

Study Number	AN	Sex/Age	Drug/Total Daily Dosage at Time of AE	Study Day	Adverse Experience	Duration	Intensity	Drug Relation	Therapy Discontinuation
Placebo/Alemdronate 10 mg (Cont.)									
037015	2241	F/62	Off D 1 day/10 mg	1635	Death	1 day	Severe	Def not	NA
037016	2388	F/60	Off D 1 day/10 mg	1635	Respiratory failure	1 day	Severe	Def not	Yes
037016	2423	F/60	On/10 mg	1098	Melanoma	1 day	Moderate	Prob not	No
037018	2570	F/78	On/10 mg	1738	Suffocates	3 hours	Severe	Prob not	No
			Off D 1 day/10 mg	1777	Death	1 day	Severe	Def not	NA
			Off D 1 day/10 mg	1777	Death	1 minute	Severe	Def not	Yes
Alemdronate 5 mg									
035001	0336	F/74	On/5 mg	1286	Neoplasm, intestinal, malignant	10 days	Severe	Def not	No
035001	0355	F/82	On/5 mg	1098	Fracture, hip, rt	29 days	Severe	Def not	No
			On/5 mg	1497	Heart failure	7 days	Moderate	Def not	No
035003	0165	F/71	On/5 mg	1798	Blood pressure decreased	2 days	Moderate	Def not	No
035005	0092	F/68	Off D 1 day/5 mg	1442	Neoplasm, gallbladder	11 days	Moderate	Prob not	No
035007	0121	F/63	On/5 mg	1259	Neoplasm, breast, malignant	31 day	Mild	Def not	No
			On/5 mg	1290	Neoplasm, breast, malignant	2 days	Severe	Def not	No
035007	0137	F/77	On/5 mg	1548	Neoplasm, skin, malignant	85 days	Mild	Def not	No
			On/5 mg	1739	Neoplasm, skin, malignant	1 day	Mild	Def not	No
035007	0142	F/55	On/5 mg	1472	Neoplasm, skin, malignant	1 day	Mild	Def not	No
035009	0279	F/60	On/5 mg	1323	Neoplasm, skin, malignant	1 day	Mild	Def not	No
035009	0281	F/65	Off D 1 day/5 mg	1421	Neoplasm, breast, malignant	17 days	Severe	Def not	No
035012	0451	F/73	On/5 mg	1575	Cholelithiasis	17 days	Severe	Def not	No
035012	0464	F/52	On/5 mg	1187	Neoplasm, skin, malignant	80 days	Moderate	Def not	No
035016	0362	F/61	Off D 1 day/5 mg	1065	Myocardial infarction	30 minutes	Severe	Def not	No
035016	0371	F/69	On/5 mg	1273	Anemia	7 days	Severe	Prob not	No

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Alendronate 5 mg (Cont.)									
035016	0384	F/67	D/5 mg	1355	Fracture, femur, R	117 days	Severe	Def not	No
			D/5 mg	1620	Neoplasm, skin, malignant	1 day	Mild	Def not	No
			D/5 mg	1620	Fracture, hip, R	67 days	Severe	Prob not	No
035017	0049	F/68	D/5 mg	1578	Bronchitis, chronic	231 days	Severe	Def not	No
			D/5 mg	1632	Carcinoma, squamous cell, metastatic	177 days	Severe	Def not	Yes
			Off D 175 days/5 mg	1807	Pneumonia	2 days	Severe	Def not	No
			Off D 176 days/5 mg	1808	Death	1 day	Severe	Def not	NA
035018	0292	F/71	Off D 1 day/5 mg	1796	Hypokalemia	15 days	Severe	Def not	No
			Off D 1 day/5 mg	1796	Asthma	15 days	Severe	Def not	No
037003	2315	F/59	Off D 1 day/5 mg	1174	Cardiac arrest	1 day	Severe	Def not	Yes
			Off D 1 day/5 mg	1174	Death	1 day	Severe	Def not	NA
037009	2551	F/61	D/5 mg	1491	Tinnitus	4 days	Mild	Def not	No
037010	2367	F/59	D/5 mg	1391	Myocardial infarction	24 days	Severe	Def not	No
037011	2007	F/50	D/5 mg	1236	Headache	9 days	Severe	Prob not	No
			D/5 mg	1236	Vomiting	9 days	Severe	Prob not	No
037015	2322	F/69	Off D 1 day/5 mg	1405	Cholecystitis	38 days	Severe	Def not	No
			Off D 1 day/5 mg	1405	Abscess	38 days	Severe	Prob not	No
037019	2589	F/58	D/5 mg	1345	Lymphangitis	10 days	Severe	Def not	No
Alendronate 10 mg									
035001	0353	F/68	D/10 mg	1215	Pneumonia	16 days	Severe	Def not	No
035002	0192	F/61	D/10 mg	1111	Epistaxis	4 days	Moderate	Def not	No

