Appendix 13. Narrative summary of deaths in the rofecoxib program.

1- AN 2395, Study 029-10. 72 year-old white man, history or CAD but no active angina, MI and CABG 15 years prior to entering the study, randomized to diclofenac, 150 mg a day . On 11/4/96 he reported having two episodes of tachycardia of 30 min duration. He received cardizem and digoxin. On 12/5/99 he underwent coronary artery redo surgery and coronary bypass. The patient died on 12/29/96 (day 88 of therapy). The episode was considered definitively not related to study drug.

2- AN 5599, Study 034. 79-year-old woman with a history of angina pectoris and congestive heart failure, placed on diclofenac 150 mg/day, on 4/11/97. Concomitant therapy included thyroxine sodium, premarin, furosemide, caffeine citrate, nifedipine, glyceryl trinitrate and diazepam. On 4/17/97 the cardiologist suggested that the drug therapy might have worsened the angina. On 4/21/97 therapy was discontinued by the patient herself; she felt the medication wasn't helping and that it was worsening the angina—she withdrew consent. The patient died on 5/2/97, 11 days after discontinuing study treatment. The cause of death was myocardial infarction. The reporting physician felt that myocardial infarction and death were probable not related to study drug. No blood tests were done on the patient, therefore no CK-MB, CPK Isoenzymes results.

3- AN 5068, Study 034. 55-year-old woman with a history of depression and suicide attempt, randomized to diclofenac, 150 mg/day on 3/6/97. Concomitant therapy included citalopram 20 mg daily, flunitrazepam 1 mg daily and bromazepam 6 mg daily for depression. On 6/19/97, the patient committed suicide by taking probably large amount of citalopram, flunitrazepam and bromazepam or other medications prescribed by psychiatrist . Her psychiatrist said that the suicide attempt was premeditated. The investigator felt that suicide attempt was definitely not related to study drug.

4- AN 5320, Study 034. 78-year-old woman with a history of hypertension, randomized to diclofenac, 150 mg/ day. She had a hemorrhagic cerebrovascular accident 2 months into the treatment. Patient was in a coma and died 1 day later. The episode was not considered to be drug related..

5- AN 5761, Study 034C. 75 year-old white female, randomized to diclofenac 150 mg, on day 225 of therapy died of postoperative complications (cardiorespiratory arrest after coronary bypass grafting). The episode was considered definitively not related to study drug.

6- AN 7517, Study 035. A 69 year-old white female randomized to diclofenac 150 mg/day collapsed in her house. The patient was in ventricular fibrillation when CPR began, and was subsequently pronounced dead in the emergency room. The cause of death was cardiac arrest. This experience occurred after 85 days of study therapy, and was considered possibly drug related.

7- AN 7588, Study 035. 79 year-old white female, history of hypertension and hypothyroidism, MI in 1985 and known LBBB, on methyldopa/hctz, estrogen, levothyroxine, vitamin C and vitamin K, randomized to MK 12.5mg a day on 2/4/97. The patient was seen by friends in her usual state of health on 5/23/97 (52 days of study treatment). A few hours later she was found dead. The cause of death was listed in the CRF as unspecified natural causes. No autopsy was performed. The episode was considered definitely not drug related. Review of CRF shows that on 4/30/97 she had a decreased potassium (3.1) attributed to concomitant medications. No other information is available. (In Appendix 14.4.1, (narrative) the cause of death was reported to be sudden cardiac death).

8- AN 7922, Study 035. A 75 year-old white male died suddenly while driving a tractor. The cause of death was advanced systemic atherosclerosis. This experience occurred after 175 days of study therapy (diclofenac) and was considered probably not drug related. The patient had suffered a syncopal episode of unknown etiology 5 weeks before his death.

9- AN 9415, Study 040. 80-year-old female with history of hypertension and varices, randomized to 12.5 mg ROFECOXIB, died of a pulmonary embolism 8 days after sustaining a hip fracture. The patient had discontinued from the study 2 weeks prior to the hip fracture due to a clinical adverse event (nonserious

facial rash, possibly related to study drug). Neither the hip fracture nor the pulmonary embolism were determined by the investigator to be drug related.

10- AN 9089, Study 072 (orthopedic pain) 87-year-old female, with history of HTN, Atrial fibrillation, previous DVT and CVA on warfarin, randomized to the naproxen sodium/placebo group. The patient died of multiple organ failure and bacterial sepsis on Day 16 following a femoral fracture on Day 7, bacterial sepsis, cardiac arrest, and pulmonary embolism starting on Day 9. The death was considered not related to study drug.

Data provided with 120-day safety update:

AN 0282, a patient in the placebo group in the multinational endoscopy study protocol 045, was diagnosed with metastatic adenocarcinoma of the colon 151 days after his last study dose.

AN 7932, Study 035, a patient with cardiac risk factors experienced a myocardial infarction 35 days after his last dose of study drug. This patient had been withdrawn due to recurrent intermittent hives after 2 weeks of taking diclofenac 50 mg TID.

AN 1283, Study 058, 86 year-old white female with a history of atrial fibrillation, died from a cardiac arrest. (day 46 on rofecoxib 12.5 mg QD).

AN 1502, Study 058, 87 year-old white female died from multiple organ failure secondary to bacterial sepsis (day 127, on rofecoxib 12.5 mg QD).

AN 1614, Study 058, 87 year-old white female with cardiac risk factors, experienced a myocardial infarction complicated by pneumonia 28 days after her last dose of nabumetone 500 mg TID. She had been 43 days on treatment.

AN 2190 (rofecoxib 50 mg, study 068, dose ranging study in RA). 70 year old woman with severe R.A., with history of interstitial lung disease, entered the protocol on 3/30/98. Concomitant medications included methotrexate. On 4/16/98 presented to the investigator with flu-like symptoms and SOB and was found to have scattered ronchi on the right lung base. Study drug was discontinued. On 4/20/98 patient presented to the E.R. with increasing SOB, fever and was found to have a WBC of 20.000. She received multiple medications (including furosemide, digoxin, antibiotics, solumedrol) for treatment of presumptive CHF, CAD, atrial fibrillation, and pneumonitis. Patient died on 5/10/98. A limited autopsy was performed. The cause of death was respiratory failure with pulmonary fibrosis as a contributing factor. Additional finding was mediastinal emphysema.

Appendix 14. Clinical adverse events. Most frequent adverse experiences (NDA Clinical Documentation, E.2. Clinical Safety in OA, page E-243)

