Dropouts for Laboratory Abnormalities: Seventeen of 778 patients (2%) discontinued due to laboratory adverse experiences. Fourteen of these 17 patients (82%) were randomized to diclofenac. Nearly all of the discontinuations in the diclofenac treatment group were related to abnormal liver function tests.

The following patients were discontinued from the trial because of proteinuria or serum creatinine increased:

AN 7937 was a 66 years old female, treated with MK-0966 12.5 mg, who developed proteinuria 332 mg/24 hr (normal range 0 to 150 mg/24 hr), and was discontinued from the trial on day 88, the patient recovered.

AN 7535 was a white male 75 years old who had an increase in his serum creatinine to 2.1 mg/dl (normal range: 0.7 to 1.4 mg/dl) resulting in his discontinuation on day 53 of treatment with diclofenac 150 mg, the patient recovered.

AN 8080 was a 67 years old white female male who was discontinued after 141 days of treatment with diclofenac because his serum creatinine increased to 2.1 mg/dL (normal range: 0.7 to 1.4 mg/dl), the patient recovered.

Adverse Event Incidence Tables: The number (%) of patients who had Cardiovascular, Urogenital or Body as a Whole/Site Unspecified clinical adverse experiences are presented in Table 6-035. Patients receiving MK-0966 had rates of occurrence that were similar to diclofenac-treated patients.

Table 6-035. Number (%) Of Patients With Cardiovascular, Urogenital And Body As A Whole/Site Unspecified Clinical Adverse Experiences

	MK-0966 12.5 mg (N=259) n (%)	MK-0966 25 mg (N=257) n (%)	Diclofenac 150 mg (N=268) n (%)
Cardiovascular System	18 (6.9)	31 (12.1)	26 (9.7)
Urogenital System	24 (9.3)	25 (9.7)	23 (8.6)
Body as a Whole/Site Unspecified	100 (38.6)	107 (41.6)	97 (36.2)

[Adapted from NDA 21-042, Vol. 1.139, Table 41, page 146.]

Edema-related clinical adverse experiences[6] 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[7]. Hypertension-related[8] clinical adverse experiences were also identified to occur with a higher incidence with MK-0966 than with diclofenac.

Tables 7-035 and 8-035 summarize, by treatment group, hypertension- and edema-type adverse experiences, respectively. MK-0966 treatment, at 25 mg, was associated with higher rates of edema-type adverse experiences than diclofenac. Edema-type adverse experiences occurred in a dose-dependent manner with MK-0966.

[6] 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.

[7] NDA 21-042, Vol. 1.142, APPENDIX 4.36, pages 2141-2142.

[8] 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 7-035. Table ?. Number (%) Of Patients With Edema

	MK-0966 12.5 mg (N=259) n (%)	MK-0966 25 mg (N=257) n (%)	Diclofenac 150 mg (N=268) n (%)
Peripheral edema	2 (0.8)	4 (1.6)	2 (0.7)
Edema	1 (0.4)	5 (1.9)	3 (1.1)
Fluid retention	1 (0.4)	6 (2.3)	1 (0.4)
Lower extremity edema	15 (5.8)	14 (5.4)	15 (5.6)
Upper extremity edema	1 (0.4)	1 (0.4)	1 (0.4)
Hand swelling	4 (1.5)	1 (0.4)	1 (0.4)
ΣEdema	**24 (9.3)**	**31 (12.1)**	**24 (8.9)**

[Adapted from NDA 21-042, Vol. 1.139, Table 58, page 208. ΣEdema = Peripheral Edema+Edema+Fluid retention+Lower extremity edema+Upper extremity edema+Hand swelling.]

Hypertension-related clinical adverse experiences occurred with a higher incidence with MK-0966 25 mg than with diclofenac (Table 8-035). MK-0966 administration caused a dose-dependent increase in the incidence rate of hypertension-type adverse events.

Table 8-035. Number Of Patients With Hypertension

	MK-0966 12.5 mg (N=259) n (%)	MK-0966 25 mg (N=257) n (%)	Diclofenac 150 mg (N=268) n (%)
Blood pressure increased	1 (0.4	4 (1.6)	5 (1.9)
Hypertension	10 (3.9)	14 (5.4)	6 (2.3)
ΣHypertension	**11 (4.2)**	**18 (7.0)**	**11 (4.1)**

[Adapted from NDA 21-042, Vol. 1.132, Table 60, page 211. ΣHypertension = Blood pressure increased+Hypertension.]

Table 9-035 provides clinical information, i.e., history of hypertension, changes in medications, association with edema, etc., for the patients with hypertension-type adverse events.

