Table 1

Accounting of Patients in the GIOP Extension Studies (082/083) and Reasons for Non-participation in Extension Studies

	N	% of Original Cohort
Original study cohort	**560**	**100**
Double-blind extension patients	**203**	**36**
Open-label extension patients	14	3
Non-extension patients	343	61
Discontinued prior to Month 12	84	15
Site Closed	97	17
Glucocorticoid dose <7.5 mg/day	87	16
No consent	75	13

[1] This table contains counts of patients. Although a patient may not be taking part in the extension for more than one reason, the patient was counted only once. The following hierarchy determined which reason would be shown in the table: Month 12 discontinuation, site closed, glucocorticoid dose <7. 5 mg and no consent.

Patients who received PBO, 5- or 10- mg alendronate in the first 12 months continued to receive the same double-blind treatment during the extension (Table 2). Patients who received 2.5 mg in Year 1 were blindly switched to 10 mg.

Table 2
Study Design

Month 0 to Month 12	Month 12 to 24
Placebo	Placebo
Alendronate 2.5 mg	Alendronate 10 mg
Alendronate 5 mg	Alendronate 5 mg
Alendronate 10 mg	Alendronate 10 mg

2. Description of Vertebral Fracture Assessment

The primary method for assessing vertebral fractures in these studies, as prespecified in the Data Analysis Plan, was morphometric analysis [1]. Morphometric vertebral fractures were primarily determined by computerized digitization [2] of spine radiographs and defined as a decrease of ≥20% and ≥4 mm in the anterior, middle, or posterior height of any vertebra (L1 to L5 and T4 to T12) between Months 0 and 12 and 0 and 24.

A binary, semiquantitative (SQ) visual assessment of vertebral deformity was used to verify the digitized measurements [3,4]. This method grades vertebrae on visual inspection without direct vertebral measurement as follows: normal (grade 0);

borderline deformed (grade 0.5); mildly deformed (grade 1, approximately 20 to 25% reduction in anterior, middle, and/or posterior height and a reduction of area 10 to 20%); moderately deformed (grade 2, approximately 25 to 40% reduction in any height and a reduction in area 20 to 40%); and severely deformed (grade 3, approximately 40% reduction in any height and area). An incident (occurring during the study) vertebral fracture was defined as a change in SQ grade of ≥1 from baseline to follow up. The morphometric results are based on computer-generated calculations, while the semiquantitative technique relies on the radiologist's visual interpretation of plane radiographs.

These methods were unchanged relative to the original one-year study.

3. **Vertebral Morphometry - Incidence of Vertebral Fractures Between Month 0 and Month 24 - Double-blind Extension Cohort**

In the original 12-month study, 5 of 134 (3.7%) of patients in the placebo group had a vertebral fracture, compared with 6 of 266 patients (2.3%) in the alendronate-treated (5- and 10-mg) patients (Appendix 1, Table 1).

Five patients continuing into double-blind extension had at least one new vertebral fracture between Month 0 and Month 24, as determined from the change in digitized vertebral heights (Table 3). Four of 57 (7.0%) patients in the placebo group had a new vertebral fracture, compared with 1 of 140 patients (0.7%) in the alendronate-treated (5-, 10- or 2.5/10- mg) group. Although the study was not specifically powered to demonstrate fracture risk reduction, the higher incidence of vertebral fractures in the placebo group versus the alendronate group was statistically significant (p-value <0.05).

