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By Lynne Peterson

SUMMARY

Doctors consider the various bisphosphenates fairly equivalent, though dosing and administration regimens vary, and less frequent dosing may have advantages. However, bisphosphenate use is likely to increase as doctors pull back from hormone therapy after the findings of the Women's Health Initiative. Doctors are excited about parathyroid hormone (PTH), but most plan to use it only for selected, high risk patients with significant osteoporosis. Amgen/NPS Pharmaceuticals' calcimimetic, AMG-073, which is in Phase II trials, looks promising. NPS/GlaxoSmithKline's calcilytic is further away but also worth watching.

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Among the key topics examined at this meeting were bisphosphenates, parathyroid hormone, hormone replacement therapy, calcimimetics, and calcilytics.

BISPHOSPHENATES

The bisphosphenate marketing wars raged at this meeting. Each company presented data that made it appear its drug was the best, safest, most effective, etc. In terms of efficacy, most sources believe that daily products are equal to weekly, and that all are fairly comparable in terms of efficacy. A head-to-head study of risedronate vs. alendronate is underway and should determine if there are any real differences, at least between those two agents. That data should be available in about a year.

Intermittent therapy for bisphosphenates also got a lot of attention at the meeting. A U.K. researcher said, "Most bisphosphenates probably can be given daily, weekly or monthly to achieve the same cumulative dose to produce an equivalent effect – provided a high enough dose is used. However, there may be differences when they are given over longer intervals."

When bisphosphenates are given weekly, it has been at the daily dose times seven. Interestingly, a Japanese study showed that a daily PTH dose given weekly instead of daily is just as effective as the daily dose. That might mean the PTH dose could be cut by $1/7^{th}$. The University of California, San Francisco, has NIH approval for a study of weekly PTH at this dose level, but has not yet arranged funding for the study.

Most doctors were unimpressed with the marketing claims for the bisphosphenates. They already recognize the benefits of bisphosphenates, and prescribe them for a majority of the post-menopausal women with -- or at risk of – osteoporosis, and they insisted there is little difference among the agents, particularly between Actonel and Fosamax. All described the claims as marketing maneuvers.

An epidemiologist comparing these agents said the reduction in risk of hip fractures is:

- ~50% with Fosamax
- ~30% with Actonel
- None with Evista at four years, according to speakers at this meeting
- Inconclusive with calcitonin
- 40%-60% with estrogen when taken continuously, though he noted, "Despite the HERS and the Women's Health Initiative (WHI) studies, There are no

randomized trials of HRT in hip fractures among women with osteoporosis…In HERS-1, no matter what we did, we couldn't tease out any effect on clinical fractures. It was a null finding. In HERS-2, there was a trend to an increase of hip fractures in the estrogen plus progestin group, but it wasn't statistically significant. The WHI results were a big surprise, showing a 34% decrease in risk with HRT…A hypothesis for why HERS and WHI results differed is that estrogen prevents fractures in younger women. The average age of women in WHI was 63, and it was 67 in HERS…Another hypothesis is that in women with coronary heart disease, the effects of the estrogen on bone are blocked."

On average, doctors at this meeting (and it must be remembered that few of these are OB/GYNs) estimated that, of their new osteoporosis patients starting on drug therapy,

- 65% will get a bisphosphenates, and all said they are splitting their use equally between Actonel and Fosamax.
- 28% will get a selective estrogen receptor modulator (SERM), which means Eli Lilly's Evista (raloxifene)
- 7% will take HRT. A doctor said, "I am prescribing HRT for individual patients who would benefit who may not encounter some of the other potential risks and who understand the benefits and risks. Patients are very concerned (about the safety of HRT)…But for women where hip fracture is a great concern and risk, it does provide another option."

MERCK's Fosamax (alendronate)

➢ **Long term data.** Ten-year safety data reinforced the safety profile of this agent. In addition, the randomized, triple-blind, placebo-controlled Early Postmenopausal Interventional Cohort (EPIC) Study of 1,609 women showed a prolonged benefit to therapy. That study found women who received the drug (5 mg daily) for six years had normalized bone turnover and preserved bone density during the treatment period. Bone loss resumed when alendronate was discontinued after four years but at a rate slower than that following estrogen-progestin therapy. A researcher said, "In contrast to withdrawal of estrogen, catch-up loss is not observed following alendronate…BMD at the end of six years remained significantly higher in women who previously received alendronate 5 mg for four years than in those who were never treated with alendronate."

