Table 5-033. Listing of Patients Discontinued Due to Clinical Adverse Experiences

AN	Gender	Race	Age	Relative Day of Onset	Adverse Experience	Duration of AE	Relative Day of Discontinuation	Action Taken	Outcome
Placebo									
6384	M	White	63	25	Cerebrovascular accident	3.75 months	37	Discontinued PRx†	Recovered
MK-0966 12.5 mg									
6388	F	White	63	12	Coronary artery disease	Continuing	12	Discontinued PRx	Not recovered‡
6337	F	Black	66	4	Lower extremity edema	7 days	9	Discontinued PRx	Recovered
7013	F	Black	55	3	Edema	14 days	5	Discontinued PRx	Recovered
6357	F	White	69	2	Chest pain	0.75 hours	2	Discontinued PRx	Recovered
7227	F	Black	56	21	Edema	4 hours	22	Discontinued PRx	Recovered
MK-0966 25 mg									
6631	M	White	45	12	Chest pain	3 days	12	Discontinued PRx	Recovered
6998	F	White	78	19	Atrial arrhythmia	4 days	18	Discontinued PRx	Recovered
6504	F	White	49	4	Lower extremity edema	11 days	6	Discontinued PRx	Recovered
7023	F	White	69	2	Unstable angina	6 days	2	Discontinued PRx	Recovered
Ibuprofen 2400 mg									

[Adapted from NDA 21-042, Vol. 1.129, Table 45, pages 159-161. †PRx = Study medication. ‡Not recovered = Adverse experience was continuing at last follow-up. § The patient had the experience on Relative Day 19, and the last dose of study medication had been taken on Relative Day 18.]

Adverse Events Incidence Tables: Cardiovascular- and renal-related adverse experiences with an incidence ≥2.0% (in one or more treatment group) are summarized in Table 6-033. Because the terminology used by the investigators in reporting adverse events related to "fluid retention" or "hypertension" varied, they were incorporated by the sponsor into the following all-inclusive categories: Edema- and Hypertension-Type Adverse events (Tables 7-033 and 8-033).

Table 6-033. Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence ≥2.0% in 1 or More Treatment Groups) by Body System

	Placebo	MK-0966		Ibuprofen
		12.5 mg	25 mg	2400 mg
	(N=69)	(N=219)	(N=227)	(N=221)
	n (%)	n (%)	n (%)	n (%)
Body as a Whole/Site Unspecified				
Lower extremity edema	0 (0.0)	7 (3.2)	14 (6.2)*	15 (6.8)*
Cardiovascular System				
Blood pressure increased	0 (0.0)	6 (2.7)	5 (2.2)	2 (0.9)
Hypertension	1 (1.4)	1 (0.5)	5 (2.2)	3 (1.4)

[Adapted from NDA 21-042, Vol. 1.129, Table 41, pages 145 and 146. * p<0.05 vs. placebo. 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.]

Table 7-033 summarizes both the number and the percentage of patients with specific edema-type adverse experiences. MK-0966 treatment was associated with a dose-dependent incidence of edema-type adverse events. At any dose of MK-0966 there was a higher rate of occurrence for edema-type adverse experiences than in the placebo group. However, the rate of occurrence of edema-type adverse experiences in the Ibuprofen group was numerically higher than in the MK-0966 groups.

Table 7-033. Number (%) of Patients With Specific Edema-Type Adverse Experiences

	Placebo	MK-0966		Ibuprofen
		12.5 mg	25 mg	2400 mg
	(N=69)	(N=219)	(N=227)	(N=221)
	n (%)	n (%)	n (%)	n (%)
Edema	1 (1.4)	4 (1.8)	3 (1.3)	0 (0)
Fluid retention	0 (0)	0 (0)	0 (0)	3 (1.4)
Hand swelling	0 (0)	2 (0.9)	3 (1.3)	1 (0.5)
Lower extremity edema	0 (0)	7 (3.2)	14 (6.2)*	15 (6.8)*
Peripheral edema	0 (0)	0 (0)	0 (0)	2 (0.9)
ΣEdema	**1 (1.4)**	**12 (5.5)**	**19 (8.4)**	**21 (9.5)**

[Adapted from NDA 21-042, Vol. 1.129, Table 55, page 192. * p<0.05 vs. placebo. ΣEdema = Edema+ Fluid retention+ Hand swelling+ Lower extremity edema+ Peripheral edema.]

Table 8-033 summarizes both the number and the percentage of patients with specific hypertensive-related adverse experiences. MK-0966 treatment was associated with a higher rate of events than placebo and Ibuprofen. Hypertension-type adverse events with MK-0966 occurred in a dose-dependent manner.

Table 8-033. Number (%) of Patients With Specific Hypertension-Type Adverse Experiences

	Placebo	MK-0966		Ibuprofen
		12.5 mg	25 mg	2400 mg
	(N=69)	(N=219)	(N=227)	(N=221)
	n (%)	n (%)	n (%)	n (%)
Blood pressure increased	0 (0.0)	6 (2.7)	5 (2.2)	2 (0.9)
Hypertension	1 (1.4)	1 (0.5)	5 (2.2)	3 (1.4)
ΣHypertension	**1 (1.4)**	**7 (3.2)**	**10 (4.4)**	**5 (2.3)**

[Adapted from NDA 21-042, Vol. 1.129, Table 57, page 194. ΣHypertension = Blood pressure increased+ Hypertension.]

The number and percent of patients exceeding predefined limits of change on diastolic and systolic blood pressure are summarized in Table 9-033. There was a dose-related increase in the percent of patients exceeding predefined limits of change of both diastolic and systolic blood pressure in the MK-0966. As compared with placebo, MK-0996 was associated with a higher rate of patients exceeding the predefined limit of change of systolic blood pressure.

