UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, DC 20549

FORM 10-K

(Mark One)

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2021

OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from __to __.

Commission file number 001-38556

Entera Bio Ltd.

(Exact Name of Registrant as Specified in Its Charter)

Israel	**00-0000000**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification No.)**

Kiryat Hadassah
Minrav Building – Fifth Floor
Jerusalem, Israel 9112002

(Address of Principal Executive Offices) (Zip Code)

972-2-532-7151

(Registrant's Telephone Number, Including Area Code)

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	Trading Symbol	Name of Each Exchange on Which Registered
Ordinary shares, par value NIS 0.0000769 per share	ENTX	**Nasdaq Capital Market**
Warrants to purchase ordinary shares	ENTXW	**Nasdaq Capital Market**

Securities registered pursuant to Section 12(g) of the Act:

None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act.

Yes ☐ No ☒

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act.

Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days.

Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files).

Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, smaller reporting company or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	☐	Accelerated filer	☐
Non-accelerated filer	☒	Smaller reporting company	☒
		Emerging growth company	☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant has fi led a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting fi rm that prepared or issued its audit report. ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act).

Yes ☐ No ☒

The aggregate market value of the voting stock held by non-affiliates of the registrant was approximately $142.1 million as of June 30, 2021.

As of March 1, 2022, the registrant had 28,804,411 ordinary shares, par value NIS 0.0000769 per share ("Ordinary Shares") outstanding.

Documents Incorporated by Reference

Portions of the registrant's definitive proxy statement for its 2022 Annual Meeting of Stockholders, which is to be filed with the Securities and Exchange Commission no later than 120 days following December 31, 2021, are incorporated by reference in Part III of this Annual Report on Form 10-K to the extent stated herein.

CAUTIONARY STATEMENT REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K (this "Annual Report") contains "forward-looking statements," as that term is defined under the Private Securities Litigation Reform Act of 1995 ("PSLRA"), Section 27A of the Securities Act of 1933, as amended (the "Securities Act"), and Section 21E of the Securities Exchange Act of 1934, as amended (the "Exchange Act"). Various statements in this report are "forward-looking statements" within the meaning of the PSLRA and other U.S. Federal securities laws. In addition, historic results of scientific research and clinical and preclinical trials do not guarantee that the conclusions of future research or trials would not be different, and historic results referred to in this Annual Report may be interpreted differently in light of additional research and clinical and preclinical trial results. Forward-looking statements include all statements that are not historical facts. We have based these forward-looking statements largely on our management's current expectations and future events and financial trends that we believe may affect our financial condition, results of operations, business strategy and financial needs. Forward-looking statements involve substantial risks and uncertainties. All statements, other than statements of historical facts, included in this report regarding our strategy, future operations, future financial position, projected costs, prospects, plans and objectives of management are forward-looking statements. These statements are subject to risks and uncertainties and are based on information currently available to our management. Words such as, but not limited to, "anticipate," "believe," "contemplates," "continue," "could," "design," "estimate," "expect," "intend," "likely," "may," "ongoing," "plan," "potential," "predict," "project," "will," "would," "seek," "should," "target," or the negative of these terms and similar expressions or words, identify forward-looking statements. The events and circumstances reflected in our forward-looking statements may not occur and actual results could differ materially from those projected in our forward-looking statements. These factors include those described in "Item 1A-Risk Factors" of this Annual Report on Form 10-K. Meaningful factors which could cause actual results to differ include, but are not limited to:

- the scope, progress and costs of developing our product candidates such as EB613 for Osteoporosis and EB612 for Hypoparathyroidism, including without limitation any changes to the design of the Phase 3 clinical trial of EB613;
- the accuracy of our estimates regarding expenses, capital requirements, the sufficiency of our cash resources and the need for additional financing;
- our ability to raise additional funds on commercially reasonable terms, including via our ATM Program (as defined in Part II, Item 7 "Management's Discussion and Analysis of Financial Condition and Results of Operation—Liquidity and Capital Resources" of this Annual Report);
- our ability to develop, advance product candidates into, and successfully complete, clinical studies such as our Phase 2 clinical trial of EB613 in osteoporosis;
- our reliance on third parties to conduct our clinical trials and on third-party suppliers to supply or produce our product candidates;
- our interpretation of U.S. Food and Drug Administration (the "FDA") feedback and guidance and how such guidance may impact our clinical development plans, specifically our ability to utilize the 505(b)(2) pathway for the development and potential approval of EB613 and any other product candidates we may develop;
- our expectations regarding licensing, business transactions and strategic collaborations, including our ongoing collaboration with Amgen;
- our ability to use and expand our drug delivery technology to additional product candidates;
- our operation as a development stage company with limited operating history and a history of operating losses and our ability to fund our operations going forward;
- our ability to continue as a going concern absent access to sources of liquidity;
- our ability to obtain and maintain regulatory approval for any of our product candidates;
- our competitive position, especially with respect to Forteo® and other products on the market or in development for the treatment of osteoporosis;
- our ability to establish and maintain development and commercialization collaborations;

- any potential commercial launch of current or future product candidates, and the timing, cost or other aspects of such commercialization;
- our ability to manufacture and supply sufficient amounts of material to support our clinical trials and any potential future commercial requirements;
- the safety and efficacy of therapeutics marketed by competitors that are targeted toward indications for which we are developing product candidates;
- the size of any market we may target and the adoption of our product candidates, if approved, by physicians and patients;
- our ability to obtain, maintain and protect our intellectual property and operate our business without infringing misappropriating or otherwise violating any intellectual property rights of others;
- our ability to retain key personnel and recruit additional qualified personnel;
- the possibility that competing products or technologies may make any product candidates we may develop and commercialize or our oral delivery technology obsolete;
- the pricing and reimbursement of our product candidates, if approved;
- our ability to develop a sales, marketing and distribution infrastructure, if any;
- our ability to manage growth; and
- the duration and severity of the coronavirus (COVID-19) pandemic, the actions that may be required to contain the coronavirus or treat its impact, and its impact on our operations and workforce, including our research and development and clinical trials.

All forward-looking statements contained in this Annual Report are expressly qualified in their entirety by the cautionary statements contained or referred to in this section. We caution investors not to rely too heavily on the forward-looking statements we make or that are made on our behalf. Except as required by applicable law, we are under no duty, and expressly disclaim any obligation, to update or revise publicly any forward-looking statements, whether as a result of new information, future events or otherwise. You are advised, however, to consult any further disclosures we make on related subjects in any annual, quarterly or current reports that we may file with the Securities and Exchange Commission (“SEC”).

We encourage you to read the discussion and analysis of our financial condition and our consolidated financial statements contained in this Annual Report. We also encourage you to read Item 1A of this Annual Report, entitled “Risk Factors,” and Part II, Item 7 “Management’s Discussion and Analysis of Financial Condition and Results of Operation—Liquidity and Capital Resources” of this Annual Report for additional discussion of the risks and uncertainties associated with our business. There can be no assurance that the actual results or developments anticipated by us will be realized or, even if substantially realized, that they will have the expected consequences to, or effects on, us. Therefore, no assurance can be given that the outcomes stated in such forward-looking statements and estimates will be achieved.

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PART I

Unless the context otherwise requires, all references in this Annual Report on Form 10-K to the "Company," "Entera," "we," "our," "ours," and "us" refer to Entera Bio Ltd., an Israeli company, including its consolidated subsidiaries.

ITEM 1. BUSINESS

Overview

We are a clinical-stage biopharmaceutical company focused on the development and commercialization of orally delivered large molecule therapeutics for use in areas with significant unmet medical need and where adoption of injectable therapies is limited due to cost, convenience and compliance challenges for patients. We were organized under the laws of the State of Israel on September 30, 2009 and commenced operations on June 1, 2010. We have developed a proprietary platform that enables the oral delivery of injectable proteins and large molecules. Our platform has been tested successfully on numerous molecules of broad characteristics and size. We have completed Phase 2 of our lead oral PTH product, EB613 for the treatment of osteoporosis and are preparing to initiate a Phase 3 (potentially pivotal) study in H2/2022. In December 2018, we entered into a research collaboration and license agreement with Amgen for the use of Entera's oral delivery platform in the field of inflammatory diseases.

Our lead product candidates are EB613 for the treatment of osteoporosis and EB612 for the treatment of hypoparathyroidism. Both EB613 and EB612 are oral formulations of human parathyroid hormone (1-34), or PTH. An injectable formulation of PTH has been approved in the United States for more than a decade for both of these indications (PTH 1-34 for Osteoporosis and PTH 1-84 for Hypoparathyroidism). Currently, the leading products are administered via injection. In total, more than 260 healthy volunteers and patients have received multiple doses of various formulations of our oral PTH (1-34) in clinical trials.

Osteoporosis is a disease characterized by low bone mass and structural deterioration of bone tissue, which leads to greater fragility of bones and an increase in fracture risk. Forteo® is a once-daily subcutaneous injectable form of PTH (1-34) marketed by Eli Lilly and Company ("Eli Lilly"), that was approved by the U.S. Food and Drug Administration (the "FDA") in 2002 for the treatment of osteoporosis in the United States and is widely considered one of the most effective treatments due to its ability to build bone. Because our product candidate EB613 is delivered in a patient-friendly oral formulation, we believe it will reduce the treatment and cost burden on patients and lead to significantly higher patient and physician acceptance compared to injectable PTH. In 2020, we engaged a third-party firm to conduct two primary market research studies with clinicians who treat osteoporosis patients. In these two studies, the responses to the prospect of prescribing an oral PTH with demonstrated safety and efficacy were overwhelmingly positive and driven by expected improvements in patient compliance, ease of administration and reduced costs.

In November 2018, we had a pre- Investigational New Drug ("IND") meeting with the FDA to discuss the EB613 for the treatment of osteoporosis program, and, in December 2020, we announced that the FDA had reviewed our IND application for EB613 and informed us that we may proceed with our U.S. clinical trial.

We have completed two, multi-stage Phase 1 clinical trials of EB613 and a Phase 2 double-blind, placebo-controlled, dose-ranging trial of EB613 in patients with osteoporosis. The Phase 2 trial studied five once-daily doses of EB613 (0.5mg, 1.0mg, 1.5mg and 2.5mg) and placebo for six months and assessed safety, tolerability, bone biomarkers and bone mineral density (BMD). Based on these trials, EB613 appears to be safe and well tolerated with no serious drug-related adverse events reported and produced clinically and statistically significant increases in BMD at month six. The adverse events seen in these trials are consistent with those seen in other published third party trials of PTH (1-34). In December 2021 we held an end-of-Phase 2 meeting with the FDA to review the Phase 2 results and proposed Phase 3 protocol, including various aspects of our nonclinical and clinical development plan and the use of BMD, rather than fracture incidence, as the primary endpoint to support a New Drug Application, or NDA.

Hypoparathyroidism is a rare condition in which the body fails to produce sufficient amounts of PTH or the PTH produced lacks biologic activity. Historically, the treatments for hypoparathyroidism have been calcium supplements, active vitamin D analogs (calcitriol or similar drugs) and occasionally phosphate binders, the chronic use of which results in serious side effects and significant costs to patients and the healthcare system. A once-daily injectable form of PTH (1-84), marketed as Natpara®, has been approved for the treatment of hypoparathyroidism; however, Natpara is currently the subject of an FDA recall and is not currently avaialble. Our lead product candidate for hypoparathyroidism, EB612, is delivered orally and can be administered in customized doses several times a day. Studies performed by researchers at the National Institutes of Health, or NIH, have shown that dosing PTH multiple times per day significantly increases the efficacy of therapy and may be more effective for treating hypoparathyroidism. These studies found that the total daily PTH dose required to maintain serum calcium in the normal or near-normal range was reduced by 50% with twice-daily PTH (1-34) and also demonstrated that twice-daily dosing achieved better control over serum calcium and urinary calcium excretion as compared to once-daily dosing. In addition, based on the market research we conducted in osteoporosis, we believe patients generally prefer orally-administered drugs. For these reasons, we believe EB612 dosed two or more times during the day may be clinically superior to the existing daily therapy and has the potential to become the standard of care, if approved, for hypoparathyroidism.

In 2015, we successfully completed a Phase 2a trial for EB612. Although our Phase 2a trial involved a smaller number of patients, was conducted for a shorter duration and did not include an initial dose optimization period, in each case in comparison to the design of the pivotal trial used for regulatory approval of Natpara (the REPLACE trial), our trial showed the potential for similar efficacy. In the third quarter of 2019, we reported the results of a second Phase 2 clinical trial that included one day of dosing with EB612 to evaluate the pharmacokinetic/pharmacodynamics, or PK/PD, profile of various EB612 dose regimens compared with Natpara. The results from this study demonstrated that EB612 was effectively delivered into the blood stream and activated PTH-dependent biological pathways that are inadequately activated in patients with hypoparathyroidism. In addition, the various dosing regimens demonstrated positive impacts on serum calcium, urine calcium and serum phosphate levels. No serious adverse events were reported. We have developed an improved formulation of EB612 based on new intellectual property and optimization of the PK profile for hypoparathydoidism and are evaluating this in preclinical and human PK/PD studies in 2022. These data will help determine the design of a pivotal Phase 2b or Phase 3 trial of EB612 in patients with hypoparathyroidism in which the dose frequency would be titrated to control hypocalcemia, normalize serum phosphate and reduce renal calcium excretion.

In the future, after the completion of additional formulation and development activities, we expect to initiate a multi-site Phase 2b/3 clinical trial of EB612 for the treatment of hypoparathyroidism, which will further evaluate the dosage, effectiveness and safety profile of EB612 in an expanded population of patients with hypoparathyroidism. We expect that this Phase 2b/3 trial, when initiated, will be designed to replicate the REPLACE trial in many aspects and to achieve a significant reduction in urinary calcium. The phase 2b/3 clinical trial of EB612 in hypoparathyroidism may potentially support a submission for regulatory approval of EB612, if successful.

In addition to the utilization of our technology to develop our own internal drug candidates, we intend to use our technology as a platform for the oral delivery of other novel protein and large molecule therapeutics. We believe our proprietary technology has advantages over alternative delivery options, and may enable us to create a potential pipeline of products across a range of therapeutic indications. We have generated data on a number of additional proteins and peptides in molecules as large as 150 kilodaltons, or kDa, and may develop these candidates further internally, or explore potential business development collaborations to advance these therapies through clinical development and generate funding.

In December 2018, we entered into a research collaboration and license agreement with Amgen, Inc, or Amgen. Under the agreement, we and Amgen have agreed to collaborate on the development and discovery of clinical candidates in the field of inflammatory disease and other serious illnesses. Specifically, we and Amgen have agreed to use our proprietary drug delivery platform to help Amgen develop oral formulations for up to three large molecule drug candidates within Amgen's pipeline. Further, under the terms of the agreement, we have agreed to conduct preclinical development activities, at Amgen's expense, and Amgen will be responsible for research, clinical development, manufacturing and commercialization of any of the resulting programs, at its expense. We will be eligible to receive from Amgen aggregate payments of up to $270 million upon achievement of various clinical and commercial milestones or Amgen's exercise of its option to select up to two additional programs to include in the collaboration, as well as tiered royalty payments based on percentages ranging from the low to mid-single digits based on the level of Amgen's net sales of any applicable products, if approved. We will retain all intellectual property rights to our drug delivery technology, which under this collaboration will be licensed to Amgen exclusively for Amgen's selected drug targets. Amgen will retain all rights to its large molecules, including any subsequent improvements.

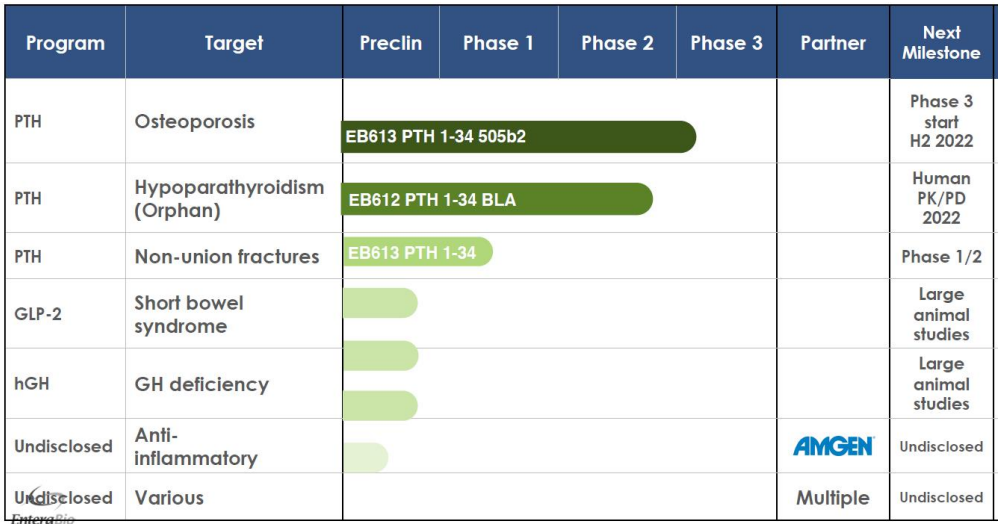
In February 2021, we announced that we initiated a new research program for an oral glucagon-like peptide-2 (GLP-2) analog based on the Company's platform technology. GLP-2, a peptide produced in the intestine and the central nervous system via the brainstem and hypothalamus, is known to enhance intestinal absorption, specifically the increased absorption of nutrients. The only GLP-2 analog currently on the market, teduglutide, was approved in 2012 as a once daily injection for the treatment of short bowel syndrome in the United States and Europe, registering global sales of $613 million in 2020. In preclinical models, our oral formulation of a GLP-2 analog has shown a comparable pharmacokinetic profile to a subcutaneous injection. In addition, GLP-2 analogs are an important category of new therapies for many metabolic diseases and therefore we believe this product candidate is well positioned for partnering opportunities.

Our Pipeline

Drug development globally has shifted towards the use of biologics such as peptides, proteins and other large molecules for the treatment of various diseases including orphan indications. For example, approximately 30% of the drugs approved by the FDA between 2015 and 2019 were biologics. Currently, most large molecule therapeutics can be delivered only via injections and other non-oral pathways because oral administration typically leads to poor absorption into the blood stream, as well as enzymatic degradation within the gastrointestinal tract. Oral drug delivery has the potential to reduce the treatment burden by providing a more patient-friendly alternative relative to injectable drugs and may provide significantly more flexibility, both in size and number of doses per day, than injectable drugs. Our proprietary oral drug delivery technology is designed to address the issues of poor absorption, high variability, and difficulties delivering such large molecules to the targeted location in the body by utilizing a combination of a synthetic absorption enhancer, to facilitate the enhanced absorption of large molecules, and protease inhibitors to prevent enzymatic degradation.

We have initially focused on the development of products which are based on previously approved therapeutic agents. We believe this will allow us to more efficiently and predictably advance product candidates through the development cycle based on well-defined clinical and regulatory pathways. We have conducted initial feasibility studies with a number of candidates and intend to commence preclinical and clinical development for our next, non-PTH product candidate in 2022.

The following chart summarizes the current stage of development of each of our current product candidates, as well as their indications.



Our Strategy

Our goal is to become a leading biopharmaceutical company focused on the development and commercialization of orally delivered large molecule therapeutics in indications with significant unmet medical needs. The key elements of our strategy to achieve this goal are to:

- *Advance EB613, potentially the first oral anabolic drug into Phase 3 for the treatment of osteoporosis*: We successfully completed and reported the results of the randomized, double-blind, placebo controlled dose ranging Phase 2 clinical trial of EB613 for the treatment of osteoporosis. The results of the Phase 2 study support the selection of the 2.5 mg dose for a pivotal Phase 3 study. We are planning to initiate a Phase 3 (potentially pivotal) trial in 2022.

- *Advance EB612 through clinical development for the treatment of hypoparathyroidism*: To date we have completed two Phase 2 clinical trials of EB612 for the treatment of hypoparathyroidism. We reported positive results from the first trial in the third quarter of 2015, and then conducted a Phase 2 PK/PD trial in 2019 to evaluate the profile of various EB612 dose regimens. After the completion of additional formulation and development activities to determine our final formulations, and subject to available funds, we expect to initiate a Phase 2b/3 clinical trial of EB612 for the treatment of hypoparathyroidism. The FDA and the European Medicines Agency, or EMA, have granted EB612 orphan drug designation for the treatment of hypoparathyroidism.

- *Establish global and regional commercial partnerships, or selectively develop commercial capabilities for our lead oral PTH product candidates*: For our oral PTH product candidates that target orphan indications (EB612 for hypoparathyroidism and GLP-2 for short bowel syndrome), we may determine to retain commercialization rights within key territories, including the United States, because of the ability to commercialize efficiently with a small sales and marketing organization. For product candidates that target indications with larger patient populations, such as osteoporosis, we may choose to partner with larger biopharmaceutical companies ahead of late stage development and commercialization, license our technology to third parties for additional indications or seek other potential collaborations. We are currently building a corporate and business development capability to determine the appropriate development and commercial strategies for our current and future product candidates.

- *Leverage our technology to develop more effective novel large molecule therapeutics through collaborations with other biotechnology or pharmaceutical companies*: Oral drug delivery lowers the treatment burden on patients relative to injectable drugs, leading to higher patient and physician acceptance and compliance, and at a lower cost to patients. However, certain peptides, proteins and other large molecule therapeutics can currently be delivered only via injections and other non-oral pathways because oral administration leads to negligible absorption into the blood stream as well as enzymatic degradation within the gastrointestinal tract. In December 2018, we entered into a research collaboration and license agreement with Amgen, and we intend to explore additional collaborations to further validate our technology and potentially generate value through funding from such collaborations. COVID-19 may impact our ability to conduct research and development activities or to develop data that may lead to potential future collaborations (see “Item 1A. Risk Factors—Risks Related to Our Business and the Development of Our Product Candidates—The COVID-19 pandemic could adversely affect our business, financial condition, and results of operations.”).

- *Identify and develop additional products based on FDA-approved injectable large molecule therapeutics*: We intend to leverage our technology platform by applying it to the development of known large molecule therapeutics, and we believe we can reduce the development and regulatory risks by working on FDA-approved large molecule therapeutic agents with known mechanisms of action. We believe this will allow us to advance our product candidates efficiently and predictably through the development cycle thereby offering us the option either to develop these products on our own or to collaborate with the companies that originally developed the injectable form of the drug. For example, in February 2021, we announced that we initiated a new research program for an oral glucagon-like peptide-2 (GLP-2) analog based on the Company’s platform technology.

Our Technology

We are focused on the development and commercialization of product candidates that leverage our proprietary platform technology for the oral delivery of large molecule therapeutics. In recent years, drug development has shifted towards the use of peptides, proteins and other large molecules for the treatment of various diseases. By lowering the treatment burden on patients, oral drug delivery leads 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 by preset injection pen and only once per day. Oral tablets are also less costly to manufacture than injectable biologics, which we expect will lower the cost of our therapies to patients, thereby expanding access to a greater population of patients who can afford these therapies.

Historically, peptides, proteins and other large molecule therapeutics have typically been delivered via injections and other non-oral pathways because oral administration leads to poor absorption into the blood stream (bioavailability) due to enzymatic degradation within the gastrointestinal tract and poor permeability though the intestinal wall. Most oral drug delivery technologies attempting to overcome this hurdle only manage to attain very low bioavailability (less than 1%), which generally results in high variability of dose exposure, both between patients and within the same patient at different times of administration. These variability issues are due to the fact that small changes in the level of absorption lead to significant changes in the bioavailability. As a result, absorption variability generally decreases as drug bioavailability increases. Oral formulations of large molecules must therefore ensure that the large molecule is able to pass through the intestinal wall so that it can be absorbed into the bloodstream and that the large molecule therapeutic is not exposed to enzymatic degradation in order to protect its biological activity and availability for absorption.

Our proprietary technology is designed to address both of these issues by utilizing a combination of a synthetic absorption enhancer, or carrier molecule, to facilitate the enhanced absorption of large molecules, and protease inhibitors to prevent enzymatic degradation. By designing our product candidates to address both the issues of absorption and degradation, we have been able to significantly increase bioavailability and decrease the variability of the PTH dose delivered in our clinical trials to date. Our carrier molecule is designed to create a weak association with our chosen large molecule therapeutic agents, leaving the therapeutic agent chemically unmodified. The carrier molecule enables transport across the intestinal membrane via transcellular absorption without compromising the integrity of the intestinal wall. Because of the weak association between the carrier molecule and the therapeutic agent, the interaction is designed to be reversible and occurs spontaneously by simple dilution on entering the blood. We select protease inhibitors that act by specifically inhibiting a number of gastrointestinal enzymes designed to assist in the degradation and digestion of proteins without interfering with normal gastrointestinal activity.

In order for large molecule therapeutics to benefit from the use of our oral delivery technology, they must demonstrate a number of specific characteristics, including:

- having the appropriate size, as measured by molecular weight, and other chemical/physical characteristics;
- having a mechanism of action that favors delivery through the gastrointestinal tract rather than through injections; and
- having a dosing schedule that requires dosing one or more times per day for at least three months.

Based on these criteria, we chose to focus initially on product candidates related to oral delivery of PTH molecules, which have the potential for therapeutic use in a number of indications, including hypoparathyroidism and osteoporosis. We have also explored the use of our technology in other molecules such as a GLP-2 analog and a number of other macromolecules, up to approximately 150 kDa in size. We believe our platform technology has the potential for use in biologics, which represented approximately 30% of all FDA drug approvals between 2015 and 2021 and over $20 billion in annual sales across that same period.

We have entered into 5 ‘funded’ Material Transfer Agreements (“MTAs”) with other pharma and biotech companies to demonstrate the utility of Entera’s platform to orally deliver large molecules, where the third parties are paying for Entera’s costs. We believe the data generated from these MTA’s will be the basis for entering into licensing agreements that generate non-dilutive funding.

Our Product Candidates

The following table summarizes important information about our current oral PTH product candidates, including their respective indications and current stages of development. We have not out-licensed any intellectual property rights to our oral PTH product candidates listed below, and, therefore, have retained the ability to pursue their worldwide commercialization, or potential commercial collaborations.

Program	Indication	Description	Stage of Development	Status
EB613	Osteoporosis	Oral PTH (1-34)	Phase 3	Phase 2 dose ranging clinical trial completed and final BMD results reported in Q2 2021 End-of-Phase 2 Meeting with FDA Dec 2021 Phase 3 initiation expected in 2022
EB612	Hypoparathyroidism	Oral PTH (1-34)	Phase 2	Phase 2a successfully completed (results reported 2015) Phase 2b PK/PD clinical trial head to head with Natpara in hypoparathyroid patients results reported in Q3 2019 Improved formulation selected in Q4 2021

Oral PTH Therapeutics

PTH is a hormone that regulates the levels of calcium and phosphorus in the blood. The naturally occurring form of PTH that is found in the human body is composed of 84 amino acids, although only the first 34 amino acids are believed to be responsible for its biological effects. A recombinant injectable form of PTH that is composed of only the first 34 amino acids, or PTH (1-34), is used as a treatment for a number of indications, including hypoparathyroidism, osteoporosis and non-union fractures. A subcutaneous injectable form of human PTH (1-34), marketed under the name Forteo®, has been approved in the United States since 2002 and has been used by more than one million patients for the treatment of osteoporosis. An injectable form of full length human PTH (1-84), marketed under the name Natpara®, has been approved for the treatment of hypoparathyroidism, but it is currently the subject of an FDA recall. We are developing multiple oral formulations of PTH (1-34) that can be used for a number of proposed indications. We believe that our oral PTH product candidates, EB613 and EB612, if approved, have the potential to become the standard of care for patients with osteoporosis, hypoparathyroidism and non-union fractures.

PTH regulates calcium and phosphate homeostasis and bone metabolism in the body. In normal healthy individuals, PTH is generally produced at very low basal levels that produce a blood concentration of 15 - 25 pg/mL. On top of the basal PTH levels, there are physiological pulses two to three times per day that result in transient increases in PTH levels reaching up to 65 pg/mL. The changes in PTH secretion are in response to ionized calcium concentration in blood plasma that result from the entry of calcium from nutrients in the intestine and resorption of calcium from bone. The pulses help encourage bone turnover through activation of both osteoblasts and osteoclasts, which are the two main types of cells that are responsible for the process through which bones are remodeled. In the absence of adequate parathyroid function producing these pulses in response to decreasing blood calcium, it is difficult for the body to regulate normal homeostatic processes.

EB613 for Osteoporosis

Osteoporosis

We are developing an oral PTH program, EB613, for the treatment of osteoporosis. Osteoporosis is a systemic skeletal disease characterized by low bone mass, deterioration of the microarchitecture of bone tissue and increased bone fragility and susceptibility to fracture. It most commonly affects older populations, primarily postmenopausal women. All bones are subject to an ongoing process of formation and degradation, whereby bone tissue is removed from the skeleton and new bone tissue is formed. Two main types of cells are responsible for this process: osteoclasts, which break down bone tissue; and osteoblasts, which secrete new bone tissue. In healthy individuals, bone resorption is matched by new bone formation. Osteoporosis develops as the delicate balance between bone resorption by osteoclasts and bone formation by osteoblasts is not maintained, and not enough bone tissue is formed, leading to frail and fracture-prone bones. Moreover, in many types of osteoporosis, the overall rate of bone turnover is accelerated, increasing the rate of bone loss. The weak and brittle bones become susceptible to fractures caused by fall, mild stress or even a cough that would cause no harm to normal bones. The complications of fractures and treatment in frail elderly individuals can in limited instances be fatal (for example, due to pulmonary embolism, pneumonia or urosepsis).

Osteoporosis often leads to loss of mobility, admission to nursing homes and dependence on caregivers resulting in substantial costs to the healthcare system. The prevalence of osteoporosis is growing due to the aging of populations in developed countries, and, according to the National Osteoporosis Foundation, or NOF, is significantly under-recognized and under-treated. While the aging of the population is a primary driver of an increase in prevalence, osteoporosis is also increasing from the use of drugs that induce bone loss, such as the chronic use of glucocorticoids and aromatase inhibitors that are increasingly used for the treatment of breast cancer and the hormone deprivation therapies used for the treatment of prostate cancer.

Market opportunity

The NOF has estimated that over eight million women in the United States already have osteoporosis and another approximately 44 million may have low bone mass, placing them at increased risk for osteoporosis. In U.S. women 55 years of age and older, the hospitalization burden of osteoporotic fractures and population facility-related hospital cost is greater than that of myocardial infarction, stroke, or breast cancer. Furthermore, the NOF expects that the number of fractures in the United States due to osteoporosis will rise to three million by 2025, resulting in an estimated $25.3 billion in costs each year. Worldwide, osteoporosis affects an estimated 200 million women according to the International Osteoporosis Foundation, or IOF, and causes more than 8.9 million fractures annually, which is equivalent to an osteoporotic fracture occurring approximately every three seconds. The IOF has estimated that 1.6 million hip fractures occur worldwide each year, and by 2050 this number could reach between 4.5 million and 6.3 million. The IOF estimates that in Europe alone, the annual cost of osteoporotic fractures could surpass €76 billion by 2050.

Limitations of current treatments for osteoporosis

The goal of pharmacological treatment of osteoporosis is to maintain or increase bone strength, to prevent factures 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 that increase the rate of bone formation, and, at least in part, restore lost bone. The global osteoporosis drug market was dominated for many years by bisphosphonates that inhibit bone resorption, although bisphosphonates' market share in the United States has declined over recent years due to fear of the occurrence of rare but potentially serious side effects. In addition, anabolic drugs like Forteo (human PTH (1-34)), and abaloparatide (Tymlos ®) which is a synthetic PTH receptor agonist, have become more frequently used. Both of these drugs are taken via subcutaneous injection and are used for only one to two-year periods with patients subsequently transitioned to an antiresorptive drug. More recently, the market has seen the introduction of newly developed pharmacological treatments that also inhibit bone resorption, including the RANK-ligand inhibitor denosumab (Prolia ®) and the anti-sclerostin antibody, romosozumab (Evenity®)

The primary current treatments for osteoporosis are summarized in the table below:

Class of Drug	Name (Producer)	Method of Action	Known Side Effects	2020 Branded Sales (in millions)
Injectable PTH	Forteo (Eli Lilly)	Increases bone mineral density by, increasing bone formation.	Decrease in blood pressure, increase in serum, calcium in the blood; nausea, joint aches, pain, leg cramps, injection site reactions	$1,046
Monoclonal antibody	Prolia (Amgen)	Blocks bone resorption by osteoclasts by binding RANK-L a protein that is essential to activate osteoclasts	Hypocalcemia, serious infections, dermatologic adverse reactions, osteonecrosis of the jaw, atypical femoral fractures, back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis	$2,763
	EVENITY® (Amgen)	Increases bone formation and, to a lesser extent, decreases bone resorption by inhibiting the action of sclerostin, a regulatory factor in bone metabolism. Note: limited duration of use to 12 monthly doses.	Heart attack, stroke, Hypersensitivity reactions, including angioedema, erythema multiforme, dermatitis, rash, and urticaria; hypocalcemia; osteonecrosis of the jaw; atypical femoral fracture;	$350
Injectable abaloparatide	Tymlos (Radius Health)	Similar to PTH, binds to PTH receptors and results in bone formation and increased bone mineral density	Osteosarcoma, Orthostatic hypotension, hypercalcemia, hypercalciuria, dizziness, nausea, headache, palpitations, fatigue, upper abdominal pain and vertigo	$219
Bisphosphonate	Fosamax (Merck) Actonel, Boniva Zometa (IV) (Novartis)	Prevent bone loss by inhibiting osteoclasts. Effects reversible at low doses but high intravenous causes apoptosis.	Irritation of the gastrointestinal mucosa, hypocalcemia, severe musculoskeletal pain, osteonecrosis of the jaw, atypical femoral fractures	N/A (Generic)

In osteoporosis patients, who have normal basal levels of PTH, therapeutic administration of PTH initially activates osteoblasts, but eventually activates osteoclasts after several months of treatment. While both types of cells are activated when PTH is administered, osteoblasts are activated to a greater extent, increasing net bone formation and bone mass. Injectable PTH (1-34), in the form of Eli Lilly's Forteo, is therefore one of the most effective osteoporosis medications on the market today and demonstrably more efficacious in reducing the risk of spine fractures than bisphosphonates. Forteo is particularly advantageous in glucocorticoid-induced osteoporosis, a known side effect of drugs like prednisone. A study published in the New England Journal of Medicine found that, over a period of 18 months, BMD in the lumbar spine in a group of patients with glucocorticoid-induced osteoporosis treated with Forteo increased twice as much as that in the group treated with a bisphosphonate.

Unlike our oral delivery system, Forteo is administered by subcutaneous injection, which has significant drawbacks, including the discomfort and local irritation associated with a daily injectable regimen. Additionally, subcutaneous injection of Forteo has been shown to induce antibodies to the drug in approximately 3% of the patient population. Based on our market research, we believe an oral form of PTH (1-34) would significantly improve patient and physician acceptance. We also believe that the desire for a more patient friendly route of administration is why Eli Lilly has evaluated several collaborations with developers of alternative delivery systems, including a micro needle patch system and an intranasal delivery system. However, these collaborations have yet to result in a successful commercial product. While a patch technology may reduce the discomfort associated with an injection, we believe patients will prefer an oral form of PTH (1-34) over a patch form of delivery. In addition, several pharmaceutical companies have previously attempted to develop an orally administered form of PTH, but none have been successful to date due to issues including variability and low bioavailability.

Other oral delivery technologies for the treatment of osteoporosis

We believe that our oral delivery technology is superior to other oral peptide delivery technologies that were and still may be in development for osteoporosis patients. The table below presents a comparison and integration of available clinical trial results to date:

Company/Technology	Molecule	API MW (g/mole)	Bioavailability (F)
Entera Bio	PTH (1-34)	4118	1.5%
Novartis/Emisphere (Eligen - CNAC) [(1)]	PTH (1-34)	4118	0.2 - 0.5%
Enteris Biopharma - Unigen (Peptelligence) [(2)]	PTH (1-31)	3719	0.52%
Multiple manufacturers[(3)]	Desmopressin	1069	0.16%
Chiasma (TPE)[(4)]	Octreotide	1019 (Cyclic peptide)	0.67%
Proxima Concepts (AXCESS)[(5)]	Insulin	5733	0.7%

(1) Source: The single dose pharmacokinetic profile of a novel oral human parathyroid hormone formulation in healthy postmenopausal women Sibylle P. Hämmerle, et al. Bone. 2012 Apr;50(4):965-73. doi: 10.1016/j.bone.2012.01.009. Epub 2012 Jan 25.

(2) Source: Pharmacokinetics of oral recombinant human parathyroid hormone rhPTH (1-31)NH2 in postmenopausal women with osteoporosis. Sturmer A1 et el. Clin Pharmacokinet. 2013 Nov;52(11):995-1004. doi: 10.1007/s40262-013-0083-4.

(3) Source: Public Assessment Report, Desmopressin Acetate 100 Microgram Tablet PL 24668/0177 and Desmopressin Acetate 200 Microgram Tablet PL 24668/0178. Medicines and Healthcare Products Regulatory Agency.

(4) Source: Pharmacokinetic Modeling of Oral Octreotide (Octreolin™) in Healthy Volunteers and Dosing Regimen Optimization for Acromegaly Patients. Shmuel Tuvia et al. Endocrine Society's 94th Annual Meeting June 2012, OR29-6-OR29-6. Source: The glucose lowering effect of an oral insulin (Capsulin) during an isoglycaemic clamp study in persons with type 2 diabetes S. D. Luzio et al. Diabetes Obes Metab. 2010 Jan;12(1):82-7. doi: 10.1111/ j.1463-1326.2009.01146.x. Epub 2009 Sep 25.

Preclinical and Clinical Development of EB613

In multiple clinical trials conducted to date, more than 260 subjects have received formulations of EB613. Furthermore, in these trials, EB613 exhibited no serious drug related adverse events and displayed compelling PK and PD properties although different than the published data from Forteo and other PTH products. Adverse events across all trials in subjects receiving EB613 were consistent with those seen in other clinical trials of PTH and included: mild hypercalcemia; tachycardia; and headache. Other adverse events observed were typical of those observed in the placebo groups of our studies and other clinical trials, and included anemia, musculoskeletal and connective tissue event of knee cramps, nausea, muscle aches, and dizziness.

Completed Phase 2 Trial and Planned Clinical Development

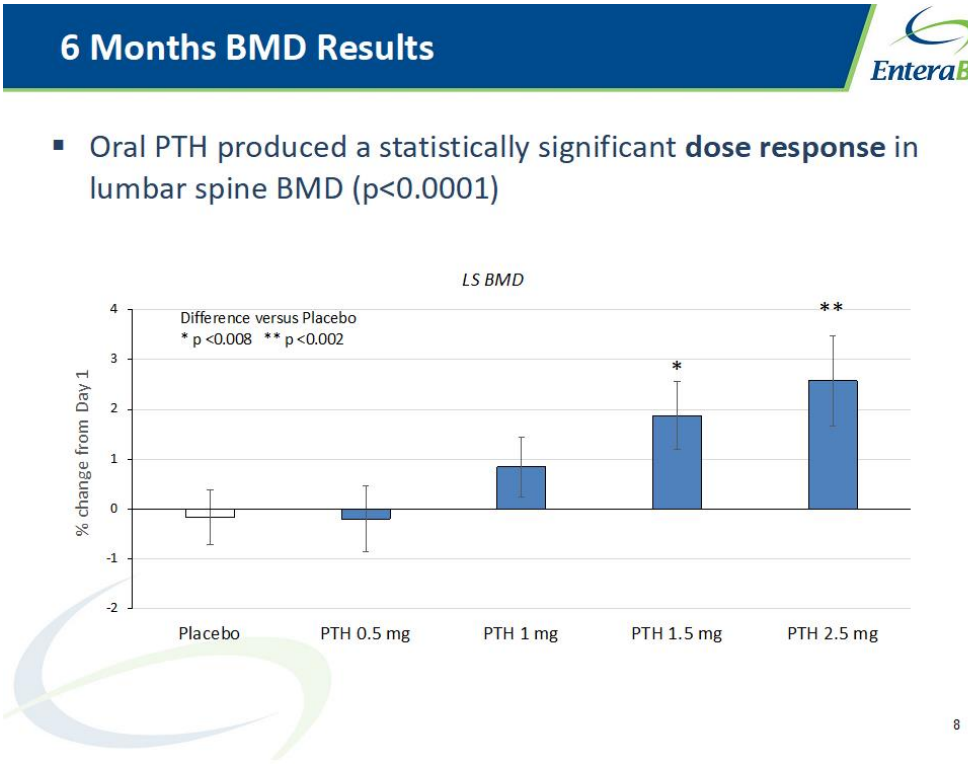
Developers of osteoporosis drugs that contain new chemical entities are required to conduct extensive clinical studies that employ an endpoint that measures the reduction in fractures. These trials often require thousands of patients over a multi-year period, and typically cost hundreds of millions of dollars. However, once fracture risk reduction has been demonstrated, the FDA and other regulatory agencies have allowed new formulations or treatment regimens of the same active ingredient to be approved using BMD as the primary efficacy endpoint under the 505(b)(2) regulatory pathway in the United States or the comparable regulation in other countries. In November 2018, we held a pre-IND meeting with the FDA to discuss our development plan for oral PTH for the treatment of osteoporosis and in December 2020, we announced that the FDA had accepted the IND submission for EB613. After successful completion of the Phase 2 dose ranging study of EB613, we held an end-of-Phase 2 meeting with FDA to discuss various aspects of the nonclinical and clinical development plan, the meeting focused on the potential use of BMD, rather than fracture incidence, as the primary endpoint to support a new drug application, or NDA.

In July 2019, we initiated a six-month Phase 2 trial of EB613 in Israel with a target enrollment of 160 subjects. The Phase 2 clinical trial was designed to evaluate both the safety of EB613 and to identify the optimal dose that we will select to advance into a single Phase 3 pivotal trial. Based on the pre-IND meeting and the interim data from the Phase 2 trial of EB613, we submitted an IND for EB613 to the FDA in November 2020. In December 2020, we announced that the FDA had reviewed our IND application for EB613 and informed us that we may proceed with our proposed U.S. clinical trial.

The Phase 2 clinical trial of EB613 was a dose-ranging, placebo-controlled study in postmenopausal female subjects with osteoporosis or low BMD conducted at four leading medical centers in Israel. The trial evaluated BMD, multiple bone markers, including P1NP and Osteocalcin - bone formation markers, CTX – a bone resorption marker, and various safety endpoints. We completed enrollment in this trial in November 2020 upon the randomization of the 161st subject. The demographics for the EB613 Phase 2 clinical trial such as age, body mass index, or BMI, and baseline levels of bone markers were generally consistent with demographics from comparable osteoporosis studies.

	N	Mean	Median
Age	161	61	61
Weight (Kg)	161	67	66
BMI	161	26	26

The 6-month Lumbar Spine BMD change from baseline (mean, standard error) are summarized below:



In March 2021, we announced complete 3-month biomarker data from this trial. The complete 3-month results from the trial showed a significant increase in the P1NP biomarker in the 2.5 mg dose group after 3 months of treatment (P <0.04) as compared to placebo. The change in P1NP at 3-months was the primary endpoint the Phase 2 trial. Similar to the increase in P1NP, a significant increase in Osteocalcin was also observed in the 2.5 mg group after 3 months (P <0.01). In line with a potential anabolic effect, a significant decrease in CTX was observed after 3 months and 6 months of treatment (P <0.015). The decrease in CTX taken together with the increase in P1NP and Osteocalcin would indicate a potential positive impact on BMD.

Biomarker data from the Placebo and EB613 2.5mg dose group are summarized below:

- A significant increase in P1NP from baseline versus placebo at month 3 (P <0.04) as well as significant increases at months 1 (P <0.0001) and 2 (P <0.003);
- A significant increase in Osteocalcin from baseline versus placebo at month 3 (P<0.006) as well as significant increases at months 1 (P<0.0001) and 2 (P<0.0001);
- A significant decrease in CTX from baseline versus placebo at month 3 and month 6)both timepoints, P <0.015 versus placebo) as well as a significant decrease at month 1 (P <0.001)

Study medication, EB613 or placebo was generally well tolerated through 6 months of treatment. Common adverse events resembled those known to be associated with teriparatide by subcutaneous injection including dizziness, headache, palpitations, and nausea. There were no adverse events that were severe in intensity in any treatment group and no serious drug-related adverse events.

Conclusions from this Phase 2 study of postmenopausal women with osteoporosis or low BMD that included six months of treatment with oral PTH 2.5 mg, included:

- Increased lumbar spine, femoral neck and total hip BMD compared to placebo, and compared to start of treatment;
- The increase in spine BMD was similar in magnitude to that previously reported with Forteo®;
- Increases in total hip and femoral neck were greater than those previously reported with Forteo®;
- Reduced serum CTX compared to placebo;
- Adverse event profile similar to that observed with Forteo®, and typical of orthostatic hypotension;
- Was not associated with serum calcium increases or Hypercalcemia adverse events; and
- Greater than 90% of subjects tolerated the 2.5 mg dose well, after titration starting with the 1.5 mg, and progressing through 2.0 mg doses,

The results of the Phase 2 study supported the selection of the 2.5 mg dose for the pivotal Phase 3 study. The six-month increases in BMD with the 2.5 mg dose position EB613 as potentially the first oral anabolic treatment.

We are also conducting several nonclinical safety assessment studies to support our regulatory filings and to enable the start of a Phase 3 clinical trial in 2022 using sites in the United States, Israel, Europe and other territories. See "Item 1A. Risk Factors—Risks Related to Our Business and the Development of Our Product Candidates—The COVID-19 pandemic could adversely affect our business, financial condition, and results of operations."

EB612 for Hypoparathyroidism

Hypoparathyroidism

Our product candidate for hypoparathyroidism, EB612, is an oral formulation of PTH (1-34). We believe that EB612, if approved, has the potential to become the standard of care for hypoparathyroidism. Hypoparathyroidism is a rare condition in which the parathyroid glands fail to produce sufficient amounts of PTH. In addition, there are rare genetic diseases where mutations in the PTH gene results in PTH that lacks biologic activity. Individuals with a deficiency of parathyroid hormone may exhibit hypocalcemia and hyperphosphatemia. Hypocalcemia can cause one or more of a variety of symptoms, including weakness, muscle cramps, excessive nervousness, headaches and uncontrollable twitching and cramping spasms of muscles such as those of the hands, feet, arms, legs and face, which is known as tetany. Numbness and tingling around the mouth and in the fingers and toes can also occur. Acute hypocalcemia can result in cardiac failure, failure of nervous system functions and death. Hyperphosphatemia can result in soft tissue calcium deposition, which may lead to severe issues, including damage to the circulatory and central nervous systems. The most common cause of hypoparathyroidism is damage to, or removal of, the parathyroid glands due to surgery for another condition. Hypoparathyroidism can also be caused by autoimmune process idiopathic reasons or occur in association with a number of different underlying disorders. In rare cases, hypoparathyroidism may occur as a genetic disorder where mutations in the PTH gene results in the production of PTH that lacks biologic activity.

Market opportunity

The prevalence of hypoparathyroidism is estimated to be 37 per 100,000 persons in the United States, with 70% of cases caused by surgery, 8% due to genetic disorder and 7% due to idiopathic origin. Although incidence rates have been difficult to quantify, it is estimated that chronic hypoparathyroidism, which affects patients for more than six months, affects approximately 58,700 insured individuals in the United States, with an estimated 43% of these chronic cases characterized as mild, 39% characterized as moderate, and 18% characterized as severe. The FDA has granted orphan drug designation to our oral PTH for the treatment of hypoparathyroidism.

Limitations of current treatments for hypoparathyroidism

Historically, the treatments for hypoparathyroidism have been calcium supplements, vitamin D supplements and phosphate binders. Although calcium and vitamin D can help alleviate hypocalcemia, their chronic use results in many serious side effects with significant costs to the healthcare system. Hypoparathyroid patients often need to take large doses of calcium throughout the day in order to maintain serum calcium near the lower limit of the normal range. Moreover, ordinary vitamin D is generally insufficient as the body cannot produce adequate quantities of 1,25-dihydroxyvitamin D, the active hormone derived from vitamin D. Drugs like calcitriol and alfacalcitol must be prescribed to stimulate calcium absorption. If excess calcium is absorbed, it then falls upon the kidneys to dispose of excess calcium. Endogenous PTH normally regulates renal calcium excretion, but this regulation is defective in patients with hypoparathyroidism. Over many years of treatment, kidney stones may develop, and ultimately kidney failure may occur due to either kidney stones or deposition of calcium phosphate in kidney tissue (called nephrocalcinosis). Despite the use of calcium and vitamin D supplements and other medications, many patients with hypoparathyroidism continue to experience physical and cognitive symptoms.

