

Update Report

December 16, 2020

D.N.A (TLV:DNA)

Entera Bio ([NASDAQ:ENTX](#)), subsidiary of D.N.A, announced, as expected on enrollment completion in its ongoing Phase 2 clinical trial of EB613 in osteoporosis and FDA approval for its IND; price target is unchanged

Sector: Healthcare

Industries: Biotechnology and Medical Devices

Stock Target Price: NIS 2.62

Closing price: 0.72 NIS

52 Week Range: 0.45-0.96

Market cap: NIS 22 M

of shares: 30.8M

Stock performance (3 mos.): 27%

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Conclusion

Entera Bio: 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 that enable personalized care.

On its third quarter report and after the company announced the following:

- On December 10, 2020, Entera Bio announces FDA Approval of IND Application for EB613
- As expected, Completed Enrollment with 161 Subjects
Randomized in the Phase 2 Study of EB613 in Osteoporosis: EB613 is an orally delivered, human parathyroid hormone (1-34) (PTH) and is positioned as the first potential, oral bone building product to treat osteoporosis.
- Positive Interim Data in Phase 2 Clinical Trial of EB613: During the third quarter, Entera announced 6-month interim biomarker and BMD data from the first 50%, or 80 patients, enrolled in its Phase 2 clinical trial of EB613. The data indicate EB613 has a meaningful and positive impact on lumbar spine BMD in a dose dependent manner.
- Continued Pipeline Development: Entera is identifying new targets for preclinical development based on its oral drug delivery platform, as well as developing optimal formulations for EB612 in preparation for a potential Phase 2b or Phase 3 study in hypoparathyroidism in 2021 or 2022. Entera has previously completed one successful Phase 2a study of EB612 in this indication.
- Amgen Collaboration Agreement: Several studies have been completed using Entera's technology to evaluate different formulations of Amgen's drug.

On 30 November, 2020, Entera Bio Appoints Spiros Jamas as Chief Executive Officer

In our view and based on our July [Initiation Report of Entera](#), Entera bio seeks potential partnerships with 1) leading injectable franchises that are now facing a growing threat from biosimilars 2) biologics and proteins that may prove to be complementary to Entera's oral delivery platform, as demonstrated by the strategic research collaboration Entera signed with Amgen in 2018 3) opportunities to license EB613 or EB612 globally, or in certain regions.

Executive Summary

Entera

Entera 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. 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 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)	\$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).

The company's main focus is applying its technology to develop an oral formulation of human parathyroid hormone (1-34), or PTH. PTH has been approved in the U.S. and EU for more than 15 years in injectable form, for the treatment of osteoporosis and currently generated revenue in excess of \$1.6 billion/ year.

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 low¹. Their lead oral PTH candidates are EB613 for the treatment of osteoporosis and EB612 for the treatment of hypoparathyroidism (Figure 1). 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'.

- **EB613 for Osteoporosis:** 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.