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Alendronate 10 mg (Cont.)									
035003	0160	F/64	D/10 mg	1129	Neoplasm, intestinal, malignant	27 days	Severe	Prob not	Yes
035005	0117	F/67	Off D 1 day/10 mg	1341	Infection, respiratory, upper	3 days	Moderate	Def not	No
035006	0001	F/72	D/10 mg	1782	Neoplasm, lung, malignant	19 days	Severe	Prob not	Yes
035010	0487	F/63	Off D 3 days/10 mg	1280	Neoplasm, ovary, benign	1 day	Moderate	Prob not	No
035010	0500	F/70	Off D 1 day/10 mg	1633	Arthritis	1 day	Mild	Prob not	No
035012	0469	F/56	D/10 mg	1617	Fracture, leg, multiple	86 days	Severe	Def not	No
035015	0317	F/61	Off D 1 day/10 mg	1788	Aneurysm, aortic	1 day	Severe	Def not	No
035017	0060	F/62	D/10 mg	1173	Neoplasm, skin, malignant	1 day	Severe	Def not	No
035018	0297	F/75	D/10 mg	1602	Rectocele	71 days	Mild	Prob not	No
			D/10 mg	1602	Urinary incontinence	205 days	Mild	Prob not	No
035018	0328	F/67	D/10 mg	1509	Neoplasm, skin, malignant	21 days	Mild	Prob not	No
			D/10 mg	1637	Urinary incontinence	41 days	Moderate	Prob not	No
037001	2129	F/70	Off D 1 day/10 mg	1499	Pain, hip	2 days	Severe	Prob not	No
037001	2344	F/64	D/10 mg	1655	Pain, abdominal	2 days	Severe	Prob not	No
037004	2501	F/64	D/10 mg	1504	Occlusion, aorta	7 days	Mild	Def not	No
			D/10 mg	1511	Occlusion, aorta	7 days	Moderate	Def not	No
037008	2132	F/61	D/10 mg	1428	Fracture, femur, neck, R	17 days	Severe	Def not	No
			D/10 mg	1518	Valvular disorder	10 days	Moderate	Def not	No
037010	2353	F/56	D/10 mg	1568	Neoplasm, anal/rectal, malignant	141 days	Moderate	Def not	No
037010	2359	F/76	D/10 mg	1651	Pain, back	18 days	Moderate	Def not	No
037014	2336	F/37	Off D 1 day/10 mg	1286	Cystocele	2 days	Mild	Def not	No
037016	2189	F/64	Off D 1 day/10 mg	1799	Cholelithiasis	1 day	Severe	Prob not	No

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Alendronate 20/5 mg									
035001	0348	F/64	D/5 mg	1802	Mass, ovarian	5 days	Severe	Def not	No
035004	0061	F/52	D/5 mg	1482	Rectocele	108 days	Moderate	Def not	No
			D/5 mg	1482	Cystocele	108 days	Moderate	Def not	No
035005	0095	F/64	D/5 mg	1736	Obstruction, carotid artery	3 days	Moderate	Def not	No
035007	0125	F/70	Off D 1 day/5 mg	1752	Osteoarthritis, hip	6 days	Severe	Def not	No
035009	0276	F/58	D/5 mg	1728	Neoplasm, skin, malignant	32 days	Mild	Def not	No
035009	0286	F/72	Off D 1 day/5 mg	1625	Reflux esophagitis	115 days	Moderate	Def not	No
035011	0423	F/57	Off D 10 days/5 mg	1404	Chronic obstructive pulmonary	10 days	Severe	Prob not	Yes
			Off D 10 days/5 mg	1404	Heart failure	10 days	Severe	Prob not	Yes
			Off D 10 days/5 mg	1404	Embolism/infarction, pulmonary	10 days	Severe	Prob not	Yes
035012	0455	F/70	D/5 mg	1372	Hernia, inguinal	4 days	Moderate	Def not	No
			D/5 mg	1688	Neoplasm, skin, malignant	106 days	Moderate	Def not	No
035013	0410	F/66	D/5 mg	1515	Displacement, disc, intervertebral	48 days	Severe	Def not	No
035015	0303	F/56	D/5 mg	1278	Uterine disorder	109 days	Moderate	Def not	No
035016	0367	F/58	D/5 mg	1339	Neoplasm, skin, malignant	68 days	Mild	Def not	No
035018	0300	F/72	D/5 mg	1688	Neoplasm, skin, malignant	16 days	Moderate	Prob not	No
037003	2319	F/60	D/5 mg	1759	Corticoadrenal insufficiency	5 days	Severe	Prob not	No
			D/5 mg	1820	Corticoadrenal insufficiency	6 days	Severe	Prob not	No