	Placebo[a]	MK-0966					Comparators		
		5 mg	12.5 mg	25 mg	50 mg	125 mg	Diclofenac	Ibuprofen	Nabumetone
	n/m[b] (%)	n/m[b] (%)	n/m[b] (%)	n/m[b] (%)	n/m[b] (%)	n/m[b] (%)	n/m[b] (%)	n/m[b] (%)	n/m[b] (%)
Body as a Whole/Site Unspecified									
Upper respiratory infection									
6 Week	24/412 (5.8)	7/149 (4.7)	36/725 (5.0)	43/735 (5.9)	2/97 (2.1)	10/74 (13.5)	NA	13/470 (2.8)	7/115 (6.1)
6 Month	37/371 (10.0)	NA	49/490 (10.0)	113/879 (12.9)	35/379 (9.2)	NA	41/498 (8.2)	36/377 (9.5)	NA
1 Year	NA	NA	82/490 (16.7)	95/489 (19.4)	NA	NA	64/498 (13.9)	NA	NA
6 Month to 86 Week	NA	NA	54/415 (13.0)	55/435 (12.6)	10/75 (13.3)	NA	48/409 (11.7)	NA	NA
Digestive System									
Diarrhea									
6 Week	24/412 (5.8)	7/149 (4.7)	33/725 (4.6)	42/735 (5.7)	8/97 (8.2)	3/74 (4.1)	NA	23/470 (4.9)	9/115 (7.8)
6 Month	29/371 (7.8)	NA	21/490 (4.3)	87/879 (9.9)	41/379 (10.8)	NA	53/498 (10.6)	37/377 (9.8)	NA
1 Year	NA	NA	31/490 (6.3)	51/489 (10.4)	NA	NA	61/498 (12.2)	NA	NA
6 Month to 86 Week	NA	NA	18/415 (4.3)	17/435 (3.9)	3/75 (4.0)	NA	18/409 (4.4)	NA	NA
Eyes, Ears, Nose, and Throat									
Sinusitis									
6 Week	6/412 (1.5)	3/149 (2.0)	16/725 (2.2)	12/735 (1.6)	4/97 (4.1)	3/74 (4.1)	NA	7/470 (1.5)	0/115 (0.0)
6 Month	10/371 (2.7)	NA	21/490 (4.3)	28/879 (3.2)	17/379 (4.5)	NA	12/498 (2.4)	8/377 (2.1)	NA
1 Year	NA	NA	29/490 (5.9)	22/489 (4.5)	NA	NA	22/498 (4.4)	NA	NA
6 Month to 86 Week	NA	NA	21/415 (5.1)	19/435 (4.4)	8/75 (10.7)	NA	17/409 (4.2)	NA	NA
Nervous System									
Headache									
6 Week	26/412 (6.3)	5/149 (3.4)	16/725 (2.2)*	33/735 (4.5)	4/97 (4.1)	9/74 (12.2)	NA	20/470 (4.3)	3/115 (2.6)
6 Month	33/371 (8.9)	NA	29/490 (5.9)	56/879 (6.4)	30/379 (7.9)	NA	40/498 (8.0)	32/377 (8.5)	NA
1 Year	NA	NA	33/490 (6.7)	35/489 (7.2)	NA	NA	51/498 (10.2)	NA	NA
6 Month to 86 Week	NA	NA	8/415 (1.9)	15/435 (3.4)	3/75 (4.0)	NA	14/409 (3.4)	NA	NA

[a] Placebo group in the 6-Month Studies had one-third less exposure than the MK-0966 groups.
[b] n/m=Number of patients with the adverse experience/total number of patients treated.
*p≤0.05; there were no other statistically significant differences observed between treatment groups in the 6-Week Studies. For details see Section 2.3.1.1.
No statistical testing was performed on the 6-Month, 1-Year or 6-Month-to-86-Week Studies groups.
[P010: P029; P033; P040; P058; P034; P035; P044; P045; P029C; P034C]

Appendix 15. Clinical adverse events. Number of patients with AE different from placebo in 6 week studies. Incidence of these AE in the 6 week, 6 month, 1 year and 6 month to 86 week OA studies. (Clinical Documentation. E.2. Page E-244)

	Placebo[†]	MK-0966					Comparators		
	n/m[‡] (%)	5 mg n/m[‡] (%)	12.5 mg n/m[‡] (%)	25 mg n/m[‡] (%)	50 mg n/m[‡] (%)	125 mg n/m[‡] (%)	Diclofenac n/m[‡] (%)	Ibuprofen n/m[‡] (%)	Nabumetone n/m[‡] (%)
Body as a Whole/Site Unspecified									
Abdominal pain									
6 Week	7/412 (1.7)	2/149 (1.3)	15/725 (2.1)	22/735 (3.0)	3/97 (3.1)	0/74 (0.0)	NA	18/470 (3.8)	1/115 (0.9)
6 Month	25/371 (6.7)	NA	14/490 (2.9)	44/879 (5.0)	26/379 (6.9)	NA	29/498 (5.8)	21/377 (5.6)	NA
1 Year	NA	NA	16/490 (3.3)	13/489 (2.7)	NA	NA	33/498 (6.6)	NA	NA
6 Month to 86 Week	NA	NA	6/415 (1.4)	9/435 (2.1)	0/75 (0.0)	NA	8/409 (2.0)	NA	NA
Lower extremity edema									
6 Week	4/412 (1.0)	4/149 (2.7)	24/725 (3.3)*	25/735 (3.4)*	5/97 (5.2)	5/74 (6.8)	NA	19/470 (4.0)	5/115 (4.3)
6 Month	5/371 (1.3)	NA	20/490 (4.1)	37/735 (4.2)	25/379 (6.6)	NA	17/498 (3.4)	13/377 (3.4)	NA
1 Year	NA	NA	30/490 (6.1)	24/489 (4.9)	NA	NA	20/498 (4.0)	NA	NA
6 Month to 86 Week	NA	NA	11/415 (2.7)	11/435 (2.5)	2/75 (2.7)	NA	4/409 (1.0)	NA	NA
Cardiovascular System									
Hypertension									
6 week	2/412 (0.5)	1/149 (0.7)	12/725 (1.7)	16/735 (2.2)*	0/97 (0.0)	0/74 (0.0)	NA	9/470 (1.9)	0/115 (0.0)
6 Month	8/371 (2.2)	NA	22/490 (4.5)	49/879 (5.6)	39/379 (10.3)	NA	8/498 (1.6)	16/377 (4.2)	NA
1 Year	NA	NA	33/490 (6.7)	37/489 (7.6)	NA	NA	24/498 (4.8)	NA	NA
6 Month to 86 Week	NA	NA	17/415 (4.1)	25/435 (5.7)	6/75 (8.0)	NA	19/409 (4.6)	NA	NA
Digestive System									
Dyspepsia									
6 Week	6/412 (1.5)	7/149 (4.7)	13/725 (1.8)	19/735 (2.6)	3/97 (3.1)	4/74 (5.4)	NA	18/470 (3.8)	0/115 (0.0)
6 Month	15/371 (4.0)	NA	24/490 (4.9)	43/879 (4.9)	17/379 (4.5)	NA	20/498 (4.0)	22/377 (5.8)	NA
1 Year	NA	NA	26/490 (5.3)	28/489 (5.7)	NA	NA	23/498 (4.6)	NA	NA
6 Month to 86 Week	NA	NA	6/415 (1.4)	10/435 (2.3)	2/75 (2.7)	NA	5/409 (1.2)	NA	NA
Epigastric discomfort									
6 Week	0/412 (0.0)	0/149 (0.0)	16/725 (2.2)*	21/735 (2.9)*	2/97 (2.1)	1/74 (1.4)	NA	25/470 (5.3)	1/115 (0.9)
6 Month	22/371 (5.9)	NA	24/490 (4.9)	47/879 (5.3)	31/379 (8.2)	NA	27/498 (5.4)	53/377 (14.1)	NA
1 Year	NA	NA	27/490 (5.5)	22/489 (4.5)	NA	NA	33/498 (6.6)	NA	NA
6 Month to 86 Week	NA	NA	7/415 (1.7)	11/435 (2.5)	2/75 (2.7)	NA	13/409 (3.2)	NA	NA
Nausea									
6 Week	8/412 (1.9)	3/149 (2.0)	27/725 (3.7)	37/735 (5.0)*	5/97 (5.2)	1/74 (1.4)	NA	23/470 (4.9)	5/115 (4.3)
6 Month	15/371 (4.0)	NA	20/490 (4.1)	63/879 (7.2)	34/379 (9.0)	NA	37/498 (7.4)	37/377 (9.8)	NA
1 Year	NA	NA	25/490 (5.1)	32/489 (6.5)	NA	NA	46/498 (9.2)	NA	NA
6 Month to 86 Week	NA	NA	11/415 (2.7)	15/435 (3.4)	8/75 (10.7)	NA	12/409 (2.9)	NA	NA
Oral Ulcer									
6 Week	0/412 (0.0)	1/149 (0.7)	5/725 (0.7)	11/735 (1.5)*	2/97 (2.1)	0/74 (0.0)	NA	4/470 (0.9)	0/115 (0.0)
6 Month	0/371 (0.0)	NA	4/490 (0.8)	8/979 (0.9)	7/379 (1.8)	NA	3/498 (0.6)	3/377 (0.8)	NA
1 Year	NA	NA	4/490 (0.8)	3/489 (0.6)	NA	NA	5/498 (1.0)	NA	NA
6 Month to 86 Week	NA	NA	0/415 (0.0)	1/435 (0.2)	1/75 (1.3)	NA	3/409 (0.7)	NA	NA
Psychiatric Disorder									
Depression									
6 Week	0/412 (0.0)	0/149 (0.0)	3/725 (0.4)	9/735 (1.2)*	0/97 (0.0)	0/74 (0.0)	NA	1/470 (0.2)	1/115 (0.9)
6 Month	1/371 (0.3)	NA	6/490 (1.2)	13/879 (1.5)	9/379 (2.4)	NA	8/498 (1.6)	3/377 (0.8)	NA
1 Year	NA	NA	13/490 (2.7)	14/489 (2.9)	NA	NA	12/498 (2.4)	NA	NA
6 Month to 86 Week	NA	NA	9/415 (2.2)	9/435 (2.1)	3/75 (4.0)	NA	4/409 (1.0)	NA	NA
Respiratory System									
Bronchitis									
6 Week	1/412 (0.2)	2/149 (0.3)	5/725 (0.7)	10/735 (1.4)	0/97 (0.0)	0/74 (0.0)	NA	2/470 (0.4)	0/115 (0.0)
6 Month	5/371 (1.3)	NA	15/490 (3.1)	26/879 (3.0)	10/379 (2.6)	NA	16/498 (3.2)	10/377 (2.7)	NA
1 Year	NA	NA	25/490 (5.1)	22/489 (4.5)	NA	NA	24/498 (4.8)	NA	NA
6 Month to 86 Week	NA	NA	13/415 (3.1)	12/435 (2.8)	4/75 (5.3)	NA	12/409 (2.9)	NA	NA

