Table 13-044. (Cont'd)

Urine protein (mg/dL)	Increase >1*f*	Placebo	15/162	--	9.3
		MK0966 25 mg	30/188	**24.1**	16.0
		MK0966 50 mg	35/178	**25.0**	19.7
		Ibuprofen	15/171	**12.7**	8.8

[Adapted from NDA 21-042, Vol. 1.151, Tables 63 and 68, pages 256 and 270, and Vol. 1.154, Appendix 4.17.2, pages 1907-1910. *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.]

SUMMARY/COMMENTS

Study protocol #044 compared the effects of 6 months treatment with MK-0966 25 mg and 50 mg with 2400 mg of ibuprofen, in adult men and women, ≥40 years old, with clinical and radiographic diagnosis of OA of the knee or hip.

Edema- and hypertension-type, serum creatinine increased, hyperkalemia and proteinuria adverse events outline the cardiovascular and renal safety profile of MK-0966 in this study. 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).

16.2.4 Protocol #045[16]: 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 multicenter, multinational (seventy-five centers worldwide: 39, United States; 36, international sites), double-blind (with in-house blinding), parallel-group design. The effect of MK-0966 25 mg once daily, MK-0966 50 mg once daily, ibuprofen 800 mg three times daily, or placebo on the incidence of gastric and/or duodenal ulcer following 12-24 weeks of treatment in patients with OA was investigated. Patients randomized into the trial were male and female patients (≥50 years of age) with OA and free of gastric and/or duodenal ulceration at the time of randomization. They were scheduled to undergo esophagogastroduodenoscopy at baseline and following 6, 12, and 24 weeks of treatment.

The primary therapy period was from January 13, 1997 to February 18, 1998. The in-house case report form cutoff was June 3, 1998

The main objectives of the study included:

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 three times daily (2400 mg), and placebo;
ii. To provide data for a pooled analysis of the incidence of gastric and/or duodenal ulcers (≥3 mm) on placebo and MK-0966;
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 three times daily (2400 mg);

[16] NDA 21-042, Vol. 1.156-1.160, Reference P045.

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 three 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 three times daily (2400 mg); and

vii. To perform analyses similar to those described above considering gastroduodenal ulcers ≥5 mm as the endpoint.

RESULTS

Demographics: Baseline patient characteristics are shown in Table 1-045 by treatment group. Approximately 75% of the patient population were female, two-third were White with a mean age of >61 years.

Table 1-045. Baseline Patient Characteristics by Treatment Group

	Placebo	MK-0966		Ibuprofen
		25 mg	50 mg	2400 mg
	(N=194) n (%)	(N=195) n (%)	(N=193) n (%)	(N=193) n (%)
Gender				
Female	146 (75.3)	151 (77.4)	139 (72.0)	143 (74.1)
Male	48 (24.7)	44 (22.6)	54 (28.0)	50 (25.9)
Race				
Asian	0 (0.0)	2 (1.0)	1 (0.5)	1 (0.5)
Black	3 (1.5)	2 (1.0)	4 (2.1)	4 (2.1)
European	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)
Hispanic American	54 (27.8)	53 (27.2)	56 (29.0)	53 (27.5)
Multi-Racial	3 (1.5)	2 (1.0)	2 (1.0)	2 (1.0)
White	134 (69.1)	135 (69.2)	129 (66.8)	133 (68.9)
Age				
Mean± SD	62.1±7.40	61.5±8.30	61.3±7.28	61.1±8.25
Prior NSAID use				
No	101 (52.06)	93 (47.69)	94 (48.70)	104 (53.89)
Yes	93 (47.94)	102 (52.31)	99 (51.30)	89 (46.11)

[Adapted from NDA 21-042, Vol. 1.156, Tables 8 and 9, pages 65 and 68.]

Safety: 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. A life-table approach was used by the sponsor to assess the incidence of adverse experiences in this trial. The clinical adverse experience profile is presented by treatment group and for both up to Week 18 of treatment and for the entire study.

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 were reported postrandomization.

Other Serious Adverse Events: Serious adverse experiences related to edema, the cardiovascular and renal systems are summarized in Table 2-045. The most common serious adverse events were cardiovascular, the investigators as serious clinical adverse events did not report edema- or hypertension-type.