Study Number	AN	Sex/Age	Drug/Total Daily Dosage at Time of AE	Study Day	Adverse Experience	Duration	Intensity	Drug Relation	Therapy Discontinuation
Alendronate 20/5 mg (Cont.)									
037005	2465	F/54	D/5 mg	1190	Pain, abdominal	42 days	Severe	Def not	No
			D/5 mg	1190	Distention, abdominal	42 days	Severe	Def not	No
			D/5 mg	1190	Neoplasm, malignant	42 days	Severe	Def not	Yes
037008	2173	F/76	D/5 mg	1113	Pneumonia	19 days	Mild	Def not	No
037009	2556	F/55	D/5 mg	1382	Osteoarthritis	2 days	Moderate	Def not	No
037012	2153	F/66	D/5 mg	1770	Rectocele	2 days	Moderate	Def not	No
			D/5 mg	1770	Cystocele	2 days	Moderate	Def not	No
037012	2167	F/60	D/5 mg	1341	Neoplasm, skin, malignant	39 days	Mild	Def not	No
			D/5 mg	1519	Neoplasm, skin, malignant	50 days	Mild	Def not	No
			Off D 1 day/5 mg	1602	Periarthritis	1 day	Moderate	Def not	No
037014	2543	F/73	D/5 mg	1768	Herpes zoster, ophthalmic	15 days	Severe	Def not	No
037015	2245	F/67	D/5 mg	1447	Neoplasm, skin, malignant	2 days	Moderate	Def not	No
037016	2225	F/63	D/5 mg	1746	Hernia, inguinal	1 day	Moderate	Prob not	No
Drug codes: D = Alendronate P = Placebo									
Drug Relation: Def not = Definitely not Prob not = Probably not									
Therapy Discontinuation: No = Not Discontinued Yes = Discontinued									
li = left rt = right NA = Not available									

Comments: Without a placebo control, it is difficult to draw conclusions regarding long-term safety. Nonetheless, there is no apparent dose effect and there are no increases in serious adverse events in any treatment category. Furthermore, there are no salient increases in any particular type of adverse event over that which might be expected in a population of this age.

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Comments (cont.): In 035 there were 14 cases of malignant skin neoplasms, with 3, 5, 2, and 4 cases in the placebo/10mg, 5-mg, 10-mg, and 20/5-mg groups respectively. However, in 037 there were 4 cases, with 2, 0, 0, and 2 in the placebo/10 mg, 5 mg, 10 mg, and 20/5 mg groups, respectively.

In the open-label group, there were 11 patients (18%) with serious AE's. There was one malignant skin neoplasm; this occurred in the placebo/10 mg group. There was no obvious pattern of excess AE's in any specific category. None of the cases was judged to be related to alendronate.

Deaths: There were 5 deaths in the double blind group and 2 in the open label group. None was judged by the investigator to be related to alendronate treatment. The causes of death, and case summaries, are provided in the NDA. Briefly, the causes were: trauma (assault, 77 y.o. on 10 mg); squamous cell carcinoma, metastatic in a 68-y.o. woman on 5 mg, probably from a primary lesion in the lung; heart failure due to IHD (59 y.o. on 5 mg); respiratory failure due to unknown cause (62 y.o. on 10 mg); death due to unknown cause (78 y.o. on 10 mg). There were 2 deaths in the open-label group: a 68 y.o. on 10 mg had a CVA; a 70 y.o. on 10 mg had an acute MI.

Discontinuation due to clinical AE's:

Nineteen patients (2.6%) discontinued treatment due to a clinical AE, vs 59 patients (5.9%) who discontinued treatment due to a clinical AE during the first 36 months of the study. Ten (3.5%), 3 (2.1%), 4 (2.6%), and 2 (1.4%) patients discontinued in the placebo/10-, 5-, 10-, and 20-/5-mg treatment groups, respectively. Seven of these patients withdrew from treatment due to AE's that were considered drug related by the investigator. A summary of these adverse experiences appears in the table below:

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Patients Discontinued From Therapy Due to Clinical Adverse Experiences

Study Number	AN	Sex/Age	Drug/Total Daily Dosage at Time of AE	Day AE/ Discontinued Study Drug/ Discontinued Study	Adverse Experience	Serious	Duration	Intensity	Drug Relation
Placebo/Alendronate 10 mg									
035005	0108	F/77	D/10 mg	1281/1281/1281	Trauma	Yes	1 day	Severe	Def not
035006	0255	F/69	D/10 mg	1327/1543/1658	Myalgia	No	78 days	Moderate	Definitely
037003	2458	F/66	D/10 mg	1661/1662/1739	Neoplasm, breast, malignant	Yes	15 days	Severe	Def not
037010	2363	F/74	D/10 mg	1718/1720/1834	Neoplasm, breast, malignant	Yes	4 days	Severe	Def not
037014	2565	F/62	Off D 5 days/10 mg	1265/1302/1362	Colitis	Yes	78 days	Severe	Def not
037015	2341	F/62	Off D 1 day/10 mg	1635/1634/1635	Respiratory failure	Yes	1 day	Severe	Def not
037016	2182	F/67	D/10 mg	1464/1496/1499	Nausea	No	33 days	Moderate	Possibly
			D/10 mg	1464/1496/1499	Discomfort, pharyngeal	No	36 days	Moderate	Possibly
			D/10 mg	1464/1496/1499	Vomiting	No	33 days	Moderate	Possibly
037016	2391	F/64	D/10 mg	1106/1109/1135	Dyspepsia	No	18 days	Moderate	Possibly
			Off D 15 days/10 mg	1124/1109/1135	Ulcer, gastric	No	12 days	Moderate	Possibly
037018	2570	F/78	Off D 1 day/10 mg	1771/1776/1777	Death	Yes	1 minute	Severe	Def not

