AN 5068, a 55-year-old woman with a history of depression and suicide attempt, committed suicide after 106 days of study treatment. The patient's depression was under treatment at the time of suicide.

AN 5320, a 78-year-old woman with a history of hypertension, experienced a hemorrhagic cerebrovascular accident. Patient was in a coma and died 1 day later.

Other Serious Adverse Events: Serious adverse experiences occurred in 42 of 693 patients (6.1%). The events related to the cardiovascular or urogenital systems are summarized in Table 3-034. No laboratory adverse experiences were considered serious by the investigator.

Table 3-034. Listing Of Patients With Serious Edema, Cardiovascular Or Urogenital Clinical Adverse Experiences

AN	Gender	Race	Age	Day of Onset	Adverse Experience	Duration	Action Taken	Outcome
MK-0966 12.5mg								
5383	F	Multiracial	58	133	Myocardial infarction	1.50 hours	Interrupted PRx	Recovered
5641	F	White	65	61	Syncope	0.08 hours	PRx continued	Recovered
5641	F	White	65	148	Atrial fibrillation	2 days	PRx continued	Recovered
5493	M	White	51	102	Chest pain	4 days	Interrupted PRx	Recovered
5105	F	White	58	69	Cerebrovascular accident	15 days	Discontinued PRx	Recovered
5387	F	White	74	108	Pyelonephritis	7 days	Discontinued PRx	Recovered
5055	M	White	76	150	Urinary retention	1 day	Interrupted PRx	Recovered
MK-0966 25 mg								
5246	F	Hispanic	75	44	Transient ischemic attack	1 hour	Discontinued PRx	Recovered
5646	F	White	48	96	Angina pectoris	10 days	PRx continued	Recovered
5277	F	Hispanic	68	9	Atrial fibrillation	4 days	PRx continued	Recovered
5423	F	White	78	108	Atrial fibrillation	3 days	PRx continued	Recovered
5548	M	White	68	138	Acute myocardial infarction	3 days	Interrupted PRx	Recovered
5431	F	White	73	159	Urinary retention	3 days	PRx continued	Recovered
Diclofenac 150 mg								
5599	F	White	79	22	Myocardial infarction	1 day	PRx continued	Not recovered
5320	F	Hispanic	78	56	Cerebrovascular accident	2 days	Discontinued PRx	Not recovered

[Adapted from NDA 21-042, Vol. 1.132, Table 45, pages 150-152. PRx: denotes study medication.]

Overall Profile of Dropouts: One hundred and sixty nine (73.1%), 183 (78.9%), and 174 (75.6%) patients continued in the trial from 12.5-mg, 25-mg MK-0966, and diclofenac groups, respectively. A total of fifty-four (7.8%) patients were discontinued due to clinical adverse experiences. The percents of patients who discontinued therapy due to clinical adverse experiences were 7.7, 6.0, and 9.6% in the 12.5-mg, 25-mg MK-0966, and diclofenac groups, respectively (Table 4-034). The rates of discontinuation in the MK-0966 groups were significantly lower than in the diclofenac group ($p<0.05$; Table 4-034).

Table 4-034. Summary of Discontinuations

	MK-0966 12.5 mg (N=231) n (%)	MK-0966 25 mg (N=232) n (%)	Diclofenac 150 mg (N=230) n (%)
Total Withdrawals	62 (26.8)	49 (21.1)	56 (24.3)
Discontinuations due to:			
Clinical adverse experience	18 (7.7)*	14 (6.0)*	22 (9.6)
Laboratory adverse experience	0 (0)*	1 (0.4)*	10 (4.3)
Deviation from protocol	8 (3.4)	6 (2.6)	2 (0.9)
Patient withdrew consent	8 (3.4)	3 (1.3)	4 (1.7)
Lost to follow-up	2 (0.9)	2 (0.9)	2 (0.9)
Lack of efficacy	22 (9.5)	19 (8.2)	13 (5.6)
Other reasons	4 (1.7)	4 (1.7)	3 (1.3)

[Adapted from NDA 21-042, Vol. 1.132, Table 19, page 85. *denotes: $p<0.05$ vs. diclofenac.]

Adverse Events Associated with Dropout: The listing of patients discontinued due to edema, cardiovascular or urogenital clinical adverse experiences are described in Table 5-034.