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Table 3

Incident Vertebral Fractures (Morphometric) Between Month 0 and Month 24
GIOP Extension Studies (082/083)
Double-Blind Extension
Incidence by Prevalent Vertebral Fracture and by Gender/Menopausal Status

	Placebo	Alendronate
Overall *	4/57 (7.0%)	1/140 (0.7%)
By Prevalent Fracture at Baseline		
No prevalent fracture	2/51 (3.9%)	1/122 (0.8%)
With prevalent fracture	2/ 6 (33.3%)	0/ 17 (0.0%)
By Gender/Menopausal Status		
Men	0/17 (0.0%)	0/45 (0.0%)
Women	4/ 38 (10.5%)	1/95 (1.0 %)
* Premenopausal	1/17 (5.9%)	0/ 34 (0.0%)
Postmenopausal	3/23 (13.0%)	1/61 (1.6%)
By First Occurrence of Fracture		
Month 12	1/57 (1.8%)	1/140 (0.7%)
Month 24	3/55 (5.5%)	0/140 (0.0%)
* P- value (Fisher's Exact Test) = 0.023		

4. Semiquantitative Binary Assessment of Vertebral Fracture - Incidence Between Month 0 and Month 24 - Double-blind Extension Cohort

A binary, semiquantitative (SQ) visual assessment of vertebral deformity was used to verify the digitized measurements as described above. As shown in Table 4, results of the semiquantitative assessment for the patients who participated in the double-blind extension are consistent with the morphometric results.

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Table 4

Incident Vertebral Fractures (Semiquantitative Binary Assessment)
Between Month 0 and Month 24
GIOP Extension Studies (082/083)
Double-Blind Extension

	Placebo	Alendronate
Overall *	5/58 (8.6%)	2/142 (1.4%)
* P-value (Fisher's Exact Test) = 0.020		
By Menopausal Status		
Men	0/17 (0.0%)	1/46 (2.2%)
Women	5/ 38 (13.2%)	1/96 (1.0%)
Premenopausal	1/17 (5.9%)	0/ 34 (0.0%)
Postmenopausal	4/24 (16.7%)	1/62 (1.6%)

5. Clinical Nonvertebral Fractures as Adverse Experiences

Investigators reported symptomatic nonvertebral fractures as clinical adverse experiences (Table 5). In the original 12-month studies, the incidence of nonvertebral fractures was 4.4% (7 patients) in the placebo group and 4.4% (14 patients) in the alendronate 5- and 10-mg groups (Appendix 1, Table 2).

In the extension cohort, from Month 0 to Month 24, the incidence of nonvertebral fractures was 10.2% in the placebo group (6 patients) and 5.6% in the combined alendronate group (8 patients) (p=0.229). A listing of the individual fractures and their precipitating event is provided in Appendix 2. There is no consistent dose trend in nonvertebral fractures, even when rib fractures are excluded from the analysis.

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Table 5

Summary of All Non-Vertebral Fracture Adverse Experiences
Between Month 0 and Month 24
GIOP Extension Studies (082/083)
Double-Blind Extension

	PBO (N=59)	ALN Combined (N=144)	ALN 5 mg (N= 62)	ALN 10 mg (N= 54)	ALN 2.5/10 mg (N= 28)
	n (%)	n (%)	n (%)	n (%)	n (%)
Number (%) of patients with one or more non-vertebral fracture adverse experiences	(2) 3% 6 (10.2)	(6) 4.2 8 (5.6)	3 5.1 4 (6.6)	2 4% 3 (5.6)	1 (3.6)
Fracture, ankle/lower leg	0 (0)	2 (1.4)	1 (1.6)	1 (1.7)	0 (0)
Fracture, foot	1 (1.7)	0 (0)	0 (0)	0 (0)	0 (0)
Fracture, hip/femur	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Fracture, hand	1 (1.7)	0 (0)	0 (0)	0 (0)	0 (0)
Fracture, rib	4 (6.8)	3 (2.1)	1 (1.6)	1 (1.9)	1 (3.6)
Fracture, wrist/arm	0 (0)	3 (2.1)	1 (1.6)	1 (1.9)	1 (3.6)
Fracture, other (pelvis, knee)	0 (0)	1 (0.7)	1 (1.6)	0 (0)	0 (0)

No significant differences between treatment groups were observed.
Note: Patients with more than one fracture adverse experience are counted only once in the overall total.

