Potential first-in-class osteoporosis drug speeds through trials

In the case of osteoporosis, a bone disease notoriously difficult to treat, doctors have hailed each new kind of drug as a major therapeutic advance. In 1999, the US Food and Drug Administration approved Merck's bisphosphonate drug Fosamax (alendronate)—which, along with other similar agents, quickly became the standard of care—and, just two years ago, the agency cleared Amgen's targeted RANK ligand inhibitor Prolia (denosumab). In some ways, the drugs have succeeded: Fosamax's sales reached \$3 billion a year before the drug's patent ran out, and Prolia has improved upon the efficacy of earlier drugs. But highly publicized side effects are causing patients to shy away from bisphosphonates, and Prolia, an injectable drug, can be a nuisance to take.

Now, on the heels of these struggles in the osteoporosis market, there's a new potential frontrunner: odanacatib. The oral drug inhibits the bone resorption enzyme cathepsin K and, if approved, will be the first in its class to reach the market. Although Fosamax and Prolia can increase bone mass by shutting down cells known as osteoclasts, they also hinder the creation of new bone. Odanacatib, which comes out of Merck's labs, seems to inhibit bone resorption without any such drawback. "This is a unique drug that may have less of an impact on inhibiting bone formation or, in some cases, actually stimulate bone formation," says Sundeep Khosla, an osteoporosis researcher at the Mayo Clinic in Rochester, Minnesota. "This could be something new and different to offer our patients."

Last month, after an outpouring of positive, early data from a pivotal trial on odanacatib, Merck announced that it was taking steps to close the trial early and move along, ahead of schedule, with regulatory applications. The trial, which launched in 2007, included more than 16,000 post-menopausal women over the age of 65. The interim analysis data have not yet been released, but recently published data on odanacatib from primate studies and from a phase 2 human trial (*J. Bone Miner. Res.* doi:10.1002/jbmr.1695, 2012) indicated that, compared with Fosamax, the new drug leads to almost twice as much an increase in bone mineral density in some bones and less reduction in serum markers

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Finding a niche: New osteoporosis drugs target different pathways that influence bone formation.

of bone formation. Merck, headquartered in Whitehouse Station, New Jersey, plans to file for regulatory approval in the US and the EU early next year.

A fraction of the fractures

Previous cathepsin K inhibitors from both Novartis and GlaxoSmithKline were halted because of side effects—particularly in the skin, where the enzyme is expressed in addition to bone. Merck has not reported an unusual rate of side effects with odanacatib, but many physicians are reserving judgment until long-term data from ongoing trials are released. "We need to await the results of this exceptionally large trial to make conclusions as far as the overall safety

and efficacy is concerned," says Henry Bone, an osteoporosis researcher at the Michigan Bone and Mineral Clinic in Detroit involved in ongoing odanacatib trials for Merck. "But I

think clinicians will be greatly influenced by the actual fracture data [showing a benefit] when they see it." Clinicians are also keeping a close eye on data from other cathepsin K inhibitors: Japan-based Ono Pharmaceutical's ONO-5334 is in phase 3 trials, and Sweden's Medivir has a drug now in phase 1 testing. Meanwhile, California-based Amgen has an experimental osteoporosis agent that inhibits the protein sclerostin, known to play a part in inhibiting bone formation. The antibody drug, AMG785, which kicked off phase 3 trials earlier this year, is the furthest along in development in its class.

For now, odanacatib is still the experimental osteoporosis drug closest to reaching the market, and if it meets benchmarks on safety and efficacy, market analysts at Credit Suisse in New York project the drug will offer a competitive alternative to bisphosphonates. The drug can be offered as both a first-line osteoporosis treatment and an option for patients who have hit the five-year mark with bisphosphonates and are no longer seeing an effect, the analysts say in a report published 25 June.

Sarah C P Williams

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Osteoporosis drugs in ongoing or recently completed phase 3 trials

Drug	Lead company	Target
BA058	Radius Health	Parathyroid hormone receptor
Femivia	EndoCeutics	Androgen receptors, estrogen
Odanacatib	Merck & Co.	Cathepsin K
Ostora	Tarsa Therapeutics	Calcitonin receptor
Romosozumab	Amgen	Sclerostin

Source: BioMedTracker