Trends-in-Medicine

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By Lynne Peterson

SUMMARY

In one-year Phase II data Amgen's AMG-162 beat placebo at all doses, and beat Merck's Fosamax at all but the lowest dose. ♦ Amgen's calcimimetic Sensipar (cinacalcet) needs more data for FDA approval in primary hyperparathyroidism, but it is being well accepted in the more limited, approved indications. ♦ Chugai's nasal spray hPTH (1-34) is proceeding to a dose-finding Phase II trial, but patent issues with Lilly loom and safety questions remain. ♦ At three years Lilly's Forteo continues to decrease fractures as well as alter progression of osteoporosis. ♦ The bisphosphenate marketing wars continue. Merck's Fosamax beat out Proctor & Gamble's Actonel on BMD in a head-to-head trial, but some sources believe Actonel may be a better pre-treatment for PTH. ♦ Johnson & Johnson/Alza is working on a transdermal patch delivery system for Forteo – Macroflex-ThPTH – which looks very interesting. ♦ Bad news is on the near horizon for Kyphon – a study to be published shows a 25% adjacent fracture risk within two months.

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In the U.S. one of two women and one of four men will have an osteoporosis-related fracture in their lifetime. In Europe, eight of 20 women and three of 20 men will have an osteoporosis-related fracture. Annually, there are 1.5 million total fractures in the U.S.:

- 700,000 vertebral fractures.
- 300,000 hip fractures.

A large percentage of osteoporotic fractures occur in elderly, postmenopausal women with low bone mass (T-score >-2.5). Other clinical risk factors include body size (taller), frail, on certain medications (e.g., sedatives, anticonvulsants, antihypertensive), diabetes, peripheral neuropathy, dementia, and/or a history of falls, prior fractures, stroke, or recent weight loss.

Dr. Ethel Siris of Columbia University said, "About 25% of these require subsequent long-term nursing home care, and about 50% are unable to resume normal walking, never regaining the level of independence they enjoyed before the fracture. There also is a 20%-25% increased mortality in the year following a hip fracture…Fractures beget fractures. A previous vertebral fracture or distal forearm fracture increases the risk of a hip fracture, and patients who have had a hip fracture have a six-fold increased risk of fracturing the second hip within the next year." She offered some frightening statistics:

- In 2000, of 170 women admitted to a New York hospital with a hip fracture, only 5% left the hospital with a prescription for an osteoporosis drug.
- In 2002, a Canadian hospital study of 311 patients with a hip fracture found only 11% left the hospital with a prescription for an osteoporosis medication.
- In 2002, a study at four Midwestern hospitals found BMD tests were performed in only 15% of patients after a fracture, only 14% were given calcium, and only 21% were given an antiresorptive.
- In 2003, at a Colorado hospital, 25% of 118 patients with a hip fracture received a prescription for osteoporosis at discharge.

In the National Osteoporosis Risk Assessment (NORA) study of 163,955 postmenopausal women, 80% of the 440 new hip fractures occurred in women age 65-99, and 20% occurred in women age 50-64 (53% of the subjects).

Compliance and persistence with current osteoporosis drug therapy is relatively poor, with about 40% of patients stopping therapy. An expert commented, "Persistence with therapy is woeful…In a database (study) of ~200,000 patients, 48%

had adequate persistence." The main reasons patients stop taking antiresorptives are:

- GI side effects 33%
- Other side effects 29%
- Lack of efficacy 29%

Osteoporosis Therapies

Approved Agents	Lumbar spine BMD change from baseline	Relative risk of vertebral fracture
Lilly's Forteo (PTH 1-34)	9.7%	0.65
Lilly's Evista (raloxifene)	2.5%	0.60
Merck's Fosamax (alendronate)	7.5%	0.52
Novartis's Aredia (pamidronate)	N/A	N/A
Proctor & Gamble's Actonel (risedronate)	4.5%	0.64
Proctor & Gamble's Didronel (etidronate)	N/A	N/A
Roche's Boniva (ibandronate) – daily	N/A	N/A
Agents in Development		
Amgen's AMG-162		
Novartis's Zometa (zoledronic acid) yearly IV		
NPS Pharmaceuticals' Preos (rhPTH 1-84)		
Roche's Boniva (ibandronate) – monthly		

A respective medical record review at a VA hospital looked at compliance (computed as the cumulative months with a bisphosphenate prescription divided by the months the prescription was refilled) among 63 patients. The study suggests that where a patient is treated affects compliance.

Treatment location	Fosamax compliance	Actonel compliance
Pharmacotherapy clinic	82.6%	71.8%
Other clinics	70.1%	62.3%

A GlaxoSmithKline-sponsored study found that weekly administration is better than daily dosing with bisphosphenates – but still suboptimal. The study was a 211,319-patient longitudinal cohort from a U.S. retail pharmacy database, and it found less frequent dosing was associated with better persistence regardless of age, method of payment, or patterns of past osteoporosis medical use.

Medication possession ratio (MPR) ≥80	Daily dosing	Weekly dosing
Continuing patients	35.2%	48.1%
New patients	13.2%	25.2%
Switching patients	15.4%	35.8%
All patients	33.3%	44.8%

Unanswered Questions

Among the questions and issues still facing antiresorptive therapy in 2004 are:

- Mechanisms of fracture reduction.
- Potential differences between bisphosphenates.
- Duration and reversibility of action.
- How long to treat with bisphosphenates. This was a hot topic at the meeting, and two sessions on this topic could not accommodate all the people who wanted to get in.
- Possible over-suppression of bone turnover. A speaker said, "Probably this is not a problem, but it needs to be debated."
- Combination or sequential therapy (e.g., PTH + bisphosphenates).
- Optimizing other applications (e.g., cancer).
- How to determine if a bisphosphenate is working. An expert said, "We use biochemical markers – serum CTX and urine NTX – because BMD takes two years to show an effect. The big problem with both those biochemical markers is the diurnal and food effects…Markers are not ready for prime time with primary care physicians."

Cost effectiveness of antiresorptives and PTH

Asked what he prescribes for naïve osteoporosis patients, one expert said, "80% get a bisphosphenate, 10% raloxifene, and 10% PTH. I haven't written a Miacalcin (Novartis, calcitonin-salmon nasal spray) prescription in the last three years…If Forteo cost the same as alendronate, then I'd prescribe 80% Forteo and 10% alendronate…The best drug at first fracture may be PTH, but cost prevents that."

Several posters addressed this issue. Among the most interesting were:

- A University of Minnesota study found Fosamax is not likely to be cost-effective in osteopenic postmenopausal women without additional BMD-independent fracture risk factors at the current price (using ≤$50,000 per QALY as cost-effective). Researchers concluded the results should be generalizable to other antiresorptive drugs of similar cost and efficacy.

Fosamax Cost Per QALY

Age	Baseline T-score		
	-1.5	-2.0	-2.4
50	$138,192	$98,454	$83,213
60	$117,318	$81,501	$62,858
70	$116,798	$87,751	$69,555
80	$154,749	$114,787	$92,250

- A Bayesian analysis by Australian researchers found bisphosphenate treatment of postmenopausal women with low BMD or established osteoporosis can reduce the risk of a hip fracture by 25%-60%. To prevent one additional hip fracture over placebo, 99 patients need to be treated for three years.

PTH issues

The key issues holding back more use of PTH include:

- FDA two-year limit on Forteo administration.
- Subcutaneous injections.
- Cost. An expert said, "Cost and the insurance co-pay have been big issues."

SPECIFIC DRUGS

ABGENIX'S ABX-10241
Off to a good start, but early

Results were presented at ASBMR from a Phase I safety and tolerability study of a single, IV dose of this fully human monoclonal antibody against parathyroid hormone in 17 patients with secondary hyperparathyroidism (SHPT). The study compared two ABX-10241 doses (30 mg and 100 mg) with placebo, finding:

- A dose-dependent suppression of unbound iPTH.
- A dose-dependent reduction in serum calcium.
- A reduction in the calcium-phosphorus product (CaP).
- No human anti-human antibodies were detected in any subject at any time point.

