Table 22	Placebo		Alendron 2.5/10		Alendronate 5 mg		Alendrona10mg		AlendronCombnd	
56 Hormone E status Row 2	Males 0/19 PreMen1/17=5.9% PosM4/24=16.7%								1/47=2.1% 0/35=0 1/63=1.6%	
59 O&E	Total NV	10	2		7		8		17	
	R only	6	0		1		1		2	
Row 3	NVR	4	2		6		7		15	
60 pt/yr @risk E	4/104 pt-yrs		1/52.9		4/108		3/95.3		8/256.2	
61 Life table E	4/61	=6.6%							8/147	=5.7%
62 48wk E & 24mo	2/61 2	=3.2% =3.2%	0 1/29	=6.8%	5/63 1	=8.0% =1.6%	7/55 0	=9.1%	12/147 3	=8.3% =2.1%
63 Row 7 O&E	4/159	=2.6%	2/83	=2.4%	6/161	=3.6%	7/157	=4.4%	15/401	=3.6%
64 8 48wk & 24mo	2/159 2/61	=1.3% =3.3%	1/83 1/29	=1.2% =3.4%	5/161 1/63	=3.1% =1.6%	7/157 0/55	=4.5%	13/401 2/147	=1312% =1.4%
65pt-yr risk O&E	**4/178**	**2.2%**	**2/96**	**2.1%**	**6/183**	**3.3%**	**7/178**	**3.9%**	**15/457.0**	**3.2%**
66 Life tabl O&E	**4/159**	**=2.5%**							**15/401**	**=3.7%**

This table (10 rows.) is very much like the previous one, and needs only a little explanation.
O=original GIOP study. E = Extension study.
Source Tables from the NDA submission are listed at the left (**T56-T66**).
Row 4 includes # of fractures and total patient-years of study participation, separated by /.
Row 9 is patient-years of risk/% with fractures.
Line 10 in Table 21 has the number of patients with non-vertebral, non-rib fractures (in bold) and the percent of subjects with these fractures.
Line 9 in Table 22 has the number of patient-years and percent (number of these fractures per 100 patient-years of therapy).

Table 23 Listing all subjects with fractures, pooled, original and extension studies

Patient #	Gender/Age	Day	Fracture location	Event	T59 Underlying disease
Placebo					
682	F76	300	Rib	No trauma	Rheumatoid Arthritis
1879	F61	216	9 ribs	Fell	Polymyalgia Rheumatica
604	F72	452	Foot, stress	No trauma	
1016	F46	183	2 ribs	Kicked by a child	Rheumatoid Arthritis
833	M67	279	3 ribs	Bicycling	Giant Cell Arteritis
242	F23	314	Humerus	Skiing	Crohn's Disease
43*	F66	643	2 metacarpals	Fell from hosp bed	
541	M47	29	Rib	No trauma	Syst Lupus Erythematosus
538*	M37	581	Rib	No trauma, shoveling snow	
84		405	Rib	Tried to lift heavy load	
473	F59	52	Elbow	Trauma	Rheumatoid Arthritis
Total patients with NV fractures = 10, with only rib = 6, NV, NRib fractures = 4					
Alendronate 2.5 mg/10 mg					
184	M57	180	2 ribs & sternum	Fell	Nephrotic Syndrome
108*	M56	574	Wrist	Alcohol fall	
		577	Rib	Alcohol fall	
Total patients NV fractures = 2, only rib fractures =0, NV, NRib fractures = 2					
Alendronate 5 mg					
720	F51	37	Tibia, stress frx		Rheumatoid Arthritis
1006	M47	510	Patella	Fell on knee	
853	F76	212	Ankle	Fell on ice	Polymyalgia Rheumatica
1055	F75	114	Pelvis	Fell onto coffee table	Polymyalgia Rheumatica
546	M65	239	Rib	Fell	Pemphigus
225	M40	291	Ulna	Knocked while playing	Nephrotic Syndrome
33	F79	34	Humerus	Fell on ice	Polymyalgia Rheumatica
Total patients with NV fractures = 7, with only rib fractures = 1, with NV, NRib fractures = 6					
Alendronate 10 mg					
1107	F69	157	Knee, hairline	Knocked over by a dog	Sarcoidosis
647	F59	141	Wrist	Fell	Polymyalgia Rheumatica
1044	F58	270	Foot	No trauma	Rheumatoid Arthritis
1140	F32	280	Elbow	Fell	Syst Lupus Erythematosus
93	F71	142	Hip	No trauma	Polymyalgia Rheumatica
2401	F56	7	Foot, phalanx	Trauma	Asthma
526	F47	8	Ankle	Tripped while walking	Rheumatoid Arthritis
52	M57	91	3 ribs	Fell	Pemphigus
Total patients with NV fractures = 8, with only rib fractures = 1, with NV, NRib fractures = 7					