Table 9-035. Number (%) of Patients With Specified Increases in Blood Pressure† And Hypertension Adverse Experiences

	MK-0966 12.5 mg (N=259) n (%)	MK-0966 25 mg (N=257) n (%)	Diclofenac 150 mg (N=268) n (%)
Total	**11 (4.2)**	**18 (7.0)**	**11 (4.1)**
Number (%) of Patients:			
With a history of hypertension	10 (3.9)	9 (3.5)	6 (2.2)
Taking antihypertensives at Visit 1	9 (3.5)	9 (3.5)	6 (2.2)
Changing antihypertensive medication‡:			
with a history of hypertension	6 of 10 (2.3)	7 of 9 (2.7)	5 of 6 (1.9)
without a history of hypertension	1 of 1 (0.4)	6 of 9 (2.3)	1 of 5 (0.4)
Discontinued for adverse experience	0 (0)	1 (0.4)	1 (0.4)
Adverse experience rated severe§	0 (0)	0 (0)	0 (0)
With an edema-related adverse experience	2 (0.8)	5 (1.9)	2 (0.7)
Exceeding blood pressure predefined limits of changeϕ	1 (0.4)	5 (1.9)	4 (1.5)

[Adapted from NDA 21-042, Vol. 1.139, Table 61, page 212. †Includes all patients as delineated in Table 60. ‡Represents either a change in dose and/or initiation of antihypertensive therapy. §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 for systolic and diastolic blood pressure are summarized in Table 10-035. No statistically significant differences were noted for blood pressure parameters.

Table 10-035. Patients Exceeding the Predefined Limits of Change on One or More Visits Diastolic And Systolic Blood Pressure (Intention-to-Treat Analysis)

Vital Sign	Predefined Limit of Change	Treatment	Measurements	
			One or More Visits Number†/Total‡(%)	Two or More Visits Number†/Total‡ (%)
Systolic blood pressure (mm Hg)	Increase >20 and value >140	MK-0966 12.5 mg	55/257 (21.4)	20/244 (7.8)
		MK-0966 25 mg	54/256 (21.1)	18/236 (7.0)
		Diclofenac 150 mg	45/266 (16.9)	17/256 (6.4)
Diastolic blood pressure (mm Hg)	Increase >15 and value >90	MK-0966 12.5 mg	12/257 (4.7)	0/244 (0.0)
		MK-0966 25 mg	19/256 (7.4)	1/236 (0.4)
		Diclofenac 150 mg	12/266 (4.5)	4/256 (1.5)

[Adapted from NDA 21-042, Vol. 1.134, Table 57, page 206. †Number of patients meeting the predefined limit criteria. ‡Total number of patients with valid values of vital sign test.]

Laboratory Findings: Laboratory adverse experiences were reported by the investigators in 117 (15.0%) of 778 patients. The laboratory adverse experience profile is summarized in Table 10-035. The 12.5- and 25-mg MK-0966 group demonstrated significantly smaller ($p<0.001$ and $=0.039$, respectively) incidences of laboratory adverse experiences than the diclofenac group. Both the 12.5- and 25-mg MK-0966 groups demonstrated significantly lower incidences ($p<0.05$) of discontinuations due to laboratory adverse experiences compared with diclofenac.

Tables 11-035 and 12-035 present a summary of laboratory adverse experiences and the number (%) of patients with specific laboratory adverse experiences by laboratory test category, respectively.

Table 10-035. Summary Of Laboratory Adverse Experiences

	MK-0966 12.5 mg (N=259) n (%)	MK-0966 25 mg (N=257) n (%)	Diclofenac 150 mg (N=268) n (%)
Number of patients with at least one laboratory test postbaseline	257	255	266
Number (%) of patients:			
With one or more adverse experiences	25 (9.7)*	36 (14.1)**	56 (21.1)
Discontinued due to adverse experiences	1 (0.4)*	2 (0.8)*	14 (5.3)

[Adapted from NDA 21-042, Vol. 1.139, Table 51, page 179. *$p<0.001$ vs. diclofenac. **$p=0.039$ vs. diclofenac.]

Three, 7, and 9 patients in the 12.5-, 25-mg MK-0966 and diclofenac groups, respectively, had laboratory adverse experiences of increased serum creatinine (Table 11-035). Proteinuria was reported by the investigators in both the MK-0966 and diclofenac groups.

Table 11-035. Summary Of Laboratory Adverse Experiences[♦]

	MK-0966 12.5 mg (N=257) n/N (%)	MK-0966 25 mg (N=259) n/N (%)	Diclofenac 150 mg (N=268) n/N (%)
Uric acid increased	1/257 (0.4)	4/254 (1.6)	1/266 (0.4)
Hyperuricemia	0/257 (0.0)	1/254 (0.4)	2/266 (0.8)
Serum creatinine increased	3/257 (1.2)	7/254 (2.8)	9/266 (3.4)
Blood urea nitrogen increased	2/257 (0.8)	7/254 (2.8)	5/266 (1.9)
Hypokalemia	1/257 (0.4)	0/254 (0.0)	3/266 (1.1)
Hyperkalemia	0/257 (0.0)	2/254 (0.8)	2/266 (0.8)
Hyponatremia	0/257 (0.0)	1/254 (0.4)	0/266 (0.0)
Albuminuria	1/257 (0.4)	0/255 (0.0)	1/265 (0.4)
Proteinuria	2/257 (0.8)	5/255 (2.0)	4/265 (1.5)

Table 11-035. (Cont'd)

Hematuria	2/186 (1.1)	2/178 (1.1)	1/181 (0.6)
Glycosuria	1/257 (0.4)	1/255 (0.4)	0/265 (0.0)

[Adapted from NDA 21-042, Vol. 1.139, Table 52, pages 181-182. *Partial listing. 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.]

