patents containing substantially the same claims as those in the applications, would contain method of treatment claims covering the use of orally administered PTH for the treatment of osteoporosis, hypoparathyroidism, and bone fractures and related conditions.

Entera Bio's oral delivery technology is a drug carrier platform that can be applied to an array of molecular and biological solutions. The company addresses large biological substances with proven therapeutic and side effect profiles that are commonly given as injections for under-attended diseases, in an attempt to provide even greater efficacy to the injectable treatments. Their carrier platform consists of two key product features, the first being ***a molecular protection system*** preventing drug breakdown and lengthening the half-life of the therapeutic drug delivered into the gut, and the second component being ***an absorption enhancer*** which enable the absorption of a therapeutically active agent in a controlled manner.

The first two products in the company's pipeline are targeted towards osteoporosis and hypoparathyroidism, and are both based on a formulation of recombinant parathyroid hormone (PTH (1-34)), an important hormone in bone remodeling and serum calcium regulation. (1) ***EB613 for osteoporosis***- Entera Bio is set to perform a phase 2a dose ranging study in patients. The company aims to use the 505(b)(2) regulatory pathway for EB613 development as an osteoporosis treatment. The 505(b)(2) pathway is a much faster route for approval, less data is needed which means significantly lower costs. Following a successful phase 2a study, Entera Bio plans to perform only one pivotal study. ***From a strategic point of view***, after completing the phase 2a study, Entera Bio can choose to sell or co-develop that asset, eliminating the need for more capital, or Entera Bio can continue the development 505(b)(2) pathway with relatively small amounts of capital and a rapid data read out[47]. (2) ***EB612 for Hypoparathyroidism-*** A phase 2a study was completed successfully and the company is headed towards an end of phase 2 meeting with the FDA in 2020. (3) The third indication in the company's pipeline, based upon the first product, addresses non-union fractures, an indication currently without an established conclusive clinical treatment. The concept is that PTH (1-34), which is a

[46] DNA Biomedical Solutions, Financial Report for 2016. (2017)
[47] Entera Bio investors presentation 2019

bone building hormone, will help to reduce the amount of non-unions occurring each year and can help in the bone healing process for people who suffer from non-union.

EB613 (PTH 1-34) for Osteoporosis

Background

Osteoporosis is a progressive systemic skeletal disease, characterized by a reduced bone mass and poor bone quality. Bone remodeling is an ongoing process that consists of two stages – bone resorption and bone formation. Resorption occurs when osteoclasts are recruited to the site of fatigued or damaged bone and digest the bone forming cavities. Osteoblasts are recruited to these cavities and form new bone while a large number of hormones and messenger systems are involved in the feedback loops that regulate bone remodeling. The entire process takes a minimum of 3 months.

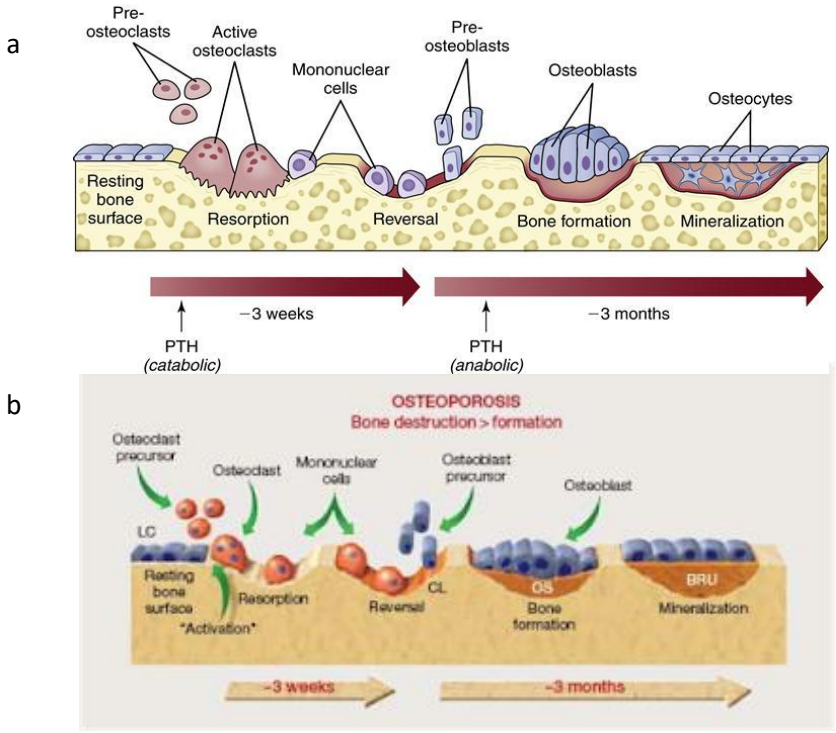


Figure 5: Bone remodeling pathway in (a) healthy subjects[48] and (b) osteoporosis patients[49]

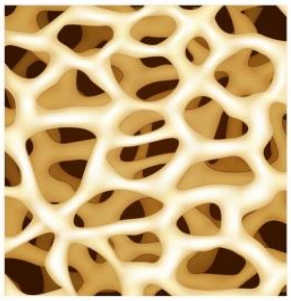
Decrease in bone density results from loss of minerals from the bone, primarily calcium. Consequently, bone strength decreases, resulting in fragile bones and increased risk of bone fractures. Osteoporosis shows no symptoms until a fracture actually occurs. Osteoporotic fractures occur in areas where healthy people would normally not break a bone, most commonly in the hip, wrist or spine. These fractures increase dramatically with age, and often cause rapid deterioration in health, resulting in death. Sometimes this phenomenon runs in families as it is inherited. Due to the asymptomatic nature of the condition, many mild-to-moderate patients are hesitant to take currently available therapies, or may not even know that they are at risk.

There are multiple types of osteoporosis:

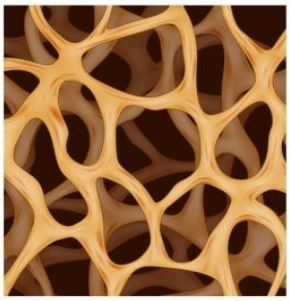
1. Post-menopausal osteoporosis is hormonal in origin and occurs only in women
2. Senile osteoporosis is a consequence of the natural aging process and occurs in men as well as women
3. Secondary osteoporosis is caused by another condition/disease or drug and occurs in men as well as women
4. Idiopathic juvenile osteoporosis occurs in children from unknown causes

[48] https://basicmedicalkey.com/structure-and-function-of-the-musculoskeletal-system/
[49] http://thescopepopculturescience.blogspot.com/2016/06/osteoporosis-dying-osteocyte.html

- About 200 million people worldwide are affected by osteoporosis – about 80% are women[50]
- Over 10 million patients are affected in the US[51]
- Every second woman and every fifth man over 50 years of age suffers an osteoporotic fracture [52]
- Approximately 30% of all postmenopausal women in the U.S. and in Europe have osteoporosis
- At least 40% of these women and 15-30% of men will sustain one or more fragility fractures in their remaining lifetime[53]



Normal Bone



Bone with Osteoporosis

- Caucasian (white) and Asian women, especially those who are post-menopausal, are at highest risk[54].
- Worldwide, a bone breaks due to osteoporosis every three seconds[55].
- In Europe, India, Japan and the USA alone, there are an estimated 125 million people with osteoporosis.
- Osteoporotic fractures cause an annual global loss of 5.8 million healthy life years to disability[56].
- In women over 45 years of age, osteoporosis accounts for more days in hospitals than diabetes, heart attacks or breast cancer.
- Current direct costs of hip fracture treatment in the US are up to $18 billion. By 2020, the cost of hip fracture treatments is expected to range from $31 billion to $62 billion. The cost of all osteoporosis related fractures is currently equivalent to the costs of cardiovascular disease and asthma[53].