Until recently, hypoparathyroidism was the only hormonal insufficiency state that did not have an approved hormone replacement therapy. Natpara, which is administered once daily with a pre-set injection pen, was approved by the FDA and launched commercially in the United States in 2015. Natpara was originally developed by NPS Pharmaceuticals, Inc., which was acquired by Shire plc in 2015 and is now a part of Takeda Pharmaceuticals, as a result of its 2019 acquisition of Shire. Natpara is a recombinant form of human PTH (1-84) that was developed as an injectable hormone replacement therapy for the underlying cause of hypoparathyroidism, which is a lack of PTH. In the FDA's advisory committee meeting for Natpara, a number of observations were highlighted, including that Natpara had limited clinical benefit in controlling excessive calcium in the urine, or hypercalciuria, a condition commonly associated with hypoparathyroidism and the most commonly identifiable cause of calcium kidney stone disease. Additional analysis by the FDA also noted that, due to a change in trial protocol that was made after the initiation of the trial, the responder rate for the pivotal single-dose trial's primary efficacy endpoint was 32.1% under the original trial protocol versus the 54.8% that was ultimately reported. The FDA stated in its briefing report that the results of this alternate analysis may be more clinically relevant, particularly if a clinician's goal is to keep a patient's serum calcium in the lower half of the normal range.

EB612 for the treatment of hypoparathyroidism

We believe EB612 may offer several advantages over Natpara for the following reasons:

- *EB612 is designed to be dosed multiple times a day*. Studies performed by the NIH have shown that dosing PTH multiple times per day significantly increases the efficacy of therapy and would be more effective for treating hypoparathyroidism than a once-per-day regimen. These studies found that the total daily PTH dose required to maintain serum calcium in the normal or near-normal range was reduced by 50% with twice-daily PTH (1-34) and also demonstrated that twice-daily dosing achieved better control over serum calcium and urinary calcium excretion as compared to once-daily dosing.

- *EB612 is designed to be dosed according to patient needs.* The hypoparathyroid population is heterogeneous, and patients have highly variable responsiveness to PTH. Therefore, the ability to customize PTH dosing throughout the day with an oral tablet is an advantage over a once-daily preset injection pen.

- *EB612 is expected to have fewer adverse events of hypercalcemia.* Our planned treatment regimen would be increased gradually and in parallel to increases in serum calcium. As a result, calcium supplements and active vitamin D metabolites (e.g., calcitriol) would be reduced gradually, while maintaining a relatively stable level of serum calcium. This is in contrast with Natpara's initially high dose, which requires an immediate reduction in supplements in anticipation of a rapid increase in serum calcium levels. Furthermore, this immediate and prolonged increase in serum calcium increases the risk of prolonged hypercalcemia compared to EB612. Moreover, the target serum calcium level would be the lower end of the normal range. If serum calcium were at, or greater than, the middle of the normal range, calcium supplements, active vitamin D metabolites and oral PTH dose would be reduced.

- *EB612 can be administered in a more convenient manner.* Natpara is administered by subcutaneous injection, must be stored under restrictive conditions (refrigeration required with no freezing or shaking) and has a multi-step preparation that must be performed every two weeks. EB612 will not require such additional preparations and will have no significant storage restrictions.

As a result of its dose flexibility and the generally greater patient acceptance of oral formulations, we believe EB612, if approved, will address a larger segment of the hypoparathyroid population than Natpara. For these reasons, we believe that EB612, if approved, has the potential to become the standard of care for patients with hypoparathyroidism.

To date, no oral PTH formulation has been successfully developed because PTH, like many other hormonally active peptides, degrades rapidly in the intestinal tract when taken orally. EB612 is a synthetic form of the first 34 amino acids of human PTH to which we have applied our proprietary technology. This technology permits oral administration, enabling more frequent dosing throughout the day and greater sensitivity and flexibility in dosing than injectable formulations of PTH. The carrier molecule and selection of protease inhibitors that are used in our technology are well-characterized and have been used in large clinical trials. We have attempted to optimize EB612 to enable the most cost effective and safest formulation while maintaining the required effect. These components, when used separately, have been shown to be safe in doses significantly higher than those used in the clinical trials for our current product candidates.

We believe that EB612 will have inherent advantages compared to injectable forms, including convenience of administration without any special preparation of the medication and convenience of storage (room temperature or refrigeration for long term storage). Additionally, based on the results of our preliminary studies, we believe that EB612 will have an enhanced clinical profile as compared to Natpara, with an additional positive effect on elevated urinary calcium, as well as reduced side effects. If our preliminary results are borne out in additional clinical trials, we believe this combination of advantages and long term clinical benefits will be compelling to both patients and physicians.

EB612 Hypoparathyroidism Clinical Trials

We demonstrated with earlier formulations of what now is EB613 a large body of evidence in Phase 1 studies, which included a Phase 1a clinical trial with multiple formulations of our oral PTH to evaluate safety and collect bioavailability and PK and PD data in 42 healthy volunteers, as well as in an extended Phase 1b clinical trial in an additional 30 volunteers to test a variety of manufacturing technologies with multiple formulations, administration parameters and dosing regimens of our oral PTH. These earlier data and oral PTH formulations led to several Phase 2 studies evaluating a number of EB612 formulations in hypoparathyroidism patients.

Phase 2a Clinical Trial

In 2015, we successfully completed a multicenter Phase 2a clinical trial of EB612 in hypoparathyroidism patients. This study demonstrated the safety and tolerability of EB612 administered four times daily for 16 weeks to patients with hypoparathyroidism. In this study, patients were titrated up to a maximum of 12 EB612 0.75 mg tablets a day (total daily dose of 9 mg) by the investigator, according to each subject's albumin-adjusted serum calcium (ACa), and supplement treatment regimen. Of the 19 enrolled subjects, 17 completed the trial (of which 15 were per protocol). No drug-related serious adverse events were reported and most of the adverse events were not considered study drug-related.

The study achieved its primary and secondary endpoints, including a reduction in calcium supplements, reductions in serum phosphate and 24-hour urine calcium excretion, maintenance of ACa within the reference range, and an improvement in quality of life. Specific results of this trial included:

- A significant reduction of 42% (p=0.001) from baseline in median calcium supplement use;
- Maintenance of median ACa levels above the lower target level for HypoPT patients (>7.5 mg/dL) throughout the study;
- A rapid decline of 23% (p=0.0003) in median serum phosphate levels 2 hours following the first dose that was maintained within the normal range for the duration of the study;
- A notable median decrease of 21% (p=0.07) in 24-hour urine calcium excretion between the first and last treatment days; and
- An increase in quality of life score of 5% (p=0.03) from baseline by the end of the treatment period.

Based on a review of the clinical data presented in Natpara's REPLACE trial and our Phase 2a results, we believe EB612 potentially provides a more favorable therapy for hypoparathyroidism patients than currently available therapies. Although our Phase 2a trial involved a smaller number of patients (N=15 vs. N=84 + 40 placebo), lasted for a shorter duration (four months vs. six months) and did not include a dose optimization period of ~2 - 16 weeks prior to treatment initiation, in each case as compared to the REPLACE trial, our results showed a greater absolute reduction in calcium supplements (1278 ±880mg vs. 1152 ±1219mg) while the patients' albumin adjusted serum calcium increased slightly as opposed to a slight decrease in the REPLACE trial (baseline vs. end of treatment). The results of this trial were published in the *Journal of Bone and Mineral Research* in the first quarter of 2021.

Phase 2 PK/PD Clinical Trial

We initiated a two-part Phase 2 PK/PD trial in 2014. This trial was designed to provide a bridge from one of our completed Phase 2a trials, which was conducted prior to the marketing approval of Natpara, and our planned future clinical trials, and to also allow us to better understand the relative strength and dose of our product as compared to the marketed product, Natpara. This trial was also intended to provide valuable comparative data to Natpara that will further inform the design of a potential Phase 2b/3 clinical trial. The relevant endpoints for the PK/PD trial included an examination of levels of PTH (1-34), PTH (1-84) (Natpara), serum calcium, serum phosphate, urinary calcium and urinary phosphate.

In November 2018 we announced the completion of part I of this Phase 2 PK/PD trial to evaluate the PK/PD profile of various EB612 dose regimens, while comparing such various dose regimens with Natpara. In Part I of the trial, ten patients with hypoparathyroidism completed two three-day in-patient visits. Throughout each of these three-day visits, patients remained on their current standard medications. On the first day of each visit (baseline) patients received no additional treatments. On day two, patients were randomized to receive one of three treatments: EB612 twice a day (BID), four times a day (QID), or Natpara once a day (QD). On day three, patients did not receive any additional treatments. In the second three-day visit, patients were again randomized on day two to receive one of the treatment regimens they had not received previously. Throughout the three-day visits, patients were continuously monitored clinically, and PTH, calcium, phosphate, and the hormonal metabolite of vitamin D (1,25- dihydroxyvitamin D) levels were measured. PTH has several well-known physiological effects. It increases serum calcium, decreases serum phosphate, increases reabsorption of calcium in the kidney, where it also increases 1,25-dihydroxyvitamin D synthesis.

Results from Part 1 of the PK/PD trial of Oral PTH (1-34) (QID) treatment included: (i) an increase in the serum calcium by an average of approximately 0.3 mg/dL over baseline, with such increase maintained over a 24-hour period; (ii) a decrease in serum phosphate by an average of 0.5 mg/dL below baseline with such decrease maintained over a 24-hour period; (iii) an increase in average levels of serum active vitamin D of approximately 90% on the day of treatment as compared to baseline; and (iv) a decrease in average levels of 24-hour urinary calcium of approximately 30% on the day of treatment as compared to baseline. An initial analysis of the Part 1 data suggested that the QID regimen provided a greater effect on all of the parameters measured as compared to the BID regimen. The concentration of PTH (1-34) in blood after administration of Oral PTH (1-34) in the current trial was sufficient to produce the observed pharmacodynamic effects and did not induce hypercalcemia. No serious adverse events were reported in the trial.

The second and final part of this PK/PD trial evaluated a variety of dosing treatment regimens with a high and low dose of EB612 as well as Natpara with patients also receiving calcium supplements and either alfacalcidol or calcitriol. In September 2019, we presented the results of Part 2 of this PK/PD trial at the American Society for Bone and Mineral Research (ASBMR) Annual Meeting. The trial conclusions noted that EB612 2.25 mg QID for one day is associated with an increase in serum albumin-corrected calcium and 1,25(OH)2D (1,25-dihydroxyvitamin D), a decrease in serum phosphate, and a decrease in urinary calcium in patients with hypoparathyroidism. EB612 produced similar biological effects to Natpara 100 µg QD, the highest dose of hPTH (1-84) currently indicated for use in patients with hypoparathyroidism, on serum calcium, phosphate and vitamin D. Additionally, EB612 resulted in a decrease in urinary calcium. These changes in serum PD parameters were sustained over the 24-hour period of observation from time zero. BID, TID and QID regimens showed a dose-dependent increase in 1,25(OH)2D indicating that the long-term treatment, even with the less frequent dosing regimens, may be an effective treatment option for those patients suffering from less severe hypoparathyroidism. Furthermore treatment with Oral hPTH (1-34) dosed at multiple times during the day has the potential to reduce calciuria generally associated with maintenance of serum calcium within the normal range using calcium supplements and calcitriol analogs alone. There were no treatment-emergent adverse events of hypercalcemia, as well as no treatment-emergent serious adverse events reported in the trial.

Planned Additional Clinical Development and Regulatory Pathway

After the completion of additional formulation and development activities to inform our final formulations, and subject to available funds, we expect to initiate a Phase 2b/3 clinical trial of EB612 for the treatment of hypoparathyroidism, which will further evaluate the dosage, effectiveness and safety profile of EB612 in an expanded population of patients with hypoparathyroidism conducted at multiple trial sites. We expect that this Phase 2b/3 trial, when initiated, will be designed to replicate the REPLACE trial in many aspects and to achieve a significant reduction in urinary calcium. The phase 2b/3 clinical trial of EB612 in hypoparathyroidism, if successful, may potentially support a submission for regulatory approval of EB612.

The Phase 2b/3 trial will likely be designed as a placebo controlled trial with a "rescue" provision for patients who have substantial persistent symptoms, hyperphosphatemia, hypocalcemia or hypercalciuria. The planned primary endpoints will be the proportion of patients obtaining a serum calcium and phosphate within a "target" range, reducing hypercalciuria and from a safety perspective, the incidence of clinically important hypercalcemia and decreased renal function adverse events. The trial will also compare the reduction in calcium intake, reduction in active vitamin D in each treatment group. Secondary endpoints include mean absolute levels of serum calcium and serum phosphate.

In April 2014, we received orphan drug designation from the FDA for our oral PTH in hypoparathyroidism. If a product receives the first FDA approval of that product for the indication for which it has orphan designation, the product is entitled to orphan drug exclusivity, which means that FDA may not approve any other application to market the same drug for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity or where the manufacturer is unable to assure sufficient product quantity. In January 2015, the FDA approved Natpara, an injectable form of PTH, for hypoparathyroidism, and awarded Natpara orphan drug exclusivity until January 23, 2022. While Natpara has orphan drug exclusivity for hypoparathyroidism, we believe that we will be able to demonstrate that our oral formulation of PTH is clinically superior to Natpara in that it demonstrates greater effectiveness is safer than Natpara or that it otherwise makes a major contribution to patient care. Therefore, we believe that Natpara's orphan drug exclusivity will not prevent the FDA from approving our BLA for EB612. In June 2016, we received approval from the EMA granting orphan status to our oral PTH in Europe.

Development and License Agreements

In addition to the development of our product candidates, we have a research collaboration and license agreement with Amgen, combining our proprietary drug delivery platform with drugs selected by Amgen to create new products. Pursuant to the agreement, in January 2019, we received a non-refundable and non-creditable initial technology access fee of $725,000 from Amgen, of which $500,000 was attributed to the right to use our intellectual property, and $225,000 was attributed to the pre-clinical R&D services that we are obligated to perform under the agreement. We are eligible to receive from Amgen aggregate payments of up to $270 million upon achievement of various clinical and commercial milestones or Amgen's exercise of options to select up to two additional programs to include in the collaboration, as well as tiered royalty payments based on percentages ranging from the low to mid-single digits based on the level of Amgen's net sales of the applicable products. During 2020 through March 16, 2021, we received an additional aggregate amount of $518,000 from Amgen for research and development services. The agreement is exclusive only to the specific drug candidates that are developed and discovered under the collaboration program, leaving us the rights to commercialize and develop products with other drugs using our proprietary technology while also allowing Amgen to retain all rights to its certain large molecules and any subsequent improvements. The first prospective product under the agreement with Amgen is currently in the preclinical and research and development phase. Under the agreement, we will engage in preclinical development at Amgen's expense and Amgen will conduct all research, clinical development, manufacturing and commercialization activities.

Additional Research and Development

Future Development of Orally Delivered Large Molecule Therapeutics

We intend to use our technology as a platform for the oral delivery of low-bioavailability therapeutics, which may include proteins and other large molecule therapeutics, as well as small molecules with very low absorption due to poor permeability properties (BCS class 3 drugs). We have conducted initial feasibility studies with a number of product candidates, and intend to commence clinical development for our next, non-PTH, product candidate in the future.

We expect that the key criteria in selecting our next clinical candidate will include: the size of the molecule and other chemical characteristics that would benefit from our technology, whether the molecule is best delivered through the intestinal tract rather than through injection, and the drug's dosing schedule, more specifically, whether it is prescribed for at least three months and would likely be best administered at least once a day. Additionally, we may target large proteins that are prone to inducing damaging immune responses when injected subcutaneously. In some cases, the immune response to the injection is so severe as to reduce or eliminate all physiological effect of the drug upon the illness. We are also considering whether to partner the development of any such additional product candidates and are in early stage discussions with a number of external parties.

Bone Healing/Non-Union Fractures

Currently, no pharmacological treatments are available that have been approved to either stimulate bone healing, treat delayed union fractures or treat patients with non-union following a fracture. A number of studies suggest that PTH could be beneficial in the treatment of such fractures, to potentially speed union and/or reduce the risk of non-union. This is due to the fact that PTH increases the activity and number of osteoblasts, which are responsible for bone formation, making it a potential treatment when bone healing is delayed. While surgery is generally required to treat patients with established fracture non-union, PTH might improve likelihood of a favorable surgical outcome. PTH could thus be a potentially new treatment option for the induction of bone healing after a fracture. Non-union fractures occur when the normal process of bone healing fails or is greatly delayed. Note the fracture malunion refers to a fracture that heals, but with an important abnormal structure or alignment of the bone fragments. By definition, a non-union fracture will not heal on its own. Most non-union fractures require surgery, which can involve bone grafts or stabilizing the affected bone by affixing rods, plates or screws. Risks of surgery include neurovascular injury, infection and hemorrhage.

In the United States, 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 costs vary from approximately $25,000 to $45,000.

Depending on the nature of the fracture, non-surgical solutions can include electrical stimulation or fitting external braces. Other more experimental techniques exist as well, including ultrasound stimulation, which has been approved by the FDA for treating fresh fracture since the 1990s. Unlike the rigorous requirements for new drug approval, the FDA has not required the same level of evidence for the efficacy of devices used to treat a medical condition. The major drawbacks of the more traditional methods are invasiveness and the risks inherent with surgery. In addition, bone grafting is associated with considerable morbidity, including chronic pain, injury to nerves and muscle and blood loss. Surgical cost is another significant concern. Experimental techniques, such as stimulation of the bone with electricity or sound show some promise for healing, but data demonstrating its effectiveness remains limited.

Our Potential Solution for Non-union or Delayed-Union of Fractures

We intend to investigate the efficacy of EB613 for delayed-union or non-union fractures. We may either pursue fracture treatment as an additional use of EB613 or further modify the formulation if studies suggest we could achieve a PK profile that is more efficacious for bone fractures. As treatment of non-union fractures and bone healing may entail three to six months of treatment, we believe the acceptance of oral PTH will be higher than other potential pharmacological alternatives that require injections.

Intellectual Property

Our success depends in part on our ability to protect the proprietary nature of our product candidates, technology, and know-how; operate without infringing on the proprietary rights of others, and prevent others from infringing on our proprietary rights. We seek to protect our proprietary position by, among other methods, seeking patent protection in the United States and in certain other jurisdictions for our product candidates and other technology that we consider important to the development of our business, where such protection is available. We believe that our success will depend in part on our ability to obtain patent protection for our intellectual property. We also intend to rely on trade secret protection, know-how and the exploitation of in-licensing opportunities to develop our proprietary position.

Patent Rights

As of March 1, 2022, our global patent portfolio included the following patents and patent applications:

Patents claiming compositions comprising a protein, an absorption enhancer and a protease inhibitor as well as methods for oral administration of a protein with an enzymatic activity, which compositions cover EB612 and EB613, have been issued in the United States, Australia, Japan, China, Hong Kong, Israel, Canada, New Zealand and Russia and have been granted by the European Patent Office (EPO) and validated accordingly in Belgium, France, Germany, Great Britain, Ireland, Italy, Liechtenstein, Luxembourg, Netherlands, Spain, Sweden, and Switzerland. Related patent applications are pending before the European Patent Office (EPO) and in the United States, Hong Kong, Brazil, China and India. Patents specifically covering PTH have already been granted in the United States, Hong Kong, Israel, Russia and Japan, and have been granted by the EPO and validated in Belgium, France, Germany, Great Britain, Ireland, Italy, Liechtenstein, Luxembourg, Netherlands, Spain, Sweden, and Switzerland. In addition, patent applications which specifically cover PTH are currently pending in Hong Kong, Brazil, China and India. The current issued patent in China is limited to insulin. This issued patent and any patent that may issue from the pending patent applications are currently expected to expire in August 2029, assuming all annuity and maintenance payments are paid thereon. Rights to these patents and patent applications were assigned to us pursuant to the Patent Transfer Agreement with Oramed.

Three patent applications filed in various jurisdictions, which we believe, if issued as patents containing substantially the same claims as those in the applications, would cover certain oral administration technologies. The mentioned technologies include compositions and drug delivery devices which utilize an absorption enhancer to enable the absorption of a therapeutically active agent in a controlled manner. We believe that certain of the pending claims contained in these patent applications, if issued in substantially the same form, would cover the formulations of EB612 and EB613. An application covering certain formulations with a controlled absorption profile was filed with the EPO and in the United States, Canada, Hong Kong, Israel and Mexico. Another application covering certain formulations for co-administration with an antacid or protease inhibitor was filed with the EPO and in the United States, Canada and Hong Kong (the application in the United States has been granted, and a divisional application has been filed therein). Any patents that issue from these patent applications are expected to expire in February 2036, assuming all annuity and maintenance payments are paid thereon. Another application covering certain formulations and regimens was filed with the EPO and in the United States, Australia, Brazil, Canada, China, Hong Kong, India, Israel, Japan, Mexico, New Zealand, Singapore, South Africa and South Korea. Any patents that issue from this patent application are expected to expire in August 2037, assuming all annuity and maintenance payments are paid thereon.

Three patent applications filed in various jurisdictions, which we believe, 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 (filed with the EPO and in the United States, Canada, China, Hong Kong, Israel and Japan; the application in Japan has been granted, and a divisional applications has been filed therein), hypoparathyroidism (filed with the EPO and in the United States, Brazil, Canada, Hong Kong, Israel and Japan; the application in Japan has been granted, and a divisional applications has been filed therein) and bone fractures and related conditions (filed with the EPO and in the United States, Canada and Hong Kong). Any patents that issue from these patent applications are expected to expire in February 2036, assuming all annuity and maintenance payments are paid thereon, and while not considering patent term extension when applicable.

Eleven provisional patent applications have been filed in 2022, which we believe, if issued as patents containing substantially the same claims as those in the applications, would cover new discoveries for the oral delivery of large molecules. Any patents that issue from these patent applications are expected to expire in February 2043, assuming all annuity and maintenance payments are paid thereon and while not considering patent term extension when applicable.

The term of individual patents depends upon the legal term for patents in the countries in which they are granted. In most countries, including the United States, the patent term is generally 20 years from the earliest claimed filing date of a non-provisional patent application in the applicable country. In the United States, a patent's term may, in certain cases, be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the USPTO in examining and granting a patent, or may be shortened if a patent is terminally disclaimed over a commonly owned patent or a patent naming a common inventor and having an earlier expiration date. The Hatch-Waxman Act, permits a patent term extension of up to five years beyond the expiration date of a U.S. patent as partial compensation for the useful patent term lost, if any, during the FDA regulatory review process. However, a patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of the product's approval by the FDA. The patent term extension period is generally one-half the time between the effective date of the IND and the submission date of the NDA for the product, plus the time between the submission date of the NDA and the approval of the application. Only one patent applicable to an approved drug is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. Only those claims covering the approved drug, a method for using it or a method for manufacturing it may be extended. Moreover, we may not receive an extension because of, for example, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements. Similar provisions are available in the EU and certain other foreign jurisdictions to extend the term of a patent that covers an approved drug. However, the length of any extension, if granted, could be less than we request.

Trade Secrets

In addition to patent rights, we also rely on unpatented trade secrets and know-how to protect our proprietary technology. However, trade secrets can be difficult to protect. We seek to protect our proprietary technology, in part, by entering into confidentiality agreements with our employees, consultants, contractors, manufacturers, outside scientific collaborators and sponsored researchers, members of our board of directors, technical review board and other advisors upon their engagement. These agreements generally provide that all confidential information developed or made known to the individual during the course of the individual's relationship with us is to be kept confidential and not to be disclosed to third parties except in specific limited circumstances. We also generally require signed confidentiality or material transfer agreements from any company that is to receive our confidential information. In the case of employees, consultants, and contractors, the agreements also generally provide that all inventions conceived by the individual while rendering services to us shall be assigned to us as our exclusive property. There can be no assurance, however, that we have entered into agreements with all applicable parties, that all persons who we desire to sign such agreements will sign, or if they do, that such agreements will not be breached, that we would have adequate remedies for any breach, or that our unpatented trade secrets or know-how will not otherwise become known or be independently developed by competitors. Additionally, to the extent that our commercial partners, collaborators, employees, and consultants use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions. For this and a more comprehensive discussion of risks related to our intellectual property, see "Item 1A.–Risk Factors—Risks Related to Our Intellectual Property."

Commercialization Strategy

Our current main focus is developing an oral PTH (1-34) for the treatment of osteoporosis and orphan indications, and, specifically, EB613 for the treatment of osteoporosis and EB612 for the treatment of hypoparathyroidism. EB613 and EB612 are two drug candidates based on oral PTH (1-34) with significantly distinct treatment approaches. In the future, we may also conduct clinical trials of EB613 for the treatment of non-union fractures. We are also investigating the application of our oral drug delivery platform to other FDA-approved proteins or large molecule therapeutics where oral dosing could either increase the total addressable market or capture a large share of an existing market due to the potential improvements in convenience, compliance and cost resulting from an orally delivered drug relative to an injectable product. In addition, we intend to explore additional collaborations that leverage our technology platform, such as our collaboration agreement with Amgen. Under the agreement with Amgen, we have agreed to collaborate with Amgen for the development and discovery of clinical candidates in the field of inflammatory disease and other serious illnesses. Further, under the terms of the agreement, we will use our proprietary drug delivery platform to develop oral formulations for up to three large molecule biological drug candidates currently being developed by Amgen.

We have not yet established sales, marketing or product distribution operations because our product candidates are in clinical development. We may seek a partner to develop EB613 and EB612, and we anticipate that any such partner would be responsible for, or substantially support, late stage clinical trials of both of these lead clinical candidates, as well as submitting applications for regulatory approvals and registrations. In our collaboration with Amgen, Amgen is responsible for the research, clinical development, manufacturing and commercialization of any of the resulting programs.

Competition

The medical and pharmaceutical industries in which we operate are highly competitive and subject to rapid and significant technological change and changes in practice. While we believe that our technology, knowledge, experience and scientific resources provide us with competitive advantages, we face competition from many different sources, including large pharmaceutical, specialty pharmaceutical, biotechnology, and generic drug companies and academic and government institutions. We believe that the key competitive factors that will affect the development and commercial success of our oral PTH product candidates for hypoparathyroidism, osteoporosis and non-union fractures, and any other product candidates that we develop, are the efficacy, safety and tolerability profile, convenience in dosing, product labeling, price and availability of reimbursement from the government and other third-parties. Our commercial opportunity could be reduced or eliminated if our competitors have products that are better in one or more of these categories.

We expect that, if approved, our oral PTH product candidates for hypoparathyroidism, osteoporosis and non-union fractures, and other product candidates that we develop, would compete with a number of existing products. Furthermore, we believe that we face competition with regard to our oral drug delivery platform, as we believe that other non-invasive medical drug delivery technologies, including alternative oral delivery systems as well as transdermal patches, are being developed by other parties. Many of our potential competitors have substantially greater financial, technical, commercial and human resources than we do and significantly more experience in the discovery, development and regulatory approvals of product candidates, and the commercialization of those products. Accordingly, our competitors may be more successful than us in obtaining FDA approval for product candidates and achieving widespread market acceptance. See “Item 1A.–Risk Factors—Risks Related to Commercialization of Our Product Candidates.”

EB613 for Osteoporosis

Current treatments for osteoporosis generally fall into two categories: antiresorptive medications to slow bone loss; and anabolic medications to increase the rate of bone formation. The global osteoporosis drug market has traditionally been dominated by bisphosphonates, which slow bone loss. Although bisphosphonates’ market share has declined due to the occurrence of serious side effects, as well as the introduction of newly developed pharmacological treatments, many of the new drugs have serious side effects of their own. Eli Lilly’s Forteo, is one of the most effective osteoporosis medications, and newer products such as Prolia® and EVENITY® have been launched by Amgen. If Approved, we anticipate that our product candidate, EB613, will compete with Forteo, Prolia and EVENITY®. We believe that EB613 may prove to be superior to Forteo due to its oral administration, potentially leading to greater patient acceptance and its sharper pharmacokinetic profile which is expected to have more potent anabolic effect. However, our competitors in this market are large pharmaceutical companies with greater resources than us and the alternatives therapies have been on the market for many years and have widespread market acceptance.

EB612 for Hypoparathyroidism

Historically, the treatments for hypoparathyroidism have been calcium supplements, vitamin D supplements and phosphate binders. However there are many serious side effects that result from the chronic use of high doses of these products. Our product candidate EB612 is designed to deliver PTH to hypoparathyroid patients to directly address the underlying PTH deficiency. Because our product would be a branded pharmaceutical, in contrast to the over-the-counter supplements currently used by those with the condition, we believe that the market acceptance will be strongest among patients whose disease is not well-controlled by over-the-counter supplements, or in those patients who continue to suffer from side effects associated with therapy or symptoms associated with poor management of their condition.

We believe that our key competitor in hypoparathyroidism treatment is Natpara, an injectable bioengineered recombinant form of PTH (1-84) that was approved by the FDA in January 2015. Natpara has been granted orphan drug designation for hypoparathyroidism by the FDA as the first approved product for this indication and has orphan drug market exclusivity for seven years in the United States. Orphan drug market exclusivity means that the FDA may not approve any other application to market the same drug for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity or where the manufacturer is unable to assure sufficient product quantity. Therefore, we will be able to obtain regulatory approval for EB612, which also has orphan drug designation for hypoparathyroidism, only if we demonstrate EB612's clinical superiority over Natpara. For example, EB612 would need to demonstrate either greater effectiveness or safety than Natpara or that it otherwise makes a major contribution to patient care. We believe that we will be able to demonstrate that our oral formulation of PTH is clinically superior to Natpara in terms of efficacy and safety, and therefore, that Natpara's orphan drug exclusivity will not prevent the FDA from approving our NDA for oral PTH prior to the expiration of Natpara's market exclusivity period in 2022 and subject to the successful completion of clinical development and acceptance of our NDA. In 2019, Natpara was recalled due to certain product format issues, and, while Takeda has disclosed its efforts to reintroduce Natpara to the market, it has not yet been successful in doing so.

In addition, Ascendis Pharma has reported that it is developing a long-acting, oral prodrug formulation of PTH for the treatment of hypoparathyroidism. In 2020, Ascendis reported top-line results from a global Phase 2 trial that indicated potential use of its product, TransCon PTH. Transcon PTH is delivered as a once-a-day injection that demonstrated normalization of quality of life and its potential as a hormone replacement therapy for hypoparathyroidism. Ascendis Pharma has initiated a global Phase 3 study of Transcon PTH that is planned to enroll 76 patients. Other companies and groups that are developing or commercializing therapies for hypoparathyroidism include Chugai Pharmaceutical Co., Ltd. (conducting a Phase 1 study), Extend Biosciences Inc. (initiating a Phase 1 study), Massachusetts General Hospital, Amolyt (formerly known as Alizé Pharma) which is working on a Parathyroid Cell Transplant starting Phase 1 with AZP-3601 and Eli Lilly.

The Israeli Innovation Authority (IIA) Grants

We have received grants of approximately $0.5 million from the IIA to partially fund our research and development. The grants are subject to certain requirements and restrictions under the Israeli research law, which we refer to as the Research Law. In general, until the grants are repaid with interest, royalties are payable to the Israeli government in the amount of 3% on revenues derived from sales of products or services developed in whole or in part using the IIA grants, including EB612, EB613 and any other oral PTH product candidates we may develop. The royalty rate may increase to 5%, with respect to approved applications filed following any year in which we achieve sales of over $70 million.

The amount that must be repaid may be increased up to six times the amount of the grant received, and the rate of royalties may be accelerated if manufacturing of the products developed with the grant money is transferred outside of the State of Israel. As of December 31, 2021, the total royalty amounts payable to the IIA, including accrued interest, was approximately $0.5 million. As of December 31, 2021, we had paid royalties in the amount of $79,000 to the IIA.

In addition to paying any royalties due, we must abide by other restrictions associated with receiving such grants under the Research Law that continue to apply even following repayment to the IIA. These restrictions may impair our ability to outsource manufacturing, engage in change of control transactions or otherwise transfer our "know-how" (in its meaning under the Research Law) in or outside of Israel, and may require us to obtain the approval of the IIA for certain actions and transactions and pay additional royalties and other amounts to the IIA. We may not receive the required approvals for any proposed transfer and, even if received, we may be required to pay the IIA a portion of the consideration that we receive upon any transfer of such technology to a non-Israeli entity up to 600% of the grant amounts and the interest. The IIA approved the Company's Research Collaboration and License Agreement with Amgen Inc. as of December 2018, subject to payments to the IIA in the rate of 5.38% out of any payment received from Amgen for the license and up to a total amount of six times the amount of the IIA funding and the interest. In addition, as disclosed under "—Manufacturing", we have signed a contract with a U.K.-based contract manufacturing organization to produce and supply pills for trials performed worldwide. We believe that, because production is not being done for commercial purposes, the entry into the production agreement in the U.K. will not affect the royalty rates to be paid to the IIA. Should it turn out that this position is not acceptable to the IIA, the maximum royalties to be paid to the IIA will be three times the amount of the grants and the interest. In addition, any change of control and any change of ownership of our Ordinary Shares that would cause a non-Israeli citizen or resident to become an interested party as defined in the Research Law (which includes any person who holds 5% or more of our outstanding shares) requires written notice to the IIA. Such a non-Israeli interested party is required to sign an undertaking towards the IIA in which it undertakes to comply with the Research Law. If we fail to comply with the Research Law, we may be forced to return the grants and/or be subject to other payments to the IIA, monetary fines and/or criminal charges.

Oramed Patent Transfer Agreement

In 2010, in connection with our establishment as a joint venture between D.N.A Biomedical Solutions Ltd. ("D.N.A Biomedical") and Oramed Ltd. ("Oramed"), a subsidiary of Oramed Pharmaceuticals, Inc., we entered into a patent license agreement with Oramed pursuant to which Oramed granted us a worldwide, royalty-bearing, exclusive, irrevocable, perpetual and sub-licensable license under certain Oramed patent rights, to develop, manufacture and commercialize products for certain indications to be specified by us and Oramed, other than diabetes, obesity and influenza. In February 2011, D.N.A Biomedical and Oramed entered into a share purchase agreement for the sale by Oramed to D.N.A Biomedical of 47% of our Ordinary Shares at the time of the transaction in February 2011. In connection with this transaction, in February 2011 we entered into a Patent Transfer Agreement with Oramed to replace the original 2010 license agreement.

Pursuant to the terms of the Patent Transfer Agreement, Oramed assigned to us all of its right, title and interest in the previously licensed patent rights, and, in return, we granted to Oramed a worldwide, royalty-free, exclusive, irrevocable, perpetual and sublicensable license under the assigned patent rights to develop, manufacture and commercialize products or otherwise exploit such patent rights in the fields of diabetes and influenza. Additionally, we agreed not to engage, directly or indirectly, in any activities in the fields of diabetes and influenza. In consideration for such assignment, we agreed to pay Oramed royalties equal to 3% of our net revenues generated, directly or indirectly, from exploitation of the assigned patent rights, including the sale, lease or transfer of the assigned patent rights or sales of products or services covered by the assigned patent rights. Either party may terminate the Patent Transfer Agreement for the other party's uncured material breach upon 45 days' written notice (and immediately upon written notice in the event of an incurable breach), or if the other party undergoes certain insolvency-related events. The royalty obligations imposed on us will survive termination of the Patent Transfer Agreement.

Manufacturing

We do not own or operate facilities for large scale product manufacturing, storage and distribution, or testing, nor do we expect to in the future. Our current facility is limited to small-mid scale manufacturing, storage and distribution of materials and oral drug formulations for clinical studies. Our facility has ISO:9001:2015 quality management systems accreditation from The Standards Institution of Israel for the production and development of functional excipients for oral drug formulations to be used in clinical trials. The facility includes a dedicated Class D clean room for tablet production and a dedicated chemical synthesis room designed to meet ISO 8 specifications.

Our manufacturing activities include the chemical synthesis of one of our non-active but functional drug components in our facility. In addition, we have a contract with a U.K.-based contract manufacturing organization, to produce and supply pills for trials performed worldwide, including formulation and production of the final drug, packaging, storage and distribution. The UK facility is an FDA/EMA inspected-GMP site and we expect future clinical studies with our oral PTH (1-34) tablets, as well as the potential commercial supply, if approved, will be provided by the same subcontractor. This contract is not exclusive and we may enter into additional contracts. Our QA/QC analytical laboratory performs part of the release and stability testing for PTH tablets manufactured by the U.K.-based contract manufacturing facility. In addition, our research and development team supports the manufacturing activities and develops/optimizes analytical methods used by the contract manufacturer in order to meet regulatory requirements for our clinical trials. Various materials included in the drug formulation and materials procured for the chemical synthesis are commercially available from various accredited suppliers. We do not have supply contracts with all such vendors and are not bound to any specific vendor at this point in time. However, it is our intention to complete such contracts in anticipation of commercial manufacturing activities, so that if approved, we will have such contracts in place.

Government Regulation and Product Approval

Government authorities in the United States, at the federal, state and local level, and in other countries and jurisdictions, including the EU, extensively regulate, among other things, the research, development, testing, manufacture, pricing, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, and import and export of pharmaceutical products. The processes for obtaining regulatory approvals in the United States and in other countries and jurisdictions, along with subsequent compliance with applicable statutes and regulations and other regulatory authorities, require the expenditure of substantial time and financial resources.

Review and Approval of Drugs in the United States

In the United States, our product candidates are regulated by the FDA as drugs under the Federal Food, Drug, and Cosmetic Act, or the FDCA, the Public Health Service Act, or the PHSA, and regulations implemented by the FDA. The failure to comply with the applicable requirements at any time during the product development process, including preclinical testing, clinical testing, the approval process or post-approval process, may subject an applicant to delays in the conduct of clinical trials, regulatory review and approval, and/or administrative or judicial sanctions. These sanctions may include, but are not limited to, the FDA's refusal to allow an applicant to proceed with clinical testing, refusal to approve pending applications, license suspension or revocation, withdrawal of an approval, warning letters, adverse publicity, customer notifications, product recalls, product seizures, refusal to grant export or import approval total or partial suspension of production or distribution, consent decrees, injunctions, fines, and civil or criminal investigations and penalties brought by the FDA or Department of Justice, or other governmental entities.

The process required by the FDA before a new drug or biologic may be marketed in the United States generally involves satisfactorily completing each of the following steps:

- preclinical laboratory tests, animal studies and formulation studies all performed in accordance with the FDA's Good Laboratory Practice regulations;
- submission to the FDA of an IND application for human clinical testing, which must become effective before human clinical trials may begin;
- approval by an independent IRB, representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled clinical trials to establish the safety and efficacy of the product candidate for each proposed indication for use and conducted in accordance with Good Clinical Practice, or GCP, requirements;
- submission of data supporting safety and efficacy as well as detailed information on the manufacture and composition of the product in clinical development and proposed labeling;
- preparation and submission to the FDA of a New Drug Application, or an NDA, or Biologics License Application, or BLA;
- review of the product by an FDA advisory committee, where appropriate or if applicable;
- satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities, including those of third parties, at which the product, or components thereof, are produced to assess compliance with current Good Manufacturing Practice, or cGMP, standards and to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity;

- satisfactory completion of any FDA audits of the non-clinical and clinical trial sites to assure compliance with GCP requirements and the integrity of clinical data in support of the NDA or BLA;

- payment of user fees and securing FDA approval of the NDA or BLA for the proposed indication; and

- compliance with any post-approval requirements, including risk evaluation and mitigation strategies, or REMS, and any post-approval studies required by the FDA.

Preclinical Studies and Investigational New Drug Application

Preclinical tests include laboratory evaluations of product chemistry, formulation and stability, as well as animal studies to evaluate the potential for efficacy and toxicity. The conduct of the preclinical tests and formulation of the compounds for testing must comply with federal regulations and requirements. The results of the preclinical tests, together with manufacturing information and analytical data, are submitted to the FDA as part of an IND application. Some preclinical tests may continue even after submission of the IND application. The IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions about the product or conduct of the proposed clinical trial, including concerns that human research volunteers will be exposed to unreasonable health risks. In that case, the IND sponsor and the FDA must resolve any outstanding FDA concerns before the clinical trial can begin.

As a result, submission of the IND may result in the FDA not allowing the clinical trials to commence or allowing the clinical trial to commence on the terms originally specified by the sponsor in the IND. If the FDA raises concerns or questions either during this initial 30-day period, or at any time during the IND process, it may choose to impose a partial or complete clinical hold. This order issued by the FDA would delay either a proposed clinical trial or cause delay in initiation of our Phase 3 clinical trial, until all outstanding concerns have been adequately addressed and the FDA has notified the company that investigations may proceed. This could cause significant delays or difficulties in completing planned clinical trials in a timely manner.

Clinical Trials

Clinical trials involve the administration of the investigational product candidate to healthy volunteers or patients with the disease to be treated under the supervision of a qualified principal investigator in accordance with GCP requirements. Clinical trials are conducted under trial protocols detailing, among other things, the objectives of the clinical trial, inclusion and exclusion criteria, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND.

A sponsor who wishes to conduct a clinical trial outside the United States may, but need not, obtain FDA authorization to conduct the clinical trial under an IND. If a clinical trial outside the United States is not conducted under an IND, the sponsor may submit data from the clinical trial to the FDA in support of a NDA so long as the clinical trial is conducted consistent with GCP and in compliance with an international guideline for the ethical conduct of clinical research known as the Declaration of Helsinki and/or the laws and regulations of the country or countries in which the clinical trial is performed, whichever provides the greater protection to the participants in the clinical trial.

Further, each clinical trial must be reviewed and approved by an IRB either centrally or individually at each institution at which the clinical trial will be conducted. The IRB will consider, among other things, clinical trial design, patient informed consent, ethical factors, the safety of human subjects and, where appropriate, the protection of privacy of the human subjects. An IRB must operate in compliance with the FDA regulations. The FDA, IRB, the clinical trial sponsor, or the principal investigator may suspend or discontinue a clinical trial at any time for various reasons, including a finding that the clinical trial is not being conducted in accordance with FDA requirements or the subjects or patients are being exposed to an unacceptable health risk. Clinical testing also must satisfy extensive GCP rules and the requirements for informed consent. Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data and safety monitoring board or committee. This group may recommend continuing the clinical trial as planned, make changes in clinical trial conduct, or cessation of the clinical trial at designated check points based on access to certain data from the clinical trial.

Clinical trials typically are conducted in three sequential phases, but the phases may overlap or be combined. Annual progress reports detailing the results of the clinical trials must be submitted to the FDA. Additional studies may be required after approval.

- *Phase 1* clinical trials are initially conducted in a limited population to test the product candidate for safety, including adverse effects, dose tolerance, absorption, metabolism, distribution, excretion and pharmacodynamics in healthy humans. For some products for severe or life-threatening diseases, especially if the product may be too toxic to administer to healthy humans, the initial clinical trials may be conducted in individuals having a specific disease for which use the tested product is indicated.

- *Phase 2* clinical trials are generally conducted in a limited patient population to identify possible adverse effects and safety risks, evaluate the efficacy of the product candidate for specific targeted indications and determine dose tolerance and optimal dosage. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more costly Phase 3 clinical trials.

- *Phase 3* clinical trials proceed if the Phase 2 clinical trials demonstrate that a dose range of the product candidate is potentially effective and has an acceptable safety profile. Phase 3 clinical trials are undertaken to further evaluate, in a larger number of patients, dosage, provide substantial evidence of clinical efficacy and further test for safety in an expanded and diverse patient population at multiple, geographically dispersed clinical trial sites. A well-controlled, statistically robust Phase 3 trial may be designed to deliver the data that regulatory authorities will use to decide whether or not to approve, and, if approved, how to appropriately label a drug: such Phase 3 studies are referred to as “pivotal.”

In some cases, the FDA may approve a NDA or BLA for a product candidate but require the sponsor to conduct additional clinical trials to further assess the drug’s safety and effectiveness after NDA or BLA approval. Such post-approval trials are typically referred to as Phase 4 clinical trials. These studies are used to gain additional data from the treatment of patients in the intended therapeutic indication and to document a clinical benefit in the case of drugs approved under accelerated approval regulations. If the FDA approves a product while a company has ongoing clinical trials that were not necessary for approval, a company may be able to use the data from these clinical trials to meet all or part of any Phase 4 clinical trial requirement or to request a change in the product labeling. Failure to exhibit due diligence with regard to conducting Phase 4 clinical trials could result in withdrawal of approval for products.

Compliance with Current Good Manufacturing Practice Requirements

Before approving a NDA or BLA, the FDA typically will inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in full compliance with cGMP requirements and able to assure consistent production of the product within required specifications. The PHSA emphasizes the importance of manufacturing control for products like biologics whose attributes cannot be precisely defined.

Manufacturers and others involved in the manufacture and distribution of products must also register their establishments with the FDA and certain state regulatory bodies. Both U.S. and non-U.S. manufacturing establishments must register and provide additional information to the FDA upon their initial participation in the manufacturing process. Any product manufactured by or imported from a facility that has not registered, whether U.S. or non-U.S., is deemed misbranded under the FDCA. Establishments may be subject to periodic unannounced inspections by government authorities to ensure compliance with cGMPs and other laws. Inspections must follow a “risk-based schedule” that may result in certain establishments being inspected more frequently. Manufacturers may also have to provide, on request, electronic or physical records regarding their establishments. Delaying, denying, limiting, or refusing inspection by the FDA may lead to a product being deemed to be adulterated.

Review and Approval of a New Drug Application and Biologics License Application

The results of product candidate development, preclinical testing and clinical trials, including negative or ambiguous results as well as positive findings, are submitted to the FDA as part of a NDA or BLA requesting approval to market the product. The NDA or BLA also must contain extensive manufacturing information and detailed information on the composition of the product and proposed labeling as well as payment of a user fee.

Under the Prescription Drug User Fee Act, or PDUFA, as amended, each NDA or BLA must be accompanied by a user fee, which the FDA adjusts on an annual basis. Fee waivers or reductions are available in certain instances, such as a waiver of the application fee for an initial application filed by a small business. Moreover, no user fees are assessed on NDAs or BLAs for products designated as orphan drugs, unless the product has a non-orphan indication for use.

The FDA has 60 days after submission of the application to conduct an initial review to determine whether it is sufficient to accept for filing based on the agency's threshold determination that it is sufficiently complete to permit substantive review. Once the submission has been accepted for filing, the FDA begins an in-depth review of the application. Under the goals and policies under the PDUFA, the FDA has ten months from the filing date in which to complete its initial review of a standard application and respond to the applicant, and six months for a priority review of the application. The FDA does not always meet its PDUFA goal dates for standard and priority applications. The review process may often be significantly extended by FDA requests for additional information or clarification. The review process and the PDUFA goal date may be extended by three months if the FDA requests, or the applicant otherwise provides additional information or clarification regarding information already provided in the submission within the last three months before the PDUFA goal date.

Under the FDCA and the PHSA, the FDA may approve a NDA or BLA if it determines that the product is safe, pure and potent and the facility where the product will be manufactured meets standards designed to ensure that it continues to be safe, pure and potent.

On the basis of the FDA's evaluation of the application and accompanying information, including the results of the inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. If the application is not approved, the FDA will issue a complete response letter, which will contain the conditions that must be met in order to secure final approval of the application, and, when possible, will outline recommended actions the sponsor might take to obtain approval of the application. Sponsors that receive a complete response letter may submit to the FDA information that represents a complete response to the issues identified by the FDA. Such resubmissions are classified under PDUFA as either Class 1 or Class 2. The classification of a resubmission is based on the information submitted by an applicant in response to an action letter. Under the goals and policies agreed to by the FDA under PDUFA, the FDA has two months to review a Class 1 resubmission and six months to review a Class 2 resubmission from the date of receipt. The FDA will not approve an application until issues identified in the complete response letter have been addressed.

The FDA may also refer the application to an advisory committee for review, evaluation and recommendation as to whether the application should be approved. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

If the FDA approves a new product, it may limit the approved indications for use of the product. It may also require that contraindications, warnings or precautions be included in the product labeling. In addition, the FDA may call for post-approval studies, including Phase 4 clinical trials, to further assess the product's safety after approval. The agency may also require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including a REMS, to help ensure that the benefits of the product outweigh the potential risks. A REMS can include medication guides, communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patent registries. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, many types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

The Drug Price Competition and Patent Term Restoration Act, or the Hatch-Waxman Act, added Section 505(b)(2) to the FDCA, allowing a company to submit an NDA application that relies on clinical trial data not conducted by or for the application, such as published scientific literature and prior FDA findings of safety and efficacy of another company's drug. An NDA application under Section 505(b)(2) is typically used when the applicant product modifies or improves a predicate drug leading to a new drug product. Because an application under Section 505(b)(2) can rely on prior clinical trial data and published scientific literature, FDA approval is generally quicker than a normal NDA application. However, an application under Section 505(b)(2) can also be delayed if the predicate drug is still under patent or exclusivity protections.

Fast Track, Breakthrough Therapy and Priority Review Designations

The FDA is authorized to designate certain products for expedited review if they are intended to address an unmet medical need in the treatment of a serious or life-threatening disease or condition, or in the event of an emergency. These programs are fast track designation, breakthrough therapy designation and priority review designation.