➢ **Weekly data.** Weekly Fosamax is superior to daily risedronate, claimed a speaker at a Merck-sponsored seminar. He said, weekly Fosamax lowered bone resorption more and increased BMD at the hip and spine more than risedronate, but he admitted the marketed dose of Fosamax is higher than the risedronate dose. He said, "In Europe and Canada, risedronate uses between-meal dosing, which is not approved in the U.S. Another trial comparing the two drugs when taken after fasting has just finished enrollment."

➢ **Combination therapy.** Alendronate plus hormone replacement therapy (HRT) is better than either agent alone at preserving bone mineral density (BMD). In a study of 485 women aged 65 and older, alendronate+HRT(estrogen+ progestin) was compared to alendronate alone, HRT alone or placebo. Researchers found that combination therapy showed a 1.5%-4% greater increase in bone mass than single therapy – regardless of the site where BMD was measured. A researcher concluded, "Monotherapy with alendronate is superior to HRT and combination therapy is superior to either alone…If HRT is an option, then combination therapy with a bisphosphenate can (safely) be considered. (However) It would be hard to do a trial (like this) now (because of patients concerns with the safety of HRT)."

Increase in BMD	Alendronate + HRT	Alendronate Alone	HRT alone
Hip	5.9%	4.2%	3.0%
Spine	+10.4%	+7.7%	+7.1%

PROCTOR & GAMBLE/AVENTIS's Actonel (risedronate)

Sales of this agent have been very strong, but most doctors said this is mostly marketing, not any superior effect from the drug. One source commented, "Actonel has good GI tolerability, build bone rapidly, and it has a labeling advantage in terms of reduction of spinal fractures."

Two multicenter, double-blind studies – VERT-MN and VERT-MA – compared risedronate to placebo in a total of 1,994 postmenopausal women with osteoporosis. Researchers found that Actonel (5 mg qw) reduced the risk of non-vertebral fractures as early as six months, and it significantly decreased the risk of moderate or severe vertebral fractures in postmenopausal women with osteoporosis at one year, an effect that was sustained for three years. A researcher said, "Fosamax has not shown this (fracture benefit) at one year."

Event in first year	Risedronate 5 mg n=1002	Placebo n=992	Risk reduction in vertebral fractures
Severe vertebral fracture	1.4%	4.6%	70.7% in moderate-severe 64% in mild-severe

HOFFMAN-LA ROCHE's Bondronat/Bonviva (ibandronate)

➢ **Oral therapy.** Oral therapy is as good as IV therapy in terms of vertebral fracture risk. A three-year, Phase III trial of almost 3,000 women, found that 2.5 mg of ibandronate daily reduced the risk of new vertebral fractures by 62% compared with placebo.

➢ **Weekly dosing.** A study found that weekly dosing (35 mg) with ibandronate was as effective as daily dosing, and the side effect profiles were similar to placebo with relatively no GI upset.

➢ **Intermittent therapy.** Intermittent oral therapy also reduces new vertebral fractures. The same Phase III study found that 20 mg of ibandronate given orally every other day for 24 days then stopped for 9-10 weeks also reduced the risk of new vertebral fractures by 50% compared with placebo. A researcher said, "20 mg won't be the final dose, and this won't be the final dosing regimen. The company is studying a once-a-month oral dose…The advantage of ibandronate over zoledronate is that it is an oral."

NOVARTIS' Zometa (zoledronate, zoledronic acid)

Once-yearly dosing for osteoporosis continues to look promising. Many doctors are very enthusiastic about Zometa, but some worry that healthy women will be squeamish about an infusion, even a 15 minute infusion.

A study of 351 postmenopausal women age 45-80 with low BMD found all doses of zoledronate (.25 mg, .5 mg and 1 mg) given once every three months or 4 mg given once a year in a 15-minute infusion were equally effective in their effect on BMD, and all were significantly better than placebo. The viability of this dosing regimen will depend on fracture data, which will not be available until 2005. The zoledronate fracture study -- the HORIZON-PFT trial -- will look at 7,406 patients, age 65-89 with low BMD and/or a previous vertebral fracture. Patients will not be excluded for current or previous HRT or SERM use, but PTH use is an exclusion. The patients in this trial will be divided into two groups:

- stratum 1 – 3,106 patients not receiving usual care osteoporosis treatment at baseline
- stratum 2 – patients receiving usual care meds (HRT, SERM, calcitonin, calcitriol, etc.)