SUMMARY/COMMENTS

Study protocol #035 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 characterized mainly by edema- and hypertension-type adverse events.

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 following discontinuations: one patient treated with MK-0966 25 mg (AN 8419) and another patient receiving diclofenac 150 mg (AN 8274).

Patient AN 7937, treated with MK-0966 12.5 mg, developed proteinuria and was discontinued from the trial.

16.2.3 Protocol #044[9]: A Multicenter, Randomized, Parallel-Group, Active- And Placebo-Controlled, Double-Blind Study, Conducted Under In-House Blinding Conditions, To Determine The Incidence Of Gastroduodenal Ulceration After 12 Weeks Of Treatment With MK-0966, Ibuprofen, Or Placebo With A 12-Week Continuation Period

METHODS

This study had a double-blind (with in-house blinding), multicenter (34 sites in the United States), parallel-group design; to investigate the effect of MK-0966 25 mg once daily, MK-0966 50 mg once daily, ibuprofen 800 mg 3 times daily (2400 mg), or placebo on the incidence of gastroduodenal ulcer following 12 weeks of treatment in patients with osteoarthritis. Male and female patients (≥50 years of age) with osteoarthritis and without gastroduodenal ulceration were scheduled to undergo esophagogastroduodenoscopy at baseline and following 6, 12, and 24 weeks of treatment.

The primary therapy period was from 13-Jan-1997 to 09-Feb-1998. The in-house case report form cutoff date was 11-May-1998.

The main objectives of the study:

i. To determine the comparative incidence of gastroduodenal ulcers (≥3 mm) following administration over 12 weeks of MK-0966 25 mg once daily, MK-0966 50 mg once daily, ibuprofen 800 mg 3 times daily (2400 mg), and placebo;
ii. To provide data for a pooled analysis of the incidence of gastroduodenal ulcers (≥3 mm) on placebo and MK-0966 25 mg once daily;
iii. To assess the general tolerability of MK-0966;
iv. To determine the comparative incidence of gastroduodenal ulcers (≥3 mm) following administration over 24 weeks of MK-0966 25 mg once daily, MK-0966 50 mg once daily, and ibuprofen 800 mg 3 times daily (2400 mg);

[9] NDA 21-042, Vol. 1.151-1.154, Reference P044.

v. To determine the comparative incidence of gastroduodenal erosions following administration over 12 weeks of MK-0966 25 mg once daily, MK-0966 50 mg once daily, ibuprofen 800 mg 3 times daily (2400 mg), or placebo;
vi. To determine the comparative incidence of gastroduodenal erosions following administration over 24 weeks of MK-0966 25 mg once daily, MK-0966 50 mg once daily, and ibuprofen 800 mg 3 times daily (2400 mg); and
vii. To perform analyses similar to those described above considering gastroduodenal ulcers ≥5 mm as the endpoint.

RESULTS

Demographics: Patient characteristics at baseline are summarized in Table 1-044. The patient population in this study was primarily composed of White females with a mean age of 61 years.

Table 1-044. Baseline Patient Characteristics

	Placebo (N=177) n (%)	MK-0966 25 mg (N=195) n (%)	MK-0966 50 mg (N=186) n (%)	Ibuprofen 2400 mg (N=184) n (%)
Gender				
Male	61 (34.5)	61 (31.3)	58 (31.2)	63 (34.2)
Female	116 (65.5)	134 (68.7)	128 (68.8)	121 (65.8)
Age (years)				
Mean± SD	61.3±7.71	61.5±7.86	61.7±7.72	62.2±8.31
Race				
Asian	1 (0.6)	1 (0.5)	0 (0.0)	2 (1.1)
Black	22 (12.4)	17 (8.7)	16 (8.6)	20 (10.9)
Eurasian	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Hispanic American	6 (3.4)	13 (6.7)	11 (5.9)	7 (3.8)
Indian	2 (1.1)	0 (0.0)	0 (0.0)	1 (0.5)
Native American	2 (1.1)	1 (0.5)	2 (1.1)	1 (0.5)
White	144 (81.4)	162 (83.1)	157 (84.4)	153 (83.2)
Prior NSAID Use				
No	32 (18.08)	33 (16.92)	33 (17.74)	27 (14.75)
Yes	145 (81.92)	162 (83.08)	153 (82.26)	156 (85.25)

[Adapted from NDA 21-042, Vol. 1.151, Tables 8 and 9, pages 61 and 64.]

Hypertension, drug allergy, and postmenopausal status as well as hysterectomy, tonsillectomy, and appendectomy were the most common secondary diagnoses. There were no differences between treatment groups for any secondary diagnoses by body system or for specific secondary diagnoses[10] or prior therapies.