Study Number	AN	Sex/Age	Drug/Total Daily Dosage Time of AE	Day AE/ Discontinued Study Drug/ Discontinued Study	Adverse Experience	Serious	Duration	Intensity	Drug Relation
Placebo/Alendronate 10 mg (Cont.)									
037019	2382	F/69	D/10 mg	1111/1171/1281	Acid regurgitation	No	147 days	Severe	Possibly
			D/10 mg	1162/1171/1281	Dysuria	No	46 days	Severe	Prob not
			D/10 mg	1162/1171/1281	Pain, abdominal	No	47 days	Moderate	Prob not
Alendronate 5 mg									
035017	0049	F/68	D/5 mg	1632/1632/1808	Carcinoma, squamous cell, metastatic	Yes	177 days	Severe	Def not
037003	2315	F/59	Off D 1 day/5 mg	1174/1173/1174	Cardiac arrest	Yes	1 day	Severe	Def not
037014	2546	F/57	D/5 mg	1105/1243/1272	Lichen planus	No	168 days	Mild	Probably
Alendronate 10 mg									
035003	0160	F/64	D/10 mg	1129/1131/1368	Neoplasm, intestinal, malignant	Yes	27 days	Severe	Prob not
035006	0264	F/61	Off D 1 day/10 mg	1081/1269/1269	Flu-like illness	No	180 days	Moderate	Possibly
035008	0001	F/72	D/10 mg	1782/1782/1800	Neoplasm, lung, malignant	Yes	19 days	Severe	Prob not
037015	2375	F/63	D/10 mg	1461/1468/1656	Pain, abdominal	No	15 days	Severe	Probably

Study Number	AN	Sex/Age	Drug/Total Daily Dosage Time of AE	Day AE/ Discontinued Study Drug/ Discontinued Study	Adverse Experience	Serious	Duration	Intensity	Drug Relation
Alendronate 20 mg/5 mg									
035011	0423	F/57	Off D 10 days/5 mg	1404/1394/1413	Chronic obstructive pulmonary disease	Yes	10 days	Severe	Prob not
			Off D 10 days/5 mg	1404/1394/1413	Heart failure	Yes	10 days	Severe	Prob not
			Off D 10 days/5 mg	1404/1394/1413	Embolism/infection, pulmonary	Yes	10 days	Severe	Prob not
037005	2465	F/54	D/5 mg	1190/1199/1247	Neoplasm, malignant	Yes	42 days	Severe	Def not

Drug codes:
D = Alendronate

Drug Relation:
Def not = Definitely not
Prob not = Probably not

Comments: The discontinuation rate is quite small and does not appear to be related to the dose of the drug. Very few patients discontinued due to AE's that were plausibly related to alendronate use.

Upper gastrointestinal AE's:

Alendronate use has been associated with upper GI AE's of varying severity. During this 2-year extension study, 138 patients (19%) had at least one upper GI adverse experience. In comparison, in the first 36 months of the study, 392 patients (39%) had upper GI AE's. Of the 138 patients with GI AE's, in 37, or 26%, the AE's were considered to be drug-related by the investigators. Four upper GI adverse experiences were considered serious, none of which was considered drug related.

Comments: These 4 were: 1) Serious GI bleeding with anemia requiring blood transfusion occurred in a 66-y.o. woman taking 10 mg of alendronate. The source of the bleeding was not found. 2) a 72 y.o. woman with history of stomach ulcer on 5mg alendronate had also taken aspirin. She had chest pain due most likely to gastroesophageal reflux. She was taken off the alendronate and was discharged from the hospital. 3) A 72 y.o. woman with unstable angina on multiple medications including 10 mg alendronate was diagnosed with esophageal candidiasis. She was successfully treated and kept on the alendronate. 4) A 50 y.o. woman with migraine was hospitalized for vomiting and headache. Workup revealed no primary GI disorder, and it was concluded that the source of the vomiting was a reaction to an antibiotic.

It should be noted that alendronate use has been associated with GI bleeding at sites other than the esophagus and stomach. One cannot exclude alendronate as a cause of serious GI bleeding in patient #1. The cause of the reflux and reflux symptomatology in patient #2 is not clear; again, alendronate cannot be ruled out with certainty. In the third and fourth cases, the involvement of alendronate seems unlikely.

Four patients discontinued due to an upper GI AE considered related to alendronate. None of the cases was serious. The difference between proportion of patients experiencing an adverse experience (five categories) in the 5- and 10-mg groups was tested using Fisher's exact test. A significant positive difference was observed between the groups taking 5 and 10 mg during Years 4 and 5 for abdominal pain ($p=0.027$). For AE's considered to be drug-related, there were no significant trends, including abdominal pain.

The following table shows the number of patients with specific GI adverse experiences, by treatment group:

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Upper Gastrointestinal Adverse Experience Summary—Patient Count (%)

	PBO/ALN 10 mg (N=288)	ALN 5 mg (N=145)	ALN 10 mg (N=151)	ALN 20 mg/5 mg (N=143)
Number (%) of patients with one or more upper GI adverse experiences	59 (20.5)	23 (15.9)	34 (22.5)	22 (15.4)
Body as a Whole/Site Unspecified				
Distention, abdominal	1 (0.3)	3 (2.1)	1 (0.7)	1 (0.7)
Hernia, diaphragmatic	6 (2.1)	0	1 (0.7)	1 (0.7)
Pain, abdominal*	14 (4.9)	4 (2.8)	14 (9.3)	8 (5.6)
Digestive System Disorders				
Acid regurgitation	7 (2.4)	1 (0.7)	6 (4.0)	2 (1.4)
Dyskinesia, esophageal	1 (0.3)	1 (0.7)	1 (0.7)	0
Dyspepsia	15 (5.2)	3 (2.1)	7 (4.6)	6 (4.2)
Dysphagia	2 (0.7)	0	0	1 (0.7)
Erosive esophagitis	1 (0.3)	1 (0.7)	1 (0.7)	0
Eructation	0	0	2 (1.3)	1 (0.7)
Esophagitis	6 (2.1)	0	1 (0.7)	0

