

**8.1.5.4 Tertiary Objectives and Endpoints**

Tertiary efficacy endpoints are:

- ✓ LS BMD in all patients (PD, LD, and EX users),
- ✓ hip and total body BMD in all patients
- ✓ height loss measured at baseline and month 12,
- ✓ phalangeal BMD to evaluate the technology,
- ✓ progression of rheumatoid arthritis by radiograph

Tertiary objectives: To assess the effect of Alendronate on vertebral morphometric endpoints of height loss(stature by Harpenden stadiometer), fracture and clinical fractures (vertebral deformity, fractures, and clinically significant fractures). Also to assess the effect on radiographic disease progression and percent change in phalangeal bone mass in rheumatoid arthritis patients.

A tertiary endpoint was change in LS BMD across MN and US, but numbers were small, so analyses at each time point were done in "all patients."

"All patients" were:

permitted dose (PD=at least 7.5 mg prednisone equivalent/day), plus low dose (LD=less than 7.5 mg/d); plus

ex-users (EX=off glucocorticoids >4 consecutive weeks prior to visit 4 or later).

Ex-users remained in the study if they had a T score <-1 at entry.

**8.2 Results/Accounting and Baseline**

**8.2.1 Patient Accounting**

**8.2.1.1 Dropouts at or before month 12 (during original study)**

T9

560 patients were randomized to treatments in the original study.

9 were treated with open-label Alendronate:

6 due to error of the central BMD lab,

1 because investigator ordered it without permission

2 because they were fast bone losers.

208 patients (plus 9 open-label patients) continued into the extension study,

T9.

343 did not continue. 61%

84 discontinued before month 12. 25%

75 did not consent. 22%

87 had glucocorticoid use below 7.5 mg/day. 25%

97 were at sites that closed. 28%

T24,25

**8.2.1.2 Discontinuations from Extension Study**

(Months 12 to 24)

**Table 1 Reasons for Discontinuations**

	Placebo	5mg	10mg	2.5/10mg	
Clinical adverse experience	4	2	4	1	
Patient withdrew consent	3	3	2	1	
Investigator's or sponsor's discretion	0	0	0	0	
Protocol violation	0	1	1	2	
Lost to follow-up	2	2	0	0	
Glucocorticoid discontinued	3	4	4	3	
Other	1	3	0	0	
46 patients discontinued from EG	13	15	11	7	
171 patients completed the extension.					
At month 24, # in ITT analysis of LS	53	59	51	27	190
# in Per protocol	38	35	30	18	121
					<b>Totals</b>

8212 cont

**Table 2** Reasons that individual patients were not included in the per-protocol analysis:

Treatment	N	Placebo 61	5mg 63	10mg 55	2.5/10mg 29
Corticoid less than 7.5mg/d		7	13	12	7
Chg dose estrogen/testosterone		2	6	6	2
25 OH D low		1	0	0	0
No baseline data		0	1	0	0
No data in relative day range		9	8	4	0
Totals		19	28	22	9

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8.2.2 Baseline

8.2.2.1 Distribution of OG subjects to EG and to Subgroups in EG

The 9 open label extension patients were not included in the following table.

Table 3 Distribution of patients to EG, non-EG, treatment groups

Study T10,11,12 N	Original, combined 560*	Extension 208	EG 343	Non-extension 343
<b>Treatment group</b>				
Placebo	159=28%	61=29%		92=27%
2.5/10 mg	83=15%	29=14%		52=15%
5 mg	161=29%	63=30%		98=29%
10 mg	157=28%	55=26%		101=29%
<b>Gender, Menopausal status</b>				
Men	176=31%	66=32%		105=31%
Premenopausal	119=21%	52=25%		67=20%
Postmenopausal	265=47%	90=43%		171=50%
<b>Stratum</b>				
I New	191=34%	66=32%		121=35%
II Intermediate	118=21%	44=21%		73=21%
III Chronic	251=45%	98=47%		149=43%
<b>Glucocorticoid-Requiring Disease</b>				
Dermatologic	50=9%	22=11		27=8%
Gastrointestinal	30=5%	3=1%		25=7%
Pulmonary	67=12%	15=7%		50=15%
Renal	17=3%	12=6%		5=1%
Rheumatologic	380=68%	145=70%		231=67%
Other	16=3%	11=5%		5=1%