3-Week Phase I Study of ABX-10241

Measurement	Placebo n=5	ABX-10241 30 mg n=4	ABX-10241 100 mg n=8
Adverse events	40%	100%	75%
Drug-related adverse events	0	0	0
Serious adverse events	20%	50%	25%
Drug-related serious adverse events	0	0	0
Patients with unbound iPTH ≤300 pg/ml at Week 1	20%	~ 50%	88%
Serum bAP change from baseline in patients with elevated bAP at baseline			
Week 1	Down ~ 5%	Down ~ 6%	Down ~ 28%
Week 2	Up <1%	Up ~ 5%	Down ~ 20%
Week 3	Up ~ 1%	N/A	Down ~ 3%

AMGEN'S AMG-162
Good news for this subcutaneous antiresorptive agent with once-every-six-months (Q6M) dosing

Based on the results of a Phase II trial, AMG-162 looks as if this monoclonal antibody could become a much more convenient alternative to the existing bisphosphenates and SERMs, but AMG-162 is still in early stage development. It appears Amgen is developing it for osteoporosis and bone metastases from solid tumors as well as other indications. The optimal dose is believed to be 60 mg subcutaneously once every six months. AMG-162 may compete most directly with a once-yearly infusion formulation of Novartis's Zometa (zoledronic acid), but an expert noted, "AMG-162 is easier for doctors to administer." Another expert said, "AMG-162 is fascinating. Other things in the clinical pipeline are me-too or different forms of administration, not really new agents… SERMs will never be big without non-vertebral fracture reduction."

AMG-162 is a follow-on product to OPG-FC, which was dropped after a randomized, double-blind, placebo-controlled, Phase I PK and PD dose-escalation study in healthy postmenopausal women found a rapid effect with sustained bone resorptive activity but a transient neutralizing antibodies against OPG in one patient. Amgen then made the decision to concentrate on a monoclonal antibody. Interestingly, several times Amgen officials and experts referred to AMG-162 as addressing "an unmet medical need," which may hint at the FDA approach the company plans to take.

Osteoporosis

AMG-162, a fully-human monoclonal antibody to RANKL, was tested in a two-year (extended to four years), randomized, double-blind, placebo-controlled, multicenter (29 sites), dose-ranging study of 412 women with low BMD (T score ≤1.8). All subjects have completed one year of treatment, and the trial is ongoing. One of the reasons the trial was extended past two years is to enable Amgen to be sure there is no hyper-responses. An Amgen official said, "What we observed from the Year 1 data is that, as the 60 mg regimen wears off in Months 5 and 6, you have a gradual increase in bone turnover. It doesn't look like a hyper-response but more of a resumption that would be expected in a normal setting, but we need longer-term follow-up on that."

There are nine different treatment arms in this trial:

1. Placebo
2. 6 mg SC every 3 months
3. 14 mg SC every 3 months
4. 30 mg SC every 3 months
5. 14 mg SC every 6 months
6. 60 mg SC every 6 months
7. 100 mg SC every 6 months
8. 210 mg SC every 6 months
9. Open label arm: Fosamax 70 mg weekly

Other interesting findings about AMG-162 and this Phase II trial from investigators and Amgen officials:

➢ **Serum levels.** After one 60 mg dose, there are very low but detectable levels in serum out to seven months. An Amgen official said there is no known condition where a patient ***needs*** to be off AMG-162.

➢ **Dosing.** A 14 mg dose has as much suppression as a 210 mg dose, but the durability is shorter with 14 mg. The 60 mg dose is the dose going forward.

➢ **Biopsies.** Biopsies were done in at least some of the Phase II patients, but that data has not been released.

➢ **Speed of action.** In BMD, both AMG-162 and Fosamax increased suppression of bone resorption markers. At three days, there was a full effect with AMG-162, but just a little with Fosamax, which was not fully effective until 1-3 months. There is no evidence that there is any cumulative suppression with AMG-162.

➢ **Combination therapy.** There is no rationale for combining AMG-162 with other antiresorptives, such as Fosamax or raloxifene. However, animal studies suggest that there is an additive effect of AMG-162 and PTH. Amgen is considering a three-arm trial comparing AMG-162, PTH, and the combination of AMG-162+PTH.

➢ **Comparison to PTH.** It appears AMG-162 has a more positive effect on cortical bone than PTH, but PTH has a bigger kick.

➢ **Discontinuations.** Withdrawals in this Phase II trial were described as due to "patient reluctance to be in a placebo-controlled trial, not due to tolerability or side effects."

➢ **Antibodies.** Two patients developed non-neutralizing antibodies to AMG-162, but they were transient, had no effect on the PK of the drug in these patients, and did not block the antiresorptive effects of AMG-162:

- A patient on low dose who had detectable titers once but continued on therapy and thereafter had undetectable levels.
- A patient who developed detectable antibody levels at Month 12 but who is still in the study and became non-detectable.

➢ **Side effects.** Injection site reactions are generally mild. There were no clinical or EKG changes. There was no difference in the number of adverse events, serious adverse events, or withdrawals due to adverse events. There also was no evidence of a negative effect on the immune system.

If AMG-162 was approved today, an investigator said the appeal for him, as a clinician, would be AMG-162's:

- Targeting of a unique pathological problem in osteoporosis.
- Rapidity of action.

Planned 1-Year Analysis of Phase II AMG-162 Results

Measurement	Placebo n=46	All patients on AMG-162 n=319	Fosamax n=47
Completers	41	283	45
% completing	89.1%	88.7%	95.7%
Withdrew prematurely	10.9%	11.3%	4.3%
Average age	63.7	62.3	62.8
Years postmenopausal	12.3	14.8	14.2
Average BMI	25.9	26.4	26.7
Baseline lumbar spine BMD T-score	-2.3	-2.1	-2.0
Baseline total hip BMD T-score	-1.4	-1.4	-1.6
Baseline serum CTX (ng/mL)	.68	.65	.68
Baseline bone-specific alkaline phosphatase (µg/L)	11.9	12.4	12.4
Primary endpoint: **Lumbar spine BMD (% change from baseline at Year 1)**			
Every-6-month AMG-162 dosing regimen	---	All doses better than placebo (p<.001)	14 mg AMG-162 worse than Fosamax (p<.05)
Every-3-month AMG-162 dosing regimen	---	All doses better than placebo (p<.0001)	30 mg AMG-162 dose better than Fosamax (p<.01)
Total hip BMD (%(change from baseline)			
Every-6-month AMG-162 dosing regimen	---	All doses better than placebo (p<.0001)	60 mg AMG-162 better than Fosamax (p<.01); other doses comparable
Every-3-month AMG-162 dosing regimen	---	All doses better than placebo (p<.0001)	30 mg AMG-162 better than Fosamax (p<.05); other doses comparable
Distal 1/3 Radius BMD (% change from baseline)			
Every-6-month AMG-162 dosing regimen	---	All doses better than placebo (p<.0001)	60, 100, and 210 mg AMG-162 better than Fosamax (p<.05)
Every-3-month AMG-162 dosing regimen	---	All doses better than placebo (p<.0001)	30 mg AMG-162 better than Fosamax (p<.05)
Other Results			
Serum CTX (ng/mL)	Relatively unchanged	Reduced 60%-80% except 14 mg dose	---
Bone-specific alkaline phosphatase (µg/L)	N/A	N/A	N/A
Total body BMD (without head)	---	All doses better than placebo (p>.05)	14 mg AMG-162 worse than Fosamax

- Every-six-month dosing, which is likely to improve persistence and adherence.
- No worry about long-term suppression.

The two issues with this agent are likely to be:

1. **Injections.** Some patients will balk at injections, but an expert said more balk at the ***perception*** of GI problems with oral bisphosphenates.
2. **Cost.** Price will be an issue. There is no indication how Amgen intends to price this.