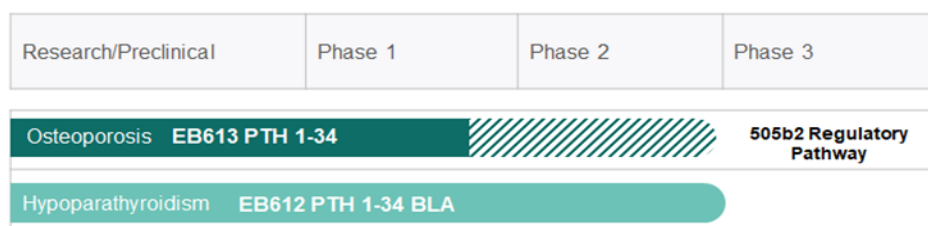
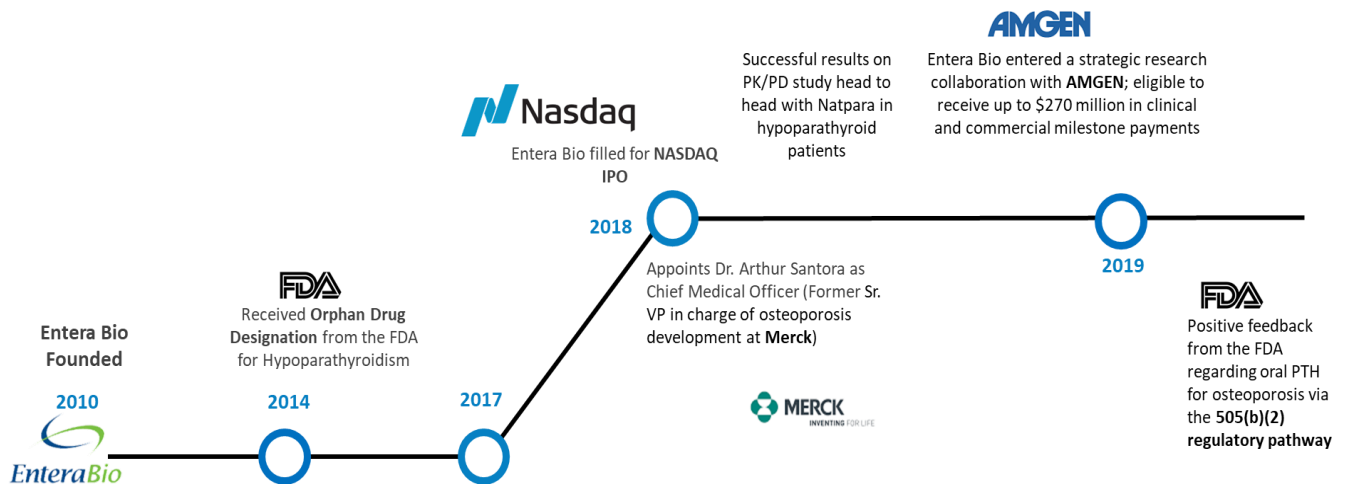


Figure 1: Entera Bio LTD. Lead candidates (Source: Investors presentation 2019)

¹ <https://selfhacked.com/blog/parathyroid-hormone-pt/>



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 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.² Entera will be eligible to receive up to \$270 million in milestone payments, for the development of three different molecules.

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's clinical development and promising results along with the Amgen agreement emphasize the potential commercial opportunities that exist for the company. Entera's orally delivered PTH hormone may substituted the current injectable hormone, providing a combination of efficacy, tolerability, and convenience. 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, granting 7 years of market exclusivity. Alongside this, Entera's long-term pipeline is set to develop solutions for indications that presently lack treatment and to license its technology to other companies.

² <https://investors.enterabio.com/news-releases/news-release-details/entera-bio-and-amgen-enter-strategic-research-collaboration>

Entera Bio - Upcoming Potential Catalysts

Program	Indication	Event	Significance	Timeline
EB613: PTH (1-34)	Osteoporosis 505(b)(2)	IND submission	Medium	Achieved
		Initiation of phase 2a trial- dose ranging study	High	Achieved
		Dose ranging study- bone marker data	High	Achieved
		Dose ranging study- bone mineral density (BMD) data ³	High	Achieved
		Report interim biomarker data from 2.5 mg Dose	High	H2-2021
		End of phase 2 meeting with the FDA	High	H2-2021
		Pivotal phase 3, multicenter study BMD endpoint study comparing Oral PTH with Forteo®	Medium	H1 2021
		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
		PK/PD study completion	Medium	Achieved
		Submit IND Multi National Study	Medium	H2 2020
		Dose ranging study	Medium	H1-2021
		Phase 2b/3 clinical trial	High	H1-2021
		Expected commencement of sales	High	2023

Sources: Frost & Sullivan Analysis; DNA Biomedical Solutions Ltd.

³ Based on the three-month interim biochemical marker and safety data, the Phase 2 protocol was amended in July 2020 to discontinue the two lower doses (0.5 mg and 1.0 mg) and add a 2.5 mg dose of EB613. The clinical trial is currently enrolling subjects in the 2.5 mg, 1.5 mg and placebo groups, with completion of enrollment for the targeted 160 patients expected by the end of the third quarter.

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