\*Includes the 9 open-label EX patients

T10,T11,T12

Table 3 Baseline Distribution to Extension, non-extension

#/Total in study=%	Original Study	Extension	Non-Extension
LS BMD T-score<-1	309/560=57%	112/208=55%	190/343=58%
T-score>-1	234/560=43%	93/208=45%	140/343=42%
<b>Vertebral fractures morphometric</b>			
# yes	463/560=83% 13	180/208=87% 2	275/343=80% 10
# unknown			
# no	84=15%	26=13%	58=17%
<b>History of ulcers or upper GI bleed</b>			
# No	503=90%	185=89%	309=90%
# Yes	57=10%	23=11%	34=10%

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### 8.2.2.2 Baseline characteristics

The extension study admitted patients from Jan 95, and last patient was in therapy until Dec 97 (US) or Jan 98.

The extension cohort was only 30 percent made up of patients continuing from the US study; the nonextension cohort was 50% from the US study.

Fast bone losers, based on their visit 6 BMD, were put on open-label 10 mg Alendronate and followed for safety.

82-90% of subjects were white.

Summary by the sponsor: "The extension cohort was representative of the original study cohort and, as expected, differed from the nonextension cohort only in that glucocorticoid use was greater and fewer patients had serious adverse experiences in the original studies."

#### 8.2.2.2.1 The Extension Population Baseline characteristics, # of patients

Table 4 Gender, Prior Use, Age

Treatment Groups:	Placebo	5mg	10mg	2.5/10mg	
Gender	Ns	61	63	55	29
Men		19	18	15	14
Premenopausal women		17	16	14	5
Postmenopausal women on estrogen		7	10	8	2
Postmenopausal women not on estrogen		18	19	18	8
Previous exposure					
Stratum 1		18	18	19	11
Stratum 2		13	13	13	5
Stratum 3		30	32	23	13
Age					
10-29years		4	4	5	0
30-39		10	8	4	5
40-49		14	14	15	3
50-59		6	9	3	9
60-69		17	20	8	5
>70		10	8	10	7

Table 5

#### 8.2.2.2.2 More Extension Population Baseline Characteristics

Treatment Groups:	Placebo	5mg	10mg	2.5/10mg	
Total # patients	61	63	55	29	
Fractures, Ca & D, and Stature					
Prior non-vert fractures	16	16	17	8	T14
Prior vertebral fractures	7	7	9	3	T15
% with vertebral fractures	11	11	16	10	T16
Baseline mean vitamin D	32.9	35.0	30.3	26.6	
Calcium intake	751	780	698	851 mg/day	
Baseline Height, mm	1633	1617	1626	1630 mm	
Baseline Weight, kg	70	71	72	69 kg	

8.2.2.2.3

Underlying disease	T17			
Rheumatic	42=69%	45=71%	37=67%	21=72%
Pulmonary	3=5%	3=5%	8=15%	1=3%
Gastrointestinal	1=2%	2=3%	0	0
Dermatologic	5=8%	8=13%	5=9%	4=14%
Renal	1=2%	4=6%	5=9%	2=7%
Other	9=15%	1=2%	0	1=3%

A higher proportion of subjects had pulmonary and GI diseases and a lower proportion had dermatologic, renal, and other diseases in the extension than in the non-extension cohort. In each cohort, the proportion with rheumatic diseases made up about 2/3 of the cohort. There was a history of GI ulcers or upper GI bleeding in 57=10% of 503 OG subjects, 23=11% of 185 EG, and in 34=10% of the 309 patients of the nonextension cohort. Intake of glucocorticoid was less in the nonextension cohort. Calcium intake was similar.