	PBO/ALN 10 mg Oral (N=288)	ALN 5 mg Oral (N=145)	ALN 10 mg Oral (N=151)	ALN 20 mg/5 mg Oral (N=143)
Digestive System Disorders (Cont.)				
Gastritis	4 (1.4)	2 (1.4)	2 (1.3)	1 (0.7)
Gastritis, atrophic	1 (0.3)	0	2 (1.3)	0
Gastroenteritis	2 (0.7)	1 (0.7)	1 (0.7)	3 (2.1)
Melena	0	0	0	1 (0.7)
Nausea	14 (4.9)	6 (4.1)	5 (3.3)	3 (2.1)
Reflux esophagitis	3 (1.0)	2 (1.4)	3 (2.0)	2 (1.4)
Ulcer, duodenal	1 (0.3)	0	0	0
Ulcer, gastric	3 (1.0)	0	2 (1.3)	0
Vomiting	5 (1.7)	4 (2.8)	3 (2.0)	1 (0.7)
* Between-group treatment test (5 and 10 mg). p-Value = 0.027 for Years 4 and 5.				
Although a patient may have had two or more upper GI adverse experiences, the patient is counted only once in "Number (%) of patients with one or more upper GI adverse experiences."				
This table does not include those adverse experiences that occurred during the first 3 years of treatment.				

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Comments: There was no evidence of a treatment group-related effect on AE incidence, except for abdominal pain. The incidence of GI adverse experiences during this phase of the study is not greater than that found during the first 3 years. In addition, there is no change in the pattern of specific GI adverse experiences that would raise concern. Again, the absence of a placebo control group reduces the cogency of the results. In

any case, there were very few instances of serious GI adverse events during this study, irrespective of whether these events were truly "drug-related." Warnings about the type and severity of GI events that occurred in this trial are currently included in the Fosamax label.

Fractures:

Comments: Fracture occurrence is a potential concern with long-term use of any drug that resides in bone for many years. Although alendronate preferentially inhibits osteoclastic bone resorption, osteoblast function is secondarily slowed, as a new steady state (or balance) is achieved. An excellent indication of this process is provided by the sponsor's biochemical bone turnover data, presented above. Alendronate treatment reduces biochemical markers of bone resorption and formation. As a new steady state is approached, bone mineral density increases, because resorption is initially inhibited more than formation. This is especially true of trabecular bone, where the turnover rate is higher than in cortical bone.

Alendronate treatment should theoretically reduce fracture occurrence, and data from other studies thus far support this favorable outcome. However, longer treatment with this agent might retard fracture healing. Further, it is possible that long-term treatment with alendronate might even promote fractures, particularly in cortical bone. The role of secondary hypersecretion of PTH is also of theoretical concern, although this seems to have been adequately addressed in the data provided herein (see above).

To address these issues, the sponsor has conducted a thorough analysis of fracture occurrence in the two-year extension study. This analysis has provided safety data extending through a total of five years of treatment.

Thirteen (4.5%), 6 (4.1%), 5 (3.3%), and 9 (6.3%) patients had a vertebral fracture in the placebo/10-, 5-, 10-, and 20-/5-mg groups, respectively. The rate of vertebral fracture per 100 patient years at risk was not calculated due to the qualitative, not quantitative, method of vertebral fracture assessment.

Vertebral fractures for 2 patients at the same study site were considered drug related by the investigator, who apparently thought that lack of drug efficacy may have caused the fractures. The sponsor thought that it was unclear why the investigator thought that the fractures were drug related. Summaries of the cases are included in the NDA.

Comments: As indicated above, there are few objective grounds for determining whether many individual AE's are drug-related. Thus it is often difficult to accept investigator opinions without further corroboration. In the case of these two patients, it certainly is unclear why one should

believe that the vertebral fractures were drug-related. On the other hand, why is a case of serious gastrointestinal bleeding in an alendronate-treated patient with no identifiable anatomic source of bleeding (see description of patient above) *not* drug-related?

