Other fractures were elbow and arm in placebo patients and foot/toe, ankle, leg, patella, hip, wrist, elbow, arm and other in Alendronate patients. The number of patients in the extension cohort was 61 placebo and 118 drug-treated subjects. There were **9 and 7 new fractures during the second year, 6 and 6 of them vertebral and 1 and 0 rib**. The other fractures were foot/toe and hand /finger in placebo, patella in Alendronate-treated patients.

The reason that year one and year 2 do not add up in number of fractures to equal the number in the Total for year 1 and year 2 seems to be that the patients in the total category are only those who entered the extension. That is, first-year data are dropped for all those who did not continue. These data are not very helpful, because there were so few fractures after the first 48 weeks. Looking only at the extension patients, it is clear that the excess of non-vertebral, non-rib fractures is about the same at 2 years, as it was at 1 year. The **total fracture rate in the placebo group is 10, 15, 25% in the 3 periods, and is 7, 6, and 14% in the Alendronate group.**

Morphometric vertebral fractures were determined in 082/083 (560 pts x 1-2 yrs), 035/037 (994 pts x 3 yrs), and 051 (6459 pts x 3-4yrs). They yielded relative risks of 0.39, 0.52, and 0.54 with the **upper limits of the 95% confidence intervals 1.04, 0.95, and 0.66**. RR and 95% CI for 082/083 and FIT for clinical (symptomatic) fractures were 0.65 and 0.82 RR and 1.49 and 0.93.

Note: All clinical fractures were subjected to an adjudication process in which "all nonosteoporotic fractures (pathologic fractures and those judged to have the potential to occur in a nonosteoporotic person) were excluded from the analysis. This adjudication process was conducted blinded, but it should be possible to rely on the randomization process to eliminate any imbalance in the distribution of these fractures. It is just another possible source of bias that would best be eliminated.

Conclusions drawn by Merck:

- ✓ Data support an excellent safety profile for Alendronate.
- ✓ The incidence of clinical and laboratory AEs is numerically greater only in individual studies.
- ✓ 5 and 10 mg doses have similar AE profiles, except for slightly higher rates of abdominal pain and acid regurgitation in Alendronate subjects.
- ✓ Upper GI AEs were common in long-term clinical trials but similar in drug and placebo groups.
- ✓ Esophageal AEs were more numerous in drug than placebo groups, but serious events were only about 0.1%.
- ✓ Gastric and duodenal PUBs were similar in incidence, and gastric mucosa protects the stomach against caustic secretions and other irritants.
- ✓ Fracture results demonstrate a consistent reduction in fracture risk in vertebral and nonvertebral sites.
- ✓ Alendronate was well tolerated, and effected reduction of fractures.

Conclusions Drawn by Reviewer

Points Considered:

Concerns about Rationale

1. Bone recycling is suppressed by glucocorticoids. The osteoblast is inhibited, and the osteoclast continues at the normal rate, resulting in an imbalance so that less bone is formed than is resorbed. Adding Alendronate decreases resorption to try to match the abnormally reduced bone production.

2. The application says that glucocorticoid therapy is reported to result in doubling of the fracture rate and a near tripling of the hip fractures; glucocorticoid also results in fractures at a higher BMD than in patients with involutional osteoporosis, a disassociation of bone density and fracture rate that argues against Merck's implications that this condition parallels postmenopausal osteoporosis.

Effectiveness of Alendronate for glucocorticoid-induced osteoporosis:

3. Alendronate is effective at increasing BMD of the Lumbar Spine, and it may reduce vertebral fracture rate in patients with glucocorticoid-induced osteoporosis.

4. Effectiveness for prevention of GIOP has not been demonstrated.

5. The changes in lumbar spine BMD are modest:3.61 and 4.62% (5 and 10 mg doses).

6. The trochanter, an area rich in trabecular bone, and of perhaps greater importance for hip fractures, experiences greater BMD increases than other parts of the hip: 3.37 and 5.12% the first year, 1.42 and 1.78 the second year.