Table 9-033. Predefined Limits of Change on Diastolic and Systolic Blood Pressure (Intention-to-Treat Approach)

Vital Sign	Predefined Limit of Change	Treatment	Number/Total (%)
Diastolic Blood Pressure (mm Hg)	Increase > 15.0 and Value > 90.0	Placebo	1 /69 (1.45%)
		MK-0966 12.5 mg	3 /217 (1.38%)
		MK-0966 25 mg	8 /226 (3.54%)
		Ibuprofen	4 /221 (1.81%)
Systolic Blood Pressure (mm Hg)	Increase > 20.0 and Value > 140.0	Placebo	3 /69 (4.35%)
		MK-0966 12.5 mg	17 /217 (7.83%)
		MK-0966 25 mg	31 /226 (13.72%)
		Ibuprofen	43 /221 (19.46%)

[Adapted from NDA 21-042, Vol. 1.132, APPENDIX 4.18, page 1850. Pairwise Comparison p-Value, Systolic Blood Pressure: 25 mg vs. Ibuprofen 0.381 (-1.25, 4.71), 12.5 mg vs. Ibuprofen >0.999 (-2.77, 1.92), 25 mg vs. 12.5 mg 0.222 (-0.71, 5.02), 12.5 mg vs. Placebo >0.999 (-3.29, 3.15), 25 mg vs. Placebo 0.690 (-1.62, 5.80), Ibuprofen vs. Placebo >0.999 (-2.96, 3.68); Systolic Blood Pressure: 25 mg vs. Ibuprofen 0.126 (-12.62, 1.14), 12.5 mg vs. Ibuprofen <0.001 (-17.95, -5.30), 25 mg vs. 12.5 mg 0.048 (0.15, 11.62), 12.5 mg vs. Placebo 0.423 (-2.51, 9.48), 25 mg vs. Placebo 0.032 (2.79, 15.95), Ibuprofen vs. Placebo 0.002 (8.01, 22.21).]

Laboratory Findings: The number (%) of patients with specific laboratory adverse experiences by laboratory test category are described in Table 10-033. The small number of laboratory adverse experiences reported by the investigators prevents a valid commentary on the subject.

Table 10-033. Number (%) of Patients With Specific Laboratory Adverse Experiences by Laboratory Test Category

	Placebo	MK-0966		Ibuprofen
		12.5 mg	25 mg	2400 mg
	(N=69) n/N (%)†	(N=219) n/N (%)	(N=227) n/N (%)	(N=221) n/N (%)
Hyperkalemia	0/69 (0.0)	1/216 (0.5)	0/226 (0.0)	0/221 (0.0)
Hyperuricemia	0/69 (0.0)	1/216 (0.5)	0/226 (0.0)	0/221 (0.0)
Hypokalemia	0/69 (0.0)	1/216 (0.5)	0/226 (0.0)	1/221 (0.5)
Serum creatinine increased	0/69 (0.0)	1/216 (0.5)	0/226 (0.0)	1/221 (0.5)
Uric acid increased	0/69 (0.0)	1/216 (0.5)	1/226 (0.4)	1/221 (0.5)
Bacteriuria	0/32 (0.0)	1/119 (0.8)	0/140 (0.0)	0/125 (0.0)
Hematuria	0/68 (0.0)	2/216 (0.9)	1/226 (0.4)	0/220 (0.0)
Leukocyturia	0/32 (0.0)	2/121 (1.7)	1/140 (0.7)	1/127 (0.8)
Proteinuria	0/68 (0.0)	0/216 (0.0)	1/226 (0.4)	1/220 (0.5)
Pyuria	0/32 (0.0)	0/121 (0.0)	1/140 (0.7)	1/127 (0.8)

[Adapted from NDA 21-042, Vol. 1.129, Table 50, page 169. †n/N = number (%) of patients with laboratory adverse experience/number of patients for whom the laboratory test was recorded. N = total number of patients per treatment group. Although a patient may have had two or more laboratory adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.]

In Table 11-033 the numbers of patients (%) exceeding the predefined limits of change for laboratory chemistry are summarized. There was a dose-related increase in the percentage of patients with increase serum potassium and urine protein in the MK-0966 groups.

Table 11-033. Number (%) of Patients Exceeding the Predefined Limits of Change: Laboratory Chemistry (Intention-to-Treat Approach)

		Treatment	Number/Total (%)
Serum creatinine (mg/dL)	Increase >= 0.5 and Value > ULN	Placebo	0 /68 (0.00%)
		MK-0966 12.5 mg	0 /216 (0.00%)
		MK-0966 25 mg	1 /225 (0.44%)
		Ibuprofen	1 /221 (0.45%)
Serum potassium (mEq(K)/L)	Decrease >= 0.8 and Value < LLN	Placebo	0 /68 (0.00%)
		MK-0966 12.5 mg	1 /216 (0.46%)
		MK-0966 25 mg	0 /225 (0.00%)
		Ibuprofen	2 /221 (0.90%)
	Increase >= 0.8 and Value > ULN	Placebo	4 /68 (5.88%)
		MK-0966 12.5 mg	3 /216 (1.39%)
		MK-0966 25 mg	10 /225 (4.44%)
		Ibuprofen	5 /221 (2.26%)
Serum uric acid (mg/dL)	Increase >= 50.0% and Value > ULN	Placebo	0 /68 (0.00%)
		MK-0966 12.5 mg	2 /216 (0.93%)
		MK-0966 25 mg	4 /225 (1.78%)
		Ibuprofen	1 /221 (0.45%)
Urine protein (quant) (mg/dL)	Increase >= 1.0*f*	Placebo	17 /67 (25.37%)
		MK-0966 12.5 mg	41 /216 (18.98%)
		MK-0966 25 mg	56 /224 (25.00%)
		Ibuprofen	41 /218 (18.81%)

[Adapted from NDA 21-042, Vol. 1.132, APPENDIX 4.18, pages 1857-1861. *f*Specification includes both character and numeric values.]

SUMMARY/COMMENTS

Study protocol #033 compared the effects of 6 weeks treatment with MK-0966 12.5 mg and 25 mg, with 2400 mg of Ibuprofen, and placebo in adult men and women, ≥40 years old, with clinical and radiographic diagnosis of OA of the knee or hip.

The cardiovascular and renal safety profile of MK-0966 was highlighted by a dose-dependent increase in the incidence of both edema- and hypertension-type adverse events. MK-0996 treatment resulted in discontinuation due to edema-type adverse events in three patients receiving 12.5 mg and in one patient in the 25 mg group.