Safety: According to the sponsor, "the primary assessment of safety data was by life-table method, up to Week 18 (placebo treatment group was terminated at Week 16 with a follow-up visit at Week 18) and during the entire 26-week study. Ninety-five percent of the placebo treatment group discontinued per protocol at Week 16, with a follow-up visit at Week 18; the rest of the patients were to complete 24 weeks of treatment. Therefore, comparisons between the three active treatment groups and the placebo group can only be made meaningfully up to Week 18. In contrast to Phase III clinical trials designed to assess the efficacy of MK-0966 for the treatment of osteoarthritis, a life-table approach was used to assess the incidence of adverse experiences in this trial. The ibuprofen treatment group experienced a high discontinuation rate, relative to the other treatment groups, because of many patients reaching the endpoint of endoscopic ulcer. The net effect was to markedly reduce the number of patient-months of exposure during the study period for the ibuprofen group. To address this potential for bias in the evaluation of adverse experiences, the primary analysis of the safety data was by life-table method, up to both Week 18 and during the entire study. Unless otherwise stated, incidence rates presented in this section are life-table

[10] NDA 21-042, Vol. 1.151, Tables 10 and 11.

rates." The mean number of days on treatment was 95, 133.2, 130.0, and 100.2 for patients in the placebo, MK-0966 25-mg, MK-0966 50-mg, and ibuprofen treatment groups, respectively.

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.

Deaths: No deaths occurred in this study.

Other Serious Adverse Events: The most common serious adverse experiences were cardiovascular or cerebrovascular (suspected and confirmed): 0, 3 (ANs 5324, 5972, 6118), 6 (ANs 5012, 5034, 5179, 5194, 5257, 5570) and 2 (ANs 5678, 5804) patients in the placebo, MK-0966 25-mg, MK-0966 50-mg and ibuprofen groups, respectively. One patient in the MK-0966 25 mg, AN 5257, and another in the ibuprofen group, AN 5804, were reported by the study investigators to have hypertension as a serious adverse experience (Table 2-044).

Table 2-044. Listing Of Patients With Serious Cardiovascular Clinical Adverse Experiences

AN	Gender	Race	Age	Day of Onset	Adverse Experience	Duration	Action Taken	Outcome
Placebo								
MK-0966 25 mg								
5324	F	White	66	9	Coronary artery disease	CONT	Discontinued PRx	Not recovered
5972	F	Black	70	63	Chest pain	23.00 day	PRx continued	Recovered
6118	F	Hispanic	50	174	Chest pain	2.00 day	PRx continued	Recovered
MK-0966 50 mg								
5012	F	White	66	38	Chest pain	3.00 day	PRx continued	Recovered
5034	F	White	64	8	Cerebrovascular accident	CONT	Discontinued PRx	Not recovered
5179	F	White	65	106	Cerebrovascular accident	1.00 day	Discontinued PRx	Recovered
5194	F	Black	70	46	Cerebrovascular accident	5.00 hr	Discontinued PRx	Recovered
5257	F	White	56	97	Hypertension	20.00 hr	PRx continued	Recovered
5570	F	White	58	12	Chest pain	2.00 hr	PRx continued	Recovered
Ibuprofen 2400 mg								
5678	M	White	67	35	Congestive heart failure	CONT	Discontinued PRx	Not recovered
5804	F	White	87	22	Hypertension	5.00 day	Discontinued PRx	Recovered

[Adapted from NDA 21-042, Vol. 1.151, Table 48, pages 187-188. CONT: denotes continuing. PRx: denotes study medication.]

Overall Profile of Dropouts: Withdrawals due to clinical adverse experiences and other reasons are summarized in Table 3-044[11]. Both active treatments had a rate of discontinuation due to adverse events higher than placebo. Patients in the ibuprofen group were discontinued at rates that were higher than placebo and MK-0966.

Table 3-044. Summary of Discontinuations

	Placebo (N=177) n (%)	MK-0966 25 mg (N=195) n (%)	MK-0966 50 mg (N=186) n (%)	Ibuprofen 2400 mg (N=184) n (%)
Total Withdrawals	58 (32.8)	59 (30.2)	64 (34.4)	112 (60.9)
Discontinuations due to:				
Clinical adverse experience	12 (6.8)	20 (10.3)	22 (11.8)	21 (11.4)
Laboratory adverse experience	2 (1.1)	0 (0.0)	1 (0.5)	6 (3.3)
Lack of efficacy	16 (9.0)	6 (3.1)	4 (2.2)	9 (4.9)
Lost to follow up	1 (0.6)	3 (1.5)	0 (0.0)	3 (1.6)
Patient moved	1 (0.6)	3 (1.5)	0 (0.0)	0 (0.0)
Patient withdrew consent	7 (4.0)	13 (6.7)	14 (7.5)	11 (6.0)
Deviation from protocol	9 (5.1)	3 (1.5)	4 (2.2)	8 (4.3)
Study endpoint[12]§	10 (5.6)	11 (5.6)	19 (10.2)	54 (29.3)

[Adapted from NDA 21-042, Vol. 1.151, Table 19, page 85. Total includes a patient who was allocated by two different study centers: first as AN 5450 at site 016 (placebo treatment group) and again as AN 5013 at site 001 (ibuprofen treatment group). The second enrollment period has been excluded from all analyses of study endpoints; both enrollments are included in the analyses of safety data. §Includes 4 patients (ANs 5264, 5368, 5379, 5779) who discontinued due to development of gastroduodenal erosions.]