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8.4 Results/Safety

The following safety issues are identified as problems associated with other bisphosphonates and addressed for their relevance to Alendronate.

1. Calcium and **phosphate** homeostasis effects have been reported with bisphosphonates; increased skeletal pain, impaired fracture healing, atypical and focal osteomalacia, and mineralizing defects have been reported with etidronate; and mineralization defect and osteomalacia have been seen with i.v. pamidronate.
2. Severe **bronchoconstriction** in asthmatics with aspirin-sensitive allergy to diphosphonate have been seen with clodronate and etidronate.
3. **Rashes**, erythroderma, epidermal necrolysis, vasculitis, erythema multiforme have been reported with a variety of different bisphosphonates: pamidronate, tilutronate, clodronate, and sodium diphosphonate.
4. Acute **hearing loss, uveitis, iritis, episcleritis, scleritis, and optic neuritis** have been reported with pamidronate, etidronate, and risedronate.
5. Bisphosphonates, etidronate, tiludronate, and clodronate have been associated with acutely **impaired renal function**, transient proteinuria.
6. Glucocorticoids may increase the risk of upper GI adverse experiences. The combination of glucocorticoids and NSAIDs is especially likely to increase this risk, so **upper GI adverse events** were carefully evaluated, and investigators were instructed to question patients about adherence to proper dosing instructions.
7. Bone histomorphometry was done in programs for osteoporosis, Paget's and GIOP patients.
8. Fracture healing was studied in dogs and showed normal strength in healed bone. Nothing is said about time required for healing.

8.4.1 AE-collection and incidence

Investigators asked patients if there were any adverse events, but no events were suggested to the patients.

Adverse events were classified as **mild, moderate or severe** based on whether it was easily tolerated, uncomfortable enough to interfere with usual activity, or incapacitating, and serious if patient was discontinued from the study, and event was likely related to drug.

Sponsor's **definition of serious** includes that the AE is judged to be drug-related. Adverse events should be classified as to severity without regard to their supposed relationship to drug, because an investigator's guess about drug relatedness is not meaningful. Many times, an investigator will consider a particular adverse event-drug to be related based on whether it is known to cause the event. Relative information should be included. For instance if no drug was taken or if it had not been given prior to onset of AE, or if the AE was related to trauma or other circumstance, these facts should be mentioned. Sponsor must submit as serious, any event that is reasonably considered serious regardless of purported drug relationship.

If **corrected serum calcium** was received, no recalculation was done. If calcium was not corrected, Merck corrected as follows:

Corrected serum calcium (CU)=serum calcium (mg/dL)+0.8(4-albumin {g/dL}) & C.

Corrected, serum calcium (SI) = serum calcium (mmol/L)+ 0.02(40-albumin {g/L}).

In the **extension study** (ITT):

67 patients were **treated with placebo** for a mean of 610 days.
610 x 67=40870 patient-days of placebo.
40870/30=1362 patient –months on placebo.
40870/365=112 patient-years of placebo.
157 patients were **treated with Alendronate** for a mean of 624 days.
157 x 624 days is 97968 patient days on alendronate.
97968 /30 = 3266 patient-months of alendronate.
97968/365 =268 patient years of alendronate.
191/208 (92%) patients had at least one **clinical AE.**
47 (23%) had **serious adverse events**.
(4.3%) were **withdrawn due to clinical AE.**
3 (1.4%) had serious AEs that resulted in discontinuation from therapy.
2 patients **died**.