Specifically, the FDA may designate a product for fast track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. For fast track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a fast track product's application before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a fast track product may be effective. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information and the sponsor must pay applicable user fees. However, the FDA's time period goal for reviewing a fast track application does not begin until the last section of the application is submitted. In addition, the fast track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Second, in 2012, Congress enacted the Food and Drug Administration Safety and Innovation Act, or FDASIA. This law established a new regulatory scheme allowing for expedited review of products designated as "breakthrough therapies." A product may be designated as a breakthrough therapy if it is intended, either alone or in combination with one or more other products, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA may take certain actions with respect to breakthrough therapies, including holding meetings with the sponsor throughout the development process; providing timely advice to the product sponsor regarding development and approval; involving more senior staff in the review process; assigning a cross-disciplinary project lead for the review team; and taking other steps to design the clinical trials in an efficient manner.

Third, the FDA may designate a product for priority review if it is a product that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA determines, on a case-by-case basis, whether the proposed product represents a significant improvement when compared with other available therapies. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment-limiting product reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, and evidence of safety and effectiveness in a new subpopulation. A priority designation is intended to direct overall attention and resources to the evaluation of such applications, and to shorten the FDA's goal for taking action on a marketing application from ten months to six months.

Fourth, the Secretary of Health and Human Services may authorize unapproved drugs and biologics to be marketed in the event an actual or potential emergency has been designated by the U.S. government. After an emergency has been designated, the FDA may issue an Emergency Use Authorization, or EUA, for the use of a specific product based on criteria established by the FDCA. An EUA is product specific and is subject to specific conditions and restrictions. Once the emergency underlying the EUA ends, then the EUA terminates.

Accelerated Approval Pathway

The FDA may grant accelerated approval to a product for a serious or life-threatening condition that provides meaningful therapeutic advantage to patients over existing treatments based upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. The FDA may also grant accelerated approval for such a condition when the product has an effect on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, or IMM, and that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. Products granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.

For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. An intermediate clinical endpoint is a measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a product, such as an effect on IMM. The FDA has indicated that intermediate clinical endpoints generally may support accelerated approval where the therapeutic effect measured by the endpoint is not itself a clinical benefit and basis for traditional approval, if there is a basis for concluding that the therapeutic effect is reasonably likely to predict the ultimate clinical benefit of a product.

The accelerated approval pathway is most often used in settings in which the course of a disease is long and an extended period of time is required to measure the intended clinical benefit of a product, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly.

The accelerated approval pathway is usually contingent on a sponsor's agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the product's clinical benefit. As a result, a product candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase 4 or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or confirm a clinical benefit during post-marketing studies, would allow the FDA to withdraw the product from the market on an expedited basis. All promotional materials for product candidates approved under accelerated regulations are subject to prior review by the FDA.

Post-Approval Regulation

Once regulatory approval for marketing of a product or new indication for an existing product is obtained, the sponsor will be required to comply with post-approval regulatory requirements, including any post-approval requirements that the FDA may have imposed as a condition of approval. The sponsor will be required to report certain adverse reactions and production problems to the FDA, provide updated safety and efficacy information and comply with requirements concerning advertising and promotional labeling requirements. Drug manufacturers and certain of their subcontractors are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with ongoing regulatory requirements, including cGMP regulations, which impose certain procedural and documentation requirements upon drug manufacturers. Accordingly, the sponsor and its third-party manufacturers must continue to expend time, money and effort in the areas of production and quality control to maintain compliance with cGMP regulations and other regulatory requirements.

A product may also be subject to official lot release, meaning that the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release, the manufacturer must submit samples of each lot, together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot, to the FDA. The FDA may in addition perform certain confirmatory tests on lots of some products before releasing the lots for distribution. Finally, the FDA will conduct laboratory research related to the safety, purity, potency, and effectiveness of pharmaceutical products.

After an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a Risk Evaluation and Mitigation Strategies, or REMS, program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product license approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs and biologics may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

Orphan Drug Designation

Orphan drug designation in the United States is designed to encourage sponsors to develop drugs intended for rare diseases or conditions. In the United States, a rare disease or condition is statutorily defined as a condition that affects fewer than 200,000 individuals in the United States, or that affects more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making available the drug for the disease or condition will be recovered from sales of the drug in the United States.

Orphan drug designation qualifies a company for tax credits, waiver of the NDA user fee and may confer market exclusivity for seven years following the date of the drug's marketing approval, if granted by the FDA, if a product that has orphan designation subsequently receives the first FDA approval of that drug for the disease for which it has such designation. This means that the FDA may not approve any other applications, including an NDA to market the same drugs or even in a different formulation for the same indication for seven years, except in limited circumstances such as a showing of clinical superiority over the product with orphan drug exclusivity or where the manufacturer is unable to assure sufficient product quantity. An application for designation as an orphan product can be made any time prior to the filing of an application for approval to market the product. A product becomes an orphan product when it receives orphan drug designation from the Office of Orphan Products Development, or OOPD, at the FDA based on acceptable confidential requests made under the regulatory provisions. The product must then go through the review and approval process like any other product.

A sponsor may request orphan drug designation of a previously unapproved product or new orphan indication for an already marketed product. In addition, a sponsor of a product that is otherwise the same product as an already approved orphan drug may seek and obtain orphan drug designation for the subsequent product for the same rare disease or condition if it can present a plausible hypothesis that its product may be clinically superior to the first, approved product. More than one sponsor may receive orphan drug designation for the same product for the same rare disease or condition, but each sponsor seeking orphan drug designation must file a complete request for designation, and only the first sponsor that obtains approval for that drug for the orphan indication will obtain market exclusivity, effectively preventing the FDA from approving products under development by competitors for the same drug and same indication, unless the competitor is able to demonstrate that the product under development is clinically superior to the approved product or the approved product is not available in sufficient quantities. To permit the FDA to end another manufacturer's orphan exclusivity period, the FDA must determine that the manufacturer has demonstrated clinical superiority by showing the later drug is safer, more effective, or otherwise makes a major contribution to patient care.

The period of exclusivity begins on the date that the marketing application is approved by the FDA and applies only to the indication for which the product has been designated. The FDA may approve a second application for the same product for a different use or a subsequent application for a different drug for the same indication. Orphan drug designation neither shortens the development time or regulatory review time of a drug nor gives the drug any advantage in the regulatory review or approval process.

Biosimilars and Exclusivity

The ACA, which was signed into law on March 23, 2010, included a subtitle called the Biologics Price Competition and Innovation Act of 2009 or BPCIA. The BPCIA established a regulatory scheme authorizing the FDA to approve biosimilars and interchangeable biosimilars. The FDA has issued several draft guidance documents outlining an approach to review and approval of biosimilars. Complexities associated with the larger, and often more complex, structures of biological products, as well as the processes by which such products are manufactured, pose significant hurdles to implementation, which are still being worked out by the FDA.

Under the BPCIA, a manufacturer may submit an application for licensure of a biologic product that is "biosimilar to" or "interchangeable with" a previously approved biological product or "reference product." In order for the FDA to approve a biosimilar product, it must find that there are no clinically meaningful differences between the reference product and proposed biosimilar product in terms of safety, purity, and potency. For the FDA to approve a biosimilar product as interchangeable with a reference product, the agency must find that the biosimilar product can be expected to produce the same clinical results as the reference product, and (for products administered multiple times) that the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic.

Under the BPCIA, an application for a biosimilar product may not be submitted to the FDA until four years following the date of approval of the reference product. The FDA may not approve a biosimilar product until 12 years from the date on which the reference product was approved. Even if a product is considered to be a reference product eligible for exclusivity, another company could market a competing version of that product if the FDA approves a full BLA for such product containing the sponsor's own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity and potency of their product. The BPCIA also created certain exclusivity periods for biosimilars approved as interchangeable products.

Patent Term Extension

A patent claiming a new drug or biologic product may be eligible for a limited patent term extension under the Hatch-Waxman Act, which permits a patent extension of up to five years beyond the expiration date of a U.S. patent as partial compensation for the useful patent term lost, if any, during the FDA regulatory review process. However, a patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of the product's approval by the FDA. The patent term extension period granted is typically one-half the time between the effective date of the first IND and the submission date of the NDA for the product, plus the time between the submission date of the NDA and the approval of that application. Only one patent applicable to an approved product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple products for which approval is sought can only be extended in connection with one of the products. The USPTO reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

Regulation Outside the United States

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy that govern, among other things, clinical trials, marketing authorization, commercial sales and distribution of drug products. Whether or not it obtains FDA approval for a product, the company would need to obtain the necessary approvals by the comparable non-U.S. regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. The approval process ultimately varies between countries and jurisdictions and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries and jurisdictions might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country or jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country or jurisdiction may negatively impact the regulatory process in others.

Regulation and Marketing Authorization in the European Union

The European Medicines Agency, or EMA, is the scientific agency of the European Union, or EU, that coordinates the evaluation and monitoring of new and approved medicinal products such as drugs and biologics. It is responsible for the scientific evaluation of applications for EU marketing authorizations, as well as the development of technical guidance and the provision of scientific advice to sponsors.

The process regarding approval of medicinal products in the EU follows roughly the same lines as in the United States and likewise generally involves satisfactorily completing each of the following:

- preclinical laboratory tests, animal studies and formulation studies all performed in accordance with the applicable EU Good Laboratory Practice regulations;
- submission to the relevant regulatory agencies in EU member states, or national authorities, of a clinical trial application, or CTA, for each clinical trial, which must be approved before human clinical trials may begin;
- performance of adequate and well-controlled clinical trials to establish the safety and efficacy of the product for each proposed indication;
- submission to the relevant national authorities of a Marketing Authorisation Application, or MAA, which includes the data supporting safety and efficacy as well as detailed information on the manufacture and composition of the product in clinical development and proposed labeling;
- satisfactory completion of an inspection by the relevant national authorities of the manufacturing facility or facilities, including those of third parties, at which the product is produced to assess compliance with cGMP;
- potential audits of the non-clinical and clinical trial sites that generated the data in support of the MAA; and
- review and approval by the relevant national authority of the MAA before any commercial marketing, sale or shipment of the product.

Preclinical Studies

Preclinical tests include laboratory evaluations of product chemistry, formulation and stability, as well as studies to evaluate the potential efficacy and toxicity in animals. The conduct of the preclinical tests and formulation of the compounds for testing must comply with the relevant EU regulations and requirements. The results of the preclinical tests, together with relevant manufacturing information and analytical data, are submitted as part of the CTA when seeking approval to start a clinical trial, and with the MAA when seeking marketing authorization.

Clinical Trial Approval

Requirements for the conduct of clinical trials in the EU including cGCP, are implemented in the currently Clinical Trials Directive 2001/20/EC and the GCP Directive 2005/28/EC. Pursuant to Directive 2001/20/EC and Directive 2005/28/EC, as amended, a system for the approval of clinical trials in the EU has been implemented through national legislation of the EU member states. Under this system, approval must be obtained from the competent national authority in which a trial is planned to be conducted, or in multiple member states if the clinical trial is to be conducted in a number of member states. To this end, a CTA is submitted, which must be supported by an investigational medicinal product dossier, or IMPD, and further supporting information prescribed by Directive 2001/20/EC and Directive 2005/28/EC and other applicable guidance documents. Furthermore, a clinical trial may only be started after a competent ethics committee has issued a favorable opinion on the clinical trial application in that country.

On January 31, 2022, the Clinical Trials Regulation (EU) No. 536/2014 replaced the current Clinical Trials Directive 2001/20/EC. To ensure that the rules for clinical trials are identical throughout the EU, the Clinical Trials Regulation (EU) No. 536/2014 was passed as a regulation which is directly applicable in all EU member states. The Clinical Trials Directive 2001/20/EC will, however, still apply three years from the date of entry into application of the Clinical Trials Regulation to (i) clinical trials applications submitted before the entry into application and (ii) clinical trials applications submitted within one year after the entry into application if the sponsor opts for the old system.

Regulation (EU) No 536/2014 aims to simplify and streamline the approval of clinical trial in the EU. The main characteristics of the regulation include:

- A streamlined application procedure via a single entry point, known as the Clinical Trials Information System;
- A single set of documents to be prepared and submitted for the application as well as simplified reporting procedures which will spare sponsors from submitting broadly identical information separately to various and different national authorities;
- A harmonized procedure for the assessment of applications for clinical trials, which is divided in two parts;
- Strictly defined deadlines for the assessment of clinical trial application; and
- The involvement of the ethics committees in the assessment procedure in accordance with the national law of the member state concerned but within the overall timelines defined by the Regulation (EU) No 536/2014.

Marketing Authorization

Authorization to market a product in the member states of the EU proceeds under one of four procedures: a centralized procedure, a mutual recognition procedure, a decentralized procedure or a national procedure.

Centralized Procedure

The centralized procedure enables applicants to obtain a marketing authorization that is valid in all EU member states based on a single application. Certain medicinal products, including products developed by means of biotechnological processes must undergo the centralized authorization procedure for marketing authorization, which, if granted by the European Commission, based on the opinion of the EMA, is automatically valid in all EU member states. Sponsors may elect to file an MAA through the centralized procedures for other classes of products.

The centralized procedure is mandatory for certain types of products such as, medicines derived from biotechnology processes such as genetic engineering, advanced-therapy medicines such as gene-therapy or tissue engineered medicine, orphan medicines, and medicinal products containing a new active substance indicated for the treatment of HIV, AIDS, cancer, diabetes, neurodegenerative disorders, autoimmune and other immune dysfunctions, and viral diseases. The centralized authorization procedure is optional for other medicinal products if they contain a new active substance, if the applicant shows that the medicinal product concerned constitutes a significant therapeutic, scientific or technical innovation, or that the granting of authorization is in the public interest of the EU.

Administrative Procedure

Under the centralized procedure, the EMA's Committee for Human Medicinal Products, or CHMP serves as the scientific committee that renders opinions about the safety, efficacy and quality of medicinal products for human use on behalf of the EMA. The CHMP is composed of experts nominated by each member state's national authority for medicinal products, with one of them appointed to act as Rapporteur for the coordination of the evaluation with the possible assistance of a further member of the Committee acting as a Co-Rapporteur. After approval, the Rapporteur(s) continue to monitor the product throughout its life cycle. The CHMP has 210 active days to adopt an opinion as to whether a marketing authorization should be granted. The process usually takes longer in case additional information is requested, which triggers clock-stops in the procedural timelines. The process is complex and involves extensive consultation with the regulatory authorities of member states and a number of experts. When an application is submitted for a marketing authorization in respect of a drug which is of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation, the applicant may, pursuant to Article 14(9) Regulation (EC) No 726/2004, request an accelerated assessment procedure. If the CHMP accepts such request, the time-limit of 210 days will be reduced to 150 days but it is possible that the CHMP can revert to the standard time-limit for the centralized procedure if it considers that it is no longer appropriate to conduct an accelerated assessment. Once the procedure is completed, a European Public Assessment Report, or EPAR, is produced. If the opinion is negative, information is given as to the grounds on which this conclusion was reached. After the adoption of the CHMP opinion, a decision on the MAA must be adopted by the European Commission, after consulting the EU member states, which in total can take more than 60 days. After a drug has been authorized and launched, it is a condition of maintaining the marketing authorization that all aspects relating to its quality, safety and efficacy must be kept under review.

Conditional Approval

In specific circumstances, EU legislation (Article 14(7) Regulation (EC) No 726/2004 and Regulation (EC) No 507/2006 on Conditional Marketing Authorisations for Medicinal Products for Human Use) enables applicants to obtain a conditional marketing authorization prior to obtaining the comprehensive clinical data required for an application for a full marketing authorization. Such conditional approvals may be granted for products (including medicines designated as orphan medicinal products), if (1) the risk-benefit balance of the product is positive, (2) it is likely that the applicant will be in a position to provide the required comprehensive clinical trial data, (3) the product fulfills unmet medical needs, and (4) the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required. A conditional marketing authorization may contain specific obligations to be fulfilled by the marketing authorization holder, including obligations with respect to the completion of ongoing or new studies, and with respect to the collection of pharmacovigilance data. Conditional marketing authorizations are valid for one year, and may be renewed annually, if the risk-benefit balance remains positive, and after an assessment of the need for additional or modified conditions and/or specific obligations. The timelines for the centralized procedure described above also apply with respect to the review by the CHMP of applications for a conditional marketing authorization.

Marketing Authorization Under Exceptional Circumstances

As per Article 14(8) Regulation (EC) No 726/2004, products for which the applicant can demonstrate that comprehensive data (in line with the requirements laid down in Annex I of Directive 2001/83/EC, as amended) cannot be provided (due to specific reasons foreseen in the legislation) might be eligible for marketing authorization under exceptional circumstances. This type of authorization is reviewed annually to reassess the risk-benefit balance. The fulfillment of any specific procedures/obligations imposed as part of the marketing authorization under exceptional circumstances is aimed at the provision of information on the safe and effective use of the product and will normally not lead to the completion of a full dossier/approval.

Period of Authorization and Renewals

A marketing authorization will be valid for five years in principle, and the marketing authorization may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the EMA or by a national authority. To this end, the marketing authorization holder must provide the EMA or the competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorization was granted, at least nine months before the marketing authorization ceases to be valid. Once renewed, the marketing authorization will be valid for an unlimited period, unless the European Commission or the national authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal. Any authorization that is not followed by the actual placing of the drug on the EU market (in case of centralized procedure) or on the market of the authorizing member state within three years after authorization will cease to be valid, the so-called "sunset clause."

Orphan Drug Designation and Exclusivity

The European Commission can grant orphan medicinal product designation to products for which the sponsor can establish that it is intended for the diagnosis, prevention, or treatment of (1) a life-threatening or chronically debilitating condition affecting not more than five in 10,000 people in the EU, or (2) a life threatening, seriously debilitating or serious and chronic condition in the EU and that without incentives it is unlikely that sales of the drug in the EU would generate a sufficient return to justify the necessary investment. In addition, the sponsor must establish that there is no other satisfactory method approved in the EU of diagnosing, preventing or treating the condition, or if such a method exists, the proposed orphan drug will be of significant benefit to patients.

Orphan drug designation provides a number of benefits, including fee reductions, regulatory assistance, and the possibility to apply for a centralized EU marketing authorization (see "—Government Regulation and Product Approval—Regulation Outside the United States—Centralized Authorization Procedure"), as well as 10 years of market exclusivity following a marketing authorization. During this market exclusivity period, neither the EMA, nor the European Commission nor the Member States can accept an application or grant a marketing authorization for a medicinal product containing a similar active substance or substances as contained in an authorized orphan medicinal product, and which is intended for the same therapeutic indication. The market exclusivity period for the authorized therapeutic indication may be reduced to six years if, at the end of the fifth year, it is established that the orphan drug designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity. In addition, a competing similar medicinal product may be authorized prior to the expiration of the market exclusivity period, including if it is shown to be safer, more effective or otherwise clinically superior to the already approved orphan drug or if the holder of the marketing authorization for the already approved orphan drug is unable to supply sufficient quantities of the product.

If the MAA of a medicinal product designated as an orphan drug includes the results of all studies conducted in compliance with an agreed PIP, and a corresponding statement is subsequently included in the marketing authorization granted, the ten-year period of market exclusivity will be extended to twelve years.

Regulatory Data Protection

EU legislation also provides for a system of regulatory data and market exclusivity. Upon receiving marketing authorization, new chemical entities approved on the basis of complete independent data package benefit from eight years of data exclusivity and an additional two years of market exclusivity. Data exclusivity prevents regulatory authorities in the EU from referencing the innovator's data to assess a generic or biosimilar (abbreviated) application. During the additional two-year period of market exclusivity, a generic or biosimilar marketing authorization can be submitted, and the innovator's data may be referenced, but no generic or biosimilar medicinal product can be marketed until the expiration of the market exclusivity. The overall ten-year period will be extended to a maximum of eleven years if, during the first eight years of those 10 years, the marketing authorization holder, or MAH, obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be a new chemical entity and the innovator is able to gain the period of data exclusivity, another company nevertheless could also market another version of the drug if such company obtained marketing authorization based on an MAA with a complete independent data package of pharmaceutical test, pre-clinical tests and clinical trials. However, products designated as orphan medicinal products enjoy, upon receiving marketing authorization, a period of 10 years of orphan market exclusivity (see also "—Government Regulation and Product Approval—Regulation and Marketing Authorization in the European Union—Orphan Drug Designation and Exclusivity"). Depending upon the timing and duration of the EU marketing authorization process, products may be eligible for up to five years' supplementary protection certificates, or SPCs. Such SPCs extend the rights under the basic patent for the drug.

Regulatory Requirements After a Marketing Authorization Has Been Obtained

If we obtain authorization for a medicinal product in the EU, we will be required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of medicinal products:

Pharmacovigilance and Other Requirements

We will, for example, have to comply with the EU's stringent pharmacovigilance or safety reporting rules, pursuant to which post-authorization studies and additional monitoring obligations can be imposed.

Other requirements relate to, for example, the manufacturing of products and APIs in accordance with good manufacturing practice standards. EU regulators may conduct inspections to verify our compliance with applicable requirements, and we will have to continue to expend time, money and effort to remain compliant. Non-compliance with EU requirements regarding safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population, can also result in significant financial penalties in the EU. Similarly, failure to comply with the EU's requirements regarding the protection of individual personal data can also lead to significant penalties and sanctions. Individual EU member states may also impose various sanctions and penalties in case we do not comply with locally applicable requirements.

Manufacturing

The manufacturing of authorized drugs, for which a separate manufacturer's license is mandatory, must be conducted in compliance with the EMA's cGMP requirements and comparable requirements of other national authorities, which mandate the methods, facilities and controls used in manufacturing, processing and packing of drugs to assure their safety and identity. The EMA enforces its cGMP requirements through mandatory registration of facilities and inspections of those facilities. The EMA may have a coordinating role for these inspections while the responsibility for carrying them out rests with the member states competent authority under whose responsibility the manufacturer falls. Failure to comply with these requirements could interrupt supply and result in delays, unanticipated costs and lost revenues, and could subject the applicant to potential legal or regulatory action, including but not limited to warning letters, suspension of manufacturing, seizure of product, injunctive action or possible civil and criminal penalties.

Marketing and Promotion

The marketing and promotion of authorized drugs, including industry-sponsored continuing medical education and advertising directed toward the prescribers of drugs and/or the general public, are strictly regulated in the EU. The applicable regulations aim to ensure that information provided by holders of marketing authorizations regarding their products is truthful, balanced and accurately reflects the safety and efficacy claims authorized by the EMA or by the national authority of the authorizing member state. Failure to comply with these requirements can result in adverse publicity, warning letters, corrective advertising and potential civil and criminal penalties.

Clinical Testing in Israel

In order to conduct clinical trials on humans in Israel, prior authorization must be obtained from the medical director of the institution (i.e., the Director of Hospital – DOH) in which the clinical trials are scheduled to be conducted. All clinical trials must first be approved by the Institutional Review Board (IRB) / Independent Ethics Committee (IEC) which may request additional prior approval from the Israeli Ministry of Health (IMOH), as required under the Guidelines for Clinical Trials in Human Subjects implemented pursuant to the Israeli Public Health Regulations (Clinical Trials in Human Subjects), 5740-1980, as amended from time to time. Pursuant to the Israeli Public Health Regulations, such authorization generally cannot be granted unless, among other things, the relevant institutions ethics committee has provided its prior approval of the testing and that the trial complies with the standards set forth by the Declaration of Helsinki. The Ministry of Health has provided emergency guidance associated with COVID-19 in March 2020 for ongoing clinical trials, which we are complying with, and may issue additional guidance that may impact our ability to complete our ongoing clinical trials of EB613 in Osteoporosis.

The IRB/IEC and IMOH prioritizes the safety, rights and the wellbeing of the participants are addressed, as well as among other things, evaluating the anticipated benefits that are likely to be derived from the project to determine if it justifies the risks and inconvenience to be inflicted on the participating human subjects. The institution may also conduct audits to insure that all international GCP and IMOH guidelines are being adhered to in order to maintain the proper conduct and accuracy of the information gathered in the course of the clinical testing.

Other Healthcare Laws

Health care providers, physicians and third-party payers play a primary role in the recommendation and prescription of drug products that are granted marketing approval. Arrangements with third-party payers and customers are subject to broadly applicable fraud and abuse and other health care laws and regulations. In the United States, such restrictions under applicable federal and state healthcare laws and regulations, include the following:

- the federal Anti-Kickback Statute prohibits, among other things, the knowing and willful offer, payment, solicitation or receipt of any form of remuneration in return for, or to induce, (i) the referral of a person, (ii) the furnishing or arranging for the furnishing of items or services reimbursable under the Medicare, Medicaid or other governmental programs, or (iii) the purchase, lease or order or arranging or recommending purchasing, leasing or ordering of any item or service reimbursable under the Medicare, Medicaid or other governmental programs. A person or entity does not need to have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it to have committed a violation; in addition, items or services resulting from a violation of the federal Anti-Kickback Statute may constitute a false or fraudulent claim for purposes of the False Claims Act;

- the federal False Claims Act imposes civil penalties, and provides for civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;

- the Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any health care benefit program or making false statements relating to health care matters. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it to have committed a violation;

- the federal false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for health care benefits, items or services;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, which governs the conduct of certain electronic healthcare transactions and protects the security and privacy of protected health information that is stored or transmitted electronically;

- the Physician Payments Sunshine Act, created under the ACA, and its implementing regulations, which requires specified manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program, with specific exceptions, to report annually to the Centers for Medicare & Medicaid Services, or CMS, information related to payments or other "transfers of value" made to physicians. All such reported information is publicly available;

- analogous state and non-U.S. laws and regulations, such as state anti-kickback and false claims laws which may apply to items or services reimbursed by any payer, including commercial insurers; state laws that require pharmaceutical companies to comply with the industry's voluntary compliance guidelines and the applicable compliance guidance promulgated by the federal government or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws that require pharmaceutical manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts; and

- regulation by the Centers for Medicare and Medicaid Services and enforcement by the U.S. Department of Health and Human Services Office of Inspector General or the U.S. Department of Justice.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our future business activities could be subject to challenge under one or more of such laws. Efforts to ensure that our business arrangements with third parties will comply with applicable laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other health care laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, exclusion from government funded health care programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other providers or entities with whom we expect to do business are found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded health care programs.

Environmental, Health and Safety

We are further subject to various foreign, national, federal, state and local laws and regulations relating to environmental, health and safety matters, in a number of jurisdictions, governing, inter alia, (i) the use, storage, registration, handling, emission and disposal of chemicals, waste materials and sewage; and (ii) chemical, air, water and ground contamination, air emissions and the cleanup of contaminated sites, including any contamination that results from spills due to our failure to properly dispose of chemicals, waste materials and sewage. Our operations at our Jerusalem research and development facility use chemicals and produce waste materials and sewage. Our activities require permits from various governmental authorities including, local municipal authorities, the Ministry of Environmental Protection and the Ministry of Health. The Ministry of Environmental Protection and the Ministry of Health, local authorities and the municipal water and sewage company may conduct periodic inspections in order to review and ensure our compliance with the various regulations.

Although we do not believe that we will be required to make material operating or capital expenditures in connection with such laws and regulations, we may be required to incur significant costs to comply with these laws and regulations in the future, and complying with these laws and regulations may result in a material adverse effect upon our business, financial condition and results of operations. Further, our failure to comply with such laws and regulations could have a material adverse effect on our business and reputation, result in an interruption or delay in the development or manufacture of our products, or increase the costs for the development or manufacture of our products.

In addition, laws and regulations relating to environmental, health and safety matters are often subject to change. In the event of any changes or new laws or regulations, we could be subject to new compliance measures or to penalties for activities which were previously permitted. For instance, Israeli regulations were promulgated in 2011 relating to the discharge of industrial sewage into the sewer system. These regulations establish new and potentially significant fees for discharging forbidden or irregular sewage into the sewage system.

Pharmaceutical Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any drug products for which we plan to seek regulatory approval. Sales of any of our product candidates, if approved, will depend, in part, on the extent to which the costs of the products will be covered by third-party payors, including government health programs such as Medicare and Medicaid, commercial health insurers and managed care organizations. Concerns about drug pricing have been expressed by both members of the United States Congress and the administration. The process for determining whether a payer will provide coverage for a drug product may be separate from the process for setting the price or reimbursement rate that the payer will pay for the drug product once coverage is approved. Third-party payers may limit coverage to specific drug products on an approved list, or formulary, which might not include all of the approved drugs for a particular indication.

In order to secure coverage and reimbursement for any product that might be approved for sale, we may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA, EMA or other comparable regulatory approvals. Our product candidates may not be considered medically necessary or cost-effective. A payer's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Third-party reimbursement may not be sufficient to enable us to maintain price levels high enough to realize an appropriate return on our investment in product development.

The containment of healthcare costs has become a priority of governments, and the prices of drugs have been a focus in this effort. Third-party payers are increasingly challenging the prices charged for medical products and services and examining the medical necessity and cost effectiveness of medical products in addition to their safety and efficacy. If these third-party payors do not consider our products to be cost-effective compared to other available therapies, they may not cover our products if approved under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our products at a profit. The U.S. government, state legislatures and non-U.S. governments have shown significant interest in implementing cost containment programs to limit the growth of government-paid health care costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs. Adoption of such controls and measures, and tightening of restrictive policies in jurisdictions with existing controls and measures, could limit payments for pharmaceuticals such as the product candidates that we are developing and could adversely affect our net revenue and results.

Pricing and reimbursement schemes vary widely from country to country. Some countries provide that drug products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular product candidate to currently available therapies. The conduct of such studies could be expensive and result in delays in our commercializing efforts. The EU provides options for its member states to restrict the range of drug products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. EU member states may approve a specific price for a drug product or may instead adopt a system of direct or indirect controls on the profitability of the company placing the drug product on the market. Other member states allow companies to fix their own prices for drug products, but monitor and control company profits. The downward pressure on health care costs in general, particularly prescription drugs, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert competitive pressure that may reduce pricing within a country. There can be no assurance that any country that has price controls or reimbursement limitations for drug products will allow favorable reimbursement and pricing arrangements for any of our products.

The marketability of any products for which we receive regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. In addition, emphasis on managed care in the United States has increased and we expect will continue to increase the pressure on drug pricing. Coverage policies, third-party reimbursement rates and drug pricing regulation may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Health Care Reform

In the United States, there have been and continue to be a number of significant legislative initiatives to contain healthcare costs. The ACA was enacted in the United States in March 2010 and contains provisions that may reduce the profitability of drug products, including, for example, increased rebates for drugs subject to the Medicaid Drug Rebate Program, extension of Medicaid rebates to Medicaid managed care plans, mandatory discounts for certain Medicare Part D beneficiaries and annual fees based on pharmaceutical companies' share of sales to federal health care programs.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. These changes included aggregate reductions to Medicare payments to providers of 2% per fiscal year, effective April 1, 2013 and, due to subsequent legislative amendments to the statute, will stay in effect through 2027, unless additional Congressional action is taken; however, pursuant to the CARES Act, and subsequent legislation, these reductions are suspended from May 1, 2020 through March 31, 2022 due to the COVID-19 pandemic. In January 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, reduced Medicare payments to several providers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These laws may result in additional reductions in Medicare and other healthcare funding, which could have a material adverse effect on customers for our drugs, if approved, and, accordingly, our financial operations.

Moreover, recently there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their commercial products. There have been several recent U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the cost of drugs under Medicare, and reform government program reimbursement methodologies for drugs. The FDA released a final rule on September 24, 2020, effective November 30, 2020, providing guidance for states to build and submit importation plans for drugs from Canada. Further, on November 20, 2020, the U.S. Department of Health and Human Services, or HHS, finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. Although a number of these, and other proposed measures may require authorization through additional legislation to become effective, Congress has indicated that it will continue to seek new legislative measures to control drug costs.

Additionally, CMS issued a final rule, effective on July 9, 2019, that requires direct-to-consumer advertisements of prescription drugs and biological products, for which payment is available through or under Medicare or Medicaid, to include in the advertisement the Wholesale Acquisition Cost, or list price, of that drug or biological product if it is equal to or greater than $35 for a monthly supply or usual course of treatment. Prescription drugs and biological products advertisements that are in violation of these requirements will be included on a public list.

Any adopted health reform measure could reduce the ultimate demand for our products, if approved, or put pressure on our product pricing. Individual states in the United States have also become increasingly active in passing legislation and implementing regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs. We expect that additional state and federal healthcare reform measures will be adopted in the future.

We expect that additional state and federal healthcare reform measures, as well as legal changes by foreign governments, will be adopted in the future, any of which could limit the amounts that governments will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

Employees

As of December 31, 2021, we had 21 employees and consultants based in Israel, including 18 full-time employees, two part time employees, and one part-time consultant who serves as our Israel-based CFO. In addition, we had one employee and four consultants based in the United States, including Chief Executive Officer, our Chief Medical Officer and our U.S-based CFO. Six of our employees and consultants have either PhDs or MDs. The distribution of our full-time employees according to main areas of activity is set forth in the following table:

	Employees
Area of Activity:	
Research and development	16
General and administrative	3
Total	19

Israeli labor laws govern the length of the workday and workweek, minimum wages for employees, procedures for hiring and dismissing employees, determination of severance pay, annual leave, sick days, advance notice of termination, payments to the National Insurance Institute, and other conditions of employment and include equal opportunity and anti-discrimination laws. While we are not, and none of our employees is, party to any collective bargaining agreements, certain provisions of the collective bargaining agreements between the Histadrut (General Federation of Labor in Israel) and the Coordination Bureau of Economic Organizations (including the Industrialists' Associations) are applicable to our employees in Israel by order of the Israeli Ministry of the Economy. These provisions primarily concern pension fund benefits for all employees, insurance for work-related accidents, recuperation pay and travel expenses. We generally provide our employees with benefits and working conditions beyond the required minimums. We have never experienced any employment-related work stoppages and believe our relationships with our employees are good.

Facilities

For more information regarding our facilities, see "Item 2—Properties."

Legal Proceedings

For more information regarding legal proceedings, see 'Item 3—Legal Proceedings."

Additional Information

Our website is at www.enterabio.com. We make available, free of charge, on our investor relations section under the heading "SEC Filings" our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and any amendments to those reports filed with or furnished to the SEC pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. Our website address is included in this report only as an inactive textual reference. Information contained on, or available through, our website is not incorporated by reference in, or made a part of, this report.

ITEM 1A. RISK FACTORS

You should carefully consider the risks described below, as well as other information contained in this Annual Report, including the consolidated financial statements and the notes thereto and "Item 7-Management's Discussion and Analysis of Financial Condition and Results of Operations." The occurrence of any of the events discussed below could significantly and adversely affect our business, prospects, results of operations, financial condition, and cash flows.

Any investment in our securities involves a high degree of risk. You should consider carefully the following factors and all other information contained in this Annual Report before you make a decision to invest in our Ordinary Shares and publicly traded warrants to purchase our Ordinary Shares listed on the Nasdaq under the symbol ENTXW (the "IPO Warrants"). If any of the negative events referred to below occur, our business, prospects, financial condition and results of operations could be materially and adversely affected. In any such case, the trading price of our Ordinary Shares could decline, and you could lose all or part of your investment.

Risk Factor Summary

Our business is subject to a number of risks, including risks that may prevent us from achieving our business objectives or may adversely affect our business, financial condition, results of operations, cash flows and prospects. These risks are discussed more fully later in this Item 1A, and include, but are not limited to, the following:

- We have incurred significant losses since our inception and anticipate that we will continue to incur substantial losses for the next several years;
- Management has performed an analysis of our ability to continue as a going concern and our independent registered public accounting firm has raised substantial doubt as to our ability to continue as a going concern;
- All of our product candidates, including EB613 and EB612, are in preclinical or clinical development and we have not yet successfully completed the development of any product candidates;
- If serious adverse, undesirable or unacceptable side effects are identified during the development of our product candidates, marketing approval may be delayed or we may need to abandon our development of such product candidates, and if such side effects are identified following regulatory approval, any approved product label may be limited or we may be subject to other significant negative consequences;
- The COVID-19 pandemic could adversely affect our business, financial condition, and results of operations;
- The commencement and completion of clinical trials can be delayed or prevented for a number of reasons;
- The results of previous clinical trials may not be predictive of future results, our progress in trials for one product candidate may not be indicative of progress in trials for other product candidates, and our trials may not be designed so as to support regulatory approval;
- Even if regulatory approvals are obtained for our product candidates, we will be subject to ongoing government regulation. If we fail to comply with applicable current and future laws and government regulations, it could delay or prevent the promotion, marketing or sale of our products;
- Healthcare legislative changes may harm our business and future prospects;
- We are subject to manufacturing risks that could substantially increase our costs and limit supply of our products;
- We are highly dependent upon our ability to enter into agreements with collaborators to develop, commercialize and market our products;
- We may fail to establish, maintain, defend and enforce intellectual property rights with respect to our technology;
- The price of our Ordinary Shares and IPO Warrants may be volatile, and holders of our Ordinary Shares and IPO Warrants could lose all or part of their investment; and
- Security, political and economic instability in the Middle East may harm our business.

Risks Related to Our Financial Position

We have incurred significant losses since our inception and anticipate that we will continue to incur substantial losses for the next several years.

We have incurred net losses in each year since our inception, including net losses of $12.2 million in 2021 and $11.2 million in 2020. As of December 31, 2021 we had an accumulated deficit of $82.4 million. We expect to continue to incur substantial losses for the next several years, and we expect these losses to increase as we continue our development of and potentially seek regulatory approval for, EB613 and EB612 and potentially develop future product candidates, including a new oral GLP-2 analog research program. In addition, if we receive regulatory approval to market EB613 or any of our other current or future product candidates, we will incur additional losses as we scale-up manufacturing and potentially prepare to commercialize any approved products. We anticipate that our net losses and accumulated deficit for the next several years will be significant as we conduct our planned operations. Given our current development plans, we anticipate that our existing cash and cash equivalents and will be sufficient to fund our operations into the fourth quarter of 2022. Accordingly, these factors, among others, raise substantial doubt about our ability to continue as a going concern. Because of the numerous risks and uncertainties associated with the development and commercialization of our product candidates, we are unable to accurately predict the timing or amount of the development and clinical expenses or when, or if we will be able to achieve, or maintain, profitability. In addition, our expenses could increase if we are required by the FDA or comparable foreign regulatory authorities to perform preclinical or clinical studies or trials in addition to those currently expected, or if there are any delays in completing our clinical trials or the development and potential commercialization of EB613 or any other product candidates. The amount of our future net losses will depend, in part, on the amount and timing of our expenses, our ability to generate revenue and our ability to raise additional capital. These net losses have had, and will continue to have, an adverse effect on our stockholders' equity and working capital.

Management has performed an analysis of our ability to continue as a going concern. In addition, our independent registered public accounting firm has raised substantial doubt as to our ability to continue as a going concern.

Based on its assessment, management has raised substantial doubt about our ability to continue as a going concern. In addition, our independent registered public accounting firm expressed substantial doubt as to our ability to continue as a going concern in their report accompanying our audited consolidated financial statements. As of March 1 2022, we had cash and cash equivalents of approximately $21.7 million. Our ability to continue as a going concern will depend on our ability to obtain additional financing. Management is in the process of evaluating various financing alternatives including public or private equity offerings, debt financings, strategic collaborations and grant funding to finance future research and development activities and general and administrative expenses. A going concern opinion could impair our ability to finance our operations through public or private equity offerings or debt financings, or a combination of one or more of these funding sources. Any additional equity or debt financing could be extremely dilutive to our current shareholders. Additional capital may not be available on reasonable terms, or at all, and we may be required to terminate or significantly curtail our operations, or enter into arrangements with collaborative partners or others that may require us to relinquish rights to certain aspects of our product candidates, or potential markets that we would not otherwise relinquish. If we are unable to obtain capital, our business, including our ability to conduct studies and develop our product candidates, would be jeopardized and we may not be able to continue operations.

Due to our limited resources and access to capital, we must and have in the past decided to prioritize development of certain product candidates; these decisions may prove to have been wrong and may adversely affect our current and any potential future revenues.

Because we have limited resources and access to capital to fund our operations, we must decide which product candidates to pursue and the amount of resources to allocate to each product candidate. As such, we are currently primarily focused on the development of EB613 and EB612 for the treatment of osteoporosis and hypoparathyroidism, respectively and in February 2021, we initiated a new oral GLP-2 analog research program. Our decisions concerning the allocation of research, collaboration, management and financial resources toward particular compounds, product candidates or therapeutic areas may not lead to the development of viable commercial products and may divert resources away from better opportunities. Similarly, our current or potential decisions to delay, terminate or collaborate with third parties with respect to certain product development programs may also be sub-optimal and could cause us to miss valuable opportunities. If we make incorrect determinations regarding the market potential of our product candidates or misread trends in the biopharmaceutical industry, our business, financial condition and results of operations could be materially adversely affected.

We will require substantial additional funding, which may not be available to us on acceptable terms, or at all, and, if not available, may require us to delay, reduce or cease our product development activities and operations.

We are currently advancing our lead product candidate EB613 through clinical development. Developing therapeutics, including conducting preclinical studies and clinical trials, is expensive. We will require substantial additional capital in order to complete filings with the regulatory agencies including the FDA and European Medicines Agency, or the EMA, secure commercial manufacturing supply for and commercialize EB613 and conduct the research and development and clinical and regulatory activities necessary to bring other product candidates to market. If the FDA or comparable foreign regulatory authorities require that we perform additional preclinical studies or clinical trials at any point, our expenses would further increase beyond what we currently expect, and the anticipated timing of any future clinical development activities and potential regulatory approvals may be delayed depending upon our allocation of resources and available funding. The recent outbreak of COVID-19 has significantly disrupted world financial markets and may reduce opportunities for us to seek out additional funding. Additional funds may not be available when we need them on terms that are acceptable to us, or at all. If adequate funds are not available to us on a timely basis, or on acceptable terms, we may be required to delay, limit, reduce or terminate preclinical studies, clinical trials or other development activities for one or more of our product candidates or delay, limit, reduce or terminate our establishment of manufacturing, sales and marketing capabilities or other activities that may be necessary to commercialize our product candidates.

We expect that we would need to raise additional funds to support the execution of our long-term growth strategy, including for a potential Phase 3 trial comparing EB613 with Forteo®, additional non-clinical studies for EB613, and further development of our technology platform and product pipeline, including our new oral GLP-2 analog research program. We can provide no assurance that additional funding will be available on a timely basis, on terms acceptable to us, or at all. Because successful development of our product candidates is uncertain, we are unable to estimate the actual amount of financing we will require to complete research and development and to commercialize our product candidates. We may also require additional financing if we are forced to delay and curtail our research activities and clinical trials due to the impact of COVID-19. The amount and timing of our funding requirements will depend on many factors, including but not limited to:

- the number and characteristics of product candidates that we pursue;
- the scope, progress, timing, cost and results of research, preclinical development, and clinical trials;
- the costs, timing and outcome of seeking and obtaining approvals from the FDA, EMA or other regulatory agencies;
- the costs associated with manufacturing our product candidates and establishing sales, marketing, and distribution capabilities;
- the costs associated with obtaining, maintaining, expanding, defending and enforcing the scope of our intellectual property portfolio, including the amount and timing of any payments we may be required to make in connection with the licensing, filing, defense and enforcement of any patents or other intellectual property rights;
- the extent to which we acquire or in-license other products or technologies;
- the economic and other terms, timing of and success of any collaboration, licensing, or other arrangements into which we entered or may enter in the future, including the timing of achievement of milestones and receipt of any milestone or royalty payments under these agreements;
- our need and ability to hire additional management, scientific, and medical personnel;
- the effect of competing products that may limit market penetration of our product candidates;
- the amount and timing of revenues, if any, we receive from commercial sales of any product candidates for which we receive marketing approval in the future;
- our need to implement additional internal systems and infrastructure, including financial and reporting systems to support our current operations as a public company; and
- the impact of COVID-19 on our clinical trials, regulatory timelines, business operations and financial stability.

Many of these factors are outside of our control. Based upon our currently expected level of operating expenditures, we believe that we will be able to fund our operations into the fourth quarter of 2022. Our expectations are based on management's current assumptions, clinical development plans and regulatory submission timelines, which may prove to be wrong, and we could spend our available financial resources much faster than we currently expect. This period could be shortened if there are any unanticipated increases in spending on development programs or other unanticipated increases in spending related to circumstances outside of our control, including, without limitation, costs associated with litigation or other legal proceedings, hiring of additional consultants and personnel or procurement of additional raw materials. Our existing cash and cash equivalents will not be sufficient to obtain regulatory approval for any of our product candidates. Accordingly, we continue to require substantial additional capital. In order to fund our future capital needs, we may seek additional funding through equity or debt financings, development partnering arrangements, lines of credit or other sources. These conditions raise substantial doubt about our ability to continue as a going concern, and we will be required to raise additional funds, seek alternative means of financial support, or both, in order to continue operations. The accompanying financial statements have been prepared assuming that we will continue as a going concern and do not include adjustments that might result from the outcome of this uncertainty. If we are unable to raise the requisite funds, we will need to curtail or cease operations.

Our fundraising efforts in the future to secure additional financing will divert our management from our day-to-day activities, which may adversely affect our ability to develop and commercialize our product candidates. In addition, we cannot guarantee that future financing will be available in sufficient amounts or on terms acceptable to us, if at all. If we are unable to raise additional capital when required or on acceptable terms, we may be required to significantly delay, reduce or discontinue the development or commercialization of one or more of our product candidates or curtail our operations, which will have an adverse effect on our business, operating results and prospects.

We have a limited operating history and no history of commercializing pharmaceutical products, which may make it difficult to evaluate the prospects for our future viability and making an investment in our Ordinary Shares unsuitable for many investors.

We began operations in 2010. Our operations to date have been limited to financing and staffing our company, developing our drug delivery technology and developing our product candidates. We have not yet demonstrated an ability successfully to complete a large-scale, pivotal clinical trial, obtain marketing approval, manufacture a commercial scale product or conduct sales and marketing activities necessary for successful product commercialization. Consequently, predictions about our future success or viability may not be as accurate as they could be if we had a history of successfully developing and commercializing pharmaceutical products.

Raising additional capital may cause dilution to our shareholders, and these financings, or disputes with shareholders in connection therewith, may restrict our operations or require us to relinquish substantial rights or result in unanticipated legal or other costs.

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our cash needs through a combination of public or private equity offerings, debt financings, strategic collaborations and grant funding. We do not have any committed external sources of funds and we will need to raise additional capital. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will be diluted, and the terms of these new securities may include liquidation or other preferences that adversely affect the rights of a holder of our Ordinary Shares. Debt financing, if available at all, may involve agreements that include covenants limiting or restricting our ability to take specific actions such as incurring additional debt, making capital expenditures, or declaring dividends, and may be secured by all or a portion of our assets. Further, we may incur substantial costs in pursuing future capital and/or financing, including investment banking fees, legal fees, accounting fees, printing and distribution expenses and other costs and such efforts may divert our management from their day-to-day activities, which may compromise our ability to develop and market our product candidates. We may also be required to recognize non-cash expenses in connection with certain securities we may issue, such as convertible notes and warrants, which could cause our operating results to fluctuate on a quarterly basis.

Shareholders who invested prior to the Company's initial public offering, or IPO, lenders whose indebtedness converted upon consummation of the IPO into our Ordinary Shares or shareholders who invested in our January 2018 private placement offering may raise claims concerning their pre-existing contractual rights as lenders or shareholders or oppose actions taken by the Company with respect to the terms of existing or future financing transactions. Any such dispute could be time-consuming or costly to the Company or require us to seek alternative financing arrangements.

If we raise additional funds through collaborations, strategic alliances, or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, product candidates, or future revenue streams, or grant licenses on terms that are not favorable to us. We cannot assure you that we will be able to obtain additional funding if and when necessary. If we are unable to obtain adequate financing on a timely basis, we could be required to delay, scale back or eliminate one or more of our development programs or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

The requirements of being a public company may strain our resources and distract our management, which could make it difficult to manage our business, particularly after we are no longer an Emerging Growth Company.

As a public company, we are required to comply with various regulatory and reporting requirements, including those required by the SEC. Complying with these reporting and regulatory requirements are time consuming, result in increased costs to us and could have a negative effect on our business, results of operations and financial condition.

We are subject to the reporting requirements of the Exchange Act, and the requirements of the Sarbanes-Oxley Act of 2002, as amended, or the Sarbanes-Oxley Act. These requirements may place a strain on our systems and resources. The Exchange Act requires that we file annual and current reports with respect to our business and financial condition. The Sarbanes-Oxley Act requires that we maintain effective disclosure controls and procedures and internal control over financial reporting. We are implementing procedures and processes for the purpose of addressing the standards and requirements applicable to public companies. Complying with these requirements is costly and time consuming. In the event that we are unable to demonstrate compliance with our obligations as a public company in a timely manner, or are unable to produce timely or accurate financial statements, we may be subject to sanctions or investigations by regulatory authorities, such as the SEC or Nasdaq, investors may lose confidence in our operating results and the price of our Ordinary Shares could decline. These activities may divert management's attention from other business concerns, which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

As an emerging growth company, we may take advantage of certain temporary exemptions from various reporting requirements including, but not limited to, not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act and the rules and regulations of the SEC thereunder. We plan to take advantage of these exemptions but we cannot guarantee that we will not be required to implement these requirements sooner than budgeted or planned and thereby incur unexpected expenses. We will remain an emerging growth company until the earliest of: (a) the last day of our fiscal year during which we have total annual gross revenues of at least $1.07 billion; (b) the last day of our fiscal year following the fifth anniversary of the completion of our IPO, specifically, December 31, 2023; (c) the date on which we have, during the previous three-year period, issued more than $1.0 billion in non-convertible debt; or (d) the date on which we are deemed to be a large accelerated filer, or Large Accelerated Filer, under the Exchange Act with at least $700 million of equity securities held by non-affiliates. We cannot predict or estimate the amount of additional costs we may incur as a result of no longer being an Emerging Growth Company or the timing of such costs.