8.2.2.2.4 Secondary Diagnoses: T18

100% of the 208 extension patients had at least one secondary diagnosis. Of special interest are the Musculoskeletal and Digestive System Disorders. 84-85% of the 118 patients in the 5 and 10 mg Alendronate groups had secondary diagnoses of musculoskeletal disorders. The most common in placebo, 5 and 10 mg groups, respectively were: rheumatoid arthritis 31, 36 and 49%, lupus Erythematosus in 13, 16 and 4% and polymyalgia rheumatica in 16, 10 and 11%. The most common GI secondary diagnoses were acid regurgitation (6=10%, 9=14% and 7=13%), appendectomy (13=21%, 9=14% and 9=16%) and biliary surgery (5=8%, 11=18%, and 6=11%). Perhaps the drug increases appendectomies and decreases biliary surgery. Increase in abdominal pain might result in more appendectomies and/or more biliary surgery. It may have no effect on the frequency of the conditions.

More interesting were reflux esophagitis, duodenal and gastric ulcer.

**Table 6**

	Placebo	5mg	10mg	2.5/10mg	
N	61	63	55	29	T18
Reflux esophagitis	3=5%	1=2%	3=6%	0	
Duodenal ulcer	1=2%	3=5%	1=2%	2=7%	
Gastric ulcer	0	4=6%	0	3=10%	T19

All 208 randomized patients and the 9 open-label patients in EG had received prior therapies; 26% had taken anti-inflammatory drugs and 42% used gastrointestinal drugs T20

8.2.2.2.5 Concomitant use was common, with 41% taking anti-inflammatory and 59% gastrointestinal drugs.

**Table 7**

GI Drug use	Placebo	5 mg	10 mg	2.5/10 mg
Prior GI drugs	36=42%	24=38%	19=34%	13=42%
Concomitant GI drug	43=70%	32=51%	27=49%	19=65%

**8.3 Results/Efficacy, Per hypothesis and other BMD**

**8.3.1.1 Primary – LSBMD**

BMD analyses are last time patient was on PD. Both ITT and per protocol analyses were done. Also, analyses included both months 12 to 24 (OG) and Months 0 to 24(OG). "Baseline"= Month 0.

**Note:** The following two tables show BMD data from the two GIOP efficacy studies submitted in the original IND submission.

- ✓ They provide information on efficacy during the first year to compare with the effectiveness of the drug beyond one year.
- ✓ It is unfortunate that during the second year there was not a group of patients who were randomly removed from drug and observed on placebo or continued on drug. This is a problem because of the known tendency for patients who are put on corticosteroid therapy to lose bone rapidly during the first 6 months and to lose much less rapidly thereafter.
- ✓ I do not want to imply that BMD is the defining factor in osteoporosis, but since it is the thing that is measured commonly, and it is the factor used to identify candidates for drug therapy, it is the surrogate that must be addressed in drug review and labeling.
- ✓ Alendronate was modestly effective for restoring bone during the first year of treatment; it did very little during the second year, but there was no tendency to lose the density gained during the first year.
- ✓ Given a potentially toxic, and certainly unpleasant drug to take, it may be preferable in practice to discontinue alendronate after 12 months and continue calcium and vitamin D (particularly the latter) in adequate amounts after that time, and possibly to add HRT or raloxifene.

**Table 8 Original Study MN(082)BMD % Change from baseline and difference from placebo**

BMD change & difference	Placebo	Alendronate 2.5 mg	Alendronate 5 mg	Alendronate 10 mg	
Lumbar Spine	N: 75	78	78	76	OG T12
%Change	-0.72	0.70	2.03**	2.96**	
Difference		1.47*	2.65**	3.70**	
Femoral Neck	N: 75	71	78	79	OG T13
%Change	-0.69	0.26	2.24**	1.68**	
Difference		1.00	2.75**	2.33**	
Trochanter	N: 75	71	78	79	OG T14
Change	-0.25	1.20*	1.95**	3.33**	
Difference		1.35	2.09*	3.49**	
Total Hip	N: 52	48	56	54	OG T15
Change	-0.03	0.63	1.53**	1.70**	
Difference		0.58	1.46*	1.65**	
Total Body	N: 64	61	67	64	OG T16
Change	-0.13	1.01*	0.23	0.51*	
Difference		1.11	0.43	0.63	