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Table 24 Selected Adverse Events

OG & EG	Original Studies 0-12 mo			Extension Studies 0-24 mo			
No/% patients	Placbo	5mg Al	10mgA	Placbo	5mg Al	10mgA	2.5/10
N=	159	161	157	61	63	55	29
Total events	126/79	129/80	131/83	55/90	59/94	51/93	26/90
Digestive Systm	50/31	43/27	52/33	28/46	20/32	21/38	6/21
Skin& appendag	34/21	28/17	42/27	22/36	24/38	18/33	10/35
Special sense	13/8	14/9	21/13	19/31	12/19	10/18	5/17
Extension only; Specific events number/percent							
Acid regurgitatn				3/ 4.9	1/1.6	5/9.1	0
Constipation				1/1.6	4/6.3	5/9.1	1/3.4
Gastritis				2/3.3	1/1.6	3/5.5	1/3.4
Refluxesophagit		P=.008		0	0	4/7.3	0
Hemic & Lymph				1/1.6	5/7.9	4/7.3	4/14
Anemia				1/1.6	4/6.3	2/3.6	1/3.4
Osteopenia				2/3.3	2/3.2	5/9.1	5/17
URI				9/15	11/18	11/20	3/10
Influenza				8/13	2/3.2	4/7.3	1/3.4
Bronchitis				12/20	8/13	4/7.3	0
Pneumonia				0	4/6.3	3/5.5	0
Cataract				5/8.2	5/7.9	4/7.3	2/6.9
Nervousness		P=.028		0	0	3/5.5	0
Asthma		P=.021		0	1/1.6	4/7.3	1/3.4
Vaginitis		P=.021		0	1/1.6	4/7.3	1/3.4
Abdominal pain	0	3/1.9	5/3.2	1/1.6	0	2/3.6	1/3.4
Acid regurgitatn	2/1.3	3/1.9	4/2.5	1/1.6	1/1.6	3/5.5	0
Melena	0	0	2/1.3	0	0	2/3.6	0
Gastric ulcer	1/0.6	0	0	1/1.6	0	1/1.8	0
Esophagitis	1/0.6	0	0	1/1.6	0	1/1.8	0

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Discontinuations

- ✓ 537 (**7.7%**) **placebo** and 719 (**7.4%**) **Alendronate** patients) discontinued participation in the **13 double-blind trials** because of adverse reactions. 187 and 205 of these reasons for withdrawal were classified as **serious.**
- ✓ 324 placebo and 296 alendronate withdrawals were from the VFS and CFS sections of the **FIT study (051)**. These population totals represent **46 and 33% of the total patients** in these 13 studies. 537 and 719 **discontinuations are 7.7 and 7.4%** 0f the total populations (placebo and drug).
- ✓ When the **12 studies other than FIT** are grouped and looked at together, this total population minus the 3223 and 3236 patients in FIT totals 3795 placebo and 6514 Alendronate-treated patients. The **213 placebo and 423 Alendronate dropouts are 5.6% of placebo and 6.5%** of drug patients in the study population.

Note: Possible explanations for the FIT study failing to observe severe GI events reported by patients and physicians in practice:

- ✓ From the large number of reports we have seen on GI events, it is not easy to believe that the blinding was completely successful. It may be obvious to many of the women that they have been taking more than a placebo.
- ✓ The FIT study probably recruited more recently than most of the other studies, by which time, exclusions (mainly for prior GI disease) and instructions for taking and remaining upright may have been enforced more stringently.
- ✓ Criteria for hospital admissions have become more strict, and hospitalization is one of the criteria for designating an event serious. As a result, hospitalization is not as likely for events that patients and physicians consider serious, such as events that involve large GI bleeds but are treated as outpatients with endoscopy, fluids, drugs, and blood.

Caution: To separate the FIT and non-FIT populations, I got the number of subjects studied in FIT from a different table. It is likely that the population total was different from that represented here.

Laboratory Events

The number of serious laboratory adverse experiences was low and depended on the number of tests being performed. Incidences did not vary between drug and placebo groups. The number of serious AEs seemed to be less than withdrawals for AEs.