Administration of MK-0966 12.5 mg was associated with a patient's discontinuation due to edema and hypertension (AN 5519).

Table 5-034. Listing Of Patients Discontinued Due To Edema, Cardiovascular Or Urogenital Clinical Adverse Experiences

AN	Gender	Race	Age	Day of Onset	Adverse Experience	Duration	Day of Discontinuance	Action Taken	Outcome
MK-0966 12.5mg									
5387	F	White	74	108	Pyelonephritis	7 days	108	Discontinued PRx	Recovered
5519	F	White	56	143	Edema	29 days	162	Discontinued PRx	
				162	Hypertension	11 days	162	Discontinued PRx	Recovered
5071	F	White	64	116	Angina pectoris	2 months	121	Discontinued PRx	Recovered
5105	F	White	58	69	Cerebrovascular accident	15 days	64	Discontinued PRx	Recovered
MK-0966 25 mg									
5246	F	Hispanic	75	44	Transient ischemic attack	1 hours	45	Discontinued PRx	Recovered
5277	F	Hispanic	68	3	Palpitation	4 days	5	Discontinued PRx	Recovered
Diclofenac 150 mg									
5599	F	White	79	2	Unstable angina	20 days	11	Discontinued PRx	Recovered
5320	F	Hispanic	78	56	Cerebrovascular accident	2 days	56	Discontinued PRx	Not recovered
5768	F	White	73	2	Urolithiasis	Continuing	4	Discontinued PRx	Not recovered

[Adapted from NDA 21-042, Vol. 1.132, Table 48, pages 158-161.]

Adverse Event Incidence Tables: The number (%) of patients who had Cardiovascular, Urogenital and Body as a Whole/Site Unspecified clinical adverse experiences are presented in Table 6-034. Patients receiving MK-0966 had rates of occurrence for cardiovascular adverse experiences significantly higher than diclofenac-treated patients did.

Table 6-034. Number (%) of Patients With Cardiovascular, Urogenital and Body as a Whole/Site Unspecified Clinical Adverse Experiences

	MK-0966 12.5 mg (N=231) n (%)	MK-0966 25 mg (N=232) n (%)	Diclofenac 150 mg (N=230) n (%)
Cardiovascular System	29 (12.6)*	28 (12.1)*	13 (5.7)
Urogenital System	26 (11.3)	22 (9.5)	16 (7.0)
Body as a Whole/Site Unspecified	64 (27.7)	72 (31.0)	67 (29.1)

[Adapted from NDA 21-042, Vol. 1.132, Table 42, page 139. *p<0.05 vs. diclofenac.]

Edema-related clinical adverse experiences[2] classified in the category Body as a Whole/Site Unspecified, as was the case in other studies, were selected because they were noted to occur with MK-0966 at higher rates than with diclofenac. Cardiovascular and Urogenital clinical adverse experiences occurring with an incidence of >0% were summarized by the sponsor[3]. Hypertension-related[4] clinical adverse experiences were identified also to occur with a higher incidence with MK-0966 than with diclofenac.

Tables 7-034 and 8-034 summarize, by treatment group, hypertension- and edema-type adverse experiences, respectively. MK-0966 treatment, at any dose, was associated with higher rates of edema-type adverse experiences than diclofenac.

Table 7-034. Number (%) Of Patients With Edema

	MK-0966 12.5 mg (N=231) n (%)	MK-0966 25 mg (N=232) n (%)	Diclofenac 150 mg (N=230) n (%)
Peripheral edema	0 (0.0)	2 (0.9)	1 (0.4)
Edema	4 (1.7)	2 (0.9)	0 (0.0)
Fluid retention	0 (0.0)	0 (0.0)	1 (0.4)
Lower extremity edema	4 (1.7)	4 (1.7)	2 (0.9)
Hand swelling	0 (0.0)	1 (0.4)	0 (0.0)
ΣEdema	**8 (3.5)**	**8 (3.4)**	**4 (1.7)**

[Adapted from NDA 21-042, Vol. 1.132,Table 59, pages 199. ΣEdema = peripheral edema+edema+fluid retention+lower extremity edema.]