Adverse Events Associated with Dropout: The listing of patients discontinued due to edema, cardiovascular or urogenital clinical adverse experiences are described in Table 4-044. Administration of MK-0966 25 mg was associated with patients' discontinuation due to edema (ANs 5352, 5603, 5640,) and hypertension (AN 5676). Two patients receiving 50 mg of MK-0966 withdrew due to edema (ANs 5334, 5524). Ibuprofen treatment resulted in three discontinuations due to hypertension-type adverse experiences (ANs 5706, 5804, 5844) and one patient was discontinued due to edema (AN 5322).

Adverse Event Incidence Tables: During the entire study, clinical adverse experiences were reported by 567 (76.4%—crude rate) of 742 randomized patients[13].

The number (%) of patients who had Cardiovascular, Urogenital or Body as a Whole/Site Unspecified clinical adverse experiences are presented in Tables 5-044 and 6-044.

[11] Standard crude rate analyses are employed because the rates of discontinuation derived by life-table and by crude rate analyses yield similar results.

[12] The incidence of gastroduodenal ulcers, ≥3 mm, was the primary endpoint.

[13] NDA 21-042, Vol. 1.154, APPENDIX 4.24, Table 4.24, pages 1985-1992, & 1985-1992.

Table 4-044. 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
Placebo									
5064	F	White	65	28	Palpitation	3.00 day	31	Discontinued PRx	Recovered
MK-0966 25 mg									
5324	F	White	66	9	Coronary artery disease	CONT	9	Discontinued PRx	Not recovered
5352	F	White	63	5	Lower extremity edema	18.00 day	6	Discontinued PRx	Recovered
5603	F	White	65	31	Fluid retention	CONT	46	Discontinued PRx	Not recovered
5640	F	Black	59	65	Peripheral edema	1.02 mo	84	Discontinued PRx	Recovered
5676	F	Black	5	43	Hypertension	CONT	42	Discontinued PRx	Not recovered
5972	F	Black	70	61	Chest pain	2.00 day	60	Discontinued PRx	Recovered
MK-0966 50 mg									
5034	F	White	64	8	Cerebrovascular accident	CONT	10	Discontinued PRx	Not recovered
5179	F	White	65	106	Cerebrovascular accident	1.00 day	106	Discontinued PRx	Recovered
5194	F	Black	70	46	Cerebrovascular accident	5.00 hr	46	Discontinued PRx	Recovered
5334	F	White	64	74	Lower extremity edema	1.54 mo	77	Discontinued PRx	Recovered
				76	Edema	1.48 mo	77	Discontinued PRx	Recovered
5524	F	White	49	12	Edema	5.00 day	14	Discontinued PRx	Recovered
Ibuprofen 2400 mg									
5706	F	Black	70	65	Blood pressure increased	23.00 day	64	Discontinued PRx	Recovered
5322	M	White	63	68	Lower extremity edema	1.05 mo	84	Discontinued PRx	Recovered
5678	M	White	67	35	Congestive heart failure	CONT	35	Discontinued PRx	Not recovered
5804	F	White	87	22	Hypertension	5.00 day	24	Discontinued PRx	Recovered
5844	F	White	59	22	Hypertension	CONT	92	Discontinued PRx	Not recovered

[Adapted from NDA 21-042, Vol. 1.151, Table 50, pages 207-210.]

Table 5-044. Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence ≥2.0% in One or More Treatment Groups) by Body System Week 18

System	Placebo N=177			MK-0966 25 mg N=195			MK-0966 50 mg N=186			Ibuprofen 2400 mg N=184		
	n	Life Table Rate†	Crude Rate‡	n	Life Table Rate†	Crude Rate‡	n	Life Table Rate†	Crude Rate‡	n	Life Table Rate†	Crude Rate‡
Body As A Whole												
Lower extremity edema	2	1.2	1.1	10	5.6*	5.1	12	7.0*	6.5	6	3.9	3.3
Upper extremity edema	1	0.6	0.6	2	1.0	1.0	4	2.3	2.2	1	0.6	0.5
Cardiovascular												
Hypertension	1	0.6	0.6	9	5.3*	4.6	12	7.2*	6.5	8	5.7*	4.3
Urogenital												
Urinary tract infection	6	4.2	3.4	1	0.5	0.5	2	1.1	1.1	6	4.4	3.3

[Adapted from NDA 21-042, Vol. 1.151, Table 44, pages 154-158. *p≤0.05 vs. placebo. †Life-table rate = cumulative life-table rate, based on the probability that an event occurs by the time point. ‡Crude rate = number of patients within the clinical adverse experience category/total number of patients randomized into the treatment group, as percent. 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 6-044. Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence ≥2.0% in One or More Treatment Groups) by Body System Entire Study

System	Placebo N=177			MK-0966 25 mg N=195			MK-0966 50 mg N=186			Ibuprofen 2400 mg N=184		
	n	Life Table Rate†	Crude Rate‡	n	Life Table Rate†	Crude Rate‡	n	Life Table Rate†	Crude Rate‡	n	Life Table Rate†	Crude Rate‡
Body As A Whole												
Lower extremity edema	2	--	1.1	11	6.4	5.6	16	12.0	8.6	6	3.9	3.3
Upper extremity edema	1	--	0.6	2	1.0	1.0	4	2.3	2.2	1	0.6	0.5
Cardiovascular												
Hypertension	1	--	0.6	11	6.8	5.6	14	9.8	7.5	9	8.2	4.9
Urogenital												
Urinary tract infection	6	--	3.4	2	2.1	1.0	5	3.7	2.7	7	7.0	3.8

[Adapted from NDA 21-042, Vol. 1.151, Table 45, pages 159-163. †Life-table rate = cumulative life-table rate, based on the probability that an event occurs by the time point. ‡Crude rate = number of patients within the clinical adverse experience category/total number of patients randomized into the treatment group, as percent. 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.]