The global osteoporosis treatment market was valued at $11.74 billion in 2016, and is expected to reach $16.5 billion by 2025, expanding at a CAGR of 3.9% from 2017 to 2025[57]. (See scheme on page 15)

The parathyroid hormone (PTH) is one of the two major hormones modulating calcium and phosphate homeostasis in the body. It is an anabolic agent, in which therapies using it results in new bone formation. Intermittent administration of recombinant human PTH has been shown to stimulate bone formation. The first 34 amino acids (the bioactive portion of the complete hormone molecule containing 84 amino acids) have already been used in the treatment of some forms of osteoporosis by the drug Teriparatide (brand name Forteo®) since 2002, given as an injection. The drug is also occasionally used off-label to speed fracture healing. Entera Bio's EB613 utilizes PTH (1-34), the same active molecule as Forteo®, but for oral treatment of osteoporosis.

The World Health Organization (WHO) has proposed criteria for the diagnosis of osteopenia (low bone mass), osteoporosis, and severe osteoporosis in women. All classifications of bone density incorporate the results of a BMD test.

[50] https://www.iofbonehealth.org/facts-statistics
[51] http://www.qscience.com/doi/pdf/10.5339/jlghs.2016.2
[52] http://www.iofbonehealth.org/facts-statistics.
[53] https://www.iofbonehealth.org/epidemiology
[54] https://www.nof.org/preventing-fractures/general-facts/what-women-need-to-know/
[55] https://www.iofbonehealth.org/facts-statistics
[56] https://www.iofbonehealth.org/sites/default/files/media/PDFs/Fact%20Sheets/2014-factsheet-osteoporosis-A4.pdf
[57] https://www.researchandmarkets.com/reports/4431604/global-osteoporosis-treatment-market-size-market

Table 1 T-Scores and WHO Diagnostic Criteria for Osteoporosis[4,14]	
Interpretation	**T-Score***
Normal	–1.0 and higher
Osteopenia	–1.0 to –2.5
Osteoporosis	–2.5 and lower
Severe osteoporosis	–2.5 and lower with one or more fragility fractures
* Reference values vary by geographical location. WHO = World Health Organization.	

Figure 6: T-Scores and WHO Diagnostic criteria

There are two principal types of osteoporosis. ***Primary osteoporosis*** is often associated with age and sex hormone deficiency. Age-related osteoporosis results from the continuous deterioration of the trabeculae in bone. In addition, the reduction of estrogen production in postmenopausal women causes a significant increase in bone loss. In men, sex-hormone-binding globulin inactivates testosterone and estrogen as aging occurs, which may contribute to the decrease in BMD with time. ***Secondary osteoporosis*** is caused by several comorbid diseases and/or medications. Diseases implicated in osteoporosis often involve mechanisms related to the imbalance of calcium, vitamin D, and sex hormones[53].

Treatment of osteoporosis is strictly related to severity of pathology. Initially, it is important to prevent fragility fractures with an active lifestyle and adequate nutritional supplements, including daily calcium and vitamin D intake, performing weight bearing activities, avoiding or stopping smoking, and avoiding heavy alcohol consumption. Depending on bone density, several pharmacological treatments could be used with the aim of increasing bone mass and strength by inhibiting bone resorption or promoting bone formation[58].

The patients who need pharmacologic therapy are the following:

- Patients with a history of a fracture of the hip or spine
- Patients without a history of fractures but with a T-score of −2.5 or lower
- Patients with a T-score between −1.0 and −2.5 if FRAX* (major osteoporotic fracture probability) is ≥20% or hip fracture probability is ≥3%[59].

Currently, no treatment can completely reverse established osteoporosis. Early intervention can prevent osteoporosis in most people. For patients with established osteoporosis, medical intervention can halt its progression. Therapy should be individualized based on each patient's clinical scenario, with the risks and benefits of treatment discussed between the clinician and patient.

Clinical Data for EB613

Entera Bio completed two separate Phase 1 pharmacokinetic studies in which the patients received commercial subcutaneous (SC) PTH (1-34) injection or the oral formulation of PTH (EB613). The pharmacokinetic profile of EB613 was characterized by rapid absorption and disappearance rates hence leading to short pharmacokinetic exposure to the drug (Cmax of the oral PTH (1-34) formulation was dose dependent reaching up to approximately two-fold higher than the Cmax of the injection).

**** In February 2008, a tool called FRAX was released by the WHO. FRAX is the best effort to date to incorporate risk factors into determination of fracture risk and is more effective in conjunction with BMD than without. Important risk factors—risks that are amenable to intervention—can be determined easily. FRAX can be used for men as well as women and is validated globally, with output and utility of results adaptable to individual populations or regional/national standards, but there are also major limitations.***

[58] https://www.frontiersin.org/articles/10.3389/fphar.2017.00803/full#B40
[59] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4876714/pdf/nihms787529.pdf

Entera Bio's development combines the proven efficacy of PTH in increasing bone formation in osteoporosis patients with the additional benefit of permitting oral administration, which reduces the treatment burden on patients, leading to higher patient and physician acceptance. Each dose of oral PTH has the potential to trigger a Cmax peak, stimulating osteoclasts and osteoblasts, thereby increasing overall bone formation (bone homeostasis is maintained by a balance between bone resorption by osteoclasts and bone formation by osteoblasts; osteoblasts not only play a central role in bone formation by synthesizing multiple bone matrix proteins, but regulate osteoclast maturation by soluble factors and cognate interaction, resulting in bone resorption)[60].

Cyclic AMP (cAMP) levels are an indicator for PTH's activity. They can be measured in the plasma and used as a biological marker of PTH activity. The graph below shows that the pharmacodynamics profiles for EB613 are compelling and very similar to Forteo® (SC-PTH).

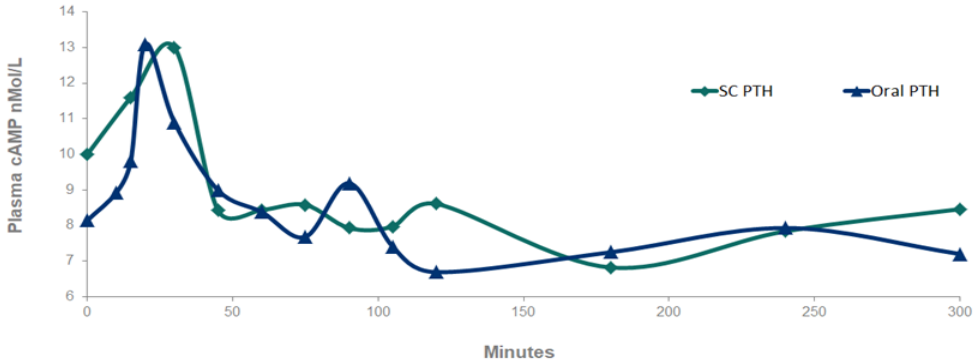
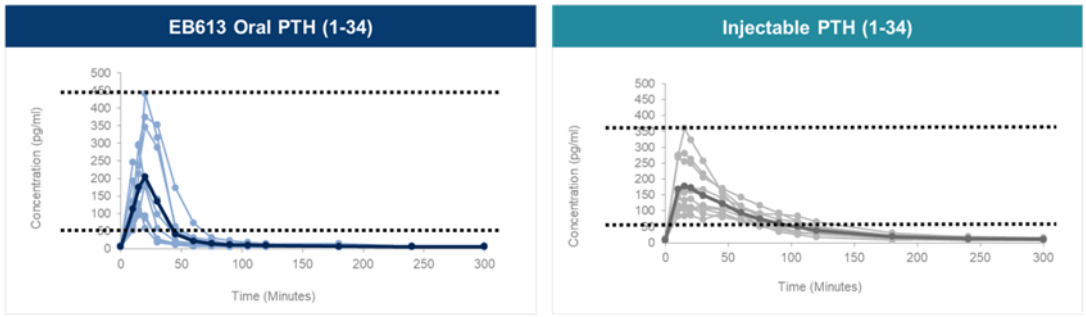


Figure 7a: The pharmacodynamics of EB613 (oral PTH) versus Forteo® (SC PTH) (Source: Entera Bio investor's presentation)

Pharmacokinetic studies in both the injectable PTH (1-34) and oral PTH (1-34) show a rapid increase in plasma concentrations followed by a fast elimination phase. This is significant for attaining the **desired anabolic effect** by transiently activating the biological pathways and possibly even more so with Entera Bio's oral PTH as its profile is **sharper** than the injection with a more rapid return to baseline ((Hypercalcemia, higher blood calcium, is a potential side effect of injected PTH that can potentially be reduced by taking the oral version of PTH). The prolonged increase in PTH levels following an injection may reduce the desired anabolic effect. This gives an advantage to oral PTH (1-34) versus the injectable version.