* p≤0.05 versus placebo. For details see Section 2.3.1.1. Statistical testing was performed for 12.5- and 25-mg MK-0966 groups versus placebo only.

† Placebo group in the 6-Month Studies had one-third less exposure than the MK-0966 groups.

‡ n/m=Number of patients with the adverse experience/total number of patients treated.

No statistical testing was performed on the 6-Month, 1-Year, or 6-Month-to-86-Week Studies groups.

[P010; P029; P033; P040; P058; P034; P035; P044; P045; P029C; P034C]

Appendix 16.1. Patient discontinuation due to clinical adverse experiences 6-week phase III OA studies.

	Placebo (N=412)		MK-0966 12.5 mg (N=725)		MK-0966 25 mg (N=735)		Ibuprofen* 2400 mg (N=470)		Nabumetone* 1500 mg (N=115)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients with one or more adverse experiences	14	(3.4)	34	(4.7)	40	(5.4)	29	(6.2)	8	(7.0)
Patients with no adverse experience	398	(96.6)	691	(95.3)	695	(94.6)	441	(93.8)	107	(93.0)
Body as a whole/site unspecified	4	(1.0)	12	(1.7)	8	(1.1)	8	(1.7)	1	(0.9)
Cardiovascular system	1	(0.2)	4	(0.6)	7	(1.0)	0	(0.0)	1	(0.9)
Digestive system	3	(0.7)	11	(1.5)	19	(2.6)	17	(3.6)	2	(1.7)
Eyes, ears, nose, and throat	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Immune system	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.2)	0	(0.0)
Metabolism and nutrition	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Musculoskeletal system	3	(0.7)	0	(0.0)	1	(0.1)	2	(0.4)	0	(0.0)
Psychiatric disorder	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Respiratory system	0	(0.0)	1	(0.1)	2	(0.3)	0	(0.0)	2	(1.7)
Skin and skin appendages	3	(0.7)	4	(0.6)	0	(0.0)	1	(0.2)	2	(1.7)
Urogenital system	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

* Statistical comparisons were only performed between the placebo and MK-0966 groups.
Although a patient may have had two or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

[P010; P029; P033; P040; P058]

Appendix 16.2. Patient discontinuation due to clinical adverse experiences (6-w, phase II

E-23

Number (%) of Patients With Clinical Adverse Experiences by Body System
Phase II Osteoarthritis Studies (Protocols 010 and 029)

	Placebo (N=217)		MK-0966 5 mg (N=149)		MK-0966 12.5 mg (N=144)		MK-0966 25 mg (N=210)		MK-0966 50 mg (N=97)		MK-0966 125 mg (N=74)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients with one or more adverse experiences	94	(43.3)	81	(54.4)	74	(51.4)	118	(56.2)	61	(62.9)	42	(56.8)
Patients with no adverse experience	123	(56.7)	68	(45.6)	70	(48.6)	92	(43.8)	36	(37.1)	32	(43.2)
Body as a whole/site unspecified	31	(14.3)	28	(18.8)	25	(17.4)	48	(22.9)	17	(17.5)	24	(32.4)
Cardiovascular system	5	(2.3)	7	(4.7)	9	(6.2)	9	(4.3)	5	(5.2)	3	(4.1)
Digestive system	28	(12.9)	29	(19.5)	16	(11.1)	40	(19.0)	25	(25.8)	15	(20.3)
Eyes, ears, nose, and throat	14	(6.5)	9	(6.0)	12	(8.3)	17	(8.1)	15	(15.5)	6	(8.1)
Hemic and lymphatic system	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.4)
Immune system	1	(0.5)	0	(0.0)	2	(1.4)	2	(1.0)	2	(2.1)	0	(0.0)
Metabolism and nutrition	4	(1.8)	0	(0.0)	0	(0.0)	2	(1.0)	2	(2.1)	4	(5.4)
Musculoskeletal system	20	(9.2)	13	(8.7)	10	(6.9)	24	(11.4)	12	(12.4)	4	(5.4)
Nervous system	22	(10.1)	14	(9.4)	15	(10.4)	15	(7.1)	10	(10.3)	14	(18.9)
Psychiatric disorder	0	(0.0)	2	(1.3)	3	(2.1)	3	(1.4)	2	(2.1)	0	(0.0)
Respiratory system	2	(0.9)	3	(2.0)	1	(0.7)	7	(3.3)	2	(2.1)	2	(2.7)
Skin and skin appendages	8	(3.7)	9	(6.0)	10	(6.9)	17	(8.1)	7	(7.2)	2	(2.7)
Urogenital system	7	(3.2)	4	(2.7)	6	(4.2)	8	(3.8)	6	(6.2)	2	(2.7)

Although a patient may have had two or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

[P010; P029]

Appendix 16.3. Clinical Adverse experiences. Patient discontinuation due to clinical adverse experiences in 6 month OA trials

.2.2 Patients Discontinued Due to Clinical Adverse Experiences—6-Month Studies (Cont.)