Tables 7-044 and 8-044 summarize the number (%) of patients with edema[14]- and hypertension[15]-type clinical adverse experiences up to Week 18 and for the entire study, respectively. Both clinical adverse events, regardless the time period, occurred at a higher rate with any dose of MK-0966 than placebo, and in a dose-dependent manner. At 50 mg MK-0966 was associated, regardless the time period, with rates of occurrence for the aforementioned adverse events higher than with ibuprofen.

Table 7-044. Number (%) Of With Clinical Hypertension-Type Or Edema-Type Adverse Experiences Week 18 (Intention-To-Treat Approach)

Clinical Adverse Experience	Treatment	Number‡/Total§	Life Table Rateϕ (%)	Crude Rate¶ (%)
ΣHypertension	Placebo	4/173	**2.6**	2.3
	MK0966 25 mg	11/184	**6.5**	5.6
	MK0966 50 mg	14/172	**8.6***	7.5
	Ibuprofen	10/174	**7.1**	5.4
ΣEdema	Placebo	4/173	**2.4**	2.3
	MK0966 25 mg	12/183	**6.7**	6.2
	MK0966 50 mg	19/167	**11.0***	10.2
	Ibuprofen	7/177	**4.4**	3.8

[Adapted from NDA 21-042, Vol. 1.151, Tables 69, 70, 74, and 75, pages 273, 274, 283, 284. ΣHypertension = Blood pressure increased+Borderline hypertension+ Hypertension+Uncontrolled hypertension. ΣEdema = Edema+Fluid retention+Lower extremity edema+Peripheral edema+Upper extremity edema. *p≤0.05 vs. placebo. ‡Number of patients meeting the predefined limit criteria. §Total number of patients with valid values of the laboratory or vital sign test. ϕLife-table rate = cumulative life-table rate, based on the probability that an event occurs by the time point. ¶Crude rate = number of patients within the clinical adverse experience category/total number of patients randomized into the treatment group, as percent.]

Table 8-044. Number (%) Of Patients With Clinical Hypertension-Type Or Edema-Type Adverse Experiences Entire Study (Intention-To-Treat Approach)

Clinical Adverse Experience	Treatment	Number‡/Total§	Life Table Rateϕ (%)	Crude Rate¶ (%)
ΣHypertension	Placebo	4/173	--	2.3
	MK0966 25 mg	13/182	**8.1**	6.7
	MK0966 50 mg	16/170	**11.2**	8.6
	Ibuprofen	11/173	**9.6**	6.0
ΣEdema	Placebo	4/173	--	2.3
	MK0966 25 mg	13/182	**7.4**	6.7
	MK0966 50 mg	23/163	**16.0**	12.4
	Ibuprofen	9/175	**7.0**	4.9

[Adapted from NDA 21-042, Vol. 1.151, Tables 69, 70, 74, and 75, pages 273, 274, 283, 284. ΣHypertension = Blood pressure increased+Borderline hypertension+ Hypertension+Uncontrolled hypertension. ΣEdema = Edema+Fluid retention+Lower extremity edema+Peripheral edema+Upper extremity edema. ‡Number of patients meeting the predefined limit criteria. §Total number of patients with valid values of the laboratory or vital sign test. ϕLife-table rate = cumulative life-table rate, based on the probability that an event occurs by the time point. ¶Crude rate = number of patients within the clinical adverse experience category/total number of patients randomized into the treatment group, as percent.]

Laboratory Findings: Nine of 742 patients (1.2%, crude rate) discontinued due to laboratory adverse experiences. Compared to the MK-0966 25-mg, MK-0966 50-mg or placebo treatment groups, ibuprofen

[14] 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.

[15] 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).

was associated with a greater number of laboratory adverse experiences resulting in discontinuation (6 patients). Four of the six adverse experiences in the ibuprofen group that resulted in discontinuation reflected changes in renal function (blood urea nitrogen increased, serum creatinine increased, or hyponatremia). A single patient from the MK-0966 50-mg treatment group was discontinued due to an elevation in blood urea nitrogen (BUN); this patient's serum creatinine was unchanged from baseline at the time of discontinuation (Table 9-044).