The number of patients with vertebral fractures, by treatment group, is presented in the table below:

Vertebral Fractures
Patient Count (%)

	PBO/ALN 10 mg (N=288)	ALN 5 mg (N=145)	ALN 10 mg (N=151)	ALN 20/5 mg (N=143)
Number (%) of patients with one or more vertebral fractures	13 (4.5)	6 (4.1)	5 (3.3)	9 (6.3)
Musculoskeletal Disorders				
Fracture, vertebra	1 (0.3)	0	0	0
Fracture, vertebra, L1	4 (1.4)	2 (1.4)	0	0
Fracture, vertebra, L2	0	0	1 (0.7)	3 (2.1)
Fracture, vertebra, L3	2 (0.7)	0	0	0
Fracture, vertebra, L4	0	0	1 (0.7)	0
Fracture, vertebra, T10	2 (0.7)	0	1 (0.7)	2 (1.4)
Fracture, vertebra, T11	2 (0.7)	2 (1.4)	2 (1.3)	3 (2.1)
Fracture, vertebra, T12	2 (0.7)	2 (1.4)	0	0
Fracture, vertebra, T4	1 (0.3)	0	0	0
Fracture, vertebra, T5	1 (0.3)	1 (0.7)	0	1 (0.7)
Fracture, vertebra, T6	2 (0.7)	0	1 (0.7)	0
Fracture, vertebra, T7	0	0	0	1 (0.7)
Fracture, vertebra, T8	1 (0.3)	1 (0.7)	0	0
Fracture, vertebra, T9	0	0	0	5 (3.5)

Although a patient may have had two or more adverse experiences, the patient is counted only once in "Number (%) of patients with one or more vertebral fractures."

This table does not include those adverse experiences that occurred during the first 3 years of treatment.

Non-vertebral fractures:

The clinical significance of non-vertebral fractures is generally greater than that of vertebral fractures. Compared to vertebral fractures, non-vertebral fractures are certainly easier to diagnose unequivocally. During the extension study, 16 (5.6%), 7 (4.8%), 7 (4.6%), and 5 (3.5%) patients had a nonvertebral fracture in the placebo/10-, 5-, 10-, and 20-/5-mg groups, respectively. Tabulation of nonvertebral fractures by treatment group is given below:

Nonvertebral Fractures
Patient Count (%)

	PBO/ ALN 10 mg (N=288)	ALN 5 mg (N=145)	ALN 10 mg (N=151)	ALN 20/5 mg (N=143)
Number (%) of patients with one or more nonvertebral fractures	16 (5.6)	7 (4.8)	7 (4.6)	5 (3.5)
Musculoskeletal Disorders				
Fracture, ankle, lt	1 (0.3)	0	0	0
Fracture, ankle, rt	1 (0.3)	0	0	0
Fracture, femur, lt	0	1 (0.7)	0	0
Fracture, femur, neck, rt	0	0	1 (0.7)	0
Fracture, femur, rt	1 (0.3)	0	0	0
Fracture, fibula	0	0	1 (0.7)	0
Fracture, foot	1 (0.3)	0	0	0
Fracture, foot phalanx, lt	1 (0.3)	0	0	0
Fracture, foot, lt	0	1 (0.7)	0	0
Fracture, hand phalanx, lt	1 (0.3)	1 (0.7)	0	0
Fracture, hip, rt	2 (0.7)	2 (1.4)	0	0
Fracture, humerus, rt	0	0	0	1 (0.7)
Fracture, leg, multiple	0	0	1 (0.7)	0
Fracture, metacarpal, lt	1 (0.3)	1 (0.7)	0	0
Fracture, metatarsal, rt	1 (0.3)	0	0	0
Fracture, nose	0	0	0	1 (0.7)
Fracture, patella, rt	0	0	1 (0.7)	0
Fracture, pelvis	1 (0.3)	0	0	0
Fracture, radius, lt	1 (0.3)	1 (0.7)	0	1 (0.7)
Fracture, rib	1 (0.3)	0	1 (0.7)	0
Fracture, rib, 5th, rt	0	0	0	1 (0.7)
Fracture, rib, 8th, rt	0	0	0	1 (0.7)
Fracture, shoulder, lt	1 (0.3)	0	0	0
Fracture, sternum	2 (0.7)	0	1 (0.7)	1 (0.7)
Fracture, stress, foot	0	0	1 (0.7)	0
Fracture, wrist, lt	1 (0.3)	1 (0.7)	0	0
Fracture, wrist, rt	0	1 (0.7)	0	0

Although a patient may have had two or more nonvertebral fractures, the patient is counted only once in "Number (%) of patients with one or more nonvertebral fractures."

This table does not include those adverse experiences that occurred during the first 3 years of treatment.

The sponsor calculated the number of fractures per 100 patient-years at risk by treatment group and study period (Years 0 to 3 double-blind study and Years 4 to 5 extension). The number of patients at risk of nonvertebral fractures in the beginning of the first year were 397, 202, 196, and 199 in the placebo/10-, 5-, 10- and 20-/5-mg treatment groups, respectively. Comparing the two treatment intervals (Years 0-3 vs Years 4-5) the rates of nonvertebral fractures per 100 patient years at risk were the same or slightly less during the extension period, in each treatment group and in the pooled alendronate groups. Thus no detectable evidence of an increase in the rate of nonvertebral fractures with continuing treatment was observed.

The crude nonvertebral fracture rates, in which a patient was allowed to be at risk for fracture only once during the 5-year period, are given in the table below.