Formulation	Participants	Cmax (pg/ml)	Tmax (min)	Coefficient of Variation (%)
EB613 Oral PTH	10	235.6 ± 36	16.5 ± 1.2	48
Injectable PTH	10	184.2 ± 26	16 ± 1.8	45

Figure 7b: The pharmacokinetic of EB613 (oral PTH) versus Forteo® (Injectable PTH)[61]

Entera Bio's next step in this clinical development program is to conduct a Phase 2a multi-center dose-ranging study (low dose, middle, high and placebo) in approximately 160 osteoporosis patients in four separate sites, in order to study both safety and the optimal dose to advance into a phase 3 pivotal study. This dose ranging study will include

[60] http://www.eurekaselect.com/90600/article
[61] Entera Bio investor's presentation, 2019

multiple bone markers and various additional safety endpoints. The Company will be conducting several nonclinical safety assessment studies in parallel. Entera Bio can choose to sell or co-develop that asset eliminating the need for more capital.

Assuming a favorable outcome of these studies, the Company is planning a single Phase 3, multicenter study comparing Oral PTH with Forteo® over a 12-month treatment period, to begin in 2020. The study is likely to be conducted in the U.S. and Europe, and potentially enroll between 600 and 800 patients in total, depending on statistical powering assumptions. In the pre-IND meeting with the FDA (November 2018), Entera Bio discussed its development plan of Oral PTH for the treatment of osteoporosis. In addition to discussing various aspects of the nonclinical and clinical development plan, the meeting focused on the 505(b)(2) regulatory pathway and the use of bone mineral density (BMD) rather than fracture incidence as the primary endpoint to support a biologics license application (BLA).

Currently, there are no new drugs under development that are given orally for the treatment of osteoporosis. This fact positions Entera Bio as the first oral bone-building therapy for Osteoporosis.

EB613 for Non-Union Fractures

An additional indication treatment in the Company's pipeline, that makes use of EB613, addresses non-union fractures, an indication which currently has no proven treatment solution. Non-union of fractures occurs when normal bone healing is interrupted and a fracture does not heal properly, if at all. This complication may result from a fracture's movements, poor blood supply or infection. The most common reported risk factor is an open fracture.

Various factors increase the risk of non-union bone fractures: severe fracture, smoking, the use of anti-inflammatory or opioid drugs, poor nutrition, and the use of anticoagulant drugs. Many of these risk factors interfere with the body's ability to produce new blood vessels (the process of vasculogenesis) that are essential for healing. Without vasculogenesis, the body cannot deliver the molecular building blocks and the specialized cells needed to form new bone in the void caused by the fracture[62].

Bone healing failure occurs in 5-10% of all fractures.[63] In the U.S., there are approximately seven million new fractures each year, with approximately 300,000 delayed union or non-union fractures. Estimates for the average non-union treatment cost vary from approximately $25,000 to $45,000. These are primarily fractures of the pelvis and hip, which involve extended hospital stays and result in very high costs to patients.

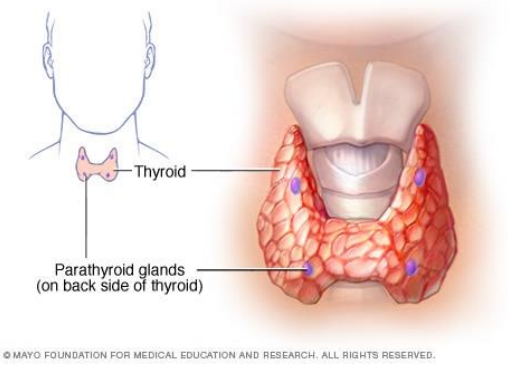
Studies have suggested that PTH can accelerate bone healing. PTH increases the activity and number of osteoblasts, which are responsible for bone formation, making it a potential treatment when bone healing is delayed.

Entera Bio aims to investigate the efficacy of EB613 for delayed-union or non-union fractures by either pursuing fracture treatment as an additional use of EB613 or further modifying the formulation if studies suggest they could achieve a PK profile that is more efficacious for bone fractures. Entera Bio's management believes that they will be able to use the PK data generated with EB613 in phase 1 clinical trials relating to osteoporosis to progress directly to a phase 2a clinical trial for oral PTH product candidates for non-union or delayed-union bone fractures.

[62] https://www.nature.com/articles/550S193a
[63] Zura R, et al. JAMA Surg. 2016

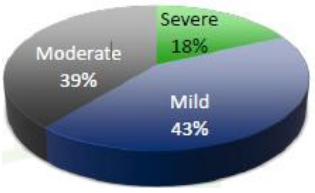
EB612 (PTH 1-34) for Hypoparathyroidism

Hypoparathyroidism is an uncommon condition in which the parathyroid glands in the neck are either missing entirely, or secrete abnormally low levels of parathyroid hormone (PTH). PTH is key to regulating and maintaining a balance of two important minerals - calcium and phosphorus. The level of calcium in the blood is sensed through the calcium-sensing receptor in the parathyroid chief cells that secrete the parathyroid hormone accordingly. Magnesium is required for PTH secretion as well. PTH acts on several organs to increase calcium levels: it increases calcium absorption in the bowel, prevents calcium excretion, increases phosphate release in the kidney and in bones, and increases calcium through bone resorption.



The main symptoms of hypoparathyroidism result from low blood calcium levels (also known as hypocalcemia), which interfere with normal muscle contraction and nerve conduction, often causing cramping and twitching of muscles or tetany (involuntary muscle contraction), peripheral neuropathies, electrolyte imbalances, and can even be fatal in severe cases. Risk factors for contracting the condition may include family history, recent neck surgery (particularly if involving the thyroid), and certain autoimmune or endocrine disorders.[64] [65] The diagnosis is made with blood tests, and other investigations such as genetic testing.

A healthy diet, as well as calcium or vitamin D replacement can ameliorate the symptoms, but can increase the risk of kidney stones and chronic kidney disease. Severe hypocalcaemia, a potentially life-threatening condition, is treated with intravenous calcium (e.g. as calcium gluconate). Overall, the treatment of hypoparathyroidism is limited. The only available approved drug treatment is a daily injection of a recombinant complete parathyroid hormone (PTH-1-84)[66], which was developed by NPS (acquired by Shire in 2015), and has since traded under the brand name Natpara. It is usually administered in more severe cases of low blood calcium levels[**].



Hypoparathyroidism is considered a heavy burden illness, with 72% of patients experiencing more than ten symptoms on a daily basis (such as weakness, muscle cramps, headache, and brain fog)[67]. It has a high economic impact as 78% of the patients report six missed work days per year and many are unemployed. Chronic hypoparathyroidism affects approximately 180,000 patients worldwide. Of those, approximately 60,000 are in the US: approximately 18% of patients are classified as severe, 39% as moderate and 43% as mild. Entera Bio estimates that its drug candidate will extend the treatment to a broader range of patients, and can treat patients across the spectrum of severity.

The global hypoparathyroidism treatment landscape that only gained much significance post the FDA approval of Natpara in 2015 is projected to grow at a rather robust CAGR of approximately 8% through 2026. The valuation of the global hypoparathyroidism treatment market is expected to stand at $663.7 million throughout 2019. The global

****The recombinant human parathyroid hormone (1-34) and natural human parathyroid hormone (1-84) in a human body have a same amino acid sequence of first-34th amino acids at the C-terminal, and have same biological activities and physiologic and pharmacologic characteristics. The recombinant human parathyroid hormone (1-34) has the advantages of simple technology, good reappearance and suitableness for the industrialized production[45].**

[64] https://www.enterabio.com/pipeline/bone-healing
[65] http://www.mayoclinic.org/diseases-conditions/hyperparathyroidism/symptoms-causes/dxc-20319888
[66] https://patents.google.com/patent/CN103451219A/en
[67] Hadker N, et al., Endocr Pract. (2014) 20, 671-679

hypoparathyroidism treatment market holds the potential to exceed $ 1.1 billion in revenues by 2026.[68] As of March 2019, there are around 47 known ongoing clinical programs, globally, at different stages of development, wherein, 43 are interventional studies and 19 involve APIs with high potential market equity.