**Table 9**

Original Study US (083) BMD Change from baseline and difference from placebo

BMD change & difference	Placebo	Alendronate 5 mg	Alendronate 10 mg	
Lumbar Spine	N 67	68	69	OG T12
%Change	-0.04	2.24**	2.78**	
Difference		2.17**	2.94**	
Femoral Neck	N 67	68	66	OG T13
%Change	-1.71*	-0.03	0.22	
Difference		1.49	1.80*	
Trochanter	N 67	68	66	OG T14
%Change	-1.27	0.05	1.84*	
Difference		1.14	3.25**	
Total Hip	N 54	53	55	OG T15
%Change	-0.91	0.28	0.66	
Difference		0.98	1.41	
Total Body	N 45	43	49	OG T16
%Change	0.12	0.57	1.02*	
Difference		0.31	0.97*	

Note: Tables 8 and 9 are similar (data from Original GIOP studies), but from MN and US studies, respectively. MN reported better results at all sites than US (exception: total body where all changes were less than 1%). For total hip, all changes were less than 2%. At Tr in US, 5 mg/d Alendronate yielded 1.14% increase in BMD compared to placebo. It is apparent that much of the improvement in BMD (compared to placebo) comes from a decline in BMD of the placebo group. It must be presumed that the treated groups would have lost BMD similar to the loss in the placebo group and that the difference between drug and placebo represents the true benefit of the drug. Efficacy of Alendronate for LS BMD during the first year of Alendronate treatment is substantial.

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**Table 10** BMD results at spine, hip, and total body for Original study and extension study

Per cent change	Placebo	5mg Alendronate	10mg Alendronate	2.5/10mg Alendronate
OG from month 0				
EG from month 12				
Lumbar Spine				
OG	-0.77 n=53	2.84** n=59	3.85** n=51	3.69** T29 n=27
EG	-0.18 n=53	0.95 n=59	0.52 n=51	2.81° T30 n=27
Femoral Neck				
OG	-2.93 n=53	0.11* n=57	0.61* n=51	0.43 T32 n=22
EG	-1.63 n=53	-0.69 n=57	-0.82 n=51	-0.53 T33 n=22
Trochanter				
OG	-1.21 n=53	2.16** n=57	3.91** n=51	1.73° T34 n=22
EG	-0.19 n=53	1.23 n=57	1.59 n=51	0.86 T35 n=22
Total Hip				
OG	-1.57 n=45	1.64** n=47	2.69** n=40	1.50* T36 n=19
EG	-0.66 n=45	0.85 n=47	1.45* n=40	0.71 T37 n=19
Total Body				
OG	-0.36 n=45	0.77* n=47	1.09 n=40	0.99 T38 n=19
EG	-0.15 n=40	0.26 n=44	0.01 n=41	0.07 T39 n=19

\*\*Different from placebo, p<0.001

\*Different from placebo, p=(various as shown in Table 9)

°Other significant differences:

- LS EX(2.5/10,10mg) p=0.013 **Note: 2.5/10>10mg**
- Trochanter EX(2.5/10,10mg) p=0.047

**Table 11** Placebo-Alendronate, difference months 0 to 24 and 12 to 24

Per cent change	Placebo	5mg Alendronate	10mg Alendronate	2.5/10mg Alendronate
OG from Mo 0				
EG from Mo12				
Lumbr Spine (LS)				
OG	-0.77	3.61**	4.62**	4.46 p<0.001
EG	-0.18	1.13	0.70	2.99 p=0.002
Femoral Neck (FN)				
OG	-2.93	3.04 p=0.002	3.54**	3.36
EG	-1.63	0.94	0.81	1.10
Trochanter (Tr)				
OG	-1.21	3.37**	5.12**	2.94
EG	-0.19	1.42	1.78 p=0.036	1.05
Total Hip (TH)				
OG	-1.57	3.21**	4.26**	3.07 p=0.02
EG	-0.66	1.51 p=0.03	2.11 p=0.005	1.37
Total Body (TB)				
OG	-0.36	1.13 p=0.025	1.45 p=0.009	1.35 p=0.042
EG	-0.15	0.41	0.16	0.22

The 2.5/10mg group is not considered in the following discussion, because the switch from an inadequate 2.5mg to the 10 mg dose produced a response similar to that of initiating therapy (like the first 48 weeks of the trials).