16.1.4 Protocol #040[6]: A Placebo- and Active–Comparator-Controlled, Parallel-Group, 6-Week, Double-Blind Study, Conducted Under In-House Blinding Conditions, to Assess the Safety and Efficacy of MK-0966 Versus Ibuprofen in Patients With Osteoarthritis of the Knee or Hip

METHODS

Study #040 had the following design: double blind (with in-house blinding), multicenter (Fifty-two centers, multinational, non-U.S.) placebo and active comparator controlled, parallel group. Healthy men or women of nonchildbearing potential ≥40 years old, with clinical and radiographic diagnosis of OA of the knee or hip for greater than 6 months. Two types of patients were evaluated: (1) patients with a history of response to NSAIDs who demonstrated increased pain and worsening of disease status at the Flare/Randomization Visit (Visit 2) following withdrawal of prior NSAID therapy; and (2) patients who regularly used paracetamol instead of NSAIDs for the treatment of OA of the study joint who demonstrated consistently moderate or greater pain at both the Screening and Flare/Randomization Visits measured by prespecified criteria. Three- to 15-day nonsteroidal anti-inflammatory drug (NSAID) washout period, followed by a 6-

[6] NDA 21-042, Vol. 1.146-1.148, Reference 040.

week treatment period with 12.5 mg MK-0966 daily, 25 mg MK-0966 daily, 800 mg ibuprofen 3 times daily, or placebo.

The primary therapy period was from 14MAY97 to 07JAN98. The in-house case report form cutoff date was 09APR98.

The main objectives of the study were: (1) To demonstrate clinical efficacy of 25 mg MK-0966 compared with ibuprofen in the treatment of osteoarthritis (OA) of the knee and hip during a 6-week treatment period; (2) To confirm the safety and tolerability of MK-0966 administration for a 6-week treatment period; (3) To demonstrate clinical efficacy of 25 mg MK-0966 superior to placebo in the treatment of OA of the knee and hip during a 6-week treatment period; (4) To demonstrate clinical efficacy of 12.5 mg of MK-0966 superior to placebo in the treatment of OA of the knee and hip during a 6-week treatment period; (5) To explore the safety and clinical efficacy of MK-0966 in patients who regularly use acetaminophen for the treatment of OA of the knee or hip; (6) To compare the clinical efficacy and safety of 12.5 mg versus 25 mg MK-0966 in the treatment of OA of the knee or hip; (7) To compare the clinical efficacy and safety of 12.5 mg MK-0966 versus ibuprofen in the treatment of OA of the knee or hip; (8) To compare MK-0966 versus ibuprofen in the incidence of spontaneous gastrointestinal adverse experiences which are consistent with NSAID use.

The percent of patients with adverse experiences and those exceeding the predefined limits of change in laboratory values and vital signs was assessed using Fisher's exact test.

RESULTS

Demographics: Table 1-040 summarizes patient characteristics at baseline by treatment group. The patient population studied were predominantly White female with a mean age of >60 years.

The average duration of OA and the percentage distribution of specific secondary diagnoses (with the exception of HEENT and Hepatobiliary systems) or prior therapies were similar among the groups.

Table 1-040. Baseline Patient Characteristics by Treatment Group

	Placebo	MK-0966		Ibuprofen
		12.5 mg	25 mg	2400 mg
	(N=74)	(N=244)	(N=242)	(N=249)
Gender				
Female	63 (85.14)	198 (81.15)	191 (78.93)	195 (78.31)
Male	11 (14.86)	46 (18.85)	51 (21.07)	54 (21.69)
Race				
Asian	0 (0.00)	1 (0.41)	1 (0.41)	0 (0.00)
Black	1 (1.35)	4 (1.64)	4 (1.65)	4 (1.61)
Hispanic 21	(28.38)	69 (28.28)	72 (29.75)	70 (28.11)
Multiracial	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.40)
Native Am	0 (0.00)	1 (0.41)	1 (0.41)	0 (0.00)
Polynesian	0 (0.00)	1 (0.41)	0 (0.00)	0 (0.00)
White	52 (70.27)	168 (68.85)	164 (67.77)	174 (69.88)
Age †				
Mean (SD)	63.1 (9.65)	64.0 (8.35)	62.8 (9.29)	64.1 (8.34)

[Adapted from NDA 21-042, Vol. 1.146, Table 12, page 69.]

Safety: Clinical and laboratory adverse events occurring postrandomization are summarized below. This is followed by an analysis of clinical and laboratory safety measures.

Deaths: There was only one death reported: AN 9415 (MK-0966, 12.5 mg) an 80-year-old female, died of a pulmonary embolism 8 days after sustaining a hip fracture. According to the sposnor, the patient had discontinued from the study 2 weeks before the hip fracture due to an unrelated, nonserious clinical adverse event.

Other Serious Adverse Experiences: Cardiovascular serious adverse experiences occurred in 2 patients: 0, 1, 1, and 0 in the placebo, 12.5 mg and 25 mg MK-0966, and ibuprofen, respectively. MK-0966 AN 9415 (12.5 mg) died of a pulmonary embolism and is described above under the category of Deaths. AN 9457 (25 mg) had a history of ischemic heart disease, atrial fibrillation, ventricular extrasystoles and ventricular tachycardia. The patient presented with ventricular tachycardia 2 days after completing study medication per protocol. The patient was subsequently diagnosed with a myocardial infarction and pneumonia. The patient underwent angioplasty and recovered.

Overall Profile of Dropouts: The incidence of discontinuation due to a clinical or a laboratory adverse experience was significantly less in the placebo and 25 mg MK-0966 groups compared with ibuprofen (Table 2-040).

Table 2-040. Patient Accounting

	Placebo (N=74) n (%)	MK-0966 12.5 mg (N=244) n (%)	MK-0966 25 mg (N=242) n (%)	Ibuprofen 2400 mg (N=249) n (%)
DISCONTINUED:				
Clinical adverse experience	1 (1.4)	10 (4.1)	9 (3.7)**	21 (8.4)*
Laboratory adverse experience	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)
Who died	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

[Adapted from NDA 21-042, Vol. 1.146, Tables 46 & 51, pages 142 & 166. * $p<0.05$ vs. placebo. **$p<0.05$ vs. ibuprofen.]

Adverse Events Associated with Dropout: Table 3-040 provides the listing of patients discontinued due to clinical adverse experiences. Of note, patient AN 8748 was discontinued by the study investigator because of edema.

Table 3-040. Listing of Patients Discontinued Due to Clinical Adverse Experiences

AN	Gender	Race	Age	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Relative Day of Discontinuation	Action Taken	Outcome
Placebo									
MK-0966 12.5 mg									
9183	F	White	81	19	Palpitation	Continuing	19	Discontinued PRx	Not recovered

Table 3-040. (Cont'd)

MK-0966 25 mg									
8748	F	White	54	24	Edema	13.00 days	27	Discontinued PRx	Recovered
Ibuprofen 2400 mg									

[Adapted from NDA 21-042, Vol. 1.146, Table 47, pages 157-159.]