7. During the second year, changes were small, even in the lumbar spine where they were 1.13 and 0.70 (5 and 10 mg doses). It would be interesting to know whether calcium and vitamin D would suffice to prevent bone loss during the second year.

8. Small BMD losses in placebo groups demonstrate that bone loss is not rampant in many of the untreated patients. That the BMD losses are small may result from the supplemental calcium and vitamin D provided to subjects in these trials.

9. Decrease in stature of glucocorticoid-treated patients was not prevented and was only trivially retarded by alendronate.

10. Blinding might be difficult with a drug of this type. I would not be surprised to learn that many patients knew if they were taking drug.

11. FIT: The Clinical Fracture Cohort had 2 more "all Clinical Fractures" per 100 patient-years in the placebo than in the Alendronate group. In no group were the differences between drug and placebo patients greater than 4%.

12. Some literature characterizes GIOP as causing both rib and vertebral fractures. This characterization seems reasonable, because both are rich in trabecular bone. I have used this classification of fractures in this review.

Fracture safety of Alendronate for glucocorticoid-induced osteoporosis:

13. The number of fractures actually prevented is a very small proportion of the population treated.

14. Alendronate has not been shown to reduce the fracture rate of bones other than spine in glucocorticoid-treated patients.

15. A trend toward an increase in fracture rate of bones composed mostly of cortical bone (total fractures exclusive of spine and ribs) is seen.

16. A potential bias is introduced by adjudicating nonvertebral fractures and eliminating those that could occur in non-osteoporotic patients, rather than counting all fractures.

17. Multiple end-points are named (24), a number that would make a statistically positive result very likely. Any labeling requests that rely on this data would have to have the p value adjusted.

Gastrointestinal safety of Alendronate for glucocorticoid-induced osteoporosis:

18. Alendronate seems to carry only a small risk of serious gastrointestinal adverse events if used as instructed and observing the exclusions set by Merck for Alendronate clinical trials.

19. Exclusions (prior or present) from Merck Clinical Trials: major GI disease, peptic ulcer, dyspepsia, delayed esophageal emptying.

20. Gastritis and reflux esophagitis were more frequent in Alendronate than in placebo patients.

21. Concomitant and prior use of GI drugs was slightly greater in the placebo than in the Alendronate-treated patients. They were, therefore at greater risk of GI disease during the trial.

Summary: If all that is asked of this drug is that it increase BMD of the Lumbar Spine, then it is effective. If it need only be not often fatal, then it is safe.

It is disappointing and perplexing that stature is not effectively treated by a drug that reduces fractures of the spine. If it doesn't reduce the height loss, what does it do for patients, besides improve the appearance of lateral x-rays of the spine? In the FIT data (PMO, not GIOP), a small subgroup that experienced new vertebral fractures did seem to benefit, so that a centimeter or two of height might be preserved, when the drug is taken for 5 years. Spinal fractures have been considered to be of consequence for their effect on height, as most of them are otherwise asymptomatic. The information in this application causes me to question the endpoint (new vertebral fractures) on which our approval process has relied for all drugs so far.approved for PMO (with commitment to obtain and submit adequate fracture data post-marketing).

Prevention of symptomatic fractures is the ultimate goal of osteoporosis treatments. If they are reduced, the drug is effective. This application analyses "all clinical fractures," a category that includes all fractures except the asymptomatic spinal fractures, whereas most fracture studies count all vertebral fractures and do not include non-vertebral fractures. When symptomatic spinal fractures

and non-vertebral fractures were combined, there was not a statistically significant difference between drug and placebo; when only non-vertebral, non-rib fractures were counted, the number was greater for Alendronate-treated patients, but the difference was not statistically significant. Actual numbers were 4/178 pt-yrs for placebo and 6/183 and 7/178 pt-yrs for 5 and 10 mg doses of Alendronate. This is 2.2% vs 3.3 and 3.9% for 5 and 10 mg doses.