The incidence of nonvertebral fractures from Month 0 to 12 (Year 1) is compared to the incidence from Month 12 to 24 (Year 2) and is shown in Table 6. There is no increase in nonvertebral fractures in placebo patients from Year 1 to Year 2. However, there are 50% fewer fractures in alendronate patients in Year 2 compared with Year 1. As shown in Table 6, the highest dose alendronate treatment group (10 mg) had no nonvertebral fractures during Year 2, while the placebo group had 2 fractures.

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Table 6
Summary of All Non-Vertebral Fracture Adverse Experiences
Year 1 vs. Year 2 For Patients Who Entered the Double-Blind GIOP Extension Studies (082/083)

Fracture Site	PBO (N=59)		ALN Combined (N=144)		ALN 5 mg (N=62)		ALN 10 mg (N=54)		ALN 2.5/10 mg (N=28)	
	Year 1	Year 2	Year 1	Year 2	Year 1	Year 2	Year 1	Year 2	Year 1	Year 2
Number of patients with one or more non-vertebral fracture AEs	3 (5.1%)	3 (5.1%)	6 (4.2%)	2 (1.4%)	3 (4.8%)	1 (1.6%)	3 (5.6%)	0	0	1 (3.6%)
ankle/lower leg	0	0	2 (1.4%)	0	1 (1.6%)	0	1 (1.9%)	0	0	0
foot	0	1 (1.7%)	0	0	0	0	0	0	0	0
hand	0	1 (1.7%)	1 (1.7%)	0	0	0	0	0	0	0
rib	3 (5.1%)	1 (1.7%)	2 (1.4%)	1 (0.7%)	1 (1.6%)	0	1 (1.9%)	0	0	1 (3.6%)
wrist/arm	0	0	1 (0.7%)	1 (1.9%)	1 (1.6%)	0	1 (1.9%)	0	0	1 (3.6%)
other (pelvis, knee)	0	0	0	1 (1.9%)	0	1 (1.6%)	0	0	0	0

0 2 4 2 2 1

6. Supportive analyses : Incidence of Fractures During Treatment - All patients Randomized at Month 0 to Double-Blind Study Therapy

Incidence of fractures during double-blind treatment for the 560 patients randomized to the one-year study is presented below. The counts reflect all fractures which occurred in any patient during the 24-month study period except those occurring during the study extension in patients receiving open-label alendronate. This includes fractures that occurred between Month 0 and Month 12 (Year 1) in patients who did not participate in the extension, or who were taking alendronate open-label during extension, as well as fractures that occurred between Month 0 and Month 24 (Years 1 and 2) in patients who continued into the double-blind extension.

The crude incidence of vertebral morphometric fracture was 5.9% in the placebo versus 2.4% in the alendronate group (Table 7).

Table 7

Crude Incidence of Vertebral Fractures (Morphometric) During Double-Blind Treatment
GIOP Original and Extension Studies (082/083)
All Patients (N=560)
Months 0 to 24

	Placebo	Alendronate
Incidence of Vertebral Fractures (Morphometric)	8/ 136 (5.9%)	8/ 340 (2.4%)

The incidence of nonvertebral fractures for the entire GIOP extension study cohort was 6.3% in the placebo group versus 4.2% on alendronate (Table 8). Table 8 provides an assessment of fractures occurring during the first or second year of the study in patients who entered the extension study. A specific lifetable analysis to analyze these data accoring to the precise time of occurrence of fracture is planned.