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Gastrointestinal Adverse Events

The incidence of GI events was generally slightly greater in patients on higher doses. In 035/037 the rates (% of patients with the specified event) are presented in the following table for 5, 10, and 20 mg during the first 3 years. The 20 mg subjects were switched to 5 mg during year 3.

Table 34 **V12P110T60 and V12P111T61**

035/037 and 054 Original Studies (Years 1-3): % of subjects with events								
Events	Placebo		5 mg dose		10 mg dose		20/5 mg dose	
	035/37	054	035/7	054	035/7	054	035/7	054
Total UGI Events	39	40	37	35	43	42	40	37
Serious GI Evnts	0.8	2.2	1.0	0	0.5	1.1	3.0	2.2
Withdrew for AE	2.0	1.1	3.5	2.3	1.0	3.4	2.0	5.4
Gastric duodenal	0.5	2.2	0	0	1.5	1.1	2.5	0
Serious Event	0.3	0	0	0	0.5	0	0	0
Esophageal Event	2.0	2.2	2.0	1.2	4.6	4.5	6.5	0
Serious Event	0.3	2.2	0	0	0	0	0.5	0
Total	**44.9**	**49.5**	**43.5**	**38.4**	**51.1**	**51.7**	**54.5**	**44.2**

The incidence of patients with one or more upper GI adverse experiences ranged from 5.8 to 47.5% across all treatment groups. Serious events were less common, but comparable across groups. GI AEs in 082/083 (**V12P109T59**). The following discussion includes totals from both studies (082 &083), placebo, 5 and 10 mg Alendronate-treated patients, but not 2.5 mg patients. 5 and 10 mg subjects are combined. Year 1 (48 weeks) is presented alongside year 2 results. Upper GI AEs, total, serious, and resulting in withdrawal are presented with gastric and duodenal PUBs total and serious, and esophageal total and serious.

Table 35 **GI Adverse events in GIOP 5 and 10 mg only combined** **V12P109T59**

Table GI AEs	082/083, year 1		082/083, year 2	
Treatment	Placebo	Alendronate	placebo	Alendronate
Total Ns	159	318	61	118
Total UGIAEs	26=16%	70=44%	19=31%	30=51%
Serious	2=1.3%	2=1.3%	3=4.9%	1=1.8%
withdrew	0	3=1.9%	0	1=1.8%
Abdom pain	8=15%	24=15%	9=15%	10=17%
Acid regurgit	4=2.5%	14=8.8%	3=4.9%	6=11%
Dyspepsia	3=1.9%	7=4.4%	2=3.3%	4=6.8%
Nausea	6=3.8%	11=7%	3=4.9%	6=10%
Vomiting	2=1.3%	1=0.6%	1=1.6%	0
GsDuo PUBs	2=1.3%	5=3.1%	1=1.6%	4=7.3%
Serious	0	1=06%	0	1=1.8%
Esophageal	4=2.5%	8=5%	3=4.9%	9=16%
Serious	0	0	0	0

Table 36 GI Adverse events in postmenopausal osteoporosis, GIOP V12P110T60

Table GI AEs	082/083,	year 1	035/037,	years 1-3
Treatment	placebo	Alendronate	placebo	Alendronate
Total Ns	159	318	397	398
Total UGIAEs	26=16%	70=22%	155=39%	158=40%
Serious	2=1.3%	2=0.6%	3=0.8%	3=0.8%
withdrew	0	3=0.8%	8=2.0%	9=2.3%
Abdom pain	8=15%	24=7.5%	55=14%	76=19%
Acid regurgit	4=2.5%	14=4.4%	24=6.0%	17=4.3%
Dyspepsia	3=1.9%	7=2.2%	38=9.6%	40=10%
Nausea	6=3.8%	11=3.5%	59=15%	42=11%
Vomiting	2=1.3%	1=0.3%	22=5.5%	25=6.3%
GsDuo PUBs	2=1.3%	5=1.6%	2=0.5%	3=0.8%
Serious	0	1=03%	1=0.3%	1=0.3%
Esophageal	4=2.5%	8=2.5%	8=2.0%	9=2.3%
Serious	0	0	1=0.3%	0

These 4 tables, 2 above and 2 below, were an attempt to look at the rates for various events. Number of events is given and followed by rate. Where it says %, the rate is per 100 patients, and where it says "by patient years of exposure", the rate is per 10,000 patient years. However, the patient years are obtained from **V12P22T3** and will not represent the specific population on which the rates in these tables are calculated.