Our Ordinary Shares and IPO Warrants are listed on Nasdaq. As a public company listed on Nasdaq, we incur significant legal, accounting and other expenses. In addition, changing laws, regulations and standards, in the United States or Israel, relating to corporate governance and public disclosure and other matters, may be implemented in the future, which may increase our legal and financial compliance costs, make some activities more time consuming and divert management's time and attention from revenue-generating activities to compliance activities. If our efforts to comply with new laws, regulations and standards differ from the activities intended by regulatory or governing bodies due to ambiguities related to practice, regulatory authorities may initiate legal proceedings against us and our business may be harmed. Furthermore, because we are a publicly traded company in the United States and subject to U.S. rules and regulations, it is more expensive for us to obtain director and officer liability insurance, and we may be required to accept reduced coverage or incur substantially higher costs to obtain coverage. These factors may also make it more difficult for us to attract and retain qualified members of our board of directors, particularly to serve on our audit committee, and qualified executive officers.

Risks Related to Our Business and the Development of Our Product Candidates

All of our product candidates are in preclinical or clinical development and we have not yet successfully completed the development of any product candidates.

We are a clinical-stage company focused on the development of orally delivered protein therapeutics to treat unmet medical needs. We were formed in 2009 and have a limited operating history. Since inception we have devoted substantially all of our resources to the development of our technology platform, the clinical and preclinical advancement of our product candidates, the creation, licensing and protection of related intellectual property rights and the provision of general and administrative support for these operations. We have not yet obtained regulatory approval for any product candidates in any jurisdiction or generated any revenues from product sales. If any of our current or future product candidates fails in clinical trials or preclinical development, or does not gain regulatory approval, or if our product candidates following regulatory approval, if any, do not achieve market acceptance, we may never become profitable or sustain profitability.

We commenced our first clinical trials with our oral PTH candidates in osteoporosis and hypoparathyroidism, and we have a limited operating history of developing products upon which our business and prospects can be evaluated. In addition, our Phase 2 clinical trial for EB613 for osteoporosis was the largest clinical trial we have conducted to date, and we have never conducted clinical trials of a size required for regulatory approvals. Furthermore, we have not yet demonstrated an ability to successfully overcome many of the risks and uncertainties frequently encountered by companies in rapidly evolving fields, such as the oral delivery of protein therapeutics.

To become and remain profitable, we must succeed in developing and commercializing products that generate significant revenues. This will require us to be successful in a range of challenging activities for which we are only in the preliminary stages, including developing product candidates, completing pre-clinical and clinical trials for such product candidates, obtaining regulatory approval for them, and manufacturing, marketing and selling those products for which we may obtain regulatory approval. We may never succeed in these activities and, even if we do, we may never generate revenue from product sales that is significant enough to achieve profitability. Our ability to generate future revenue from product sales depends heavily on our success in many areas, including but not limited to:

- the completion of future development efforts for EB613, EB612 or other product candidates;
- securing additional funding as may be needed to continue the development of EB613 or any other product candidates;
- obtaining required regulatory and marketing approvals for the manufacturing and commercialization of EB613 and any other product candidates we may develop, including a new Oral GLP-2 analog research program;
- obtaining adequate reimbursement from third-party payors for any product that may be commercialized, if approved;
- managing our spending as costs and expenses increase due to the preparation of regulatory filings, potential regulatory approvals, manufacturing scale-up and potential commercialization;
- continuing to build and maintain our intellectual property portfolio;
- recruiting and retaining qualified executive management and other personnel;
- building and maintaining appropriate research and development, clinical, sales, manufacturing, financial reporting, distribution and marketing capabilities on our own or through third parties;
- gaining market acceptance for our product candidates;
- developing and maintaining successful strategic relationships and collaborations;
- developing a sustainable and scalable manufacturing process for any approved product candidates and maintaining supply and manufacturing relationships with third parties that can support clinical development and market demand for our product candidates, if approved;
- establishing sales, marketing, and distribution capabilities in the United States and the EU;
- obtaining market acceptance for any of our product candidates that receive marketing approval, if any, as viable treatment options;
- addressing any competing technological and market developments;
- negotiating favorable terms in any collaboration, licensing, or other arrangements into which we may enter; and
- attracting, hiring and retaining qualified personnel.

If we are unsuccessful in accomplishing any of these objectives, we may not be able to develop product candidates, raise capital, expand our business or continue our operations. Even if one or more of the product candidates that we develop is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product candidate. Because of the numerous risks and uncertainties with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve profitability. Even if we achieve profitability in the future, we may not be able to sustain profitability in subsequent periods. Our failure to become or remain profitable would depress our market value and could impair our ability to raise capital, expand our business, develop other product candidates, or continue our operations. A decline in the value of our company could also cause you to lose all or part of your investment.

We depend on enrollment of patients in our clinical trials for our product candidates. If we are unable to enroll an adequate number of volunteers or patients in our clinical trials, our research and development efforts could be materially adversely affected.

Successful and timely completion of clinical trials will require that we enroll enough volunteers in early studies, or patients with a specific disease in later trials. Trials may be subject to delays as a result of enrollment taking longer than anticipated or subject withdrawal. Enrollment depends on many factors, including the size and nature of the patient population, eligibility criteria for the trial, the proximity of patients to clinical sites, the design of the clinical protocol, the number of competing clinical trials, the availability of drugs approved for the indication the clinical trial is investigating, and clinicians' and patients' perceptions as to the potential advantages of the product being studied in relation to other available therapies. Our most advanced programs, EB613 and EB612 may compete with marketed drugs, such as Forteo (in Osteoporosis) and Natapara (in hypoparathyroidism) or other clinical trials for drugs in development to treat such conditions. Furthermore, EB612 has orphan drug designation in the United States and in the European Union, or the EU, which means that the potential patient population is limited. These factors may make it difficult for us to enroll enough subjects to complete our clinical trials in a timely and cost-effective manner. Delays in the completion of any clinical trial of our product candidates will increase our costs, slow down development of our product candidates and any potential approvals and delay or potentially jeopardize our ability to commence product sales and generate revenue. In addition, some of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates.

We may not be successful in our efforts to use and expand our drug delivery technology to other product candidates.

A key element of our strategy is to combine our oral drug delivery technology platform with a variety of proteins and large molecule active pharmaceutical ingredients, or APIs, to build a pipeline of product candidates and progress these product candidates through clinical development for the treatment of a variety of different types of diseases. We intend to use our technology in combination with known APIs, to validate our platform and potentially minimize risk and development timelines.

Our initial product candidates combine our oral drug delivery technology with PTH, a hormone that has been used in injectable form for many years for the treatment of osteoporosis and hypoparathyroidism. Our business is substantially dependent on our ability to complete the development of, obtain regulatory approval for, and successfully commercialize our oral PTH product candidates in a timely manner. If we are unable to validate our oral drug delivery technology with our PTH product candidates, in particular our lead candidate EB613, we may be unsuccessful in leveraging our oral drug delivery technology for use with other APIs. In addition, we may significantly modify the formulation of oral PTH to develop new formulations for applications in hypoparathyroidism and other indications. If we are not successful in optimizing the formation of our PTH product candidates for additional indications, or if we are not otherwise able to obtain regulatory approval for them or successfully commercialize them, our business and prospects may be severely limited.

In addition, our technology makes use of synthetically bioengineered ingredients. Although our product candidates utilize a synthesized PTH molecule with a known mechanism of action, they may cause patients to exhibit safety or immune responses that do not match the biological effect of a human protein produced by the parathyroid gland. Such responses could result in increased regulatory scrutiny, delays or other impediments to our planned development or the public acceptance and commercialization of our products. Even if we are successful in expanding our drug delivery technology to other APIs for other indications, the potential product candidates that we identify may not be suitable for clinical development, to the extent they are shown to have harmful side effects or other characteristics that indicate that they are unlikely to be products that will receive marketing approval and achieve market acceptance. We may never successfully develop or commercialize our technology with other APIs, which could limit our business and prospects.

If serious adverse, undesirable or unacceptable side effects are identified during the development of our product candidates, marketing approval may be delayed or we may need to abandon our development of such product candidates, and if such side effects are identified following regulatory approval, any approved product label may be limited or we may be subject to other significant negative consequences.

All of our product candidates are still in clinical or non-clinical development and although our product candidates have undergone or will undergo safety testing, not all adverse effects of drugs can be predicted or anticipated. Unforeseen side effects from any of our product candidates could be recognized either during clinical development or, if such side effects are rare, after our product candidates have been approved by regulatory authorities and the approved product has been marketed, resulting in the exposure of additional patients. While our oral PTH has exhibited no serious drug related adverse events in our clinical trials to date, the results of future clinical trials may show that our product candidates cause undesirable or unacceptable side effects, which could interrupt, delay or halt clinical trials, and result in delay of, or failure to obtain, marketing approval from the FDA, the EMA and other regulatory authorities, or result in marketing approval from the FDA, the EMA and other regulatory authorities with restrictive label warnings or potential product liability claims. For instance, other PTH products have been issued with labels that disclose a potential risk of osteosarcoma based on non-clinical studies.

Additionally, the FDA and foreign regulatory agency regulations require that we report certain information about adverse medical events if our products may have caused or contributed to those adverse events. The timing of our obligation to report would be triggered by the date on which we become aware of the adverse event as well as the nature of the event. We may fail to report adverse events we become aware of within the prescribed timeframe. We may also fail to appreciate that we have become aware of a reportable adverse event, especially if it is not reported to us as an adverse event or if it is an adverse event that is unexpected or removed in time from the use of our products. If we fail to comply with our reporting obligations, the FDA or a foreign regulatory agency could take action including criminal prosecution, the imposition of civil monetary penalties or seizure of our products.

If any of our product candidates receives marketing approval and we or others later identify undesirable or unacceptable side effects caused by such products:

- regulatory authorities may require us to take these products off the market;
- regulatory authorities may require the addition of labeling statements, specific warnings, a contraindication or field alerts to physicians and pharmacies;
- we may be required to change the way the product is administered, conduct additional clinical trials or change the labeling of the product;
- we may be subject to limitations on how we may promote the product;
- sales of the product may decrease significantly;
- we may be subject to litigation or product liability claims; and
- our reputation may suffer.

Any of these events could prevent us or any potential collaborators from achieving or maintaining market acceptance of the affected product or could substantially increase commercialization costs and expenses, which in turn could delay or prevent us from generating significant revenue from the sale of our products.

We manage our business and develop our technology with a small number of employees and key consultants, and, in the event of their loss or unavailability, we may not be able to grow our business or develop and commercialize our products.

We currently depend upon the efforts and abilities of our senior executives, including Spiros Jamas, our Chief Executive Officer, Dr. Phillip Schwartz, our President of R&D and Executive Vice President, Hillel Galitzer, our Chief Operating Officer, and a small number of employees and key consultants. Our success depends upon the continued contributions of these senior executives, employees and consultants, many of whom have substantial scientific and technical experience with, and have been instrumental for, us and our technology platform. Furthermore, recruiting and retaining new executive talent and qualified scientific personnel to perform future research and development work will be critical to our success. Competition for skilled personnel is intense and turnover rates are high, and our ability to attract and retain qualified personnel may be limited. The loss or unavailability of the services of any of our key employees and consultants for any significant period of time or our inability to attract and retain qualified skilled personnel could have a material adverse effect on our business, technology, prospects, financial condition and results of operations. We do not maintain “key man” life insurance policies for any of our employees.

We expect to grow our organization, particularly in the United States, specifically to supplement and expand our senior management, clinical development and regulatory capabilities and marketing infrastructure, and we may experience difficulties in managing these changes and this growth, which could disrupt our operations.

As our clinical development and commercialization plans and strategies develop, we expect to supplement and expand our employee base, particularly in the United States, for clinical development, regulatory, operational, sales, marketing, financial and other capabilities and with senior managers who are either based in the United States or who have significant U.S. public company experience. These changes may result in significant shifting of responsibilities or replacement of key personnel. The need to identify, recruit, maintain, motivate and integrate additional employees and senior members of management, including senior executives, is expected to impose significant responsibilities on our senior executives and may divert a disproportionate amount of their attention away from our day-to-day activities. The addition of such employees and managers may have an impact on the decisions that we make over time.

In conjunction with the addition of these employees and senior members of management, we intend to grow our company. Due to our limited financial resources and the limited experience of our management team, it is possible that our management, finance, development personnel, systems and facilities currently in place may not be adequate to support this future growth. We may not be able to effectively manage the expansion of our operations, which may result in weaknesses in our infrastructure, give rise to operational errors, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Our expected growth could require significant expenditures and may divert financial resources from other projects, such as the development of existing and additional product candidates. If we are unable to effectively manage our expected growth, our expenses may increase more than expected, our ability to generate or grow revenue could be reduced and we may not be able to implement our strategy. Our future financial performance and our ability to develop our product candidates and compete effectively with others in our industry will depend, in part, on our ability to effectively manage any future growth. In addition, pursuant to both Israeli law and Nasdaq rules, we have appointed independent directors, which may result in a change in the company’s direction over time.

We are increasingly dependent on information technology systems, infrastructure and data, and our internal computer systems, or those of our collaborators, third-party clinical research organizations or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product development programs.

We are increasingly dependent upon information technology systems, infrastructure and data. Despite the implementation of security measures, our internal computer systems and those of our development partners, third-party clinical research organizations, data management organizations and other contractors and consultants are vulnerable to damage from service interruption or destruction, computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. In addition, such systems are subject to compromise from internal threats, such as theft, misuse, unauthorized access or other improper actions by employees, third-party service providers and other third parties with otherwise legitimate access to our systems. Cyber-attacks are increasing in their frequency, sophistication and intensity, and have become increasingly difficult to detect. Cyber-attacks could include the deployment of harmful malware, denial-of service, social engineering and other means to affect service reliability and threaten data confidentiality, integrity and availability. It is possible that we may not be able to anticipate, detect, appropriately react and respond to, or implement effective preventative measures against all cybersecurity incidents. Our key business partners face similar risks, and a security breach of their systems could adversely affect our security posture.

While we have not experienced any such system failure, accident or security breach to date, if such an event were to occur and cause interruptions in our operations, it could cause damage or destroy assets, compromise business systems, or otherwise result in a material disruption of our programs and business operations. Security breaches further pose a risk that sensitive data, including intellectual property, clinical data, trade secrets or personal information may be exposed to unauthorized persons or to the public, altered or lost. For example, the loss of clinical trial data for any of our product candidates could delay our ability to report such data, result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach results in a loss of or damage to our data or applications or other data or applications relating to our technology or product candidates, or inappropriate disclosure of confidential or proprietary information, we could incur liabilities, damages or damage to our reputation and the further development of our product candidates could be delayed. We do not currently maintain a cyber insurance policy and therefore the successful assertion of one or more large claims against us in connection with a breach or other cybersecurity-related matter could materially adversely affect our business, financial condition and operating results.

We rely on email and other messaging services in connection with our operations. We may be targeted by parties using fraudulent spoofing and phishing emails to misappropriate passwords, payment information or other personal information or to introduce viruses through Trojan horse programs or otherwise through our networks, computers, smartphones, tablets or other devices. Despite our efforts to mitigate the effectiveness of such malicious email campaigns through a variety of control and non-electronic checks, spoofing and phishing may damage our business and increase our costs. Any of these events or circumstances could materially adversely affect our business, financial condition and operating results.

We may be required to expend significant capital and other resources to protect against, respond to, and recover from any potential, attempted, or existing cybersecurity incidents. As cybersecurity incidents continue to evolve, we may be required to expend significant additional resources to continue to modify or enhance our protective measures or to investigate and remediate any information security vulnerabilities. In addition, our remediation efforts may not be successful. Moreover, there could be public announcements regarding any cybersecurity incidents and any steps we take to respond to or remediate such incidents, and if securities analysts or investors perceive these announcements to be negative, it could, among other things, have a substantial adverse effect on the price of our Ordinary Shares. There can be no assurance that our efforts will prevent service interruptions, or identify breaches in our systems, that could adversely affect our business and operations and/or result in the loss of critical or sensitive information or the illegal transfer of funds to unknown persons, which could result in financial, legal, business or reputational harm, and may harm our relationships with third parties.

Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements and insider trading.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with the regulations of the FDA or foreign regulators, failure to provide accurate information to regulatory authorities, failure to comply with manufacturing standards we have established, failure to comply with federal and state health care fraud and abuse laws and regulations in the United States and abroad, failure to report financial information or data accurately, disclose unauthorized activities to us or failure to comply with our own internal company policies. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and cause harm to our reputation. We have adopted a code of business conduct and ethics, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

In addition, during the course of our operations, our directors, executives and employees may have access to material, nonpublic information regarding our business, our results of operations or potential transactions we are considering. We may not be able to prevent a director, executive or employee from trading in our Ordinary Shares on the basis of, or while having access to, material, nonpublic information. If a director, executive or employee was to be investigated or an action was to be brought against a director, executive or employee for insider trading, it could have a negative impact on our reputation and our stock price. Such a claim, with or without merit, could also result in substantial expenditures of time and money and divert attention of our management team from other tasks important to the success of our business.

The results of the United Kingdom's exit from the European Union, commonly referred to as "Brexit," may have a negative effect on global economic conditions, financial markets and our business.

The United Kingdom, or the U.K., exited the EU on January 31, 2020. The U.K.'s withdrawal from the EU occurred on January 31, 2020, but the U.K. remained in the EU's customs union and single market for a transition period that expired on December 31, 2020. On December 24, 2020, the U.K. and the EU entered into a trade and cooperation agreement (the "Trade and Cooperation Agreement"), which was applied on a provisional basis from January 1, 2021. While the economic integration does not reach the level that existed during the time the U.K. was a member state of the EU, the Trade and Cooperation Agreement sets out preferential arrangements in areas such as trade in goods and in services, digital trade and intellectual property. Negotiations are expected to continue in relation to the relationship between the U.K. and the EU in certain other areas which are not covered by the Trade and Cooperation Agreement.

Since a significant proportion of the regulatory framework affecting the pharmaceutical and biotechnology industries in the U.K. is derived from the EU directives and regulations, Brexit, the Trade and Cooperation Agreement and any future agreements between the U.K. and the EU could materially impact the regulatory regime with respect to the approval of our product candidates in the U.K. and/or the EU. For example, as a result of the uncertainty surrounding Brexit, the EMA relocated to Amsterdam from London. This transition may cause disruption in the administrative and medical scientific links between the EMA and the U.K. Medicines and Healthcare products Regulatory Agency, including delays in granting clinical trial authorization or marketing authorization, disruption of import and export of active substance and other components of new drug formulations, and disruption of the supply chain for clinical trial product and final authorized formulations. The cumulative effects of the disruption to the regulatory framework may add considerably to the development lead time to marketing authorization and commercialization of products in the U.K. and/or the EU. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in the U.K. and/or the EU, and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occurs, we may be forced to restrict or delay efforts to seek regulatory approval in the U.K. and/or EU for our product candidates, which could significantly and materially harm our business.

The COVID-19 pandemic could adversely affect our business, financial condition, and results of operations.

Given the continued spread of COVID-19, including the emergence of COVID-19 variants, such as the recent Delta and Omicron variants, and the resultant personal, economic and governmental reactions, we may have to take additional actions in the future that could adversely affect our business, financial condition, and results of operations, including a return to a fully remote workforce.

We continue to monitor our operations and government regulations, guidelines and recommendations and may need to temporarily close our office space to protect our employees. In addition, hospitals may reduce staffing and have begun to reduce or postpone certain treatments in response to the spread of an infectious disease, including our clinical trials.

Disruptions to our supply chain will prevent us from receiving necessary materials from manufacturers for our research and may also delay third-party laboratories with which we work from performing research tasks. If individuals or site staff who, as healthcare providers, may have heightened exposure to COVID-19, choose not to participate in or leave clinical trials being conducted by us or our collaboration partners due to concerns over infection risk or if Israeli authorities fully close or curtail access to the hospital facilities where many of our clinical trials are conducted for a prolonged time, our clinical trial operations could be significantly and adversely affected. The diversion of healthcare resources away from the conduct of clinical trials to focus on pandemic concerns, including the attention of physicians serving as our clinical trial investigators, diversion of hospitals and medical centers or sites serving as our clinical trial sites and hospital or other staff supporting the conduct of our clinical trials may significantly disrupt our research activities. Israeli authorities have begun repurposing certain medical institutions to function as centers for COVID-19 treatment, including two centers where we conduct trials.

Limitations on travel could interrupt key trial activities, such as clinical trial site initiations and monitoring of ongoing stability studies or other such experiments associated with our upcoming preclinical studies or future collaborations, domestic and international travel by employees, contractors or patients to clinical trial sites, including any government-imposed travel restrictions or quarantines that may impact the ability or willingness of patients, employees or contractors to travel to our clinical trial sites or secure visas or entry permissions, any of which could delay or adversely impact the conduct or progress of our clinical trials. At this time, our employees are largely following a work from home policy and will be required to adapt or change their current participation in our research as evolving government directives are released, including the cessation of non-essential business activity, which may be interpreted by Israeli authorities to include our clinical trials. Limitations on or the closure of mass transit may impact our business operations or delay necessary interactions with local regulators, ethics committees and other important agencies and contractors.

As a result, the expected timeline for data readouts of our preclinical studies and clinical trials and certain regulatory filings will likely be negatively impacted, which would adversely affect our ability to obtain regulatory approval for our product candidates, increase our operating expenses and have a material adverse effect on our financial results. We may require additional capital to continue our research activities, which funding may not be available entirely or at attractive terms.

In addition, our management team has spent, and will likely continue to spend, significant time, attention, and resources monitoring the COVID-19 pandemic and associated global economic uncertainty and seeking to manage its effects on our business and workforce. The degree to which COVID-19 will affect our business, financial condition, and results of operations will depend on future developments that are highly uncertain and cannot currently be predicted. These developments include, but are not limited to, the duration, extent, impact and severity of the COVID-19 pandemic in different geographies, the effectiveness of our transition from work-from-home arrangements to a gradual return to our offices, actions taken to contain the COVID-19 pandemic, the long-term efficacy, global availability and acceptance of vaccines, related restrictions on economic activity and domestic and international trade, and the extent of the impact of these and other factors on our employees, suppliers, and customers.

These and other factors arising from the COVID-19 pandemic could worsen in countries that are already afflicted with COVID-19, could continue to spread to additional countries, or could return to countries where the pandemic has been partially contained, each of which could further adversely impact our ability to conduct clinical trials and our business generally, and could have a material adverse impact on our operations and financial condition and results. In addition, the trading prices for our Ordinary Shares and other biopharmaceutical companies have been highly volatile as a result of the COVID-19 pandemic. The extent to which the coronavirus impacts our business will depend on future developments, which are highly uncertain and cannot be predicted, including new information which may emerge concerning the severity and geographic reach of the coronavirus and the effectiveness of actions to contain the coronavirus or treat its impact, among others.

We are subject to risks related to restrictive data privacy regulations governing the collection, use, processing and cross-border transfer of personal information.

In the ordinary course of our business, we may collect, process, use, store or transfer sensitive data in our data centers and on our networks, including intellectual property, proprietary business information (both ours and that of our customers, suppliers and business partners) and personally identifiable information, including in connection with conducting clinical trials. We are subject to strict data privacy laws and regulations in the United States, EU, Israel and other jurisdictions in which we operate, as well as contractual obligations, governing the collection, transmission, storage and use of personal information. The legislative and regulatory landscape for data privacy and protection continues to evolve around the world and are increasingly rigorous, with new and constantly changing requirements applicable to our business, including the U.S.'s federal Health Insurance Portability and Accountability Act of 1996, as amended, or HIPAA, the EU General Data Protection Regulation ((EU) 2016/679), or the GDPR, the Israeli Privacy Protection Law, 5741-1981, and other laws and regulations governing the collection, use, disclosure and transmission of data. The enforcement practices of these laws and regulations are likely to remain uncertain for the foreseeable future. These laws and regulations may be interpreted and applied differently over time and from jurisdiction to jurisdiction, and it is possible that they will be interpreted and applied in ways that may have a material adverse effect on our results of operations, financial condition and cash flows.

For example, in the United States, various federal and state regulators have adopted, or are considering adopting, laws and regulations concerning personal information and data security. Certain state laws may be more stringent or broader in scope, or offer greater individual rights, with respect to personal information than federal, international or other state laws, and such laws may differ from each other, all of which may complicate compliance efforts. For example, the California Consumer Privacy Act, or the CCPA, which increases privacy rights for California residents and imposes obligations on companies that process their personal information, came into effect on January 1, 2020. Among other things, the CCPA requires covered companies to provide new disclosures to California consumers and provide such consumers new data protection and privacy rights, including the ability to opt-out of certain sales of personal information. On November 3, 2020, California voters approved a new privacy law, the California Privacy Rights Act, or CPRA, which significantly modifies the CCPA, including by expanding consumers' rights with respect to certain personal information and creating a new state agency to oversee implementation and enforcement efforts. Many of the CPRA's provisions will become effective on January 1, 2023. The CCPA provides for civil penalties for violations, as well as a private right of action for certain data breaches that result in the loss of personal information. This private right of action may increase the likelihood of, and risks associated with, data breach litigation. In addition, laws in all 50 U.S. states require businesses to provide notice to consumers whose personal information has been disclosed as a result of a data breach. State laws are changing rapidly and there is discussion in Congress of a new comprehensive federal data privacy law to which we would become subject if it is enacted.

In addition, outside the United States, laws, regulations and standards in many jurisdictions apply broadly to the collection, use, retention, security, disclosure, transfer and other processing of personal information. For example, the GDPR greatly increased the European Commission's jurisdictional reach of its laws and adds a broad array of requirements for handling personal data. EU member states are tasked under the GDPR to enact, and have enacted, certain implementing legislation that adds to and/or further interprets the GDPR requirements and potentially extends our obligations and potential liability for failing to meet such obligations. The GDPR, together with national legislation, regulations and guidelines of the EU member states governing the processing of personal data, impose strict obligations and restrictions on the ability to collect, use, retain, protect, disclose, transfer and otherwise process personal data. Specifically, the GDPR's requirements including having legal bases for processing personal information relating to identifiable individuals and transferring such information outside of the European Economic Area, including to the United States, and other countries providing details to those individuals regarding the processing of their personal information, keeping personal information secure, having data processing agreements with third parties who process personal information, responding to individuals' requests to exercise their rights in respect of their personal information, reporting security breaches involving personal data to the competent national data protection authority and affected individuals, appointing data protection officers, conducting data protection impact assessments and record-keeping. The GDPR imposes additional responsibilities and liabilities in relation to personal data that we process and authorizes fines for certain violations of up to 4% of global annual revenue or €20 million, whichever is greater. The U.K. has transposed the GDPR into domestic law, with its version of the GDPR that took effect on January 1, 2021, which could expose us to two parallel regimes, each of which potentially authorizes similar fines for certain violations. As such, we may be required to put in place additional mechanisms ensuring compliance with the new data protection rules.

All of these evolving compliance and operational requirements impose significant costs, such as costs related to organizational changes, implementing additional protection technologies, training associates and engaging consultants, which are likely to increase over time. In addition, such requirements may require us to modify our data processing practices and policies, distract management or divert resources from other initiatives and projects. Any failure or perceived failure to comply with the requirements of privacy laws and regulations, including the CCPA, GDPR and related national data protection laws of the member states of the EU and the U.K., may result in damage to our reputation and our relationship with our customers, as well as proceedings or litigation by governmental agencies or customers, including class action privacy litigation in certain jurisdictions, which would subject us to significant fines, sanctions, awards, penalties or judgments, which could have a material adverse effect on our business, prospects, financial condition and results of operations.

Risks Related to Regulatory Approval of Our Product Candidates

Clinical drug development is expensive, time consuming and uncertain. Development programs are subject to unanticipated delays and we may ultimately not be able to obtain regulatory approvals for the commercialization of our product candidates.

Our lead product candidates are orally delivered tablet formulations of the synthetic form of the first 34 amino acids of human PTH. We are developing EB613 to treat osteoporosis and EB612 to treat hypoparathyroidism. These product candidates have not yet reached late-stage clinical development and are subject to the risks of failure inherent in drug development. The clinical development, manufacturing, quality assurance, labeling, storage, record-keeping, advertising, promotion, pharmacovigilance, import, export, marketing and distribution of our product candidates is subject to extensive regulation by the FDA in the United States and by comparable authorities in foreign markets. We are not permitted to market our product candidates in the United States until we receive approval of a new drug application, or NDA, or biologics license application, or BLA, from the FDA or in any other country until we receive marketing approval from the applicable regulatory authorities in such countries. We have not yet submitted a marketing application, or received marketing approval, for any of our product candidates and have limited experience in conducting and managing the clinical trials necessary to obtain regulatory approvals. The process of obtaining regulatory approvals is expensive, often takes many years, and can vary substantially based upon the type, complexity, and novelty of the products involved, as well as the target indications. Approval policies or regulations may change and the regulatory agencies have substantial discretion in the approval process for products, including the ability to delay, limit or deny approval of a product candidate for many reasons. Obtaining approval of an NDA, BLA, or other marketing application can be a lengthy, expensive and uncertain process. Despite the time and expense invested in clinical development of product candidates, regulatory approval is never guaranteed.

The FDA or comparable foreign regulatory authorities can delay, limit or deny approval of a product candidate for many reasons, including:

- such authorities may disagree with the number, design, size, conduct or implementation of our clinical trials or any of our collaborators' clinical trials;
- we or any of our development partners may be unable to demonstrate to the satisfaction of the FDA or other regulatory authorities that a product candidate is safe and effective for any indication;
- the results of clinical trials may not meet the level of statistical significance or clinical significance required by the FDA, EMA or other regulatory agencies for approval;
- such authorities may not accept clinical data from trials which are conducted at clinical facilities or in countries where the standard of care is potentially different from that authority's jurisdiction;
- the data collected from non-clinical studies and clinical trials of our product candidates may not be sufficient to support the submission of an application for regulatory approval;
- the results of clinical trials may not demonstrate the safety or efficacy required by such authorities for approval;
- we or any of our future development partners may be unable to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks;
- such authorities may disagree with our interpretation of data from preclinical studies or clinical trials or the use of results from studies that served as precursors to our current or future product candidates;
- such authorities may find deficiencies in our manufacturing processes or facilities or those of third-party manufacturers with which we or any of our future development partners contract for clinical and commercial supplies;
- the FDA may require development of a Risk Evaluation and Mitigation Strategy, or REMS, as a condition of approval; and
- the approval policies or regulations of such authorities may significantly change in a manner rendering our or any of our future development partners' clinical data insufficient for approval.

Each of our oral PTH product candidates, including EB613 and EB612, are still in clinical development and face a variety of risks and uncertainties, including the following:

- future clinical trial results may show that our oral PTH is not effective, including if our drug delivery technology is not effective, our product candidates are not effective, our clinical trial designs are flawed, or clinical trial investigators or subjects do not comply with trial protocols;
- our product candidates may not be well tolerated or may cause negative side effects;
- our ability to complete the development and commercialization of our oral PTH for our intended uses may be significantly dependent upon our ability to obtain and maintain experienced and committed collaborators to assist us with obtaining clinical and regulatory approvals for, and the manufacturing, marketing and distribution of, our oral PTH;
- even if our oral PTH is shown to be safe and effective for its intended purposes, we may face significant or unforeseen difficulties in obtaining or manufacturing sufficient quantities at reasonable prices, or at all;
- even if our oral PTH is successfully developed, commercially produced and receives all necessary regulatory approvals, there is no guarantee that there will be market acceptance;
- even if our oral PTH is successfully developed, commercially produced and receives all necessary regulatory approvals for the treatment of Osteoporosis, there is no guarantee that we will successfully develop and commercialize it for other indications, including hypoparathyroidism and delayed union fractures; and
- our competitors may develop therapeutics or other treatments that are superior to or less costly than our own with the result that our products, even if they are successfully developed, manufactured and approved, may not generate significant revenues.

If we are unsuccessful in dealing with any of these risks, or if we or a potential partner are unable to successfully commercialize our oral PTH or any other product candidates we may develop in the future, it would likely have a material adverse effect on our business, prospects, financial condition and results of operations. In addition, in the event we are able to successfully commercialize our oral PTH, we may sell the tablets at a discounted sales price for the initial period in order to gain market acceptance of the product, which could adversely affect our financial condition and results of operations.

In addition, before we can submit an application for regulatory approval in the United States, we must conduct a pivotal trial that will be substantially broader than our completed Phase 2a trial in hypoparathyroidism and our ongoing Phase 2 trial in osteoporosis. We will also need to agree on a protocol with the FDA for a Phase 3 clinical trial before commencing the trial. The outbreak of COVID-19 may impact whether the FDA would consider our Phase 2 clinical trial data to be sufficient for purposes of commencing a Phase 3 clinical trial for osteoporosis. Phase 3 clinical trials frequently produce unsatisfactory results even when prior clinical trials were successful. Therefore, even if the results of our Phase 2 trials are successful, the results of the additional trials that we conduct may or may not be successful. Further, our product candidates may not be approved even if they achieve their primary endpoints in Phase 3 clinical trials. For example, there is no FDA guidance on the acceptable level of variability of absorption of orally delivered products with large molecule APIs, and, therefore we are unable to be certain that we are designing our product candidates or clinical trials to satisfy the FDA in this regard. The FDA, EMA or other regulatory agencies may require that we conduct additional clinical, nonclinical, manufacturing validation or drug product quality studies beyond those planned and submit data from such trials before considering or reconsidering the application. Depending on the extent of these or any other studies, approval of any applications that we submit may be delayed by several years or may require us to expend more resources than we have available. It is also possible that additional studies, if performed and completed, may not be considered sufficient by the FDA, EMA or other regulatory agencies. If any of these outcomes occur, we would not receive approval for our oral PTH tablet or other product candidates we may develop in the future.

In addition, the FDA, EMA or other regulatory agencies may also approve a product candidate for fewer or more limited indications than we request, may impose significant limitations related to use restrictions for certain age groups, warnings, precautions or contraindications or may grant approval contingent on the performance of costly post-marketing clinical trials or risk mitigation requirements. The FDA, EMA or other regulatory agencies may also not accept the labeling claims that we believe would be necessary or desirable for the successful commercialization of our product candidates.

The commencement and completion of clinical trials can be delayed or prevented for a number of reasons.

EB613 is currently in a Phase 2 clinical trial for the treatment of osteoporosis and we had a Pre-IND meeting for EB613 with the FDA in November 2018. Following FDA guidance on our proposed preclinical and clinical development plans, we intend to further develop EB613 and conduct the required nonclinical studies and clinical trials in order to attain regulatory approval in the United States and other countries. In addition, we plan to initiate a Phase 2b/3 clinical trial of EB612 in hypoparathyroidism that would potentially support a submission for regulatory approval of EB612. Furthermore, in February 2021, we initiated a new oral GLP-2 analog research program based on our platform technology. Drug development is a long, expensive and uncertain process, and delay or failure can occur at any stage of any of our clinical trials for a number of reasons including:

- difficulties obtaining regulatory approval to commence a clinical trial or complying with conditions imposed by a regulatory authority regarding the scope or term of a clinical trial;
- delays in reaching or failing to reach agreement on acceptable terms with prospective contract research organizations, or CROs, contract manufacturing organizations, and trial sites, the terms of which can be subject to extensive negotiation and may vary significantly;
- failure of our third-party contractors, such as CROs and contract manufacturing organizations, or our investigators to comply with regulatory requirements or otherwise meet their contractual obligations in a timely manner;
- insufficient or inadequate supply or quality of a product candidate or other materials necessary to conduct our clinical trials;
- difficulties obtaining institutional review board, or IRB, or ethics committee approval to conduct a clinical trial at a prospective site;
- the FDA, EMA or other regulatory authority may require changes to any of our trial designs, our pre-clinical strategy or our manufacturing plans;

- various challenges recruiting and enrolling subjects to participate in clinical trials, including size and nature of subject population, proximity of subjects to clinical sites, eligibility criteria for the trial, budgetary limitations, nature of trial protocol, the patient referral practices of physicians, changes in the readiness of subjects to volunteer for a trial, the availability of approved effective treatments for the relevant disease and competition from other clinical trial programs for similar indications;

- difficulties in maintaining contact with subjects who withdraw from the trial, resulting in incomplete data;

- governmental or regulatory delays and changes in regulatory requirements, policy and guidelines;

- the FDA or other regulatory authorities may impose a clinical hold, or we or our investigators, IRBs, or ethics committees may elect to suspend or terminate clinical research or trials;

- varying interpretations of data by the FDA and foreign regulatory agencies; and

- inaccurate interpretations by us of the FDA's guidance for the clinical and regulatory path for our product candidates.

If changes in regulatory requirements and guidance occur, we may need to significantly amend clinical trial protocols or submit new clinical trial protocols with appropriate regulatory authorities to reflect these changes. Amendments may require us to renegotiate terms with CROs or investigators, or resubmit clinical trial protocols to IRBs or ethics committees for re-examination, which may impact the costs, timing or successful completion of a clinical trial. Our clinical trials may be suspended or terminated at any time by the FDA (for trials in the United States), other regulatory authorities (for trials conducted outside the United States), the IRB /ethics committee overseeing any given clinical trial, any of our clinical trial sites with respect to that site, or us, due to a number of factors, including:

- failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols;

- failing to establish clinical endpoints acceptable to the FDA and other regulatory authorities;

- findings of an inspection of the clinical trial operations or trial sites by the FDA or other regulatory authorities;

- unforeseen issues, including serious adverse events associated with a product candidate, or lack of effectiveness or any determination that a clinical trial presents unacceptable health risks;

- lack of adequate funding to continue the clinical trial due to unforeseen costs or other business decisions; and

- upon a breach or pursuant to the terms of any agreement with, or for any other reason by, current or future collaborators that have responsibility for the clinical development of any of our product candidates.

Moreover, principal investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time and receive compensation in connection with such services. Under certain circumstances, we are required to report some of these relationships to the FDA. The FDA may conclude that a financial relationship between us and a principal investigator has created a conflict of interest or otherwise affected the investigator's conduct of the trial. The FDA may therefore question the integrity of the data generated at the applicable clinical trial site and the utility of the clinical trial itself may be jeopardized. This could result in a delay in approval, or rejection, of our marketing applications by the FDA and may ultimately lead to the denial of marketing approval of one or more of our product candidates.

If we do not succeed in conducting and managing our non-clinical development activities or clinical trials, or in obtaining regulatory approvals, we might not be able to commercialize our product candidates, or might be significantly delayed in doing so, which could have a material adverse effect on our business, prospects, financial condition and results of operations.

The results of previous clinical trials may not be predictive of future results, our progress in trials for one product candidate may not be indicative of progress in trials for other product candidates, and our trials may not be designed so as to support regulatory approval.

We currently have no products approved for sale and we cannot guarantee that we will ever have marketable products. Clinical failure can occur at any stage of clinical development. Clinical trials may produce negative or inconclusive results, and we or any of our current and future collaborators may decide, or regulators may require us, to conduct additional clinical or non-clinical testing. We will be required to demonstrate with substantial evidence through well-controlled clinical trials that our product candidates are safe and effective for use in a diverse population before we can obtain regulatory approvals for their commercial sale. Success in early clinical trials does not mean that future clinical trials will be successful because product candidates in later-stage clinical trials may fail to demonstrate sufficient safety and efficacy to the satisfaction of the FDA and other regulatory authorities despite having progressed through initial clinical trials. Product candidates that have shown promising results in early clinical trials may still suffer significant setbacks in subsequent clinical trials. Similarly, the outcome of non-clinical testing and early clinical trials may not be predictive of the success of later clinical trials, and interim results of a clinical trial do not necessarily predict final results. Progress in trials of one product candidate does not indicate that we will make similar progress in additional trials for that product candidate or in trials for our other product candidates. A number of companies in the pharmaceutical industry, including those with greater resources and experience than us, have suffered significant setbacks in advanced clinical trials, even after obtaining promising results in earlier clinical trials.

The design of a clinical trial can determine whether its results will support approval of a product. We may be unable to design and/or execute a clinical trial to support regulatory approval. Flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced or completed. In addition, we or our investigators may have little control over whether subjects comply with important aspects of clinical trial protocols. In particular, in trials of our oral PTH, if subjects do not comply with restrictions on eating and drinking before and after administration of our product candidates, interaction between the drug and food in the gastrointestinal tract, or a "food effect," may decrease the bioavailability and increase the variability of drug delivered to the subject, which may negatively impact efficacy.

In some instances, there can be significant variability in safety and/or efficacy results between different trials of the same product candidate due to numerous factors, including changes in trial protocols, differences in size and type of the patient populations, adherence to the dosing regimen and other trial protocols, modifications in the formulation throughout the course of development and the rate of dropout among clinical trial participants. While we have not had any serious adverse events in our clinical trials to date that are believed to be related to our oral PTH product candidates, we may need to change future trial designs in response to adverse events that occur during future clinical development. We do not know whether any Phase 2, Phase 3 or other clinical trials we or any of our collaborators may conduct will demonstrate consistent or adequate efficacy and safety to obtain regulatory approval to market our product candidates.

Even if regulatory approvals are obtained for our product candidates, we will be subject to ongoing government regulation. If we fail to comply with applicable current and future laws and government regulations, it could delay or prevent the promotion, marketing or sale of our products.

Even if marketing approval is obtained for our product candidates, a regulatory authority may still impose significant restrictions on a product's indications, conditions for use, distribution or marketing or impose ongoing requirements for potentially costly post-market surveillance, post-approval studies or clinical trials, all of which may result in significant expense and limit our ability to commercialize our products. Our products will also be subject to ongoing requirements governing the labeling, packaging, storage, advertising, distribution, promotion, recordkeeping and submission of safety and other post-market information, including adverse events, and any changes to the approved product, product labeling or manufacturing process. In addition, manufacturers of drug products and their facilities are subject to continual review and periodic inspections by the FDA and other regulatory authorities for compliance with cGMP, requirements and other regulations.

If we, our drug products or the manufacturing facilities for our drug products, fail to comply with applicable regulatory requirements, a regulatory agency may:

- issue warning letters or untitled letters or take similar enforcement actions;
- seek an injunction or impose civil or criminal penalties or monetary fines;
- suspend or withdraw marketing approval;
- suspend any ongoing clinical trials;
- refuse to approve pending applications or supplements to applications;
- suspend or impose restrictions on operations, including costly new manufacturing requirements;
- seize or detain products, refuse to permit the import or export of products, exclude products from federal healthcare programs, or request that we initiate a product recall; or
- refuse to allow us to enter into supply contracts, including government contracts.

We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad, and compliance with such regulation may be expensive and consume substantial financial and management resources. If we or any future marketing collaborators or contract manufacturers are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies or are not able to maintain regulatory compliance, it could delay or prevent the promotion, marketing or sale of our products, which would adversely affect our business and results of operations.

In order to obtain FDA approval for EB612 prior to the expiration of Natpara's orphan drug exclusivity in 2022, we may need to show that EB612 is clinically superior or otherwise makes a major contribution to patient care. Moreover, although we have obtained orphan drug designation for EB612 for the treatment of hypoparathyroidism, we may be unable to maintain the benefits associated with orphan drug designation, including the potential for market exclusivity.

Regulatory authorities in some jurisdictions, including the United States and Europe, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a product candidate as an orphan drug if it is a drug intended to treat a rare disease or condition, which is generally defined as a condition that affects fewer than 200,000 individuals in the United States or that affects more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making available the drug for the disease or condition will be recovered from sales of the drug in the United States. In the EU, the European Commission may designate a product candidate as an orphan medicinal product if it is a medicine for the diagnosis, prevention or treatment of life-threatening or very serious conditions that affects not more than five in 10,000 persons in the EU, or it is unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development and no satisfactory method of diagnosis, prevention or treatment of the condition concerned is authorized, or, if such method exists, that the medicinal product will be of significant benefit to those affected by the condition. We have received orphan drug designation for oral PTH, specifically human PTH (1-34), for the treatment of hypoparathyroidism from the FDA, but orphan drug designation may not ensure that we have market exclusivity in a particular market and there is no assurance we will be able to receive orphan drug designation for any additional oral PTH product candidates for the treatment of other diseases. Further, the granting of a request for orphan drug designation does not alter the standard regulatory requirements and process for obtaining marketing approval, including the development time or regulatory review time of a drug.

Generally, if a product candidate with an orphan drug designation receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which, subject to certain exceptions, precludes the FDA from approving another drug with the same active moiety for the same indication for that time period or precludes the EMA, and other national authorities in the EU, from accepting the marketing application for a similar medicinal product for the same indication. The applicable period is seven years in the United States and 10 years in the EU. The EU period can be reduced to six years if, at the end of the fifth year of marketing exclusivity, a product no longer meets the criteria for orphan drug designation, for instance if the product is sufficiently profitable so that market exclusivity is no longer justified. In the EU, orphan exclusivity may also be extended for an additional two years (i.e., a maximum of 12 years orphan exclusivity) if the product is approved on the basis of a dossier that includes pediatric clinical trial data generated in accordance with an approved pediatric investigation plan. Orphan drug exclusivity may be lost in the United States if the FDA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition.

Orphan drug exclusivity may not effectively protect the product from competition because exclusivity can be suspended under certain circumstances. In the United States, even after an orphan drug is approved, the FDA can subsequently approve another drug with the same active moiety for the same condition if the FDA concludes that the later drug is clinically superior in that it is shown to be safer, more effective or otherwise makes a major contribution to patient care. In the EU, orphan exclusivity will not prevent a marketing authorization being granted for a similar medicinal product in the same indication if the new product is safer, more effective or otherwise clinically superior to the first product or if the marketing authorization holder of the first product is unable to supply sufficient quantities of the product.

We believe that our key competitor in hypoparathyroidism treatment is Takeda Pharmaceutical Company Ltd., whose product Natpara, an injectable bioengineered recombinant form of PTH (1-84), was approved by the FDA in January 2015, and conditionally approved by the EMA in April 2017. Natpara had been granted orphan drug designation for hypoparathyroidism by the FDA which expired on January 23, 2022, and has 10 years market exclusivity after receipt of market approval in the EU. We believe that we will be able to demonstrate to the satisfaction of the EMA that our formulation of PTH is clinically superior to Natpara, and therefore we do not believe that the EMA will be precluded from approving a marketing application prior to Natpara's expiration of orphan exclusivity, but there can be no assurance that we will be able to demonstrate that EB612 is clinically superior to Natpara or otherwise makes a major contribution to patient care, under the applicable EMA standards and obtain regulatory approval even if EB612 would otherwise satisfy each regulator's standards for approval. On September 5, 2019, Natpara was recalled in the United States due to certain manufacturing issues. Natpara is currently undergoing post-approval studies and the recall may be lifted at any time.

Even if we obtain regulatory approval of EB612, we may not enjoy the benefits of our orphan designation for EB612 for hypoparathyroidism. Regulatory approval of EB612 would not create exclusivity vis-a-vis Natpara, and we would still have to compete with Natpara for market acceptance and on other factors that contribute to commercial success, such as reimbursement. Moreover, even if we obtain orphan drug exclusivity for EB612 vis-à-vis other products in development, that exclusivity may not effectively protect EB612 from competition because different drugs with different active moieties can be approved for the same condition. Even after an orphan drug is approved, the FDA or EMA can subsequently approve the same drug with the same active moiety for the same condition if the FDA or EMA concludes that the later drug is safer, more effective, or otherwise makes a major contribution to patient care.

Healthcare legislative changes may harm our business and future prospects.

Healthcare costs have risen significantly over the past decade. Globally, governments are becoming increasingly aggressive in imposing health care cost-containment measures. Certain proposals, if passed, would impose limitations on the prices we will be able to charge for the products that we are developing, or the amounts of reimbursement available for these products from governmental agencies or third-party payors. These limitations could in turn reduce the amount of revenues that we will be able to generate in the future from sales of our products and licenses of our technology.

In the United States, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or MMA, changed the way Medicare covers and pays for pharmaceutical products. The MMA expanded Medicare coverage for outpatient drug purchases by those covered by Medicare under a new Part D and introduced a new reimbursement methodology based on average sales prices for Medicare Part B physician-administered drugs. In addition, the MMA authorized Medicare Part D prescription drug plans to limit the number of drugs that will be covered in any therapeutic class. As a result of this legislation and the expansion of federal coverage of drug products, we expect that there will be additional pressure to contain and reduce costs. These cost reduction initiatives and other provisions of the MMA could decrease the coverage and price that we receive for any approved products and could seriously harm our future business prospects. While this law applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates, and any reduction in reimbursement that results from this law may result in a similar reduction in payments from private payors.