Amgen officials declined to provide many details on the "very large," pivotal Phase III trial in osteoporosis, but an investigator said it is a randomized (1:1), three-year, placebo-controlled trial in both prevention and treatment, using the 60 mg every-six-month dosing regimen. "Large" was defined by an Amgen official as somewhere between the 7,705-patient Evista MORE trial or the 1,035-patient FACT trial (comparing Fosamax and Actonel) – suggesting the AMG-162 Phase III trial is >1,000 patients, and probably at least 2,000.

The Phase III primary endpoint is fracture reduction, but it is likely that BMD also is an endpoint. The trial got underway earlier this year, and enrollment is still ongoing (that is, the trial is not yet fully enrolled). No data is expected to be released until the trial is completed; there are no planned interim data analyses or presentations. Asked for more details, an official said, "Look at what the regulatory authorities have said in their guidance documents…The clinical trial design will be very, very similar to the regulatory guidance."

The pivotal Phase III patients being enrolled:

- Are not purely osteoporotic.
- Include patients at increased risk. The new WHO estimation of fracture risk that is expected to be released in mid-2005 will be based on the level of risk, not just BMD, and this trial incorporates that. This means, patients with low BMD are being enrolled, but so are patients with normal BMD with other risk factors.

Phase II trials also have been initiated in rheumatoid arthritis (RA), and other, large-scale, global registration trials are believed to be underway, looking at key patient populations, including:

- Post menopausal osteoporosis (including hip fractures).
- Amelioration of hormone ablation-induced bone loss. For this, BMD is likely to be an endpoint.
- Treatment of metastatic bone disease.

Amgen is looking at a variety of other possible indications for AMG-162. An Amgen official said, "This is something we are actively discussing…We are continuing to look at the data and see the best and most efficient (regulatory) pathway…We will study the indications carefully. We really must understand the risk:benefit profile of the molecule so we know what is going into the marketplace. There are faster ways to get there, and ones that will take a little longer. But our commitment is to understand the risk:benefit profile…We can't do everything at the same time…and we are really pondering our options right now."

Bone metastases

Bone metastases are a significant problem in cancer patients, and a speaker at an Amgen-sponsored symposium called bone mets "an unmet medical need." He added, "Current therapies have limitations…IV bisphosphenates have side effects. About one-third of patients have acute phase reactions, there is renal toxicity, osteonecrosis, and inconvenience." In contrast, he said, AMG-162 is a more sustained inhibitor of bone turnover than pamidronate and is administered subcutaneously.

Androgen-replacement therapy for prostate cancer also is thought to increase the fracture risk, but the published studies in this have been small, with no control group. A researcher reported on a large Medicare fracture study looking at a random sample of 5% of Medicare beneficiaries, designed to simulate a randomized clinical trial. This study identified 10,617 prostate cancer patients, with men with bone mets censored. This was a patient-based analysis, not an event-based analysis (only one fracture counted for each patient). The researcher concluded, "It is clear that GnRH antagonists do increase the risk of fracture…They should be considered high risk medications, perhaps on a par with glucocorticoids."

Incidence of Skeletal Events in Cancer Patients

Measurement	Breast	Myeloma	Prostate	Lung/ others
Skeletal Events in Cancer Randomized Clinical Trials				
Total skeletal-related events	64	51	49	46
Fractures	52	37	25	22
Relative Risk for High Urinary NTx				
Skeletal-related events	3.6	---	5.3	2.9
Progression	3.2	---	2.3	2.2
Death	6.7	---	3.5	5.9
Medicare Fracture Study				
Primary endpoint: Risk of any fracture	---	1.25 (p<.001)	---	---
Risk of hip fracture	---	1.46 (p=.008)	---	---
Risk of vertebral fracture	---	1.63 (p<.001)	---	---

Another study of AMG-162 is underway in non-metastatic prostate cancer, the HALT Fracture Prevention Study. The primary endpoint in this 968-patient trial is BMD at one year, and the secondary endpoint is vertebral fractures. The trial will compare AMG-162 at 60 mg subcutaneously every six months to placebo. A prior randomized trial with other therapies found lumbar spine BMD and total hip BMD were

improved at one year best by IV Zometa (7.8% spine, 3.9% hip) than by IV pamidronate (3.8% spine, 2.0% hip) or Evista (2% spine, 3.7% hip).

The HALT Breast Cancer trial is a comparable study in breast cancer. It has the same design, but is smaller (208 patients). The primary endpoint is lumbar spine BMD.

Metastatic Bone Disease

Cancer type	Incidence of bone mets	Median survival in months
Bladder	40%	6-9
Breast	65% - 75%	19-25
Lung	30% - 40%	6-7
Melanoma	14% - 45%	6
Myeloma	70% - 95%	6-54
Prostate	65% - 75%	12-53
Renal	20% - 25%	12
Thyroid	60%	48

AMGEN'S Sensipar (cinacalcet, AMG-073)
Off to a good start

Amgen's focus at ASBMR was AMG-162 not Sensipar, a new calcimimetic approved by the FDA in March 2004 in 30 mg, 60 mg, and 90 mg doses. The potential uses for Sensipar in the U.S. are:

- 300,000 secondary HPT patients on dialysis. **(FDA approved)** A speaker said MediCal recently approved reimbursement for Sensipar in these patients. She said her dialysis unit has been using calcitriol rather than Bone Care International's Hectoral (doxercalciferol) or Abbott's oral Zemplar (paricalcitol) – because of cost… Cinacalcet is better than either Hectoral or Zemplar." Another expert said, "We are switching from calcitriol to Zemplar in our dialysis patients if the CAP is high because there is a lower cardiovascular risk with Zemplar than Hectoral."
- 500 parathyroid cancer patients. **(FDA approved)**
- 1-1.5 million primary hyperparathyroid (PHPT) patients. **(FDA approvable letter)** A speaker said the FDA wants data on more patients with this condition. About 25% of PHPT patients are seen by endocrinologists; the others are seen mostly by primary care physicians. PCPs tend to refer the most severe patients.
- 8 million CKD patients. **(Not FDA approved)** This is the largest potential market.

Among the features of Sensipar that were discussed at ASBMR were:

- The maximum effect occurs 2-6 hours after a dose.
- There are no interactions with calcium or Genzyme's Renagel (sevalamer), but 5% of dialysis patients have seizures, so they need to be monitored carefully.
- Hypocalcemia is the key issue with Sensipar, and it should not be started if serum calcium is <8.4 mg/dL, but when hypocalcemia occurs it is rarely symptomatic and is easily managed with calcium and vitamin D.
- Over three years, 80% of patients on Sensipar have normalized serum calcium.
- Most sources believe vitamin D should be reduced when Sensipar is prescribed, but phosphate binders do not need to be reduced.

Parathyroid cancer. A poster addressed the safety in an ongoing trial of Sensipar in patients with refractory, metastatic parathyroid carcinoma. Researchers concluded:

- Medical management is challenging due to the resistance of the cancer to therapy.
- Patients with parathyroid cancer have a poor prognosis, especially when surgery has proven unsuccessful.
- Cinacalcet effectively treats hypercalcemia in these patients and can fill an "unmet medical need" in this setting; 71% of patients had a reduction in serum calcium of ≥1 mg/dL. Reductions in serum calcium were maintained for up to three years in some patients.
- Three patients withdrew due to adverse events – nausea and vomiting for two; hives for one.

Another poster from Columbia University reported on a 10-patient study in inoperable parathyroid cancer treated with Sensipar and found:

- Nausea and vomiting occurred in 6 of the 10 (4 moderate, 2 severe).
- Five developed hip fractures.
- Three died on the drug (1 CHF, 1 respiratory arrest, and 1 from a hip fracture complication). Two patients died (from hypercalcemia) after the Sensipar was stopped.
- Conclusions: "It is premature to comment on the effects of the natural history of parathyroid cancer, including tumor burden, fracture rate, and mortality. However, cinacalcet is potentially an effective treatment for hypercalcemia in patients with inoperable parathyroid cancer."