In sum, the incidence of adverse experiences of hypertension, systolic hypertension, and increased blood pressure was 7.4, 5.6, and 1.7% in the 12.5-mg, 25-mg MK-0966, and diclofenac groups, respectively (Table 8-034).

[2] Because the terminology used by the investigators in reporting adverse events related to "fluid retention" varied, they were incorporated by the sponsor into the following all-inclusive category: Edema-Type Adverse events.

[3] NDA 21-042, Vol. 1.134, APPENDIX 4.39, Table 42, pages 1633-1642.

[4] Because the terminology used by the investigators in reporting adverse events related to "hypertension" varied, they were incorporated by the sponsor into the following all-inclusive category: Hypertension-Type Adverse events. The incidence of hypertension in the 12.5 mg MK-0966 group was significantly greater than in the diclofenac group (p=0.007, Sponsor's analysis). The combined incidence rate of hypertension for both MK-0966 groups was 4.8%, and this rate of occurrence was significantly greater than the diclofenac rate (p=0.007, Sponsor's analysis).

Table 8-034. Number Of Patients With Hypertension

	MK-0966 12.5 mg (N=231) n (%)	MK-0966 25 mg (N=232) n (%)	Diclofenac 150 mg (N=230) n (%)
Blood pressure increased	3 (1.3)	4 (1.7)	2 (0.9)
Systolic hypertension	1 (0.4)	0 (0.0)	0 (0.0)
Hypertension	13 (5.6)	9 (3.9)	2 (0.9)
ΣHypertension	17 (7.4)	13 (5.6)	4 (1.7)

[Adapted from NDA 21-042, Vol. 1.132, Table 61, page 201. ΣHypertension = Blood pressure increased+Systolic hypertension+Hypertension.]

Table 9-034 provides clinical information, i.e., history of hypertension, changes in medications, association with edema, etc., for the patients with hypertension-type adverse events.

Table 9-034. Number (%) of Patients With Specified Increases in Blood Pressure† And Hypertension Adverse Experiences

	MK-0966 12.5 mg (N=231) n (%)	MK-0966 25 mg (N=232) n (%)	Diclofenac 150 mg (N=230) n (%)
Total	**17 (7.4)**	**13 (5.6)**	**4 (1.7)**
Number (%) of Patients:			
With a history of hypertension	11 (4.8)	3 (1.3)	3 (1.3)
Taking antihypertensives at Visit 1	10 (4.3)	2 (0.9)	3 (1.3)
Changing antihypertensive medication‡:			
with a history of hypertension	8 of 11 (3.5)	2 of 3 (0.9)	1 of 3 (0.4)
without a history of hypertension	4 of 6 (1.7)	5 of 10 (2.2)	0 of 1 (0)
Discontinued for adverse experience	1 (0.4)	0 (0)	0 (0)
Adverse experience rated severe§	1 (0.4)	0 (0)	0 (0)
With an edema-related adverse experience	2 (0.9)	2 (0.9)	0 (0)
Exceeding blood pressure predefined limits of changeϕ	4 (1.7)	2 (0.9)	2 (0.9)

[Adapted from NDA 21-042, Vol. 1.132, Table 62, page 203. †Includes all patients discontinued due to hypertension clinical adverse experience. ‡Represents either a change in dose and/or a new medication. §Defined as incapacitating, with inability to work or do usual activity. ϕA 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 > 90 mm Hg; systolic predefined limit: >20 mm Hg from baseline and >140 mm Hg.]

The number (%) of patients exceeding the predefined limits of change on diastolic and systolic blood pressure is summarized in Table 10-034. More MK-0966 patients exceeded the systolic and diastolic limits. In comparison to diclofenac, the 12.5-mg, 25-mg MK-0966 groups had a significantly higher percent (p=0.015 and p=0.007, respectively) of patients exceeding the predefined limits of change in systolic blood pressure (16, 17, and 8% in the 12.5-mg, 25-mg MK-0966, and diclofenac groups, respectively).

