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Forteo Injection May Soon Face Competition From a Pill

— Same peptide formulated for oral administration passes phase II test

by John Gever, Contributing Writer, MedPage Today
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An oral peptide drug with the same amino acid sequence as injectable teriparatide (Forteo) significantly boosted bone mineral density (BMD) in postmenopausal woman at risk for osteoporosis, a researcher reported from a dose-ranging phase II trial.

Six months of treatment with the oral agent, called EBP05, at doses of 2.5 mg/day led to a mean 2.5% increase in lumbar spine BMD versus a slight decrease in women receiving placebo ($P<0.002$), said Arthur Santora, MD, PhD, of Entera Bio's U.S. office in Boston. (The company, which is developing EBP05, is headquartered in Jerusalem.)

Santora said the drug yielded numerical improvements in BMD at the femoral neck and total hip as well in the 161-patient trial, during a late-breaking abstract session at the American Society for Bone and Mineral Research (ASBMR) annual meeting held online and in San Diego.

Mean patient age was about 60, with BMI values generally in the normal to overweight range. Mean BMD T-scores were 2.2-2.3 in the lumbar spine and total hip, and about 1.9 at the femoral neck.

Specific placebo-adjusted BMD improvements with EBP05 at 6 months were as follows:

- Lumbar spine: 3.78%
- Total hip: 1.38%
- Femoral neck: 2.42%

Only the lumbar spine BMD increase reached statistical significance in this analysis. However, Santora pointed out that, in a 2015 analysis, BMD increases with injectable teriparatide were concentrated in the lumbar spine, and the numerical increases with EBP05 at the other locations were substantially greater than with teriparatide.

Impacts on bone turnover markers included a steady decline in serum C-telopeptide of type I collagen (CTX) and an initial spike in procollagen type 1 N-terminal propeptide (P1NP) followed by decline.

In fact, P1NP changes at month 3 were the trial's primary endpoint, reported in a separate poster at the ASBMR meeting. At the end of treatment month 1, mean levels of this marker had increased more than 30% from baseline. It then fell back to about 10% over baseline by month 3, and completely returned to baseline at month 6. The same pattern was seen with osteocalcin, while CTX levels fell immediately by about 15% with treatment and stayed down throughout.

Santora's group concluded that these results were highly favorable and suggestive of better efficacy than with injectable teriparatide, which they said increases bone resorption and remodeling. In contrast, EBP05 seemed to inhibit bone resorption. Moreover, they said in the poster, "the anabolic effect on BMD may be greater than that estimated by the P1NP and osteocalcin response alone."

Teriparatide comprises the first 34 amino acids in the human parathyroid hormone protein. In its currently approved form, it's delivered by daily self-injection with a preloaded pen. Santora said, "Injections deter older patients from using the drug, contributing to a treatment gap in high-risk patients." Entera Bio has proprietary technology for making peptide molecules orally available.

There were some hiccups in the trial, Santora acknowledged, with two dosing protocol changes instituted after the study began.

As initially designed, patients ages 50 and older, at least 3 years postmenopause and with low BMD T-scores (between -2 and -3.5), were to be randomized to placebo or EBP05 at daily doses of 0.5, 1.0, or 1.5 mg/day. An interim analysis then suggested that the two lowest doses were having no effect. Recruitment for those arms was terminated and a daily 2.5-mg dose added.

Not longer afterward, however, high rates of orthostasis were observed in this high-dose group, Santora said. Seven of the 19 patients initially assigned to that arm withdrew within 3 months, and two more discontinued later without completing the full 6 months.

Consequently, the investigators began a titration regime for the 2.5-mg dose in 17 newly recruited patients: 1.5 mg/day for 1 month, 2.0 mg/day for the next month, and then 2.5 mg/day for months 3-6. That seemed to fix the problem, as only one patient in that arm withdrew prematurely. (The efficacy results Santora reported for the 2.5-mg dose included all 36 patients receiving that level.)

Other safety findings in the study were consistent with injectable teriparatide, Santora said. No excess blood calcium was noted.

Overall, the phase II results were encouraging enough that Entera is planning a phase III trial next year that will pit EBP05 directly against injectable teriparatide in a head-to-head format, Santora concluded.

John Gever was Managing Editor from 2014 to 2021; he is now a regular contributor.

Disclosures

The study was funded by Entera Bio. Santora and some co-authors were company employees.

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