Miscellaneous

- A poster from Columbia University researchers reported that parathyroid cancer patients were coming to Columbia from outside the U.S. for treatment with Sensipar, which makes them feel much better. The researchers noted that Sensipar doesn't seem to help bone density in these patients, lowering serum calcium but not increasing BMD, "which was the real hope."
- Another poster from Columbia University looked at Sensipar in juvenile dogs, reporting no observable effect on serum or urinary bone biomarkers, BMD measurements, or histopathology of the growth plate. The conclusion was that Sensipar appears safe in children.

- Asked about the effect of Sensipar on BMD, an Amgen official said, "We haven't done a lot on that. At the EDTA (European Dialysis and Transplant Association) meeting, it was reported that bone biopsies showed an increase in bone histology. But nephrologists generally don't measure BMD."
- There will be data at the American Society of Nephrology meeting in late October 2004 on vitamin D and phosphate binder use with Sensipar.

CHUGAI'S NASAL SPRAY hPTH (1-34)
A potential challenge to Forteo

Chugai is developing a nasal spray formulation of PTH that is administered using a simple device much like those used for allergic rhinitis nasal sprays – one puff daily in each nostril, any time during the day. The drug is absorbed through the nasal mucosa, and Phase I studies have shown a dose-dependent increase in plasma cyclic AMP with this formulation. Chugai also has a subcutaneous form of hPTH, but an official said the company does not plan to seek marketing approval for this.

Phase I PK Study of Nasal hPTH

Measurement	SC	Nasal
Cmax (pg/mL)	260.0	363.8
AUC	506.4	249.9
Tmax (h)	0.67	0.23
T ½ (h)	1.11	0.50

Open-label Phase II of Nasal hPTH Results at 3 Months

Measurement (change from baseline)	PTH250 n=31	PTH500 n=30	PTH1000 n=31
Lumbar spine BMD	0.1% (p=.817)	0.7% (p=.165)	2.4% (p=.012)
Serum PINP	N/A	N/A	16.7% (p<.05)
Osteocalcin	N/A	N/A	20.6% (p<.05)
Urinary CTX	N/A	Suppressed	Suppressed
Urinary NTx	N/A	Suppressed	Suppressed
Hypercalcemia (>10.4 mg/dL but <11 mg/dL) 3 hours after administration	2 patients	N/A	5 patients

A randomized, open-label Phase II study of 92 osteoporotic patients found a nasal spray of 1000 µg hPTH (1-34) produced similar peak serum concentrations as a subcutaneous injection of 20 µg. Dr. T. Matsumoto of the University of Tokushima in Japan, the principal investigator in the Phase II trial, said, "With subcutaneous administration, you expect to have a slight increase in bone resorption as well as a robust increase in bone formation…In this case, bone formation is not tremendous compared to subcutaneous, but bone resorption is suppressed very consistently, using two different resorption markers…So, there is an increase in bone formation at the same time bone resorption is suppressed…We saw positive results after just three months. Most other PTHs don't see results until six to 12 months…We had expected performance to be similar to subcutaneous, but we were surprised to find it is faster with nasal administration, though the effect on bone is not faster…The mode of action turned out to be a little different…Nasal PTH enhances bone formation a little less than subcutaneous PTH, but it suppresses bone resorption at the same time…so the net change in bone mass turned out to be similar."

Some of the potential concerns with nasal PTH include:

- **Hypercalcemia.** There is a spike in serum calcium three hours after every administration, but it comes back down. The magnitude of the increase is not in the hypercalcemic range, and it is not cumulative, Dr. Matsumoto said.
- **Effect on sinus bone.** Prior attempts by other companies to develop a nasal PTH failed, and one problem was a negative effect on sinus bone. An osteoporosis expert said, "Intranasal PTH concerns the heck out of me." Dr. Matsumoto said he had heard about reports of another nasal formulation causing bone growth in the nose, but he insisted he has never seen that problem with the Chugai formulation – either in preclinical or clinical studies – but they are watching for that.
- **Effect on smell.** A physician in the audience cautioned that nasal PTH could affect the sense of smell, and Dr. Matsumoto admitted patients were not questioned about that. However, he said no patients complained about a change in smell, adding, "That (loss of smell with other agents) may be due to the enhancer of absorption…This does not have an enhancer, and that may be why we don't see that problem."
- **Patent challenge from Lilly.** A Chugai official admitted there is likely to be a patent challenge from Lilly, but the official was confident Chugai would prevail, though the official would not explain why.
- **Dose variability.** There is greater variability with nasal than subcutaneous administration, but Dr. Matsumoto does not think that matters. He said, "We do see variability on serum concentration after nasal administration, but when we look at bone markers and BMD, the differences don't appear to be influencing the net result on bone."

The potential advantages of nasal PTH include:

- **Compliance**. Chugai is hopeful that patients will be more compliant with a nasal spray than an injectable product.
- **Cost**. Dr. Matsumoto was certain Chugai will offer this at a lower cost than Forteo.

The next step is a dose-finding Phase II study, and then Chugai plans to go into Phase III. Dr. Matsumoto estimated that it will be at least five years before this product is approved in the U.S., assuming a three-year fracture study is required for Phase III.

LILLY'S Forteo (teraparatide)
The data is holding up

A post-hoc analysis of three-year data from the Fracture Prevention Trial (FPT) showed that Forteo not only decreases the incidence of repeat fractures, but it also alters the natural history of the progression of osteoporosis. FPT was a randomized, double-blind, placebo-controlled registration study, and the new analysis looked at a subset of 931 postmenopausal women with prior vertebral fractures who took Forteo. Other trials have shown that there is an increased risk for new vertebral fractures – and non-vertebral fractures – based on the number and severity of previous fractures, but Forteo was shown to decrease this risk.

There were three arms in this trial – placebo, 20 µg Forteo, and 40 µg Forteo, and the women were followed for a median of 21 months. The 40 µg results were described as "very similar" to the 20 µg results, but only the 20 µg results were presented. The principal investigator concluded, "Placebo-treated patients with increasing number and severity of vertebral fractures had an increased risk for new vertebral fractures and for new moderate or severe vertebral fractures. These trends were not observed in teraparatide-treated patients …Placebo patients with an increased number of prior fragility fractures had an increasing risk for new non-vertebral fractures, and, again, this trend was not seen with Forteo… These results should encourage increased use of spine imaging. In the U.S. many physicians don't do a radiograph. And Forteo is an important therapeutic alternative in patients with prior fractures, especially in patients with increasing number or severity of prior fractures."

Lilly reportedly is trying to design a fracture healing trial for Forteo, but some football quarterbacks already are using it. An expert said, "I know at least two quarterbacks given Forteo, and they seem pleased with the outcome…For a claim of improved fracture healing, you need to show earlier functional improvement."

The design of the prospective, observational DANCE trial was discussed. The primary endpoint is non-vertebral fractures at 24 months. Secondary endpoints include vertebral fractures, adverse events, change in back pain, adherence, and BMD/BMC. The treatment phase is two years, and the post-treatment follow-up is another two years.

MERCK'S Fosamax (alendronate)
Beats out Actonel on BMD

Just before ASBMR, Merck released the results of the FACT trial, comparing Fosamax and Proctor & Gamble's Actonel (risedronate) in 1,042 postmenopausal osteoporotic women. In that Merck-sponsored trial, Fosamax showed significantly greater increases in BMD at all pre-specified endpoints out to 12 months, and it lowered levels of biochemical markers of bone turnover further than Actonel within three months. If it weren't for the recall of Merck's Cox-2 inhibitor, Vioxx (rofecoxib), just days before ASBMR, Merck officials and sales reps would have been in a much better mood at this meeting.