The placebo column in the above **Table 11** shows that bone loss by placebo patients during the first 48 weeks of the trial was greatest in the hip: % losses of 1.21- 2.93 in FN, Tr, and TH whereas only 0.77 and 0.36 are lost from LS and TB. Placebo subjects continue to take glucocorticoids and do not receive treatment other than calcium and vitamin D. Still, less than 1% of BMD was lost during this second month of Alendronate therapy except for FN, which lost 1.63%.

**Note:** Alendronate therapy resulted in increased BMD-placebo differences, and in significant differences from placebo although the losses in placebo patients were small. However, at 24 months the differences from placebo were not significant in LS, FN, or TB. The difference at Tr was significant only for those taking 10 mg of Alendronate. The difference from placebo was significant for TH at both doses. Although significant, the differences for Tr and TH were very small.

- ✓ The amount of bone loss observed in these trials is not persuasive that intervention other than calcium and vitamin D is warranted.
- ✓ The reason bone loss is decreased so much in the placebo group in the second year might be that when patients are put on corticoids, they lose bone rapidly during the first 6 months and much less rapidly thereafter. Benefit must be evaluated in the context of this expected improvement in the rate of bone loss.
- ✓ The effect relative to placebo is of the most importance.

The dose recommended for all but non-estrogen-using postmenopausal women is 5 mg/d. Ten mg/d is the dose proposed for postmenopausal women.

**Table 12** Observed mean BMD, & mean difference from placebo LS & FN

Mean adjusted for protocol, center, stratum												
Sources, T29 T30 T32 T33	Months 0, 12, 24 Observed mean G/cm <sup>2</sup>			Difference from placebo, Lumbar Spine %chg Adjusted Adjusted Mean Mean				Difference from placebo, Femoral Neck %chg Adjusted Adjusted Mean Mean				
	95% CI		LS	95% CI		LS	95% CI		FN	95% CI		FN
	Months:12-24		Months:0-24		Months:12-24		Months:0-24					
Placebo LS	0.95	0.95	0.94	1.14		3.70		0.93		3.17		
Placebo FN	0.72	0.71	0.70	-0.36,2.65		1.89,5.51		-0.48,2.34		1.19,5.15		
5 mg LS	0.94	0.95	0.96	0.86		5.02		0.98		4.03		
5 mg FN	0.74	0.75	0.74	-0.73,2.45		3.11,6.94		-0.50,2.46		1.95,6.12		
10 mg LS	0.96	0.99	1.00	2.94		4.42		0.24		1.23		
10 mg FN	0.75	0.76	0.75	1.12,4.76		2.37,6.46		-1.61,2.09		-1.48,3.95		
2.5/10 mg LS	0.90	0.91	0.93	2.94		4.42		0.24		1.23		
2.5/10 mg FN	0.74	0.74	0.74	1.12,4.76		2.37,6.46		-1.61,2.09		-1.48,3.95		

**Table 13** Percent of patients who achieved specified results and % minus placebo

	Change exceeded	Placebo, % of patients	5 mg dose		10 mg dose		2.5/10 mg	
			% of pts -pbo					
Lumbar spine T31	-6%	83	95	12	98	13	100	17
	-3%	70	90	20	90	20	96	26
	0%	45	78	33	86	41	93	48
	+3%	19	48	29	61	42	63	44
	+6%	8	27	19	37	29	19	11

This table includes the total response minus the placebo response (-pbo) in order to see what proportion of the responders might have obtained their response without taking drug. This is the drug-attributable effect.

1. **Note:** Differences between the percent of patients on placebo and the percent on drug who did at least as well as 0% bone density loss are the percent of patients whose maintenance of BMD can be attributed to drug.
- ✓ Using 0 change as a treatment response (no loss of bone from the lumbosacral spine), this result was obtained by 45% of placebo patients and 78% of the patients who took 5mg/d of Alendronate. This indicates that 45/78=58% of the patients who took 5 mg/d of Alendronate and had no lumbar spine bone loss, might have seen no bone loss if they were not on drug.
- ✓ Similar results might have been seen by 45/86=52% of 10 mg patients, and 45/93=48% of the 2.5/10 mg patients. In other words, about half of those who prevented bone loss with drug might have gotten the same response with placebo.
- ✓ 37% of 10 mg patients, 27% of 5 mg patients, and 8% of placebo patients achieved a 6% increase in LS BMD. Thus, 19 and 29% of those patients had a response that can be attributed to drug.