Below, Numbers after = are the **number of events per 10,000 patient years.**

Comparison of GIOP and PMO Using Patient-Years Exposure V12P22T3

Table 37 GI AEs	082/083,	year 1	035/037,	years 1-3
Treatment	placebo	Alendronate	placebo	Alendronate
Total Pt-yrs	182	462	1040	2916
Total UGIAEs	26=1429	70=1515	155=1490	158=542
Serious	2= 110	2= 43	3= 29	3= 10
Withdrew	0	3= 65	8= 77	9= 31
Gastroduode PUBs	2= 110	5= 108	2= 19	3= 10
Serious	0	1= 22	1= 9.6	1= 3
Esophageal	4=220	8= 173	8= 77	9= 31
Serious	0	0	1=9.6	0

Comparison of GI AEs (NDA studies plus FIT) by Patient-Years of Exposure Table 38
V12P98T53 and V12P110T60

	051, years 1-3		035/037, years 1-3	
Treatment	placebo	alendronate	Placebo	Alendronate
Total Pt-yrs	10622	10642	1040	2916
Total UGI AEs	1490=1403	1536=1443	155=1490	158=542
Serious	59= 56	65= 61	3= 29	3= 0
Withdrew	88= 83	102= 96	8= 77	9= 1
Gastroduode PUBs	67= 63	60= 56	2= 19	3=10
Serious	19= 18	16= 15	1= 96	1= 3
Esophageal	303=285	322= 303	8= 77	9= 1
Serious	5= 5	11= 10	1= 96	0

Numbers after = are the number of events per 10,000 patient years.

Bone Safety Across Studies

Clinical Fracture Endpoints of Protocol 051 include symptomatic vertebral fractures, non-vertebral fractures, and combined all clinical fractures.

1. **Vertebral** **Fracture Cohort** 1005 placebo &1022 drug = 2027
2. **Clinical** **Fracture Cohort** 2218 placebo & 2214 drug = 4432
3. **Osteoporotic Clinical Fracture Cohort** 1521 placebo & 1545 drug= 3066
4Combined Osteoporotic Cohort 2526pbo&2567drug=vertfx +osteoclinical fracture =1+3 = 5093
5 **Combined** **Cohort** 3223 pbo & 3236 drug = vertfx + clin fx=1+2=6459

Three groups of patients and **2 combination** groups were specified:
1) Vertebral Fracture Cohort
2) Clinical Fracture Cohort
3) Osteoporotic Clinical Fracture Cohort
4) Combined Osteoporotic Cohort
5) Combined Cohort

For each cohort, **3 kinds of fractures** are counted:
1) Clinical fractures
2) Nonvertebral fractures
3) Symptomatic vertebral fractures

The **15 resulting cohorts**/categories are split into 30 to examine **placebo and drug categories** separately.

The vertebral fracture cohort had 182 fractures/1005 placebo patients (18%) and 141/1022 drug patients (14%), giving a relative risk of 0.74 with 95% CI 0.59, 0.92, p0.007.
The vertebral fracture cohort had 147 fractures/1005 pbo pts (15%) and 123/1022 drug patients (12%) RR 0.81, CI 0.64,
The data in the following table are from Protocol 051. One of the **criteria for enrolling** in this study was a **femoral neck BMD** of ≤0.68 g/cm^2, which was thought to correspond to a **T-score of –2.0**. All BMD measurements were made using Hologic QDR-2000 dual-energy x-ray absorptiometry (DXA) instruments. It was later (after the study was fully enrolled but before it was unblinded) found that using this instrument **yielded T-score estimates substantially lower than values derived from the third US NHANES-III**. The BMD used actually corresponds to a T score of approximately –1.6, resulting in approximately 31% of the enrolled patients being **osteopenic rather than osteoporotic**. Separate analyses were made of those who met the original criteria. Other criteria included age 55-80, and at least 2 years postmenopause. Vertebral fracture was not an entry criterion, and women who had such fractures at baseline were entered into a **3-year Vertebral Fracture Study** (VFS), while those who had no vertebral fracture at baseline were entered into **a 4-year Clinical Fracture Study (CFS)**.