The company holds orphan drug designation for hypoparathyroidism from the FDA (US) and EMA (Europe) since April 2014 and June 2016, respectively, to develop the oral drug PTH (1-34). Orphan drugs are a regulatory classification granted to unique FDA approval candidates being developed to address insufficiently met medical needs for diseases affecting a relatively small share of the population (up to 200,000 people in the US). The program is designed to incentivize pharmaceutical firms to develop drugs for rare medical conditions. Such benefits include: taxation benefits; grants; government R&D subsidies; higher prices; barriers to entry for production of generic drugs; and most importantly, seven years of market exclusivity (even if the patent period ends, the company can continue operating monopolistically). Without such incentives, drug companies would be dissuaded from developing solutions with relatively high development costs, and which appeal to only a small consumer market. Accordingly the company can take advantage of the benefits above-mentioned, to drive their product to market and maximize its profitability.

Clinical Data for EB612

Entera Bio completed a multicenter, open-label, phase 2a clinical trial in hypoparathyroidism with EB612, administered three to four times daily in parallel to a baseline regimen of calcium and vitamin D. The trial included 17 hypoparathyroidism patients (postsurgical 68.4%, autoimmune 26.3% and hereditary 5.3%, while the mean age was 44.5 years) and was carried out in Israel.[69] The trial results met the primary endpoints including reduction in calcium supplements and plasma levels, demonstrating a promising safety profile. In addition, phosphate levels decreased overall as well as consistently following each dose. Importantly, PTH (1-34) is well studied, and has been administered as an **injectable drug** with the brand name Forteo® to millions of osteoporosis patients for more than a decade, which further strengthens its safe use. PTH pulsed throughout the day better mimics endogenous hormone levels. Moreover, clinical evidence supports multiple daily dosing; NIH studies have shown that multiple doses daily are superior to one dose a day (QD). All in all, phase 2a results demonstrate the potential for an improved profile versus Natpara.

The company recently completed a clinical trial to evaluate the pharmacokinetic and pharmacodynamics (PK/PD) profile of various EB612 dose regimens. After the completion and evaluation of the PK/PD, the company is expected to initiate a phase 2b/3 clinical trial for EB612 for hypoparathyroidism treatment. The trial will evaluate the dosage and examine the effectiveness and safety profile of EB612 in an expanded population of patients with hypoparathyroidism conducted at multiple trial sites. The phase 2b/3 pivotal trial will include 120-160 patients, EB612 will be individually titrated to patients. Like Natpara, it should only need one pivotal trial, conducted with the same KOLs/PI sites. In parallel to the pivotal study, a head-to-head study is planned in the US versus Natpara to show EB612's potential to be superior to Natpara and accelerate market acceptance. These milestones are defined to follow an efficient and well established pathway on the way to receiving regulatory approval for marketing EB612. The FDA and EMA have granted EB612 orphan drug designation for the treatment of hypoparathyroidism. Entera Bio aims to utilize additional funds to prepare EB612 for advanced clinical studies and ultimately for regulatory approval.

[68] https://www.prnewswire.com/news-releases/hypoparathyroidism-treatment-market-will-reach-at-a-cagr-of-8-from-2018-to-2026-837260191.html

[69] Entera Bio Official Website.

Competitive analysis

Proteins and peptides now constitute a major proportion of therapeutic modalities being pursued for the treatment of various diseases. Nearly 30% of all drugs approved by the US Food and Drug Administration (FDA) in 2015–2018 were biologics. Development of alternative strategies for the non-invasive delivery of biologics must take into consideration the molecular mass of the biologic, the therapeutic dose and the relationship between these two parameters. Biologic size and dose can limit absorption, especially for biologics that require large doses[70].

Oral delivery is the most widely used route of administration for small-molecule drugs owing to its non-invasive nature (convenient for patients and thus has high patient compliance), and to its limited dosing frequency, which has been enabled by controlled-release formulations. These advantages are present in standard oral delivery technologies such as solid dosage forms (capsules and tablets), syrups, and other oral dosage forms. Technologies that enable and facilitate the oral delivery of biologics are highly desirable but remain elusive.

Companies which are attempting to develop oral carrier systems that will be able to deliver a variety of therapeutics with minimal modification include: Emisphere (USA), Evonik (Germany), Alkermes (Ireland), Anesta Corp. (US), Generex Biotechnology (US) and Alza Corp (US). As an example, Emisphere's Eligen system has the potential to deliver therapeutics from 0.5–150 kDa by a drug–carrier system known as SNAC.[71] A second such system is the gastro intestinal mucoadhesive patch system (GI-MAPS) of Evonik [72].

Over 20 biologics are being clinically investigated for oral delivery. Five peptides (octreotide for acromegaly, semaglutide for diabetes, insulin for diabetes, salmon calcitonin for osteoporosis and desmopressin for diabetes) are in phase III trials. The peptides being clinically investigated for oral delivery are all currently approved for use via injections, which has implications for regulatory approval — peptides previously approved for other routes of administration have a history of successful approval and safe and efficacious use in the clinic.

Name (company)	Delivery approach	Biologic	Application/indication	ClinicalTrials.gov identifier
Peptides				
Mycapssa (Chiasma)	Capsule using the proprietary technology platform Transient Permeability Enhancer	Octreotide	Acromegaly	• NCT01412424 (phase III) • NCT03252353 (phase III) • NCT02685709 (phase III)
Capsulin OAD (Diabetology)	Capsule using the proprietary technology platform Axcess	Insulin	Type 2 diabetes	EudraCT numbers: • 2005-004753-95 • 2006-006251-12
NN9924 (Novo Nordisk)	Tablet with absorption-enhancing excipients	Semaglutide	Type 2 diabetes	>25 trials, including: • NCT02827708 (phase III) • NCT02161588 (phase I) • NCT02877355 (phase I)
Ovarest (Enteris)	Peptelligence: improved solubility and absorption of peptides for oral delivery	Leuprolide	Pharmacokinetic and pharmacodynamic profiles in healthy female volunteers	NCT02807363 (phase II)
ORMD-0801 (Oramed)	Oral insulin capsule that prevents enzyme degradation and enhances intestinal absorption	Insulin	Type 1 and type 2 diabetes	• NCT02094534 (phase II) • NCT02954601 (phase II) • NCT02653300 (phase II) • NCT01889667 (phase II) • NCT02535715 (phase II) • NCT02496000 (phase II) • NCT00867594 (phase II)
TTP273 (vTv Therapeutics)	Tablet	Glucagon-like peptide 1	Type 2 diabetes	NCT02653599 (phase II)
Tregopil; formerly IN-105 (Biocon)	Tablet	Novel oral insulin molecule	Type 1 diabetes	NCT01035801 (phase I)
Oral HDV Insulin (Diasome)	Capsule containing insulin targeted to the liver	Insulin	Type 2 diabetes	• NCT00814294 (phase II/III) • NCT00521378
Oshadi Icp (Oshadi Drug Administration)	Oral formulation	Insulin	Type 1 diabetes	• NCT01973920 (phase II) • NCT01772251 (phase Ib) • NCT01973920 (phase II) • NCT01120912 (phase I)
TBRIA (Tarsa Therapeutics)	Tablet	Salmon calcitonin	Postmenopausal osteoporosis in women	• NCT00959764 (phase III) • NCT01292187 (phase II) • NCT00803686 (phase II) • NCT00620854 (phase II)

Figure 8: Current clinical trials and approved products for the oral delivery of biologics[69]

[70] https://www.nature.com/articles/nrd.2018.183
[71] http://www.emisphere.com
[72] http://healthcare.evonik.com

Competitive Landscape - Osteoporosis:

The goal of pharmacological treatment of osteoporosis is to maintain or increase bone strength, to prevent fractures, and to minimize osteoporosis-related morbidity and mortality caused by fractures throughout the patient's life. Current treatments for osteoporosis generally fall into two categories: antiresorptive medications that prevent bone loss but do not restore normal bone mass and anabolic medications to increase the rate of bone formation, and at least in part, restore lost bone.