1-Year Results of FACT Trial

Measurement (change from baseline at 12 months)	Fosamax 70 mg QW n=515	Actonel 35 mg QW n=527	p-value
Primary endpoint: Hip trocanter BMD	3.4%	2.1%	<.001
Secondary endpoint #1: Total hip BMD	2.2%	1.2%	<.001
Secondary endpoint #2: Femoral neck BMD	1.6%	0.9%	<.005
Secondary endpoint #3: Lumbar spine BMD	3.7%	2.6%	<.001
Adverse events	22.5%	20.1%	0.364
Fractures	26 patients	20 patients	Nss

Fracture Prevention Trial

Baseline fracture incidence	Historical fracture data from placebo patients in MORE trial	Fracture Prevention Trial			
		Placebo n=464	Forteo n=467	Placebo n=464	Forteo n=467
	Incidence of new fractures	Risk of new vertebral fracture among all patients		Risk of new vertebral fracture among moderate/severe patients	
0	~ 5%	---	---	---	---
1 fracture	~ 13%	6.8%	3.4%	3.0%	0
2 fractures	~ 18%	15.7%	5.8%	8.8%	1.9%
≥3 fractures	~ 37%	22.6%	7.2%	17.1%	1.3%
p-value for progression	---	<.001	0.15	<.001	0.26

Most sources described FACT as another shot in the marketing wars between Merck and P&G. One expert said, "This is another example of a surrogate marker outcome study…The fracture rate was not different, but that's being ignored, and I don't think you can ignore that. There is no real difference in efficacy in the two. BMD is not enough; you need a fracture study."

Some sources suggested the FACT results were due to P&G developing a too-low dose of Actonel. An expert said, "I don't think P&G got the dose right, and that's why it

doesn't prevent hip fractures in people over age 80." However, P&G sources generally shrugged the findings off, saying they are confident the results of an ongoing head-to-head trial sponsored by P&G will show either a fracture advantage to Actonel or, at least, no disadvantage vs. Fosamax.

Merck also had positive news from a study released at ASBMR. The 13-week, prospective, single cohort, open-label EASY trial of 259 osteoporosis patients found that weekly Fosamax (70 mg) is effective in reducing bone resorption within the first five weeks of treatment.

13-Week Results of EASY Trial

Measurement	Fosamax	p-value
Discontinued	15.8%	
Lost to follow-up	8.9%	
Change in urine NTx from baseline		
At 5 weeks	Down 35.9%	<.001
At 13 weeks	Down 42.9%	<.01
In compliant patients at 5 weeks	Down 37.9%	<.001
In compliant patients at 13 weeks	Down 47.5%	<.001
In semi-compliant patients at 5 weeks	Down 38.2%	.001
In semi-compliant patients at 13 weeks	Down 39.5%	.001 (Nss vs. compliant patients at 13 weeks)
Safety		
Adverse events	10.0%	---
Dyspepsia	3.1%	---
Nausea	1.5%	---
Diarrhea	1.2%	---
Abdominal pain	0.8%	---
Serious adverse events	1.5%	---

A Japanese study in 50 consecutive rheumatoid arthritis patients suggested Fosamax may retard the radiological progression of erosion formation in RA.

Fosamax in RA

Measurement	Fosamax	Control
Change in Sharp score	3.2 (p<.001)	7.5 (p<.01)

NOVARTIS'S Zometa (zoledronic acid, zoledronate) IV Zometa also beats Actonel

An analysis of pooled data from two randomized, multicenter, double-blind, active-controlled studies of patients with Paget's disease found IV Zometa produces greater reductions in bone markers than daily, oral Actonel. Zometa has a slightly worse side effect profile for the first three days, but after three days, the side effect profiles are fairly comparable. An expert said, "The concern with Zometa is suppression of remodeling forever. We will see in Phase III if there is fracture data."

Phase III HORIZON-TOP Results: Pooled Comparison of Zoledronate and Risedronate in Paget's Disease

Measurement	Zometa single 5 mg IV n=177	Actonel 30 mg QD n=172	Relevance
Dosing	One 15-min. infusion	Oral 30 mg/day for 60 days	---
Patients completing follow-up	171	155	---
***Primary endpoint:* Non-inferiority**			
≥75% reduction in serum alkaline phosphatase (SAP) excess or its normalization at 6 months	96%	74%	Difference -.22 *
***Secondary endpoint:* Superiority**			
Study 2305: ≥75% reduction in SAP excess or its normalization at 6 months	95%	75%	p<.001
Study 2304: ≥75% reduction in SAP excess or its normalization at 6 months	97%	74%	p<.001
≥1 adverse events	83%	77%	---
Serious adverse events	9 patients	11 patients	---
Rate of clinically notable adverse events due to study drug	28%	8%	---
Total adverse events	28.2%	8.1%	---
Flu-like symptoms	11.4%	4.1%	---
Increase in serum creatinine >0.5 mg/dL	1 patient	1 patient	---

* Above .16 required to prove non-inferiority

A poster from Australian researchers suggested that Zometa may be beneficial in treatment of non-vertebral fracture patients, including in combination with OP-1. In this study, rats were given one IV dose of Zometa, which was then stopped – not followed with oral therapy.

NPS PHARMACEUTICALS' Preos (rhPTH 1-84) Comparable to Forteo

Partial two-year data from the PaTH trial – looking for the best therapy after a year of Preos – were presented at ASBMR, and there were no real surprises. The complete results are expected to be published later this year in a major medical journal (e.g, ***New England Journal of Medicine***), and those results will not be announced in advance of publication. Researchers concluded that:

- Gains in BMD with Preos are rapidly lost after PTH is discontinued.
- Fosamax following Preos leads to further gains in BMD.

- The data suggest that however long Preos is used, it probably should be followed with antiresorptive therapy, but researchers warned that the results with Fosamax should not automatically extend to other antiresorptives.

2-Year PaTH Trial Results

Year One	Preos	Preos	Preos + Fosamax	Fosamax
Year Two	**Placebo**	**Fosamax**	**Fosamax**	**Fosamax**
Change in BMD by DXA				
Spine	+4% *	+12%	+8% *	+8% *
Hip	+1.2% *	+4%	+3%	+3%
Change in BMD by QCT				
Trabecular spine	+13% *	+30%	+11% *	+7% *
Trabecular hip	+5%	+12%	N/A	N/A
Other Results				
Serum CTX	+11%	-60%	N/A	N/A
Cortical BMD	No significant change	No significant change	N/A	N/A
Cortical BMC	Down slightly	Up significantly	N/A	N/A
Cortical volume	Down slightly	Up significantly	N/A	N/A

*** p<.05 vs. baseline**

There appears little to differentiate Preos from Forteo.

➢ **Delivery.** They use different pen delivery systems, but they are equally accepted by patients and doctors. One doctor said the dropout rate with Forteo is low – <5% of patients at his hospital. He explained, "If you instruct patients properly on how to administer the agent, and they are observed doing it, and then followed up when they go home, that is the recipe for good compliance. Patients actually get used to the needle, which is very tiny…and these are very motivated patients."

➢ **Adverse events.** There is no significant safety difference between the two drugs, but there may be slightly less nausea, vomiting, and headache with Preos than Forteo. A Preos researcher said, "We didn't see any excess of nausea, vomiting, or headache with Preos."

➢ **Osteosarcoma.** There is a "no effect" dose with Preos in a two-year rat study – but not with Forteo. This may make clinicians somewhat more comfortable prescribing PTH in general and Preos in particular. A researcher commented, "A 'no effect' dose is reassuring." Another expert said, "The sarcoma issue is a rodent issue, not a human issue, but I wouldn't give PTH to patients with cancer in the past five years – more because of metastases than sarcoma." A Preos researcher said, "There are a lot of doctors concerned about the rat toxicity (with Forteo), and the Preos data may help their comfort level. I'm becoming convinced there is a difference (between Preos and Forteo) – even though I don't believe Forteo causes osteosarcoma." An NPS official said, "Sales reps may be able to use this (rat) data to say, 'Doctor, if you are concerned about the potential carcinogenicity of PTH, then Preos appears to be less carcinogenic than Forteo.'" However, sources generally agree that Preos is likely to get a black box warning like Forteo.