Table 10-034. Patients Exceeding the Predefined Limits of Change On Diastolic And Systolic Blood Pressure (Intention-to-Treat Analysis)

Vital Sign	Predefined Limit of Change	Treatment	Number†/Total‡ (%)
Systolic blood pressure (mm Hg)	Increase >20 and value >140	MK-0966 12.5 mg	37/229 (16.2)*
		MK-0966 25 mg	39/229 (17.0)*
		Diclofenac 150 mg	19/229 (8.3)
Diastolic blood pressure (mm Hg)	Increase >15 and value >90	MK-0966 12.5 mg	15/229 (6.5)
		MK-0966 25 mg	16/229 (7.0)
		Diclofenac 150 mg	11/229 (4.8)

[Adapted from NDA 21-042, Vol. 1.134, Appendix 4.23, pages 1527. *p<0.05 vs. diclofenac. †Number of patients meeting the predefined limit criteria. ‡Total number of patients with valid values of vital sign test.]

Laboratory Findings: Tables 11-034 and 12-034 present a summary of laboratory adverse experiences and the number (%) of patients with specific laboratory adverse experiences by laboratory test category, respectively.

Table 11-034. Summary Of Laboratory Adverse Experiences

	MK-0966 12.5 mg (N=231) n (%)	MK-0966 25 mg (N=232) n (%)	Diclofenac 150 mg (N=230) n (%)
Number of patients with at least one laboratory test postbaseline	229	229	230
Number (%) of patients:			
With one or more adverse experiences	29 (12.7)*	36 (15.7)	52 (22.6)
Discontinued due to adverse experiences	0 (0.0)*	1 (0.4)*	10 (4.3)

[Adapted from NDA 21-042, Vol. 1.134, Table 52, page 168. *p<0.05 vs. diclofenac.]

One (0.4%), 2 (0.9%), and 3 (1.3%) patients in the 12.5-mg, 25-mg MK-0966, and diclofenac groups, respectively, had laboratory adverse experiences of increased serum creatinine (Table 12-034). According to the sponsor, none of these patients had an adverse experience of edema or proteinuria. None had urinary protein present at the time of the creatinine increase. Of the 3 patients in the MK-0966 groups, none discontinued from the study due to elevated creatinine. In all cases, the elevations were not greater than 1.5 times the baseline value for serum creatinine. All elevations returned to baseline levels with continued patient use of study therapy. Of the 3 patients in the diclofenac groups, none discontinued from the study due to elevated creatinine. In all cases, the elevations were not greater than 1.5 times the baseline value for serum creatinine. None of these patients had an adverse experience of edema or proteinuria.

ANs 5299 and 5580 (25 mg MK-0966) had evidence of proteinuria on qualitative testing at several visits with 24-hour urinary protein of 281.6 and 730 mg/day (NR <150 mg/day).

Table 12-034. Summary Of Laboratory Adverse Experiences♦

	MK-0966 12.5 mg (N=231) n/N (%)	MK-0966 25 mg (N=232) n/N (%)	Diclofenac 150 mg (N=230) n/N (%)
Uric acid increased	0/229 (0.0)	2/229 (0.9)	1/230 (0.4)
Ionized calcium decreased	0/229 (0.0)	1/229 (0.4)	0/230 (0.0)
Serum albumin decreased	0/229 (0.0)	0/229 (0.0)	1/230 (0.4)
Total serum protein decreased	0/229 (0.0)	0/229 (0.0)	1/230 (0.4)
Serum creatinine increased	1/229 (0.4)	2/229 (0.9)	3/230 (1.3)
Blood urea nitrogen increased	2/229 (0.9)	5/229 (2.2)	5/230 (2.2)
Hyperkalemia	0/229 (0.0)	1/229 (0.4)	1/230 (0.4)
Hypokalemia	1/229 (0.4)	0/229 (0.0)	0/230 (0.0)
Microalbuminuria	0/43 (0.0)	1/49 (2.0)	0/33 (0.0)
Albuminuria	0/229 (0.0)	1/229 (0.4)	0/230 (0.0)
Proteinuria	8/229 (3.5)	6/229 (2.6)	4/230 (1.7)
Hematuria	1/229 (0.4)	1/229 (0.4)	0/230 (0.0)
Leukocyturia	1/159 (0.6)	4/159 (2.5)	3/147 (2.0)
Glycosuria	2/229 (0.9)	0/229 (0.0)	2/230 (0.9)

[Adapted from NDA 21-042, Vol. 1.134, Table 53, pages 170-171. ♦Partial listing. ‡There was no associated laboratory test or there were no patients for whom the laboratory test was recorded.]