**LS BMD by Subgroups**

**8.3.1.1 By LSBMD at Baseline by Hologic/Lunar and T-scores**

**Table 14**

	T21	Pbo N=61	5mg N=61	10mg N=54	2.5/10mg N=29
LS BMD Mean g/cm <sup>2</sup> Hologic/Lunar		0.95/0.99	0.92/1.05	0.95/1.00	0.90/0.92
12mo T-score		-1.18	-1.24	-1.14	-1.66
#/% Patients T-score>-1		28/46	24/39	28/52	13/45
-2<T-score<-1		18/30	18/30	11/20	3/10
T-score<-2		15/25	19/31	15/28	13/45

**Table 15**

	PLACEBO	5 mg	10 mg dose
With T score <-2 SD, mean change in LS BMD	+0.41(N=13)	+3.15(N=19)	+ 5.02(N=14)
T score ≥-1 SD, mean change in LS BMD	-0.74(N=24)	+2.63(N=22)	+3.39(N=26)

There are 3 treatment groups in this study, which has a large dropout. Ns are very small.

**8.3.1.2 By past exposure to glucocorticoids**

At entry to the original GIOP study (OG), patients were stratified according to their current use and past exposure to glucocorticoids.

**Stratum I:** patients with the least total exposure during the 3 years prior to study entry (less than 4 months on current regimen and not more than 6 months total in past 3 years). These patients were considered "new" users, but limited prior glucocorticoid use was allowed. This stratum showed effects on lumbar spine bone mineral density (LS BMD) that were not distinguishable from the other two strata

**Stratum II:** 4-12 months on current regimen and not more than 18 months in 3 years;

**Stratum III:** more than 12 months current and more than 18 months in 3 years.

Change in BMD of the lumbar spine in OG is compared by tertiles of the cumulative glucocorticoid dose during 3 years prior to study. The patients are also stratified according to the amount of glucocorticoid use in the past 3 years.

**NOTE:** This is the closest to studying patients who are previously untreated with glucocorticoids that I find in this report.

The proposed Package Insert, Indications section says that Alendronate is indicated for prevention of GIOP.

Table 16

OG LS BMD change	Placebo N=47	5 mg alendronate N=49	10 mg alendronate N=56
Low tertile prednisone Equivalent 295-27500 mg	-0.89%	+1.54%	+3.53%
High tertile 4005 to 33160 mg	-0.01%	+2.16%	+2.88%
Stratum 1	-1.03%	+1.45%	+2.96%
Stratum 3	+0.15%	+2.52%	+2.84%

8.3.1.2 Prior glucocorticoid use was a determinant of placebo bone loss in that for placebo patients whose duration of glucocorticoid use was less than the median, 2.37 percent was lost, but for those above the median, 0.56% was gained. However, in Alendronate 5 and 10 mg groups (Ns 24-30), bone gained was the same (2.84) above and below the median in the 5 mg group, 3.36 for those below the median, 4.39 above the median in the 10 mg group. P values for subgroup by treatment interaction were >0.1. Numbers in the subgroups were very small, as few as 11. Stratum 1 placebo patients experienced larger BMD decreases and Alendronate groups had less increase from baseline than chronic users. For total hip, placebo patients below median or stratum 1 for duration of use lost 3.58 or 5.17 compared to 0.11 loss and 0.16 gain for the chronic users (Stratum 3). Treated patients (>median or stratum 3) gained 1.20 and 1.41 at total hip.

**Note:** Glucocorticoid use was a little higher in the placebo group (10.40 g) than in the Alendronate groups (8.65 and 8.43 g, p=0.09). When the average prednisone equivalent was > 20 mg (N=8) placebo patients lost 1.76, and Alendronate patients lost 0.57 (5 mg and N=7) or gained 6.71 (10 mg and N = 7). On the other hand, if the dose was < 20 mg the Alendronate patients gained 3.30 and 3.39.(N=45 for placebo and 52, and 44). The numbers are quite small, and I do not know why tertiles should vary so much in size, or why 20 mg/d was chosen for dividing the prednisone equivalent dose. The discrepancy in glucocorticoid use could bias the results by increasing the numbers obtained for placebo bone loss.