Table 9-044. Listing of Patients Discontinued Due to Laboratory Adverse Experiences

AN	Gender	Race	Age	Relative Day of Onset	Adverse Experience	Laboratory Value and Unit	Normal Range	Relative Day of Discontinuation	Action Taken
Placebo									
MK-0966 25 mg									
MK-0966 50 mg									
5288	M	White	76	141	BUN increased	37 mg/dL	5 to 20	144	Discontinued PRx
Ibuprofen 2400 mg									
5356	F	Black	62	98	BUN increased	40 mg/dL	5 to 20	103	Discontinued PRx
5509	F	White	79	22	Serum creatinine increased	2.1 mg/dL	0.7 to 1.4	32	Discontinued PRx
5509	F	White	79	22	BUN increased	29 mg/dL	5 to 20	32	Discontinued PRx
5548	M	Black	71	32	Serum creatinine increased	2.4 mg/dL	0.7 to 1.4	31	Discontinued PRx
5938	F	White	73	25	Hyponatremia	120 mEq/L	133 to 145	26	Discontinued PRx

[Adapted from NDA 21-042, Vol. 1.151, Table 58, pages 237.]

Tables 10-044 and 11-044 number (%) of patients with specific laboratory adverse experiences by laboratory test category up to Week 18 and entire study. Hyperkalemia adverse event was identified to happen at rates higher than placebo for MK-0966 and ibuprofen.Serum creatinine increased adverse event occurred in a dose dependent manner with MK-0966, and at 50 mg MK-0966 the incidence for this event was higher than with ibuprofen. Similarly, proteinuria adverse event with MK-0966 was dose-related, and occurred at rates higher than with ibuprofen, for the entire study.

Table 10-044. Number (%) of Patients With Specific Laboratory Adverse Experiences by Laboratory Test Category Week 18

System	Placebo N=177			MK-0966 25 mg N=195			MK-0966 50 mg N=186			Ibuprofen 2400 mg N=184		
	n/N	Life Table Rate‡	Crude Rate§	n/N	Life Table Rate‡	Crude Rate§	n/N	Life Table Rate‡	Crude Rate§	n/N	Life Table Rate‡	Crude Rate§
Bicarbonate decreased	1/173	0.6	0.6	0/194	0.0	0.0	0/183	0.0	0.0	1/181	0.6	0.6
Hyperkalemia	0/173	0.0	0.0	3/194	1.7	1.5	3/183	1.9	1.6	1/181	1.1	0.6
Hypokalemia	1/173	0.7	0.6	0/194	0.0	0.0	0/183	0.0	0.0	1/181	0.6	0.6
BUN increased	0/173	0.0	0.0	1/194	0.5	0.5	0/183	0.0	0.0	3/181	1.8	1.7
Serum creatinine increased	0/173	0.0	0.0	1/194	0.5	0.5	5/183	3.4*	2.7	3/181	1.8	1.7
Erythrocyturia	1/173	0.7	0.6	0/193	0.0	0.0	0/183	0.0	0.0	0/181	0.0	0.0
Glycosuria	1/173	0.9	0.6	1/193	0.6	0.5	0/183	0.0	0.0	0/181	0.0	0.0
Hematuria	2/173	1.4	1.2	1/193	0.5	0.5	0/183	0.0	0.0	0/181	0.0	0.0
Leukocyturia	3/172	2.0	1.7	1/193	0.6	0.5	2/183	1.3	1.1	1/181	0.6	0.6
Microalbuminuria	0/10	0.0	0.0	0/18	0.0	0.0	0/19	0.0	0.0	0/10	0.0	0.0
Proteinuria	0/173	0.0	0.0	3/193	1.9	1.6	1/183	0.6	0.5	1/181	0.6	0.6

[Adapted from NDA 21-042, Vol. 1.151, Table 54, pages 225-227. *p≤0.05 vs. placebo. ‡Life-table rate = cumulative life-table rate, based on the probability that an event occurs by the time point. §Crude rate = number of patients within the laboratory adverse experience category/number of patients with one or more laboratory tests postbaseline, as percent. 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. n/N = number of patients with laboratory adverse experiences / number of patients for whom the laboratory test was recorded.]

Table 11-044. Number (%) of Patients With Specific Laboratory Adverse Experiences by Laboratory Test Category Entire Study

System	Placebo N=177			MK-0966 25 mg N=195			MK-0966 50 mg N=186			Ibuprofen 2400 mg N=184		
	n/N	Life Table Rate‡	Crude Rate§	n/N	Life Table Rate‡	Crude Rate§	n/N	Life Table Rate‡	Crude Rate§	n/N	Life Table Rate‡	Crude Rate§
Bicarbonate decreased	1/173	--	0.6	0/194	0.0	0.0	0/183	0.0	0.0	1/181	0.6	0.6
BUNincreased	0/173	--	0.0	1/194	0.5	0.5	1/183	0.8	0.5	3/181	1.8	1.7
Hyperkalemia	0/173	--	0.0	5/194	4.7	2.6	4/183	2.7	2.2	2/181	3.7	1.1
Hypokalemia	1/173	--	0.6	0/194	0.0	0.0	0/183	0.0	0.0	1/181	0.6	0.6
Serum creatinine increased	0/173	--	0.0	4/194	4.3	2.1	6/183	4.2	3.3	3/181	1.8	1.7
Erythrocyturia	1/173	--	0.6	0/193	0.0	0.0	0/183	0.0	0.0	0/181	0.0	0.0
Glycosuria	1/173	--	0.6	2/193	2.1	1.0	0/183	0.0	0.0	1/181	1.3	0.6
Hematuria	2/173	--	1.2	1/193	0.5	0.5	0/183	0.0	0.0	0/181	0.0	0.0
Leukocyturia	3/172	--	1.7	2/193	2.2	1.0	2/183	1.3	1.1	1/181	0.6	0.6
Microalbuminuria	0/10	--	0.0	0/18	0.0	0.0	1/19	1.7	5.3	0/10	0.0	0.0
Proteinuria	0/173	--	0.0	3/193	1.9	1.6	3/183	4.0	1.6	1/181	0.6	0.6