In this application, the primary endpoint is not stature or fractures, but a surrogate, BMD.

The single endpoint that fails both for safety and for efficacy is not one of the 24 listed. I do not find it safe to use Alendronate for GIOP unless there is fracture data showing that non-vertebral, non-rib fractures are not increased by Alendronate administration. I also do not find the drug effective if non-vertebral, non-rib fractures are increased, even if there are data showing that spinal fractures are decreased.

NDA 20560
Merck
Alendronate (Fosamax)
Supplement on Glucocorticoid-induced osteoporosis (GIOP)
Histomorphometry
Date 5-14-98

Addendum to Clinical Review of NDA Supplement

I did not expect that the bone histomorphometry would be given as much importance as I thought I heard at the Advisory Committee yesterday. It seemed that some of the experts expressed the opinion that if histomorphometry does not show any abnormal bone, it is safe to accept Bone Mineral Density as the principal efficacy endpoint for drugs that are to be used for GIOP. To help us evaluate the histomorphometry findings, I have prepared a more detailed review of the hispomorphometry included in the Fosamax Supplement for GIOP.

The mineral apposition rate did not differ between patients on placebo and those on drug. The other histomorphometry parameters were all less in alendronate-treated patients, including the mineralizing surface. The marked difference in mineralizing surface (1.31 vs 5.53% of the bone surface) is attributed to reduced turnover. The biopsies were done at the end of the study, and there are no baseline values to which these findings can be compared.

It appears that these findings were what Merck expected and were considered favorable to the drug. However, the report says that these histomorphometry parameters are not appropriate tools for assessing bone turnover; chemical markers are considered best for that assessment.

The next 6 pages were cut and pasted directly from the CANDA.

/S/ [redacted]

Hypotheses

Safety

Daily oral treatment with alendronate, at doses of up to 10 mg/day for at least 48 weeks in patients with GIOP:

a. Will not impair mineralization, as judged by increased OV and increased OTh relative to placebo-treated controls.

b. Will either not reduce MAR relative to placebo-treated controls, or will have a small effect within the normal range, consistent with the effect of treatment to decrease bone turnover.

c. Will not be associated with the induction of qualitative abnormalities, including woven bone and marrow fibrosis, as determined by an expert in histomorphometry.

Efficacy

Daily oral treatment with alendronate, at doses of up to 10 mg/day for at least 48 weeks in patients with GIOP, will suppress bone turnover as judged by a decrease in MS, relative to placebo-treated controls.

Table 6

Quantitative Assessment of Histomorphometry at Week 48
Combined GIOP Studies (082/083)

Parameter	Treatment	n	Mean	SD	Median
Osteoid Thickness (µm)					
	Placebo	17	8.97	2.13	9.00
	Pooled alendronate[1]	30	5.95	1.22	5.90
Mineral Apposition Rate (µm/day)					
	Placebo	14	0.54	0.09	0.57
	Pooled alendronate[1]	24	0.58	0.16	0.56
Osteoid Volume (% of Bone Volume)					
	Placebo	17	1.67	1.58	1.05
	Pooled alendronate[1]	30	0.41	0.65	0.21
Mineralizing Surface (% of Bone Surface)					
	Placebo	17	5.53	5.54	3.37
	Pooled alendronate[1]	30	1.31	3.37	0.37

[1] Alendronate 5- and 10-mg patients only.