Adverse Events Incidence Tables: Cardiovascular- and renal-related adverse experiences with an incidence ≥2.0% (in one or more treatment group) are summarized in Table 4-040.

Table 4-040. Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence ≥2.0% in One or More Treatment Groups) by Body System

	Placebo (N=74)	MK-0966 12.5 mg (N=244)	MK-0966 25 mg (N=242)	Ibuprofen 2400 mg (N=249)
Body as a Whole/Site Unspecified				
Lower extremity edema	0 (0.0)	5 (2.0)	3 (1.2)	4 (1.6)
Cardiovascular System				
Hypertension	0 (0.0)	10 (4.1)	9 (3.7)	6 (2.4)
Urogenital System				
Urinary tract infection	0 (0.0)	5 (2.0)	3 (1.2)	7 (2.8)

[Adapted from NDA 21-042, Vol. 1.146, Table 43, pages 144, 145.]

Because the terminology used by the investigators in reporting adverse events related to "fluid retention" or "hypertension" varied, they were incorporated by the sponsor into the following all-inclusive categories: Edema- and Hypertension-Type Adverse events.

Table 5-040 summarizes both the number and the percentage of patients with specific edema-type adverse experiences. MK-0966 treatment was associated with a dose-dependent incidence of edema-type adverse events. At any dose of MK-0966 there was a higher rate of occurrence for edema-type adverse experiences than in the placebo or Ibuprofen groups.

Table 5-040. Number (%) of Patients With Clinical Edema-Type Adverse Experiences

	Placebo (N=74)	MK-0966 12.5 mg (N=244)	MK-0966 25 mg (N=242)	Ibuprofen 2400 mg (N=249)
Lower extremity edema	0 (0.0)	5 (2.0)	3 (1.2)	4 (1.6)
Edema	0 (0.0)	2(0.8)	3 (1.2)	2 (0.8)
Peripheral edema	0 (0.0)	0 (0.0)	2 (0.8)	0 (0)
ΣEdema	**0 (0.0)**	**7 (2.8)**	**8 (3.3)**	**6 (2.4)**

[Adapted from NDA 21-042, Vol. 1.146, Appendix 4.33, pages 1776-1793. ΣEdema = Lower extremity+ Edema+Peripheral edema.]

Table 6-040 summarizes both the number and the percentage of patients with specific hypertension-type adverse experiences. At any dose of MK-0966 the rate of occurrence for hypertension-type adverse experiences was higher than in the placebo or Ibuprofen groups.

Table 6-040. Number (%) of Patients With Clinical Hypertension-Type Adverse Experiences

	Placebo (N=74)	MK-0966 12.5 mg (N=244)	MK-0966 25 mg (N=242)	Ibuprofen 2400 mg (N=249)
Blood pressure increased	0 (0.0)	1 (0.4)	2 (0.8)	1 (0.4)
Diastolic hypertension	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Hypertension	0 (0.0)	10 (4.1)	9 (3.7)	6 (2.4)
Hypertension uncontrolled with medication	0 (0.0)	0 (0.0)	1 (0.4)	0 (0)
ΣHypertension	**0 (0.0)**	**11 (4.5)**	**12 (4.9)**	**8 (3.2)**

[Adapted from NDA 21-042, Vol. 1.146, Appendix 4.33, pages 1776-1793. ΣHypertension = Blood pressure increased+Diastolic hypertension+Hypertension+Hypertension uncontrolled with medication.]

The number and percent of patients exceeding predefined limits of change on diastolic and systolic blood pressure are summarized in Table 7-040. There was a dose-related increase in the percent of patients exceeding predefined limits of change of systolic blood pressure with MK-0966. As compared with placebo or ibuprofen, MK-0996 at 25 mg was associated with a higher rate of patients exceeding the predefined limit of change of systolic blood pressure.

Table 7-040. Patients Exceeding* the Predefined Limits of Change On Diastolic And Systolic Blood Pressure (Intention-to-Treat Approach)

Vital Sign	Predefined Limit of Change	Treatment	Number†/Total‡ (%)
Systolic blood pressure (mm Hg)	Increase >20.0 and value >140.0	Placebo	1/66 (1.5)
		MK-0966 12.5 mg	4/236 (1.7)
		MK-0966 25 mg	8/226 (3.5)
		Ibuprofen 2400 mg	7/236 (3.0)
Diastolic blood pressure (mm Hg)	Increase >15.0 and value>90.0	Placebo	0/66 (0.0)
		MK-0966 12.5 mg	3/236 (1.3)
		MK-0966 25 mg	2/226 (0.9)
		Ibuprofen 2400 mg	0/236 (0.0)

[Adapted from NDA 21-042, Vol. 1.146, Table 59, pages 193. *Exceeded two or more times. †Number of patients meeting the predefined limit criteria. ‡Total number of patients with valid values of the laboratory or vital sign tests. ULN = Upper limit of normal range. LLN = Lower limit of normal range.]

Laboratory Findings: The number (%) of patients with specific laboratory adverse experiences by laboratory test category are described in Table 8-040. The small number of laboratory adverse experiences reported by the investigators prevents a valid commentary on the subject.

Table 8-040. Number (%) of Patients With Specific Laboratory Adverse Experiences by Laboratory Test Category

	Placebo	MK-0966		Ibuprofen
		12.5 mg	25 mg	2400 mg
	(N=74) n/N (%)†	(N=244) n/N (%)	(N=242) n/N (%)	(N=249) n/N (%)
BUN increased	1/73 (1.4)	5/243 (2.1)	3/236 (1.3)	3/246 (1.2)
Hyperkalemia	0/73 (0.0)	1/243 (0.4)	0/236 (0.0)	0/246 (0.0)
Hyperuricemia	0/73 (0.0)	0/243 (0.0)	0/236 (0.0)	1/246 (0.4)
Hypocalcemia	0/73 (0.0)	0/243 (0.0)	0/236 (0.0)	1/246 (0.4)
Hypokalemia	0/73 (0.0)	0/243 (0.0)	1/236 (0.4)	1/246 (0.4)
Serum creatinine increased	0/73 (0.0)	3/243 (1.2)	1/236 (0.4)	2/246 (0.8)
Uric acid increased	0/73 (0.0)	2/243 (0.8)	0/236 (0.0)	0/246 (0.0)
Bacteriuria	0/44 (0.0)	0/154 (0.0)	1/156 (0.6)	0/154 (0.0)
Glycosuria	0/73 (0.0)	0/243 (0.0)	0/236 (0.0)	2/246 (0.8)
Leukocyturia	0/44 (0.0)	0/154 (0.0)	1/156 (0.6)	1/154 (0.6)
Microalbuminuria	0/11 (0.0)	1/45 (2.2)	0/37 (0.0)	0/53 (0.0)
Proteinuria	0/73 (0.0)	3/243 (1.2)	0/237 (0.0)	3/246 (1.2)

