Entera Bio Announces Execution of Key Regulatory Milestones for EB613, the First Oral Anabolic Drug Proposed for the Treatment of Osteoporosis; Miranda Toledano Assumes CEO Position

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JERUSALEM, July 18, 2022 (GLOBE NEWSWIRE) -- Entera Bio Ltd. (NASDAQ: ENTX), a leader in the development of orally delivered peptides and therapeutic proteins, announced today the execution of the following key milestones:

- **The U.S. Food and Drug Administration (FDA) has granted Entera's request for a Type C Meeting based on the revised phase 3 registrational study for lead clinical asset, EB613 (oral formulation of PTH (1-34, teriparatide), as the first oral anabolic drug to treat post-menopausal women with osteoporosis. The meeting is expected in H2 2022**
- **Following its End of Phase 2 Meeting with the FDA, Entera designed the pivotal study for EB613 as an 18 month double blind placebo-controlled study, followed by a 6-month open label transition to alendronate for all patients**
- **The study's primary endpoint employs the Foundation for the National Institutes of Health Bone Quality Program (FNIH BQP) total hip Bone Mineral Density (BMD) as a surrogate endpoint to evaluate fracture risk. FDA re-confirmed that with a well-designed BMD study, EB613 approval would not require a fracture study**
- **In line with her increased executive role since earlier this year, Ms. Miranda Toledano, Entera Board Member and industry veteran with over 20 years of experience succeeds Dr. Spiros Jamas as Chief Executive Officer**

FDA Acceptance of Type C Meeting: Phase 3 Design of EB613 Under Review

During Entera's End of Phase 2 Meeting, FDA's Division of Endocrinology remarked on the FNIH BQP published meta-regression analysis which is based on patient-level BMD and fracture incidence data from more than 22 placebo-controlled fracture endpoint studies across all classes of osteoporosis drugs, including teriparatide. The FNIH BQP data indicate that changes in Total Hip BMD (in contrast to lumbar spine or femoral neck BMD measurements) provides a superior surrogate marker of an osteoporosis drug's effects on vertebral, nonvertebral and all site fracture risk. The FNIH BQP BMD data and Surrogate Threshold Effects (STEs) are in the process of qualification by the FDA to become the first surrogate endpoint for fracture risk reduction[1].

FDA suggested that Entera explore the FNIH BQP STEs and the design of a placebo-controlled study as an alternative to the originally contemplated non-inferiority design versus Forteo.® Entera has since submitted to the FDA, as part of its Type C briefing documents, a revised Phase 3 protocol. The study is expected to be an 18-month randomized, double-blind, multicenter study comparing the effects of oral PTH (1-34, teriparatide) EB613 vs. placebo on BMD in post-menopausal women with osteoporosis at high risk of fracture, followed by a 6-month open-label extension where all patients will be transitioned to alendronate, a standard of care anti-resorptive therapy.

[1] Black DM et. al. The Lancet. Diabetes & Endocrinology 2020 Eastell R et. al. JBMR 2021

FDA Approves Biomarker Qualification Plan for the First Surrogate Endpoint in Anti-Osteoporosis Drug Trials, June 1st, 2022, https://www.fnih.org/news/announcements/fda-approves-biomarkers-qualification-plan-first-surrogate-endpoint-anti

Patients will be randomized in a 2:1 ratio to receive blinded treatments with either EB613 (N=400) 2.5mg dose of oral PTH or Placebo (N=200). The 6-month extension phase of the study is intended to provide information on the transition from EB613 to a standard anti-resorptive therapy which has been shown to maintain or augment the increases in BMD following injectable PTH therapies, to preserve blinding of the prior therapy and to ensure that patients randomized to the placebo arm also receive an osteoporosis treatment.

The primary objective or endpoint of the phase 3 study will evaluate the effect of daily oral EB613 treatment on percent change in Total Hip BMD over 18 months versus placebo. Statistical methods will compare the observed treatment effect compared to pre-defined STEs associated with vertebral fracture, all site fracture and nonvertebral fracture risk reduction. The study will also look at secondary endpoints including changes in lumbar spine and femoral neck BMD and EB613's effects on biochemical markers of bone formation and resorption.

"In the past months, Entera has invested a considerable amount of time aligning our proposed Phase 3 study with FDA's EOP2 guidance, with the support of our clinical and statistical team, world-renowned scientific and clinical leaders in osteoporosis drug development, and representative institutional review boards. We are appreciative of FDA's inputs and believe that the current Phase 3 design is a much de-risked pivotal study pathway and enables us to continue to study a similar patient population, based on T-Score and other criteria, as in our Phase 2 dose ranging study which met its 3-month biomarker and 6-month BMD endpoints. We look forward to providing updates to you on the outcome of our conversation with FDA later this year," said Miranda Toledano, Entera's Chief Executive Officer.

CEO Transition

Entera's Board of Directors appointed Miranda Toledano as Chief Executive Officer (CEO) as of July 15th, 2022, succeeding Dr. Spiros Jamas.