All these patients will be randomized to either 5 mg zoledronate once yearly or placebo. The primary endpoint is vertebral fractures in Stratus 1 and hip fractures in Stratum 2.

Another study, the HORIZON-RFT trial, also will be conducted at the same time. This is a multinational, double-blind, randomized, placebo controlled, parallel group study of the effects of zoledronate on the rate of subsequent clinical fractures after a hip fracture. This trial will study 3,468 men and women age >50 who have undergone surgical repair of a low-trauma hip fracture. Patients will be given either once-yearly zoledronate 5 mg IV or placebo, with infusions at randomization and at 12 months. The primary endpoint is clinical fracture, and the secondary endpoints are serum markers of bone turnover, quality of life, ability to perform the activity of daily living, pain and cost effectiveness. The percent change in BMD of the non-fractured hip by DXA will be assess in 600 patients. The study will complete once 303 patients have been diagnosed with a clinical fracture.

HORMONE REPLACEMENT THERAPY

Bisphosphenate use has gone up in wake of the decision by the National Heart, Lung, and Blood Institute (NHLBI) to stop the Women's Health Initiative study of the use of hormone replacement therapy (HRT) for primary prevention. Indeed, the prescribing practices of endocrinologists and rheumatologists, not only obstetricians and gynecologists, has changed. Doctors at this meeting said their use of HRT for osteoporosis has dropped significantly since the trial was stopped, and they expect very few of their new osteoporosis patients to start HRT.

The National Institutes of Health (NIH) is sponsoring a forum on the WHI on October 23 and 24, 2002 in Bethesda, Maryland. However, WHI officials have been a little vague on what the meeting is expected to accomplish. One official said, "The NIH leadership felt we owe the public more of a forum. That was just one study, and you don't make recommendations from one study. Recommendations come from task forces looking at all the data." A second WHI official said, "There has been confusion among physicians about what has been found and what to do. The meeting is to discuss the meaning of the findings and how they (the agents) should be used…ERT is not over; it is important for bone, but cardiovascular use is dead."

➢ *Asked if the forum will lead to new guidelines for HRT use*, an official said, "I can't promise that. This is not a consensus conference, but pretty much a general discussion."

➢ *Asked whether there will be a discussion of the applicability of the WHI findings to other HRT products*, an official said, "I can't give good answer on that."

➢ *Asked if the approach is similar to the panel the FDA held after the decision to withdraw Pfizer's (then Warner Lambert's) Rezulin (troglitazone) from the market*, an official said, "Absolutely. That's a good analogy."

It does appear that physicians may find the forum useful. A doctor said, "The WHI study is nice, but I have a lot of women on HRT who said they feel fine and want to continue. There are a lot of questions that will be answered (by the forum). In the wake of the (WHI) findings and the halting of the arm of the trial, there was so much general concern and dismay on the part of many women and their doctors on how to use the new information that we are hoping the discussion will help to dissipate some of that doubt and confusion."

PARATHYROID HORMONE (PTH)

Doctors questioned about how they will use PTH when and if it is approved, indicated they will reserve it for selected, high risk patients who have significant osteoporosis by BMD (spine) or who have clinically significant signs/symptoms. They also plan to use it in a subset of naïve, high risk patients. However, most do not plan to use it for new patients at first. Rather, they will use it for existing patients who need additional treatment. One commented, "Lilly's pen injector makes giving the injections very easy." Another commented, "Specialists may not over use PTH, but the danger is that primary care physicians will because it is so easy."

ELI LILLY'S Forteo [teraparatide, rPTH (1-34)]

The FDA has given Eli Lilly an approvable letter for 20 mg daily injectable Forteo, with only manufacturing issues remaining, so the drug is expected to be on the market within six months. Development of Forteo was delayed a couple of years ago when a rat study found an association between Forteo and osteosarcoma. Lilly presented carcinogenicity data at the meeting from a new rat study which should lay most if not all of those concerns to rests. An ASBMR official said, "The human studies suggest no increased risk of osteosarcoma…There is nothing to suggest we will see that in humans."