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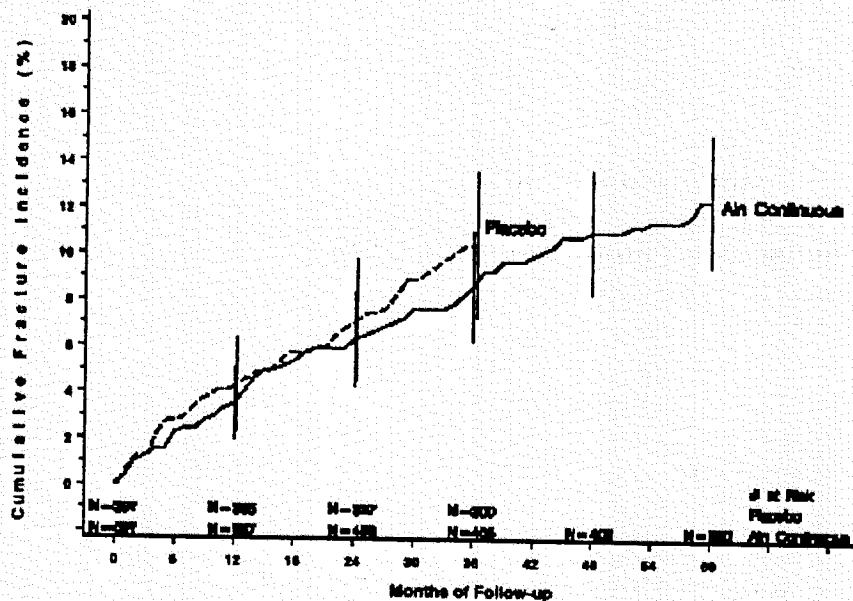
(Pooled 035/037)
Nonvertebral Fracture Crude Rates by
Treatment and Study Period
(All Patients)

Alendronate Treatment	Study Period (Years)	Cases	Patient-Years at Risk	Rate (Per 100 Patient-Year Risk)
Placebo/10 mg	0 to 3	38	1022.2	3.72
	4 to 5	16	534.0	3.00
ALN 5 mg	0 to 3	16	517.3	3.09
	4 to 5	6	259.9	2.31
ALN 10 mg	0 to 3	14	511.7	2.74
	4 to 5	7	284.6	2.46
ALN 20/5 mg	0 to 3	17	507.3	3.35
	4 to 5	4	266.8	1.50
Pooled ALN	0 to 3	47	1536.3	3.06
	4 to 5	17	811.3	2.10

Cumulative nonvertebral fracture incidence, estimated from a life table Model, is shown in the figure below. Placebo-group estimates are shown through Month 36, at which time patients were switched to open-label alendronate 10 mg; the pooled continuous alendronate group estimates are shown through Month 60. The cumulative incidences of nonvertebral fractures were seen to be generally lower in the pooled alendronate group compared with placebo in the first 3 years. The sponsor notes that the variability for lifetable estimates increases when fewer patients are at risk, as is seen in the later time points. All patients with data were included in the estimation of crude rates and incidences of fracture.

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Nonvertebral Fractures Over 5 Years
 Cumulative Incidence of First Fracture Occurrence
 With 95% Confidence Intervals
 Pooled 035/037



Comments: Again, lack of an ongoing placebo group leaves open the question whether the two curves would have converged, crossed, or retained the same trajectories at Month 60, the sponsor's reservations about variability notwithstanding.

The sponsor also determined the rates of nonvertebral fractures that were obtained when a patient could be at risk of fracture during both study periods—that is, a patient could have only one fracture in a study period but may have a fracture in both periods. This analysis also showed no evidence of an increase in the rate of nonvertebral fractures with continuing treatment (data in NDA Table 73).

Finally, the nonvertebral fracture rates through 5 years were also obtained for patients continuing in the extension studies and who were not on open label. The results, given in Appendices [4.36.9 to 4.36.11] of the NDA, were in agreement with those based on all patients in the study. In this analysis as in the others, there were no clinically meaningful differences between the U.S. and multinational cohorts in the number of nonvertebral fracture events.

Comments: Based on the data and the analyses, and within the limits of a trial that lacked a placebo arm for the last two years, there is no indication

that 60 months of alendronate treatment carries increased risk of vertebral or non-vertebral fractures within this time period.

Rash:

Rash and/or erythema have been observed in patients taking alendronate. During the two-year extension study, 24 (3.3%) of 727 patients reported rash as an adverse experience. In comparison, 93 (9.4%) of 994 patients reported rash as an adverse experience at Month 36. There were no clinically significant differences between the 5- and 10-mg treatment groups in the incidence of rash [4.36.6].

Laboratory adverse experiences:

This analysis is based on data received for all patients through 60 months of treatment. Data from open-label-treated patients are excluded. Of the 727 patients who entered the study, 25 discontinued before follow-up laboratory tests were completed. These were roughly evenly distributed among treatment groups. Of the 702 patients with protocol-specified laboratory tests, 129 (18.4%) had at least one laboratory AE. None of the laboratory AE's was considered serious by the investigators. A summary of laboratory AE's is presented in the table below:

Laboratory Adverse Experience Summary—Patient Count (%)

	PBO/ ALN 10 mg (N=288)		ALN 5 mg (N=145)		ALN 10 mg (N=151)		ALN 20/5 mg (N=143)	
Number of patients with at least one laboratory test postbaseline	278	(96.5)	136	(93.8)	151	(100)	137	(95.8)
Number (%) of patients								
with one or more adverse experiences	47	(16.9)	21	(15.4)	35	(23.2)	26	(19.0)
with drug-related adverse experiences	2	(0.7)	1	(0.7)	0		2	(1.5)
with serious adverse experiences	0		0		0		0	
with serious drug-related adverse experiences	0		0		0		0	
withdrawn from therapy due to an adverse experience	0		0		0		0	
withdrawn from therapy due to a drug-related adverse experience	0		0		0		0	
withdrawn from therapy due to a serious adverse experience	0		0		0		0	
withdrawn from therapy due to a serious drug-related adverse experience	0		0		0		0	

This table does not include those adverse experiences that occurred during the first 3 years of treatment

No serious laboratory AE's occurred in the 61 open-label-treated patients.