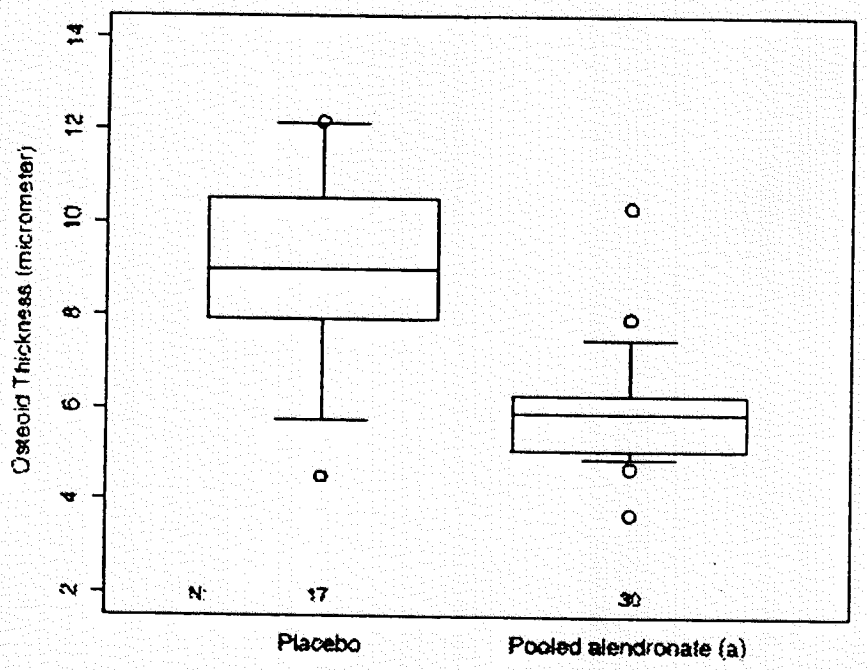
Data Source: [4.9]

1) Osteoid Thickness

The osteoid thickness data are in Figure 1, which also indicates the number of observations in each group. The mean (SD) OTh was 5.95 (1.22) µm in the pooled alendronate group compared with 8.97 (2.13) µm in the placebo group. An increase in OTh would be expected if alendronate significantly impaired the mineralization of newly formed bone; however, OTh was clearly lower in the alendronate patients than in those on placebo. This observed decrease is most likely explained by the anticipated effect of alendronate to decrease bone turnover rate.

Figure 1

Effect of Alendronate on Osteoid Thickness (µm) at Week 48
Combined GIOP Studies (082/083)



(a) Alendronate 5- and 10-mg patients only.

Note: The plot provides the median (center line), 25th and 75 percentiles (bottom and top of boxes), 10th and 90th percentiles (caps of error bars), and individual points outside those limits.

Data Source: [4.9]