Differences between Stratum 1 and Stratum 3 were very small and not significant, although they tended toward greater results in the patients that had been on corticoids for the shortest time.

### 8.3.1.3 LS BMD By Gender and Menopausal Status

Table 17

	T46					
	N	Pbo	N	5mg	N	10 mg
Men	17	+0.65	17	+4.29	14	+6.29.
Women	36	-1.43	42	+2.25	37	+2.92.
Premenopausal women	11	-0.96	15	+0.75	12	+2.34.
Postmenopausal women with estrogen replacement	7	-3.98	9	+5.36	7	+1.40.
without estrogen	18	-0.73	18	+1.95	18	+3.91.

When placebo is subtracted from the above 5 and 10 mg group results, increases are as follows:

Gender and hormonal status	Table 18	N	Alendronate 5mg	Alendronate 10 mg	T46
Men		17	3.64	Ns 17	5.64
Women		36	3.68	42	4.35
Premenopausal women		11	1.71	15	3.30
Postmenopausal women on Estrogen		7	9.34	9	5.38
Postmenopausal women;no Estrogen		18	2.68	18	4.64

These subgroups, although small, indicate that men respond better than premenopausal or postmenopausal women, except for those taking estrogen.

8.3.1.4 By underlying disease Table 19

Overall population		-0.77	+2.84	+3.85
Polymyalgia Rheumatica/GCA	Ns 6-11	-3.95	+0.64	+3.48
Rheumatoid Arthritis	Ns 16-24	-0.62	+4.65	+2.99

8.3.2 Efficacy-Secondary

8.3.2.1 Chemical Markers

Urine N-telopeptide/Creatinine decreased in 5 and 10 mg groups approximately 60% by month 3 (2.5mg group by month 12) and remained decreased through month 24, T48.

Bone -Specific Alkaline Phosphatase decreased from baseline by 13-27% of baseline value. Decrease from baseline was significantly different from placebo for 5 and 10 mg. All groups except 2.5/10 mg increased between months 12 and 24, but remained below baseline. BSAP absolute values, declined to month 9 in drug groups (9-10 down to about 7), and then went up to about 7.5 to 8ng/mL, T49.

Decrease of total alkaline phosphatase was not significant. Numerically, the 10 mg group remained below placebo (96.6), but the other groups were all between 87.4 to 87.8, T50.

8.3.2.2 Stature

Height and weight were measured at months 3, 6, 9, 12, 18, and 24.

Height was assessed by [REDACTED]

The following table is from a table in the Case Report Tabulations of the Extension Study 082/083. The table is copied by retyping it. The reason for doing the typing is that I could not read the original. That means that I interpreted the printing as best I could but cannot guarantee it is correct. What I could not read was only the right hand end of the numbers.

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Stature (mm) Analysis of Change from Baseline

Table 20		Observed Means		Change from Baseline		
Treatment	N	Baseline	Month 24	Mean	SD	Median
Placebo	55	1635	1631	-3.71***	6.29	-3
Alendronate	138	1621	1619	-2.23	6.28	-1

Within-treatment test of change—0 \*\*\*p<0.001.  
None: Within test for the mean was L-test and for the median the signed-rank test.

Between-treatment test results:	Estimate <sup>1</sup> : -1.31 95% C.I.: 1-3.21, 0.59 P-value: 0.175
Interaction p-values:	Treatment-by-center interaction: 0.884 Treatment-by-study interaction: 0.504 Treatment-by-stratum interaction: 0.848

Treatment difference: Change in stature on placebo.  
Change in stature on Alendronate (adjusted for study, center and stratum effect).

"On average, both treatment groups decreased in stature, the mean change from baseline was -3.71 and -2.23 mm in the placebo and Alendronate groups, respectively. Although the mean decrease in stature was larger in the placebo group, the difference was not significant."