[Adapted from NDA 21-042, Vol. 1.46, Table 52, pages 167, 168. †n/N (%) = number (%) of patients with laboratory adverse experiences/number of patients for whom the laboratory test was recorded. N = total number of patients per treatment group. Although a patient may have had two or more laboratory adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.]

In Table 9-040 the numbers of patients (%) exceeding the predefined limits of change for laboratory chemistry are summarized. Too few patients had abnormal values to permit a well-founded commentary.

Table 9-040. Patients Exceeding The Predefined Limits Of Change: Blood And Urine Chemistry (Intention-To-Treat Approach)

Laboratory Test	Predefined Limits of Change	Treatment	Number‡/Total§ (%)
Serum creatinine (mg/dL)	Increase ≥0.5 and value >ULN	MK0966 12.5 mg MK0966 25 mg MK0966 50 mg Ibuprofen 2400 mg	0/72 (0.0) 1/242 (0.4) 0/234 (0.0) 3/246 (1.2)
Serum potassium (mEq(K)/L)	Increase ≥0.8 and value >ULN	MK0966 12.5 mg MK0966 25 mg MK0966 50 mg Ibuprofen 2400 mg	3/72 (4.2) 7/241 (2.9) 5/234 (2.1) 3/244 (1.2)
	Decrease ≥0.8 and value <LLN	MK0966 12.5 mg MK0966 25 mg MK0966 50 mg Ibuprofen 2400 mg	0/72 (0.0) 0/241 (0.0) 2/234 (0.9) 5/244 (2.0)
Serum uric acid (mg/dL)	Increase ≥50.0% and value >ULN	MK0966 12.5 mg MK0966 25 mg MK0966 50 mg Ibuprofen 2400 mg	0/72 (0.0) 1/242 (0.4) 0/234 (0.0) 1/246 (0.4)
Urine protein (mg/dL)	Increase >1*f*	MK0966 12.5 mg MK0966 25 mg MK0966 50 mg Ibuprofen 2400 mg	1/62 (1.6) 1/83 (1.2) 1/71 (1.4) 0/61 (0.0)

[Adapted from NDA 21-042, Vol. 1.146, Appendix 4.16, pages 1520-1523. ULN = Upper limit of normal range. LLN = Lower limit of normal range. ‡Number of patients meeting the predefined limit criteria. §Total number of patients with valid values of the laboratory test. *f*Specification includes both character and numeric values.]

SUMMARY/COMMENTS

Study protocol #040 compared the effects of 6 weeks treatment with MK-0966 12.5 mg and 25 mg, with 2400 mg of Ibuprofen, and placebo in adult men and women, ≥40 years old, with clinical and radiographic diagnosis of OA of the knee or hip.

Edema- and hypertension-type adverse events essentially defined the cardiovascular and renal safety profile of MK-0966 in this study. MK-0996 treatment resulted in discontinuation due to edema-type adverse event in one patient receiving 25 mg.

16.1.5 Protocol #058[7]: An Active-Comparator- And Placebo-Controlled, Parallel-Group, 6-Week, Double-Blind Study, Conducted Under In-House Blinding, To Assess The Efficacy, Safety, And Tolerability Of MK-0966 In Patients Aged 80 And Over With Osteoarthritis Of The Knee Or Hip (With Extension)

METHODS

The study had the following design: multicenter (45 centers, U.S), double blind, placebo and active comparator controlled, and parallel group. Extension: Double blind, active comparator controlled, parallel group. Eligible patients were placed on 6-week treatment period with 12.5 or 25 mg MK-0966, nabumetone 1500 mg, or placebo daily followed by a 24-week treatment period (Extension) with 12.5 or 25 mg MK-0966 or 1500 mg nabumetone daily. The Base Study randomized healthy men or women ≥80 years old, with a clinical and radiologic diagnosis of OA of the knee (tibio-femoral joint) or hip. Extension: Patients must have completed the Base Study (Protocol 058-01) through Visit 6, and, in the opinion of the investigator, must have tolerated study medication and complied with all study procedures.

[7] NDA 21-042, Vol. 171-174, Reference 058.

The primary therapy period was from 01AUG97 to 01APR98.

The objectives of the study were: (1) To evaluate the clinical efficacy of 12.5 or 25 mg MK-0966 daily, compared with placebo for treatment of osteoarthritis (OA) in patients aged 80 years and older with hip or knee involvement. (2) To demonstrate the overall safety and tolerability of 12.5 and 25 mg MK-0966 daily, compared with nabumetone 1500 mg daily and placebo over a 6-week period in patients aged 80 years and older. (3) To evaluate the clinical efficacy of nabumetone 1500 mg daily compared with placebo for the treatment of OA in patients aged 80 years and older with hip or knee involvement. (4) To evaluate the effects of 12.5 and 25 mg MK-0966 daily, nabumetone 1500 mg daily, and placebo on body weight, blood pressure, serum albumin, serum hepatic transaminases, serum alkaline phosphatase, and serum creatinine in patients aged 80 years and older. (5) To obtain data on the safety and tolerability of concurrent therapy with MK-0966 and low-dose aspirin in patients aged 80 years and older. (6) To explore the effects of 12.5 or 25 mg MK-0966 daily versus placebo on responses by geriatric patients (with OA of the knee or hip) to the WOMAC questionnaire for measuring therapeutic changes in Pain, Stiffness, and Physical Function. (7) To evaluate the response to the SF-36 health-related Quality-of-Life questionnaire in geriatric patients treated with 12.5 mg MK-0966 or 25 mg daily, 1500 mg nabumetone daily, and placebo.