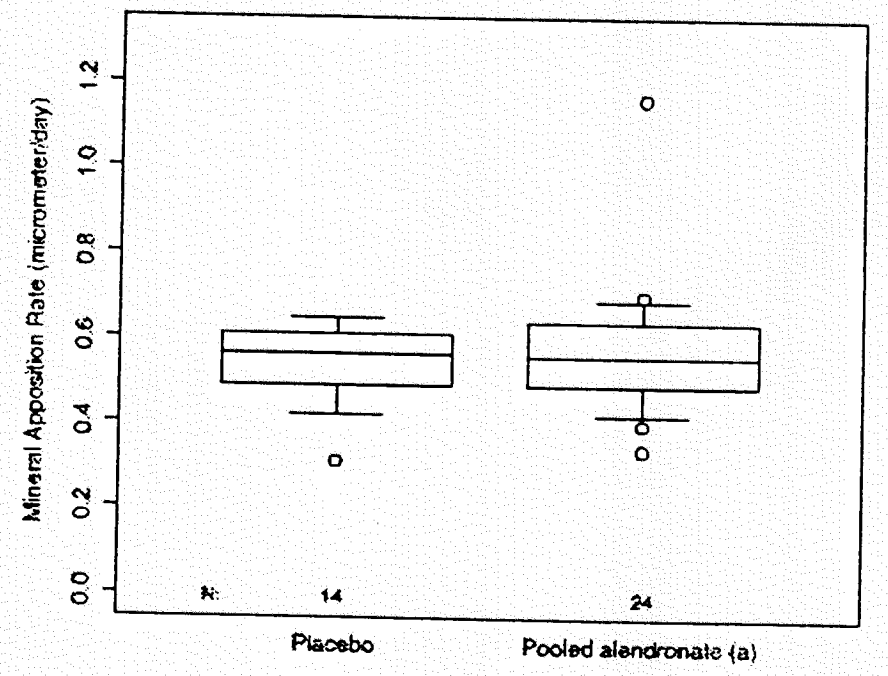
2) Mineral Apposition Rate

MAR data are in Figure 2. The mean (SD) MAR was 0.54 (0.09) µm/day in the placebo group and 0.58 (0.16) µm/day in the alendronate group. The MAR was unaffected by alendronate treatment compared with placebo treatment. Thus, there is no evidence of toxicity associated with alendronate in terms of decreasing the rate of mineralization.

0.0 0.2 0.4 0.6 0.8 1.0 1.2

Figure 2

Effect of Alendronate on Mineral Apposition Rate (µm/day) at Week 48
Combined GIOP Studies (082/083)



(a) Alendronate 5- and 10-mg patients only.

Note: The plot provides the median (center line), 25th and 75 percentiles (bottom and top of boxes), 10th and 90th percentiles (caps of error bars), and individual points outside those limits.

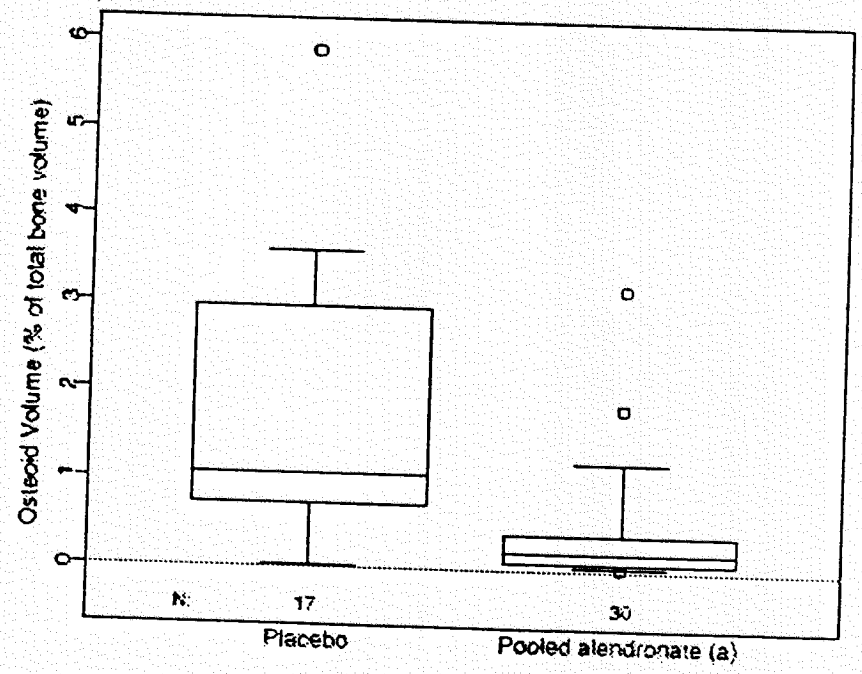
Data Source: [4.9]

Osteoid Volume

The mean (SD) OV, expressed as percent of the total bone volume, was 1.67 (1.58)% in the placebo-treated patients and 0.41 (0.65)% in the alendronate-treated patients. OV was in general lower in patients on alendronate than in patients on placebo (Figure 3). These data indicate that mineralization is not impaired by alendronate treatment.

Figure 3

Effect of Alendronate on Osteoid Volume (% of Total Bone Volume) at Week 48
Combined GIOP Studies (082/083)



(a) Alendronate 5- and 10-mg patients only.

Note: The plot provides the median (center line), 25th and 75 percentiles (bottom and top of boxes), 10th and 90th percentiles (caps of error bars), and individual points outside these limits.