In March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively, the ACA, a sweeping law intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for health care and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms. The ACA, among other things, increased rebates a manufacturer must pay to the Medicaid program, addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected, established a new Medicare Part D coverage gap discount program, in which manufacturers must provide 75% point-of-sale discounts on products covered under Part D and implemented payment system reforms including a national pilot program on payment bundling to encourage hospitals, physicians and other providers to improve the coordination, quality and efficiency of certain healthcare services through bundled payment models. Further, ACA imposed a significant annual fee on companies that manufacture or import branded prescription drug products. Substantial new provisions affecting compliance were enacted, which may affect our business practices with health care practitioners. The ACA appears likely to continue the pressure on pharmaceutical pricing and may also increase our regulatory burdens and operating costs.

In addition, other legislative changes have been proposed and adopted in the United States since the ACA was enacted. In 2011, the U.S. Congress enacted the Budget Control Act of 2011, or the Budget Control Act, which included provisions intended to reduce the federal deficit. The Budget Control Act resulted in the imposition of 2% reductions in Medicare payments to providers beginning in 2013 and, due to subsequent legislative amendments to the statute, will remain in effect through 2027 absent additional congressional action. However, pursuant to the CARES Act, and subsequent legislation, these reductions are suspended from May 1, 2020 through March 31, 2022 due to the COVID-19 pandemic. In January 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, reduced Medicare payments to several providers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding, which could have a material adverse effect on customers for our drugs, if approved, and accordingly, our financial operations. If government spending is further reduced, anticipated budgetary shortfalls may also impact the ability of relevant agencies, such as the FDA, to continue to function at current levels, which may impact the ability of relevant agencies to timely review and approve research and development, manufacturing and marketing activities, which may delay our ability to develop, market and sell any product candidates we may develop. In addition, any significant spending reductions affecting Medicare, Medicaid or other publicly funded or subsidized health programs that may be implemented, or any significant taxes or fees that may be imposed on us, as part of any broader deficit reduction effort or legislative replacement to the Budget Control Act, could have an adverse impact on our anticipated product revenues.

There have been changes and modifications to certain aspects of the ACA, and we expect such changes and modifications to continue. In 2017, the U.S. Congress enacted the Tax Cuts and Jobs Act, or the 2017 Tax Act, which eliminated the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the “individual mandate.” On January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain fees mandated by the ACA, including the so-called “Cadillac” tax on certain high cost employer-sponsored insurance plans and the annual fee imposed on certain health insurance providers based on market share. The Bipartisan Budget Act of 2018, or the BBA, among other things, amended the ACA, effective January 1, 2019, to close the coverage gap in most Medicare drug plans. In July 2018, CMS, published a final rule permitting further collections and payments to and from certain ACA qualified health plans and health insurance issuers under the ACA risk adjustment program in response to the outcome of federal district court litigation, regarding the method CMS uses to determine this risk adjustment. On January 28, 2021, President Biden issued an executive order to initiate a special enrollment period from February 15, 2021 through May 15, 2021 for purposes of obtaining health insurance coverage through the ACA marketplace. The executive order also instructs certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA. Changes and modifications to the ACA are likely to continue, with unpredictable and uncertain results.

Recently, there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their commercial products. There have been several recent U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the cost of drugs under Medicare, and reform government program reimbursement methodologies for drugs. On September 24, 2020, the FDA released a final rule providing guidance for states to build and submit importation plans for drugs from Canada. Further, on November 20, 2020, the U.S. Department of Health and Human Services, or HHS, finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

On November 20, 2020, the HHS Office of Inspector General finalized further modifications to the federal Anti-Kickback Statute. Under the final rules, the HHS Office of Inspector General added safe harbor protections under the Anti-Kickback Statute for certain coordinated care and value-based arrangements among clinicians, providers, and others, yet removed safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers. This rule (with exceptions) became effective January 19, 2021. We continue to evaluate what effect, if any, these rules will have on our business. CMS issued a final rule, effective on July 9, 2019, that requires direct-to-consumer advertisements of prescription drugs and biological products, for which payment is available through or under Medicare or Medicaid, to include in the advertisement the Wholesale Acquisition Cost, or list price, of that drug or biological product if it is equal to or greater than $35 for a monthly supply or usual course of treatment. Prescription drugs and biological products that are in violation of these requirements will be included on a public list. Any adopted health reform measure could reduce the ultimate demand for our products, if approved, or put pressure on our product pricing. Individual states in the United States have also become increasingly active in passing legislation and implementing regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs. We expect that additional state and federal healthcare reform measures will be adopted in the future.

The delivery of healthcare in the EU, including the establishment and operation of health services and the pricing and reimbursement of medicines, is almost exclusively a matter for national, rather than EU, law and policy. National governments and health service providers have different priorities and approaches to the delivery of health care and the pricing and reimbursement of products in that context. In general, however, the healthcare budgetary constraints in most EU member states have resulted in restrictions on the pricing and reimbursement of medicines by relevant health service providers. Coupled with ever-increasing EU and national regulatory burdens on those wishing to develop and market products, this could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to commercialize any products for which we obtain marketing approval. Both in the United States and in the EU, legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We do not know whether additional legislative changes will be enacted, or whether the regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be.

Our relationships with customers and payors are subject to applicable anti-kickback, fraud and abuse and other healthcare laws and regulations, which, if violated, could expose us to criminal sanctions, civil penalties, exclusion from government healthcare programs, contractual damages, reputational harm and diminished profits and future earnings.

Healthcare providers, physicians and others will play a primary role in the recommendation and prescription of any products for which we obtain marketing approval. Our future arrangements with third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations, primarily in the United States, that may constrain the business or financial arrangements and relationships through which we market, sell and distribute our products for which we obtain marketing approval. Restrictions under applicable healthcare laws and regulations, include the following:

- the federal Anti-Kickback Statute prohibits, among other things, the knowing and willful offer, payment, solicitation or receipt of any form of remuneration in return for, or to induce, (i) the referral of a person, (ii) the furnishing or arranging for the furnishing of items or services reimbursable under the Medicare, Medicaid or other governmental programs, or (iii) the purchase, lease or order or arranging or recommending purchasing, leasing or ordering of any item or service reimbursable under the Medicare, Medicaid or other governmental programs. A person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act;

- the federal False Claims Act imposes civil penalties, and provides for civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;

- HIPAA imposes criminal and civil liability for executing a scheme to defraud any health care benefit program or making false statements relating to health care matters. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;

- the federal false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for health care benefits, items or services;

- the Physician Payments Sunshine Act, created under the ACA, and its implementing regulations, which requires specified manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program, with specific exceptions, to report annually to CMS information related to payments or other "transfers of value" made to physicians. All such reported information is publicly available;

- analogous state and non-U.S. laws and regulations, such as certain state anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payor, including commercial insurers; state laws that require pharmaceutical companies to comply with the industry's voluntary compliance guidelines and the applicable compliance guidance promulgated by the federal government or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts; and

- regulation by the CMS and enforcement by the HHS Office of Inspector General or the U.S. Department of Justice.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our future business activities could be subject to challenge under one or more of such laws.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, exclusion from U.S. government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other providers or entities with whom we expect to do business with are found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

Risks Related to Commercialization of Our Product Candidates

We are likely to face significant competition, and if our competitors' products are more effective, safer or less expensive than ours, our commercial opportunities will be negatively affected. Our lead product candidates, if approved, would compete with existing products.

Our industry is highly competitive and subject to rapid and significant technological change. While we believe that our technology, knowledge, experience and scientific resources provide us with competitive advantages, we face competition from many different sources, including large pharmaceutical, specialty pharmaceutical, biotechnology and generic drug companies and academic and government institutions. These organizations may have significantly greater resources than we do and conduct similar research, seek and obtain patent protection that may impact our freedom to operate and establish collaborative arrangements for research, development, manufacturing and marketing of products that compete with our product candidates. We believe that the key competitive factors that will affect the development and commercial success of our oral PTH product candidates, and any other product candidates that we develop, are efficacy, safety and tolerability profile, convenience in dosing, product labeling, price and availability of reimbursement from the government and other third-parties. Our commercial opportunity could be reduced or eliminated if our competitors have products that are better in one or more of these categories. Furthermore, our competitors may, among other things, develop and commercialize products that are safer, more effective, less expensive, or more convenient or easier to administer, obtain quicker regulatory approval, establish superior proprietary positions, have access to more manufacturing capacity, implement more effective approaches to sales and marketing, or form more advantageous strategic alliances.

Our primary innovation is our development of an oral drug delivery technology for large peptides, protein and other large molecules. If another company develops an alternative technology for oral delivery of such molecules that is equal to or better than our technology, we may be unable to compete.

The osteoporosis market is already served by a variety of competing products based on a number of APIs. Many of these existing products have achieved widespread acceptance among physicians, patients and payors for the treatment of osteoporosis. The market has been dominated by bisphosphonates for many years, although bisphosphonates' market share has declined due to the occurrence of rare but potentially serious side effects, as well as the introduction of newly developed pharmacological treatments. Many of the new drugs have serious side effects of their own. Eli Lilly's Forteo, an injectable PTH (1-34), is one of the most effective osteoporosis medications, and newer products such as Prolia® and EVENITY® have been launched by Amgen Inc., or Amgen. We anticipate that our product candidate EB613, if approved, will compete with Forteo, Prolia, EVENITY, and the rest of the pharmacological treatments for osteoporosis. Many of these products are available on a generic basis, and EB613 may not demonstrate sufficient additional clinical benefits to physicians, patients or payors as compared to generic products. In many cases, insurers or other third-party payors, particularly Medicare, seek to encourage the use of generic products. Furthermore, our competitors in this market are large pharmaceutical companies and the alternatives have been on the market for many years and have widespread market acceptance.

We believe that our key competitor in hypoparathyroidism treatment is Natpara. If we obtain regulatory approval for EB612, it will compete with Natpara, which by that time will have been marketed for several years and may have wide-spread market acceptance that may be difficult to overcome. Moreover, although we have obtained orphan drug designation for EB612 for the treatment of hypoparathyroidism, we may be unable to maintain the benefits associated with orphan drug designation, including the potential for market exclusivity. In addition, Ascendis Pharma has reported that it is developing a long-acting, oral prodrug formulation of PTH for the treatment of hypoparathyroidism. In August 2020, Ascendis reported on top-line results from a global Phase 2 trial, and anticipates initiating a Phase 3 trial by the end of 2021 or 2022.

We are subject to manufacturing risks that could substantially increase our costs and limit supply of our products.

The process of manufacturing our products is complex, highly regulated and subject to several risks, including:

- We do not have experience in manufacturing our product candidates at commercial scale. We may not succeed in the scaling up of our final manufacturing process. We may need a larger-scale manufacturing process for our oral PTH than what we have planned, depending on the dose and regimen that will be determined in future studies. Any changes in our manufacturing processes as a result of scaling up may result in the need to obtain additional regulatory approvals. Difficulties in achieving commercial-scale production or the need for additional regulatory approvals as a result of scaling up could delay the development and regulatory approval of our product candidates and ultimately affect our success. Contract manufacturers may not have sufficient expertise to manufacture a dry oral formulation with a large molecule API, in which case we may have to establish our own commercial manufacturing capabilities, which could be expensive and delay launch of product candidates.

- The manufacturing process for large molecules is more complex and subject to greater regulation than that of other drugs. The process of manufacturing large molecules, such as our product candidates, is extremely susceptible to product loss due to contamination, equipment failure or improper installation or operation of equipment, vendor or operator error, inconsistency in yields, variability in product characteristics and difficulties in scaling the production process. Even minor deviations from normal manufacturing processes could result in reduced production yields, product defects and other supply disruptions. If microbial, viral or other contaminations are discovered in our product candidates or in the manufacturing facilities in which our product candidates are made, such manufacturing facilities may need to be closed for an extended period of time to investigate and remedy the contamination.

- The manufacturing facilities in which our product candidates are made could be adversely affected by equipment failures, labor shortages, natural disasters, power failures, outbreaks of an infectious disease such as COVID-19 and numerous other factors.

- We and our contract manufacturing organizations, or CMOs, must comply with applicable current cGMP regulations and guidelines. We and our CMOs may encounter difficulties in achieving quality control and quality assurance and may experience shortages in qualified personnel. We and our CMOs are subject to inspections by the FDA and comparable agencies in other jurisdictions to confirm compliance with applicable regulatory requirements. Any failure to follow cGMP or other regulatory requirements or delay, interruption or other issues that arise in the manufacture, fill-finish, packaging, or storage of our product candidates as a result of a failure of our facilities or the facilities or operations of third parties to comply with regulatory requirements or pass any regulatory authority inspection could significantly impair our ability to develop and commercialize our product candidates, including leading to significant delays in the availability of drug product for our clinical trials or the termination or hold on a clinical trial, or the delay or prevention of a filing or approval of marketing applications for our product candidates. Significant noncompliance could also result in the imposition of sanctions, including fines, injunctions, civil penalties, failure of regulatory authorities to grant marketing approvals for our product candidates, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of products, operating restrictions and criminal prosecutions, any of which could damage our reputation. If we are not able to maintain regulatory compliance, we may not be permitted to market our product candidates and/or may be subject to product recalls, seizures, injunctions, or criminal prosecution.

- Any adverse developments affecting manufacturing operations for our product candidates, if any are approved, may result in shipment delays, inventory shortages, lot failures, product withdrawals or recalls, or other interruptions in the supply of our products. We may also have to take inventory write-offs and incur other charges and expenses for products that fail to meet specifications, undertake costly remediation efforts or seek more costly manufacturing alternatives.

- Our product candidates that have been produced and are stored for later use may degrade, become contaminated or suffer other quality defects, which may cause the affected product candidates to no longer be suitable for their intended use in clinical trials or other development activities. If the defective product candidates cannot be replaced in a timely fashion, we may incur significant delays in our development programs that could adversely affect the value of such product candidates.

We currently have no sales, marketing or distribution infrastructure. Any failure or delay in the development of our internal sales, marketing and distribution capabilities would adversely affect the commercialization of our products. If we enter into collaborations to market and sell any approved products, our revenue may be lower and we will be dependent on the efforts of a third party.

We have not yet established sales, marketing or distribution operations because our product candidates are in the early to mid-stages of clinical development. If our product candidates are approved and we were to commercialize these products, such activities would be expensive and time consuming. If we elect to fund and undertake commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms or at all. In addition, the costs of establishing sales and marketing operations may be incurred in advance of any approval of our product candidates. Moreover, we may not be able to hire a sales force that is sufficient in size or has adequate expertise in the medical markets that we intend to target. Any failure or delay in the development of our internal sales, marketing and distribution capabilities would adversely affect the commercialization of our products.

Alternatively, we may consider entering into a collaboration to commercialize our oral PTH candidates globally or in selected regions. Any such collaborator would be responsible for, or substantially support, late stage clinical trials of our oral PTH product candidates, as well as regulatory approvals and registrations. These arrangements are typically complex and time consuming to negotiate. To the extent that we enter into collaboration agreements with respect to marketing, sales or distribution, our product revenue may be lower than if we directly marketed and sold any approved products. In addition, any revenue we receive will depend in whole or in part upon the efforts of these third-party collaborators, which may not be successful and are generally not within our control. If we are unable to enter into these arrangements on acceptable terms or at all, we may not be able to successfully commercialize any approved products. If we are not successful in commercializing any approved products, either on our own or through collaborations with one or more third parties, our future product revenue will suffer and we may incur significant additional losses.

Even if approved, if any of our product candidates do not achieve broad market acceptance among physicians, patients, the medical community and third-party payors, our revenue generated from their sales will be limited.

The commercial success of our product candidates will depend upon their acceptance among physicians, patients and the medical community. The degree of market acceptance of our product candidates will depend on a number of factors, including:

- limitations or warnings contained in the approved labeling for a product candidate;
- changes in the standard of care for the targeted indications for any of our product candidates;
- limitations in the approved clinical indications for our product candidates;
- demonstrated clinical safety and efficacy compared to other products;
- lack of significant adverse side effects;
- sales, marketing and distribution support;
- availability and extent of coverage and reimbursement from managed care plans and other third-party payors;
- timing of market introduction and perceived effectiveness of competitive products;
- the degree of cost-effectiveness of our product candidates;
- availability of alternative therapies at similar or lower cost, including generic and over-the-counter products;
- the extent to which the product candidate is approved for inclusion on formularies of hospitals and third-party payors, including managed care organizations;
- whether the product is designated under physician treatment guidelines as a first-line therapy or as a second- or third-line therapy for particular diseases;
- adverse publicity about our product candidates or favorable publicity about competitive products;
- convenience and ease of administration of our products; and
- potential product liability claims.

If any of our product candidates are approved, but do not achieve an adequate level of acceptance by physicians, patients and the medical community, we may not generate sufficient revenue from these products, and we may not become or remain profitable. In addition, efforts to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources and may never be successful.

Even if we obtain regulatory approval of any of our product candidates in a major pharmaceutical market such as the United States or the EU, we may never obtain approval or commercialize our products in other major markets, which would limit our ability to realize their full market potential.

In order to market any products in a country or territory, we must establish and comply with numerous and varying regulatory requirements of such countries or territories regarding safety and efficacy. Clinical trials conducted in one country may not be accepted by regulatory authorities in other countries, and regulatory approval in one country does not mean that regulatory approval will be obtained in any other country. Approval procedures vary among countries and can involve additional product testing and validation and additional administrative review periods. Seeking regulatory approvals in all major markets could result in significant delays, difficulties and costs for us and may require additional preclinical studies or clinical trials which would be costly and time consuming. Regulatory requirements can vary widely from country to country and could delay or prevent the introduction of our products in those countries. Satisfying these and other regulatory requirements is costly, time consuming, uncertain and subject to unanticipated delays. In addition, our failure to obtain regulatory approval in any country may delay or have negative effects on the process for regulatory approval in other countries. We do not have any product candidates approved for sale in any jurisdiction, including international markets, and we do not have experience in obtaining regulatory approval in international markets. If we fail to comply with regulatory requirements in international markets or to obtain and maintain required approvals, our target market will be reduced and our ability to realize the full market potential of our products will be harmed.

The successful commercialization of our product candidates, if approved, will depend in part on the extent to which governmental authorities and third-party payors establish adequate coverage and reimbursement levels and pricing policies.

The successful commercialization of our product candidates, if approved, will depend, in part, on the extent to which coverage and reimbursement for our products will be available from government and health administration authorities, private health insurers and other third-party payors. To manage healthcare costs, many governments and third-party payors increasingly scrutinize the pricing of new technologies and require greater levels of evidence of favorable clinical outcomes and cost-effectiveness before extending coverage. In light of such challenges to prices and increasing levels of evidence of the benefits and clinical outcomes required of new technologies, we cannot be sure that coverage will be available for our oral PTH product candidates, if approved, or any other product candidate that we commercialize and, if available, that the reimbursement rates will be adequate. If we are unable to obtain adequate levels of coverage and reimbursement for our product candidates, their marketability will be negatively and materially impacted.

Reimbursement may impact the demand for, or the price of, any product for which we obtain marketing approval. In addition, third-party payors are likely to impose strict requirements for reimbursement in order to limit off-label use of a higher priced drug. Reimbursement by a third-party payor may depend upon a number of factors, including the third-party payor's determination that use of a product is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

Third party payors may deny coverage and reimbursement status altogether of a given drug product, or cover the product but establish prices at levels that are too low to enable us to realize an appropriate return on our investment in product development. Because the coverage and reimbursement policies may change frequently, in some cases at short notice, even when there is favorable coverage and reimbursement, future changes may occur that adversely impact the favorable status. Further, the net reimbursement for drug products may be subject to additional reductions if there are changes to laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States.

The unavailability or inadequacy of third-party coverage and reimbursement could have a material adverse effect on the market acceptance of our product candidates and the future revenues we may expect to receive from those product candidates. In addition, we are unable to predict what additional legislation or regulation relating to the healthcare industry or third-party coverage and reimbursement may be enacted in the future, or what effect such legislation or regulation would have on our business.

Obtaining coverage and reimbursement approval for a product from a government or other third-party payors is a time-consuming and costly process that could require us to provide supporting scientific, clinical and cost effectiveness data for the use of our products to the payor. We may not be able to provide data sufficient to gain acceptance with respect to coverage and reimbursement. We cannot be sure that coverage or adequate reimbursement will be available for our product candidates, if approved. Also, we cannot be sure that reimbursement amounts will not reduce the demand for, or the price of, our future products. If reimbursement is not available, or is available only to limited levels, we may not be able to commercialize our product candidates, profitably or at all, even if approved.

We may become exposed to costly and damaging liability claims, either when testing our product candidates in the clinic or at the commercial stage; and our product liability insurance may not cover all damages from such claims.

We are exposed to potential product liability and professional indemnity risks that are inherent in the research, development, manufacturing, marketing and use of pharmaceutical products. Currently we have no products that have been approved for commercial sale; however, the current and future use of product candidates by us in clinical trials, and the sale of any approved products in the future, may expose us to liability claims. These claims might be made by patients that use the product, healthcare providers, pharmaceutical companies, our collaborators or others selling such products. Any claims against us, regardless of their merit, could be difficult and costly to defend and could materially adversely affect the market for our product candidates or any prospects for commercialization of our product candidates. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for any of our product candidates or products we develop;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants or cancellation of clinical trials;
- costs to defend the related litigation, which may be only partially recoverable even in the event of successful defense;

- a diversion of management's time and our resources;
- substantial monetary awards to trial participants or patients;
- regulatory investigations, product recalls, withdrawals or labeling, marketing or promotional restrictions;
- loss of revenues; and
- the inability to commercialize any products we develop.

Although the clinical trial process is designed to identify and assess potential side effects, it is always possible that a drug, even after regulatory approval, may exhibit unforeseen side effects. If any of our product candidates were to cause adverse side effects during clinical trials or after approval of the product candidate, we may be exposed to substantial liabilities. Physicians and patients may not comply with any warnings that identify known potential adverse effects and patients who should not use our product candidates.

Although we maintain limited product liability insurance for our product candidates, it is possible that our liabilities could exceed our insurance coverage. We intend to expand our insurance coverage to include the sale of commercial products if we obtain marketing approval for any of our product candidates. However, we may not be able to maintain insurance coverage at a reasonable cost or obtain insurance coverage that will be adequate to satisfy any liability that may arise. If a successful product liability claim or series of claims is brought against us for uninsured liabilities or in excess of insured liabilities, our assets may not be sufficient to cover such claims and our business operations could be impaired.

Should any of the events described above occur, this could have a material adverse effect on our business, financial condition and results of operations.

Risks Related to Our Dependence on Third Parties

We are highly dependent upon our ability to enter into agreements with collaborators to develop, commercialize and market our products.

We may enter into collaborations with third parties that we believe could provide us with funding, research support, and other milestone payments. For example, we have entered into a research collaboration and license agreement with Amgen. Under the agreement, we have agreed to collaborate with Amgen for the development and discovery of clinical candidates in the field of inflammatory disease and other serious illnesses. Further, under the terms of the agreement, we will engage in formulation and preclinical development at Amgen's expense. Amgen will be responsible for subsequent research, clinical development, manufacturing and commercialization of any of the resulting programs, at its expense. We also anticipate seeking a collaborator to develop EB613 for osteoporosis and that any such collaborator would be responsible for, or substantially support, late stage clinical trials of EB613 as well as regulatory approvals and registrations and any potential commercialization activities.

We face significant competition in seeking appropriate collaborators. Our ability to reach a definitive agreement for a collaboration will depend upon, among other things, our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. These factors may include the design or results of clinical trials, the likelihood of approval by the FDA, the EMA or similar regulatory authorities, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing products, the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge and industry and market conditions generally. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available for collaboration and whether such a collaboration could be more attractive than the one with us for our product candidate.

Collaborations are complex and time-consuming to negotiate and document. If we are unable to reach agreements with suitable collaborators on a timely basis, on acceptable terms, or at all, we may have to curtail the development of a product candidate, reduce or delay one or more of our other development programs, delay potential commercialization of a product candidate or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities ourselves, we may not be able to further develop our product candidates or bring them to market or continue to develop our technology platforms and our business may be materially and adversely affected.

Any collaboration we enter into may pose a number of risks, including the following:

- Collaborators may have significant discretion in determining the efforts and resources that they will apply to these collaborations;

- Collaborators may not perform their obligations as expected;

- Collaborators may not pursue development and commercialization of any product candidates that achieve regulatory approval or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborators' strategic focus or available funding, or external factors, such as an acquisition, that divert resources or create competing priorities;

- Collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;

- Collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our products or product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;

- Product candidates discovered in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to cease to devote resources to the commercialization of our product candidates;

- A collaborator with marketing and distribution rights to one or more of our product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of such product or products;

- Disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development, might cause delays or termination of the research, development or commercialization of product candidates, might lead to additional responsibilities for us with respect to product candidates, or might result in litigation or arbitration, any of which would be time-consuming and expensive;

- Collaborators may not properly obtain, maintain, defend or enforce our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation or other intellectual property-related proceedings, including proceedings challenging the scope, ownership, validity and enforceability of our intellectual property. For example, Amgen has the first right to enforce or defend certain of our intellectual property rights under our research collaboration and license agreement, and although we may have the right to assume the enforcement and defense of such intellectual property rights if Amgen does not, our ability to do so may be compromised by Amgen's actions;

- Collaborators may own or co-own intellectual property covering our product candidates or research programs that results from our collaboration with them, and in such cases, we may not have the exclusive right to commercialize such intellectual property or such product candidates or research programs;

- Collaborators may infringe, misappropriate or otherwise violate the intellectual property rights of third parties, which may expose us to litigation and potential liability;

- Collaborators may fail to comply with applicable laws, rules or regulations when performing services for us, which may expose us to legal proceedings and potential liability;

- Collaborations may be terminated for convenience by the collaborator and, if terminated, we may suffer from negative publicity and we may find it more difficult to attract new collaborators. For example, at any point in the research and development process, subject to certain conditions, Amgen can terminate our research collaboration and license agreement in its entirety or with respect to a specific development program; and

- The outbreak of COVID-19 may cause us to fail to meet contractually obligated deadlines with our collaboration partners or otherwise strain our relationships with current collaborators or other business partners.

If we enter into collaborations to develop and potentially commercialize any product candidates, we may not be able to realize the benefit of such transactions if we or our collaborator elects not to exercise the rights granted under the agreement or if we or our collaborator are unable to successfully integrate a product candidate into existing operations and company culture. In addition, if our agreement with any of our collaborators terminates, our access to technology and intellectual property licensed to us by that collaborator may be restricted or terminate entirely, which may delay our continued development of our product candidates utilizing the collaborator's technology or intellectual property or require us to stop development of such product candidates completely. We may also find it more difficult to find a suitable replacement collaborator or attract new collaborators, and our development programs may be delayed or the perception of us in the business and financial communities could be adversely affected. All of the risks relating to product development, regulatory approval and commercialization described in this Annual Report also apply to the activities of any of our future program collaborators.

Exclusivity and other governance provisions within our research collaboration and license agreement with Amgen may prevent us from pursuing certain alternative product candidates and exercising complete control over our product candidates' development.

During certain periods under our research collaboration and license agreement with Amgen, we may not, alone or with a third party, research, develop, manufacture or commercialize certain products primarily interacting with the targets of the applicable collaboration programs. Further, our collaboration with Amgen is governed by a joint research committee, or JRC, made up of equal representatives of us and Amgen. The JRC may establish additional subcommittees to oversee particular projects or activities. Subject to limitations specified in the agreement, if the JRC is unable to make a decision by consensus, the disagreement is to be resolved through escalation to specified senior executive officers of the parties, although Amgen has the final decision-making ability with respect to certain specified issues. These exclusivity and governance provisions may inhibit our development efforts and could have a material adverse effect on our business, prospects, financial condition and results of operations.

We may not be able to secure and maintain research institutions to conduct our clinical trials.

We rely on research institutions to conduct our clinical trials. Specifically, the limited number of centers experienced with pharmaceutical product candidates heightens our dependence on such research institutions. Our reliance upon research institutions, including hospitals and clinics, provides us with less control over the timing and cost of clinical trials and the ability to recruit subjects. If we are unable to reach agreements with suitable research institutions on acceptable terms, if any resulting agreement is terminated, if research institutions are closed down by public authorities for reasons outside of our control, such as during the current COVID-19 pandemic, or if we cannot fulfill contractual commitments due to the impact of the COVID-19 pandemic, we may be unable to quickly replace the research institution with another qualified institution on acceptable terms. Furthermore, we may not be able to secure and maintain suitable research institutions to conduct our clinical trials.

Independent clinical investigators and CROs that we engage to conduct our clinical trials may not devote sufficient time or attention to our clinical trials or be able to repeat their past success.

We expect to continue to depend on independent clinical investigators and CROs to conduct our clinical trials. CROs may also assist us in the collection and analysis of data. There is a limited number of third-party service providers that specialize or have the expertise required to achieve our business objectives. Identifying, qualifying and managing performance of third-party service providers can be difficult, time consuming and cause delays in our development programs. These investigators and CROs will not be our employees and we will not be able to control, other than by contract, the amount of resources, including time, which they devote to our product candidates and clinical trials. If independent investigators or CROs fail to devote sufficient resources to the development of our product candidates, or if their performance is substandard, it may delay or compromise the prospects for approval and commercialization of any product candidates that we develop. In addition, the use of third-party service providers requires us to disclose our proprietary information to these parties, which could increase the risk that this information will be misappropriated. Further, the FDA and other regulatory authorities require that we comply with standards and GCP requirements for conducting, recording and reporting clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial subjects are protected. Regulatory authorities enforce these GCPs through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of our CROs fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, EMA or comparable regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with GCP regulations. In addition, our clinical trials must be conducted with product produced under cGMP regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. Failure of clinical investigators or CROs to meet their obligations to us or comply with GCP procedures could adversely affect the clinical development of our product candidates and harm our business.

If the third parties or consultants that assist us in conducting our clinical trials do not perform their contractual duties or obligations, experience work stoppages, do not meet expected deadlines, terminate their agreements with us or need to be replaced, or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical trial protocols or GCPs, or for any other reason, we may need to conduct additional clinical trials or enter into new arrangements with alternative third parties, which could be difficult, costly or impossible, and our clinical trials may be extended, delayed or terminated or may need to be repeated. If any of the foregoing were to occur, we may not be able to obtain, or may be delayed in obtaining, regulatory approval for the product candidates being tested in such trials, and will not be able to, or may be delayed in our efforts to, successfully commercialize these product candidates.

We contract with third parties for the supply of materials used in drug formulation for clinical testing and expect to contract with third parties for the manufacturing of our product candidates for large-scale testing. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or products or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.

We anticipate continuing our engagement of third parties to provide our clinical supply as we advance our product candidates into and through clinical development. We expect in the future to use third parties for the manufacture of our product candidates for clinical testing, as well as for commercial manufacture. We plan to enter into long-term supply agreements with several manufacturers for commercial supplies. We may be unable to reach agreement on satisfactory terms with contract manufacturers to manufacture our product candidates. Additionally, the facilities to manufacture our product candidates must be the subject of a satisfactory inspection before the FDA, the EMA or other regulatory authorities approve an NDA or grant a marketing authorization for the product candidate manufactured at that facility. We will depend on these third-party manufacturers for compliance with the FDA's and EMA's requirements for the manufacture of our finished products. We do not control the manufacturing process of, and are completely dependent on, our contract manufacturers for compliance with cGMPs. If our manufacturers cannot successfully manufacture material that conforms to our specifications and the FDA, European Commission and other regulatory authorities' cGMP requirements, they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities. In addition, we have no control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA or a comparable foreign regulatory authority does not approve these facilities for the manufacture of our product candidates or if it withdraws any such approval in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our product candidates, if approved, and may subject us to recalls or enforcement action for products already on the market.

Our failure or the failure of our third party subcontractors and suppliers to comply with applicable regulations could result in sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our product candidates that we may develop.

Reliance on third-party manufacturers entails risks to which we would not be subject if we manufactured the product candidates ourselves, including:

- the possibility of a breach of the manufacturing agreements by the third parties because of factors beyond our control;
- the possibility that the supply is inadequate or delayed;
- the risk that the third party may enter the field and seek to compete and may no longer be willing to continue supplying;
- the possibility of termination or nonrenewal of the agreements by the third parties before we are able to arrange for a qualified replacement third-party manufacturer; and
- the possibility that we may not be able to secure a manufacturer or manufacturing capacity in a timely manner and on satisfactory terms in order to meet our manufacturing needs.

Any of these factors could cause the delay of approval or commercialization of our product candidates, cause us to incur higher costs or prevent us from commercializing our product candidates successfully. Furthermore, if any of our product candidates are approved and contract manufacturers fail to deliver the required commercial quantities of finished product on a timely basis and at commercially reasonable prices, and we are unable to find one or more replacement manufacturers capable of production at a substantially equivalent cost, in substantially equivalent volumes and quality and on a timely basis, we would likely be unable to meet demand for our products and could lose potential revenue. It may take several years to establish an alternative source of supply for our product candidates and to have any such new source approved by the FDA, the EMA or any other relevant regulatory authorities.

Risks Related to Our Intellectual Property

If we fail to establish, maintain, defend and enforce intellectual property rights with respect to our technology, our business, prospects, financial condition and results of operations may be materially adversely affected.

Our success depends in large part on our ability to obtain and maintain protection with respect to our intellectual property and proprietary technology. Our product candidates utilize our proprietary technology relating to the oral delivery of large molecules for the treatment of certain conditions with oral PTH. We seek to protect our proprietary position by filing patent applications in the United States and certain foreign jurisdictions relating to our product candidates and technologies that are important to our business. This process is expensive, complex and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. If we do not adequately obtain, maintain, protect and enforce our proprietary rights in our technologies, competitors may be able to use our technologies and erode or negate any competitive advantage we may have, which could have a material adverse effect on our business and our ability to achieve profitability.

We have limited patent protection with respect to our product candidates and technologies. We have been issued a patent that contains claims directed to compositions comprising a protein, an absorption enhancer and a protease inhibitor, as well as methods for oral administration of a protein with an enzymatic activity in each of the United States, Australia, Canada, Japan, New Zealand, China, Israel and Russia. Related patent applications are pending in the United States, the EU, Hong Kong, Brazil, China and India. We have also filed six patent applications in various jurisdictions that currently contain claims directed to oral administration technologies, including compositions and drug delivery devices utilizing an absorption enhancer and methods of treating osteoporosis, hypoparathyroidism and bone fractures and related conditions with orally administered parathyroid hormone. We cannot be certain that patents will be issued or granted with respect to any of our pending or future patent applications, or that issued or granted patents will not later be found to be invalid or unenforceable. The patent position of pharmaceutical companies is generally uncertain because it involves complex legal and factual considerations. The standards applied by the United States Patent and Trademark Office, or USPTO, and foreign patent offices in granting patents are not always applied uniformly or predictably, and can change. For example, there is no uniform worldwide policy regarding patentable subject matter or the scope of claims allowable in pharmaceutical or biotechnology patents. Even if our pending patent applications issue as patents, such patents may not cover our product candidates in the United States or in other countries. Accordingly, we cannot predict whether additional patents protecting our technology will issue in the United States or in non-U.S. jurisdictions, or whether any patents that do issue will have claims of adequate scope to provide us with a competitive advantage.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or in patent claims being narrowed, invalidated or held unenforceable, which could limit our ability to stop others from using or commercializing technology and products similar or identical to ours, or limit the duration of the patent protection covering our technology and product candidates. In addition, patents have a limited lifespan. In the United States and most foreign jurisdictions, the natural expiration of a patent is generally 20 years after its effective filing date. Various extensions may be available; however, the life of a patent and the protection it affords is limited. For example, the Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, permits a patent term extension of up to five years beyond the expiration date of a U.S. patent as partial compensation for the useful patent term lost, if any, during the FDA regulatory review process. However, a patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of the product's approval by the FDA, only one patent applicable to an approved drug is eligible for the extension, and only those claims covering the approved drug, a method for using it or a method for manufacturing it may be extended. We may not be granted an extension because we may fail to satisfy applicable requirements and even if we are granted an extension, the applicable time period or the scope of patent protection afforded could be less than we request. In addition, if we encounter delays in obtaining regulatory approvals, the period of time during which we could market a product under patent protection could be reduced. Even if patents covering our product candidates are obtained, once such patents expire, we may be vulnerable to competition from similar or generic products. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, we cannot provide any assurance that any of our issued patents or any patents that may be issued to us in the future will provide sufficient protections for our technology or product candidates, in whole or in part, or will effectively prevent competitors from commercializing similar or identical technologies and products.

Our issued patents may not be sufficient to provide us with a competitive advantage. For example, competitors and other third parties may be able to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner. We may also grant licenses under our intellectual property that may limit our ability to exploit such intellectual property. For example, we are party to a patent transfer agreement, or the Patent Transfer Agreement, with Oramed Ltd., or Oramed, pursuant to which we have granted Oramed an exclusive, worldwide, royalty-free, irrevocable and perpetual license, with the right to sublicense, under certain of our patent rights to develop, manufacture and commercialize covered products or otherwise exploit such patent rights in the fields of diabetes and influenza and we have agreed not to, directly or indirectly, engage in any activities within the fields of diabetes and influenza. Even if such agreement were to be terminated, Oramed would retain its exclusive license under such patent rights.

In the future, we may enter into additional collaborative agreements or license agreements with third parties which may subject us to obligations that must be fulfilled and require us to manage complex relationships with third parties. If we are unable to meet our obligations or manage our relationships with our collaborators under these agreements, our revenue may decrease. From the standpoint of our future strategic collaborators, the strength of the intellectual property under which we may grant licenses can be a determinant of the value of these relationships. If we are unable to secure, protect and enforce our intellectual property, it may become more difficult for us to attract strategic collaborators. The loss or diminution of our intellectual property rights could also result in a decision by future third-party collaborators to terminate their agreements with us. In addition, these agreements may be complex and may contain provisions that could give rise to legal disputes, including potential disputes concerning financial obligations or ownership of intellectual property and data under such agreements. Such disputes can lead to lengthy, expensive litigation or arbitration, requiring us to divert management time and resources to such dispute. Any such development could have a material adverse effect on our business, prospects, financial condition and results of operations.

We may become involved in proceedings to protect or enforce our proprietary rights, which could be expensive and time consuming, and may ultimately be unsuccessful.

Competitors or other third parties may infringe or otherwise violate our patents, trademarks, copyrights or other intellectual property rights. To counter infringement or other violations, we may be required to file claims, which can be expensive and time consuming. Any such claims could provoke these parties to assert counterclaims against us, including claims alleging that we infringe their patents or other intellectual property rights. In addition, in a patent infringement proceeding, a court may decide that one or more of the patents we assert is invalid or unenforceable, in whole or in part, construe the patent's claims narrowly or refuse to prevent the other party from using the technology at issue on the grounds that our patents do not cover the technology. In any intellectual property litigation, even if we are successful, any award of monetary damages or other remedy we receive may not be commercially valuable. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. Third parties may also raise challenges to the validity of our patent claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, post-grant review and *inter partes* review proceedings and equivalent proceedings in foreign jurisdictions such as opposition proceedings. If third parties have prepared and filed patent applications in the United States that also claim technology to which we have rights, we may have to participate in interference proceedings in the USPTO, to determine priority of invention for patent applications filed before March 16, 2013, or in derivation proceedings to determine inventorship for patent applications filed after such date. Such proceedings could result in the revocation of, cancellation of, or amendment to our patents in such a way that they no longer cover our product candidates or provide us with any competitive advantage.

In addition, we may be subject to third-party challenges regarding our exclusive ownership of our intellectual property. If a third party were successful in challenging our exclusive ownership of any of our intellectual property, we may lose our right to use such intellectual property, such third party may be able to license such intellectual property to other third parties, including our competitors, and third parties could market competing products and technology.

In addition, during the course of this kind of litigation or proceedings, there could be public announcements of the results of hearings, motions or other interim proceedings or developments or public access to related documents. If investors perceive these results to be negative, the market price for our Ordinary Shares could be significantly harmed. Any of the foregoing could have a material adverse effect on our competitive position, business, financial conditions, results of operations, and prospects.

Our commercial success depends significantly on our ability to operate without infringing the patents and other proprietary rights of third parties. We may face claims that we are violating the intellectual property rights of others.

Our success will depend in part on our ability to operate without infringing the proprietary rights of third parties. Other entities may have or obtain patents or other proprietary rights that could limit our ability to make, use, sell, offer for sale or import our product candidates and future approved products or impair our competitive position. We may face claims, including from direct competitors, asserting that the commercial use of our technology infringes or otherwise violates the intellectual property rights of others. We cannot be certain that our technologies and processes do not violate the intellectual property rights of others. Third parties may assert infringement claims against us based on existing or future intellectual property rights. We expect that we may increasingly be subject to such claims as our product candidates approach commercialization, and as we gain greater visibility as a public company. We may not be aware of all such intellectual property rights potentially relating to our product candidates and their uses. Thus, we do not know with certainty that our oral PTH (1-34) tablet or any other product candidate, or our commercialization thereof, does not and will not infringe or otherwise violate any third party's intellectual property.

If we were found to infringe or otherwise violate the intellectual property rights of others, we could face significant costs to implement work-arounds, and we cannot provide any assurance that any such work-around would be available or technically equivalent to our current technology. In such cases, we might need to license a third party's intellectual property, and such required licenses might not be available on acceptable terms, or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us and could require us to make substantial licensing and royalty payments. We could be forced, including by court order, to cease commercializing the infringing technology or product. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees if we are found to have willfully infringed a patent or other intellectual property right. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could expose us to similar liabilities and have a similar negative impact on our business.

The pharmaceutical and biotechnology industries have produced a significant number of patents, and it may not always be clear to industry participants, including us, which patents cover various types of products or methods of use. The coverage of patents is subject to interpretation by the courts, and the interpretation is not always uniform or predictable. There is a substantial amount of litigation involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries generally, and these lawsuits can be very time consuming and costly. If we are sued for patent infringement, we would need to demonstrate that our products or methods either do not infringe the patent claims of the relevant patent or that the patent claims are invalid, and we may not be successful in doing so. Proving invalidity is difficult. For example, in the United States, proving invalidity requires a showing of clear and convincing evidence to overcome the presumption of validity enjoyed by issued patents. Even if we are successful in these proceedings, we may incur substantial costs and divert management's time and attention in defending these proceedings, which could have a material adverse effect on our business.

Also, to the extent that our agreements provide that we will defend and indemnify our suppliers, service providers, future strategic collaborators or any other party for claims against them relating to any alleged infringement of the intellectual property rights of third parties in connection with such suppliers', service providers', strategic collaborators' or other parties' use of our technologies, we may incur substantial costs defending and indemnifying such parties to the extent they are subject to these types of claims. Any claims brought against us, any suppliers, service providers, future strategic collaborators or any other party indemnified by us alleging that we have violated the intellectual property of others could have a material adverse effect on our business, prospects, financial condition and results of operations.

We may not be able to protect and enforce our intellectual property rights throughout the world.

We currently have limited patent protection for our product candidates and technologies, and filing, prosecuting, maintaining and defending patents on product candidates in all countries throughout the world would be prohibitively expensive. In addition, we may not pursue or obtain patent protection in all major markets. In addition, the legal systems of some countries, particularly developing countries, do not favor the enforcement of patents and other intellectual property protection, especially those relating to life sciences. This could make it difficult for us to stop the infringement of our other intellectual property rights. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to certain third parties. Furthermore, many countries limit the enforceability of patents against third parties, including government agencies or government contractors. In these countries, patents may provide limited or no benefit.

Competitors may use our technologies in jurisdictions where we have not obtained or are unable to adequately enforce patent protection to develop or commercialize their own products. These products may compete with our future products, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing. Proceedings to enforce our patent rights in such jurisdictions, whether or not successful, could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly, put our patent applications at risk of not issuing and provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

In addition, changes in the law and legal decisions by courts in the United States and foreign countries may affect our ability to obtain adequate protection for our technology and to enforce our intellectual property.

Changes in U.S. patent law could diminish the value of our future patents, if issued, thereby impairing our ability to protect our product candidates.

As is the case with other pharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the pharmaceutical industry involve both technological and legal complexity. Therefore, obtaining and enforcing pharmaceutical patents is costly, time-consuming and inherently uncertain. In addition, the United States has recently enacted wide-ranging patent reform legislation, which includes provisions that affect the way patent applications are prosecuted, redefine prior art, may affect patent litigation, and switch the U.S. patent system from a "first to invent" system to a "first inventor to file" system. It is not clear what, if any, impact such legislation will have on the operation of our business. Additionally, the United States Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by the U.S. Congress, the federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of any U.S. patents that may issue to us in the future, all of which could have a material adverse effect on our business and financial condition.

Intellectual property litigation may lead to unfavorable publicity that harms our reputation and causes the market price of our Ordinary Shares to decline.

During the course of any intellectual property litigation, there could be public announcements of the results of hearings, rulings on motions, and other interim proceedings. If securities analysts or investors regard these announcements as negative, the perceived value of our product candidates or future products, services or intellectual property could be diminished and the market price of our Ordinary Shares may decline as a result. Furthermore, such negative publicity could severely impair our capability to enter into future agreements with key commercial collaborators.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by government patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance fees, renewal fees, annuity fees and various other government fees on patents and/or applications will be due to be paid to the USPTO and various government patent agencies outside of the United States over the lifetime of our owned patents and/or applications and any patent rights we may own or license in the future. The USPTO and various non-U.S. government patent agencies require compliance with several procedural, documentary, fee payment and other similar provisions during the patent application process. In many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. There are situations, however, in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, potential competitors might be able to enter the market and this circumstance could have a material adverse effect on our business.

Under applicable employment laws, we may not be able to enforce covenants not to compete and therefore may be unable to prevent our competitors from benefiting from the expertise of some of our former employees. In addition, our Israeli employees may be entitled to seek compensation for their inventions irrespective of their contractual agreements with us.

Our agreements with our employees and key consultants generally include non-competition provisions. These provisions prohibit such employees and key consultants, if they cease working for us, from competing directly with us or working for our competitors or clients for a limited period of time. We may be unable to enforce these provisions under the laws of the jurisdictions in which our employees and consultants work and it may be difficult for us to restrict our competitors from benefitting from the expertise our former employees or consultants developed while working for us. For example, Israeli courts have required employers seeking to enforce non-compete undertakings of a former employee to demonstrate that the competitive activities of the former employee will harm one of a limited number of material interests of the employer which have been recognized by the courts, such as the secrecy of a company's confidential commercial information or the protection of its intellectual property. If we cannot demonstrate that such interests will be harmed, we may be unable to prevent our competitors from benefiting from the expertise of our former employees or consultants and our ability to remain competitive may be diminished. In addition, a significant portion of our intellectual property has been developed by our employees and consultants in the course of their employment or consulting relationship with us. Under the Israeli Patent Law, 5727-1967, inventions conceived by an employee or consultant during the scope of his or her employment or consulting relationship with a company are regarded as "service inventions." Even when our agreements with our employees and consultants include provisions regarding the assignment and waiver of rights to additional compensation in respect of inventions created within the course of their employment or consulting relationship with us, including in respect of service inventions, we cannot guarantee that such provisions will be upheld by Israeli courts, as a result of uncertainty under Israeli law with respect to the efficacy of such provisions. If we are required to pay additional compensation or face disputes relating to service inventions, our results of operations could be adversely affected.

We may not be able to protect the confidentiality of our technology, which, if disseminated, could negatively impact our plan of operations.

In addition to seeking patent protection, we also rely on trade secret protection and confidentiality agreements to protect proprietary know-how that may not be patentable, processes for which patents may be difficult to obtain and/or enforce, and other elements of our technology. Any disclosure to or misappropriation by third parties of our confidential proprietary information could enable competitors to quickly duplicate or surpass our technological achievements, which would harm our competitive position. While we strive to maintain systems and procedures to protect the confidentiality of our trade secrets and technical know-how, these systems and procedures may fail to provide an adequate degree of protection. For example, although we generally enter into agreements with our employees, consultants, advisors, and other collaborators restricting the disclosure and use of trade secrets, technical know-how and confidential information, we cannot provide any assurance that these agreements will be sufficient to prevent unauthorized use or disclosure of our trade secrets and technical know-how, that these agreements will not be breached or that we have executed agreements with all parties who may have had access to our proprietary information. We may not have adequate remedies in the case of a breach of any such agreements, and our competitors or others may independently develop substantially equivalent or superior proprietary information and techniques or otherwise gain access to our trade secrets or know-how. Monitoring and policing unauthorized use and disclosure of intellectual property is difficult. Further, the laws of certain foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States. As a result, we may encounter significant problems in protecting and defending our intellectual property both in the United States and abroad. If we are unable to prevent material disclosure of the intellectual property related to our technologies to third parties, or if our competitors or other third parties independently develop any of our trade secrets, we will not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, results of operations and financial condition.