The analysis of urinalysis data was also carried out based on between-treatment group comparisons of percent of patients exceeding predefined limits of change in urine protein. No statistically significant differences were noted. However, 5, 4, and 1 patient in the 12.5-mg, 25-mg MK-0966, and diclofenac groups, respectively, exceeded the predefined limits of change for proteinuria at 2 or more visits and did not have resolution of these changes.

Table 13-034. 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	MK-0966 12.5 mg MK-0966 25 mg Diclofenac 150 mg	0/228 (0.0) 0/229 (0.0) 4/229 (1.75)
Serum potassium (mEq(K)/L)	Increase ≥8.0 and value >ULN	MK-0966 12.5 mg MK-0966 25 mg Diclofenac 150 mg	10/228 (4.39) 13/229 (5.68) 13/229 (5.68)
Serum uric acid (mg/dL)	Increase ≥50.0% and value >ULN	MK-0966 12.5 mg MK-0966 25 mg Diclofenac 150 mg	5/228 (2.19) 3/229 (1.31) 1/229 (0.44)
Urine Protein (mg/dL)	Increase ≥1.0*f*	MK-0966 12.5 mg MK-0966 25 mg Diclofenac 150 mg	33/228 (14.5) 27/229 (11.8) 24/229 (10.5)

[Adapted from NDA 21-042, Vol. 1.134, Appendix 4.19, pages 1461-1463. ‡Number of patients meeting the predefined limit criteria. §Total number of patients with valid values of vital sign test. *f*Specification includes both character and numeric values.]

SUMMARY/COMMENTS

Study protocol #034 compared the effects of 6 months treatment with MK-0966 12.5 mg and 25 mg, and with 150 mg of diclofenac, 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 in this study is highlighted by edema- and hypertension-type adverse events. One patient (AN 5519) receiving MK-0966 12.5 mg withdrew from the study due to a combined adverse experience of hypertension and edema/fluid retention.

16.2.2 Protocol #035[5]: 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 study was carried out in sixty-nine centers in United States, and had a double blind (with in-house blinding), active comparator (diclofenac sodium) controlled, and parallel group study. Three to 15-day nonsteroidal anti-inflammatory (NSAID) washout period, followed by a 52-week treatment period with 12.5 mg MK-0966, 25 mg MK-0966 once daily, or 50 mg diclofenac sodium 3 times daily.

The primary therapy period was from 15NOV96 to 10NOV97. The in-house case report form cutoff date was 05FEB98.

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

The subjects enrolled in the study were 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. According to the sponsor 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 acetaminophen instead of NSAIDs

[5] NDA 21-042, Vol. 1.139-1.142, Reference 035.

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 1 year †;
ii. o 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 acetaminophen for the treatment of OA of the knee or hip;
iv. 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;
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.

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

RESULTS

Demographics: Patient characteristics at baseline are summarized in Table 1-035. The population studied in the trial was composed primarily White female patients with a mean age of 62 years.

Table 1-035. Baseline Patient Characteristics by Treatment Group

	MK-0966 12.5 mg (N=259) n (%)	MK-0966 25 mg (N=257) n (%)	Diclofenac 150 mg (N=268) n (%)
Gender			
Female	169 (65.3)	175 (68.1)	185 (69.0)
Male	90 (34.8)	82 (31.9)	83 (31.0)
Race			
Asian	0 (0.0)	0 (0.0)	1 (0.4)
Black	19 (7.3)	23 (8.9)	23 (8.6)
Hispanic American	3 (1.2)	4 (1.6)	7 (2.6)
Polynesian	1 (0.4)	1 (0.4)	0 (0.0)
White	236 (91.1)	229 (89.1)	237 (88.4)
Age (mean±SD)	62.8±10.2	62.8±10.3	62.5±10.2
Prior NSAID Use			
Acetaminophen only	19 (7.3)	19 (7.4)	26 (9.7)
NSAID	240 (92.6)	238 (92.6)	242 (90.3)

[Adapted from NDA 21-042, Vol. 1.139, Tables 12 and 13, pages 69-70.]