Data Source: [4.9]

Histomorphometric qualitative analysis of bone biopsies obtained from 88 patients enrolled in the Multinational and U.S. studies showed that alendronate preserved the normal lamellar architecture of bone in glucocorticoid users. Alendronate did not induce woven bone, marrow fibrosis, or any other structural abnormality.

As expected, alendronate decreased the rate of bone turnover, shown by a decrease in OTh and MS. However, bone turnover was not completely suppressed. Bone mineralization was not impaired, as shown by the lack of effect of alendronate on the MAR. Moreover, OV decreased (as a result of the decreased bone turnover rate), a change opposite to that expected for an agent inhibiting bone mineralization [1.2.4].

These data demonstrate alendronate treatment decreases bone turnover while preserving bone quality in glucocorticoid-treated patients. These effects on bone turnover have important clinical implications. There is some evidence that the relationship between bone density and the occurrence of vertebral fractures may be different in GIOP compared with patients with involutional osteoporosis. The occurrence of fractures in glucocorticoid users in the presence of higher bone densities suggests that glucocorticoids affect not only bone quantity but also bone quality. Thus, the histomorphometric data suggest that alendronate may be able to prevent the microarchitectural deterioration of bone and reduce fracture risk to a greater extent than predicted by its effect on BMD.

Hedin

MAR 23 1998

NDA 20560/SEI-012 BM
Merck
Alendronate (Fosamax)
Dated 3-6-98 and stamped 3-9-98
Received 3-16-98
Reviewed 3-17-98

This submission is in response to questions asked of the sponsor by the Division.

Section I describes the possible **animal models** of glucocorticoid-induced osteoporosis (GIOP). Their conclusion is that no suitable animal is adequately validated.

Section II responds to our request for information on which they rely to conclude that **GIOP is sufficiently similar to post-menopausal osteoporosis** (PMOP) that validation in PMOP can be extrapolated to GIOP.

Similarities:

1. **Bone resorption** relative to formation results in net bone loss.
2. Excessive **osteoclastic bone resorption** relative to osteoblastic bone formation is the key pathophysiologic mechanism underlying the bone loss.
3. **Negative bone balance** is attributable to 3 factors: 1) effects on osteoblasts lead to decreased bone formation, 2) secondary hyperparathyroidism due to decreased intestinal absorption and decreased renal tubular reabsorption of calcium leads to increases in both resorption and formation, and 3) gonadal hormone deficiency results in increased resorption and formation.
4. **Bone resorption is increased** in both GIOP and PMOP, and the cellular mechanisms are the same: mediated by the osteoclast.
5. Many **small studies** demonstrate the efficacy of bisphosphonates in male osteoporosis, immobilization, hyperthyroidism, idiopathic juvenile osteoporosis and osteogenesis imperfecta, indicating that beneficial effects on bone mass relate to specific effects of bisphosphonates as inhibitors of bone resorption **irrespective of mechanism of stimulating bone resorption.**
6. Alendronate **has consistent effects on bone mineral density.**
7. Absorptiometric measurements are **predominantly measures of cortical bone quality.**

8. Bone turnover is more rapid in cancellous bone, so **changes in bone density can be seen first at more cancellous sites.**
9. Bone mineral density **GIOP data are consistent with PMOP** data, as are data for men and pre and post menopausal women and data for the different GIOP underlying illnesses. Data are presented for PMOP phase II, FIT, EPIC and GIOP studies for spine and hip.
10. Effects (excess bone resorption) of **bone markers** are consistent for GIOP and PMOP.
11. **Bone turnover** (BSAP and NTx) is **greater in women who fracture** regardless of use of alendronate.
12. **Histomorphometry** does not reveal any failure of mineralization (osteoid volume, mineral apposition rate, mineralizing surface).