➢ **Bone quality.** This is one area where Preos may differentiate itself from Forteo. Biopsy data indicates Preos is still forming bone at 18 months, something not seen with other compounds. A researcher said, "As a clinician, it is very, very important to have good quality bone. We want to know that after treatment with a given therapy, the quality of that bone is good."

➢ **Hypercalcemia.** This appears to be similar with the two agents (11% with Forteo, 12% with Preos). With Forteo, a doctor said she does a blood calcium a month after starting Forteo, though that is not required. However, one source who has experience with both products warned that the hypercalcemia appears to be higher with Preos.

➢ **C-terminus concept.** A speaker said, "Clearly, there is something at the mid or carboxyl end (of PTH 1-34) that binds to osteosarcoma cells. It's possible 53-84 could interfere with that binding." A Preos researcher said, "There is no 1-34 PTH in biology; it is man-made. There must be a reason the body makes 1-84. It could be non-skeletal effects. So, the concept of C-terminus is appealing."

➢ **Pre- and post-Preos therapy.** There also is a growing sense among experts here that PTH is best given before an antiresorptive, though that is not always clinically possible. An expert said, "It doesn't make a lot of sense to shut down bone turnover when you want to get bone going, so you may want to be more circumspect in the casual use of antiresorptives when considering PTH."

Yet, not every expert agrees with this. Dr. Robert Lindsay of Helen Hayes Hospital said, "I still think combination therapy (PTH+bisphosphenate) is better than sequential therapy, but I can't raise enough money for that study…Combination therapy may be better for fracture risk than for BMD…We give PTH on top of a bisphosphenate. I used to switch bisphosphenates when a patient got a fracture on one bisphosphenate – or I'd try raloxifene. Now, we add PTH. It isn't true that PTH doesn't work in the presence of a bisphosphenate, but cost is an issue."

If an antiresorptive is given before PTH, another expert suggested that Proctor & Gamble's Actonel (risedronate) may be the best choice of the currently available products and Lilly's Evista (raloxifene) may be the worst choice. Among the comments by PaTH researchers about this were:

- "In my practice...patients with severe osteoporosis…I start on PTH, and then after 18 months put on a potent antiresorptive. At this meeting, I've seen that some antiresorptives, like raloxifene, may not be as potent in maintaining the improvements in bone mass."

- "Theoretically, risedronate might not lead to the same delay (in efficacy) as alendronate…The antiresorptives that don't shut down bone turnover to the same degree are less likely to delay the effect of PTH. The story of risedronate is still up in the air…In those patients who are on alendronate or risedronate, should you wait for a period of time – 3, 6, or 12 months – to let the bones recover? We have no data. I would guess it will not make any difference for alendronate because we know bone markers continue to be depressed for five years after cessation of alendronate, so there is no rationale for waiting in the case of alendronate. With risedronate, there is reason to think bone turnover will bounce back much more quickly when it is stopped."

A potent bisphosphenate should be prescribed as soon as either Preos or Forteo is stopped, and one researcher suggested Actonel again may be the preferred choice, "You may want to use PTH a second time, so using risedronate after the first course of PTH may make the most sense."

Using Fosamax prior to either PTH causes early delay in bone turnover response and a smaller BMD increase after 18 months. Women treated with HRT, who take a course of PTH, and who continue the HRT after the PTH, generally maintain their bone mass at the spine and hip, and Evista appears to do the same thing. Thus, pre-treatment with Evista does not appear to blunt the response to PTH, but post-treatment with HRT only maintains bone mass; it doesn't increase it.

➢ **Cost.** NPS has not announced the pricing for Preos, but if it is substantially lower than Forteo, that is likely to spur use. PTH is expensive (Forteo costs about $7,000 a year), and that is a barrier to use for many patients. For example, Dr. John Bilezikian of Columbia University sees very severe osteoporosis patients, and he is a strong believer in PTH therapy, but only about 10% of his osteoporosis patients are on Forteo. Another expert said, "I don't know that we can differentiate between Forteo and Preos until there is a head-to-head study. I suspect the only difference will be price – with Preos lower."

➢ **Switching.** An expert could cite no real reason to switch patients from one of these agents to the other, unless the patient is intolerant to one, but he didn't see any reason a patient couldn't be switched.

➢ **Pulse or intermittent therapy.** Studies are underway with PTH to see if pulse therapy or intermittent therapy will work. An NIH-funded study is exploring weekly PTH, and Columbia University researchers are looking at administering it once every three months. A head-to-head study will compare the use of alendronate or risedronate and then subsequent PTH therapy.

For comparison purposes, here are the one-year results of the PaTH trial that were presented at ASBMR in 2003.

1-Year PaTH Trial Results

Measurement	Preos 100 µg n=119	Preos 100 µg + Fosamax 10 mg QD n=59	Fosamax 10 mg QD n=60
Change in BMD by DXA			
Spine	+6.2%	+6.1% *	+4.6% *
Hip	+0.8%	+1.8% *	+2.0%
Change in BMD by QCT			
Trabecular spine	+23.8%	+11.3%	+7.6%
Total hip	-2.4%	-0.%	+1.2%
Other Results			
Serum CTX	+104%	-14%	-73%

At the American College of Rheumatology in October 2004, there will be data from the TOP trial. TOP uses a Preos dose of 100 µg/day, and it is designed to look at vertebral fracture outcomes. The trial enrolled ~2,500 patients ***without*** the most severe osteoporosis, just low BMD, not prior fractures. This is different from the Forteo (and other antiresorptives) pivotal trials, which enrolled patients based on vertebral fracture history. If the TOP data is positive, researchers hope it will broaden PTH use to include all osteoporosis patients, not just those at greatest risk of fracture.

At ASBMR 2005, some results from the NIH-funded PARSIMONY trial of once-weekly Preos (100 µg) will be presented.

PFIZER'S Lasoxifene
A newer, better SERM?

Lasoxifene is a next-generation SERM in development for the prevention and treatment of osteoporosis in postmenopausal women. A PK study in 65 healthy Japanese women found that adverse events were frequent but mostly mild and included headache, diarrhea, pain, and rhinitis.

Lasoxifene PK Study

Measurement	Lasoxifene 0.25 mg		Lasoxifene 0.5 mg	
	Fed n=16	Unfed n=16	Fed n=17	Unfed n=16
AUC	16.9	16.3	31.3	28.8
Cmax	.239	.227	.435	.432
Tmax	12	8	18	12

A two-year comparison of lasoxifene and Lilly's Evista (raloxifene) in 410 postmenopausal women found lasoxifene was statistically more effective than either placebo or Evista in lipid metabolism and markers of cardiac risk.

2-Year Lipid and Cardiac Results of Lasoxifene Trial

Measurement	Placebo n=83	Lasoxifene 0.25 mg/day n=82	Lasoxifene 1.0 mg/day n=82	Evista 60 mg/day n=163
LDL-C Change from Baseline				
At 6 months	- 7.2%	- 21.4% *#	- 22.2% *#	- 15.2%*
At 1 year	- 3.5%	- 20.0% *#	- 18.9% *#	- 9.9%*
At 2 years	- 3.2%	- 20.6% *#	- 19.7% *#	- 12.1%*
2-Year Results in Other Markers (change from baseline)				
Total cholesterol	- 1.2%	- 11.3% *#	- 9.3% *#	- 6.7%*
Apo B-100	+ 2.3%	- 11.7% *#	- 8.8%*	- 5.0%*
Apo A-1	- 2.5%	+ 5.5% *#	+ 4.5%*	+ 1.6%*
Lp(a)	- 19.1%	- 37.7%*#	- 27.1% *#	- 25.6%
CRP	0	- 4.1%	- 6.8%	+ 1.0%
Fibrinogen	- 2.86%	- 19.6% *#	- 15.9% *#	- 13.7%*
Safety				
Adverse events	93%	96% - 99%		96%
Hot flushes	16%	21% - 27%		21%
Leg cramps	8%	13% - 15%		9%
Leukorrhea (vaginal moisture)	4%	7% - 11%		2%
Discontinuations for hot flushes	1%	4% - 7%		5%
Discontinuations for leg cramps	0	0 – 2%		1%

* p≤.05 vs. placebo # p≤.05 vs. Evista

PROCTOR & GAMBLE'S Actonel (risedronate)
Down but not out

New data on five year treatment with Actonel showed the drug maintains bone mineralization at the same level it is at three years. Long-term therapy also did not cause hypermineralization. There also was suggestion of a "healthy level" of bone turnover under long-term treatment.