A Lilly researcher said this new study was not required by the FDA for Forteo's approval, but it was designed in consultation with the FDA. An ongoing monkey study won't be finished for 3.5 years. He said the new rat study looked at three things:

- **Effects of dose.** "In a nutshell, it is clear that dose is important. The 5 µg/kg and 30 µg/kg doses used were three-times and 20-times, respectively, greater than the typical human dose. In both the original and this newer study we found that the incidence of bone changes was dose-responsive, which was expected."
- **Duration.** How long the rats are treated -- the percent of their lifespan during which they receive the medication – has a clear influence on the incidence of bone changes. In the new study, rats were treated for varying periods of time – from 20% of their life to 70%-80% of their life. "The new study shows that…if you control the dose and the duration, you don't get bone neoplasms. We were able to treat rats for 70% of life with three times the human dose, and there were no bone tumors…Our follow-up data shows that even after cessation (of Forteo), fracture efficacy remains. Forteo is intended only for a limited duration of treatment – two years. It is likely that in the marketplace, this drug will be followed with an antiresorptive (bisphosphenate)."
- **When in the lifespan treatment began.** "We found that you don't have to treat the rats early in life for them to develop tumors. The hypothesis in the community was that starting treatment early would be a factor, but it is not the case. Even old rats started on treatment could have a problem with a high enough dose and a long enough duration of treatment…If you start a rat on therapy at six months and treat to 2 months (which is this rat's lifespan), that is in the range of 70% of lifespan." Asked what happens if treatment is started at 20 months at high doses, he said, "We haven't done those studies, but the data so far indicates there is no issue."

Other miscellaneous Forteo points:

- Another Lilly official insisted his company is not working on a weekly version of Forteo or on alternate delivery systems.
- A small pilot study presented at the meeting found that bone strength increased with Forteo.

GLAXO SMITH KLINE/UNIGENE'S UG-17841

Glaxo and Unigene signed a deal in April 2001, with Glaxo agreeing to handle clinical development of UG-17841 (an rPTH (~1-34 analog). It is an oral agent with a proprietary delivery technology. Phase I clinical trials of UG-17841 are expected to begin in 2003.

NPS PHARMACEUTICALS' Preos [recombinant parathormone, parathyroid hormone, PTH (1-84)]

Preos is in Phase III development, with more than 2,600 patients enrolled so far. There was no new data on this injectable agent at the meeting.

An NPS official said, "We are doing the same tox studies Lilly did, and we are about half-way through. At one year, there was no sign of carcinogenicity, but Lilly didn't see it at that point either. If it happens, it will be at 15-18 months. We'll be looking at the data again at two years – in August 2003." Asked if other PTHs have carcinogenicity issues, a Lilly official said there is no data directly comparing the NPS compound and Lilly's Forteo, but he added, "The FDA in two public guidances (our advisory committee guidance and another draft guidance) indicated the carcinogenicity had been seen with other PTHs, but we don't know if that includes (the NPS compound)."

A large, NIH-sponsored study of the combination of Preos and Fosamax, and NPS is conducting a European study of Preos plus estrogen in women on HRT.

CALCIMIMETICS

There are two kinds of hyperparathyroidism:

- Primary, which usually results from a single adenoma and is characterized by elevated plasma PTH and hypercalcemia.
- Secondary, which is a natural response to a failing kidney and is characterized by elevated plasma PTH and normocalcemia or hypocalcemia.

Therapies have all treated the hypercalcemia rather than the elevated serum PTH, and in some cases made the disease worse. Calcimimetic compounds act on the calcium receptor to inhibit PTH secretion. There are two types of calcimimetics:

- Type I – true agonists.
- Type II – allosteric activators which need extracellular calcium to work.

NPS PHARMACEUTICALS

NPS's first clinical calcimimetic was NPS-568, a Type II calcimimetic, which was modified and led to NPS-1493 (KRN-1493). NPS-1493 was licensed to Amgen and became AMG073. The two key reasons that NPS-568 was dropped in

favor of AMG-073 were the CYP2D liability and bioavailability differences.

AMG073 is in Phase III for secondary HPT and in Phase II for primary hyperparathyroidism (PHPT). It also may have a role in metastatic parathyroid cancer. One study showed it improved quality of life, lowered plasma PTH (from baseline, though it still remained too high), and lowered markers of bone tumors.

AMG-073 is about half-way through a Phase III clinical trial, but the data is not likely to be available until either the Endocrine Society or ASBMR meeting in 2004. There is supposed to be new data (including five abstracts) at the American Society of Nephrology meeting in Philadelphia October 30-November 4, 2002. A source said, "The data looks great. It makes people smarter on cognitive test scores for quality of life."