Chairman of the Board Mr. Jerry Lieberman said, "The management transition reflects a strategic reorientation of Entera as we embark on pivotal clinical development and ongoing strategic discussions. I am thrilled to announce Miranda as our new CEO. Her fundamental understanding of Entera's pipeline and transaction-focused track record in the industry is aligned to the current stage of the Company. Her contributions as an independent board member for the last 4 years also demonstrate her passion and commitment to establishing Entera as a leading biopharmaceutical entity. On behalf of Entera's Board, we would like to recognize and thank Dr. Spiros Jamas for his contributions to Entera and advancement to success across our core programs."

Ms. Toledano stated, "We are laser focused on unlocking the value of Entera's oral delivery platform and core therapeutic assets. Both of our lead oral PTH drug candidates, EB613 for the treatment of osteoporosis and EB612 for the treatment of hypoparathyroidism are highly differentiated with the potential to meaningfully change the treatment paradigm and the lives of patients in their respective indications. I am excited to take on the challenge of leading Entera at this critical time and help the Company forge forward which is why I first took more executive responsibility a few months ago. We believe that Entera's science has poised it as one of the leading entities in transforming the profile of therapeutic proteins to an oral route of administration. We further believe that this is especially valuable in chronically treated indications such as osteoporosis where most patients are under-treated because of the high cost and their reluctance to take injectable drugs. EB613 is positioned as a viable anabolic (bone formation) option to potentially lower the risk of fractures for a much wider population of post-menopausal osteoporotic women versus SC injected PTH drugs. We believe EB613 will deliver a tablet form (oral) PTH to fulfill the promise of this validated therapeutic class."

Dr. Jamas said, "I'm very proud of the significant progress we made advancing Entera's lead oral PTH asset, EB613 for the treatment of osteoporosis towards a pivotal Phase 3 study, including successfully completing the Phase 2 study. We demonstrated and presented data on the utility of Entera's oral delivery platform with other peptides, filed IP on a new and improved oral delivery platform and strengthened the management team. I support this transition and have full confidence that the team will realize Entera's full potential."

Ms. Toledano has served as a Member of the Board of Directors at Entera since 2018, and as Member of the Scientific Advisory Committee since February 2022. In May 2022, she also joined as Entera's Chief Business Officer and Chief Financial Officer. Previously, Miranda served as Chief Operating Officer, Chief Financial Officer, and Director of TRIGR Therapeutics, an oncology focused, clinical stage bispecific antibody company acquired by Compass Therapeutics (Nasdaq: CMPX) in June 2021 just 3 years after its establishment with her co-founder George Uy. At TRIGR, Miranda oversaw the clinical development of lead asset TR009 (now CTX-009) and led strategic execution, including a $117 million China License Transaction and acquisition by CMPX. Previously, Ms. Toledano served as Head of Healthcare Investment Banking at MLV & Co. (acquired by B. Riley FBR & Co.), where she completed biotech equity financings (IPOs, ATMs, and follow-ons) totaling over $4 billion in aggregate value. Earlier in her career, Ms. Toledano served as vice president in the investment group of Royalty Pharma. Ms. Toledano is also a member of the board of directors of Journey Medical (Nasdaq: DERM) and NEXGEL (Nasdaq: NXGL). Ms. Toledano holds a B.A. in Economics from Tufts University and an MBA in Finance and Entrepreneurship from the NYU Stern School of Business.

About EB613

Parathyroid hormone (PTH) is an 84-amino acid hormone and the primary regulator of calcium and phosphate metabolism in bone and kidney. EB613 is an oral formulation of synthetic hPTH (1-34), (teriparatide), a peptide consisting of the first 34 amino acids of PTH which represent the functional region. Subcutaneous Forteo® (teriparatide injection) has been the leading anabolic treatment of osteoporosis since 2002. EB613 utilizes Entera's oral drug delivery platform which promotes enteric absorption and stabilizes teriparatide in the gastrointestinal tract. Entera's Oral PTH formulations have been administered collectively to a total of 225 subjects in two Phase 1 studies and 3 phase 2 studies (including 35 in 2 phase 2 hypoparathyroidism studies). The most recent study was a dose ranging Phase 2 study in postmenopausal women with low bone mass. This study met primary and key secondary endpoints and was presented in a late-breaker oral presentation at the ASBMR 2021 conference. For the primary efficacy endpoint: a statistically significant increase in P1NP (a bone formation marker) at 3 months was achieved. A significant dose response was observed for 0.5, 1.0, 1.5 and 2.5 mg oral PTH doses on P1NP, Osteocalcin and bone mineral density (BMD). Subjects receiving the 2.5 mg dose of EB613 showed significant increases in dose-related BMD at the lumbar spine, total hip, and femoral neck at 6 months. Subjects receiving the 2.5 mg dose of EB613 daily for 6 months had a significant placebo adjusted increase of 3.78% in lumbar spine BMD ($p<0.008$) which is similar to the 3.9% increase in lumbar spine BMD seen with Forteo® in clinical studies reported in the literature[2]. Increases in total hip and femoral neck BMD were greater than those previously reported with Forteo®. EB613 exhibited an excellent safety profile, with no drug related serious adverse events. The most common adverse events included mild nausea, moderate back pain, moderate headache, and moderate upper abdominal pain.