5-Year Actonel Data

Bone mineral ratio	Actonel	Premarin
Baseline	33.7 *	11.9
3 years	9.4	
5 years	15.6	

* p<.05

ROCHE/GLAXOSMITHKLINE'S Boniva (ibandronate)
Monthly dosing looks promising

Roche received FDA approval in May 2003 for a 2 mg immediate-release, once-daily tablet formulation of Boniva but never launched it and apparently has no plans to try to market it against weekly Fosamax or Actonel. However, Roche and Glaxo (which are co-developing Boniva) expect to have FDA approval for a monthly oral formulation of Boniva (probably at 150 mg) by spring 2005.

Roche has come up with a clever way to encourage use and compliance with monthly Boniva. The idea is to have a specialty drug distributor mail one pill to users each month. The company also has been considering monthly phone calls to users, but the mail approach appears a better idea, though perhaps both phone calls and mail will be used. Of course, patients will have to give their consent for either of these programs. A competitor commented, "That (mailing) is very ingenious. I think people will like that. It's much better than a bottle in the medicine cabinet that they might forget about."

New, two-year data from the randomized, double-blind MOBILE trial confirmed that oral, monthly Boniva is at least equivalent to the QD Boniva in increasing spine and hip BMD and in reducing bone resorption. A supplemental new drug application (sNDA) for once-monthly dosing was submitted to the FDA in May 2004 for the treatment and prevention of postmenopausal osteoporosis. MOBILE compared two monthly doses of Boniva (100 mg and 150 mg) to the approved daily regimen of 2.5 mg Boniva in 1,609 postmenopausal women with osteoporosis.

How will monthly Boniva compete with other bisphosphenates? An expert said, "Weekly bisphosphenates have no fracture data. There is only fracture data on daily administration. Weekly products got on the market with pharmacodynamic studies. Alendronate and risedronate looked at bone remodeling between doses and showed it was suppressed. If ibandronate shows consistent suppression, then it can predict a fracture benefit…As you increase the inter-dose duration, it is more important to have fracture data." Another expert who is currently using Fosamax and Actonel evenly said, "I'll ask patients what they prefer – weekly or monthly. In a year, I'd guess that a third of patients will be on weekly Fosamax, a third on weekly Actonel, and a third on monthly Boniva, but I'm not sure Boniva will be that high. Roche did a preference study which said patients would prefer a monthly pill, but I don't believe that."

The one-year results of MOBILE were highlighted in a number of posters, and that trial showed:

- Both monthly and daily Boniva reduced bone resorption (as measured by serum CTX) to normal pre-menopausal levels within three months of initiation, and maintained this suppression with continued therapy.
- Women taking monthly Boniva had at least an equal reduction in bone resorption, compared to women who received daily Boniva.
- A greater proportion of women in the 150 mg/month group achieved pre-defined reductions (>30%, 50%, and 70% below baseline levels) serum CTX, vs. those in the QD dose group.

- Women taking monthly Boniva had at least an equal increase in BMD of the lumbar spine and hip compared to women who received daily Boniva, with those taking the 150 mg/month dose having the greatest increase in BMD.
- More women in the 100 mg/month and 150 mg/month groups achieved increases above baseline in lumbar spine and total hip BMD after one year vs. those in the daily dose group.
- Monthly dosing was generally well-tolerated and similar to daily dosing in terms of adverse effects. With daily dosing, the most commonly reported adverse events were hypertension, dyspepsia, and nausea; with monthly dosing the most common adverse events were hypertension, dyspepsia, and arthralgia.

WYETH'S Lrp5
Is no news good news?

There was no new data on Wyeth's efforts to produce an Lrp5 blocker. Creighton, Genome Therapeutics, and Wyeth were collaborating on high throughput screening to find an agent that will block the Lrp5 protein receptor. At ASBMR last year, a researcher said agents had been identified and are now being evaluated at the chemistry level. This year, a Wyeth researcher said the company has a "two-pronged approach, and they are both working."

VERTEBRAL BODY AUGMENTATION

KYPHON'S Kyphoplasty
Bad news on the near horizon

An article will appear in October 2004 in the journal ***Spine*** which says that Kyphon's kyphoplasty is associated with a 25% adjacent fracture incidence within two months of the procedure. There will also be an accompanying review by an expert who will slam Kyphon/kyphoplasty. This information was not formally presented, but there was a buzz among experts about this. One commented, "The pendulum appears to be swinging back from kyphoplasty." Another osteoporosis expert, who refers patients only for kyphoplasty, said these findings "are very concerning and may have an impact on kyphoplasty use."

The reviewer who does zero kyphoplasty at his medical center, just vertebroplasty, commented, "I don't think the (kyphoplasty) balloon does anything...The kyphoplasty balloon actually may be harmful." His belief also is that less cement is better, so he uses only 2-5 ml for a vertebroplasty.

Here at ASBMR, he presented his own prospective study of 46 consecutive patients (49 procedures for 66 painful vertebral compression fractures). The patients had a mean age of 74, with a mean fracture age of 2.5 months. The study showed that vertebral height restoration achieved with vertebroplasty did **not** result in additional pain relief or improved quality of life beyond cement fixation alone. The researcher concluded, "The rationale and desire to restore vertebral height and sagittal alignment during percutaneous vertebroplasty are compelling, but these initial data do not demonstrate additional benefit to pain relief or quality of life over six months when incomplete vertebral height restoration is achieved." He insisted these findings apply to kyphoplasty as well.

Value of Height Restoration in Vertebroplasty

Measurement	All patients	Height restoration patients	p-value
VAS Pain Score			
Baseline	7.7	7.7	Nss
1 day post-procedure	2.8 (p<.001)	4.1	Nss
6 months	2.8 (p<.001)	4.1	Nss
5 Quality of Life Domains			
Week 2	Substantially increased	Substantially increased	Nss
6 months	Substantially increased (p=.007)	Substantially increased (p=.007)	Nss

Other interesting comments on this topic included:

- Reportedly, a randomized trial comparing kyphoplasty and vertebroplasty is already underway in Sweden, and there were rumors that other orthopedic surgeons are planning randomized clinical trials.
- The reviewer said Spineology's approach may be helpful for patients with a large vertebral cavity (huge, empty vertebral frames), which he estimated is about 45% of vertebral fractures if its bone chip bag were more malleable. He met with Spineology last month.

None of the sources questioned were aware of Medtronic's new vertebral augmentation device.

OTHER INTERESTING NEWS FROM ASBMR

JOHNSON & JOHNSON/ALZA'S Macroflex-ThPTH, a transdermal PTH patch

Though this poster was presented with no fanfare, it was one of the most interesting posters at the meeting. Alza researchers described delivering Lilly's Forteo with its Macroflex technology as a "product under development." However, Lilly sources insisted they knew nothing about this.

The poster claimed that, compared to Forteo, the patch is:

- Bioequivalent.
- Absorbed faster.
- Bioactive.

- Well tolerated and safe.

First-in-Man Study of Macroflex-ThPTH in Healthy Adult Women

Measurement	Subcutaneous Forteo 40 µg n=20	Macroflex-Th-0229PTH 30 µg n=20
Cmax (pg/mL)	167	305
Tmax (h)	.594	.131
AUC_c	494	661
AUC_{inf}	870	837
Adverse events	33% at 20 µg 70% at 40 µg	50%

SANOFI-AVENTIS' Acomplia (rimonabant)

Early but interesting data suggest Acomplia may have a role in osteoporosis as well as diet and smoking cessation. A study (in cells, mice, and rabbits) from the University of Aberdeen, Scotland, found endocannabinoids are a novel therapeutic target for the prevention and treatment of bone diseases associated with osteoclast activation. They concluded that cannabinoid receptor inverse agonists – like Acomplia – represent a new class of antiresorptive drugs.