Comparison of NPS Calcimimetics

Characteristic	NPS-568	AMG-073
Potency	27 nM	28 nM
MoA	Allosteric	Allosteric
CYP2D liability	Yes	No
Bioavailability	<5%	>5%

In early studies in PHPT, AMG-073 produced a very rapid effect that also came back quickly, indicating this is a reversible chemical action. Data presented at the Endocrine Society meeting earlier this year found that daily dosing with AMG-073 over one year (compared to placebo) was associated with a decrease in plasma levels of PTH, which in turn were associated with a decrease in levels of circulating calcium. An NPS official concluded, "The calcimimetics are quite good in treating PHPT."

In secondary HPT, in which vitamin D and plasma calcium levels are down but plasma phosphatase and PTH levels are up, the current treatment is diet, calcium supplements, phosphate binders, calcitriol (Roche's Rocaltrol) and surgery (parathyroidectomy) in very severe cases. A study of a single oral dose of NPS-568 in dialysis patients with moderate to severe secondary HPT found rapid lowering of serum PTH, indicating the agent is effective in decreasing circulating PTH in dialysis patients.

Phase II data on once-daily, oral AMG-073 showed that, over 12 weeks, dialysis patients experienced a dose-dependent decrease in plasma levels of PTH which were maintained. An NPS official said, "One of the problems in secondary HPT is that it varies from mild to severe disease, and the data showed that, regardless of the severity of the disease, one dose lowered the PTH level…And there is a decrease in the calcium/phosphate ratio, which is something you want to do because we are gaining an appreciation that an increased ratio results in soft tissue calcification."

Standard therapy today for secondary HPT is Calcitriol, and a calcimimetic may have advantages over this. For instance, a calcimimetic is likely to affect renal bone disease differently.

However, an expert in the field cautioned: "The ideal approach (to PHPT) is to use allosteroid modulators. The 52-month data indicate AMG073 sustains its effect up to a year, but the data are still not conclusive or compelling. We don't believe any medical therapy is sufficiently definitive to recommend in clinical practice – yet."

Calcimimetic vs. Calcitriol

Calcimimetic	Calcitriol
Acts on cell surface receptor	Acts on genomic receptor
Inhibits PTH secretion	Inhibits PTH synthesis
Rapid onset (minutes) and recovery (hours)	Slow onset and recovery takes days to weeks
Decreases CaxP products	Increases CaxP products
Pulsatile effect	Slow effect over days pulsatile decrease

CALCILYTICS

Calcilytics should increase PTH secretion. They need to be short-acting and orally active. The major concern in finding one is calcilytic-induced parathyroid hyperplasia.

NPS and **GLAXO SMITH KLINE** are collaborating on calcilytics. NPS's first generation calcilytic was NPS-2143. In vitro data showed it is an allosteric inhibitor that stimulates PTH secretion. Researchers reported that the drug showed no effects at low levels, but when infused at medium levels (300 nM), there was a profound and rapid effect, with PTH levels rising and staying up. Rat studies showed it increased both bone formation and bone resorption, so there was no net increase in BMD, but when given with estradiol it increased BMD without causing parathyroid cell hyperplasia. Currently, NPS-2143 is in Phase I trials.

Other interesting findings at this meeting:

Vitamin D. A study at the University of Chicago confirmed an inverse relationship between serum vitamin D levels and blood pressure: People with low serum vitamin D tend to have high blood pressure. A researcher said, "We found vitamin D suppressed the renin-angiotensin system…vitamin D suppresses renin production in the body, keeping the appropriate level. In a vitamin D deficient suppresses renin production…This helps explain why insufficient sunlight exposure and vitamin D state..gets the system out of control and leads to hypertension…But too much vitamin D further definite risk factors for hypertension and underscores the importance of nutritional vitamin D supplementation. And it opens the possibility of using vitamin D analogs as a hypertension treatment in the future." A source commented,

"This is the first connection between vitamin D and blood pressure, and African Americans tend to have more hypertension and lower vitamin D levels."

AMGEN's OPG (osteoprotegrin). An Amgen official reported that this is not likely to be the agent finally approved. The company has a follow-on agent that is likely to replace the current OPG and be the one that reaches market. This source said the "new" OPG will be administered subcutaneously, have more and longer suppression of osteoclasts, and require less frequent treatment. Phase I data with the new OPG is being analyzed now, and a Phase II trial is expected to start shortly, but any OPG is at least six to seven years away from market, according to the Amgen official.