The current osteoporosis treatment landscape is mostly antiresorptive comprising five principal classes of agents: bisphosphonates (Reclast, Fosamax, Bonviva), estrogens (Premarin), selective estrogen receptor modulators (Viviant, Evista), calcitonin (Miacalcin), and monoclonal antibodies (Prolia®). Each of these acts by reducing loss of bone mineral. The second type of treatment includes PTH therapy, which results in new bone formation (anabolic agent).

Bisphosphonates are oral drugs with proven anti fracture efficacy and a good safety profile that inhibits the bone resorption process, and are the most widely used first-line antiresorptive therapy.[73] However, bisphosphonates are characterized by GI disturbances and the risk of osteonecrosis of the jaw. In 2007 the total worldwide sales of the top ten bisphosphonate products reached almost $8 billion, but dramatically decreased to about $2 billion by 2015.[74]

Company	Brand	Pharmacological Class
AMGEN	• Prolia	• Anti-receptor activator of nuclear factor-kappaB ligand MAb
Lilly	• Forteo	• Parathyroid hormone
	• Edirol	• Vitamin D3 analogue
Pfizer	• Premarin	• Oestrogen agonist
NOVARTIS	• Reclast	• Bisphosphonate
Pfizer	• Caltrate	• Calcium supplement

The two most effective osteoporosis drugs on the market today are injections. The most recent entrant-**Prolia® (Denosumab)** is a monoclonal antibody that blocks a cascade of signals causing bone breakage, given as an injection every 6 months to prevent bone loss. In 2017, its sales reached approximately $2 billion, and are expected to increase further. The second type of drug, **Forteo®**, developed by Eli Lilly, is the only anabolic osteoporosis agent on the US market that increases bone mineral density by increasing bone formation. Forteo® is a recombinant form of PTH, administered by daily subcutaneous injections and recommended for people with osteoporosis who are at high risk for fractures. 2017 worldwide sales of Forteo® were $1.7 billion.

Recently the FDA has approved **EVENITY™** (romosozumab-aqqg) for the treatment of osteoporosis in postmenopausal women at high risk for fracture. EVENITY is the first and only bone builder with a unique dual effect that both increases bone formation and to a lesser extent reduces bone resorption (or bone loss) to rapidly reduce the risk of fracture.[75]

[73] Chen JS, et al., Nat Rev Endocrinol. (2011) 6;8(2), 81-91

[74] Evaluate Pharma

[75] https://www.amgen.com/media/news-releases/2019/04/fda-approves-evenity-romosozumabaqqg-for-the-treatment-of-osteoporosis-in-postmenopausal-women-at-high-risk-for-fracture/

The following table presents the total worldwide market value of the top 10 available products:

	Annual Sales (Indication) - WW - Sales								Growth per Year (%)						
Product	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2024**	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2024**
Prolia(Amgen)	1,968	2,243	2,477	2,677	2,840	2,927	2,983	3,001	+14%	+10%	+8%	+6%	+3%	+2%	+1%
Viviant (Pfizer)	206	277	340	393	443	489	526	564	+35%	+23%	+15%	+13%	+10%	+8%	+7%
Forteo (Eli Lilly)	1,749	1,698	1,404	1,053	844	716	608	515	**-3%**	**-17%**	**-25%**	**-20%**	**-15%**	**-15%**	**-15%**
Premarin (Pfizer)	469	438	424	413	402	391	380	370	-7%	-3%	-3%	-3%	-3%	-3%	-3%
Prolia (Daiichi Sankyo)[76]	209	253	286	315	335	346	357	368	+21%	+13%	+10%	+6%	+3%	+3%	+3%
Caltrate (Pfizer)	320	326	333	339	346	352	359	365	+2%	+2%	+2%	+2%	+2%	+2%	+2%
Abaloparatide TD (Radius Health)	-	-	-	-	4	76	207	321	-	-	-	n/a	n/a	+173%	+55%
Edirol (Taisho)	229	246	256	265	270	275	280	285	+7%	+4%	+4%	+2%	+2%	+2%	+2%
Tymlos (Radius Health)	12	98	186	263	310	291	256	243	+709 %	+90%	+42%	+18%	-6%	-12%	-5%
Estriol (Sino Biopharmaceutical)	125	152	165	177	189	200	212	224	+21%	+8%	+7%	+7%	+6%	+6%	+6%
other	**2,058**	**2,014**	**2,092**	**2,050**	**1,971**	**1,905**	**1,828**	**1,772**	**-2%**	**+4%**	**-2%**	**-4%**	**-3%**	**-4%**	**-3%**

Source: Evaluate Pharma. All Financial data in US $ (million)

Tymlos (Radius Health) is an Injectable abaloparatide which is similar to PTH in that it binds to PTH receptors and result in bone formation and increased bone mineral density. The drug was launched in April 2017 which resulted in $12.1 million in sales.

PF708 is being developed as a therapeutic equivalent candidate to Forteo®, which is approved and marketed by Eli Lilly and Company for the treatment of osteoporosis in certain patients with a high risk of fracture. Forteo® achieved $1.6 billion in global product sales in 2018[77]. The FDA agreed to review the 505(b)(2) New Drug Application (NDA) for the Company's lead product candidate, PF708. On February 28th 2019, Pfenex Inc. and Alvogen Ltd. announced entering into agreements expanding their collaboration to develop and commercialize Pfenex's lead product candidate, PF708 to the EU, to certain countries in Middle East, and North Africa (MENA) the ROW territories[78].

Except for the commercially available drugs for the treatment of osteoporosis, there are numerous drugs under development. Our search identified 45 drug candidates from stage I to late clinical or pre-registration stages.[79]

Other than Entera Bio, several other companies are developing oral delivery treatments of osteoporosis. Among them, **RGB-10** is a biosimilar of teriparatide (PTH) given as a subcutaneous injection, under development by Gedeon Richter (Hungary) for the treatment of osteoporosis. RGB-10 is the first biosimilar teriparatide granted marketing authorization in January 2017 by the European Medicines Agency.[80]

Ostora is a recombinant oral salmon calcitonin (rsCT) once-daily tablet at a preregistration stage, under development by Tarsa Therapeutics for the treatment of osteoporosis. It was previously under development by

[76] https://www.amgen.com/media/news-releases/2007/07/amgen-and-daiichi-sankyo-announce-agreement-for-denosumab-in-japan/
[77] https://www.globenewswire.com/news-release/2019/02/19/1734258/0/en/Pfenex-Announces-FDA-Acceptance-of-NDA-for-PF708.html
[78] https://www.marketwatch.com/press-release/pfenex-and-alvogen-expand-development-and-commercialization-collaboration-for-pf708-a-therapeutic-equivalent-candidate-to-forteorforsteor-to-the-eu-mena-and-row-2019-02-28
[79] Pharmaprojects-a drug development database
[80] http://www.gabionline.net/layout/set/print/Biosimilars/Research/Biosimilar-teriparatide-approved-for-the-treatment-of-osteoporosis

Unigene Laboratories, Inc., a biopharmaceutical company in the US, which develops oral and nasal drug delivery technologies.[81]

Lasofoxifene (phase 3) is the lead compound in a series of partial estrogen agonists based upon Ligand's intracellular technology research, developed by Pfizer, for the treament of postmenopausal osteoporosis. It was also under development for vaginal atrophy. Currently it is at the phase III clinical stage.

K-5211, Ligandrol (LGD-4033) is a novel selective androgen receptor modulator (SARM), discovered by Ligand Pharmaceuticals for the treatment of sarcopenia, muscle wasting, cachexia and osteoporosis. The drug was licensed to Viking Therapeutics, and is currently in phase II.

Donesta® by Mithra (phase 2) is a product candidate for a new generation of hormone therapy, with the oral administration of Estetrol (E4) for Vasomotor Menopausal Symptoms (VMS) relief[82]. E4 has a positive action on bone metabolism and could therefore be used in the context of the prevention or treatment of osteoporosis.