E-38

Number (%) of Patients Discontinued With Clinical Adverse Experiences by Body System
6-Month Osteoarthritis Studies

	Placebo† (N=371)		MK-0966 12.5 mg (N=490)		MK-0966 25 mg (N=879)		MK-0966 50 mg (N=379)		Ibuprofen 2400 mg (N=377)		Diclofenac 150 mg (N=498)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients with one or more adverse experiences	19	(5.1)	47	(9.6)	68	(7.7)	40	(10.6)	39	(10.3)	57	(11.4)
Patients with no adverse experience	352	(94.9)	443	(90.4)	811	(92.3)	339	(89.4)	338	(89.7)	441	(88.6)
Body as a whole/site unspecified	4	(1.1)	11	(2.2)	19	(2.2)	7	(1.8)	11	(2.9)	10	(2.0)
Cardiovascular system	2	(0.5)	5	(1.0)	8	(0.9)	6	(1.6)	5	(1.3)	10	(2.0)
Digestive system	7	(1.9)	18	(3.7)	25	(2.8)	18	(4.7)	18	(4.8)	22	(4.4)
Eyes, ears, nose, and throat	0	(0.0)	2	(0.4)	3	(0.3)	0	(0.0)	0	(0.0)	1	(0.2)
Hemic and lymphatic system	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Hepatobiliary system	0	(0.0)	0	(0.0)	2	(0.2)	0	(0.0)	0	(0.0)	1	(0.2)
Metabolism and nutrition	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Musculoskeletal system	2	(0.5)	2	(0.4)	1	(0.1)	2	(0.5)	0	(0.0)	2	(0.4)
s system	1	(0.3)	2	(0.4)	2	(0.2)	3	(0.8)	0	(0.0)	5	(1.0)
tric disorder	0	(0.0)	1	(0.2)	1	(0.1)	1	(0.3)	0	(0.0)	1	(0.2)
atory system	1	(0.3)	4	(0.8)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Skin and skin appendages	1	(0.3)	2	(0.4)	5	(0.6)	1	(0.3)	2	(0.5)	5	(1.0)
Urogenital system	0	(0.0)	3	(0.6)	1	(0.1)	1	(0.3)	3	(0.8)	3	(0.6)

† Placebo group had one-third less exposure than the MK-0966 groups.

Although a patient may have had two or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

[P034; P035; P044; P045]

Appendix 17. 1. Laboratory Adverse Experiences. Patients exceeding the predefined limits of change from baseline in all OA studies.

Laboratory test	Predefined limit	Treatment	6-week studies	6-month studies	6- mo to 86 w plus 29-10, 58-10
Hemoglobin (gm/dL)	Decrease ≥2.0 gm/dL	Placebo	2/398 (0.5)	5/346 (1.4)	NA
		MK-0966 5 mg	3/142 (2.1)	NA	NA
		MK-0966 12.5 mg	2/711 (0.3)	8/485 (1.6)	12/540 (2.2)
		MK-0966 25 mg	8/720 (1.1)	16/858 (1.9)	28/540 (5.2)
		MK-0966 50 mg	1/93 (1.1)	23/360 (6.4)	12/119 (10.1)
		MK-0966 125 mg	2/73 (2.7)	NA	NA
		Ibuprofen 2400 mg	14/464 (3.0)	25/353 (7.1)	NA
		Diclofenac 150 mg	NA	29/495 (5.9)	31/434 (7.1)
		Nabumetone 1500 mg	0/114 (0.0)	NA	1/85 (1.2)
Hematocrit (%)	Decrease ≥6.0% (absolute decrease)	Placebo	8/397 (2.0)	4/346 (1.2)	NA
		MK-0966 5 mg	5/142 (3.5)	NA	NA
		MK-0966 12.5 mg	11/710 (1.5)	3/485 (0.6)	26/540 (4.8)
		MK-0966 25 mg	23/720 (3.2)	24/858 (2.8)	40/539 (7.4)
		MK-0966 50 mg	11/93 (11.8)	37/360 (10.3)	24/119 (20.2)
		MK-0966 125 mg	8/72 (11.1)	NA	NA
		Ibuprofen 2400 mg	27/464 (5.8)	38/353 (10.8)	NA
		Diclofenac 150 mg	NA	18/495 (3.6)	39/434 (9.0)
		Nabumetone 1500 mg	0/114 (0.0)	NA	1/85 (1.2)
C count (10^3/microL)	Decrease ≥20.0% and value <LLN	Placebo	15/397 (3.8)	34/346 (9.8)	NA
		MK-0966 5 mg	5/142 (3.5)	NA	NA
		MK-0966 12.5 mg	40/711 (5.6)	67/485 (13.8)	49/540 (9.1)
		MK-0966 25 mg	47/720 (6.5)	118/858 (13.8)	49/540 (9.1)
		MK-0966 50 mg	4/93 (4.3)	54/360 (15.0)	5/119 (4.2)
		MK-0966 125 mg	2/73 (2.7)	NA	NA
		Ibuprofen 2400 mg	28/464 (6.0)	31/353 (8.8)	NA
		Diclofenac 150 mg	NA	69/495 (13.9)	47/434 (10.8)
		Nabumetone 1500 mg	9/114 (7.9)	NA	6/85 (7.1)
Lymphocyte count (10^3/microL)	Decrease ≥20.0% and value <LLN	Placebo	13/389 (3.3)	29/340 (8.5)	NA
		MK-0966 5 mg	1/142 (0.7)	NA	NA
		MK-0966 12.5 mg	46/697 (6.6)*	57/477 (11.9)	43/525 (8.2)
		MK-0966 25 mg	49/711 (6.9)*	128/849 (15.1)	55/536 (10.3)
		MK-0966 50 mg	3/93 (3.2)	49/350 (14.0)	3/119 (2.5)
		MK-0966 125 mg	0/73 (0.0)	NA	NA
		Ibuprofen 2400 mg	38/455 (8.4)	47/350 (13.4)	NA
		Diclofenac 150 mg	NA	64/488 (13.1)	28/430 (6.5)
		Nabumetone 1500 mg	16/111 (14.4)	NA	10/79 (12.7)
Platelet count (10^3/microL)	Decrease ≥25.0% and value <LLN	Placebo	3/396 (0.8)	9/346 (2.6)	NA
		MK-0966 5 mg	0/142 (0.0)	NA	NA
		MK-0966 12.5 mg	8/710 (1.1)	17/485 (3.5)	13/540 (2.4)
		MK-0966 25 mg	9/719 (1.3)	26/857 (3.0)	11/539 (2.0)
		MK-0966 50 mg	0/92 (0.0)	18/360 (5.0)	3/119 (2.5)
		MK-0966 125 mg	0/73 (0.0)	NA	NA
		Ibuprofen 2400 mg	3/463 (0.6)	7/353 (2.0)	NA
		Diclofenac 150 mg	NA	19/495 (3.8)	8/434 (1.8)
		Nabumetone 1500 mg	3/114 (2.6)	NA	4/85 (4.7)

Appendix 17. (cont). Patients exceeding the predefined limits of change from baseline in all OA studies.