The overall safety and tolerability of MK-0966 in both the 12.5- and 25-mg groups was assessed by comparing the proportions of patients with: adverse experiences (AEs) among treatment groups; a predefined list of digestive system AEs; AEs in specific body systems; any individual AE occurring in more than 2% of patients; and changes in individual laboratory and vital sign tests that exceeded predefined limits.

RESULTS

Demographics: Over ninety percent of the enrolled patients were White and almost two-thirds were female (Table 1-058). All patients were ≥80 years of age when randomized. The groups were well balanced concerning secondary diagnosis and prior drug therapies.

Table 1-058. Baseline Patient Characteristics by Treatment Group Base Study

	Placebo	MK-0966		Nabumetone
		12.5 mg	25 mg	1500 mg
	(N=52) n (%)	(N=118) n (%)	(N=56) n (%)	(N=115) n (%)
Gender				
Female	34 (65.4)	77 (65.3)	32 (57.1)	74 (64.3)
Male	18 (34.6)	41 (34.7)	24 (42.9)	41 (35.7)
Age				
Mean	83.0	83.3	83.8	83.1
SD	3.01	3.06	3.23	2.90
Race				
Asian	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Black	3 (5.8)	3 (2.5)	5 (8.9)	3 (2.6)
Hispanic American	1 (1.9)	0 (0.0)	0 (0.0)	3 (2.6)
Native American	0 (0.0)	3 (2.5)	0 (0.0)	2 (1.7)
White	48 (92.3)	112 (94.9)	51 (91.1)	106 (92.2)

[Adapted from NDA 21-042, Vol. 1.166, Table 15, page 72.]

Safety: Clinical and laboratory adverse events occurring postrandomization are summarized below. This is followed by an analysis of clinical and laboratory safety measures.

Deaths: No deaths occurred in the study.

Other Serious Clinical Adverse Experiences: The most common type of serious adverse experience was cardiovascular which was reported in 4 patients; three in the MK-0966 12.5 mg group and one in the nabumetone group. Patient AN 1248 (MK-0966 12.5 mg), 86 year-old female with hypertension and hypercholesterolemia, had a vasovagal reaction after 19 days of therapy. AN 1259 (MK-0966 12.5 mg), 81

year-old male with hypertension, angina pectoris, cardiomegaly, and NIDDM experienced a MI after 18 days of therapy. AN 1307(MK-0966 12.5 mg), 80 year-old male with hypertension, was hospitalized with congestive heart failure after 44 days of therapy. An 1291, 81 year-old male with atrial fibrilation, a history of coronary bypass surgery and benign prostatic hypertrophy developed a rapid ventricular response and was hospitalized for congestive heart failure after 23 days of therapy.

Overall Profile of Dropouts: Twenty-one (6.2%) of 341 patients discontinued from therapy due to a clinical adverse experience (Table 2-058). MK-0966 and nabumetone had similar rate of discontinuation, but higher rates of discontinuation than placebo.

Table 2-058. Patient Accounting

	Placebo	MK-0966		Nabumetone
		12.5 mg	25 mg	1500 mg
	(N=52) n/N (%)†	(N=118) n/N (%)	(N=56) n/N (%)	(N=115) n/N (%)
COMPLETED 6-WEEK BASE STUDY:	43 (82.6)	101 (85.6)	48 (85.7)	100 (87.0)
DISCONTINUED:	9 (17.3)	17 (14.4)	8 (14.3)	15 (13.0)
Clinical adverse experience	1 (1.9)	8 (6.8)	4 (7.1)	8 (7.0)
Laboratory adverse experience	0 (0)	1 (0.8)	1 (1.8)	0 (0)
Deviation from protocol	0 (0)	1 (0.8)	0 (0)	1 (0.9)
Patient withdrew consent	2 (3.8)	4 (3.4)	1 (1.8)	3 (2.6)
Lost to follow-up	0 (0)	1 (0.8)	0 (0)	0 (0)
Lack efficacy	6 (11.5)	2 (1.7)	0 (0)	2 (1.7)
Other reasons	0 (0)	0 (0)	1 (1.8)	1 (0.9)
Patient moved	0 (0)	0 (0)	1 (1.8)	0 (0)

[Adapted from NDA 21-042, Vol. 1.166, Table 22, page 91.]

No patient discontinued due to an adverse experience of hypertension, or edema/fluid retention. Only two patients were discontinued due to cardiovascular adverse experiences. AN 1737 (MK-0966 25 mg), an 81-year-old man, discontinued due to congestive heart failure following 67 days of therapy.

AN 1181 (Nabumetone 1500 mg), 80-year-old woman with hypertension, congestive heart failure, borderline cardiomegaly, mild/minimal aortic and mitral insufficiency, and hyperlipidemia, discontinued due to worsening congestive heart failure which occurred following 165 days of therapy. The patient's nonstudy medications included simvastatin, loratadine, conjugated estrogenic hormones, albuterol, cisapride, and enalapril. The patient had symptoms of shortness of breath, a productive cough, and mild headache. The patient presented to an emergency room but was not hospitalized. Study drug was discontinued on Day 172. The patient returned for a discontinuation visit on Day 178 and was diagnosed with pneumonia. The worsening congestive heart failure was considered by the investigator to be possibly drug related.

Adverse Events Incidence Tables: Clinical adverse experiences were reported by 194 (56.9%) of 341 randomized patients. Because the terminology used by the investigators in reporting adverse events related to "fluid retention" or "hypertension" varied, they were incorporated by the sponsor into the following all-inclusive categories: Edema- and Hypertension-Type Adverse events. Tables 3-058 and 4-058 summarize, by treatment group, hypertension- and edema-type adverse experiences. MK-0966 treatment, at any dose, was associated with higher rates of edema-type adverse experiences than placebo or nabumetone. The incidence of edema-type adverse experiences with MK-0966 was dose-dependent.

Table 3-058. Number (%) of Patients With Edema-Type Adverse Experiences

	Placebo (N=52) n/N (%)†	MK-0966		Nabumetone 1500 mg (N=115) n/N (%)
		12.5 mg (N=118) n/N (%)	25 mg (N=56) n/N (%)	
Edema	0 (0.0)	0 (0.0)	1 (1.8)	1 (0.9)
Fluid retention	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Hand swelling	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)
Lower extremity edema	3 (5.8)	9 (7.6)	3 (5.4)	5 (4.3)
Peripheral edema	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)
ΣEdema	**3 (5.8)**	**9 (7.6)**	**6 (10.7)**	**7 (6.1)**

[Adapted from NDA 21-042, Vol. 1.171,Table 53, page 185. ΣEdema = Peripheral edema+Edema+Fluid retention+Lower extremity edema+Hand swelling.]