We currently have relationships with different consultants who perform research and development activities for us and who are not employed by us, and we may enter into additional relationships of such nature in the future. We have limited control over the activities of these consultants and can expect only limited amounts of their time to be dedicated to our activities. These persons may have consulting, employment or advisory arrangements with other entities that may conflict with or compete with their obligations to us. We typically require our consultants to sign agreements that require such consultants to treat our proprietary information and results of studies as confidential. However, in connection with each such relationship, we may not be able to maintain the confidentiality of our technology, the dissemination of which could hurt our competitive position and results of operations. To the extent that our scientific consultants develop inventions or processes independently that may be applicable to our product candidates, disputes may arise as to the ownership of the proprietary rights to such information, and we may expend significant resources in such disputes and we may not win those disputes.

We may be subject to claims by third parties asserting that we or our employees, consultants or contractors have misappropriated their intellectual property, or claiming ownership of what we regard as our own intellectual property.

Certain of our employees, consultants and contractors were previously employed at other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees, consultants and contractors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or these employees, consultants or contractors have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such employee's, consultant's or contractor's former employer. Litigation may be necessary to defend against these claims and, even if we are successful in defending ourselves, could result in substantial costs to us or be distracting to our management. If we do not succeed with respect to any such claims, in addition to paying monetary damages and possible ongoing royalties, we may lose valuable intellectual property rights or personnel. Any of the foregoing could have a material adverse effect on our competitive position, business, financial conditions, results of operations, and prospects.

In addition, while we typically require our employees, consultants and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own. Further, such assignment agreements may not be self-executing, may be insufficient in scope or may be breached, and we may be forced to bring claims against third parties, or defend claims they may bring against us, to determine the ownership of what we regard as our intellectual property.

If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to management.

If trademarks and trade names related to our product candidates are not adequately protected, then we may not be able to build name recognition in our markets of interest and our business may be adversely affected.

We do not currently own or use any registered trademarks for our product candidates. In the future, our registered or unregistered trademarks or trade names may be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. We may not be able to protect our rights to these trademarks and trade names, which we need to build name recognition by potential collaborators or customers in our markets of interest. Any unauthorized use of these trademarks could harm our reputation or commercial interests. In addition, our enforcement against third-party infringers or violators may be unduly expensive and time-consuming, and the outcome may be an inadequate remedy. Over the long term, if we are unable to establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively and our business may be adversely affected.

Risks Related to Our Ordinary Shares and IPO Warrants

The price of our Ordinary Shares and IPO Warrants may be volatile, and holders of our Ordinary Shares and IPO Warrants could lose all or part of their investment

The price of securities for publicly traded emerging biopharmaceutical and drug discovery and development companies has been highly volatile and is likely to remain highly volatile in the future. The market price of our Ordinary Shares and IPO Warrants on Nasdaq may fluctuate as a result of a number of factors, some of which are beyond our control, including, but not limited to:

- our clinical trial results and the timing of the release of such results;
- the amount of our cash resources and our ability to obtain additional funding;
- the announcement of research activities, business developments, technological innovations or new products, or acquisitions or expansion plans by us or our competitors;
- the success or failure of our research and development projects or those of our competitors;
- our entering into or terminating strategic relationships;
- changes in laws or government regulation;
- actual or anticipated fluctuations in our and our competitors' results of operations and financial condition;
- regulatory developments and the decisions of regulatory authorities as to the approval or rejection of new or modified products;
- the departure of our key personnel;
- disputes related to intellectual property and proprietary rights, including patents, litigation matters and our ability to obtain intellectual property protection for our technologies;
- our sale, or the sale by our significant shareholders, of Ordinary Shares, IPO Warrants or other securities in the future;
- public concern regarding the safety, efficacy or other aspects of the products or methodologies we are developing;
- market conditions in our industry and changes in estimates of the future size and growth rate of our markets;
- market acceptance of our products;
- the mix of products that we sell and related services that we provide;
- the success or failure of our licensees to develop, obtain approval for and commercialize our licensed products, for which we are entitled to contingent payments and royalties;
- the publication of the results of preclinical or clinical trials for EB613, EB612 or any other product candidates we may develop, including a new Oral GLP-2 analog research program;
- the failure by us to achieve a publicly announced milestone;
- delays between our expenditures to develop and market new or enhanced products and the generation of sales from those products;
- changes in the amounts that we spend to develop, acquire or license new products, technologies or businesses;
- changes in our expenditures to promote our products;
- variances in our financial performance from the expectations of market analysts;
- the limited trading volume of our Ordinary Shares and IPO Warrants; and
- general economic and market conditions, including factors unrelated to our industry or operating performance.

In addition, the stock market in general has recently experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of individual companies. Broad market and industry factors may materially affect the market price of companies' stock, including ours, regardless of actual operating performance.

We do not know whether a market for our Ordinary Shares or IPO Warrants will be sustained and as a result, it may be difficult for holders of our Ordinary Shares or IPO Warrants to sell their securities.

Although our Ordinary Shares and IPO Warrants are listed on Nasdaq, an active trading market for our Ordinary Shares and IPO Warrants may not be sustained. The lack of an active market may impair the ability of holders of our Ordinary Shares or IPO Warrants to sell their Ordinary Shares or IPO Warrants at the time they wish to sell them or at a price that they consider reasonable. The lack of an active market may also reduce the value of our Ordinary Shares or IPO Warrants, and may cause the trading price of our Ordinary Shares or IPO Warrants to be more volatile. An inactive market may also impair our ability to raise capital by selling Ordinary Shares and may impair our ability to acquire other companies by using our Ordinary Shares or IPO Warrants as consideration**.**

Our stock price may continue to be volatile, and securities class action litigation has often been instituted against companies following periods of volatility of their stock price. Any such litigation, if instituted against us, could result in substantial costs and a diversion of our management's attention and resources.

In the past, following periods of volatility in the overall market and the market price of a particular company's securities, securities class action litigation has often been instituted against these companies. Although there is no such shareholder litigation currently pending or threatened against the Company, such litigation, if instituted against us, could result in substantial costs and a diversion of our management's attention and resources.

The IPO Warrants are speculative in nature and are a risky investment. You may not be able to recover your investment in the IPO Warrants, and the IPO Warrants may expire worthless.

The value of the IPO Warrants will depend on the value of our Ordinary Shares, which will depend on factors related and unrelated to the success of our clinical development program or other factors as detailed above and cannot be predicted at this time.

If the price per share of our Ordinary Shares does not increase to an amount sufficiently above the applicable exercise price of the IPO Warrants during the period the IPO Warrants are exercisable, and if a public market for our IPO Warrants does not develop, the IPO Warrants may not have any value, and you may be unable to recover any or all of your investment in the IPO Warrants. There can be no assurance that the market price of the Ordinary Shares will ever equal or exceed the exercise price of the IPO Warrants, and consequently, whether it will ever be profitable for holders of the IPO Warrants to exercise the IPO Warrants.

Holders of the IPO Warrants will have no rights as shareholders until they acquire our Ordinary Shares.

Until a holder of an IPO Warrant acquires our Ordinary Shares upon exercise of the IPO Warrants, the holder will have no rights with respect to our Ordinary Shares issuable upon exercise of the IPO Warrants, except as set forth in the IPO Warrants. Upon exercise of your IPO Warrants, the holder will be entitled to exercise the rights of a shareholder only as to matters for which the record date occurs on or after the exercise date, unless the IPO Warrants are settled via "cashless exercise" in which case you will be entitled to exercise such rights only after the end of the relevant calculation period as defined in our Registration Statement on Form F-1 (File No. 333-221472) filed with the SEC on June 27, 2018, under "Description of IPO Warrants - Exercisability, Exercise Price and Term."

Future sales by our shareholders may adversely affect our stock price and our ability to raise funds in new stock offerings.

Sales of our Ordinary Shares or IPO Warrants in the public market could lower the market price of our Ordinary Shares or IPO Warrants. Sales may also make it more difficult for us to sell equity securities or equity-related securities in the future at a time and price that our management deems acceptable or at all. Most of our outstanding Ordinary Shares and IPO Warrants are not restricted from resale. In the event of a sale of Ordinary Shares or IPO Warrants offered by selling shareholders, the price of our Ordinary Shares or IPO Warrants could decline, and such decline could be material.

The market price of our Ordinary Shares and IPO Warrants could be negatively affected by future sales of our securities.

If our shareholders, particularly our directors or our executive officers and their affiliates, that in aggregate, beneficially own approximately 2.9% of our Ordinary Shares as of March 1, 2022, sell substantial amounts of our Ordinary Shares or IPO Warrants in the public market, or if there is a public perception that these sales may occur in the future, the market price of our Ordinary Shares or IPO Warrants may decline. The perception in the public market that our shareholders might sell our Ordinary Shares or IPO Warrants could also depress the market price of our Ordinary Shares or IPO Warrants and could impair our future ability to obtain capital, especially through an offering of equity securities. In addition, our sale of additional Ordinary Shares or other similar securities in order to raise capital might have a similar negative impact on the share price of our Ordinary Shares or IPO Warrants. A decline in the price of our Ordinary Shares may impede our ability to raise capital through the issuance of additional Ordinary Shares, IPO Warrants or other equity securities, and may cause holders of our Ordinary Shares or IPO Warrants to lose part or all of their investment.

We have never paid, and we currently do not intend to pay dividends.

We have never declared or paid any cash dividends on our Ordinary Shares. We currently intend to retain any future earnings to finance operations and to expand our business and, therefore, do not expect to pay any cash dividends in the foreseeable future. As a result, capital appreciation, if any, of our Ordinary Shares will be investors' sole source of gain for the foreseeable future. In addition, Israeli law may limit our declaration or payment of dividends, and may subject our dividends to Israeli withholding taxes.

As of January 1, 2022, we are required to report as a U.S. domestic issuer and the benefits of a "foreign private issuer" are no longer available to us, which will likely result in additional costs and expenses for us.

As of January 1, 2022, we have lost our status as a "foreign private issuer" and are required to adjust our disclosure and reporting to comply with the requirements for domestic U.S. companies. As a result:

- we are required to report on forms that are applicable to U.S. companies, such as Forms 10-K, 10-Q and 8-K, rather than the forms formerly used us, such as Forms 20-F and 6-K;
- we are required to include substantially more information in proxy statements than previously provided;
- we can no longer make use of the shelf registration statement on Form F-3 that was declared effective on July 22, 2020, and will need to file a new registration statement on the relevant form applicable to domestic issuers should we wish to engage in public capital raising activities, including capital raising under our ATM Program;
- if we engage in capital raising activities, there is a higher likelihood that investors may require us to file resale registration statements with the SEC as a condition to any such financing; and
- we may be required to modify certain of our policies to comply with accepted governance practices associated with U.S. domestic issuers.

We expect that complying with these additional requirements would increase our legal and audit fees which in turn, could have a material adverse effect on our business, financial condition and results of operations. In addition, as a result of being considered a "domestic issuer" for reporting and disclosure requirements:

- we are no longer exempt from certain of the provisions of U.S. securities laws such as (i) Regulation FD, which restricts the selective disclosure of material information, (ii) exemptions for filing beneficial ownership reports under Section 16(a) of the Exchange Act for executive officers, directors and 10% shareholders (Forms 3, 4, and 5), and (iii) the Section 16(b) short swing profit rules;
- we are no longer permitted to disclose compensation information for our executive officers on an aggregate rather than an individual basis, although such exemption may still be available to us as long as we remain an "emerging growth company"; and
- we have lost the ability to rely upon exemptions from Nasdaq corporate governance requirements that are available to foreign private issuers.

As a foreign private issuer, we were permitted to follow, and had followed through December 31, 2021, certain home country corporate governance practices instead of those otherwise required under the Nasdaq Stock Market for domestic U.S. issuers. For instance, we followed home country practice in Israel with regard to (a) the quorum requirement for shareholder meetings, (b) the lack of need for independent director oversight of director nominations and for a nominating and governance committee; (c) the lack of need for separate executive sessions of independent directors and non-management directors; and (d) the lack of need to obtain shareholder approval for certain dilutive events such as (i) the establishment or amendment of certain equity-based compensation plans and (ii) certain transactions other than a public offering involving issuances of a 20% or more interest in the company.

We may not have sufficient insurance to cover our liability in any current or future litigation claims either due to coverage limits or as a result of insurance carriers seeking to deny coverage of such claims.

We may face a variety of litigation-related liability risks. Our amended Articles of Association, or Articles, other applicable agreements and/or Israeli law may require us to indemnify (and advance expenses to) our current and past directors and officers and employees from reasonable expenses related to the defense of any action arising from their service to us, including circumstances under which indemnification is otherwise discretionary. While our directors and officers are included in a director and officer liability insurance policy, which covers all our directors and officers in some circumstances, our insurance coverage does not cover all of our indemnification obligations and may not be adequate to cover any indemnification or other claims against us. In addition, the underwriters of our present coverage may seek to avoid coverage in certain circumstances based upon the terms of the respective policies. If we incur liabilities that exceed our coverage under our directors and officers insurance policy or incur liabilities not covered by our insurance, we would have to self-fund any indemnification amounts owed to our directors and officers and employees in which case our results of operations and financial condition could be materially adversely affected. Further, if D&O insurance becomes prohibitively expensive to maintain in the future, we may be unable to renew such insurance on economic terms or unable renew such insurance at all. The lack of D&O insurance may make it difficult for us to retain and attract talented and skilled directors and officers to serve our company, which could adversely affect our business.

There is a risk that we may be a passive foreign investment company, for U.S. federal income tax purposes for any taxable year, which generally would result in certain adverse U.S. federal income tax consequences to our U.S. investors.

There is a risk that we may be treated as a passive foreign investment company, or PFIC, for any taxable year. The application of the PFIC rules to a company like us is subject to uncertainties, and for the reasons described below, we cannot express a view as to whether we will be a PFIC for the current or any future taxable year. In general, a non-U.S. corporation is a PFIC for any taxable year in which (i) 75% or more of its gross income consists of passive income, or the income test, or (ii) 50% or more of the average value of its assets consists of assets (generally determined on a quarterly basis) that produce, or are held for the production of, passive income, or the assets test. Generally, passive income includes interest, dividends, rents, royalties and certain gains, and cash is generally treated as a passive asset that produces passive income for PFIC purposes. The assets shown on our balance sheet consist, and are expected to continue to consist, primarily of cash and cash equivalents for the foreseeable future. Therefore, whether we will satisfy the assets test for the current or any future taxable year will depend largely on the quarterly value of our goodwill and on how quickly we utilize our cash in our business. Because (i) the value of our goodwill may be determined by reference to the market price of our Ordinary Shares, which has been, and may continue to be volatile given the nature and early stage of our business, (ii) we hold, and expect to continue to hold, a significant amount of cash, and (iii) a company's annual PFIC status can be determined only after the end of each taxable year, we cannot express a view as to whether we will be a PFIC for the current or any future taxable year. In addition, it is not clear how to apply the income test to a company like us, which is still developing its key intangible assets and whose overall losses from research activities significantly exceed the amount of its income (including passive income). If our losses from research and development activities are disregarded for purposes of the income test, we may be a PFIC for any taxable year if 75% or more of our gross income (as determined for U.S. federal income tax purposes) for the relevant year is from interest and financial investments. Because the revenue shown on our financial statements is not calculated based on U.S. tax principles, and because for any taxable year we may not have sufficient (or any) non-passive revenue, there is a risk that we may be or become a PFIC under the income test for any taxable year. If we were a PFIC for any taxable year during which a U.S. investor owned our Ordinary Shares (or under proposed Treasury regulations, IPO Warrants), such U.S. shareholder generally will be subject to certain adverse U.S. federal income tax consequences, including increased tax liability on gains from dispositions of the Ordinary Shares (or IPO Warrants) and certain distributions and a requirement to file annual reports with the Internal Revenue Service. U.S. investors should consult with their tax advisers regarding the application of the PFIC rules as they may relate to an investment in our company.

We are an emerging growth company and a smaller reporting company, and our compliance with the reduced reporting and disclosure requirements applicable to emerging growth companies and smaller reporting companies could make our Ordinary Shares less attractive to investors and may make it more difficult to raise capital as and when we need it.

We are an emerging growth company, as defined in the Jumpstart our Business Startups Act of 2012, referred to as the JOBS Act, and we expect to take advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies, including the auditor attestation requirements of Section 404, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements, exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved and extended adoption period for accounting pronouncements.

Even after we no longer qualify as an emerging growth company, we may still qualify as a "smaller reporting company," which would allow us to continue to take advantage of many of the same exemptions from disclosure requirements, including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act and reduced disclosure obligations regarding executive compensation in this prospectus and our periodic reports and proxy statements.

We cannot predict whether investors will find our Ordinary Shares less attractive as a result of our reliance on these exemptions. If some investors find our ordinary shares less attractive as a result, there may be a less active trading market for our ordinary shares and our stock price may be more volatile.

Additionally, because of the exemptions from various reporting requirements provided to us as an emerging growth company, we may be less attractive to investors and it may be difficult for us to raise additional capital as and when we need it. Investors may be unable to compare our business with other companies in our industry if they believe that our reporting is not as transparent as the reporting of other companies in our industry. If we are unable to raise additional capital as and when we need it, our financial condition and results of operations may be materially and adversely affected.

Our Ordinary Shares may be delisted from the Nasdaq Capital Market if we are unable to maintain compliance with Nasdaq's continued listing standards.

Nasdaq imposes, among other requirements, continued listing standards including a minimum bid requirement. The price of our Ordinary Shares must trade at or above $1.00 to comply with the minimum bid requirement for continued listing on the Nasdaq Capital Market. If the closing bid price of our Ordinary Shares fails to meet Nasdaq's minimum closing bid price requirement for a period in excess of 30 consecutive days, or if we otherwise fail to meet any other applicable requirements of the Nasdaq Capital Market and we are unable to regain compliance, Nasdaq may make a determination to delist our Ordinary Shares. Any delisting of our Ordinary Shares would likely adversely affect the market liquidity and market price of our Ordinary Shares and our ability to obtain financing for the continuation of our operations or result in the loss of confidence by investors.

If we fail to maintain an effective system of internal control over financial reporting, we may not be able to accurately report our financial results or prevent fraud. As a result, shareholders could lose confidence in our financial and other public reporting, which would harm our business and the trading price of our Ordinary Shares.

Effective internal controls over financial reporting are necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, are designed to prevent fraud among other objectives. Any failure to implement required new or improved controls, or difficulties encountered in their implementation could cause us to fail to meet our reporting obligations. In addition, any testing by us conducted in connection with Section 404 of the Sarbanes-Oxley Act of 2002, or any subsequent testing by our independent registered public accounting firm, may reveal deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses or that may require prospective or retroactive changes to our financial statements or identify other areas for further attention or improvement. Inferior internal controls could also subject us to regulatory scrutiny and sanctions, impair our ability to raise revenue and cause investors to lose confidence in our reported financial information, which could have a negative effect on the trading price of our Ordinary Shares.

We are required to disclose changes made in our internal controls and procedures and our management is required to assess the effectiveness of these controls annually. However, for as long as we are an "emerging growth company" under the JOBS Act, our independent registered public accounting firm will not be required to attest to the effectiveness of our internal controls over financial reporting pursuant to Section 404. An independent assessment of the effectiveness of our internal controls could detect problems that our management's assessment might not. Undetected material weaknesses in our internal controls could lead to financial statement restatements and require us to incur the expense of remediation.

If securities or industry analysts do not publish research or reports or publish unfavorable research about our business, our share price and trading volume could decline.

The trading market for our Ordinary Shares depends in part on the research and reports that securities or industry analysts publish about us or our business. We do not have control over these analysts and we do not have commitments from them to write research reports about us. If securities or industry analysts do not commence coverage of our company, the trading price for our shares may be negatively affected. In the event we obtain securities or industry analyst coverage, if one or more of the analysts who covers us downgrades our shares, our shares price would likely decline. If one or more of these analysts ceases to cover us or fails to publish regular reports on us, interest in the purchase of our shares could decrease, which could cause our share price or trading volume to decline.

Risks Relating to Our Incorporation and Location in Israel

The Israeli government grants we have received for research and development expenditures restrict our ability to manufacture products and transfer technologies outside of Israel and require us to satisfy specified conditions. If we fail to satisfy these conditions, we may be required to refund grants previously received together with interest and penalties or to pay other amounts according to the formulas set out in the relevant laws.

Our research and development efforts have been financed, in part, through the grants that we have received from the Israeli Innovation Authority (formerly known as the Office of Chief Scientist of the Israeli Ministry of Economy), or the IIA. Pursuant to these grants, we must comply with the requirements of the Encouragement of Industrial Research, Development and Technological Innovation in Industry Law 5744-1984 and the IIA regulations, or the Research Law. Until the grants are repaid with interest, royalties are payable to the IIA in the amount of 3% on revenues derived from sales of products or services developed in whole or in part using the IIA grants, including EB612, EB613 and any other oral PTH product candidates we may develop. The royalty rate may increase to 5%, with respect to approved applications filed following any year in which we achieve sales of over $70 million.

Under the Research Law, we are prohibited from manufacturing products developed using these grants outside of the State of Israel without special approvals. We may not receive the required approvals for any proposed transfer of manufacturing activities. Even if we do receive approval to manufacture products developed with government grants outside of Israel, the royalty rate may be increased and we may be required to pay up to three times the grant amounts and the interest, depending on the manufacturing volume that is performed outside of Israel. This restriction may impair our ability to outsource manufacturing or engage in our own manufacturing operations for those products or technologies. For additional information, see "Item 1—Business—The Israeli Innovation Authority (IIA) Grant."

Additionally, under the Research Law, we are prohibited from transferring in any manner (including by way of license), the IIA-financed technologies and related rights (including know-how and other intellectual property rights) in or outside of the State of Israel, except under limited circumstances and only with the approval of the IIA. We may not receive the required approvals for any proposed transfer and, even if received, we may be required to pay the IIA a portion of the consideration that we receive upon any transfer of such technology to a non-Israeli entity up to 600% of the grant amounts and the interest. The scope of the IIA support received, the royalties that we have already paid to the IIA, the amount of time that has elapsed between the date on which the know-how or other intellectual property rights were transferred and the date on which the IIA grants were received and the sale price and the form of transaction will be taken into account in order to calculate the amount of the payment to the IIA. Approval to transfer the technology to residents of the State of Israel is also required, and may be granted in specific circumstances only if the recipient abides by the provisions of applicable laws, including the restrictions on the transfer of know-how and the obligation to pay royalties. No assurance can be made that approval to any such transfer, if requested, will be granted. Transfer of know-how or rights outside of the state of Israel without IIA approval is a criminal offense.

These restrictions may impair our ability to sell our technology assets or to perform or outsource manufacturing outside of Israel, engage in change of control transactions or otherwise transfer our know-how outside of Israel and may require us to obtain the approval of the IIA for certain actions and transactions and pay additional royalties and other amounts to the IIA. In addition, any change of control and any change of ownership of our Ordinary Shares that would make a non-Israeli citizen or resident an interested party, as defined in the Israeli Securities Law, 5728-1968, as amended, requires written notice to the IIA, and our failure to comply with this requirement could result in monetary fines. Such non-Israeli interested parties, which include 5% shareholders and shareholders who have the right to appoint a director to our board of directors, are required to sign an undertaking towards the IIA in which they would undertake to comply with the Research Law. Shareholders that purchased Ordinary Shares in our IPO would not be required to sign such an undertaking.

These restrictions will continue to apply even after we have repaid the full amount of the grants and the interest. If we fail to satisfy the conditions of the Research Law, we may be required to refund grants previously received together with interest and penalties, to make other payments to the IIA or become subject to criminal charges.

Security, political and economic instability in the Middle East may harm our business.

Our principal research and development facilities are located in Israel. In addition, part of our key employees, officers and directors are residents of Israel. Accordingly, political, economic and military conditions in the Middle East may affect our business directly. Since the establishment of the State of Israel in 1948, a number of armed conflicts have occurred between Israel and its neighboring countries, Hamas (an Islamist militia and political group in the Gaza Strip) and Hezbollah (an Islamist militia and political group in Lebanon). Recent political uprisings, social unrest and violence in various countries in the Middle East, including Israel's neighbor Syria, are affecting the political stability of those countries. This instability may lead to deterioration of the political relationships that exist between Israel and certain countries and have raised concerns regarding security in the region and the potential for armed conflict. In addition, Iran has threatened to attack Israel. Iran is also believed to have a strong influence among the Syrian government, Hamas and Hezbollah. These situations may potentially escalate in the future into more violent events which may affect Israel and us. These situations, including conflicts which involved missile strikes against civilian targets in various parts of Israel have in the past negatively affected business conditions in Israel.

Any hostilities involving Israel or the interruption or curtailment of trade between Israel and its present trading partners could have a material adverse effect on our business. Although such hostilities did not have a material adverse impact on our business in the past, we cannot guarantee that hostilities will not be renewed and have such an effect in the future. The political and security situation in Israel may result in parties with whom we have contracts claiming that they are not obligated to perform their commitments under those agreements pursuant to force majeure provisions. These or other Israeli political or economic factors could harm our operations and product development. Any hostilities involving Israel or the interruption or curtailment of trade between Israel and its present trading partners could adversely affect our operations and could make it more difficult for us to raise capital. We could experience disruptions if acts associated with this conflict result in any serious damage to our facilities. Furthermore, several countries, as well as certain companies and organizations, continue to restrict business with Israel and Israeli companies, which could have an adverse effect on our business and financial condition in the future. Our business interruption insurance may not adequately compensate us for losses, if at all, that may occur as a result of an event associated with a security situation in the Middle East, and any losses or damages incurred by us could have a material adverse effect on our business.

Our operations may be disrupted by the obligations of personnel to perform military service.

Our employees in Israel, including executive officers, generally, may be called upon to perform up to 42 days (and in some cases more) of annual military reserve duty until they generally reach the age of 45 (or older in some cases) and, in emergency circumstances, could be called to active duty. In response to increased tension and hostilities, since September 2000 there have been occasional call-ups of military reservists, including in connection with the mid-2006 war in Lebanon and the December 2008, November 2012 and July 2014 conflicts with Hamas, and it is possible that there will be additional call-ups in the future. Our operations could be disrupted by the absence of a significant number of our employees related to military service or the absence for extended periods of one or more of our key employees for military service. Such disruption could materially adversely affect our operations, business and results of operations.

Our business is subject to currency exchange risk and fluctuations between the U.S. dollar and other currencies may negatively affect our earnings and results of operations.

The U.S. dollar is both our functional and reporting currency. As a result, our results of operations may be adversely affected by exchange rate fluctuations between the U.S. dollar and the NIS. A significant portion of the expenses associated with our Israeli operations, including personnel and facilities related expenses, are incurred in NIS. Consequently, inflation in Israel will have the effect of increasing the cost of our operations in Israel unless it is offset on a timely basis by a devaluation of the NIS relative to the U.S. dollar. In addition, if the value of the U.S. dollar decreases against the NIS, our earnings may be negatively impacted. Moreover, exchange rate fluctuations in currency exchange rates in countries other than Israel where we operate, perform our clinical trials or conduct business may also negatively affect our earnings and results of operations. We cannot predict any future trends in the rate of inflation or deflation in Israel or the rate of devaluation or appreciation of the NIS against the U.S. dollar. If the dollar cost of our operations in Israel increases, our dollar-measured results of operations will be adversely affected. For example, in 2021, the value of the NIS appreciated against the U.S. dollar by 3.27%, which appreciation was partially offset by inflation in Israel of 02.8%. In 2020, the value of the NIS appreciated against the U.S. dollar by 6.97%, the effect of which was partially offset by inflation in Israel at a rate of approximately 0.7%. As a result of these fluctuations, our NIS denominated expenses were affected.

Potential future revenue may be derived from abroad, including outside of the United States. As a result, our business and share price may be affected by fluctuations in foreign exchange rates with these other currencies, which may also have a significant impact on our reported results of operations and cash flows from period to period. Currently, we do not have any exchange rate hedging arrangements in place. Foreign currency fluctuations could materially adversely affect our results of operations or could positively affect our results of operations in ways that may not necessarily be repeated in future periods.

It may be difficult to enforce a U.S. judgment against us or our officers and directors, to assert U.S. securities laws claims in Israel or to serve process on our officers and directors.

We are incorporated under the laws of the State of Israel. Service of process upon us, our directors and officers and the Israeli experts, if any, a significant number of whom reside outside the United States, may be difficult to obtain within the United States. Furthermore, because the majority of our assets and investments, and substantially all of our directors, officers and such Israeli experts, if any, are located outside the United States, any judgment obtained in the United States against us or any of them may be difficult to collect within the United States. In addition, such judgment may not be enforced by an Israeli court.

In addition, it may also be difficult for an investor to effect service of process on these persons in the U.S. or to assert U.S. securities law claims in original actions instituted in Israel. Israeli courts may refuse to hear a claim based on an alleged violation of U.S. securities laws reasoning that Israel is not the most appropriate forum to bring such a claim. In addition, even if an Israeli court agrees to hear a claim, it may determine that Israeli law and not U.S. law is applicable to the claim. If U.S. law is found to be applicable, the content of applicable U.S. law must be proved as a fact, which can be a time-consuming and costly process. Certain matters of procedure will also be governed by Israeli law. There is little binding case law in Israel addressing the matters described above. See the section in our Registration Statement on Form F-1 filed under the Securities Act with the SEC on June 27, 2018, entitled “Enforceability of Civil Liabilities.” As a result of the difficulty associated with enforcing a judgment against us in Israel, holders of our Ordinary Shares may not be able to collect any damages awarded by either a U.S. or foreign court.

Provisions of Israeli law and our Articles may give rise to withholding obligations or delay, prevent or make difficult a change of control and therefore depress the price of our shares.

Israeli corporate law regulates mergers, requires tender offers for acquisitions of shares above specified thresholds, requires special approvals for transactions involving directors, officers or significant shareholders and regulates other matters that may be relevant to these types of transactions. For example, under Israel's Companies Law, 5759-1999, as currently amended or the Companies Law, upon the request of a creditor of either party to a proposed merger, the court may delay or prevent the merger if it concludes that there exists a reasonable concern that as a result of the merger the surviving company will be unable to satisfy the obligations of any of the parties to the merger. Additionally, a tender offer for all of a company's issued and outstanding shares can only be completed if the acquirer receives positive responses from the holders of at least 95% of the issued share capital. Completion of the tender offer also requires approval of a majority of the offerees that do not have a personal interest in the tender offer unless, following consummation of the tender offer, the acquirer would hold more than 98% of the company's outstanding shares. Furthermore, the shareholders, including those who indicated their acceptance of the tender offer, may, at any time within six months following the completion of the tender offer, petition an Israeli court to alter the consideration for the acquisition, unless the acquirer stipulated in its tender offer that a shareholder that accepts the offer may not seek such appraisal rights.

Furthermore, Israeli tax considerations may make potential transactions unappealing to us or to our shareholders whose country of residence does not have a tax treaty with Israel exempting such shareholders from Israeli tax. For example, Israeli tax law does not recognize tax-free share exchanges to the same extent as U.S. tax law. With respect to mergers, Israeli tax law allows for tax deferral in certain circumstances that makes the deferral contingent on the fulfillment of numerous conditions, including a holding period of two years from the date of the transaction during which sales and dispositions of shares of the participating companies are, subject to certain exceptions, restricted. Moreover, with respect to certain share swap transactions, the tax deferral is limited in time, and when the time expires, tax then becomes payable even if no actual disposition of the shares has occurred.

Our Articles provide that our directors are elected on a staggered basis such that a potential acquirer cannot readily replace our entire board of directors at a single general shareholders meeting.

These provisions could cause our Ordinary Shares to trade at prices below the price for which third parties might be willing to pay to gain control of us. Third parties who are otherwise willing to pay a premium over prevailing market prices to gain control of us may be unable or unwilling to do so because of these provisions of Israeli law and our amended Articles.

Your rights and responsibilities as a shareholder are governed by Israeli law, which may differ in some respects from the rights and responsibilities of shareholders of U.S. companies.

We are incorporated under Israeli law. The rights and responsibilities of the holders of our Ordinary Shares are governed by our Articles and Israeli law. These rights and responsibilities differ in some respects from the rights and responsibilities of shareholders in typical U.S.-based corporations. In particular, a shareholder of an Israeli company has a duty to act in good faith and in a customary manner in exercising its rights and performing its obligations towards the company and other shareholders and to refrain from abusing its power in the company, including, among other things, in voting at the general meeting of shareholders on matters such as amendments to a company's articles of association, increases in a company's authorized share capital, mergers and acquisitions and interested party transactions requiring shareholder approval. In addition, a shareholder who knows that it possesses the power to determine the outcome of a shareholder vote or to appoint or prevent the appointment of a director or executive officer in the company has a duty of fairness toward the company with regard to such vote or appointment. There is limited case law available to assist us in understanding the implications of these provisions that govern shareholders' actions, and these provisions may be interpreted to impose additional obligations and liabilities on holders of our Ordinary Shares that are not typically imposed on shareholders of U.S. corporations.

Our business could be negatively affected as a result of actions of activist shareholders, and such activism could impact the trading value of our securities.

In recent years, certain Israeli issuers listed on United States exchanges have been faced with governance-related demands from activist shareholders, unsolicited tender offers and proxy contests. Responding to these types of actions by activist shareholders could be costly and time-consuming, disrupting our operations and diverting the attention of management and our employees. Such activities could interfere with our ability to execute our strategic plan. In addition, a proxy contest for the election of directors at our annual meeting would require us to incur significant legal fees and proxy solicitation expenses and require significant time and attention by management and our board of directors. The perceived uncertainties as to our future direction also could affect the market price and volatility of our securities.

ITEM 1B. UNRESOLVED STAFF COMMENTS.

None.

ITEM 2. PROPERTIES.

Our facilities in Israel, which house our research and developments, clinical development, clinical operations, regulatory and management functions are located in Jerusalem, Israel. Under a Lease Agreement with Unihead Biopark Ltd. as of December 31, 2021, we are leasing approximately 622 square meters of office and laboratory space pursuant to a lease agreement that will expire on June 30, 2023. Of the 622 square meters leased, we utilize approximately 527 square meters for our operations and have agreed to sublease the remaining approximately 95 square meters to a third-party until December 2022.

We believe that our current office and laboratory space in Israel is sufficient to meet our anticipated needs for the foreseeable future and is suitable for the conduct of our business. We believe that suitable additional space would be available if required in the future on commercially reasonable terms.

ITEM 3. LEGAL PROCEEDINGS.

We are not currently a party to any material legal proceedings.

ITEM 4. MINE SAFETY DISCLOSURES.

Not applicable.

PART II

ITEM 5. MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES.

Market for our Ordinary Shares and IPO Warrants

Our Ordinary Shares and IPO Warrants are traded on the Nasdaq Capital Market under the symbols "ENTX" and "ENTXW," respectively.

As of March 1, 2022, there were approximately 65 holders of record of our Ordinary Shares.This number does not include the number of persons whose shares are in nominee or in "street name" accounts through brokers.

Dividends

If the Company decides to distribute a cash dividend, Israeli residents who are individuals are generally subject to Israeli income tax at a rate of either 25% or 30%, if the recipient of such dividend is a "substantial shareholder" at the time of distribution or at any time during the preceding 12-month period, unless the cash dividend is paid out of income that has been tax exempt due to an "approved enterprise" status under the Law for the Encouragement of Capital Investments, 5719-1959, in which case the Company will be subject to corporate tax at a rate then in effect under Israeli law on the amount of cash dividend and in addition, an Israeli shareholder, corporation or individual, will be subject to a tax rate of 20% on such cash dividend distribution. In addition, Israeli resident corporations are generally exempt from Israeli corporate tax for dividends paid on our Ordinary Shares. Pursuant to the Convention Between the Government of the United States of America and the Government of Israel with Respect to Taxes on Income, as amended (the "U.S.-Israel Tax Treaty"), the maximum tax on dividends paid to a holder of our Ordinary Shares who qualifies as a resident of the United States within the meaning of the U.S.-Israel Tax Treaty is 25% or 15% in case of dividends paid out of the profits of an "approved enterprise", subject to certain conditions. Furthermore, dividends not generated by an "approved enterprise" paid to a U.S. corporation holding at least 10% of our issued voting power during the part of the tax year which precedes the date of payment of the dividend and during the whole of its prior tax year (if any), are generally taxed at a rate of 12.5%, subject to certain conditions. The Company has never declared or paid cash dividends on its Ordinary Shares.

The actual amount, timing, and frequency of future dividends, if any, will be at the sole discretion of the board of directors and will be declared based upon various factors, many of which are beyond our control. The Company's current plans are to retain future earnings primarily to finance the development of its business and for other corporate purposes.

ITEM 6. [Reserved]

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

This Annual Report on Form 10-K contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 ("PSLRA"), Section 27A of the Securities Act of 1933, as amended, (the "Securities Act"), and Section 21E of the Securities Exchange Act of 1934, as amended, (the "Exchange Act"), about our expectations, beliefs or intentions regarding our product development efforts, business, financial condition, results of operations, strategies and prospects. You can identify forward-looking statements by the fact that these statements do not relate to historical or current matters. Rather, forward-looking statements relate to anticipated or expected events, activities, trends or results as of the date they are made. Because forward-looking statements relate to matters that have not yet occurred, these statements are inherently subject to risks and uncertainties that could cause our actual results to differ materially from any future results expressed or implied by the forward-looking statements. Many factors could cause our actual activities or results to differ materially from the activities and results anticipated in forward-looking statements. These factors include those contained in "Item 1A — Risk Factors" and "Cautionary Statement Regarding Forward-Looking Statements" of this Annual Report on Form 10-K. We do not undertake any obligation to update forward-looking statements except as required by applicable law. We intend that all forward-looking statements be subject to the safe harbor provisions of PSLRA. These forward-looking statements reflect our views only as of the date they are made.

For purposes of this Item 7, references to the "Company," "we," "us" and "our" refer to Entera Bio Ltd. and its consolidated subsidiary.

Overview

We are a clinical-stage biopharmaceutical company focused on the development and commercialization of orally delivered large molecule therapeutics for use in areas with significant unmet medical need and where adoption of injectable therapies is limited due to cost, convenience and compliance challenges for patients. We were organized under the laws of the State of Israel on September 30, 2009 and commenced operations on June 1, 2010. We have developed a proprietary platform that enables the oral delivery of injectable proteins and large molecules. Our platform has been tested successfully on numerous molecules of broad characteristics and size. We have advanced our lead oral PTH product, EB613 to Phase 3 (potentially pivotal) and in December 2018 entered into a research collaboration and license agreement with Amgen for the use of Entera's oral delivery platform in the field of inflammatory diseases.

Our lead product candidates are EB613 for the treatment of osteoporosis and EB612 for the treatment of hypoparathyroidism. Both EB613 and EB612 are oral formulations of human parathyroid hormone (1-34), or PTH. An injectable formulation of PTH has been approved in the United States for more than a decade for both of these indications (PTH 1-34 for Osteoporosis and PTH 1-84 for Hypoparathyroidism). Currently, the leading products are administered via injection. In total, more than 260 healthy volunteers and patients have received multiple doses of various formulations of our oral PTH (1-34) in clinical trials.

Osteoporosis is a disease characterized by low bone mass and structural deterioration of bone tissue, which leads to greater fragility of bones and an increase in fracture risk. Forteo® is a once-daily subcutaneous injectable form of PTH (1-34) marketed by Eli Lilly and Company ("Eli Lilly"), that was approved by the U.S. Food and Drug Administration (the "FDA") in 2002 for the treatment of osteoporosis in the United States and is widely considered one of the most effective treatments due to its ability to build bone. Because our product candidate EB613 is delivered in a patient-friendly oral formulation, we believe it will reduce the treatment and cost burden on patients and lead to significantly higher patient and physician acceptance compared to injectable PTH. In 2020, we engaged a third-party firm to conduct two primary market research studies with clinicians who treat osteoporosis patients. In these two studies, the responses to the prospect of prescribing an oral PTH with demonstrated safety and efficacy were overwhelmingly positive and driven by expected improvements in patient compliance, ease of administration and reduced costs.

In November 2018, we had a pre- Investigational New Drug ("IND") meeting with the FDA to discuss the EB613 for the treatment of osteoporosis program, and, in December 2020, we announced that the FDA had reviewed our IND application for EB613 and informed us that we may proceed with our U.S. clinical trial.

We have completed two, multi-stage Phase 1 clinical trials of EB613 and a Phase 2 double-blind, placebo-controlled, dose-ranging trial of EB613 in patients with osteoporosis. The Phase 2 trial studied five once-daily doses of EB613 (0.5mg, 1.0mg, 1.5mg and 2.5mg) and placebo for six months and assessed safety, tolerability, bone biomarkers and bone mineral density (BMD). Based on these trials, EB613 appears to be safe and well tolerated with no serious drug-related adverse events reported and produced clinically and statistically significant increases in BMD at month six. The adverse events seen in these trials are consistent with those seen in other published third party trials of PTH (1-34). In December 2021 we held an end-of-Phase 2 meeting with the FDA to review the Phase 2 results and proposed Phase 3 protocol, including various aspects of our nonclinical and clinical development plan and the use of BMD, rather than fracture incidence, as the primary endpoint to support a New Drug Application, or NDA.

Hypoparathyroidism is a rare condition in which the body fails to produce sufficient amounts of PTH or the PTH produced lacks biologic activity. Historically, the treatments for hypoparathyroidism have been calcium supplements, active vitamin D analogs (calcitriol or similar drugs) and occasionally phosphate binders, the chronic use of which results in serious side effects and significant costs to patients and the healthcare system. A once-daily injectable form of PTH (1-84), marketed as Natpara®, has been approved for the treatment of hypoparathyroidism; however, Natpara is currently the subject of an FDA recall and is not currently avaialble. Our lead product candidate for hypoparathyroidism, EB612, is delivered orally and can be administered in customized doses several times a day. Studies performed by researchers at the National Institutes of Health, or NIH, have shown that dosing PTH multiple times per day significantly increases the efficacy of therapy and may be more effective for treating hypoparathyroidism. These studies found that the total daily PTH dose required to maintain serum calcium in the normal or near-normal range was reduced by 50% with twice-daily PTH (1-34) and also demonstrated that twice-daily dosing achieved better control over serum calcium and urinary calcium excretion as compared to once-daily dosing. In addition, based on the market research we conducted in osteoporosis, we believe patients generally prefer orally-administered drugs. For these reasons, we believe EB612 dosed two or more times during the day may be clinically superior to the existing daily therapy and has the potential to become the standard of care, if approved, for hypoparathyroidism.

In 2015, we successfully completed a Phase 2a trial for EB612. Although our Phase 2a trial involved a smaller number of patients, was conducted for a shorter duration and did not include an initial dose optimization period, in each case in comparison to the design of the pivotal trial used for regulatory approval of Natpara (the REPLACE trial), our trial showed the potential for similar efficacy. In the third quarter of 2019, we reported the results of a second Phase 2 clinical trial that included one day of dosing with EB612 to evaluate the pharmacokinetic/pharmacodynamics, or PK/PD, profile of various EB612 dose regimens compared with Natpara. The results from this study demonstrated that EB612 was effectively delivered into the blood stream and activated PTH-dependent biological pathways that are inadequately activated in patients with hypoparathyroidism. In addition, the various dosing regimens demonstrated positive impacts on serum calcium, urine calcium and serum phosphate levels. No serious adverse events were reported. We have developed an improved formulation of EB612 based on new intellectual property and optimization of the PK profile for hypoparathydoidism and are evaluating this in preclinical and human PK/PD studies in 2022. These data will help determine the design of a pivotal Phase 2b or Phase 3 trial of EB612 in patients with hypoparathyroidism in which the dose frequency would be titrated to control hypocalcemia, normalize serum phosphate and reduce renal calcium excretion.

In the future, after the completion of additional formulation and development activities, we expect to initiate a multi-site Phase 2b/3 clinical trial of EB612 for the treatment of hypoparathyroidism, which will further evaluate the dosage, effectiveness and safety profile of EB612 in an expanded population of patients with hypoparathyroidism. We expect that this Phase 2b/3 trial, when initiated, will be designed to replicate the REPLACE trial in many aspects and to achieve a significant reduction in urinary calcium. The phase 2b/3 clinical trial of EB612 in hypoparathyroidism may potentially support a submission for regulatory approval of EB612, if successful.

In addition to the utilization of our technology to develop our own internal drug candidates, we intend to use our technology as a platform for the oral delivery of other novel protein and large molecule therapeutics. We believe our proprietary technology has advantages over alternative delivery options, and may enable us to create a potential pipeline of products across a range of therapeutic indications. We have generated data on a number of additional proteins and peptides in molecules as large as 150 kilodaltons, or kDa, and may develop these candidates further internally, or explore potential business development collaborations to advance these therapies through clinical development and generate funding.

In December 2018, we entered into a research collaboration and license agreement with Amgen, Inc, or Amgen. Under the agreement, we and Amgen have agreed to collaborate on the development and discovery of clinical candidates in the field of inflammatory disease and other serious illnesses. Specifically, we and Amgen have agreed to use our proprietary drug delivery platform to help Amgen develop oral formulations for up to three large molecule drug candidates within Amgen's pipeline. Further, under the terms of the agreement, we have agreed to conduct preclinical development activities, at Amgen's expense, and Amgen will be responsible for research, clinical development, manufacturing and commercialization of any of the resulting programs, at its expense. We will be eligible to receive from Amgen aggregate payments of up to $270 million upon achievement of various clinical and commercial milestones or Amgen's exercise of its option to select up to two additional programs to include in the collaboration, as well as tiered royalty payments based on percentages ranging from the low to mid-single digits based on the level of Amgen's net sales of any applicable products, if approved. We will retain all intellectual property rights to our drug delivery technology, which under this collaboration will be licensed to Amgen exclusively for Amgen's selected drug targets. Amgen will retain all rights to its large molecules, including any subsequent improvements.

In February 2021, we announced that we initiated a new research program for an oral glucagon-like peptide-2 (GLP-2) analog based on the Company's platform technology. GLP-2, a peptide produced in the intestine and the central nervous system via the brainstem and hypothalamus, is known to enhance intestinal absorption, specifically the increased absorption of nutrients. The only GLP-2 analog currently on the market, teduglutide, was approved in 2012 as a once daily injection for the treatment of short bowel syndrome in the United States and Europe, registering global sales of $613 million in 2020. In preclinical models, our oral formulation of a GLP-2 analog has shown a comparable pharmacokinetic profile to a subcutaneous injection. In addition, GLP-2 analogs are an important category of new therapies for many metabolic diseases and therefore we believe this product candidate is well positioned for partnering opportunities.

We intend to utilize future funds, as available, to advance EB613 and EB612 through clinical development and ultimately towards regulatory approval. To date, we have funded our operations through sales of Ordinary Shares under our prior Equity Distribution Agreement with Canaccord Genuity LLC (the "Prior ATM Program"), our current At the Market Sales Agreement with B. Riley Securities, Inc. (the "ATM Program", and together with the Prior ATM Program, the "ATM Programs"), sales of Ordinary Shares in our IPO, private placements of our Ordinary Shares and preferred shares, warrants and convertible debt, government grants and through revenues generated from research collaboration and our license agreement with Amgen. We have no products that have received regulatory approval and have never generated revenue from product sales.

Since our inception, we have raised a total of $84.7 million, including $25.3 million through our ATM Programs, of which $21.8 million was raised in 2021, $14.3 million in our December 2019 private placement, $11.2 million in our IPO in 2018 and $33.9 million in aggregate funding from a combination of grants, exercise of options and warrants and private placements of Ordinary Shares, preferred shares and debt prior to our IPO.

Since inception, we have incurred significant losses. For the years ended December 31, 2021 and 2020, our operating losses were $12.2 million and $11.2 million, respectively, and we expect to continue to incur significant expenses and losses for the foreseeable future. As of December 31, 2021, we had an accumulated deficit of $82.4 million. Our losses may fluctuate significantly from quarter to quarter and year to year, depending on the timing of our clinical trials, our expenditures on any other research and development activities and payments under the collaboration with Amgen or any future collaborations into which we may enter.

As a result of our recurring losses from operations, negative cash flows and lack of liquidity, management is of the opinion that there is substantial doubt as to the Company's ability to continue as a going concern. Our independent registered public accounting firm included an explanatory paragraph in its report on our financial statements as of, and for the year ended, December 31, 2021, expressing the existence of substantial doubt about our ability to continue as a going concern. The audited consolidated financial statements included herein have been prepared assuming that we will continue as a going concern and do not include adjustments that might result from the outcome of this uncertainty. If we are unable to raise the requisite funds, we will need to curtail or cease operations. See "Item 1A—Risk Factors—Risks Related to Our Financial Position and Need for Additional Capital."

As of December 31, 2021, we had cash and cash equivalents of $24.9 million. In order to fund further operations, we will need to raise additional capital. We may raise these funds through a variety of means, including private or public equity offerings, debt financings, government grants, strategic collaborations and licensing arrangements. Additional financing may not be available when we need it or may not be available on terms that are favorable to us.