The sponsor also presents a complete analysis of laboratory AE's by laboratory test abnormality. Increased urine WBCs, increased serum glucose, and increased/decreased TSH were the most commonly reported laboratory adverse experiences related to protocol-required measurements and the only laboratory adverse experiences with an incidence of at least 5% in at least one treatment group. Blood glucose was found to be increased in 6.0% (9/149 patients) of the 10 mg group, as opposed to 2.9, 2.2, and 2.9% of the placebo/10mg, 5 mg, and 20/5 mg group. Urine WBC's were increased in 5.5, 3.8, 4.1, and 6.65 of the pbo/10mg, 5 mg, 10mg, and 20/5mg groups respectively. The TSH changes were found in a small number of patients; TSH was not a prespecified test. A complete listing of these events is presented in Table 77 of the NDA and will not be reproduced here.

Comments: There were no notable increases in the occurrence of any specific laboratory test abnormality in an exhaustive and inclusive battery of hematological and biochemical examinations. Fecal occult blood was not monitored as a prespecified test (apparently only one patient had this test done).

There were only 5 patients with laboratory AE's that were considered to be drug-related by the investigator. Of these, 2 were in the PBO/10 mg group, 1 was in the 5 mg group, and the remaining 2 were in the 20/5 mg group. None were in the 10 mg group. These AE's involved 2 increases in ALT, 1 in AST, 1 decreased phosphate, 1 increased GGT, and 1 increase in LDH.

No laboratory adverse experiences were considered serious, and no patients discontinued from study therapy due to laboratory adverse experiences.

c. Adverse Experiences—Other (Special Examinations)

All adverse experiences, including those found by means of other safety tests (e.g., physical examination) are discussed in the clinical adverse experience (Section II.C.4.a.) and laboratory adverse experience (Section II.C.4.b.) sections of this CSR.

d. Clinical Safety Measurements

Vital Signs

Vital signs were examined as a measure of safety. Assessment of change from baseline at Month 60 for body weight, blood pressure (systolic and diastolic), and pulse rate are in Tables 79 through 82. Significant increases of 0.9 ($p<0.001$), 1.4 ($p<0.001$), 1.0 ($p<0.010$), and 0.7 ($p<0.050$) kg of body

weight were observed in the placebo/10-, 5-, 10-, and 20-/5-mg groups, respectively. Systolic blood pressure increased over the 5-year period by 2.6, 2.7, 4.4, and 0.9 mm Hg in the placebo/10-, 5-, 10-, and 20-/5-mg groups. All changes from baseline were significant ($p < 0.010$; $p < 0.050$ for 5 mg) except for those seen in the 20-/5-mg group. There were no significant changes from baseline at Month 60 in diastolic blood pressure and pulse rate in any treatment group. No significant differences were observed between alendronate 5- and 10-mg treatment groups in weight, systolic and diastolic blood pressure, or pulse rate.

There was no significant treatment-by-protocol interaction in any of the vital signs, indicating that changes in weight, systolic and diastolic blood pressure, and pulse rate was similar across Protocols 035-10 and 037-10.

9. and 10. Conclusions regarding efficacy and safety data

This clinical trial examined the efficacy and safety of 5 years of alendronate treatment in postmenopausal osteopenic women. Of 994 patients initially enrolled in Protocols 035 and 037, 788 (79%) entered the 2-year extension study. These included 61 patients who entered open-label. The remaining patients, 727, or 73% of those initially randomized, entered the extension study double-blind. 715 patients (91%) completed the extension study, including completers among 61 patients who entered open-label or switched to open-label treatment. Thus, depending on the particular efficacy outcome measured and the number of patients excluded, analyses were done on fewer than 700 patients. For example, the ITT analysis of lumbar spine BMD was done on 644 patients (Table 21). This = 88% of the 727 who enrolled in the extension study double blind and 65% of the 994 that were initially randomized into the trials. For the femoral neck BMD outcome, roughly the same number of patients was analyzed.

In a detailed analysis of patient characteristics, the sponsor demonstrated that there were no clinically significant differences between the baseline characteristics of those patients who were initially enrolled in the first 3 years of the studies and the subset of patients who continued into the 2-year extension. Among the patients who enrolled in the extension, there were no significant differences in the baseline characteristics of patients who entered the 4 different treatment groups. Furthermore, in an examination of all patients who were eligible to enter the extension, the sponsor demonstrated that there were no significant differences between those who entered the extension and those who did not. Among potential differences that the sponsor specifically examined were changes in lumbar spine BMD during the previous 3 years of treatment with alendronate or placebo. In this and other important demographic and clinical variables,