Table 39 V12P122 T67	Vertebral fracture cohort	Clinical fracture cohort	Osteoporoti clinical fracture cohort	Combined osteoporoti cohort	Combined cohort
All Clinical Fractures					
Pbo	182/1005	312/2218	246/1521	428/2526	494/3223
%	=18%	=14%	=16%	=17%	=15%
alndronate	141/1022	272/2214	199/1545	340/2567	413/3236
%	=14%	=12%	=13%	=13%	=13%
RR	0.74	0.86	0.78	0.76	0.82
95%CI	0.59,0.92	0.73,1.01	0.65,0.94	0.66,0.88	0.72,0.93
P	0.007	0.072	0.010	<0.001	0.002
Nonvertebral Fractures					
Pbo	147/1005	294/2218	228/1521	375/2526	441/3223
%	=15%	=13%	=15%	=15%	=14%
alndronate	123/1022	261/2214	191/1545	314/2567	384/3236
%	=12%	=12%	=12%	=12%	=12%
RR	0.81	0.88	0.81	0.81	0.86
95%CI	0.64,1.03	0.74,1.04	0.67,0.99	0.70,0.94	0.75,0.98
P	0.082	0.133	0.035	0.006	0.026
Symptomatic Vertebral Fractures					
Pbo	50/1005	27/2218	25/1521	75/2526	77/3223
%	=5%	=1.2%	=1.6%	=3%	=2.4%
alndronate	24/1022	18/2214	15/1545	39/2567	42/3236
%	=2.3%	=0.8%	=1.0%	1.5%	=1.3
RR	0.46	0.66	0.59	0.50	0.53
95%CI	0.28,0.75	0.36,1.20	0.3,1.10	0.34,0.74	0.36,0.77
P	0.002	0.178	0.102	<0.001	<0.001

I note that the two categories of "symptomatic" and "nonvertebral" fractures do not add up exactly to the number of events in the category of "all clinical" fractures; this is probably because some patients had both **"symptomatic vertebral" and "nonvertebral fractures".**

The combined osteoporotic cohort is those women who met the original criterion of T-score <-2 in the VFS plus those who met this criterion in the CFS. The Combined cohort is those in the VFS plus those in the CFS. The primary endpoint in VFS was development of new vertebral fracture, and a secondary endpoint was all clinical fractures. The primary endpoint in CFS was any clinical fracture, and a secondary endpoint was new vertebral fractures. **Using "All Clinical Fractures" for the endpoint**, and treating the cohort for 3-4 years depending on whether it is the vertebral or non-vertebral cohort would **decrease the fractures** as follows:

- ✓ Vertebral fracture cohort — 2 per 3 years in 1022 pts
- ✓ Clinical fracture cohort — 4 per 4 years in 2214 pts
- ✓ Osteoporotic clinical fracture cohort — 4 per 4 years in 1545 pts
- ✓ Combined osteoporotic cohort — 4 per 3-4 yrs in 2567 pts
- ✓ Combined cohort — 2 per 3-4 yrs in 3236 pts

Note:The differences in rates between placebo and Alendronate per 100 patient years is extremely small. % used in **table 39** is the number of fractures sustained in 100 women treated for 3 or 4 years.

In this same study, **specific fracture sites** (hip, wrist, and other than spine, hip, or wrist) were looked at in the same cohorts.

In **table 40**, similar analysis for site of fractures is presented to facilitate comparison of effects on these sites with the previous vertebral and nonvertebral results.

Note: It is expected that effects will be less in absolute terms in locations other than spine, but these are all symptomatic fractures.