Laboratory test	Predefined limit	Treatment	6-week studies	6-month studies	6- mo to 86 w plus 29-10, 58-10
Serum creatinine (mg/dL)	Increase ≥0.5 and value >ULN	Placebo	1/397 (0.3)	1/346 (0.3)	NA
		MK-0966 5 mg	0/142 (0.0)	NA	NA
		MK-0966 12.5 mg	6/713 (0.8)	3/484 (0.6)	5/540 (0.9)
		MK-0966 25 mg	4/720 (0.6)	4/859 (0.5)	11/540 (2.0)
		MK-0966 50 mg	1/93 (1.1)	7/360 (1.9)	5/119 (4.2)
		MK-0966 125 mg	1/73 (1.4)	NA	NA
		Ibuprofen 2400 mg	4/467 (0.9)	6/354 (1.7)	NA
		Diclofenac 150 mg	NA	11/495 (2.2)	4/434 (0.9)
		Nabumetone 1500 mg	1/114 (0.9)	NA	1/85 (1.2)
Serum potassium (mEq[K]/L)	Decrease ≥0.8 and value <LLN	Placebo	2/395 (0.5)	4/346 (1.2)	NA
		MK-0966 5 mg	1/142 (0.7)	NA	NA
		MK-0966 12.5 mg	2/712 (0.3)	6/484 (1.2)	9/540 (1.7)
		MK-0966 25 mg	6/720 (0.8)	6/859 (0.7)	3/540 (0.6)
		MK-0966 50 mg	0/93 (0.0)	4/359 (1.1)	0/119 (0.0)
		MK-0966 125 mg	0/73 (0.0)	NA	NA
		Ibuprofen 2400 mg	7/465 (1.5)	1/354 (0.3)	NA
		Diclofenac 150 mg	NA	4/495 (0.8)	3/434 (0.7)
		Nabumetone 1500 mg	0/114 (0.0)	NA	1/85 (1.2)
	Increase ≥0.8 and value >ULN	Placebo	8/395 (2.0)	13/346 (3.8)	NA
		MK-0966 5 mg	1/142 (0.7)	NA	NA
		MK-0966 12.5 mg	23/712 (3.2)	25/484 (5.2)	24/540 (4.4)
		MK-0966 25 mg	23/720 (3.2)	73/859 (8.5)	36/540 (6.7)
		MK-0966 50 mg	3/93 (3.2)	59/359 (16.4)	4/119 (3.4)
		MK-0966 125 mg	0/73 (0.0)	NA	NA
		Ibuprofen 2400 mg	8/465 (1.7)	23/354 (6.5)	NA
		Diclofenac 150 mg	NA	29/495 (5.9)	21/434 (4.8)
		Nabumetone 1500 mg	7/114 (6.1)	NA	4/85 (4.7)
Serum alanine amino-transferase (IU[amino-transferase]/L)	Increase ≥100.0% and value >ULN	Placebo	2/397 (0.5)	8/346 (2.3)	NA
		MK-0966 5 mg	2/142 (1.4)	NA	NA
		MK-0966 12.5 mg	12/713 (1.7)	23/484 (4.8)	22/540 (4.1)
		MK-0966 25 mg	9/720 (1.3)	47/859 (5.5)	29/540 (5.4)
		MK-0966 50 mg	2/93 (2.2)	22/360 (6.1)	7/119 (5.9)
		MK-0966 125 mg	5/73 (6.8)	NA	NA
		Ibuprofen 2400 mg	4/467 (0.9)	18/354 (5.1)	NA
		Diclofenac 150 mg	NA	129/495 (26.1)	86/434 (19.8
		Nabumetone 1500 mg	0/114 (0.0)	NA	3/85 (3.5)
Serum aspartate amino-transferase (IU[amino-transferase]/L)	Increase ≥100.0% and value >ULN	Placebo	2/397 (0.5)	5/346 (1.4)	NA
		MK-0966 5 mg	1/142 (0.7)	NA	NA
		MK-0966 12.5 mg	11/713 (1.5)	14/484 (2.9)	16/540 (3.0)
		MK-0966 25 mg	6/720 (0.8)	38/859 (4.4)	20/540 (3.7)
		MK-0966 50 mg	1/93 (1.1)	22/360 (6.1)	4/119 (3.4)
		MK-0966 125 mg	4/73 (5.5)	NA	NA
		Ibuprofen 2400 mg	3/467 (0.6)	15/354 (4.2)	NA
		Diclofenac 150 mg	NA	66/495 (13.3)	42/434 (9.7)
		Nabumetone 1500 mg	0/114 (0.0)	NA	0/85 (0.0)

Appendix 18. GI clinical studies in the rofecoxib program

Protocol	Phase	Description (Study Location)	Total Daily Dose	Treatment (Weeks)	Total Number of Patients Randomized
Healthy Subjects					
Models of GI Tract Injury					
041	IIb	Small Intestinal Permeability (Multinational)	PBO MK-0966 25, 50 mg Indomethacin 150 mg	1	39
050	IIb	Fecal Red Blood Cell Loss (Multinational)	PBO MK-0966 25, 50 mg Ibuprofen 2400 mg	4	67
Upper Endoscopy					
009	I	Upper Endoscopy After 7-Day Treatment (U.S.)	PBO MK-0966 250 mg Ibuprofen 2400 mg Aspirin 2600 mg	1	170
OA Patients					
Upper Endoscopy					
044	III	Ibuprofen Comparison with Upper Endoscopy (U.S.)	PBO MK-0966 25, 50 mg Ibuprofen 2400 mg	24	742
045	III	Ibuprofen Comparison with Upper Endoscopy (U.S./Multinational)	PBO MK-0966 25, 50 mg Ibuprofen 2400 mg	24	775
Pooled Analysis - Protocol 069					

Appendix 19. Liver function tests and in OA trials. (6 week, 6 month and 6month to 86-week studies)

	Placebo* n/m (%)	MK-0966 5 mg n/m (%)	MK-0966 12.5 mg n/m (%)	MK-0966 25 mg n/m (%)	MK-0966 50 mg n/m (%)	MK-0966 125 mg n/m (%)	Comparators Diclofenac n/m (%)	Comparators Ibuprofen n/m (%)	Comparators Nabumet n/m (%
Blood Chemistry									
Alanine Aminotransferase Increase									
6 week	2/404 (0.5)	1/143 (0.7)	14/719 (1.9)	12/723 (1.7)	1/95 (1.1)	4/74 (5.4)	NA	6/467 (1.3)	0/114 (0.0
6 month	11/363 (3.0)	NA	12/486 (2.5)	29/868 (3.3)	9/372 (2.4)	NA	59/496 (11.9)	13/371 (3.5)	NA
1 year	NA	NA	16/486 (3.3)	15/483 (3.1)	NA	NA	69/496 (13.9)	NA	NA
6 month to 86 week	NA	NA	8/412 (1.9)	10/434 (2.3)	5/74 (6.8)	NA	21/406 (5.2)	NA	NA
Aspartate Aminotransferase Increased									
6 week	3/404 (0.7)	0/143 (0.0)	13/719 (1.8)	10/723 (1.4)	1/95 (1.1)	4/74 (5.4)	NA	6/467 (1.3)	1/114 (0.9
6 month	13/363 (3.6)	NA	13/486 (2.7)	26/868 (3.0)	10/372 (2.7)	NA	44/498 (8.9)	10/371 (2.7)	NA
1 year	NA	NA	17/486 (3.5)	12/483 (2.5)	NA	NA	53/496 (10.7)	NA	NA
6 month to 86 week	NA	NA	7/412 (1.7)	8/434 (1.8)	5/74 (6.8)	NA	15/406 (3.7)	NA	NA

Appendix 20. Narrative for patients with LFT > 3 ULN who did not recover while on treatment and considered possibly drug-related by the investigator.

AN 5332 (Protocol 034; 25 mg rofecoxib), a 71-year-old male, discontinued due to presumptive drug-induced hepatitis on Study Day 280. Baseline (Visit 2) laboratory tests were ALT of 23 (ULN=25 IU/L), AST of 23 (ULN=22 IU/L), serum alkaline phosphatase of 61 (ULN=72 IU/L), and total serum bilirubin of 1.21 (ULN=1.1 mg/dL). The patient developed an increased ALT of 34 IU/L and AST of 37 IU/L on Study Day 184. Maximum ALT and AST values were **223 and 225 IU/L**, respectively, on Study Day 269. Serum alkaline phosphatase and total serum bilirubin were 83 IU/L and 1.39 mg/dL at this time. There was no evidence of other causes for the increased LFT's (Viral hepatitis testing was negative and there were no clinical signs of hepatitis; the patient reported no alcohol use, new concomitant medications, intramuscular injections, intercurrent illness, or increased physical activity. No history of hepatitis or liver disease was reported). The patient discontinued treatment on Study Day 280; ALT, AST, serum alkaline phosphatase, and total serum bilirubin values were 211, 187, 71 IU/L, and 2.3 mg/dL, respectively. ALT, AST, serum alkalinephosphatase, and total serum bilirubin were 232, 236, 75 IU/L, and 2.08 mg/dL, respectively, 7 days later. Follow-up continued until approximately 2 months after discontinuation of study treatment, when ALT, AST, serum alkaline phosphatase, and total serum bilirubin were 30, 28, 71 IU/L, and 0.94 mg/dL, respectively. The investigator termed this episode "hepatitis" and it was considered by the investigator to be probably drug related.