Hypertension-type adverse events occurred in a dose dependent manner with MK-0966 (25 mg dose); with incidence rates that were higher than placebo but similar to nabumetone (Table 4-058).

Table 4-058. Number (%) of Patients With Hypertension-Type Adverse Experiences

	Placebo (N=52) n/N (%)†	MK-0966		Nabumetone 1500 mg (N=115) n/N (%)
		12.5 mg (N=118) n/N (%)	25 mg (N=56) n/N (%)	
Blood pressure increased	1 (1.9)	3 (2.5)	2 (3.6)	4 (3.5)
ΣHypertension	**1 (1.9)**	**3 (2.5)**	**2 (3.6)**	**4 (3.5)**

[Adapted from NDA 21-042, Vol. 1.171,Table 55, page 188. ΣHypertension = patients had adverse experiences under the broader term "blood pressure increased".]

Laboratory Findings: Table 5-058 presents the number (%) of patients with specific laboratory adverse experiences by laboratory test category. Of note, hyperkalemia developed only in patients receiving MK-0966 25 mg. Serum creatinine increased as identified by the investigators occurred in a dose-dependent manner with MK-0966 and at rates that were higher than with placebo or nabumetone.

Table 5-058. Number (%) of Patients With Specific Laboratory Adverse Experiences by Laboratory Test Category Base Study

	Placebo (N=52) n/N (%)†	MK-0966		Nabumetone 1500 mg (N=115) n/N (%)
		12.5 mg (N=118) n/N (%)	25 mg (N=56) n/N (%)	
BUN increased	0/52 (0.0)	2/118 (1.7)	1/54 (1.9)	0/114 (0.0)
Hyperkalemia	0/52 (0.0)	0/118 (0.0)	2/54 (3.7)	0/114 (0.0)
Hypokalemia	0/52 (0.0)	0/118 (0.0)	1/54 (1.9)	0/114 (0.0)
Serum creatinine increased	0/52 (0.0)	5/118 (4.2)	3/54 (5.6)	4/114 (3.5)
Uric acid increased	0/52 (0.0)	0/118 (0.0)	0/54 (0.0)	1/114 (0.9)
Bacteriuria	0/34 (0.0)	1/91 (1.1)	0/40 (0.0)	1/80 (1.3)
Glycosuria	1/52 (1.9)	0/118 (0.0)	1/54 (1.9)	0/114 (0.0)
Hematuria	0/52 (0.0)	0/118 (0.0)	1/54 (1.9)	0/114 (0.0)
Leukocyturia	1/34 (2.9)	2/91 (2.2)	0/40 (0.0)	0/80 (0.0)
Microscopic hematuria	0/34 (0.0)	0/91 (0.0)	0/40 (0.0)	1/80 (1.3)
Proteinuria	1/52 (1.9)	2/118 (1.7)	0/54 (0.0)	1/114 (0.9)

[Adapted from NDA 21-042, Vol. 1.171, Table 47, pages 154, 155.†n/N (%)=number of patients with laboratory adverse experiences/number (percent) of patients for whom the laboratory test was recorded. N=total number of patients per treatment group. Although a patient may have had two or more laboratory adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.]

Number (%) of patients exceeding the predefined limits of change for laboratory chemistry is described in Table 6-058. As was the case for laboratory adverse experiences, patients in the MK-0966 groups had

higher incidence of abnormally high values for serum creatinine and potassium than placebo or nabumetone. The percentage of patients exceeding the predefined limit of change for urine protein was higher in the MK-0966 groups than placebo or nabumetone.

Table 6-058. Patients Exceeding the Predefined Limits of Change–Laboratory (Intention-to-Treat Approach)

Laboratory Test	Predefined Limits of Change	Treatment	Number‡/Total§ (%)
Serum creatinine (mg/dL)	Increase≥0.5 and Value<ULN	Placebo	1/52 (1.9)
		MK-0966 12.5 mg	3/118 (2.5)
		MK-0966 25 mg	2/54 (3.7)
		Nabumetone 1500 mg	1/114 (0.9)
Serum potassium (mEq(K)/L)	Increase ≥8.0 and value >ULN	Placebo	1/52 (1.9)
		MK-0966 12.5 mg	11/118 (9.3)
		MK-0966 25 mg	5/54 (9.3)
		Nabumetone 1500 mg	7/114 (6.1)
Serum uric acid (mg/dL)	Increase ≥50.0% and value >ULN	Placebo	0/52 (0.0)
		MK-0966 12.5 mg	4/118 (3.4)
		MK-0966 25 mg	0/54 (0.0)
		Nabumetone 1500 mg	8/114 (7.0)
Urine Protein (mg/dL)	Increase ≥1.0*f*	Placebo	5/52 (9.6)
		MK-0966 12.5 mg	23/118 (19.5)
		MK-0966 25 mg	8/54 (14.8)
		Nabumetone 1500 mg	12/114 (10.7)

[Adapted from NDA 21-042, Vol. 1.171, Table 50, page 168, and Appendix 4.34, page 1896. ‡Number of patients meeting the predefined limit criteria. §Total number of patients with valid values of the laboratory or vital sign test. *f*Specification includes both character and numeric values. ULN = Upper limit of normal range. A patient may be counted only once in a category; the same patient may appear in different categories.]

SUMMARY/COMMENTS

Study protocol #058 compared the effects of 6 weeks treatment with MK-0966 12.5 mg and 25 mg, with 1500 mg of nabumetone, and placebo in adult elderly men and women, ≥80 years old, with clinical and radiographic diagnosis of OA of the knee or hip.

Edema- and hypertension-type adverse events essentially defined the cardiovascular and renal safety profile of MK-0966 in this study. No patient withdrew due to an adverse experience of hypertension, or edema/fluid retention. Of note, hyperkalemia developed only in patients receiving MK-0966 25 mg. Serum creatinine increased as identified by the investigators occurred in a dose-dependent manner with MK-0966 and at rates that were higher than with placebo or nabumetone. Similarly, patients in the MK-0966 groups had higher incidence of abnormally high values for serum creatinine and potassium than placebo or nabumetone.