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Table 8

Incidence of Non-Vertebral Fractures During Double-Blind Treatment
GIOP Original and Extension Studies (082/083)
All Patients (N=560)
Months 0 to 24

	Placebo	ALN Combined	ALN 5 mg	ALN 10 mg	ALN 2.5/10 mg
Incidence of Non-Vertebral Fractures	10/ 159 (6.3%)	17/ 401 (4.2%)	7/ 161 (4.4%)	8/ 157 (5.1)	2/ 83 (2.4%)
Year 1	7/ 159 (4.4%)	15/401 (3.7%)	6/ 161 (3.7%)	8/ 157 (5.1%)	1/ 83 (1.2%)
Year 2	3/ 59 (5.1%)	2/144 (1.4%)	1/ 62 (1.6%)	0/ 54 (0)	1/ 28 (3.6%)

7. Summary

The most common fractures seen in patients treated with glucocorticoids are vertebral and rib fractures. These were also the most common fractures in the GIOP studies and were decreased on alendronate. The overall number of fracture events was small. There is no apparent increase in nonvertebral fractures whether one looks at the extension cohort alone or the exploratory analysis that includes all patients entered into the original study.

Perhaps most importantly, these data clearly demonstrate that there is no increase in the rate of vertebral or nonvertebral fractures during the second year in GIOP patients who continued to receive alendronate. This is entirely consistent with the data from our studies in postmenopausal osteoporosis, which now extend out to five years and show that the effects of alendronate to decrease fracture incidence is consistent over time. It is also consistent with the additional bone biopsy data obtained from the GIOP study population as well as the fact that the rate of bone turnover in the GIOP population, as determined by biochemical markers, is only partially decreased to reach a new steady state for both bone formation and bone resorption with mean values well within the normal range for healthy premenopausal women.

Therefore, overall, these two-year fracture data provide further evidence of benefit of alendronate in glucocorticoid users that is highly consistent with the data from postmenopausal women with osteoporosis that have clearly demonstrated the antifracture efficacy of alendronate.

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8. List of References

1. MK-0217: Glucocorticoid-Induced Osteoporosis: Special Endpoints Report. 1997.

2. Jergas M, San Valentin R. Techniques for the assessment of vertebral dimensions in quantitative morphometry. In: Genant HK, Jergas M, van Kujik C, eds. Vertebral fracture in osteoporosis. San Francisco: Radiology Research and Education Group, 1995:163-88.

3. Genant HK, Wu CY, Van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res 1993;8(9):1137-48.

4. Genant HK, Jergas M, Palermo L, et al. Comparison of semiquantitative visual and quantitative morphometric assessment of prevalent and incident vertebral fractures in osteoporosis. J Bone Miner Res 1996;11(7):984-96.

APPENDIX 1
Original 12-Month Study

Table 1

Incident Vertebral Fractures (Morphometric) by
Gender and Menopausal Status
Combined GIOP Studies (082/083)
Month 0 to Month 12

	Placebo (N= 135)	Pooled Alendronate[1] (N=268)
Total Vertebral Fractures	3.7% (5/134)[2]	2.3% (6/266)[2]
By Gender and Menopausal Status		
Men	2.1% (1/48)	1.4% (1/74)
Women	4.7% (4/86)	2.6% (5/192)
Premenopausal	0% (0/33)	0% (0/58)
Postmenopausal	7.6% (4/53)	3.7% (5/134)

[1] Alendronate 5- and 10-mg patients only.
[2] Number of patients with incident vertebral fracture/total patients with paired spine radiographs in subgroup.

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Table 2

Summary of All Clinical Nonvertebral Fracture Adverse Experiences by Dose
Combined GIOP Studies (082/083)
Month 0 to Month 12

	PBO (N=159)	ALN 5 mg (N=161)	ALN 10 mg (N=157)
	% (n)	% (n)	% (n)
Number (%) of patients with one or more non-vertebral fracture adverse experiences	4.4 (7)	3.7 (6)	5.1 (8)
Fracture, ankle/lower leg	0	1.2 (2)	0.6 (1)
Fracture, foot	0	0	1.3 (2)
Fracture, hip/femur	0	0	0.6 (1)
Fracture, other (pelvis, knee)	0	0.6 (1)	0.6 (1)
Fracture, rib	3.1 (5)	0.6 (1)	0.6 (1)
Fracture, wrist/arm	1.3 (2)	1.2 (2)	1.3 (2)
Number (%) of patients with one or more non-vertebral fracture adverse experiences excluding rib fractures	1.3 (2)	3.1 (5)	4.5 (7)

No significant differences between treatment groups were observed.
Note: Patients with more than one fracture adverse experience are counted only once in the overall total.