So far, researchers haven't reported any toxicity concerns with OPG – no cancer, infection, or immune suppression. Early safety data in rats with cancer that metastasized to the bone indicated that OPG blocked lesions, stopped tumor burden from progressing, and is safe. A researcher said, "It doesn't harm fracture repair in normal rats, but we don't know yet if it will slow healing in osteoporotic people with fractures."

OPG is likely to be used both as monotherapy and in combination with PTH. A researcher said, "OPG and PTH work phenomenally together."

Several interesting studies were presented that continue to fuel optimism about this agent.

- A Japanese study found that serum OPG levels correlate to the severity of coronary artery calcification. The study looked at 201 patients undergoing coronary angiography and compared serum OPG levels with severity of coronary calcification and found that the serum OPG level increased as the severity of coronary calcification increased. The findings were confirmed by electron-beam CT. Researchers concluded, "OPG may be involved in progression of CAD, and serum OPG may reflect certain stages of CAD." They described OPG as a precursor for cardiac events and suggested that OPG levels should be considered a risk factor for coronary artery disease. A source called this "very provocative information."
- A "Mice in Space" study found that OPG works by lowering osteoclast surface area, indicating it is a safe and effective counter-measure for dis-use osteopenia. That means, a researcher explained, that it may be particularly useful for bedridden people, astronauts and quadriplegics.

BONE CARE INTERNATIONAL'S Hectoral (vitamin D pro hormone). This is approved for secondary PHT in chronic renal failure, but it may have value as a topical agent in psoriasis and skin cancer. A British researcher said, "It was a bit of a surprising finding. There haven't been any human clinical trials yet."

HOFFMAN-LA ROCHE's NPT-IIa. This program was stopped, at least temporarily, in December 2001.

INTERMUNE'S Actimmune (interferon-γ). A University of Rochester study suggested that IFN-γ may help prevent bone loss in arthritic patients. A researcher explained, "You need an inflammatory response for IFN-γ to have an effect, and that is present in patients with arthritis." There is no indication that Intermune is pursuing this indication – yet.

NOVARTIS

- **"Compound 1."** This cathepsin-k inhibitor is a cysteine protease. So far, there is only animal (rat and monkey) data, but it is fairly interesting and would be first-in-class. It is oral, reduces bone resorption, and is reversible.
- **PK-1166.** In cell lines and mice, this EGFR reduces the proliferation of bone mets.

TANABE's TMC-315B2. This RANKL-RANK inhibitor from a fungus proved too complex to go forward in development, but the company is looking for a simplified version.

WYETH/GENEOME THERAPEUTICS's LRP5 receptor blocker. Perhaps the most exciting finding reported at the meeting was the discovery of the importance of a specific mutation in the Lrp5 gene (on chromosome 11) that leads to increased to bone mass (density). Creighton University researchers studied 38 related patients with Osteoporosis-Pseudoglioma (OPPG) syndrome and found that an inherited autosomal trait – a gene mutation in Lrp5 – caused extremely high bone mineral content in their skeletons. A researcher called it "nature's cure for fracture," saying that no one in the family, from age 3 to age 90, had had a fracture.

Creighton, Genome Therapeutics and Wyeth are collaborating on high throughput screening to find a pharmacologic agent that will mimic this disorder by doing what the mutation does – block the Lrp5 protein receptor. A researcher said, "We know the mutation causes osteoblasts and osteocytes to live longer and increases the sensitivity of the skeleton to mechanical loading. With this mutation, you get twice the response. Our hope is that by manipulating Lrp5 (and/or the pathways through which it acts) with a pharmacologic agent, we will increase a person's bone density substantially and prevent fractures."

Although any Lrp5 receptor-blocker is years away from the market, Wyeth researchers said they hope to have an agent in human clinical trials in less than three years. One commented, "This would sop up the receptor the way Enbrel (Amgen, etanercept) sops up TNF-α."

The issues that will need to be watched in the development of this agent are vision, carcinogenicity and neurological problems. A researcher said, "This is an extremely exciting discovery, but the concern with Lrp5 is that the increases in bone could be associated with negative effects such as infections, cancer, vision problems, or neurologic problems in the Wnt signaling pathway through which this works."

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