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[2] *Leder BZ et.al. JCEM 2015*

About Entera Bio

Entera is a leader in the development 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 proprietary, oral drug delivery technology is designed to address the technical challenges of poor absorption, high variability, and the inability to deliver large molecules to the targeted location in the body through the use of a synthetic absorption enhancer to facilitate the absorption of large molecules, and protease inhibitors to prevent enzymatic degradation and support delivery to targeted tissues. The Company's most advanced product candidates, EB613 for the treatment of osteoporosis and EB612 for the treatment of hypoparathyroidism are in clinical development. The Company recently completed the phase 2 study for EB613. Entera also licenses its technology to biopharmaceutical companies for use with their proprietary compounds and, to date, has established a collaboration with Amgen Inc. For more information on Entera Bio, visit www.enterabio.com.

Cautionary Statement Regarding Forward Looking Statements

Various statements in this press release are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995 (PSLRA). All statements (other than statements of historical facts) in this press release regarding our prospects, plans, financial position, business strategy and expected financial and operational results may constitute forward-looking statements. Words such as, but not limited to, "anticipate," "believe," "can," "could," "expect," "estimate," "design," "goal," "intend," "may," "might," "objective," "plan," "predict," "project," "target," "likely," "should," "will," and "would," or the negative of these terms and similar expressions or words, identify forward-looking statements. Forward-looking statements are based upon current expectations that involve risks, changes in circumstances, assumptions and uncertainties. Forward-looking statements should not be read as a guarantee of future performance or results and may not be accurate indications of when such performance or results will be achieved.

Important factors that could cause actual results to differ materially from those reflected in Entera's forward-looking statements include, among others: changes in our interpretation of the 3-month biomarker data from the Phase 2 clinical trial of EB613, the timing of data readouts from the Phase 2

clinical trial of EB613, the full results of the Phase 2 clinical trial of EB613 and our analysis of those full results, the FDA's interpretation and review of our results from and analysis of our Phase 2 trial of EB613, unexpected changes in our ongoing and planned preclinical development and clinical trials, the timing of and our ability to make regulatory filings and obtain and maintain regulatory approvals for our product candidates; the potential disruption and delay of manufacturing supply chains, loss of available workforce resources, either by Entera or its collaboration and laboratory partners, due to travel restrictions, lay-offs or forced closures or repurposing of hospital facilities; impacts to research and development or clinical activities that Entera is contractually obligated to provide, such as those pursuant to Entera's agreement with Amgen; overall regulatory timelines, if the FDA or other authorities are closed for prolonged periods, choose to allocate resources to review of COVID-19 related drugs or believe that the amount of Phase 2 clinical data collected are insufficient to initiate a Phase 3 trial, or a meaningful deterioration of the current political, legal and regulatory situation in Israel or the United States; the availability, quality and timing of the data from the Phase 2 clinical trial of EB613 in osteoporosis patients; the size and growth of the potential market for EB613 and Entera's other product candidates including any possible expansion of the market if an orally delivered option is available in addition to an injectable formulation; the scope, progress and costs of developing Entera's product candidates including EB612 and GLP-2; Entera's reliance on third parties to conduct its clinical trials; Entera's expectations regarding licensing, business transactions and strategic collaborations; Entera's operation as a development stage company with limited operating history; Entera's ability to continue as a going concern absent access to sources of liquidity; Entera's expectations regarding its expenses, revenue, cash resources, liquidity and financial condition; Entera's ability to raise additional capital; Entera's interpretation of FDA feedback and guidance and how such guidance may impact its clinical development plans; Entera's ability to obtain and maintain regulatory approval for any of its product candidates; Entera's ability to comply with Nasdaq's minimum listing standards and other matters related to compliance with the requirements of being a public company in the United States; Entera's intellectual property position and its ability to protect its intellectual property; and other factors that are described in the "Cautionary Statement Regarding Forward-Looking Statements," "Risk Factors", "Management's Discussion and Analysis of Financial Condition and Results of Operations" sections of Entera's more recent annual, quarterly and current report and other documents filed by Entera with the SEC and available free of charge on the SEC's website at http://www.sec.gov. There can be no assurance that the actual results or developments anticipated by Entera will be realized or, even if substantially realized, that they will have the expected consequences to, or effects on, Entera. Therefore, no assurance can be given that the outcomes stated in such forward-looking statements and estimates will be achieved. The information in this release is provided only as of the date of this release, and Entera undertakes no obligation, to update or revise publicly any forward-looking statements, whether as a result of new information, future events or otherwise, except to the extent required by law.

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