As of December 31, 2021, we had 21 employees and 5 consultants who provide services to us on a part-time basis. Our operations are located in Jerusalem, Israel.

Patent Transfer, Licensing Agreements and Grant Funding

Oramed Patent Transfer Agreement

In 2011, we entered into a patent transfer agreement with Oramed, or the Patent Transfer Agreement, pursuant to which Oramed assigned to us all of its rights, title and interest in the patent rights Oramed licensed to us when we were originally organized, subject to a worldwide, royalty-free, exclusive, irrevocable, perpetual and sub-licensable license granted to Oramed under the assigned patent rights to develop, manufacture and commercialize products or otherwise exploit such patent rights in the fields of diabetes and influenza. Additionally, we agreed not to engage, directly or indirectly, in any activities in the fields of diabetes and influenza. Under the terms of the Patent Transfer Agreement, we agreed to pay Oramed royalties equal to 3% of our net revenues generated, directly or indirectly, from exploitation of the assigned patent rights, including the sale, lease or transfer of the assigned patent rights or sales of products or services covered by the assigned patent rights.

Amgen Research Collaboration and License Agreement

On December 10, 2018, we entered into a research collaboration and license agreement with Amgen, which we refer to as the Amgen Agreement, with respect to inflammatory disease and other serious illnesses. Pursuant to the Amgen Agreement, we and Amgen have agreed to use our proprietary drug delivery platform to develop oral formulations for one preclinical large molecule program that Amgen has selected. In exchange for entering into the agreement, Amgen paid us a non-refundable and non-creditable initial access fee of $725,000 in the first quarter of 2019, of which $500,000 was attributed to the right to use the intellectual property and $225,000 was attributed to the pre-clinical R&D services that we are obligated to perform under the Amgen Agreement. In addition, under the Amgen Agreement, Amgen reimburses us for additional expenses that we incur for any work we do under the collaboration. Thus far during our collaboration, Amgen has paid $968,000 for pre-clinical R&D services.

Amgen also has options, limited in time, to select up to two additional programs to include in the collaboration. Amgen is responsible for the clinical development, regulatory approval, manufacturing and worldwide commercialization of the programs. Pursuant to the terms of the Amgen Agreement, Amgen is required to make aggregate payments of up to $270 million upon achievement of various clinical and commercial milestones or its exercise of options to select the additional two programs to include in the collaboration. In addition, Amgen is required to make tiered royalty payments ranging from the low to mid-single digits as a percentage of Amgen's net sales of the applicable products covered by the Amgen Agreement. Amgen's obligation to pay royalties with respect to a product in a particular country commences upon the first commercial sale of such product in such country and expires on a country-by-country and product-by-product basis on the later of (a) the date on which the sale of the product is no longer covered by a valid claim of a patent licensed to Amgen under the Amgen Agreement, and (b) the tenth anniversary of the first commercial sale of such product in such country.

Under the Amgen Agreement, we granted Amgen an exclusive, worldwide, sub-licensable license to certain of our intellectual property relating to our drug delivery technology to develop, manufacture and commercialize the applicable products. We have retained all intellectual property rights to our drug delivery technology, Amgen will retain all rights to its large molecules and any subsequent improvements, and ownership of certain intellectual property developed through the performance of the collaboration is to be determined by U.S. patent law. Each party is responsible for the filing and prosecution of patents relating to its owned developments and, with respect to any jointly-owned developments, we are responsible for the filing and prosecution of patents solely claiming improvements to our drug delivery technology and Amgen is responsible for the filing and prosecution of any other jointly-owned developments. Amgen has the primary right to enforce any such patents against third-party infringement with respect to a product that has the same mechanism of action as one of the collaboration programs, subject to involvement by us in certain circumstances.

During certain periods covered by the Amgen Agreement, we may not alone, or with a third party, research, develop, manufacture or commercialize certain products that interact with the targets of the applicable collaboration programs. The collaboration is governed by a joint research committee, or JRC, made up of equal representatives of us and Amgen. The JRC may establish additional subcommittees to oversee particular projects or activities. Subject to certain limitations, if the JRC is unable to make a decision by consensus, the disagreement is to be resolved through escalation to specified senior executive officers of the parties, although Amgen has the final decision-making ability with respect to certain pre-defined issues.

The term of the Amgen Agreement commenced on December 10, 2018, and unless earlier terminated, continues in full force and effect, on a product-by-product basis, until expiration of the last-to-expire royalty term with respect to such product. At any point in the research, development or commercialization process, subject to certain conditions, Amgen can terminate the Amgen Agreement in its entirety or with respect to a specific development program. Both parties can terminate the agreement for a material breach by the other party that goes uncured, subject to a 90-day notice period.

The Israeli Innovation Authority Grants

We have received grants of approximately $0.5 million from the IIA to partially fund our research and development. The grants are subject to certain requirements and restrictions under the Israeli Encouragement of Research, Development and Technological Innovation in Industry Law 5477-1984, or the Research Law. In general, until the grants are repaid with interest, royalties are payable to the Israeli government in the amount of 3% on revenues derived from sales of products or services developed in whole or in part using the IIA grants, including EB613, EB612 and any other oral PTH product candidates we may develop. The royalty rate may increase to 5%, with respect to approved applications filed following any year in which we achieve sales of over $70 million.

The amount that must be repaid may be increased up to six times the amount of the grant received, and the rate of royalties may be accelerated, if manufacturing of the products developed with the grant money is transferred outside of the State of Israel. Moreover, a payment of up to 600% of the grant received may be required upon the transfer of any IIA-funded know-how to a non-Israeli entity. We signed a contract with a U.K.-based contract manufacturing organization to produce and supply pills for trials performed worldwide. We believe that, because this production is not for commercial purposes, it will not affect the royalty rates to be paid to the IIA. Should the IIA successfully take a contrary position, the maximum royalties to be paid to the IIA will be approximately $1.5 million, which is three times the amount of the original grant. Following the signing of the Amgen Agreement, we have been required to pay 5.38% of each payment by Amgen and up to 600% of the grant received. As of December 31, 2021, we had paid royalties to the IIA in the amount of $79,000 related to the Amgen Agreement.

In addition to paying any royalties due, we must abide by other restrictions associated with receiving such grants under the Research Law that continue to apply following repayment to the IIA.

Financial Overview

Revenue

To date, we have not generated any revenue from sales of our products, and we do not expect to receive any revenue from any product candidates that we develop unless and until we obtain regulatory approval and successfully commercialize our products.

Under the Amgen Agreement, during 2020 through December 31, 2021, we had received an additional aggregate amount of $743,000 from Amgen for research and development services.

Revenues including revenues under the Amgen Agreement are recognized according to ASC 606, "Revenues from Contracts with Customers”.

According to ASC 606, a performance obligation is a promise to provide a distinct good or service or a series of distinct goods or services. Goods and services that are not distinct are bundled with other goods or services in the contract until a bundle of goods or services that is distinct is created. A good or service promised to a customer is distinct if the customer can benefit from the good or service either on its own or together with other resources that are readily available to the customer and the entity’s promise to transfer the good or service to the customer is separately identifiable from other promises in the contract. Options granted to the customer that do not provide a material right to the customer that it would not receive without entering into the contract do not give rise to performance obligations. We identified two performance obligations in the agreement: the license to use the Company's proprietary drug delivery platform and pre-clinical research and development services (“pre-clinical R&D services”). The license to our intellectual property has significant standalone functionality, since we are not required to continue to support, develop or maintain the intellectual property transferred and will not undertake any activities to change the standalone functionality of the intellectual property. Therefore, we recognized the revenues related to this performance obligation in December 2018 at the point in time that control of the license was transferred to Amgen. The preclinical R&D services include discovery, research and design preclinical activities relating to the programs selected by Amgen. Revenues attributed to the preclinical R&D services are recognized during the period the pre-clinical R&D services are provided according to the input model method on a cost-to-cost basis. Each of these items met the definition of distinct performance obligation. The Company evaluated the standalone selling price of the pre-clinical R&D services at $225,000 and the right to use the intellectual property at $500,000.

Under ASC 606, the consideration that we would be entitled to upon the achievement of contractual milestones, which are contingent upon the occurrence of future events of development and commercial progress, are a form of variable consideration. When assessing the portion, if any, of such milestone-related consideration to be included in the transaction price, we first assess the most likely outcome for each milestone, and exclude the consideration related to milestones of which the occurrence is not considered the most likely outcome. We then evaluate if any of the variable consideration determined in the first step is constrained. Variable consideration is included in the transaction price if, in our judgment, it is probable that a significant future reversal of cumulative revenue under the contract will not occur. Estimates of variable consideration and determination of whether to include estimated amounts in the transaction price are based largely on an assessment of our anticipated performance and all information (historical, current and forecasted) that is reasonably available. We did not recognize any revenues from milestone payments.

An entity should recognize revenue for a sales-based or usage-based royalty promised in exchange for a license of intellectual property only when (or as) the later of the following events occurs:

- The subsequent sale or usage occurs; and
- The performance obligation to which some or all of the sales-based or usage-based royalty has been allocated has been satisfied (or partially satisfied).

We did not recognize any revenues from royalties since royalties are payable based on future commercial sales, as defined in the Amgen Agreement and there were no commercial sales as of the date of the financial statements

For the years ended December 31, 2021 and 2020, we recognized revenues from the Amgen Agreement in the total amounts of $502,000 and $365,000, respectively.

Research and Development Expenses

Research and development expenses consist of costs incurred for the development of our drug delivery technology and our product candidates. Those expenses include:

- employee-related expenses, including salaries, bonuses and share-based compensation expenses for employees and service providers in the research and development function;
- expenses incurred in operating our laboratories including our small-scale manufacturing facility;
- expenses incurred under agreements with CROs, and investigative sites that conduct our clinical trials;
- expenses related to outsourced and contracted services, such as external laboratories, consulting and advisory services;
- supply, development and manufacturing costs relating to clinical trial materials; and
- other costs associated with pre-clinical and clinical activities.

Research and development activities are the primary focus of our business. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. We expect that our research and development expenses will increase significantly in future periods as we advance EB613 and EB612 into later stages of clinical development and invest in additional preclinical candidates.

Research expenses are generally recognized as incurred. An intangible asset arising from the development of our product candidates is recognized if certain capitalization conditions are met. During the years ended December 31, 2021 and 2020, we did not capitalize any development costs.

Our research and development expenses may vary substantially from period to period based on the timing of our research and development activities, including due to the timing of initiation of clinical trials and the enrollment of patients in clinical trials. For the years ended December 31, 2021 and 2020, our research and development expenses were $6.8 million and $6.4 million, respectively. Research and development expenses for the years ended December 31, 2021 and 2020 were primarily for the development of EB613 and EB612. The successful development of our product candidates is highly uncertain. At this time, we cannot reasonably estimate the nature, timing and estimated costs of the efforts that will be necessary to complete the development of, or the period, if any, in which material net cash inflows may commence from, any of our product candidates. This is due to numerous risks and uncertainties associated with developing drugs, including:

- the uncertainty of the scope, rate of progress, results and cost of our clinical trials, nonclinical testing and other related activities;
- the cost of manufacturing clinical supplies and establishing commercial supplies of our product candidates and any products that we may develop;
- the number and characteristics of product candidates that we pursue;
- the cost, timing and outcomes of regulatory approvals;
- the cost and timing of establishing any sales, marketing, and distribution capabilities; and

- the terms and timing of any collaborative, licensing and other arrangements that we may establish, including any milestone and royalty payments thereunder.

A change in the outcome of any of these variables with respect to the development of EB613, EB612 or any other product candidate that we may develop could mean a significant change in the costs and timing associated with the development of such product candidate. For example, if the FDA or other regulatory authority were to require us to conduct preclinical and/or clinical studies beyond those which we currently anticipate will be required for the completion of clinical development, if we experience significant delays in enrollment in any clinical trials or if we encounter difficulties in manufacturing our clinical supplies, then we could be required to expend significant additional financial resources and time on the completion of the clinical development.

General and Administrative Expenses

General and administrative expenses consist principally of salaries, benefits, share-based compensation and related costs for directors and personnel in executive and finance functions. Other general and administrative expenses include D&O insurance and other insurance, communication expenses, professional fees for legal and accounting services, patent counseling and portfolio maintenance and business development expenses.

We expect that our general and administrative expenses will increase in the future as we increase our headcount and expand our administrative function to support our operations.

Financial Expenses (Income), Net

Financial expenses, net are composed primarily of interest income and exchange rate differences of certain currencies against our functional currency.

Taxes on Income

We have not generated taxable income since our inception, and as of December 31, 2021, we had carry-forward tax losses of $56.1 million. We anticipate that we will be able to carry forward these tax losses indefinitely to future tax years. Accordingly, we do not expect to pay taxes in Israel until we have taxable income after the full utilization of our carryforward tax losses. We provided a full valuation allowance with respect to the deferred tax assets related to these carry forward losses of the Company.

As of December 31, 2021, Entera Bio Inc. has no carry forward tax losses.

Results of Operations

Comparison of Years Ended December 31, 2021 and 2020

	Year Ended December 31,		Increase (Decrease)	
	2021	2020	$	%
	(In thousands, except for percentage information)			
Revenues	$ 571	$ 365	$ 206	56%
Cost of revenues	$ 373	$ 300	73	24%
Operating expenses:				
Research and development expenses, net	$ 6,771	$ 6,382	$ 398	6%
General and administrative expenses	$ 5,690	$ 4,851	$ 839	17%
Other income	$ (46)	$ -	$ (46)	100%
Operating loss	$ 12,217	$ 11,168	$ 1,049	9%
Financial expenses, net	$ 29	$ 28	$ 1	4%
Income tax (benefit) expenses	$ (59)	$ 20	$ (79)	(395)%
Net loss	$ 12,187	$ 11,216	$ 1,190	9%

Revenue

Revenues for the year ended December 31, 2021 and 2020 were $571,000 and $365,000, respectively. For 2021 and 2020, the majority of our revenues were attributable to research and development, or R&D services provided to Amgen under the Amgen Agreement and other MTA agreements. We did not generate any revenues prior to the signing of the Amgen Agreement. For the accounting treatment see "—Critical Accounting Policies and Estimates—Revenue Recognition" below.

Cost of Revenues

Cost of revenues for the year ended December 31, 2021 were $373,000 compared to $300,000 for the year ended December 31, 2020 and were primarily attributed to salaries and related expenses in connection with the R&D services provided to Amgen and other MTA agreements.

Research and Development Expenses, Net

Research and development expenses, net for the year ended December 31, 2021 were $6.8 million, as compared to $6.4 million for the year ended December 31, 2020. The increase of $0.4 million was primarily due to an increase of $0.7 million in materials and production costs, an increase of $1.2 million in pre-clinical activity as part of the preparation for our Phase 3 clinical trial for EB613 and an increase of $0.1 million in employees compensation, including share-based compensation. The increase was partially offset by a decrease of $0.9 million in other clinical trial expenses related to EB613 related to our Phase 2 trial that was completed in June 2021 and a decrease of $0.7 million in professional and consulting services expenses mainly due to submission of the IND in 2020.

General and Administrative Expenses

General and administrative expenses for the year ended December 31, 2021 were $5.7 million, compared to $4.9 million for the year ended December 31, 2020. The increase of $0.8 million was mainly attributed to an increase of $0.8 million in share-based compensation granted to executive officers, as well as the reversal of expenses related to the expiration of the former CEO's unvested options in 2020, an increase of $0.3 million in legal and accounting costs and an increase of $0.2 million in D&O insurance costs. The increase was partially offset by a decrease of $0.5 million in professional fees, mainly search fees.

Financial Expenses, Net

Financial expenses, net for the year ended December 31, 2021 was $29,000, compared to $28,000 for the year ended December 31, 2020. Our financial expenses are comprised mainly of bank commission and exchange rate differences of certain currencies against our functional currency, which is the U.S. Dollar.

Liquidity and Capital Resources

Since inception, we have incurred significant losses. As a result of our recurring losses from operations, negative cash flows from operating activities and lack of liquidity, our independent registered public accounting firm included an explanatory paragraph in its report on our financial statements as of, and for the year ended, December 31, 2021, expressing the existence of substantial doubt about our ability to continue as a going concern. For the years ended December 31, 2021 and 2020, our operating losses were $12.2 million and $11.2 million, respectively. We expect to continue to incur significant expenses and losses for the next several years as we advance our products through development and provide administrative support for our operations. As of December 31, 2021, we had an accumulated deficit of $82.4 million. Since our inception, we have raised a total of $84.7 million, including $25.3 million through our ATM Programs, of which $21.8 million was raised in 2021, $14.3 million in our December 2019 private placement, $11.2 in our IPO in 2018 and $33.9 in aggregate funding from a combination of grants, exercise of options and warrants and private placements of Ordinary Shares, preferred shares and debt prior to our IPO. In addition, through December 31, 2021, we had have received approximately $1.4 million under the Amgen Agreement. As of December 31, 2021, we had cash and cash equivalents of $24.9 million. Our primary uses of cash have been to fund research and development, general and administrative and working capital requirements, and we expect these will continue to be our primary uses of cash.

In July 2020, we entered into an equity distribution agreement with Canaccord Genuity LLC, as sales agent, to implement an ATM program under which we, from time to time, may offer and sell our Ordinary Shares, having an aggregate offering price of up to $13.9 million (the "Prior ATM Program"). The sales agent was entitled to a fixed commission of 3% of the aggregate gross proceeds as well as and reimbursement of expenses.

On July 13, 2020, we filed with the SEC a shelf registration statement on a Form F-3 for the registration of our Ordinary Shares that we may, from time to time, offer and sell in one or more offerings, our securities with an aggregate offering price of up to $100 million. In addition, certain Ordinary Shares under such Form F-3 were offered, issued and sold pursuant to Prior ATM Program and the ATM Program (as defined below). However, following our transition from foreign private issuer to domestic issuer status beginning January 1, 2022 and the filing of this Annual Report on Form 10-K, we will no longer be able to make use of such shelf registration statement on Form F-3 and will need to file a new registration statement on a form applicable to domestic issuers, such as Form S-3, should we wish to engage in further public offerings of our Ordinary Shares, including further sales pursuant to the ATM Program.

The Prior ATM Program terminated in accordance with its terms following our sale of the full dollar amount of Ordinary Shares permitted thereunder. On May 7, 2021 we entered into an At Market Issuance Sales Agreement with B. Riley Securities, Inc., as sales agent, under which we, from time to time, may offer and sell up to 5,000,000 Ordinary Shares (the "ATM Program"). The sales agent is entitled to a fixed commission of 3% of the aggregate gross proceeds as well as and reimbursement of expenses. For the year ended December 31, 2021, we sold an aggregate of 2.546,265 Ordinary Shares under the Prior ATM Program and 1,764,860 Ordinary Shares under the ATM Program, the aggregate proceeds of which amounted to $25 million, net of issuance costs.

Funding Requirements

We believe that our existing capital resources, not including potential milestone payments, will be sufficient to meet our projected operating requirements into the fourth quarter of 2022.

We have based these estimates on assumptions that may prove to be wrong, and we may use our available capital resources sooner than we currently expect. Because of the numerous risks and uncertainties associated with the development of our product candidates, and the extent to which we may enter into collaborations with third parties for development of these or other product candidates, we are unable to estimate the amounts of increased capital outlays and operating expenses associated with completing the development of our current and future product candidates. Our future capital requirements will depend on many factors, including:

- the costs, timing and outcome of clinical trials for, and regulatory review of, EB613, EB612 and any other product candidates we may develop;
- the costs of development activities for any other product candidates we may pursue;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- the impact of COVID-19 on our clinical trials, regulatory timelines, business operations and financial stability; and
- our ability to establish collaborations on favorable terms, if at all.

We are in the process of evaluating various financing alternatives in the public or private equity markets, government grants or through license of our technology to additional external parties through partnerships or research collaborations as we will need to finance future research and development activities, general and administrative expenses and working capital through fund raising. However, there is no certainty about our ability to obtain such funding.

We do not have any committed external sources of funds. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of our then-existing shareholders will be diluted, and the terms of these securities may include liquidation or other preferences that may adversely affect our existing shareholders' rights as shareholders. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends and may include requirements to hold minimum levels of funding. If we raise additional funds through collaborations, strategic alliances or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams or research programs or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings or collaborations, when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market our oral PTH product candidates and any other product candidates that we would otherwise prefer to develop and market ourselves.

Our audited consolidated financial statements for the year ended December 31, 2021, included elsewhere in this Annual Report on Form 10-K, note that there is substantial doubt about our ability to continue as a going concern as of such date; and in its report accompanying our audited consolidated financial statements included herein, our independent registered public accounting firm included an explanatory paragraph stating that our recurring losses from operations and our cash outflows from operating activities raise substantial doubt as to our ability to continue as a going concern. This means that our management and our independent registered public accounting firm have expressed substantial doubt about our ability to continue our operations without an additional infusion of capital from external sources. The audited consolidated financial statements have been prepared on a going concern basis and do not include any adjustments that may be necessary should we be unable to continue as a going concern. If we are unable to finance our operations, our business would be in jeopardy and we might not be able to continue operations and might have to liquidate our assets. In that case, investors might receive less than the value at which those assets are carried on our financial statements, and it is likely that investors would lose all or a part of their investment.

Cash Flows

Year Ended December 31, 2021 Compared to Year Ended December 31, 2020

The following table sets forth the primary sources and uses of cash for each of the periods set forth below:

	(audited) Year ended December 31,	
	2021	**2020**
	(in thousands)	
Net Cash used in operating activities	$ (9,063)	$ (10,557)
Net Cash used in investing activities	(17)	(53)
Net Cash provided by financing activities	25,381	4,051
Net (decrease) increase in cash and cash equivalents	$ 16,301	$ (6,559)

Net Cash Used in Operating Activities

Net Cash used in operating activities for the year ended December 31, 2021 was $9.1 million, consisting primarily of our operating loss of $12.2 million, which was partially offset by $1.9 million of share-based compensation and depreciation expenses and an increase of $1.3 million in our working capital.

Net Cash used in operating activities for the year ended December 31, 2020 was $10.6 million consisting primarily of our operating loss of $11.2 million and a 0.4 million decrease in our working capital which was partially offset by $0.9 million of share-based compensation, $0.1 million of depreciation expenses.

The decrease of $1.5 million in cash used in operating activities for the year ended December 31, 2021 compared to the same period in 2020 was mainly attributed to our change in loss, an increase of $1.0 million in share-based compensation and a decrease of $1.7 in working capital mainly due to a decrease in payments to suppliers and services providers, which were partially offset by an increase of $0.2 in payments to D&O insurance and an increase of $1.0 million in our operating loss.

Net Cash Used in Investing Activities

Net Cash used in investing activities for the year ended December 31, 2021 and 2020 consisted primarily of the purchase of property and equipment.

Net Cash Provided by Financing Activities

Net Cash provided by financing activities for the year ended December 31, 2021 mainly resulted from net proceeds of $21.8 million from the issuance of Ordinary Shares under our ATM Programs and $3.6 million from exercise of warrants and options.

Net Cash provided by financing activities for the year ended December 31, 2020 mainly resulted from net proceeds of $0.8 million from the issuance of the Ordinary Shares and Warrants in the final closing of our December 2019 private placement offering and net proceeds of $3.2 million from the issuance of Ordinary Shares under our Prior ATM Program.

Contractual Obligations

The following tables summarize our contractual obligations and commitments as of December 31, 2021 that will affect our future liquidity:

	Payments due by period				
Contractual Obligations	**Total**	**Less than 1 year**	**1 - 3 years**	**3 - 5 years**	**More than 5 years**
			(In thousands)		
Operating leases for facility and vehicles	$ 341	$ 224	$ 117	$ -	$ -
Total	$ 341	$ 224	$ 117	$ -	$ -

Severance Obligations

We have long-term liabilities for severance pay that are calculated pursuant to Israeli law generally based on the most recent salary of the relevant employees multiplied by the number of years of employment to the extent not covered by our regular deposits with defined contribution plans. As of December 31, 2021, our severance pay liability, net was immaterial. Because the timing of any such payments is not fixed and determinable, we have not included these liabilities in the table above.

Contingencies

We also have obligations to make future payments to third parties that become due and payable on the achievement of certain milestones, such as royalties upon sale of products or revenues from the Amgen Agreement. We have not included these commitments in our statements of financial position or in the table above because the achievement and timing of these milestones is not fixed and determinable. These potential future commitments include a commitment to pay Oramed royalties equal to 3% of our net revenues pursuant to the terms of the Patent Transfer Agreement between us and Oramed and a commitment to pay royalties to the IIA**.**

Critical Accounting Policies and Estimates

We prepare our consolidated financial statements in accordance with U.S. generally accepted accounting principles, or GAAP. The preparation of consolidated financial statements also requires us to make estimates and assumptions that affect the reported amounts of assets, liabilities, revenue, expenses and related disclosures. We base our estimates on historical experience and on various other assumptions that we believe to be reasonable under the circumstances. Actual results could differ significantly from the estimates made by our management. To the extent that there are differences between our estimates and actual results, our future financial statement presentation, financial condition, results of operations and cash flows will be affected.

While our significant accounting policies are more fully described in Note 2 to the consolidated financial statements included elsewhere in this Annual Report on Form 10-K, we believe that the following accounting policies are the most critical to assist shareholders and investors reading the consolidated financial statements in fully understanding and evaluating our financial condition and results of operations. These policies relate to the more significant areas involving management's judgments and estimates and they require our most difficult, subjective or complex judgments, often as a result of the need to make estimates about the effect of the matters that are inherently uncertain.

Revenue Recognition

With respect to the Amgen Agreement, we used our judgement to identify our deliverables in the agreement and whether the deliverables are distinct performance obligation. In addition, we use our judgement to determine the allocation of the transaction price between our identified distinct performance obligations. We also used significant judgment in order to determine the R&D services period. For a description of our revenue recognition policy see "Note 2—Summary of Significant Accounting Policies—Revenue Recognition" of our audited consolidated financial statements for the year ended December 31, 2021, included elsewhere in this Annual Report.

Share-Based Compensation

In 2013 and in 2018, we adopted share-based compensation plans for employees, directors and service providers. Our share-based compensation plan adopted in 2013 governs the issuance of equity incentive awards prior to our initial public offering, and the share-based compensation plan adopted in 2018 governs the issuance of equity incentive awards from and after the closing of our initial public offering. As part of the plans, we grant employees, directors and service providers, from time to time and at our discretion, options to purchase our Ordinary Shares and restricted share units. The fair value of the services received in exchange for the grant of the options is recognized as an expense in our statements of comprehensive loss with a corresponding adjustment to equity in our statements of financial position. The total amount is recognized as an expense ratably over the service period of the options, which is the period during which all vesting conditions are expected to be met.

We estimate the fair value of our share-based compensation to employees, directors and service providers using the Black-Scholes option pricing model, which requires the input of highly subjective assumptions, including (a) the expected volatility of our shares, (b) the expected term of the award, (c) the risk-free interest rate, (d) expected dividends and (e) the fair value of our Ordinary Shares at the date of grant.

The following table summarizes the allocation of our share-based compensation expense:

	Year ended December 31,	
	2021	2020 (1)
	(in thousands)	
Cost of revenues	$ 102	$ 51
Research and development	661	514
General and administrative	1,098	336
Total	$ 1,861	$ 901

(1) The resignation of Mr. Gridley, our Former CEO, took effect on September 7, 2020. According to the terms of Mr. Gridley's options, of which had yet to fully vest expired, 553,942 options expired and were recognized in the consolidated statement of comprehensive loss as a reverse of expense under the general and administrative line item in the amount of $0.3 million.

Recently Issued Accounting Pronouncements

Certain recently issued accounting pronouncements are discussed in Note 2 to the consolidated financial statements included elsewhere in this Annual Report on Form 10-K.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

In the ordinary course of our operations, we are exposed to certain market risks. Market risk represents the risk of loss that may impact our financial position due to adverse changes in financial market prices and rates. Our market risk exposure is primarily a result of foreign currency exchange rates.

Foreign Currency Exchange Risk

Our functional currency and reporting currency is the U.S. dollar. Although a substantial portion of our expenses (mainly salaries and related costs) are denominated in NIS, accounting for 25%, 32% and 31% of our expenses in the years ended December 31, 2021, 2020 and 2019, respectively, our revenues were generated under agreement denominated in U.S. dollars and our proceeds from the Amgen Agreement, share issuance from our 2019 private placement, our ATM programs and exercise of warrants and options, which have been the main source of our financing, are denominated in U.S. dollars. Fluctuations in the NIS to U.S. dollar exchange rate may affect our results because some of our assets and liabilities are linked to the NIS, and a portion of our operating expenses are denominated in NIS. In the future, we also may be exposed to additional currency fluctuations against the U.S. dollar. See "Item 1.A.—Risk Factors— Risks Relating to Our Incorporation and Location in Israel—Our business is subject to currency exchange risk and fluctuations between the U.S. dollar and other currencies may negatively affect our earnings and results of operations."

A decrease in value of the NIS in relation to the U.S. dollar has the effect of reducing the U.S. dollar amount of our expenses or payables that are payable in NIS, unless those expenses or payables are linked to the U.S. dollar. Conversely, any appreciation of the NIS in relation to the U.S. dollar has the effect of increasing the U.S. dollar value of our unlinked NIS expenses, which would have a negative impact on our financial results. In 2021, the value of the NIS appreciated against the U.S. dollar by 3.27%, which appreciation was partially offset by inflation in Israel of 2.8%. In 2020, the value of the NIS appreciated against the U.S. dollar by 6.97%, which appreciation was partially offset by inflation in Israel of approximately 0.7%.

Because exchange rates between the U.S. dollar and the NIS (as well as between the U.S. dollar and other currencies) fluctuate continuously, such fluctuations have an impact on our results and period-to-period comparisons of our results. The effects of foreign currency re-measurements are reported in our statements of operations.

We will continue to monitor exposure to currency fluctuations. We do not hedge our foreign currency exchange risk. In the future, we may enter into formal currency hedging transactions to decrease the risk of financial exposure from fluctuations in the exchange rates of our principal operating currencies. These measures, however, may not adequately protect us from the material adverse effects of such fluctuations.

Inflation Risk

We do not believe that inflation had a material effect on our business, financial condition or results of operations in the last two fiscal years. If our costs were to become subject to significant inflationary pressures, we may not be able to fully offset such higher costs through hedging transactions. Our inability or failure to do so could harm our business, financial condition and results of operations.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

ENTERA BIO LTD.

CONSOLIDATED FINANCIAL STATEMENTS

AS OF DECEMBER 31, 2021

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Report of Independent Registered Public Accounting Firm

To the Board of Directors and Shareholders of Entera Bio Ltd.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Entera Bio Ltd. and its subsidiary (the "Company") as of December 31, 2021 and 2020, and the related consolidated statements of operations, changes in shareholders' equity and cash flows for the years then ended, including the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2021 and 2020, and the results of its operations and its cash flows for the years then ended in conformity with accounting principles generally accepted in the United States of America.

Substantial Doubt About the Company's Ability to Continue as a Going Concern

The accompanying consolidated financial statements have been prepared assuming that the Company will continue as a going concern. As discussed in Note 1d to the consolidated financial statements, the Company has incurred recurring losses from operations and has cash outflows from operating activities that raise substantial doubt about its ability to continue as a going concern. Management's plans in regard to these matters are also described in Note 1d. The consolidated financial statements do not include any adjustments that might result from the outcome of this uncertainty

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's consolidated financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits of these consolidated financial statements in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/Kesselman & Kesselman
Certified Public Accountants (lsr.)
A member firm of PricewaterhouseCoopers International Limited

Tel-Aviv, Israel
March 8, 2022

We have served as the Company's auditor since 2010.

ENTERA BIO LTD.
CONSOLIDATED BALANCE SHEETS
(U.S. dollars in thousands, except share data)

	December 31	
	2021	**2020**
Assets		
CURRENT ASSETS:		
Cash and cash equivalents	24,892	8,593
Accounts receivable	183	255
Other current assets	254	261
TOTAL CURRENT ASSETS	25,329	9,109
NON-CURRENT ASSETS:		
Property and equipment, net	156	192
Operating lease right-of-use assets	239	374
Deferred income taxes	217	-
Funds in respect of employee rights upon retirement	46	47
TOTAL NON-CURRENT ASSETS	658	613
TOTAL ASSETS	25,987	9,722
Liabilities and shareholders' equity		
CURRENT LIABILITIES:		
Accounts payable	166	164
Accrued expenses and other payables	2,801	1,330
Current maturities of operating lease	179	189
Contract liabilities	15	158
TOTAL CURRENT LIABILITIES	3,161	1,841
NON-CURRENT LIABILITIES:		
Operating lease liabilities	123	243
Liability for employee rights upon retirement	138	128
TOTAL NON-CURRENT LIABILITIES	261	371
TOTAL LIABILITIES	3,422	2,212
COMMITMENTS AND CONTINGENCIES		
SHAREHOLDERS' EQUITY:		
Ordinary Shares, NIS 0.0000769 par value: Authorized - as of December 31, 2021 and December 31, 2020, 140,010,000 shares; issued and outstanding:- as of December 31, 2021, and December 31, 2020 28,804,411 and 21,057,922 shares, respectively	*	*
Additional paid-in capital	104,950	77,708
Accumulated other comprehensive income	41	41
Accumulated deficit	(82,426)	(70,239)
TOTAL SHAREHOLDERS' EQUITY	22,565	7,510
TOTAL LIABILITIES AND SHAREHOLDERS' EQUITY	25,987	9,722

* Represents an amount less than one thousand US dollars

The accompanying notes are an integral part of the consolidated financial statements.

ENTERA BIO LTD.
CONSOLIDATED STATEMENTS OF OPERATIONS
(U.S. dollars in thousands, except share and per share data)

	Year ended December 31	
	2021	**2020**
REVENUES	571	365
COST OF REVENUES	373	300
GROSS PROFIT	198	65
OPERATING EXPENSES:		
Research and development	6,771	6,382
General and administrative	5,690	4,851
Other income	(46)	-
TOTAL OPERATING EXPENSES	12,415	11,233
OPERATING LOSS	12,217	11,168
FINANCIAL EXPENSES , net	29	28
LOSS BEFORE INCOME TAX	12,246	11,196
INCOME TAX (BENEFIT) EXPENSE	(59)	20
NET LOSS	12,187	11,216
LOSS PER SHARE BASIC AND DILUTED	0.47	0.67
WEIGHTED-AVERAGE NUMBER OF SHARES OUTSTANDING USED IN COMPUTATION OF BASIC AND DILUTED LOSS PER SHARE	26,133,770	18,417,093

The accompanying notes are an integral part of the consolidated financial statements.

ENTERA BIO LTD
CONSOLIDATED STATEMENTS OF CHANGES IN SHAREHOLDERS' EQUITY
(U.S. dollars in thousands, except share and per share data)

	Ordinary shares					
	Number of shares issued	Amounts	Additional paid-in capital	Accumulated other Comprehensive income	Accumulated deficit	Total
BALANCE AT JANUARY 1, 2020	17,864,684	*	72,756	41	(59,023)	13,774
Net loss	-	-	-	-	(11,216)	(11,216)
Issuance of ordinary shares and warrants due to a private placement net of issuance costs	337,553	-	796	-	-	796
Issuance of shares due to the ATM program, net of issuance costs	2,802,731	-	3,187	-	-	3,187
Exercise of options to ordinary shares	31,954	-	68	-	-	68
Share-based compensation	-	-	901	-	-	901
Vested restricted share units	21,000	-	-	-	-	-
BALANCE AT DECEMBER 31, 2020	21,057,922	*	77,708	41	(70,239)	7,510
Net loss	-	-	-	-	(12,187)	(12,187)
Exercise of warrants to ordinary shares	3,175,050	-	3,158	-	-	3,158
Issuance of shares due to the ATM program, net of issuance costs	4,386,728	*	21,805	-	-	21,805
Exercise of options to ordinary shares	177,711	-	418	-	-	418
Share-based compensation	-	-	1,861	-	-	1,861
Vested restricted share units	7,000	-	-	-	-	-
BALANCE AT DECEMBER 31, 2021	28,804,411	*	104,950	41	(82,426)	22,565

* Represents an amount less than one thousand US dollars.

The accompanying notes are an integral part of these consolidated financial statements

ENTERA BIO LTD.
CONSOLIDATED STATEMENTS OF CASH FLOWS
(U.S. dollars in thousands)

	Year ended December 31	
	2021	**2020**
CASH FLOWS FROM OPERATING ACTIVITIES:		
Net loss	(12,187)	(11,216)
Adjustments required to reconcile net loss to net cash used in operating activities:		
Depreciation	53	63
Deferred income taxes	(217)	-
Share-based compensation	1,861	901
Finance expenses (income), net	18	46
Changes in operating asset and liabilities:		
Decrease in accounts receivable	72	23
Decrease (increase) in other current assets	7	(55)
Increase (decrease) in accounts payable	2	(170)
Increase (decrease) in accrued expenses and other payables	1,471	(40)
Increase (decrease) in contract liabilities	(143)	(109)
Net cash used in operating activities	(9,063)	(10,557)
CASH FLOWS FROM INVESTING ACTIVITIES:		
Purchase of property and equipment	(17)	(53)
Net cash used in investing activities	(17)	(53)
CASH FLOWS FROM FINANCING ACTIVITIES:		
Cash flows from financing activities:		
Proceeds from issuance of shares and warrants, net of issuance costs	-	796
Proceeds from issuance of shares through ATM programs, net of issuance costs	21,805	3,187
Exercise of options and warrants into shares	3,576	68
Net cash provided by financing activities	25,381	4,051
INCREASE (DECREASE) IN CASH, CASH EQUIVALENTS AND RESTRICTED CASH	16,301	(6,559)
CASH, CASH EQUIVALENTS AND RESTRICTED DEPOSITS AT BEGINNING OF THE YEAR	8,663	15,222
CASH, CASH EQUIVALENTS AND RESTRICTED DEPOSITS AT END OF THE YEAR	24,964	8,663

Reconciliation in amounts on consolidated balance sheets:

Cash and cash equivalents	24,892	8,593
Restricted deposits included in other current assets	72	70
Total cash and cash equivalents and restricted cash	24,964	8,663
SUPPLEMENTAL DISCLOSURE OF CASH FLOW TRANSACTIONS:		
Income taxes paid in cash during the year	2	89
SUPPLEMENTARY INFORMATION ON INVESTING AND FINANCING ACTIVITIES NOT INVOLVING CASH FLOWS:		
Cashless exercise of warrants	*	-
Vested restricted shares units	*	*
Operating lease right of use assets obtained in exchange for new operating lease liabilities	31	258

NOTE 1 - GENERAL

a. Entera Bio Ltd. (collectively with its subsidiary, the "Company") was incorporated on September 30, 2009 and commenced operation on June 1, 2010. On January 8, 2018 the Company incorporated Entera Bio Inc., a wholly owned subsidiary incorporated in Delaware USA. The Company is a leader in the development and commercialization of orally delivered large molecule therapeutics for use in areas with significant unmet medical need where adoption of injectable therapies is limited due to cost, convenience and compliance challenges for patients. The Company's most advanced product candidates, EB613 for the treatment of osteoporosis and EB612 for the treatment of hypoparathyroidism, are based on its proprietary technology platform and are both in Phase 2 clinical development. The Company also licenses its technology to biopharmaceutical companies for use with their proprietary compounds and, to date, has completed one such agreement with Amgen Inc.

b. The Company's securities have been listed for trading on the Nasdaq Capital Market since the Company's initial public offering in July 2018, where a total of 1,400,000 ordinary shares and 1,400,000 warrants (the "IPO warrants") to purchase up to 700,000 ordinary shares were issued in consideration of net proceeds of $9.6 million, after deducting offering expenses. The public offering price was $8.00 per unit, each of which consisted of one ordinary share and one warrant to purchase 0.5 of an ordinary share.

c. On December 10, 2018, the Company entered into agreement (the "Amgen Agreement") with Amgen Inc. ("Amgen") in inflammatory disease and other serious illnesses. Pursuant to the Amgen Agreement, the Company and Amgen have agreed to use the Company's proprietary drug delivery platform to develop oral formulations for one preclinical large molecule program that Amgen has selected. Amgen also has options to select up to two additional programs to include in the agreement. Amgen is responsible for the clinical development, regulatory approval, manufacturing and worldwide commercialization of the programs.

The Company granted Amgen an exclusive, worldwide, sublicensable license under certain of its intellectual property relating to its drug delivery technology to develop, manufacture and commercialize the applicable products. The Company will retain all intellectual property rights to its drug delivery technology, and Amgen will retain all rights to its large molecules and any subsequent improvements, and ownership of certain intellectual property developed through the performance of the agreement is to be determined by U.S. patent law. See also note 10.

d. Since the Company is engaged in research and development activities, it has not derived significant income from its activities and has incurred accumulated losses in the amount of $82.4 million through December 31, 2021 and negative cash flows from operating activities. The Company's management is of the opinion that its available funds as of December 31, 2021 will allow the Company to operate under its current plans into the fourth quarter of 2022. These factors raise substantial doubt as to the Company's ability to continue as a going concern. Management is in the process of evaluating various financing alternatives in the public or private equity markets, government grants or through license of the company's technology to additional external parties through partnerships or research collaborations as the Company will need to finance future research and development activities, general and administrative expenses and working capital through fund raising. However, there is no certainty about the Company's ability to obtain such funding.

NOTE 2 - SIGNIFICANT ACCOUNTING POLICIES

a. Basis of presentation of the financial statements

The consolidated financial statements are prepared in accordance with generally accepted accounting principles in the United States ("U.S. GAAP"). Prior to 2021, the Company prepared its financial statements in accordance with International Financial Reporting Standards ("IFRS"), as issued by the International Accounting Standards Board ("IASB"), as permitted in the United States ("U.S.") based on the Company's status as a foreign private issuer as defined by the U.S. Securities and Exchange Commission (the "SEC"). During 2021, the Company determined that it is no longer qualified as a foreign private issuer under the SEC rules. As a result, as of January 1, 2022, the Company is required to comply with all of the disclosure and reporting requirements applicable to U.S. domestic issuers.

b. Use of estimates in the preparation of financial statements

The preparation of the consolidated financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, the disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of revenues and expenses during the reporting period. Actual results may differ from those estimates.

c. Functional currency

1) Functional and presentation currency

Items included in the financial statements of the Company are measured using the currency of the primary economic environment in which the entity operates ("the functional currency"). The U.S. dollar is the currency of the primary economic environment in which the operations of the Company is conducted. The consolidated financial statements are presented in U.S. dollars.

2) Transactions and balances

Transactions and balances originally denominated in U.S. dollars are presented at their original amounts. Balances in non- U.S. dollar currencies are translated into U.S. dollars using historical and current exchange rates for non-monetary and monetary balances, respectively. For non-U.S. dollar transactions and other items in the statements of income (indicated below), the following exchange rates are used: (i) for transactions – exchange rates at transaction dates or average exchange rates; and (ii) for other items (derived from non-monetary balance sheet items such as depreciation and amortization) – historical exchange rates. Currency transaction gains and losses are presented in financial income (expenses), as appropriate.

The functional currency of the subsidiary is the U.S. dollar.

d. Principles of consolidation

The consolidated financial statements include the accounts of the Company and Entera Bio Inc. All inter-company transactions and balances have been eliminated in consolidation.

NOTE 2 - SIGNIFICANT ACCOUNTING POLICIES (continued)

e. Cash and cash equivalents

The Company considers as cash equivalents all short-term, highly liquid investments, which include short-term bank deposits with original maturities of three months or less from the date of purchase that are not restricted as to withdrawal or use and are readily convertible to known amounts of cash.

f. Restricted

Restricted cash deposited in an interest-bearing saving account which is used as a security for the Company's office rent, and credit card.

g. Fair value measurement

The Company measures fair value and discloses fair value measurements for financial assets and liabilities. Fair value is based on the price that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date. The accounting standard establishes a fair value hierarchy that prioritizes observable and unobservable inputs used to measure fair value into three broad levels, which are described below:

Level 1: Quoted prices (unadjusted) in active markets that are accessible at the measurement date for assets or liabilities. The fair value hierarchy gives the highest priority to Level 1 inputs.

Level 2: Observable inputs that are based on inputs not quoted on active markets but corroborated by market data.

Level 3: Unobservable inputs are used when little or no market data is available. The fair value hierarchy gives the lowest priority to Level 3 inputs.

h. Employee severance benefits

Under the Israeli Severance Pay Law, 1963, the Company is required to make severance payments upon dismissal of an Israeli employee or upon termination of employment in certain other circumstances. The severance payment liability to the employees located in Israel (based upon length of service and the latest monthly salary - one month’s salary for each year employed) is recorded on the Company’s balance sheet under “Liability for employee rights upon retirement.” The liability is recorded as if it was payable at each balance sheet date on an undiscounted basis.

In accordance with Section 14 of the Israeli Severance Pay Law, 1963, the Company makes regular deposits with certain insurance companies for accounts controlled by each applicable employee in order to secure the employee’s retirement benefit obligation. The Company is fully relieved from any severance pay liability with respect to each such employee after it makes the payments on behalf of the employee. The liability accrued in respect of these employees and the amounts funded, as of the respective agreement dates, are not reflected in the Company balance sheet, as the amounts funded are not under the control and management of the Company and the pension or severance pay risks have been irrevocably transferred to the applicable insurance companies (the “Contribution Plan”).

With regard to the period before December 2013, the liability is funded in part from the purchase of insurance policies or by the establishment of pension funds with dedicated deposits in the funds. The amounts used to fund these liabilities are included in the balance sheets under “Funds in respect of employee rights upon retirement.” These policies are the Company’s assets.

The amounts of severance payment expenses were $137 and $125 for the years ended December 31, 2021 and 2020, respectively.

The Company expects to contribute approximately $142 in the year ending December 31, 2022 to insurance companies in connection with its expected severance liabilities for that year.

NOTE 2 - SIGNIFICANT ACCOUNTING POLICIES (continued)

i. Leases

On January 1, 2019, the Company adopted ASU No. 2016-02, Leases (Topic 842). The Company determines if an arrangement is a lease at inception. Balances related to operating leases are included in operating lease right-of-use ("ROU") assets and current and non-current operating lease liabilities in the consolidated balance sheets.

ROU assets represent the Company's right to use an underlying asset for the lease term and lease liabilities represent the Company's obligation to make lease payments arising from the lease. Operating lease ROU assets and liabilities are recognized as of the commencement date based on the present value of lease payments over the lease term. Lease terms will include options to extend or terminate the lease when it is reasonably certain that the Company will either exercise or not exercise the option to renew or terminate the lease.

The discount rate for the lease is the rate implicit in the lease unless that rate cannot be readily determined. As the Company's leases do not provide an implicit rate, the Company's uses its estimated incremental borrowing rate based on the information available at the commencement date in determining the present value of lease payments. Lease expense for lease payments is recognized on a straight-line basis over the lease term (see also Note 4).

Sublease income is recognized on a straight-line basis over the expected lease term and is included in other income in our consolidated statements of operations.

j. Property and equipment

1) Property and equipment are stated at cost, net of accumulated depreciation and amortization.

2) The Company's property and equipment are depreciated using the straight-line method, which approximates the pattern of usage, over the term of the estimated useful life, as follows:

	Years
Computer equipment	3-5
Office furniture	10
Laboratory equipment	7-10

Leasehold improvements are amortized by the straight-line method over the shorter of (i) the expected lease term and (ii) the estimated useful life of the improvements.

NOTE 2 - SIGNIFICANT ACCOUNTING POLICIES (continued)

k. Impairment of long-lived assets

The Company tests long-lived assets for impairment whenever events or changes in circumstances indicate that the carrying amount of an asset may no longer be recoverable. Recoverability of long-lived assets is measured by comparing the carrying amount of the long-lived asset to the estimated undiscounted future cash flows expected to be generated by the asset. If the sum of the expected undiscounted cash flow is less than the carrying amount of the asset, the Company recognizes an impairment loss, which is the excess of the carrying amount over the fair value of the asset, using the expected future discounted cash flows As of December 31, 2021 and 2020, the Company did not recognize an impairment loss on its long-lived assets.

l. Share-based compensation

The Company grants share options and restricted share units ("RSU") (together "Share-Based Compensation") to its employees, directors and non-employees in consideration for services rendered.

The Company accounts for Share-Based Compensation awards classified as equity awards, including share-based option awards and restricted share units, using the grant-date fair value. The Company recognize the value of the award as an expense over the requisite service period.

The Company applies ASU 2018-07 (Topic 718) that expands the scope of Topic 718 to include Share-Based Compensation transactions for acquiring goods and services from non-employees. Under the provision of the amendment, the Company measures share-based compensation to non-employees in the same manner as share-based compensation to employees.

The Company measures compensation expenses for option awards based on estimated fair value on the date of grant using the Black-Scholes option-pricing model. This option pricing model requires estimates as to the option's expected term and the price volatility of the underlying stock. The Company measures compensation expense for the restricted share units based on the market value of the underlying share at the date of grant.