Most (99.9%) of the 784 randomized patients had at least one secondary diagnosis. According to the sponsor, no apparent trends were noted for specific secondary diagnoses between treatment groups. The most common prior drug therapies were vitamins, conjugated estrogenic hormones, and diuretics. There were no obvious differences between treatment groups in frequency or type of prior 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 2-035.

Table 2-035. Summary Of Adverse Experiences

Number (%) of patients:	MK-0966 12.5 mg (N=259) n (%)	MK-0966 25 mg (N=257) n (%)	Diclofenac 150 mg (N=268) n (%)
who died	1 (0.4)	0 (0.0)	2 (0.7)
with one or more adverse experiences	200 (77.2)	201 (78.2)	209 (78.0)
with no adverse experience	59 (22.8)	56 (21.8)	59 (22.0)
with serious adverse experiences	16 (6.2)	10 (3.9)	17 (6.3)
discontinued due to adverse experiences	29 (11.2)	25 (9.7)	35 (13.1)
discontinued due to serious adverse experiences	5 (1.9)	3 (1.2)	11 (4.1)

[Adapted from NDA 21-042, Vol. 1.139, Table 40, page 145.]

Deaths: Three deaths occurred during the study. AN 7588 (12.5 mg MK-0966) died suddenly of unknown causes. The remaining 2 deaths occurred in patients taking diclofenac. AN 7517 died due to cardiac arrest, and AN 7922 died due to advanced systemic atherosclerosis.

Other Serious Adverse Events: Table 3-035 describes patients that had serious clinical adverse events related to the cardiovascular system.

Table 3-035. Listing Of Patients With Serious Cardiovascular Clinical Adverse Experiences

AN	Gender	Race	Age	Day of Onset	Adverse Experience	Duration	Action Taken	Outcome
MK-0966 12.5mg								
7779	F	White	70	169	Myocardial infarction	3 days	Discontinued PRx	Recovered
8387	F	White	48	65	Chest pain	4 days	PRx continued	Recovered
MK-0966 25 mg								
8075	F	Black	81	97	Coronary artery disease	9 days	PRx continued	Recovered
				106	Coronary artery disease	4 days	PRx continued	Recovered
7502	M	White	68	168	Acute myocardial infarction	7 days	Discontinued PRx	Recovered
Diclofenac 150 mg								
7508	F	White	59	87	Chest pain	3 days	Discontinued PRx	Recovered
7517	F	White	69	85	Cardiac arrest	1 day	Discontinued PRx	Not recovered
7403	M	White	79	103	Myocardial infarction	10 days	Discontinued PRx	Recovered
7953	M	Hispanic	71	7	Coronary artery disease	Continuing	Discontinued PRx	Not recovered
				7	Congestive heart failure	7 days	PRx continued	
8129	F	White	73	183	Cerebrovascular accident	Continuing	Discontinued PRx	Not recovered
8259	M	White	55	90	Angina pectoris	3 days	Discontinued PRx	Recovered
7922	M	White	75	175	Atherosclerosis	1 day	Discontinued PRx	Not recovered
7462	M	White	75	78	Cardiac arrest	0.25 hours	Discontinued	PRx Recovered
				78	Aortic valve stenosis	6 days	Discontinued	PRx Recovered

[Adapted from NDA 21-042, Vol. 1.139, Table 44, pages 158-161. PRx: denotes study medication.]

Overall Profile of Dropouts: 66.6% of the patients completed the first 6-month treatment period. There were 76 (29.3%), 91 (35.4), and 95 (35.4%) patients who discontinued in the 12.5-, 25-mg MK-0966 and diclofenac treatment groups, respectively (Table 4-035). According to the sponsor, the 12.5- and 25-mg MK-0966 treatment groups demonstrated significantly fewer ($p<0.001$) incidences of discontinuations due to laboratory adverse events compared with diclofenac.