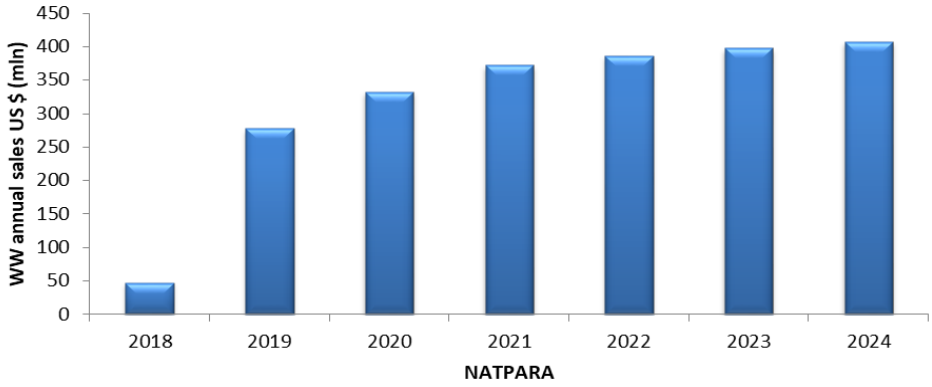
Enobosarm (phase 3) also known as ostarine, is an investigational selective androgen receptor modulator (SARM) developed by GTX Inc. for the treatment of conditions such as muscle wasting and osteoporosis, formerly under development by Merck & Company.

Competitive Landscape – Hypoparathyroidism:

The Hypoparathyroidism drugs landscape consists of a sole player -**Natpara**, developed by NPS which was acquired by Shire Pharmaceuticals (that was acquired by Takeda Pharmaceutical Company Ltd). NATPARA is a prescription parathyroid hormone used with calcium and vitamin D to control low blood calcium (hypocalcemia) in people with low parathyroid hormone blood levels (hypoparathyroidism)[83].

The drug was FDA approved in 2015, and in 2016 the drug brought in revenues of $85.3 million (only in the U.S.),[84] with U.S. market revenues forecasted to reach $441.31 million by 2022.[85] Entera Bio's orally delivered PTH hormone is intended to substitute the current Natpara solution. Moreover, the company estimates that its drug candidate will extend the treatment to a broader range of patients, and can treat moderate to severe patients, as well as mild. The market for rare-disease treatments is considered attractive, despite a small number of patients, because companies can increase prices dramatically. Despite the high cost ($100k annually), insurers are usually willing to pay for the therapies because they have few members who need them and the drugs can be lifesaving.[86]

<u>The total worldwide market value for Natpara is shown in the table below:</u>



Source: Evaluate Pharma

[81] https://www.bloomberg.com/research/stocks/private/snapshot
[82] https://www.mithra.com/en/estetrol
[83] https://www.natpara.com/
[84] Shire PLC. Annual Report 2016. (2017).
[85] Evaluate Pharma, 2017
[86] DNA Biomedical Solutions, Financial Report for 2016. (2017)

Some companies are in the pre-clinical development stage such as:

- **Alize Pharma III (AZP-3601)**- a unique PTH analog designed specifically for PTH replacement therapy in hypoparathyroidism by academic partners at the Massachusetts General Hospital and Harvard Medical School. AZP-3601 potently interacts with a specific configuration of the PTH receptor that results in prolonged activation and effects calcium metabolism[87].
- **GC Pharma** (hypoparathyroidism stem cell therapy) develops a tonsil-derived stem cell therapy that can effectively substitute non-functional parathyroid cells in the patient's body[88].
- **Extend Biosciences** (parathyroid hormone (1-34): The company indicates that their D-VITylated PTH (1-34) conjugate mimics the physiological levels of PTH, thereby returning and maintaining serum calcium and phosphate levels within the normal range[89].
- **TransCon PTH** (Ascendis Pharma) which begins phase 2 in Q1-2019[90] and has filed an IND application with the FDA, uses TransCon technology that combines the benefits of conventional prodrug and sustained release technologies and enables the creation of a platform technology that is broadly applicable to proteins, peptides and small molecules[91]. Ascendis Pharma anticipates top line results in the fourth quarter of 2019. According to Evaluate Pharma, TransCon will launch start its drug in 2023 and will achieve annual sales of $40 million.

[87] https://www.alz-pharma.com/#our-programs
[88] http://globalgreencross.com/rd/pipeline
[89] http://extendbio.com/pipeline/
[90] https://ascendispharma.com/product-pipeline/transcon-pth/
[91] https://ascendispharma.com/platform/transcon-technology/

Financial Valuation and Projections

Valuation

We start our evaluation with the company's two products:

- ***EB613 for Osteoporosis***: Entera Bio is set to perform a phase 2a dose ranging study in patients. The company aims to use the 505(b)(2) regulatory pathway, which is less expensive and a much faster route to approval.
- ***EB612 for Hypoparathyroidism***: Entera Bio successfully completed a phase 2a clinical trial in hypoparathyroidism. A pharmacokinetic/pharmacodynamic (PK/PD) cross over study of EB612 versus Natpara (*orphan drug designation*) will be reported later this year with the next planned step for clinical development being a phase 2b/3 pivotal study.

Distribution agreement:

- Osteoporosis – the company is evaluating possible partnership opportunities with a large pharmaceutical company, whereby the partner will conduct a phase 2b/3 pivotal trial, regulatory approvals, registrations, and commercialization. The potential agreement with the partner would include milestone payments and annual royalty payments from sales of the drug. We based our forecast on the following recent deals and assume future deals will generate $50M as an upfront payment with 10% royalties from sales:

Investor (Country)	*Investee (Country)*	*Amount*	*Product*	*Date*
Johnson & Johnson (US)	Protagonist Therapeutics (US)	$50M	Inflammatory Bowel Disease injectables in pill form	June 2017
Hefei (Sinopharm) (CN)	Oramed (IL)	$50M	Orally ingestible Insulin	Nov. 2015
Google Ventures, Novartis, AstraZeneca and many others (US)	Rani Therapeutics (US)	$70M	General platform, including; TNF-alpha inhibitors, interleukin antibodies, insulin and GLP-1	Feb. 2016
25 major financial institutions (US)	Chiasma (US)	$26.4M (as of August 30, 2017)	Developing and commercializing oral therapies - phase III clinical trial for the treatment of acromegaly	Via Nasdaq in 2017

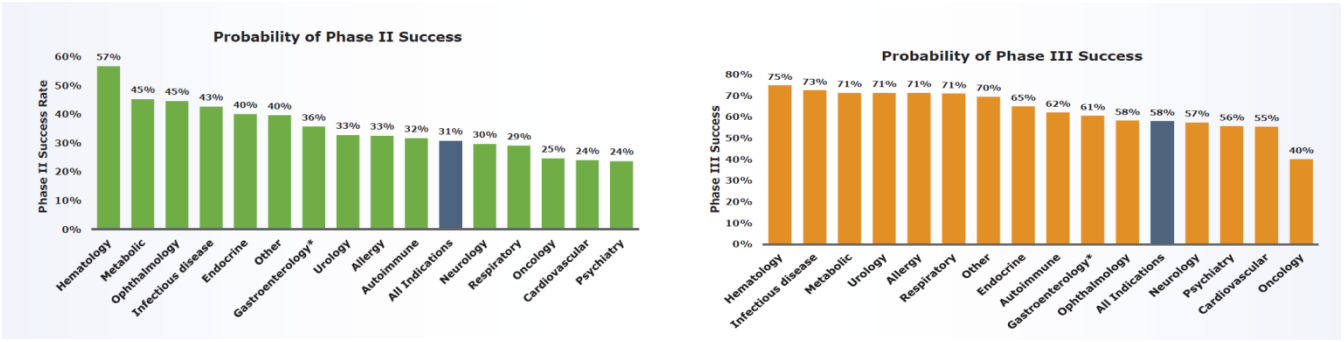
Sources: (1) (Business Insider Australia, 2017); (2) (Reuters, 2015); (3) (BioSpace, 2016); (4) (NASDAQ, 2017).

