# Osteoporosis Therapy Pipeline Is Chock Full

BY ROBERT FINN
*San Francisco Bureau*

SAN FRANCISCO — "It's a pretty exciting time for drug development in osteoporosis," Dr. Deborah Sellmeyer said at a meeting on osteoporosis sponsored by the University of California, San Francisco.

While joking that her information was "sourced from Google and rumor and various investment brochures," Dr. Sellmeyer, director of the Center for Osteoporosis at the university, listed some of the osteoporosis drugs in the pipeline.

A fracture trial for a full-length version of parathyroid hormone (PTH [1-84]) has been completed, and a new drug application (NDA) was submitted to the Food and Drug Administration in July 2005.

**Tibolone is a drug that 'likes every steroid receptor it ever met,' and was found in a recent study to not cause any average weight gain.**

Meanwhile, inhaled-powder and oral forms of PTH are in phase I and phase II trials, and at least one PTH analogue is in phase III. "Everyone's looking for the magic combination that will be able to replicate the PTH skeletal effect and get rid of the hypercalcemic effect," Dr. Sellmeyer said.

Oral calcitonin preparations are in phase I and phase II. And low-dose and ultralow-dose estrogen remain fertile areas of research. The hope is that these preparations will replicate the beneficial bone effects of estrogen while avoiding its harmful vascular effects. While two low-dose patches and one low-dose pill have already been approved for the prevention of osteoporosis and for the treatment of vasomotor symptoms, no fracture data are yet available.

Zoledronic acid, a once-a-year intravenous bisphosphonate, is currently approved for hypercalcemia of malignancy and is now in a phase III trial to determine whether it prevents osteoporotic fractures. This agent is likely to benefit people who cannot tolerate oral bisphosphonates, people in assisted-living situations, and people who have difficulty remembering to take medication.

There are several new selective estrogen receptor modulators under development, with three—lasofoxifene, bazedoxifene, and arzoxifene—in phase III or beyond. An NDA for lasofoxifene was submitted to the FDA in 2004, but the manufacturer apparently received a nonapprovable letter in September 2005, putting the drug in limbo. An NDA for bazedoxifene was submitted in 2006 for the prevention of osteoporosis, and an NDA is planned for 2007 for a combination of bazedoxifene and estrogen for osteoporosis treatment and possible premenopausal use. Results from a phase III trial of arzoxifene are not expected until 2010.

Tibolone is a drug that "likes every steroid receptor it ever met," in Dr. Sellmeyer's words. Its three metabolites separately have affinities for estrogen, progesterone, and androgen receptors. A recently completed 24-month prevention trial in 90 women showed no difference in vaginal spotting between tibolone and placebo. Interestingly, the women taking placebo experienced a 12% weight gain, while the women taking tibolone experienced no average weight gain. A multinational fracture study involving 4,000 women is expected to conclude sometime in 2006.

It's been known for decades that strontium improves bone mineral density (BMD), but it was never developed for osteoporosis prevention or treatment because it's a nonpatentable chemical element. Recently, however, a proprietary formulation of strontium—strontium ranelate—has shown some promise. A granular form has already been approved for use in Europe and the United Kingdom, and a once-a-day pill finished a phase I trial in September 2005. Strontium ranelate is likely to complicate interpretation of BMD testing, since it has a higher density than calcium.

Denosumab, also known as AMG 162, is a monoclonal antibody that appears to decrease bone resorption. Currently in a phase III fracture trial on postmenopausal women, denosumab will require two subcutaneous injections per year.

Isosorbide mononitrate, long used for the pain of angina, appears to improve several bone markers in postmenopausal women. A BMD trial is currently underway.

β-Blockers constitute another class of drugs that may well have bone effects. Most epidemiologic studies associate use of β-blockers with increases in BMD and decreases in fractures. Randomized trials are needed to determine whether β-blockers actually have a place in osteoporosis prevention or treatment.

Finally, there are several new agents with previously untried mechanisms of action in the pipeline. Among them are selective androgen receptor modulators, cathepsin K inhibitors, and calcilytics. All are in early-phase studies for osteoporosis. ■

# *Anastrozole Shaves Bone Density, But Wards Off Breast Ca Recurrence*

BY JANE SALODOF MACNEIL
*Southwest Bureau*

ATLANTA — Anastrozole decreased bone mineral density by an average of 6.1% in the lumbar spine and 7.2% in the hip over the 5 years that postmenopausal breast cancer patients were enrolled in a study presented by Dr. Robert E. Coleman at the annual meeting of the American Society of Clinical Oncology.