The Company elected to recognize compensation costs for awards granted to employees and directors conditioned only on continued service that have a graded vesting schedule using the accelerated method based on the multiple-option award approach. The Company elects to account for forfeitures as they occur.

m. Research and development expenses

Research and development expenses include costs directly attributable to the conduct of research and development programs, including the cost of salaries, share-based compensation expenses, payroll taxes and other employee benefits, lab expenses, consumable equipment and consulting fees. All costs associated with research and developments are expensed as incurred.

Grants received from Israel Innovation Authority (hereafter - "IIA") are recognized when the grant becomes receivable, provided there is reasonable assurance that the Company will comply with the conditions attached to the grant and there is reasonable assurance the grant will be received. Since at the time the grants were received, successful development of the related projects was not assured, the grant was deducted from the research and development expenses as the applicable costs are incurred, and presented in R&D expenses, net.

NOTE 2 - SIGNIFICANT ACCOUNTING POLICIES (continued)

n. Revenue recognition

The Company recognized revenue from the Amgen Agreement which was signed in December 2018 according to ASC 606, "Revenues from Contracts with Customers". Prior to the signing of the Amgen Agreement in 2018, the Company did not have revenue transactions.

ASC 606 Revenue from Contracts with Customer introduces a five-step model for recognizing revenue from contracts with customers, as follows:

1. Identify the contract with a customer.
2. Identify the performance obligations in the contract.
3. Determine the transaction price.
4. Allocate the transaction price to the performance obligations in the contract.
5. Recognize revenue when (or as) the entity satisfies a performance obligation.

According to ASC 606, a performance obligation is a promise to provide a distinct good or service or a series of distinct goods or services. Goods and services that are not distinct are bundled with other goods or services in the contract until a bundle of goods or services that is distinct is created. A good or service promised to a customer is distinct if the customer can benefit from the good or service either on its own or together with other resources that are readily available to the customer and the entity's promise to transfer the good or service to the customer is separately identifiable from other promises in the contract.

Options granted to the customer that do not provide a material right to the customer that it would not receive without entering into the contract do not give rise to performance obligations.

On December 10, 2018, the Company entered into the Amgen Agreement in inflammatory disease and other serious illnesses. As part of the agreement, the Company received non-refundable and non-creditable initial access payment of $725 from Amgen in January 2019.

The Company identified two performance obligations in the agreement: 1) License to use the Company's proprietary drug delivery platform and 2) pre-clinical research and development services ("pre-clinical R&D services"). The preclinical R&D services include discovery, research and design preclinical activities relating to the programs selected by Amgen.

The Company determined the license to the intellectual property to be a right to use that has significant standalone functionality separately from the pre-clinical R&D services since the Company is not required to continue to support, develop or maintain the intellectual property transferred and will not undertake any activities to change the standalone functionality of the intellectual property. Therefore, the license to the intellectual property is a distinct performance obligation and as such revenue is recognized at the point in time that control of the license was transferred to Amgen on December 10, 2018.

Revenues attributed to the preclinical R&Ds services are recognized during the period of the pre-clinical R&D services, over time according to the input model method on a cost-to-cost basis, since the customer benefits from the research and development services as the entity performs the service.

The Company evaluated the standalone selling price of the pre-clinical R&D services at $225 and the right to use the intellectual property at $500.

NOTE 2 - SIGNIFICANT ACCOUNTING POLICIES (continued)

n. Revenue recognition (continued)

The transaction price was comprised of fixed consideration and variable consideration (capped research and development reimbursements). Under ASC 606, the consideration that the Company would be entitled to upon the achievement of contractual milestones, which are contingent upon the occurrence of future events of development and commercial progress, are a form of variable consideration. When assessing the portion, if any, of such milestones-related consideration to be included in the transaction price, the Company first assesses the most likely outcome for each milestone and excludes the consideration related to milestones of which the occurrence is not considered the most likely outcome. The Company then evaluates if any of the variable consideration determined in the first step is constrained. Variable consideration is included in the transaction price if, in the Company's judgment, it is highly probable that a significant future reversal of cumulative revenue under the contract will not occur. Estimates of variable consideration and determination of whether to include estimated amounts in the transaction price are based largely on an assessment of the Company's anticipated performance and all information (historical, current and forecasted) that is reasonably available. As of December 31, 2021, the Company did not recognize any revenues from any potential milestone payments.

An entity should recognize revenue for a sales-based or usage-based royalty promised in exchange for a license of intellectual property only when (or as) the later of the following events occurs:

a) The subsequent sale or usage occurs; and
b) The performance obligation to which some or all of the sales based or usage-based royalty has been allocated has been satisfied (or partially satisfied).

As royalties are payable based on future commercial sales, as defined in the agreement, which did not occur as of the financial statements date, the Company did not recognize any revenues from royalties. See also note 10.

o. Income taxes

1) Deferred taxes

Deferred income taxes are computed using the asset and liability method. Under the asset and liability method, deferred income tax assets and liabilities are determined based on the differences between the financial reporting and tax bases of assets and liabilities and are measured using the currently enacted tax rates and laws. A valuation allowance is recognized to the extent that it is more likely than not that the deferred taxes will not be realized in the foreseeable future.

2) Uncertainty in income taxes

The Company follows a two-step approach in recognizing and measuring uncertain tax positions. The first step is to evaluate the tax position for recognition by determining if the available evidence indicates that it is more likely than not that the position will be sustained based on technical merits. If this threshold is met, the second step is to measure the tax position as the largest amount that has more than a 50% likelihood of being realized upon ultimate settlement.

NOTE 2 - SIGNIFICANT ACCOUNTING POLICIES (continued)

p. Loss per share

Basic loss per share is computed on the basis of the net loss, adjusted to recognize the effect of a down-round feature when it is triggered, for the period divided by the weighted average number of outstanding ordinary shares during the period.

Diluted loss per share is based upon the weighted average number of ordinary shares and of ordinary shares equivalents outstanding when dilutive. Ordinary share equivalents include outstanding stock options and warrants, which are included under the treasury stock method when dilutive. The calculation of diluted loss per share does not include options, restricted shares units and warrants, exercisable into 6,517,102 shares and 7,218,966 shares for the years ended December 31, 2021 and 2020, respectively, because the effect would be anti-dilutive.

q. Legal and other contingencies

Certain conditions may exist as of the date of the consolidated financial statements, which may result in a loss to the Company but which will only be resolved when one or more future events occur or fail to occur. The Company's management assesses such contingent liabilities, if any, and such assessment inherently involves an exercise of judgment. In assessing loss contingencies related to legal proceedings that are pending against the Company or unasserted claims that may result in such proceedings, the Company's management evaluates the perceived merits of any legal proceedings or unasserted claims as well as the perceived merits of the amount of relief sought or expected to be sought.

Management applies the guidance in ASC 450-20, "Loss Contingencies" when assessing losses resulting from contingencies. If the assessment of a contingency indicates that it is probable that a material loss has been incurred and the amount of the liability can be estimated, then the estimated liability is recorded as accrued expenses in the Company's consolidated financial statements.

Legal costs incurred in connection with loss contingencies are expensed as incurred.

r. Derivatives

Freestanding instruments are first analyzed under the provisions of ASC 480 in order to determine whether the instrument should be classified as a liability, with subsequent changes in fair value recognized in the Statements of Operations in each period.

If the instrument is not within the scope of ASC 480, it is further analyzed under the provisions of ASC 815-10 in order to determine whether the instrument is considered indexed to the entity's own stock, and can be classified within equity, or rather be classified as a liability with subsequent changes in fair value recognized in the Statements of Operations in each period.

NOTE 2 - SIGNIFICANT ACCOUNTING POLICIES (continued)

s. Newly issued and recently adopted accounting pronouncements:

Recently issued accounting pronouncements, not yet adopted

1) In November 2021, the FASB issued ASU 2021-10 “Government Assistance (Topic 832)”, which requires annual disclosures that increase the transparency of transactions involving government grants, including (1) the types of transactions, (2) the accounting for those transactions, and (3) the effect of those transactions on an entity’s financial statements. The amendments in this update are effective for financial statements issued for annual periods beginning after December 15, 2021. The Company is currently evaluating this guidance to determine the impact it may have on its consolidated financial statements.

2) In August 2020, the FASB issued ASU 2020-06 “Debt – Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging – Contracts in Entity’s Own Equity (Subtopic 815 – 40).” This guidance simplifies the accounting for certain financial instruments with characteristics of liabilities and equity, including convertible instruments and contracts on an entity’s own equity. The amendments to this guidance are effective for fiscal years beginning after December 15, 2021, and interim periods within those fiscal years. The Company is currently evaluating this guidance to determine the impact it may have on its consolidated financial statements.

3) In June 2016, the FASB issued ASU 2016-13 “Financial Instruments—Credit Losses—Measurement of Credit Losses on Financial Instruments.” This guidance replaces the current incurred loss impairment methodology with a methodology that reflects expected credit losses and requires consideration of a broader range of reasonable and supportable information to inform credit loss estimates. The guidance will be effective for Smaller Reporting Companies (SRCs, as defined by the SEC) for the fiscal year beginning on January 1, 2023, including interim periods within that year. The Company is currently evaluating this guidance to determine the impact it may have on its consolidated financial statements.

NOTE 3 - COVID-19

In March 2020, the World Health Organization declared the outbreak of COVID-19 to be a pandemic. The COVID-19 pandemic is having widespread, rapidly evolving, and unpredictable impacts on global society, economies, financial markets, and business practices. During 2021, there was a broad distribution of several vaccinations and medicines to overcome the pandemic. The Company has shifted its operations to co-exist along the pandemic with encouragement of vaccinations to all of its employees. Though the Company sees great progress to overcome the COVID-19 pandemic, still the COVID-19 pandemic may continue to impact the Company’s business operations, with outbursts of new variants of the COVID-19 from time to time, and there is uncertainty in the nature and degree of its continued effects over time.

(U.S. dollars in thousands, except share and per share amounts)

NOTE 4 - OPERATING LEASES

1) The Company leases office and research and development space under several agreements. The annual lease consideration is a total of $192 and is linked to the Israeli CPI. The lease agreement will expire on June 30, 2023.

As of December 31, 2021, the Company provided bank guarantees of approximately $42, in the aggregate, to secure the fulfillment of its obligations under the lease agreements.

2) The Company has entered into operating lease agreements for vehicles used by its employees. The lease periods are generally for three years and the payments are linked to the Israeli CPI. To secure the terms of the lease agreements, the Company has made certain prepayments to the leasing company, representing approximately three months of lease payments. The annual lease consideration is a total of $36 .

The lease cost was as follows:

	Year ended December 31, 2021	Year ended December 31, 2020
Operating lease cost	216	180

Supplemental cash flow information related to leases was as follows:

	Year ended December 31, 2021	Year ended December 31, 2020
Operating cash flows from operating leases	216	180

Supplemental balance sheet information related to operating leases was as follows:

	December 31, 2021	December 31, 2020
Operating Leases		
Operating lease right-of-use assets	239	374
Current lease liabilities	179	189
Non-current lease liabilities	123	243
Total lease liabilities	302	432
Weighted-average remaining lease term (in years)	1.53	2.53
Weighted-average discount rate	16%	16%

As of December 31, 2021, the maturity of lease liabilities under our non-cancelable operating leases were as follows:

2022	224
2023	117
Total future minimum lease payments	341
Less: interest	(39)
Present value of operating lease liabilities	302

NOTE 5 - COMMITMENTS AND CONTINGENCIES

a. Commitment to pay royalties to the government of Israel

The Company is committed to pay royalties to the IIA on proceeds from sales of products in the research and development of which the Government participates by way of grants. At the time the grants were received, successful development of the related project was not assumed. In the case of failure of the project that was partly financed by the IIA, the Company is not obligated to pay any such royalties.

Under the terms of the Company's funding from the IIA, royalties are payable on sales of products developed from projects so funded of 3% during the first three years, from commencement of revenues, 4% during the subsequent three years and 5% commencing the seventh year up to 100% of the amount of the grant received by the Company (dollar linked) with the addition of annual interest based on LIBOR. The amount that must be repaid may be increased to three times the amount of the grant received, and the rate of royalties may be accelerated, if manufacturing of the products developed with the grant money is transferred outside of the State of Israel. As to the replacement of the LIBOR benchmark rate - even though the IIA has not declared the alternative benchmark rate to replace the LIBOR, the Company does not believe it will have significant impact.

As of December 31, 2021, the total royalty amount that would be payable by the Company to the IIA, before the additional LIBOR interest and payments as described above, is approximately $460.

Following the signing of the Amgen Agreement (see note 10), the IIA determined that the Company should pay 5.38% of each payment that will be received by the Company from Amgen on the license of IP up to six times the grant received. As of December 31, 2021, the Company had paid a total amount of $79 to the IIA.

b. On June 1, 2010 D.N.A. Biomedical Solutions Ltd. ("D.N.A.") and Oramed Ltd., ("Oramed") entered into a joint venture agreement, (the "Joint Venture Agreement") for the establishment of Entera Bio Ltd. According to the Joint Venture Agreement each of D.N.A. and Oramed acquired 50% of the Company's ordinary shares. D.N.A invested $600 in the Company, and Oramed and the Company entered into a Patent License Agreement pursuant to which Oramed licensed to the Company certain of Oramed's patent (the "IPR&D").

On February 22, 2011, Oramed and the Company entered into a patent transfer agreement, (the "Patent Transfer Agreement"), that superseded the Patent License Agreement, whereby Oramed assigned to the Company all of its rights, title and interest to its patent that Oramed licensed to the Company in 2010, under certain conditions. Under this agreement, the Company is obligated to pay Oramed royalties equal to 3% of its net revenues (as defined in the Patent Transfer Agreement).

NOTE 6 - SHARE CAPITAL

1) **Rights of the Company's ordinary shares**

Each ordinary share is entitled to one vote. The holder of the ordinary shares is also entitled to receive dividends whenever funds are legally available, when and if declared by the Board of Directors.

The right to receive upon liquidation of the Company a sum equal to the nominal value of the share, and if a surplus remains, to receive such surplus, subject to the rights conferred on any class of shares which may be issued in the future. Since its inception, the Company has not declared any dividends.

2) **Changes in share capital:**

a. IPO warrants

As described in note 1b, in July 2018 the Company issued 1,400,000 IPO warrants to purchase 700,000 ordinary shares of the Company, these warrants have been listed for trading on the Nasdaq Capital Market and trading began on August 12, 2018. The IPO warrants are exercisable immediately at an initial exercise price of $8.40 per ordinary share for a period of five years, unless earlier repurchased by the Company under "Fundamental Transactions" as described in the warrant agreement or early expired as described in the warrant agreement.

The exercise price and number of ordinary shares issuable upon exercise of each warrant are subject to standard adjustments. In addition, the exercise price is subject to reduction if, within two years of the date of original issuance of the warrants which ended in July 2020, the Company sells or grants any warrant or option (except in certain circumstances as described in the warrant agreement) at an effective price per share less than $8.00 per share (as adjusted in proportion with any adjustments made from time to time), which reduction will be based on a weighted average, as described in the agreement. As described in note 6(2)b below, the Company completed financing round in a price per share lower than the $8.00, therefore, the adjusted exercise price is $5.85.

At the IPO completion date, both of the instruments (warrants and shares) were classified as equity instruments as the warrants are considered indexed to the entity's own stock based on the provision of ASC 815.

In March 2021, 4,500 IPO warrants were exercised into 2,250 ordinary shares of the Company for a total consideration of $13 at an exercise price of $5.85 per ordinary share.

As of the December 31, 2021 there are 1,395,500 traded warrants to purchase 697,750 ordinary shares of the Company with an exercise price of $5.85.

NOTE 6 - SHARE CAPITAL (continued)

b. On December 11, 2019 and December 18, 2019 ("the first and second closing"), the Company entered into subscription agreements with a selected group of accredited investors, including certain board members and their affiliates for the private placement of 5,710,153 ordinary shares for aggregate subscription proceeds to the Company of $13.5 million at a price of $2.37 per share. In addition, the Company granted 2,855,095 warrants, exercisable over a three-years period from the date of issuance, to purchase 2,855,095 ordinary shares at a per share exercise price of $2.96. In addition, the exercise price is subject to reduction if, within one years of the date of original issuance of the warrants which ended in December 2020 the Company will issue ordinary shares at an effective price per share less than $2.96.

In addition, on December 13, 2019, D.N.A Biomedical Solutions Ltd. ("DNA"), an existing shareholder of the Company, subscribed to the Private Placement (the "DNA Private Placement") to purchase 337,553 ordinary shares for aggregate consideration of $800. In connection with the transaction, the Company granted DNA warrants, exercisable over a three-year period from the date of issuance, to purchase 168,776 ordinary shares at a per share exercise price of $2.96. This investment was approved by the shareholders of the Company on February 18, 2020.

The 168,776 warrants issued in connection with the DNA Private Placement together with the 2,855,095 warrants issued in connection with the Private Placement are the "Investors Warrants"

In connection therewith, the Company entered into Placement Agency agreement with GP Numenkari Inc., a broker-dealer ("the Broker"). Based on the agreement, the Broker was entitled to the following consideration:

1. A cash fee equal to 10% of the total proceeds paid by subscribers invested through the Broker.

2. Three-years warrants to purchase ordinary shares in the amount equal to 10% of the number of shares issued to subscribers invested through the Broker at a per share exercise price of $2.37 ("Broker Warrants Type 1").

3. Three-years warrants to purchase ordinary share in the amount equal to 5% of number of shares issued to subscribers invested through the Broker at a per share exercise price of $2.96 ("Broker Warrants Type 2"), together with the Broker Warrants Type 1 (the "Broker Warrants").

Following the first and second closing of the offering, the Company issued 184,515 Broker Warrants type 1 and 92,257 Broker Warrants type 2 at per share exercise price of $2.37 to $2.96, respectively

The Company had transaction costs of approximately $1.2 million, out of which $205 are Stock-Based Compensation due to issuance of the Broker Warrants.

At the transaction date, both of the instruments (shares and warrants) were classified as equity instruments as the warrants are considered indexed to the entity's own stock based on the provision of ASC 815.

During 2020, upon issuance of shares through the Company's At-the-market equity program at a price per share lower than the exercise price, the exercise price adjusted to $1.05. See note 6(2)e.

NOTE 6 - SHARE CAPITAL (continued)

On April 21, 2021, upon satisfaction of the sale price condition pursuant to the subscription agreement signed in December 2019, the Company's Board of Directors decided to accelerate the termination date of the Investors and Broker warrants issued in December 2019 and February 2020. In accordance with the terms of the agreement, as of the notice date and until June 23, 2021 (the "Early Termination Exercise Period"), the holders may exercise their warrants and following such Early Termination Exercise Period, these warrants shall be deemed terminated.

Through June 23, 2021, all warrants holders, including the company's Chairman of the board and DNA, exercised 3,300,645 warrants into 3,172,800 ordinary shares through cash or cashless mechanism. The total consideration from the exercise of these warrants was $3,145 at an exercise price of $1.05.

As of December 31, 2021, all Investors and Broker warrants were exercised.

c. On June 13, 2020, 687,960 warrants to purchase 687,960 ordinary shares for a purchase price of $6.99 per share in accordance with the Series B preferred share purchase agreement signed in 2016 and its following amendments expired.

d. In July 2020, 340,210 warrants to purchase 340,210 ordinary shares for a purchase price of $3.69 per share in accordance with the Series A preferred share purchase agreement expired.

e. On July 4, 2020, the Company established a primary registration statement under form F-3 and at-the-market equity program (the " 2020 ATM Program") that allows the Company to issue up to $13.9 million of ordinary shares, at the Company's discretion. Distributions of the ordinary shares through 2020 ATM Program were made pursuant to the terms of an equity distribution agreement dated July 13, 2020 among the Company and Canaccord Genuity LLC (the "Agent").

As of December 31, 2020, the Company issued 2,802,731 ordinary shares for gross proceeds of $3.5 million at a weighted average price of $1.27 per ordinary share through 2020 ATM Program. The net consideration from 2020 ATM Program was $3.2 million. These transactions triggered adjustment to the exercise price of the Investors and Broker warrants issued in the Private Placement held in 2019. See note 6(2)b. The Company adjusted its net loss of 2020 for the purpose of loss per share computation in order to include the effect of the down-round trigger in a total amount of $1,042.

In February and March 2021, the Company issued additional 2,546,265 ordinary shares for net proceeds of $9.9 million at a weighted average price of $3.99 per ordinary share through 2020 ATM Program.

f. On May 7, 2021, the Company entered into a new At-the-market equity program (the "2021 ATM Program") that allows the Company to issue up to additional 5 million ordinary shares, at the Company's discretion. Distributions of the ordinary shares through the 2021 ATM Program were made pursuant to the terms of an equity distribution agreement dated May 7, 2021 among the Company and B. Riley Securities, Inc.

NOTE 6 - SHARE CAPITAL (continued)

In June and July 2021, the Company issued 1,840,463 ordinary shares for net proceeds of $12.1 million at a weighted average price of $6.74 per ordinary share through the Company's 2021 ATM Program.

g. During the twelve months ended December 31, 2021, several employees and service providers exercised 177,711 options into 177,711 ordinary shares of the Company for a total consideration of $418 at a weighted average price of $2.54 per ordinary share.

NOTE 7 - SHARE-BASED COMPENSATION

1) Share-based compensation plan

On March 17, 2013, the Company's Board of Directors approved a Share Incentive Plan (the "2013 Plan"). Under the 2013 Plan, the Company shall reserve sufficient number of ordinary shares, NIS 0.000769 par value, of the Company for allocation of stock options, restricted share units, restricted share awards and performance-based awards (the "Option"), to employees and non-employees. Each Option is exercisable for one ordinary share.

Any option granted under the 2013 Plan that is not exercised within six years from the date upon which it becomes exercisable will expire.

On July 2, 2018, the Company's board of directors and shareholders of the Company approved a new Share Incentive Plan (the "2018 Plan") and reserved 1,371,398 ordinary shares of the Company for allocation of stock options, restricted share units, restricted share awards and performance-based awards (the "Option"), to employees and non-employees for issuance under the 2018 Plan. Each Option is exercisable for one ordinary share NIS 0.0000769 par value.

Any option granted under 2018 Plan that is not exercised within 10 years from the date upon which it becomes exercisable will expire.

The options granted to employees are subject to the terms stipulated by section 102(b)(2) of the Israeli Income Tax Ordinance (the "Ordinance"). According to these provisions, the Company will not be allowed to claim as an expense for tax purposes the amounts credited to the employees as a capital gain benefit in respect of the options granted.

Options granted to related parties or non-employees of the Company are governed by Section 3(i) of the Ordinance or Non-Qualified Share Options ("NSO"). The Company will be allowed to claim as an expense for tax purposes in the year in which the related parties or non-employees exercised the options into shares.

As of December 31, 2021, 289,638 ordinary shares remain available for future grants under the Plan.

On January 1, 2022 the Company's Board of Directors approved an increase of 1,440,220 ordinary shares that may be issued under the Company's Plan.

NOTE 7 - SHARE-BASED COMPENSATION (continued)

2) share-based compensation grants to employees and directors:

a) On March 16, 2020, the Company's Board of Directors approved the following option grants, with an exercise price of $2.14 per share:

1. 250,000 options to purchase ordinary shares were granted to certain executive officers.
2. 201,600 options to purchase ordinary shares were granted to certain employees.
3. 7,500 options to purchase ordinary shares was granted to a service provider.

The options vest over 4 years from the date of grant; 25% vest on the first anniversary of the date of grant and the remaining 75% vest in twelve equal quarterly installments following the first anniversary of the applicable grant date. The fair value of the options at the date of grant was $590.

b) On April 20, 2020 options to purchase 31,502 ordinary shares granted to the former CEO with an exercise price of $1.98 per share. The options vest over 4 years from the date of grant; 25% vest on the first anniversary of the date of grant and the remaining 75% vest in twelve equal quarterly installments following the first anniversary of the applicable grant date. The fair value of the options at the date of grant was $37. Effective September 7, 2020, due to termination of the employment agreement with the former CEO, these options are forfeited and recognized as a reverse of expense under the General and Administrative line.

c) In April 2020, the Company entered into an investor relations services agreement. Under the terms of the agreement, the Company agreed to pay a monthly fee of $5 and to issue the consultant 28,000 Restricted Share Units ("RSU"), of which the first 7,000 shares vested on the signing date and the remaining 21,000 shares will vest in three equal installments until January 8, 2021. As of December 31, 2020, 21,000 shares were fully vested. The fair value of the RSU was $53 using the fair value of the shares at the grant date.

d) In November 2020, the Company entered into an amendment to business development services agreement with the business development consultant. Under the terms of the agreement, the Company agreed to pay a monthly fee of $5 and to issue the consultant 79,760 options with an exercise price of $1.06 per share. The options vests over 6 months in six equal installments from October 1, 2020. The fair value of the options at the date of grant was $35.

e) On January 4, 2021 options to purchase 1,314,218 ordinary shares were granted to the Chief Executive Officer of the Company, with an exercise price of $1.24. The options vest over 4 years from the date of grant; 25% vest on the first anniversary of the date of grant and the remaining 75% of the option will vest in twelve equal quarterly installments following the first anniversary of the grant date. The grant was subject to the approval by the shareholders of the Company, which approved the grant in March 2021. The fair value of the options at the date of grant was $1,320.

NOTE 7 - SHARE-BASED COMPENSATION (continued)

f) On April 7, 2021, the Company's Board of Directors approved the following option grants:

i. Options grants to purchase 213,000 ordinary shares to certain employees and 70,000 options granted to service providers, with an exercise price of $3.61 per share. The options vest over 4 years from the date of grant; 25% vest on the first anniversary of the date of grant and the remaining 75% of the option will vest in twelve equal quarterly installments following the first anniversary of the grant date. The fair value of the options at the date of grant was $646.

ii. Options grant to purchase 33,368 ordinary shares to a non-executive director of the Company, with an exercise price of $3.61. The options will vest over 3 years in twelve equal quarterly instalments starting on the vesting commencement date. These options were subject to the approval of the shareholders of the Company, which was approved on October 4, 2021. The fair value of the options at the shareholders' approval date was $104.

g) On April 21, 2021, options to purchase 345,000 ordinary shares were granted to several executive officers of the Company, with an exercise price of $3.15. The options vest over 4 years from the date of grant; 25% vest on the first anniversary of the date of grant and the remaining 75% of the option will vest in twelve equal quarterly installments following the first anniversary of the grant date. These options were subject to the approval of the shareholders of the Company, which was approved on October 4, 2021. The fair value of the options at the shareholders' approval date was $1,140.

h) On August 23. 2021, the Company's Board of Directors approved the following option grants which were approved by the shareholders of the Company on October 4, 2021.

i. Grants of options to purchase ordinary shares with a total fair value 0f $195 for each of the seven non-executive board member on January 1, 2022. The options will vest over 3 years in twelve equal quarterly instalments starting on January 1, 2022 the vesting commencement date. On January 1, 2022, which is considered the awards grant date, the Company granted 752,899 ordinary shares to non-executive directors with an exercise price of $2.815 per share.

ii. Grants of options to purchase ordinary shares with a total fair value 0f $65 for each of the seven non-executive board member on January 1, 2022. The options will vest over 1 year in four equal quarterly instalments starting on January 1, 2022 the vesting commencement date. On January 1, 2022, which is considered the awards grant date, the Company granted 250,964 ordinary shares to non-executive directors with an exercise price of $2.815 per share.

(U.S. dollars in thousands, except share and per share amounts)

NOTE 7 - SHARE-BASED COMPENSATION (continued)

The fair value of each option granted is estimated at the date of grant using the Black-Scholes option-pricing model, with the following weighted average assumptions:

	2021	2020
Exercise price	$ 1.24-$3.61	$ 1.06-$2.14
Dividend yield	-	-
Expected volatility	68%-71%	66.35%-71%
Risk-free interest rate	1.11%-0.94%	0.16%-0.58%
Expected life - in years	6.1-5.8	2.75-6.1

	2021		2020	
	Number of options	Weighted average exercise price	Number of options	Weighted average exercise price
Outstanding at beginning of year	2,570,109	$ 4.85	2,847,600	$ 4.74
Granted	1,975,586	1.95	570,362	$ 1.98
Exercised	(177,710)	2.37	(31,954)	2.11
Forfeited	(16,660)	2.37	(589,793)	2.7
Expired	(34,466)	4.00	(226,106)	2.68
Outstanding at end of year	4,316,859	$ 3.63	2,570,109	$ 4.85
Exercisable at end of year	2,068,067	$ 5.39	1,791,687	$ 5.49

(U.S. dollars in thousands, except share and per share amounts)

NOTE 7 - SHARE-BASED COMPENSATION (continued)

The following tables summarizes information concerning outstanding and exercisable options as of December 31, 2021, in terms of ordinary shares:

	December 31, 2021			
	Options outstanding		Options exercisable	
Exercise prices per share (USD)	Number of options outstanding at end of year	Weighted Average Remaining Contractual Life	Number of options exercisable at end of year	Weighted Average Remaining contractual Life
-	4,680	0.78	4,680	0.78
1.06	14,760	3.85	14,760	3.85
1.24	1,314,218	9.02	-	-
2.14	422,300	8.26	184,756	8.26
2.53	33,638	7.89	28,031	7.89
3.15	345,000	9.30	-	-
3.61	316,368	9.27	5,561	9.27
3.68	185,640	0.32	185,640	0.32
3.97	287,565	7.05	251,949	7.05
6.31	1,245,400	4.08	1,245,400	4.08
7.54	147,290	1.26	147,290	1.26
	4,316,859		2,068,067	

The aggregate intrinsic value of the total of the outstanding and exercisable options as of December 31, 2021, is $2,378 and $146, respectively.

The following table illustrates the effect of share-based compensation on the statements of operations:

	2021	2020
Cost of revenues	102	51
Research and development expenses	661	514
General and administrative	1,098	336
	1,861	901

(U.S. dollars in thousands, except share and per share amounts)

NOTE 8 - INCOME TAX

A. Corporate tax rate

1) Ordinary taxable income in Israel is subject to a corporate tax rate of 23%.

2) The Company's subsidiary Entera Bio, Inc. taxed separately under the U.S. tax laws at a tax rate of 29%.

B. Losses for tax purposes carried forward to future years

The balance of carryforward losses as of December 31, 2021 and 2020 are approximately $56.1 million and $44.2 million, respectively.

Under Israeli tax law, tax loss carry forward have no expiration date.

C. Tax assessments

The Company and its subsidiary have tax assessments that are considered to be final through tax year 2016.

D. Loss (income) before income taxes is composed of the following

	Year ended December 31	
	2021	**2020**
Entera Bio Ltd	12,362	11,283
Entera Bio Inc	(116)	(87)
Total loss before taxes	12,246	11,196

E. Tax expenses:

	Year ended December 31	
	2021	**2020**
Current:		
Subsidiary	158	20
Total current income tax	158	20
Deferred:		
Subsidiary	(217)	-
Total tax on income	(59)	20

(U.S. dollars in thousands, except share and per share amounts)

NOTE 8 - INCOME TAX (continued)

F. Deferred income taxes

	December 31,	
	2021	**2020**
Deferred tax assets:		
Net operating loss carry forward	12,895	10,176
Research and development	1,319	1,316
Share-based compensation	876	688
Other	152	240
Net deferred tax assets before valuation allowance	15,242	12,420
valuation allowance	(15,025)	(12,420)
Net deferred tax assets	217	-

Realization of deferred tax assets is contingent upon sufficient future taxable income during the period that deductible temporary differences and carry forward losses are expected to be available to reduce taxable income.

G. Rollforward of valuation allowance:

Balance at January 1, 2020	**9,718**
Additions	2,702
Balance at January 1, 2021	**12,420**
Additions	2,605
Balance at December 31, 2021	**15,025**

NOTE 8 - INCOME TAX (continued)

H. Reconciliation of theoretical tax expenses to actual expenses

The primary difference between the statutory tax rate of the Company and the effective rate results virtually from the changes in valuation allowance in respect of carry forward tax losses and research and development expenses due to the uncertainty of the realization of such tax benefits.

I. Uncertain tax positions

As of December 31, 2021 and 2020, the Company does not have a provision for uncertain tax positions.

NOTE 9 - SUPPLEMENTARY FINANCIAL STATEMENT INFORMATION:

Balance sheets:

	December 31,	
	2021	2020
	U.S. dollars in thousands	
b. Accounts payable - other:		
Employees and employees related	147	144
Income tax	134	-
Provision for vacation	308	263
Accrued expenses	2,212	923
	2,801	1,330

NOTE 10 - REVENUE FROM COLLABORATION AND LICENSE AGREEMENT

On December 10, 2018, the Company entered into a research collaboration and license agreement (the "Amgen Agreement") with Amgen Inc. ("Amgen") in inflammatory disease and other serious illnesses. Pursuant to the Amgen Agreement, the Company and Amgen will use the Company's proprietary drug delivery platform to develop oral formulations for one preclinical large molecule program that Amgen has selected. Amgen also has options to select up to two additional programs to include in the collaboration. Amgen is responsible for the clinical development, regulatory approval, manufacturing and worldwide commercialization of the programs.

The Company granted Amgen an exclusive, worldwide, sublicensable license under certain of its intellectual property relating to its drug delivery technology to develop, manufacture and commercialize the applicable products. The Company will retain all intellectual property rights to its drug delivery technology, and Amgen will retain all rights to its large molecules and any subsequent improvements, and ownership of certain intellectual property developed through the performance of the collaboration is to be determined by U.S. patent law.

Pursuant to the terms of the Amgen Agreement, Amgen is required to make aggregate payments of up to $270 million upon achievement of various clinical and commercial milestones or its exercise of options to select additional two programs to include in the collaboration, as well as tiered royalty payments ranging from the low to mid-single digits based on the level of Amgen's net sales of the applicable products. Amgen is required to pay for the initial program $450 for the second year of preclinical R&D services to be provided by the Company and must reimburse the Company for further expenses as shall be agreed between the parties. Preclinical R&D services includes time spent by the Company's employees performing the Company's activities under the work plan of collaboration program.

NOTE 10 - REVENUE FROM COLLABORATION AND LICENSE AGREEMENT (continued)

Amgen's obligation to pay royalties with respect to a product in a particular country commences upon the first commercial sale of such product in such country and expires on a country-by-country and product-by-product basis on the later of (a) the date on which the sale of the product is no longer covered by a valid claim of a patent licensed to Amgen under the Amgen Agreement, and (b) the tenth anniversary of the first commercial sale of such product in such country.

The term of the Amgen Agreement commenced on December 10, 2018, and unless earlier terminated, shall continue in full force and effect, on a product-by-product basis, until expiration of the last-to-expire royalty term with respect to such product.

In January 2019, as required by the Amgen Agreement, Amgen paid the Company a non-refundable and non-creditable initial technology access fee of $725. The Company evaluated the selling price of the preclinical R&D services at $225 and the right to use the intellectual property ("License fees") at $500. In December 2018, the Company recognized $500 in revenues for the right to use the intellectual property.

During the second quarter of 2021, the Company extended the agreement, pursuant to the terms, Amgen is required to pay for the third year of preclinical R&D services to be provided by the Company for a total consideration of $450.

Revenues attributed to the preclinical R&D services are recognized during the period of the pre-clinical R&D services according to the input model method on a cost-to-cost basis. During 2021 the Company received the second installment for the second year and the first installment for the third year for the pre-clinical R&D services in the amount of $450.

In 2021 and 2020, the Company recorded revenues of $502 and $365 related to services provided under the Amgen Agreement.

In addition, as of December 31, 2021 and 2020 the Company recorded a contract liability of $15 and $158, respectively.

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

None.

ITEM 9A. CONTROLS AND PROCEDURES

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our Chief Executive Officer and Israel-based Chief Financial Officer, has evaluated the effectiveness of our disclosure controls and procedures (as such term is defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act and regulations promulgated thereunder) as of December 31, 2021, which we refer to as the Evaluation Date. Based on such evaluation, those officers have concluded that, as of the Evaluation Date, our disclosure controls and procedures were effective.

Management's Report on Internal Control over Financial Reporting

Our management, under the supervision of our Chief Executive Officer and Chief Financial Officer, is responsible for establishing and maintaining adequate internal control over our financial reporting, as defined in Rules 13a-15(f) and 15d-15(f) of the Exchange Act. The Company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. Internal control over financial reporting includes policies and procedures that:

- pertain to the maintenance of records that in reasonable detail accurately and fairly reflect our transactions and asset dispositions;
- provide reasonable assurance that transactions are recorded as necessary to permit the preparation of our financial statements in accordance with generally accepted accounting principles;
- provide reasonable assurance that receipts and expenditures are made only in accordance with authorizations of our management and board of directors (as appropriate); and
- provide reasonable assurance regarding the prevention or timely detection of unauthorized acquisition, use or disposition of assets that could have a material effect on our financial statements.

Due to its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. In addition, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Our management, including our Chief Executive Officer and Chief Financial Officer, assessed the effectiveness of our internal control over financial reporting as of December 31, 2021 based on criteria established in Internal Control-Integrated Framework (2013) by the Committee of Sponsoring Organizations of the Treadway Commission (COSO).

Based on such assessment, our management concluded that the Company's internal control over financial reporting was effective as of December 31, 2021.

Changes in Internal Control over Financial Reporting

There have been no changes in our internal control over financial reporting that occurred during the last fiscal quarter that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. OTHER INFORMATION

None.

ITEM 9C. DISCLOSURE REGARDING FOREIGN JURISDICTIONS THAT PREVENT INSPECTIONS.

None.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information required by this item is incorporated by reference from our Proxy Statement to be filed in connection with our 2022 Annual Meeting of Stockholders.

We have adopted a code of business conduct and ethics, called the Code of Business Conduct and Ethics, that applies to all of our directors, officers, including our principal executive, financial and accounting officers, and employees. The full text of the Code of Business Conduct and Ethics is available in the Governance section of our website at www.enterabio.com under the tab "Governance" and is available in print to any stockholder who requests it. We intend to provide amendments or waivers to our Code of Business Conduct and Ethics for any of our directors and principal officers on our website within four business days after such amendment or waiver. The reference to our website address does not constitute incorporation by reference of any of the information contained on the website, and such information is not a part of this Annual Report on Form 10-K.

ITEM 11. EXECUTIVE COMPENSATION

The information required by this item is incorporated by reference from our Proxy Statement to be filed in connection with our 2022 Annual Meeting of Stockholders.

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED SHAREHOLDER MATTERS

The information required for this item is incorporated by reference from our Proxy Statement to be filed in connection with our 2022 Annual Meeting of Stockholders.

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE

The information required for this item is incorporated by reference from our Proxy Statement to be filed in connection with our 2022 Annual Meeting of Stockholders.

ITEM 14. PRINCIPAL ACCOUNTING FEES AND SERVICES

The information required for this item is incorporated by reference from our Proxy Statement to be filed in connection with our 2022 Annual Meeting of Stockholders.

PART IV.

Item 15. EXHIBITS, FINANCIAL STATEMENT SCHEDULES.

(a) Documents filed as part of this report:

(1) Financial statements

See Item 8 for Financial Statements included with this Annual Report.

(2) Financial Statement Schedules

None.

(3) Exhibits: See below.

Exhibit No.	Description
3.1	Amended and Restated Articles of Association of Entera Bio Ltd. (incorporated by reference to Exhibit 1.1 to the Form 20-F, filed with the SEC on March 18, 2021).
4.1	Description of rights of each applicable class of securities registered under Section 12 of the Securities Exchange Act of 1934 (incorporated by reference to Exhibit 2.2 to the Form 20-F filed with the SEC on March 18, 2021).
4.2	Specimen Form of Ordinary Share Certificate (incorporated by reference to Exhibit 4.1 to the Registration Statement on Form F-1 (File No. 333-221472) filed with the SEC on November 9, 2017)
4.3	Form of IPO Warrant (incorporated herein by reference to Exhibit 4.2 to the Company's Registration Statement on Form F-1 (File No. 333-221472) filed with the SEC on May 17, 2018)
4.4	Form of Underwriter Warrant issued by the Registrant to Maxim Group LLC (incorporated by reference to Exhibit 4.3 to the Registration Statement on Form F-1 (File No. 333-221472) filed with the SEC on May 17, 2018)
4.5	Form of Warrant issued by the Registrant to GP Nurmenkari Inc. (incorporated by reference to Exhibit 4.5 to the Registration Statement on Form F-1 (File No. 333-221472) filed with the SEC on November 9, 2017)
4.6	Form of Investor Warrant used by the Registrant pursuant to its 2019 Private Placement (incorporated by reference to Exhibit 4.27 to the Form 20-F filed with the SEC on March 18, 2021).
10.1	Amended and Restated Investor's Rights Agreement, dated as of October 4, 2017, between the Registrant and the other parties thereto (incorporated by reference to Exhibit 10.10 to the Registration Statement on Form F-1 (File No. 333-221472) filed with the SEC on November 9, 2017)
10.2	Patent Transfer Agreement, dated as of February 22, 2011, between the Registrant and Oramed Ltd. (incorporated by reference to Exhibit 10.1 to the Registration Statement on Form F-1 (File No. 333-221472) filed with the SEC on November 9, 2017)
10.3	Form of Warrant Agency Agreement (incorporated by reference to Exhibit 10.18 to the Registration Statement on Form F-1 (File No. 333-221472) filed with the SEC on June 15, 2018)
10.4	Form of Regulation D Private Placement Subscription Agreement (incorporated by reference to Exhibit 4.25 to the Form 20-F filed with the SEC on March 18, 2021).
10.5	Subscription Agreement, dated December 13, 2019, between the Registrant and D.N.A Biomedical Solutions Ltd. (incorporated by reference to Exhibit 4.26 to the Form 20-F filed with the SEC on March 18, 2021).
10.6	Registration Rights Agreement, dated December 10, 2019, between the Registrant and the other parties thereto (incorporated by reference to Exhibit 4.28 to the Form 20-F filed with the SEC on March 18, 2021).
10.7	At Market Issuance Sales Agreement, dated May 7, 2021, between Entera Bio. Ltd. and B Riley Securities, Inc. (incorporated by reference to Exhibit 1.1 to the Form 6-K filed with the SEC on June 22, 2021)
10.8††	Research Collaboration and License Agreement, dated as of December 10, 2018, between Amgen Inc. and Entera Bio Ltd. (incorporated by reference to Exhibit 4.28 to the Amended Annual Report on Form 20-F/A (File No. 001-38556) filed with the SEC on April 17, 2019)
10.9†	Form of indemnification agreement between the Registrant and its directors and executive officers (incorporated by reference to Exhibit 10.12 to the Registration Statement on Form F-1 (File No. 333-221472) filed with the SEC on November 20, 2017)
10.10†	The Entera Bio Ltd. Share Incentive Plan (incorporated by reference to Exhibit 10.4 to the Registration Statement on Form F-1 (File No. 333-221472) filed with the SEC on November 9, 2017)
10.11†	2018 Equity Incentive Plan (incorporated by reference to Exhibit 99 to the Registration Statement on Form S-8 (File No. 333-227488) filed with the SEC on September 24, 2018)
10.12†	Form of Stock Option Award Agreement under the 2018 Equity Incentive Plan (incorporated by reference to Exhibit 4.25 to the Annual Report on Form 20-F (File No. 001-38556) filed with the SEC on March 28, 2019)
10.13†	Employment Agreement, dated as of January 4, 2021 between Entera Bio Ltd. and its Chief Executive Officer and director, Dr. Spiros Jamas (incorporated by reference to Exhibit 4.30 to the Form 20-F, filed with the SEC on March 18, 2021).
21.1*	List of Subsidiaries
23.1*	Consent of Kesselman & Kesselman, an independent registered public accounting firm in Israel and a member of PricewaterhouseCoopers International Limited.
31.1*	Certification of Principal Executive Officer of Entera Bio Ltd. pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
31.2*	Certification of Principal Financial and Accounting Officer of Entera Bio Ltd. pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
32.1**	Certification of Principal Executive Officer of Entera Bio Ltd. pursuant to Section 906 of the Sarbanes-Oxley act of 2002
32.2**	Certification of Principal Financial and Accounting Officer of Entera Bio Ltd. pursuant to Section 906 of the Sarbanes-Oxley act of 2002
101.INS	Inline XBRL Instance Document
101.SCH	Inline XBRL Taxonomy Extension Schema Document
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document
104	Inline XBRL for the cover page of this Annual Report on Form 10-K, included in the Exhibit 101 Inline XBRL Document Set.

† Management contract or compensatory plan or arrangement.
* Filed herewith.
** Furnished herewith.
†† Confidential treatment granted as to portions of the exhibit. Confidential materials omitted and filed separately with the Securities and Exchange Commission.

ITEM 16. FORM 10-K SUMMARY

Not applicable.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Date: March 8, 2022

ENTERA BIO LTD.

By: /s/ Spiros Jamas
Spiros Jamas
Chief Executive Officer

KNOW ALL MEN BY THESE PRESENTS, that each of the undersigned constitutes and appoints each of Spiros Jamas and Dana Yaacov-Garbelli, or any of them, each acting alone, his true and lawful attorney-in-fact and agent, with full power of substitution and resubstituting, for such person and in his name, place and stead, in any and all capacities, to sign this Annual Report on Form 10-K, and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, each acting alone, full power and authority to do and perform each and every act and thing requisite and necessary to be done in and about the premises, as fully to all intents and purposes as he might or could do in person, hereby ratifying and confirming that any such attorney-in-fact and agent, or his substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Name	Title	Date
/s/ Spiros Jamas Spiros Jamas	Chief Executive Officer (Principal Executive Officer)	March 8, 2022
/s/ Dana Yaacov-Garbeli Dana Yaacov-Garbeli	Israel-based Chief Financial Officer (Principal Financial and Accounting Officer)	March 8, 2022
/s/ Phillip Schwartz Phillip Schwartz	Director	March 8, 2022
/s/ Gerald Lieberman Gerald Lieberman	Director	March 8, 2022
/s/ Roger J. Garceau Roger J. Garceau	Director	March 8, 2022
/s/ Ron Mayron Ron Mayron	Director	March 8, 2022
/s/ Yonatan Malca Yonatan Malca	Director	March 8, 2022
/s/ Miranda J. Toledano Miranda J. Toledano	Director	March 8, 2022
/s/ Gerald M. Ostrov Gerald M. Ostrov	Director	March 8, 2022
/s/ Sean Ellis Sean Ellis	Director	March 8, 2022

Exhibit 21.1

Entera Bio Ltd.

The following is a list of subsidiaries of Entera Bio Ltd. as of December 31, 2021:

STATE OR OTHER JURISDICTION OF INCORPORATION OR ORGANIZATION	SUBSIDIARY
Delaware	Entera Bio Inc.

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statement on Form S-8 (No. 333-227488) of Entera Bio Ltd. of our report dated March 8, 2022 relating to the financial statements, which appears in this Form 10-K.

/s/ Kesselman & Kesselman
Certified Public Accountants (lsr.)
A member firm of PricewaterhouseCoopers International Limited
Tel-Aviv, Israel
March 8, 2022

Exhibit 31.1

CERTIFICATION PURSUANT TO SECTION 302 OF THE SARBANES OXLEY ACT OF 2002

I, Spiros Jamas, certify that:

1. I have reviewed this Annual Report on Form 10-K of Entera Bio Ltd.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

    a. Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

    b. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

    c. Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

    d. Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

    a. All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

    b. Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 8, 2022

/s/ Spiros Jamas
Spiros Jamas
Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION PURSUANT TO SECTION 302 OF THE SARBANES OXLEY ACT OF 2002

I, Dana Yaacov-Garbeli, certify that:

1. I have reviewed this Annual Report on Form 10-K of Entera Bio Ltd.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

    a. Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

    b. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

    c. Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

    d. Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

    a. All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

    b. Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 8, 2022

/s/ Dana Yaacov-Garbeli
Dana Yaacov-Garbeli
Israel-based CFO
(Principal Financial and Accounting Officer)

Exhibit 32.1

CERTIFICATION PURSUANT TO SECTION 906 OF THE SARBANES OXLEY ACT OF 2002

I, Spiros Jamas, Chief Executive Officer of Entera Bio Ltd. (the "Company"), certify, pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, 18 U.S.C. Section 1350 that, to the best of my knowledge:

1. the Annual Report on Form 10-K of the Company for the year ended December 31, 2021 (the "Report") fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934 (15 U.S.C. 78m or 78o(d)); and

2. the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 8 ,2022

/s/ Spiros Jamas
Spiros Jamas
Chief Executive Officer
(Principal Executive Officer)

Exhibit 32.2

CERTIFICATION PURSUANT TO SECTION 906 OF THE SARBANES OXLEY ACT OF 2002

I, Dana Yaacov-Garbeli, Israel-based CFO of Entera Bio Ltd. (the "Company"), certify, pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, 18 U.S.C. Section 1350 that, to the best of my knowledge:

1. the Annual Report on Form 10-K of the Company for the year ended December 31, 2021 (the "Report") fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934 (15 U.S.C. 78m or 78o(d)); and

2. the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 8, 2022

/s/ Dana Yaacov-Garbeli
Dana Yaacov-Garbeli
Israel-based CFO
(Principal Financial and Accounting Officer)