- Hypoparathyroidism – We adopt the company's decision to take the drug into market without a strategic partner. Thus, managerial focus will also be on sales and on establishing a sales force. We also expect higher profit margin as the company will form a sales force. We assume, based on the company's timeline, that they will introduce this drug to market in 2023.

Success rates – the company engages in a high-risk therapeutic area in promoting its EB 612 indication. Success rate data indicate higher success rates for endocrinology (40%) in comparison with the total average of all indications (31%) from phase II to phase III. However, phase III success rate is lower (65%) than the success rate for all indications (58%). Entera Bio's drug is not considered a novel API (active pharmaceutical ingredient) but rather an intermediate between a generic and novel drug. Hence, we estimate that the success rate to be even higher, although we conservatively assume an average success rate for the endocrinology therapeutic area. We address these clinical risks in our rNPV valuation for each indication.

Osteoporosis as a relatively small therapeutic area and is categorized under "others" by drug development/financial research as presented below:

Source: Clinical Development Success Rates, 2006-2015. Biomedtracker 2016.



Capitalization rate: We calculate our discount rate at 18.5%, based on our CAPM model (see Appendix B).

Main valuation parameters for EB 612 and EB 613

Indications	Current development stage	Success Rate Phase II	Success Rate Phase III	Regulatory approval success rate	Launch	Patent period
Hypoparathyroidism	2b/3	40%	Pivotal study	65%	2022	2029
Osteoporosis	2	40%	70%	86%	2024	2029

Parameters/Indications	Hypoparathyroidism	Osteoporosis
Total market per product (000K)	663,700	10,850,000
Market Growth (CAGR)	8%	4.7%
Company share from Market (Peak Sales)	25%	5%
Royalties to the Company	12%	10%
Royalties to licensor of partial technology (Oramed)	3%	3%

Based on the aforementioned parameters, we evaluate Entera's pipeline at $36.1M

Entera Bio - Amgen Agreement

We have estimated the value of the Amgen agreement as published on December 11th, 2018 and signed on April 17th, 2019 (https://investors.enterabio.com/static-files/68453225-23d3-4e47-ac47-f712e353054c). Entera will use its proprietary drug delivery platform to develop oral formulations for preclinical large molecule programs in inflammatory diseases and other serious illnesses that Amgen has selected.

Economic outcomes are a **game changer** in our view:

1. Amgen will cover approximately $6M in 2019 and 2020 for R&D costs of all 3 molecules – below is a breakdown.
2. Based on clinical success Amgen will pay up to $70M for the first molecule and up to $100M for each of the 2 other molecules (a total of $270M). We calculate this payment based on the probability it will actually be realized (we assume a high probability of 95%) and based on clinical success rates known in the industry for endocrinology.

R&D expenses paid by Amgen per molecule		**Year**
Technology access payment	$725,000	2019
First Year R&D Payment	$225,000	2019
prepayment for the First Year R&D Payment	$225,000	2019
prepayment for the second Year R&D Payment	$225,000	2020
Second Year R&D Payment	$450,000	2020

Source: Entera Bio agreement with Amgen and Frost & Sullivan analysis

Based on the aforementioned parameters, we evaluate Amgen's agreement with the Company at approximately $60M. As the company progresses and shows clinical success, probability of occurrence will be higher and in turn Entera Bio's value will grow.

Technological Platform Valuation

Entera Bio's product pipeline is supported by the Company's broad business and technological base. Valuation of Entera Bio's "technological basis" is in fact a valuation of the company's "residual value". This valuation was conducted using the Feed Rate methodology that is common in the field of Life Sciences, rather than using the conventional terminal value, normally used by non-life-science companies, for the following reasons:

- The terminal value reflects a type of steady state in company sales with a certain fixed growth rate (g) based upon past data. This is not the case for life science companies, where the terminal value is derived from projects in development.
- The terminal value for a given company usually constitutes between 70-80% of its worth. In contrast, the main share of the value of a Life Science company is attributed to income generated during several years following product launch (for the most part, approximately 6-10 years), after which a certain decline occurs (due to expiration of a patent, the emergence of competing products etc.).

The technological platform valuation is based on the average number of new projects that a company can yield annually. Estimating the capitalization value of future projects is based on pre-clinical and clinical development aspects, assessment of unallocated costs, and a higher capitalization rate than the one used during the forecast years, due to the uncertainty of the company's future projects.[92]

Our valuation includes early clinical stage indications such as EB 613 PTH 1-34 non-union fractures and early stage trials. We view Entera Bio's technological platform as a basis for its management to carry out additional worthy technology acquisitions, and incorporate them into the company's product pipeline in advanced clinical phases.

Main technology platform valuation points:

- We assume one new project each year with an average value of $19.9M (average current value of Entera's 3 molecules)
- Unallocated costs are mainly G&A and sales costs, with a similar share from the project's value as in the current pipeline programs
- We estimate unexpected costs to be 20% of the average value
- Statutory tax rate of 15% is assumed
- The capitalization rate is higher than the one used in the pipeline valuation, reflecting increased uncertainty
- It is assumed that the "platform" generates projects for n years: in our valuation, and based on the average patent period, n=11 years. We therefore subtract all projects generated after n years from the technological platform value.

  The following formula reflects the value of the technology:

$$\mathrm{V(tech)} = \frac{(fVproject - (1+r)costs)}{r} * 1 - \frac{1}{(1+r)\text{^n}}$$

[92] Bogdan & Villiger, "Valuation in Life Science - Practical Guide", 2008, Second Edition.

Main valuation parameters of the technological platform:

Average New Projects per Year	**1.00**
Project Value ($'000)	**19,873**
Unallocated Costs ($'000)	21,859
Unexpected Costs ($'000)	-3,975
Tax	15%
Capitalization	23.5%
Terminal Technology Value ($'000)	**136,570**
Technology Value - 2019-2029 ($'000)	**13,397**
Technology Value ($'000)	**123,173**

Equity Value

Non-operational assets/liabilities and unallocated costs

As of December 31, 2018, Entera Bio has non-operational assets (cash) of approximately $11.5M with an estimated monthly burn rate of $1.4M. The company has no loans.

The equity valuation elements are presented in the table below:

Pipeline Analysis		rNPV ($K)
EB 612	Hypoparathyroidism	10,256
EB 613	Osteoporosis	25,867
Amgen partnership		59,620
Total rNPV Pipeline		**95,744**
Unallocated Costs		-21,859
Terminal Technology Value		**123,173**
Enterprise Value		**197,057**
Total Non-Operational Assets/Liabilities		**4,521**
Equity Value		**201,578**

Based on the above data we value Entera Bio at $201.6M.

Sensitivity Analysis

The table below presents Entera Bio's equity value in relation to the capitalization rate. We set a range of 0.5% change from our CAPM model (see Appendix B). Entera Bio's has 11.46M shares.

Sensitivity Analysis - Capitalization Rate vs. Equity Value

Cap. Rate	Price Target ($)
17.5%	18.7
18.0%	**18.1**
18.5%	**17.6**
19.0%	**17.1**
19.5%	16.6

We estimate Entera Bio's price target to be in the range of $18.1 to $17.1 and at a mean of $17.6

Investment Thesis and Price Forecast Risks

Biotech companies, particularly those in the research and development stage, are relatively high-risk companies. Key risks that may affect Entera Bio include:

Delay / postponement of marketing / regulatory approval decisions

In order for Entera Bio to market or out-license its products, it is necessary for them to receive marketing approval from regulatory agencies, such as the FDA (US) and EMA (EU). Our estimates regarding time to market are based on the assumption that these products will successfully complete phase II and III clinical trials without significant delays. Failure to fulfill the clinical endpoints of these experiments will force the company to conduct additional clinical trials or abandon the development of certain projects. We consider this to be the main risk factor of the company's activity at this stage.

Risks involved in obtaining sources of financing and stock trading

As a biotech company in the research and development stage, with minimal revenue from sales, Entera Bio will be required to conduct fundraising prior to becoming profitable, unless early licensing deals are made. Failure to raise funds, or fundraising under conditions that are not beneficial to the company, may affect its market value. In addition, the low level of tradability may deter some investors from buying Entera Bio's stock.