AN 5792 (Protocol 034; 25 mg rofecoxib), a 67-year-old female with a history of hypertension, discontinued due to increased ALT and AST. Baseline (Visit 2) labs showed ALT of 13 IU/L (ULN=25 IU/L), AST of 13 IU/L(ULN=22 IU/L), serum alkaline phosphatase of 93 IU/L (ULN=72 IU/L), and total serum bilirubin of 0.34 mg/dL (ULN=1.1 mg/dL). The patient's only concomitant medication was enalapril 5 mg. On Study Day 272, the patient developed increased **ALT and AST of 508 IU/L and 255 IU/L**, respectively. Maximum ALT and AST values were 548 and 240 IU/L, respectively, on Study Day 286. Serum alkaline phosphatase and total serum bilirubin were176 IU/L and 1.48 mg/dL, respectively, at that time. Study therapy was discontinued 4 days later. There was no evidence of other causes for the increased LFT's. No rescue acetaminophen was used. The patient did not exhibit any clinical signs or symptoms of hepatic illness. ALT, AST, serum alkaline phosphatase, and totalserum bilirubin were 108 IU/L, 59 IU/L, 104 IU/L, and 1.4 mg/dL, respectively, 10 days after discontinuation of study therapy. Follow-up continued until approximately 41 days after discontinuation of study therapy when ALT,AST, serum alkaline phosphatase, and total serum bilirubin were 31, 21, 95 IU/L, and 0.68 mg/dL, respectively. These laboratory adverse experiences were considered by the investigator to be possibly drug related.

AN 6952 (Protocol 033; 25 mg rofecoxib), a 69-year-old female with a history of leukopenia, migraine, and asthma, had a baseline (Visit 2) ALT of 15 IU/L (ULN=25 IU/L) and AST of 17 IU/L (ULN=22 IU/L).

Prior medications that continued postrandomization included conjugated estrogen, fluticasone, salmeterol, and albuterol sulfate. Additionally, the patient had been taking zafirlukast 40 mg daily for asthma, beginning at least 103 days prior to initiating study therapy and continuing for the duration of the study. There was no evidence of other causes for the increased LFT's. On Study Day 29, the patient developed moderate asthenia/fatigue, but otherwise did not exhibit any clinical signs or symptoms of hepatic illness. On Study Day 31, ALT and AST increased to 59 IU/L and 54 IU/L, respectively. The values obtained on **Study Day 47, the day the patient completed the study, were ALT=209 IU/L and AST=169 IU/L.** Bilirubin and alkaline phosphatase levels remained within normal limits throughout the study. Several repeat laboratory tests were done in the weeks following the last dose of study drug. Sixty (60) days after the last dose, ALT was 118 IU/L and AST was 86 IU/L. At 104 days after the last dose, ALT and AST were 30 IU/L and 25 IU/L, respectively. All LFT adverse events reported were considered probably not related to study drug; an alternative explanation was not provided.

AN 507 (Protocol 045; 25 mg rofecoxib), a 52-year-old female with a history of hypothyroidism, developed increased ALT and AST on Study Day 42. Baseline (Visit 2) labs showed mildly increased ALT of 29 IU/L (ULN=25 IU/L) and AST of 22 IU/L (ULN=22 IU/L) alkaline phosphatase 88 IU/L (ULN=72 IU/L) and total serum bilirubin 0.8 mg/dL (ULN=1.1 mg/dL). Concomitant medications included estrogenic preparations for hormone replacement therapy and thyroxine for hypothyroidism. On Study **Day 42**, ALT and AST reached their maximum values of **85 and 68 IU/L**, respectively. Alkaline phosphatase was 106 IU/L and total bilirubin 1.1. Study therapy continued uninterrupted. No associated signs or symptoms were reported. There were no other explanations for the elevated LFT's. Laboratory tests performed on Study Day 63 revealed ALT, AST, alkaline phosphatase and total bilirubin of 30 mIU/L, 21 mIU/L, 85 IU/L and 1.1 mg/dL, respectively. The patient completed the study per protocol and the last dose of drug was on Study Day 112. ALT, AST, alkaline phosphatase and total bilirubin at that timewere 52 mIU/L, 28 mIU/L, 103 IU/L and 1.1 mg/dL, respectively. Laboratory adverse experiences were determined by the investigator to be possibly related to study therapy.

AN 37 (Protocol 010; 125 mg ROFECOXIB), a 68-year-old female. Concomitant medications included lovastatin, flurazepam, calcium carbonate, zinc supplement, and estrogen vaginal cream. Laboratory values at baseline (Visit 2) were alkaline phosphatase of 61 IU/L (ULN=115 IU/L), ALT of 16 IU/L (ULN=34 IU/L), AST of 19 IU/L (ULN=34 IU/L) and total serum bilirubin of 0.7 mg/dL (ULN=1.2 mg/dL). Beginning on Study **Day 23,** the patient complained of epigastric discomfort. Laboratory tests on Study Day 29 revealed an alkaline phosphatase of 202 IU/L, ALT of 118 IU/L, and AST of 74 IU/L. On Study Day 35 the patient complained of fatigue. On Study Day 36 **demonstrated ALT of 80, AST of 58, alkaline phosphatase of 787 IU/L, and total serum bilirubin of 1.7 mg/dL.** On Study Day 38, the patient was discontinued from the study, although by that time her clinical symptoms had completely resolved. Additional studies were performed including a right upper quadrant (RUQ) ultrasound which revealed no abnormalities of liver, pancreas, gall bladder or bile ducts. Hepatitis B Surface Ag, Hepatitis A IgM, and Hepatitis C Ab were all negative. EBV and CMV laboratory results were consistent with prior exposure. Repeat laboratory testing over the next 4 months showed a gradual return of alkaline phosphatase, ALT and AST to normal levels. These laboratory adverse experiences were determined by the investigator to be possibly related to study therapy.

Appendix 21. Narrative for patients with pancreatitis.

AN 2105 (Protocol 029) was a 59-year-old woman with a history of hypertension, hypercholesterolemia, and cholecystectomy in 1977. The patient was allocated to study therapy in MK-0966 5 mg/day on 11JUN96. The patient had been taking diclofenac sodium 150 mg per day, which was discontinued 5 days prior to allocation. Other medications at the time of study entry included lisinopril 40 mg q.d., hydrochlorothiazide 25 mg q.d., estrogen/progesterone supplement, clorazepate prn insomnia, Zantac 150 q.d. prn dyspepsia. Also of note, the patient was begun on **gemfibrozil** 600 mg. P.O. b.i.d. 3 days prior to allocation. This medication was started by the patient's primary care physician for mild hypercholesterolemia. After 29 days of study therapy, the patient went for a scheduled follow-up visit. She reported that the gemfibrozil had been discontinued on July 7, due to flatulence. Her last dose of study medication had been the previous day, 08JUL96. On July 9th , approximately 30 minutes after eating, the patient developed acute pancreatitis. She was kept in P.O., treated with I.V. fluids, 50 mg of meperidine and 25 mg of hydroxyzine. The following day the serum amylase fell to 99, serum lipase fell to 340. A CT scan of the abdomen was obtained on 10JUL96. Scans through the abdomen demonstrated a 1.8 centimeter area of low attenuation in the lateral aspect of the right lobe of the liver consistent with a small cyst. Surgical clips were noted in the region of the gallbladder fossa from the previous cholecystectomy. The common bile duct was prominent. The diameter of the common bile duct in the region of the pancreatic head was greater than 1.5 centimeters. There were no evidence however of dilated intrahepatic bile ducts. Images of the pancreas demonstrated mild dilation of the pancreatic duct. There was no evidence of fluid collection with or around the pancreas. Patient was formally discontinued from the study with an AE of pancreatitis and seen for a poststudy visit without further complaint. The AE was rated as probably not related to study drug given the recent addition of gemfibrozil as a potential confounding factor.