SHIRE'S Fosrenol (lanthanum carbonate)

Three posters looked at the efficacy and safety of lanthanum, a rare earth element (heavy metal). Fosrenol was submitted to the FDA in April 2002 to treat hyperphosphatemia. In March 2003, the FDA issued an approvable letter for Fosrenol but asked Shire for additional long-term safety data. Shire submitted that data, and a decision was expected by July 26, 2004, but the FDA extended the PDUFA (action) date to October 26, 2004, after receiving additional data from Shire relating to the formulation and dosage strengths. In March 2004, Fosrenol was approved in Sweden.

A key concern about Fosrenol is whether lanthanum accumulates in the body and will pose a long-term risk like aluminum. Shire studies have found no concern, but a competitor (Genzyme) presented its own study of lanthanum at the American Society of Nephrology meeting in November 2003, and that study suggested lanthanum does accumulate in organs.

The posters at ASBMR concluded there is some organ accumulation, and the lanthanum does not wash out after cessation of treatment, but researchers were not concerned with the safety.

➢ A rat safety study by Belgian researchers found:
- Bone lanthanum levels increase, but remain low.
- The mechanism is like aluminum.
- After withdrawal of lanthanum, there is no significant wash out from bone within eight weeks.
- It is probably phosphate depletion that causes bone lesions in rates, and if you supplement with phosphates, then no lesions develop.
- Lanthanum treatment goes along with the development of a mineralization defect in bone that reverses rapidly after withdrawal of lanthanum.
- Researchers concluded: "These results support the hypothesis that the mineralization defect results from a lanthanum-induced phosphate depletion and is not the consequence of a direct effect of lanthanum on bone." A researcher added, "I really don't believe lanthanum gets into the cerebral fluid in rats with high doses…I think it is safe."

➢ Another rat safety study by Belgian researchers found:
- Lanthanum can be found at the outer edge of the mineralized bone, independent of the underlying type of renal osteodystrophy.
- There is no correlation between the mineralization defect seen with high doses (1-2 kg/mg/day) for 12 weeks in chronic renal failure rats and localization of lanthanum in the bone.
- Lanthanum is not always co-localized with the active mineralization front, but can also be found on quiescent surfaces and in resorption lacunae.
- After a four-week washout period, lanthanum localization remains unchanged. A researcher said, "When it deposits, it doesn't wash out...The explanation for the defect is the effect of phosphate depletion from the lanthanum, so the conclusions would be that it is necessary to monitor phosphate levels routinely with lanthanum, and supplement it if it is lower, lower the lanthanum dose, or stop the lanthanum…You can cause the same defect with high dose Renagel…There is lanthanum accumulation in the bone, but there are nearly undetectable levels in the brain, and no sequelae."

➢ A third study looked at bone histomorphometry in ESRD patients.

1-Year Results of Lanthanum in ESRD

Measurement	Lanthanum	Calcium carbonate
Improvement in bone-cell activation frequency	51.5%	23.3%
Improvement in % osteoclast surface vs. bone formation rate	54.5%	33.3%
Osteomalacia	0	N/A

JUVENT'S Juvent 1000

This is a dynamic motion therapy for osteoporosis. The patient stands on the device which provides repetitive vertical displacement (up and down) with about 50-60 microns of movement and 0.2-0.3 gravity acceleration. Juvent, a private company, obtained the technology from Smith & Nephew,

which decided not to pursue it. Juvent officials hope to start a clinical trial by mid-2005 or sooner if the money for the trial can be raised quicker.
For a PMA, the FDA wants a randomized, multicenter, double-blind, clinical trial in patients with a T-score >-2.0. The primary endpoint will be BMD, not fractures.

The idea might sound a little odd, but there have been some proof of concept trials, with the results published in peer-reviewed journals.

- A randomized clinical trial by Creighton University researchers of 64 patients found that patients who were compliant with the regimen – therapy 20 minutes a day at least five days a week – had statistically significant increases in BMD vs. placebo. However, there was no statistically significant benefit on an intent-to-treat basis, which an official said was due to the importance of compliance with the treatment regimen, "With less than 60% compliance, there is no effect. But there is a good effect, when compliance is above 60% – and it gets better as you get more compliant…Spine BMD goes up 7% if it is used 100% of the time, and more than a 2% increase in femoral neck BMD with 100% compliance."
- A U.K. study looked at the therapy in children with cerebral palsy.
- A Swedish study found there was no negative motion transmission from the feet to the spine.

Juvent hopes to market this device to women who either don't want to take an oral medication or who have stopped taking an oral medication. The expected purchase price is $2,000, but leases will also be available for $40/month with a $400 deposit.

Miscellaneous

- A rat study from Mayo Clinic researchers suggested that PTH treatment (with PTH 1-34) may be less effective in patients with reduced weight-bearing and impaired physical activity.
- A Swiss mouse study suggested that combining a beta blocker (propranalol) with PTH is synergistic in osteoporosis.
- A Cleveland Clinic study warned that doctors may need to adjust the calcium and vitamin D doses when Forteo is used.
- A Harvard study found that several classes of drugs were associated with lower BMD, including anticonvulsants, and opioids – but not benzodiazapines or antidepressants. Researchers said, "It is unclear whether the effect on bone metabolism is a direct or indirect effect."
- **MBC Research's MBC-11.** Preliminary in vitro data on this novel nucleotide-bisphosphenate conjugate compound suggest it is:
  - 100 times more efficacious at inhibiting breast cancer proliferation than Zometa.
  - Effective at inhibiting (reducing the incidence) of bone metastases at Day 21 (in animals).
- **Merck** researchers reported that the selective Cox-2 MF-tricyclic for osteoarthritis has (1) no effect on bone resorption, (2) decreases subchondreal bone sclerosis and osteophyte formation, and (3) has disease modifying effects in RA rat model of OA.
- **Millennium's Velcade (bortezomib).** A mouse study suggested that the beneficial effect of Velcade in multiple myeloma patients results from its ability to block bone resorption and multiple myeloma cell function.
- **Ono Pharmaceutical**
  - **ONO-4819**, a PGE_2 (EP_4 subtype agonist). A rat study found this agent can enhance bone-inducing activity of rhBMP-2 without apparent systemic adverse effects when added to the rhBMP delivery system. ONO-4819 enhanced new bone formation and significantly increased bone mass, and it acts in less than two weeks. Another poster reported that there were no adverse events in rats, the agent enhances bone healing by activation of both bone formation and bone remodeling, and a clinical trial for fracture healing is ongoing in Japan.
  - **ONO-5920 (YM-529),** a bisphosphenate in development to treat bone metastases.
- **Pfizer's Lipitor (atorvastatin).** Oregon researchers reported on a one-year, 604-patient (postmenopausal women), randomized, double-blind, placebo controlled study of 10-80 mg Lipitor (atorvastatin) vs. placebo, concluding the data do not support a role for statins in prevention or treatment of osteoporosis. There was no effect on BMD or biochemical indices of bone metabolism, and researchers called the findings "unequivocal."
- **Prostakan's PSK-3471.** Two posters suggested this new SERM – a tissue selective, bone anabolic designer estrogen – may be an improved, second generation agent that helps prevent non-vertebral fractures with good breast and uterine safety. In one study, after eight weeks PSK-3471 restored bone mass in osteopenic mice and increased dose-dependently bone strength at the level of the proximal tibia better than raloxifene, with a trend towards an increase in cortical bone.
- **SkeleTech's tormifene.** A poster found this SERM, in an ex vivo study, decreased bone turnover, prevented bone loss, and protected bone microarchitecture. Researchers postulated that, in prostate cancer patients on androgen deprivation therapy, tormifene may prevent spinal bone loss and prevent spinal fracture. ♦