4.1.19 is reference to CANDA for OG. This quote is from the cited reference in the CANDA tabulations.

**Note:** The use of stature as an end-point seems to be logical, simple, and very desirable. It is easy to make non-invasive and fairly reproducible and accurate measurements of height. Loss of height is one of the principal symptoms/findings in osteoporosis. Logically, it should be highly correlated with spinal fracture. Spinal fracture is not always painful, but loss of height is almost always an undesirable outcome. However, height is always criticized as unsuitable. The only reason that it is inappropriate may be that it does not lead to a finding of drug efficacy. Perhaps it would be appropriate to listen to what this study and a similar one in PMO are saying – Drugs are not effective in prevention of decrease in height in PMO or GIO. An exception is the women who had incident fractures in Merck's PMO fracture study. At least for this GIO study, analyses are given of new symptomatic fractures, both vertebral and non-vertebral.

8.3.2.3 Serum Calcium geometric mean % change from baseline (month 0) to month 24 was (pbo, 5, 10, and 2.5/10mg groups) -0.6, -2.1, -2.2, and +0.6%, T51. For 5 mg/placebo change p<0.05, but for 10 mg dose/placebo change p=0.095. Serum phosphate mean changes were -0.4, -5.8, -0.5 and +3.7% change from baseline. None of these changes were significant, T52.

APPEARS THIS WAY ON ORIGINAL

8.3.2.4 Table 21 Fractures

Extension Study, Results at Month 24

# = % of Subjects with Fractures	Rx Dose		5 mg		10 mg		Combined doses	
	Placebo	Alendronate	Alendronate	Placebo	Alendronate	Placebo	Alendronate	
N Subjects	59	29	63	55	147	143	147 (143)	
EX SWK 48	3	EG 54	1	17%	1	10.7%	1=0.7%	
>wk 48	4	EG 54	3	5.1%	0	0	0	
V NV	15	EG 57	4	13.8%	8	12.7%	9=16.4%	
V	6	EG 57	3	10.3%	6	9.5%	6=10.9%	
SS	7	EG 57	0	0%	1	1.6%	1=1.8%	
NV	8	EG & 58	1	3.4%	4	6.3%	2=1.4%	
RIB	19	EG 58	1	3.4%	1	1.6%	3=2.0%	
NVR	10	EG 58	2	3.2%	3	4.8%	2=3.6%	
N OG & EG	11	EG 55	7	21%	13	18%	340	
V Fx	12	EG 55	8	6.0%	0	0	6=4.3%	
							8=2.4%	

To understand the above table: I refer to the 12 rows as 1, 2, etc. to 12.

Source tables (T54-T58) from NDA submission are listed in column under "Table".

- ✓ Row 1 indicates that the table is about fractures. It contains the doses of Alendronate for each column.
- ✓ Row 2 gives the number of subjects at each dose of Alendronate and heads a column containing the table numbers from which the data are obtained in the report of Extension results
- ✓ Rows 3 and 4 begin the numbers of new fractures and percent of N. First, before (<) and after (>) week 48. Note that each patient is counted only once, and if a patient had both rib and other non-vertebral fractures, only the non-rib fracture is counted.
- ✓ Row 5 has the number of all fractures, vertebral and nonvertebral. V+NV
- ✓ Row 6 is the number of vertebral fractures. V
- ✓ Row 7 is the number of patients with symptomatic vertebral fractures. SS
- ✓ Row 8 is nonvertebral fractures. NV
- ✓ Row 9 is the number of patients who had only rib fractures. RIB
- ✓ Row 10 is nonvertebral, non-rib fractures. NVR
- ✓ Row 11 is the number of subjects who completed the original study and entered the extension. NOG & EG
- ✓ Row 12 is the number of subjects with vertebral fractures, symptomatic or nonsymptomatic. V Fx

**Note:** Row 10 is the one that concerns me, because it indicates that more fractures occur during the first year of Alendronate administration in bones that contain a relatively large amount of cortical bone. That is, bones other than vertebrae and rib, and that this fracture rate exceeds the placebo rate. The actual numbers and rates are too few to know just what they mean, but it has been reported that in certain cases, Calcium seems to be taken from hip and used for spine