AN 2231, (study 29-20/30) a 69-year-old female, developed pancreatitis following 62 weeks of study therapy (MK966 25 mg/day). The patient had a similar episode several years prior, in association with cholelithiasis. The patient was hospitalized for endoscopic evaluation which revealed an inflamed ampulla of Vater which was subsequently dilated. The adverse experience was considered probably not related to study therapy. Study therapy was interrupted during the adverse experience. **The patient resumed therapy following resolution of symptoms and remained in the study.**

AN 5126 (study 34-10). A 69 year old female with history of hypertension and osteoporosis started MK or control on Jan 22/97. Concomitant therapy included quinapril and amiloride/hydrochlorothiazide. On September 27/97 the patient was hospitalized with acute pacretitis. She had no previous history of alcohol intake or hyperlipidemia. Therapy was interrupted until 9/10/97. The reporting physician felt that the acute pancreatitis was not related to therapy.

AN 1436 (study 058), an 83-year-old man with hypertension, a history of coronary artery bypass surgery, hyperlipidemia, hypothyroidism, and dyspepsia, was hospitalized for chest pain after 6 days of therapy (rofecoxib12.5 mg). The patient's nonstudy medications at baseline included low-dose aspirin, ramipril, levothyroxine, atorvastatin, and famotidine. A negative exercise stress test ruled out a cardiac etiology for the chest pain. An endoscopy revealed gastritis and duodenal erosions, but no ulcer. A biopsy was negative for *Helicobacter pylori* and revealed chronic inflammatory changes. Also noted were mildly elevated serum amylase and lipase, **possibly consistent with pancreatitis**. The investigator attributed the erosions and gastritis to the patient's pre-study NSAID, salsalate. The etiology of the patient's chest pain was never definitively diagnosed. Study drug was discontinued due to the gastritis and duodenal erosions. Thirteen days after rofecoxib was discontinued, amylase and lipase were normal.

Appendix 22. Hypertension adverse experiences – Patients exceeding predefined limits of change from baseline for systolic and diastolic BP. OA studies 6-week, 6-month and one-year studies.

Vital Sign	Predefined Limit of Change From Baseline	Treatment	6-Week Studies (4 or 5 Postrandomization Visits) 1 or More Times Number*/ Total‡	(%)	6-Week Studies 2 or More Times Number*/ Total‡	(%)	6-Month Studies† (6 or 9 Postrandomization Visits) 1 or More Times Number*/ Total‡	(%)	6-Month Studies† 2 or More Times Number*/ Total‡	(%)	1-Year Studies‡ (11 Postrandomization Visits) 1 or More Times Number*/ Total‡	(%)	1-Year Studies‡ 2 or More Times Number*/ Total‡	(%)
Systolic blood pressure (mm Hg)	Increase >20.0 mm (mm Hg) and value > 140.0 (mm Hg)	Placebo	31/408	(7.6)	7/347	(2.0)	49/347	(14.1)	14/328	(4.3)	—	—	—	—
		MK-0966 5 mg	19/148¶	(12.8)	6/148¶	(4.1)	—	—	—	—	—	—	—	—
		MK-0966 12.5 mg	74/720	(10.3)	20/679	(2.9)	92/486	(18.9)	33/459	(7.0)	116/486	(23.9)	46/469	(9.8)
		MK-0966 25 mg	105/725	(14.5)	31/689	(4.5)	190/864	(22.0)	76/824	(9.2)	19/485	(24.5)	50/460	(10.9)
		MK-0966 50 mg	11/97¶	(11.3)	3/97	(3.1)	111/362	(30.7)	56/340	(16.5)	—	—	—	—
		MK-0966 125 mg	24/74¶	(32.4)	10/74	(13.5)	—	—	—	—	—	—	—	—
		Ibuprofen 2400 mg	69/468	(14.7)	12/439¶	(2.7)	76/357	(21.3)	33/328	(10.1)	—	—	—	—
		Nabumetone 1500 mg	14/115¶	(12.2)	4/109¶	(3.7)	—	—	—	—	—	—	—	—
		Diclofenac 150 mg	—	—	—	—	64/495	(12.9)	24/479	(5.0)	96/495	(19.4)	47/479	(9.8)
Diastolic blood pressure (mm Hg)	Increase >15.0 and (mm Hg) value > 90.0 (mm Hg)	Placebo	8/408	(2.0)	0/408	(0.0)	20/347	(5.8)	4/328	(1.2)	—	—	—	—
		MK-0966 5 mg	3/148¶	(2.0)	1/148¶	(0.7)	—	—	—	—	—	—	—	—
		MK-0966 12.5 mg	13/720	(1.8)	3/679	(0.4)	27/486	(5.6)	6/469	(1.3)	41/486	(8.4)	10/469	(2.1)
		MK-0966 25 mg	27/725	(3.7)	5/689	(0.7)	94/864	(10.9)	16/824	(1.9)	47/485	(9.7)	14/460	(3.0)
		MK-0966 50 mg	3/97¶	(3.1)	0/97¶	(0.0)	36/362	(9.9)	16/340	(4.7)	—	—	—	—
		MK-0966 125 mg	2/74¶	(2.7)	0/74¶	(0.0)	—	—	—	—	—	—	—	—
		Ibuprofen 2400 mg	11/468	(2.4)	0/468	(0.0)	36/357	(10.1)	9/328	(2.7)	—	—	—	—
		Nabumetone 1500 mg	2/115¶	(1.7)	0/115¶	(0.0)	—	—	—	—	—	—	—	—
		Diclofenac 150 mg	—	—	—	—	23/495	(4.6)	6/479	(1.3)	30/495	(6.1)	9/479	(1.9)

* Number of patients meeting the predefined limit criteria.
‡ Total number of patients with valid values of the vital sign test.
§ These treatment groups with small numbers of patients from single studies are provided for comparative purposes only.
‖ Placebo group of the 6-Month Studies had one-third less exposure than the MK-0966 groups.
¶ The first 6 months of these studies are also counted in the 6-Month Studies and the second 6 months of these studies are also counted in the 6-Month-to-86-Week Studies.
Dashes indicate the treatment group was not part of the study design.