10 Table 40 **V12P122T67 and V12P124T68**

Cohorts	VF cohort		CF cohort		OCF cohort		CO cohort		Combined	
Hip										
Difference	1.1	4.3	0.2	1.8	0.4	3.3	0.6	3.7	0.5	2.5
Pbo – drug		0.74		0.86		0.78		0.76		0.82
Relativ risk	0.49		0.79		0.71		0.60		0.64	
p-value	**0.047**		0.44		0.297		0.034		*0.059*	
Wrist										
Difference	1.9		-0.5		-0.1		0.7		0.2	
Pbo-Drug										
Relativ risk										
p-value	0.52		1.19		1.04		0.82		0.94	
	0.013		0.277		0.834		0.194		0.666	
Other										
Difference	-0.1		2.0		2.6		1.5		1.4	
Drug – pbo										
Relativ risk	1.01		0.79		0.76		0.85		0.86	
p-value	**0.002**		0.018		**0.017**		*<0.071*		*<0.058*	

The number in the **upper left of each cell (table 40)** is the **difference between placebo and drug** effects for that site and cohort. The number in the upper right of each cell in the top row of the table (hip) is the difference between drug and placebo for that cohort and "all clinical fractures." The second number in the upper right of the hip display is the **relative risk for "all clinical fractures"** in the previous table. I was looking for a result that indicated whether similar patients get good results with different sites, and with vertebral bone.

Note: The best results (in difference from placebo) for clinical fractures appears to be for "all clinical" fractures in women who have the most severe osteoporosis (previous table 4.3, 3.3, and 3.7 in the VF, Osteoporotic CF, and combined osteoporotic). The difference from placebo is numerically negative, and RR is greater than 1 in certain wrist and "other" endpoint results. The relative risk is greater than 1 for wrist at clinical fractures and osteopenic clinical fractures cohorts. The relative risk is smallest for hip and wrist fractures in vertebral fracture cohort. **The results indicate** substantial benefit for preventing asymptomatic vertebral fractures but not for preventing fractures in other bones.

Note: At the "other" sites, there are a few **more fractures in ankles of patients on drug** than in ankles of patients on placebo, but fractures at all other sites are slightly more common in patients on placebo. The only site at which there appears to be a great difference is the spine (**120 in patients on placebo and 46 in patients on alendronate**). The only study designed to determine efficacy of Alendronate for reducing the risk of fractures is 051 (FIT). Considering the Combined Cohort and All Clinical Fractures, there were 3223 placebo-treated and 3236 Alendronate patients. There were 494 women with fractures in the placebo group, 15.3%, and 413 in the Alendronate group, 12.8%. This is a difference of 2.5%. Thus, **without drug, 84.7% of the women were without fractures for the 3 years**. Page 127 of this volume says, "The pooled analyses showed **highly statistically significant and clinically meaningful reductions in relative risk** for any clinical fracture of 18% in the Combined Cohort." The study was large, and findings often (10 of 15) statistically significant. This is a **reduction of 2.5 in the number of fractures per 100 women** when Alendronate was given for 3 years to a group of women with osteoporosis severe enough that they had **spinal fractures at baseline**. The benefit in fractures prevented is very small such that even a very low incidence of severe GI adverse events should lead to a careful consideration of who should accept the risks and receive this drug.

Fractures in the GIOP studies 082/083 159 patients were treated with placebo and 318 with 5 or 10 mg/day of Alendronate for 1 year. I will not include the 2.5mg group which was not effective and was changed to 10 mg for the second year. **Ten of the fractures in the placebo and 10 of those in the Alendronate group were vertebral clinical fractures, and 5 and 2 were rib fractures.**

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Number of patients with Fractures during year 1 and year 2 of the GIOP studies

Protocol	Orig GIOP 082/083y1		Extension 082/083 y2		Total 082/083 y1+2	
Treatmnt	Placebo	Alendro	Placebo	Alendro	Placebo	Alendro
Ns	159	318	61	118	61	118
Total Fx	16=10%	23=7.2%	9=15%	7=5.9%	15=25%	17=14%
Vertebral	10=6.3%	10=3.1%	6=9.8%	6=5.1%	10=16%	12=10%
Non-vert	7=4.4%	14=4.4%	3=4.9%	1=0.9%	6=09.8%	7=5.9%
Non-v-nonrib	2=1.3%	12=3.8%	2=3.3%	1=0.9%	2=3.3%	5=4.2%