Items 1-8 above were very difficult to understand, so I may not have gotten them straight. They did not seem to make much sense in the context of whether BMD is a valid surrogate for fractures in GIOP. Mostly, they assert that BMD is similar in GIOP and PMOP without any reasonable backup in GIOP data. Of course, we are convinced that, in PMOP, BMD is correlated with spinal fracture rate, and bisphosphonates reduce the risk of vertebral fractures. However, **non-vertebral fractures in patients with GIOP** are the cause of our concern. No validation of BMD in GIOP is offered. In 9 and 10 above, the data compare BMD results of GIOP and PMOP trials, but **provide no basis for extrapolating results from PMOP to GIOP or from BMD to non-vertebral fractures in GIOP patients.** Number 11 seems to say again that turnover is increased, and alendronate will reduce it—not helpful. It is whether reducing turnover further when formation is already suppressed is making bone stronger. Number 12 is no help, because we agree that bone is mineralized, particularly axial bone, a point that can be inferred from the BMD data.

Section III is an analysis of GIOP fracture data, which is acceptable, but does not address the issue **of excess non-trabecular fractures** in alendronate-treated subjects in the GIOP trials. They do include **a list of non-vertebral fractures**, information which we already have.

Appendix 2 is referenced in this section. It consists of a **table of non-vertebral fractures**, which includes rib fractures. According to this list, there were 6 patients with rib fractures (ages 76, 67, 61, 57, 47, 46), one of whom also had the sternum fractured. There was one rib fracture in each of the treatment groups.

Non-vertebral, non-rib:

Sex age	Treatment	Fracture site	Trauma
F25	PBO	humerus	skiing accident
F59	PBO	elbow	due to trauma
F51	5mg	tibia	stress fracture
F76	5mg	ankle	fell on ice
F75	5mg	pelvis	fell on coffee table
M40	5mg	ulna	knocked while playing
F79	5mg	humerus	fell on ice
F69	10mg	knee	knocked down by dog
F59	10mg	wrist	fell
F58	10mg	foot	no trauma
F32	10mg	elbow	fell
F71	10mg	hip	no trauma
F56	10mg	foot	trauma
F47	10mg	ankle	tripped while walking

This analysis seems to support our concern. It is hard to judge the amount of trauma, but it seems most of those who fractured just fell from a standing position. One skiing accident was in the placebo group.

Section IV discusses **the calculations of study size and trial feasibility.** Based on the GIOP placebo group, a fracture incidence of 4% and 10%/year is assumed. In all patients rate was 3.7%; in patients with 3 yr exposure to glucocorticoids it was 4.2%/year; and in patients with prevalent fractures it was 9.1%/year. The drop out rate was presumed to be 20%. To have 90% chance, in a one-year study, to detect a 50% reduction in fracture rate in patients with a vertebral fracture at baseline, sample size would have to be almost 700.

They also calculate detecting 30 or 40% increase in fracture rate. I would like to see some information on the size study required to **detect a 50% or 100% increase in non-vertebral, non-rib fracture rate,** because my concern is that the 3-fold increase in the GIOP studies might be real.

I believe that the **vertebral fractures detected in this study were largely symptomatic,** because there was not a plan to determine baseline and incident vertebral fractures. The investigator or other health care provider had to get an xray of the spine because of symptoms or as a routine screening in order for it to be reported as an adverse event. It might be reasonable to count all symptomatic fractures including the spine and ribs, because there is more benefit to prevention of symptomatic fractures, but it would still be difficult to equate some vague backaches to hip or limb fractures. Only **one study with one treatment group would be required,** and more than one year should be

considered, even though patients are not on glucocorticoids that long. The sponsor seems to argue that there are many fractures when pressing to have this valuable drug approved to prevent fractures, but that there are very few who have osteoporosis more than a few months to one year. The literature seems to say that patients do go on and off of glucocorticoids, but it is hard to keep them off for long periods of time, if they have a responsive illness.

There is nothing that causes me to change my mind about the approvability of alendronate for prevention of fractures in patients with GIOP.

Recommendation: Not Approvable

/S/ [redacted]

Gloria Troendle
Orig NDA 20560
Div File
HFD-510/GTroendle/RHedin

[redacted] APPEARS THIS WAY ON ORIGINAL