[Adapted from NDA 21-042, Vol. 1.151, Table 55, pages 228-230. ‡Life-table rate = cumulative life-table rate, based on the probability that an event occurs by the time point. §Crude rate = number of patients within the laboratory adverse experience category/number of patients with one or more laboratory tests postbaseline, as percent. 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. n/N = number of patients with laboratory adverse experiences / number of patients for whom the laboratory test was recorded.]

The number and percentage of patients exceeding the predefined limits of change for laboratory parameters are shown in Tables 12-044 and 13-044. In keeping with the pattern observed for proteinuria, hyperkalemia and serum creatinine increased adverse events, Mk-0966 was associated with dose-dependent upwards changes in serum creatinine and potassium and urine protein.

Table 12-044. Patients Exceeding the Predefined Limits of Change–Laboratory Week 18 (Intention-to-Treat Approach)

Laboratory Test	Predefined Limits of Change	Treatment	Number‡/Total§	Life Table Rateϕ (%)	Crude Rate¶ (%)
Serum calcium (mg/dL)	Decrease≥1.5% and Value<LLN	Placebo	1/162	0.8	0.6
		MK0966 25 mg	1/188	0.6	0.5
		MK0966 50 mg	2/177	1.2	1.1
		Ibuprofen	1/171	0.6	0.6
Serum creatinine (mg/dL)	Increase≥0.5% and Value<ULN	Placebo	1/162	0.8	0.6
		MK0966 25 mg	1/188	0.7	0.5
		MK0966 50 mg	4/178	2.6	2.2
		Ibuprofen	5/171	3.1	2.9
Serum potassium (mEq(K)/L)	Increase ≥0.8 and Value >ULN	Placebo	9/162	7.3	5.6
		MK0966 25 mg	17/188	10.3	9.0
		MK0966 50 mg	24/177	15.6*	13.6
		Ibuprofen	12/171	9.4	7.0
Serum uric acid (mg/dL)	Increase≥50.0% and Value >ULN	Placebo	0/162	0.0	0.0
		MK0966 25 mg	4/188	2.4	2.1
		MK0966 50 mg	1/178	0.6	0.6
		Ibuprofen	3/171	2.3	1.8
Urine protein (mg/dL)	Increase ≥1*f*	Placebo	15/162	11.5	9.3
		MK0966 25 mg	22/188	13.2	11.7
		MK0966 50 mg	30/178	19.0*	16.9
		Ibuprofen	13/171	10.0	7.6

[Adapted from NDA 21-042, Vol. 1.151, Tables 62 and 67, pages 255 and 269, and Vol. 1.154, Appendix 4.17.1, pages 1903-1906. *p≤0.05 vs. placebo ‡Number of patients meeting the predefined limit criteria. §Total number of patients with valid values of the laboratory or vital sign test. ϕLife-table rate = cumulative life-table rate, based on the probability that an event occurs by the time point. ¶Crude rate = number of patients within the clinical adverse experience category/total number of patients randomized into the treatment group, as percent. *f*Specification includes both character and numeric values. ULN = Upper limit of normal range; LLN = Lower limit of normal range. A patient may be counted only once in a category; the same patient may appear in different categories.]

Table 13-044. Patients Exceeding the Predefined Limits of Change–Laboratory Entire Study (Intention-to-Treat Approach)

Laboratory Test	Predefined Limits of Change	Treatment	Number‡/Total§	Life Table Rateϕ (%)	Crude Rate¶ (%)
Serum calcium (mg/dL)	Decrease≥1.5% and Value<LLN	Placebo	2/162	--	1.2
		MK0966 25 mg	1/188	0.6	0.5
		MK0966 50 mg	4/177	5.2	2.3
		Ibuprofen	1/171	0.6	0.6
Serum creatinine (mg/dL)	Increase≥0.5% and Value<ULN	Placebo	1/162	--	0.6
		MK0966 25 mg	1/188	0.7	0.5
		MK0966 50 mg	4/178	2.6	2.2
		Ibuprofen	5/171	3.1	2.9
Serum potassium (mEq(K)/L)	Increase ≥8.0 and value >ULN	Placebo	9/162	--	5.6
		MK0966 25 mg	22/188	15.3	11.7
		MK0966 50 mg	33/177	25.5	18.6
		Ibuprofen	12/171	9.4	7.0
Serum uric acid (mg/dL)	Increase≥50.0% and value >ULN	Placebo	0/162	--	0.0
		MK0966 25 mg	4/188	2.4	2.1
		MK0966 50 mg	2/178	1.6	1.1
		Ibuprofen	3/171	2.3	1.8