[P010; P029; P033; P034; P034C; P035; P040; P044; P045; P058]

Appendix 22. cont. Hypertension adverse experiences. 6 month OA studies

	Placebo‖ (N=371)		MK-0966 12.5 mg (N=490)		MK-0966 25 mg (N=879)		MK-0966 50 mg (N=379)		Ibuprofen (N=377)		Diclofenac 150 mg (N=498)	
Hypertension Adverse Experiences												
Number of Patients with hypertension adverse experiences	13 (3.5)¶		28 (5.7)¶		60 (6.8)¶		46 (12.1)¶		18 (4.7)¶		15 (3.0)¶	
	n	(%)†	n	(%)†	n	(%)†	n	(%)†	n	(%)†	n	(%)†
change in antihypertensive medication‡	8/13	(61.5)	19/28	(67.9)	39/60	(65)	30/46	(65.2)	10/18	(55.5)	7/15	(46.6)
discontinued for adverse experience	0/13	(0.0)	1/28	(3.5)	4/60	(6.7)	3/46	(6.5)	3/18	(16.6)	1/15	(6.6)
exceeding blood pressure predefined limits of change§	2/13	(15.3)	5/28	(17.8)	16/60	(26.6)	20/46	(43.3)	6/18	(33.3)	6/15	(40.0)

† Percentage is number of patients with specified criterion/number of patients with the adverse experience.
‡ Represents either a change in dose and/or a new medication.
§ A patient is counted if they exceeded the systolic and/or diastolic predefined limits of change at 2 or more visits. Diastolic predefined limit: >15 mm Hg increase from baseline and value >90 mm Hg; systolic predefined limit: >20 mm Hg from baseline and value >140 mm Hg.
‖ Placebo group had one-third less exposure than the MK-0966 groups.
¶ The percentages are the number of patients with the adverse experience/number of patients (N) in the treatment group.

[P034; P035; P044; P045]

Appendix 23. Patients With Adverse Experiences of Renal Failure, patients discontinued due to increased BUN or creatinine and patients with doubling in serum creatinine from baseline.

1. Renal failure.

NSAIDs have been reported to cause decreases in GFR resulting in overt renal decompensation. Three patients had an adverse experience of renal failure (AN 2382 [P029, 50 mg rofecoxib]; AN 8227 [P035, 25 mg rofecoxib]- and AN 571 [P045; 2400 mg ibuprofen]- among all the Phase II/III OA studies. Although the adverse experience term used by the investigator was renal failure, none of these patients required dialysis.

AN 2382 (rofecoxib 50 mg QD) was 69 year-old female with a previous history of edema. Concomitant medications included HCTZ/triamtirene for edema. The patient had a rise in serum creatinine from a baseline of 0.8 mg/dL (ULN 1.2 mg/dL) to a maximum value of 1.3 mg/dL on Study Day 45. The rise in serum creatinine was temporally **associated with an increase in dose of hydrochlorothiazide plus triamterene.** The patient discontinued study therapy on Study Day 74 for this elevation but remained on the higher dose of diuretic. Serum creatinine was 1.2 mg/dL 184 days after last dose of study therapy. This adverse experience of renal failure was considered to be possibly drug related by the investigator.

AN 8227 (rofecoxib 25 mg QD) was a 54 year-old female with a history of proteinuria who developed acute renal failure while on treatment with rofecoxib 25 mg QD. On Study Day 214, the2 days later was hospitalized for pneumonia and treated with cefotaxime. Serum creatinine which was 0.9 mg/dL (ULN 1.5 mg/dL) at baseline and 1.0 mg/dL on Study Day 182 rose to 4.2 mg/dL on Study Day 219. Serum creatinine returned to baseline upon the discontinuation of cefotaxime. This adverse experience of renal failure was considered not drug related by the investigator.

2) Patients discontinued due to increased BUN or creatinine.

AN 4146 (rofecoxib 5 mg QD, protocol 029) was a 74 year old female with a history of hyperlipidemia and hypertension with BUN and creatinine values of 22 mg/dL and 1.2 mg/dL respectively, at baseline. Concomitant medications included verapamil, HCTX, enalapril and guanifacine hydrochloride for hypertension. Twenty two days after the initiation of study treatment BUN was 37 mg/dL and went up to 43 mg/dL after 43 days of treatment. Creatinine remained unchanged. On day 72 the patient developed right hand swelling that resolved after 27 days, while on treatment. **On day 144 the patient was discontinued due to increased BUN of 37 mg/dL.** Serum creatinine was 1.6 mg/dL at this time. It is not clear when the serum creatinine increased because it was said to be "unchanged from baseline". However, both increased serum BUN and creatinine were reported as an adverse event possibly related to study drug.

AN 2202 (rofecoxib 25 mg, protocol 029) was a 69 year old female with a history of a previous renal disorder noted during prior clinical trials with NSAIDs. Concomitant medications included levothyroxine, hydrochlorothiazide and clonidine. BUN and creatinine values at baseline were 9 mg/dL and 1.2 mg/dL respecively (normal range 0.4 to 1.2 respectively). During the study, the patient exhibited fluctuating BUN and creatinine values. Following 16 months of study therapy, the patient was **discontinued when BUN and creatinine were 47 mg/dL and 1.7 mg/dL respectively**, confirmed by repeated assessment one week later. Study medication was discontinued and three weeks after discontinuation repeat values (at a local laboratory) were 17 mg/dL and 0.6 mg/dL for BUN and creatinine respectively. (normal range 0.6 to 1.5 mg/dL respectively). The adverse experience was considered by the investigator to be possibly related to study medication.

3. Patients with doubling serum creatinine from baseline.

Six rofecoxib and 1 diclofenac patient had a doubling of serum creatinine from baseline during therapy among all the Phase II/III OA studies (AN 2067 [12.5 mg rofecoxib; Protocol 029]; AN 2308 [25 mg rofexocib; Protocol 029]; AN 2281 [25 mg/50 mg rofecoxib; Protocol 029]; AN 34 [50 mg rofecoxib; Protocol 045]; AN 2183 [50 mg rofecoxib; Protocol 029]; and AN 2446 [50 mg rofecoxib; Protocol 029]; AN 5301 [150 mg diclofenac; Protocol 035]). All patients, except AN 2446, continued study therapy and had resolution of the increase in serum creatinine (follow-up value returned to within 0.3 mg/dL of the baseline value). AN 2446 discontinued study therapy for a myocardial infarction on Study Day 66. Serum creatinine was 0.7 mg/dL (ULN=1.2 mg/dL) at baseline and 0.6 mg/dL on Study Day 57. Thirty-three days after last dose of therapy, creatinine was 1.6 mg/dL. Repeat serum creatinine obtained 8 days later was 1.1 mg/dL. This elevation in serum creatinine was not considered an adverse experience by the investigator.

Appendix 24. Neurologic AE of unclear etiology.

AN 2650 (study 068). 68 year old woman with RA, no significant past medical history, no CV risks factors, no history of previous neurologic events. Concomitant medications included: prednisone 3 mg/day (started 4 months prior to study entry and was decreased to 2 mg/day one month prior to entry), premarin/provera, calcium and ranitidine. The patient entered the study on 4/29/98 (rofecoxib 25 mg/d). On 5/24/98 she complained of lethargy, decreased memory, blurry vision and difficulty finding words. An EEG was consistent with diffuse cerebral dysfunction. A CT of the brain unspecific changes that "more likely reflect changes of microvascular ischemic disease. There was no evidence of large vessel infarct or hemorrhage. No posterior circulation infarcts were visible. The patient was discontinued from the study due to "encephalopathy". The adverse event was considered by the investigator of moderate intensity and possibly related to study drug.

AN 2083 (Study 068). 54 year old man with severe RA. Past medical history significant for hypercholesterolemia and ECG findings of an old inferior wall M.I. No history of previous neurologic symptoms. Concomitant medications included simvastatin and methotrexate 7.5 mg/week. The patient entered the study in 3/9/98 (rofecoxib 5 mg/d). On 3/12/99 he noticed intention tremor of the right hand. On 3/17/98 he noticed slurred speech. On 3/18/99 he started experiencing "mouth dropping". The CRF mentions that a CT scan of the brain did have a "white matter lesion". All symptoms resolved. A neurology consultant (after rofecoxib discontinuation) could not make a definitive diagnosis. The adverse event was coded as "possible demyelinating disease". The investigator considered this episode as possibly related to study drug.