16.2 Osteoarthritis Studies
6-Months Studies

16.2.1 Protocol #034[1]: An Active-Comparator-Controlled, Parallel-Group, 1-Year, Double-Blind Study, Conducted Under In-House Blinding Conditions, To Assess The Safety And Efficacy Of Mk-0966 Versus Diclofenac Sodium In Patients With Osteoarthritis Of The Knee Or Hip

METHODS

This was a multinational, multicenter (forty-three centers) double blind (with in-house blinding), active comparator (diclofenac sodium) controlled, and parallel group study. The protocol included a three- to 15-day nonsteroidal anti-inflammatory drug (NSAID) washout period, followed by a 52-week treatment period with 12.5 mg MK-0966 once daily, 25 mg MK-0966 once daily, or 50 mg diclofenac sodium 3 times daily.

The primary therapy period was from 15SEP96 to 05NOV97. The in-house case report form cutoff date was 20FEB98.

Reviewer's Note: Noteworthy, this report presents results for the first 6 months (in-house blinded portion) of treatment only.

The subjects enrolled in the study were primarily healthy men or women of nonchildbearing potential ≥40 years old, with clinical and radiographic diagnosis of OA of the knee or hip for greater than 6 months. Two types of patients were evaluated: (1) patients with a history of response to NSAIDs who demonstrated increased pain and worsening of disease status at the Randomization Visit (Flare) following withdrawal of prior NSAID therapy; and (2) patients who regularly used paracetamol instead of NSAIDs for the treatment of OA of the study joint who demonstrated consistently moderate or greater pain at Visit 1 and the Randomization Visit (Flare) measured by prespecified criteria.

The objectives of this clinical trial included:

i. To demonstrate clinical efficacy of 25 mg MK-0966 compared with diclofenac sodium in the treatment of osteoarthritis (OA) of the knee and hip primarily during a 12-week treatment period, secondarily to 6 months, and then to 1 year;
ii. To demonstrate the safety and tolerability of MK-0966 administration for a 1-year period;
iii. To explore the safety and clinical efficacy of MK-0966 administration in patients who regularly use paracetamol for the treatment of OA of the knee or hip;
iv. To compare the clinical efficacy and safety of 12.5 versus 25 mg MK-0966 in the treatment of OA of the knee or hip;
v. To compare the clinical efficacy and safety of 12.5 mg MK-0966 versus diclofenac sodium in the treatment of OA of the knee or hip;
vi. To evaluate radiographs of the study joint at baseline and 1 year of treatment with MK-0966 or diclofenac sodium;
vii. To compare MK-0966 versus diclofenac sodium in the incidence of spontaneous gastrointestinal adverse experiences which are consistent with NSAID use.

For the safety hypothesis, the sample size of N=200 per treatment group has 80% power to detect (at α=0.05, two-tailed) a difference of 0.10 between a pair of treatment groups in adverse experiences rates if the group with the larger percentage has a rate of 0.20 (i.e., rates of 0.20 versus 0.10), and a difference of 0.14 percentage points if the group with the larger percentage has a rate of 0.40 (i.e., rates of 0.40 versus 0.26).

[1] NDA 21-042, Vol. 1.132-1.134, Reference P034.

RESULTS

Demographics: Patient characteristics at baseline are summarized in Table 1-034. In total six-hundred and ninety three patients were randomized. Approximately 80% of the patients were female and >70% were White.

Table 1-034. Baseline Patient Characteristics by Treatment Group

	MK-0966 12.5 mg (N=231) n (%)	MK-0966 25 mg (N=232) n (%)	Diclofenac 150 mg (N=230) n (%)
Gender			
Female	187 (81.0)	180 (77.6)	188 (81.7)
Male	44 (19.0)	52 (22.4)	42 (18.3)
Race			
Asian	2 (0.9)	1 (0.4)	1 (0.4)
European	0 (0.0)	1 (0.4)	0 (0.0)
Hispanic American	58 (25.1)	57 (24.6)	56 (24.3)
Black	4 (1.7)	3 (1.3)	2 (0.9)
Multiracial	6 (2.6)	4 (1.7)	5 (2.2)
White	161 (69.7)	166 (71.6)	166 (72.2)
Age (mean±SD)	62.2±9.48	62.1±8.93	62.6±9.39
Prior NSAID Use			
Paracetamol only	26 (11.26)	24 (10.34)	25 (10.87)
NSAID	205 (88.74)	208 (89.66)	205 (89.13)

[Adapted from NDA 21-042, Vol. 1.132, Tables 12 and 13, pages 70 and 71.]

The % of patients with specific secondary diagnosis and prior therapies were well balanced among the groups. Of the 693 randomized patients, 535 (77%) took at least one medication besides study drug and paracetamol postrandomization. Analgesics, diuretics and antibiotics were the most common concomitant drug therapies. There were no apparent differences between treatment groups in frequency or type of concomitant drug therapies.

Safety: Clinical and laboratory adverse experiences occurring postrandomization are summarized below. In addition, specific adverse experiences, i.e., hypertension- and edema-type adverse events will be discussed. This is followed by an analysis of clinical and laboratory safety measures. A summary of adverse experiences is provided in Table 2-034.

Table 2-034. Summary Of Adverse Experiences

Number (%) of patients:	MK-0966 12.5 mg (N=231) n (%)	MK-0966 25 mg (N=232) n (%)	Diclofenac 150 mg (N=230) n (%)
who died	0 (0.0)	0 (0.0)	3 (1.3)
with one or more adverse experiences	161 (69.7)	160 (69.0)	162 (70.4)
with no adverse experience	70 (30.3)	72 (31.0)	68 (29.6)
with serious adverse experiences	13 (5.6)	14 (6.0)	15 (6.5)
discontinued due to adverse experiences	18 (7.8)	14 (6.0)	22 (9.6)
discontinued due to serious adverse experiences	4 (1.7)	2 (0.9)	3 (1.3)

[Adapted from NDA 21-042, Vol. 1.132, Table 41, page 138.]

Deaths: Three deaths occurred during the study in patients receiving diclofenac. No death was considered to be drug related. Brief narratives for each of these patients follows:

AN 5599, a 79-year-old woman with a history of angina pectoris and congestive heart failure, died of a myocardial infarction 11 days after discontinuing study treatment. Study treatment had been discontinued for a worsening of patient's angina pectoris.