Osteoporosis risk appeared limited to women who were osteopenic before starting treatment with anastrozole (Arimidex), an aromatase inhibitor. Less clear was the likelihood of progression to osteopenia in women who started out with normal bone mineral density (BMD).

All the women who became osteoporotic—four treated with anastrozole and one who was treated with tamoxifen—were osteopenic before they began adjuvant hormonal therapy in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial.

"No patient with normal bone at baseline became osteoporotic after 5 years of treatment," Dr. Coleman, a professor of medical oncology at Weston Park Hospital in Sheffield, England, said in his report on a subset of 167 women who were tracked for bone loss.

Among 81 patients tracked in the anastrozole arm of the trial, just 13 had normal BMD after 5 years. All but one had been classified as having normal bone before the study started.

The group of patients identified as osteopenic after 5 years was more mixed, comprising 14 women who entered the study with normal BMD and 21 who were osteopenic at the outset. Dr. Coleman calculated that 17% of patients on anastrozole progressed from normal BMD to osteopenia during the study.

About a third of the anastrozole patients had not reached 5 years of follow-up, however. They were categorized as "not recorded" in Dr. Coleman's analysis.

In a discussion of the trial, Dr. Julie Gralow, of the University of Washington, Seattle, excluded the 27 unrecorded patients, 6 of whom started out with normal BMD, from a recalculation of the data. When she looked only at patients for whom 5-year data were available, she found that 53% of the women who started with normal BMD became osteopenic on anastrozole.

That anastrozole caused bone loss was no surprise to Dr. Coleman and his coinvestigators. The 9,366-patient ATAC trial reported that the aromatase inhibitor was more effective than tamoxifen at preventing breast cancer recurrences and had fewer side effects overall. Fractures were an exception, however, occurring in 11% of women on anastrozole but in only 7.7% of those on tamoxifen (Lancet 2005;365:60-2).

"Anastrozole suppresses postmenopausal estradiol levels by about 97%, so one would anticipate it would have an effect on bone health," Dr. Coleman said, noting that the bone-loss study was planned when the trial was designed.

Tamoxifen increases estradiol levels and was associated with significantly less bone loss for 86 women in the other arm of the study. Their average BMD loss was just 2.8% in the lumbar spine and 0.7% in the hip.

Despite greater bone loss with anastrozole, he said its "superior efficacy and better overall tolerability, compared with tamoxifen" would continue to give anastrozole the advantage in a risk-benefit analysis.

AstraZeneca provided research funds and honoraria. ■

# Strontium Ranelate Shows 5-Year Benefit

TORONTO — The extension phases of two large trials evaluating strontium ranelate for the prevention of osteoporotic fractures have shown that the efficacy previously seen at 3 years holds up during years 4 and 5, Dr. Jean-Yves Reginster said at a world congress on osteoporosis.

Efficacy of strontium ranelate was confirmed for both vertebral and nonvertebral fractures, Dr. Reginster said.

**After 4 years, patients taking strontium ranelate had a significant 33% reduction in risk.**

**DR. REGINSTER**

After 4 years of treatment, patients in the Spinal Osteoporosis Therapeutic Intervention (SOTI) trial randomized to receive strontium ranelate had a significant 33% reduction in risk of new vertebral fractures compared with on placebo, said Dr. Reginster of the University of Liège, Belgium. The trial included 1,649 women with postmenopausal osteoporosis whose mean age was 69 years and whose mean lumbar spine bone mineral density T score was –3.6. They were recruited from 72 centers in 11 European countries and Australia. All had had at least one vertebral fracture.

Study patients were randomized to receive 2 g of oral strontium ranelate daily or placebo, and initially were followed for 3 years, at which time treatment was associated with a 41% risk reduction for vertebral fractures (N. Engl. J. Med. 2004;350:459-68).

In the second trial, the Treatment of Peripheral Osteoporosis (TROPOS) study, treatment with 2 g/day strontium ranelate among 5,091 postmenopausal women with osteoporosis was associated with a 16% relative risk reduction for all nonvertebral fractures at 3 years and a 39% reduction for vertebral fractures (J. Clin. Endocrinol. Metab. 2005; 90:2816-22).

At 5 years, the relative risk reduction for nonvertebral fractures was 15%, and for vertebral fractures the risk reduction was 24%.

Patients in this study were older, averaging 76.7 years, Dr. Reginster said. Mean femoral neck T score was –3.1. With regard to safety, no new concerns arose. "Among all patients at the beginning of the trials there was a slight increase in the incidence of deep vein thrombosis, but this vanished over time and was no longer apparent during years 4 and 5," he said at the meeting, sponsored by the International Osteoporosis Foundation.

**—Nancy Walsh**