General risks related to similar companies

The value of small companies in the biotech field could, to a relatively high degree, be affected by publications not related directly to their activities. Such publications may refer, for example, to competitors, macro-trends in the healthcare sector, and political events.

Contact Details & Management

Entera Bio Ltd.

Entera Bio executive officers

Dr. Phillip Schwartz has served as Entera Bio's Chief Executive Officer and as a Director since Entera Bio's inception in 2010. Dr. Schwartz has more than 20 years of biotech and pharmaceutical industry experience. He previously held multiple positions in clinical affairs and business development at Endo Pharmaceuticals plc from 2005 to 2010 and at Serono from 2002 to 2005, and held multiple positions in medical affairs, business development and clinical trial development at each of Endo Pharmaceuticals plc and Serono. He has also worked as an external consultant for a number of venture capital firms. He has also consulted privately and served as an associate of Health Advances, LLC for more than 20 large biotech and pharmaceutical companies from 2000 to 2002. He has multiple publications in tier one peer-reviewed journals and has presented papers at numerous international conferences. He has also worked in the neurobiology laboratory of Nobel Laureate Professor Torsten Wiesel of the Rockefeller University. Dr. Schwartz holds a B.A. in psychology and architecture from Columbia University, an M.Sc. in immunology while studying under Professor Irun Cohen at the Weizmann Institute, and a Ph.D. in neurobiology/development/oncology from Harvard Medical School. In addition to his scientific training, Dr. Schwartz completed numerous clinical courses as part of his program at Harvard Medical School. After completing his Ph.D., Dr. Schwartz was a fellow in pediatric oncology at the Dana Farber Cancer Institute and an officer of Harvard University Medical School.

Dr. Hillel Galitzer has served as the company's Chief Operating Officer since February 2014, and prior to that served as Entera Bio's Director of Scientific Development from July 2012. Dr. Galitzer has more than ten years of experience in medical research and molecular biology. Between August 2010 and February 2014, Dr. Galitzer was an analyst and the chief operating officer for Hadasit Bio Holdings Ltd., a publicly traded company on the Tel Aviv Stock Exchange (TASE: HDST) and OTC markets. He has more than 10 years of experience in medical research and molecular biology. He is the co-founder and former chief operating officer of Optivasive Inc. He has written numerous publications in peer-reviewed journals and has lectured and presented in international conferences and universities. Dr. Galitzer received his Ph.D. from the Hebrew University Medical School in Jerusalem, where he was mentored by two world renowned researchers in the areas of parathyroid hormone and calcium regulation, his M.B.A. from Bar Ilan University in Israel and his B.Med.Sc. from the Hebrew University Medical School in Jerusalem

Dr. Arthur Santora has served as Entera Bio's Chief Medical Officer since September 2018. Dr. Santora has more than 30 years of experience in the biopharmaceutical industry. He spent the majority of his career in the clinical research team at Merck & Co., Inc., from June 1989 to March 2017, where he was the lead clinical research physician responsible for much of the clinical development of Fosamax® (alendronate sodium), one of the world's most prescribed osteoporosis treatments. He was closely involved in the clinical development of Merck's once-weekly Fosamax Plus D (alendronate sodium/ vitamin D3 combination tablets), the first drug/vitamin combination tablet in the US. His position at Merck immediately prior to his termination of services in 2017 was Scientific Associate Vice President of Clinical Research, where he was directly responsible for the technical and scientific support for all clinical research of Fosamax/Fosamax plus D and contributed to the development of many other osteoporosis and endocrine marketed and investigational drugs. Prior to joining Merck, he served as a Medical Officer at the US FDA and subsequently was a faculty member at Wayne State University Medical School in Detroit. Dr. Santora is a Clinical Associate Professor at the clinical faculty of Rutgers Robert Wood Johnson Medical School in New Brunswick, New Jersey. He has graduate training in Internal Medicine at Emory, and its Endocrinology and Metabolism subspecialty at the NIH in Bethesda. Dr. Santora received his M.D. and Ph.D. in biochemistry from Emory University in Atlanta.

Extracted from: Entera Bio, F20 Report, 2019. pp.105.

Appendices

Appendix A - Financial Reports

Consolidated statements of financial position data:	2018	2017	2016
Cash and cash equivalents	7,506	11,746	4,163
Short-term bank deposits	4,015	-	-
Restricted deposits	-	-	1,075
Accounts receivable	725	-	-
Other current assets	220	671	195
Total current assets	12,466	12,417	5,433
Property and equipment	224	207	199
Intangible assets	651	654	654
Total assets	13,341	13,278	6,286
Accounts payable-Trade and other	1,563	2,020	657
Contract liabilities	225	-	-
Convertible Loans	-	-	9,885
Total current liabilities	1,788	2,020	10,542
Convertible loans	-	3,893	4,835
Preferred shares	-	33,455	11,031
Warrants to purchase Ordinary Shares and preferred shares		5,398	
	1,372		4,800
Liability to issue preferred shares and Warrants	-	-	273
Severance pay obligations, net	65	70	51
Total non-current liabilities	1,437	42,816	20,990
Total liabilities	3,225	44,836	31,532
Shareholders' equity (Capital deficiency)	10,116	-31,558	(25,246)

Consolidated statements of comprehensive loss:	2018	2017	2016
Revenue	500	-	-
Research and development expenses, net	8,518	2,768	2,648
General and administrative expenses	2,843	8,575	2,719
Total operating loss	10,861	11,343	5,367

Appendix B - Capitalization Rate

Entera Bio

Cost of equity capital (ke) represents the return required by investors. The capitalization rate is calculated using the CAPM (Capital Asset Pricing Model). It is based on a long-term 20-year T-bond with a market risk premium, and based on Professor Aswath Damodaran's (NY University) commonly used sample (www.damodaran.com). As of December 31, 2018, the US market risk is estimated at 5.69%. A three-year market regression Beta is 1.32, according to a sample of 426 companies representing the US biotechnology sector. We used an unleveraged beta of this sample, which is higher than a leveraged beta, due to high rate of cash versus debt. The implied CAPM is 8.3%.

CAPM model (ke) is estimated as follows: $ke = rf + \beta(rm-rf) + P$

Entera is a small cap company, in which marketability and size premiums need to be considered. Duff and Phelps data research in the years 1963-2018 indicates that a 10.24% premium needs to be added to the CAPM for small cap companies. We therefore estimate the company's CAPM to be 18.5%.

CAPM Model		Value	Source
Long-term (20 years) T-bond	R(f)	0.76%	US Department of the Treasury (20Y)
Market risk premium	R(m)- R(f)	5.69%	based on Professor Damodaran's sample (1/19)
Beta unleveraged	B	1.32	Beta sample of 426 Drugs (Biotechnology) firms (1/19)
Cost of Capital	Ke	8.3%	
Size Premium		10.24%	Duff and Phelps data, 10dz.
CAPM	CAPM	**18.5%**	

Appendix C – Key Team Bios

Dr. Tiran Rothman is the head of Frost & Sullivan Research & Consulting Ltd., a subsidiary of Frost & Sullivan in Israel. He has over 10 years of experience in research and economic analysis of capital and private markets, obtained through positions at a boutique office for economic valuations, as chief economist at the AMPAL group, and as co-founder and analyst at Bio-associate Biotech Consulting. Dr. Rothman also serves as the Economics & Management School Head at Wizo Academic College (Haifa). Tiran holds a PhD (Economics), MBA (Finance), and was a visiting scholar at Stern Business School, NYU.

Dr. Hadar Cohen Halevy, Ph.D is a healthcare consulting analyst at Frost & Sullivan. Formerly, Hadar worked at Teva Pharmaceutical as a scientist in the process development department and has extensive knowledge in biosimilar manufacturing and GMP regulation. Hadar holds a Ph.D in Biochemistry from the Weizmann Institute of Science and a M.Sc in Biotechnology and Nanotechnology from Tel Aviv University. Hadar has a broad scientific background in inter-disciplinary fields and over 10 years of experience conducting original research, with expertise in peptide synthesis and drug design.

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