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APPENDIX 2

GIOP Non-Vertebral Fractures
Year 1 and Year 2 in Patients Entering Double-Blind Treatment Extension (N=203)

Treatment Group	Study #/ AN #	Gender/ Age	Study Day	Fracture Type	Precipitating Event
Placebo					
Year 1					
	083001/ 0682	F/ 76	300	rib, 7th, lt	no known trauma
	083001/ 0879	F/ 61	216	rib, 5th, 6th, 7th, lt	due to fall
	082010/ 0541	M/ 47	29	rib, 4th, lt	no known trauma
Year 2					
	083001/ 0604	F/ 72	452	stress, foot - L	no known trauma
	082007/ 0043	F/ 66	643 643	metacarpal, lt, 4th metacarpal, lt 5th	fell from hospital bed L
	082010/ 0538	M/ 37	581 405	rib, 7th, rt rib, 10th, rt	no trauma-pain started at time patient was shoveling snow patient trying to lift heavy load
ALN 2.5/10 mg[r]					
Year 2*					
	082012/ 0108	M/ 56	574 577	wrist, lt rib, rt	L fall- alcohol induced fall- alcohol induced

APPENDIX 2 (cont'd)

GIOP Non-Vertebral Fractures
Year 1 vs. Year 2 in Patients Entering Double-Blind Treatment Extension

Treatment Group	Study #/ AN #	Gender/ Age	Study Day	Fracture Type	Precipitating Event
ALN 5 mg					
Year 1					
	083001/ 0720	F/ 51	37	tibia, rt	stress fracture
	082002/ 0546	M/ 65	239	rib, 12th, lt	patient fell
	082005/ 0225	M/ 40	291	ulna, rt	patient was knocked while playing
Year 2					
	083001/ 1006	M/ 47	511	patella, rt	fell on rt knee
ALN 10 mg‡					
Year 1					
	083008/ 0647	F/ 59	141	wrist, lt	patient fell
	082016/ 0526	F/ 47	8	ankle, lt	patient tripped while walking
	082019/ 0052	M/ 57	91	rib, 3rd, 7th, 8th, rt.	patient fell

* There were no incidents of non-vertebral fractures in Year 1
‡ Patients received ALN 10 mg during Year 2
‡ There were no incidents of non-vertebral fractures in Year 2

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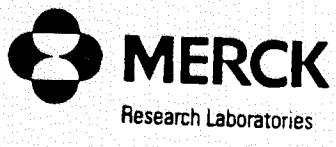
Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486-0004
Fax 610 397 2516
Tel 610 397 2905
215 652 5000

May 21, 1998



Solomon Sobel, M D., Director
Division of Metabolism and Endocrine
Drug Products, HFD-510, Room 14B04
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-560/S-012: FOSAMAX™
(Alendronate Sodium Tablets)

RESPONSE TO FDA REQUEST FOR INFORMATION

Dear Dr. Sobel:

Reference is made to the supplemental application cited above and to a facsimile communication from Mr. Randy Hedin (FDA) to Dr. Michelle Kloss (MRL) providing Agency comments on this supplemental application. With this submission, we are providing MRL's responses to these comments.

Please direct questions or need for additional information to Michelle W. Kloss, Ph.D. (610/397-2905) or, in my absence, Larry P. Bell, M.D. (610/397-2310).

Sincerely yours,

Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

Q:carnal\mk0217\giop\519resp

Attachment

FAX/Fed Ex #1

Desk Copies w/Attachment:
Mr. Randy Hedin, HFD-510, Room 14B-04 - Federal Express #1
Dr. Gloria Troendle, HFD-510, Room 14B-04 - Federal Express #1