Table 4-035. Summary of Discontinuations

	MK-0966 12.5 mg (N=259) n (%)	MK-0966 25 mg (N=257) n (%)	Diclofenac 150 mg (N=268) n (%)
Total Withdrawals	76 (29.3)	91 (35.4)	95 (35.4)
Discontinuations due to:			
Clinical adverse experience	29 (11.2)	25 (9.7)	35 (13.1)
Laboratory adverse experience	1 (0.4)*	2 (0.8)*	14 (5.2)
Deviation from protocol	6 (2.3)	6 (2.3)	7 (2.6)
Patient withdrew consent	3 (1.2)	4 (1.6)	10 (3.7)
Lost to follow-up	1 (0.4)	1 (0.4)	1 (0.4)
Lack of efficacy	34 (13.1)	50 (19.5)**	27 (10.1)
Other reasons	2 (0.8)	3 (1.2)	1 (0.4)

[Adapted from NDA 21-042, Vol. 1.139, Table 19, page 92. * $p<0.001$ vs. diclofenac. ** $p=0.003$ vs. diclofenac.]

Adverse Events Associated with Dropout: Table 5-035 provides the listing of patients who discontinued due to edema, cardiovascular or urogenital clinical adverse experiences.

Of note, the investigators because of edema-related adverse experiences discontinued two patients receiving MK-0966 12.5 mg (ANs 7653 & 7950), two treated with MK-0966 25 mg (ANs 7669 & 7879), and one patient receiving diclofenac (ANs 7947). Hypertension-type adverse experiences were responsible for the discontinuation: one patient treated with MK-0966 25 mg (AN 8419) and another patient receiving diclofenac 150 mg (AN 8274).

Table 5-035. Listing Of Patients Discontinued Due To Edema, Cardiovascular Or Urogenital Clinical Adverse Experiences

AN	Gender	Race	Age	Day of Onset	Adverse Experience	Duration	Day of Discontinuance	Action Taken	Outcome
MK-0966 12.5mg									
7653	F	White	62	162	Peripheral edema	27 days	183	Discontinued PRx	Recovered
7779	F	White	70	169	Myocardial infarction	3 days	179	Discontinued PRx	Recovered
7950	F	White	61	13	Lower extremity edema	12 days	13	Discontinued PRx	Recovered
7918	F	White	55	134	Hematuria	Continuing	182	Discontinued PRx	Not recovered
8408	F	Polynesian	77	8	Left cardiac failure	Continuing	15	Discontinued PRx	Not recovered
8019	F	White	46	83	Urinary retention	3 days	84	Discontinued PRx	Recovered
MK-0966 25 mg									
8419	F	White	70	42	Blood pressure increased	Continuing	45	Discontinued PRx	Not recovered
7669	F	White	63	1	Peripheral edema	10 days	4	Discontinued PRx	Recovered
7721	M	White	49	90	Syncope on urination	0.03 hours	89	Discontinued PRx	Recovered
7879	F	White	77	59	Lower extremity edema	9 days	60	Discontinued PRx	Recovered
7455	F	Black	64	2	Palpitation	5 days	5	Discontinued PRx	Recovered
7496	F	White	71	33	Transient ischemic attack	23 hours	33	Discontinued PRx	Recovered
7502	M	White	68	168	Acute myocardial infarction	7 days	168	Discontinued PRx	Recovered
Diclofenac 150 mg									
7508	F	White	59	87	Chest pain	3 days	86	Discontinued PRx	Recovered
7517	F	White	69	85	Cardiac arrest	1 day	85	Discontinued PRx	Not recovered
7702	F	White	53	22	Chest pain	1.50 hours	20	Discontinued PRx	Recovered
7403	M	White	79	103	Myocardial infarction	10 days	91	Discontinued PRx	Recovered
7953	M	Hispanic	71	7	Coronary artery disease	Continuing	27	Discontinued PRx	Not recovered
8129	F	White	73	183	Cerebrovascular accident	Continuing	182	Discontinued PRx	Not recovered
8259	M	White	55	90	Angina pectoris	3 days	97	Discontinued PRx	Recovered
7922	M	White	75	175	Atherosclerosis	1 day	175	Discontinued PRx	Not recovered
7947	F	White	68	2	Edema	6 days	5	Discontinued PRx	Recovered
8274	M	White	43	29	Blood pressure increased	25 days	29	Discontinued PRx	Recovered
7462	M	White	75	78	Cardiac arrest	0.25 hour	78	Discontinued PRx	Recovered
					Aortic valve stenosis	6 days	78	Discontinued PRx	Recovered

[Adapted from NDA 21-042, Vol. 1.139, Table 47, pages 153-157.]