Table 2-045. Listing of Patients With Serious Clinical Adverse Experiences

AN	Gender	Race	Age	Day of Onset	Adverse Experience	Duration	Action Taken	Outcome
Placebo								
320	M	White	69	95	Unstable angina	CONT	Interrupted PRx	Not recovered
48	F	White	64	5	Acute myocardial infarction	1 day	Discontinued PRx	Recovered
900	M	White	54	124	Myocardial infarction	1 day	PRx continued	Recovered
MK-0966 25 mg								
1008	M	White	71	134	Transient ischemic attack	0.33 hr	Interrupted PRx	Recovered
MK-0966 50 mg								
399	F	White	67	163	Deep venous thrombosis	11 day	PRx continued	Recovered
726	M	Hispa	64	78	Transient ischemic attack	23.98 hr	PRx continued	Recovered
161	M	White	57	85	Chest pain	5 day	PRx continued	Recovered
Ibuprofen 2400 mg								
310	F	White	59	30	Angina pectoris	5 day	PRx continued	Recovered
624	F	Black	49	30	Chest pain	3.00 hr	PRx continued	Recovered
681	F	White	49	94	Dizziness	0.50 hr	Discontinued PRx	Recovered
577	M	White	64	170	Sick sinus syndrome	3 day	PRx continued	Recovered

[Adapted from NDA 21-042, Vol. 1.156, Table 48, pages 196 and 197. CONT: denotes continuing. PRx: denotes study medication.]

Overall Profile of Dropouts: Of the 775 patients randomized, 497 (64.1%) completed the treatment phase. Withdrawals due to clinical adverse experiences and other reasons are summarized in Table 3-045[17]. 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 25 mg, but similar to MK-0966 at 50 mg. Discontinuation rates with MK-0966 were dose-dependent.

Table 3-045. Patient Accounting[18]

	Placebo	MK-0966		Ibuprofen
		25 mg	50 mg	2400 mg
	(N=194)	(N=195)	(N=193)	(N=193)
	n (%)	n (%)	n (%)	n (%)
COMPLETED:	152 (78.4)	138 (70.8)	127 (65.8)	80 (41.5)
DISCONTINUED:	42 (21.7)	57 (29.2)	66 (34.2)	113 (58.6)
Clinical adverse experience	7 (3.6)	10 § (5.1)	18 (9.3)	18 (9.3)
Laboratory adverse experience	0 (0.0)	1 (0.5)	3 (1.6)	1 (0.5)
Lack of efficacy	7 (3.6)	6 (3.1)	3 (1.6)	5 (2.6)
Lost to follow up	3 (1.6)	4 (2.1)	2 (1.0)	0 (0.0)
Patient moved	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)
Patient withdrew consent	13 (6.7)	15 (7.7)	16 (8.3)	10 (5.2)
Deviation from protocol	6 (3.1)	5 (2.6)	4 (2.1)	5 (2.6)
Study endpoint	5 (2.6)	15 (7.7)	19 (9.8)	73 (37.8)

[Adapted from NDA 21-042, Vol. 1.156, Table 14, page 83.]

Adverse Events Associated with Dropout: Table 4-045 provides the listing of patients discontinued due to edema, or adverse events related to the cardiovascular or urogenital systems. Two patients (ANs 0099 and 0413) receiving MK-0966 25 mg were discontinued from the trial because of edema-type adverse events. Hypertension resulted in two withdrawals (ANs 0121 and 1006) from the MK-0966 50 mg group. In the ibuprofen group on patient each withdrew because of acute renal failure (AN 0571), hypertension (AN 0407), and edema (0912).

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

[18] Includes 15 patients (AN 0096, AN 0313, AN 0533, AN 0581, AN 0583, AN 0699, AN 0701, AN 0708, AN 0718, AN 0722, AN 0773, AN 0825, AN 1021, AN 1023, AN 1024) who discontinued due to development of gastroduodenal erosions. One patient (AN 0920) was randomized and subsequently discontinued from the study due to a pretreatment adverse experience of lung malignant neoplasm that was confirmed after randomization; this patient is included here. One patient (AN 0562) was randomized and subsequently discontinued from the study due to a pretreatment adverse experience of increased WBC that was verified after randomization; this patient is included here.

Table 4-045. 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 Discontin-uation	Action Taken	Outcome
Placebo									
0048	F	White	64	5	Acute myocardial infarction	1 day	5	Discontinued PRx	Recovered
MK-0966 25 mg									
0099	F	White	67	39	Lower extremity edema	1.15 mo	66	Discontinued PRx	Recovered
0413	F	White	54	57	Fluid retention	24 day	56	Discontinued PRx	Recovered
0381	M	White	66	27	Urolithiasis	8 day	27	Discontinued PRx	Recovered
MK-0966 50 mg									
0121	M	White	56	97	Hypertension	3.88 mo	115	Discontinued PRx	Recovered
1006	F	White	68	60	Hypertension	5 day	61	Discontinued PRx	Recovered
0811	F	White	61	22	Hypotension	2 day	22	Discontinued PRx	Recovered
Ibuprofen 2400 mg									
0571	F	Hispa	61	52	Acute renal failure	21 day	59	Discontinued PRx	Recovered
0407	F	White	49	22	Hypertension	CONT‡	125	Discontinued PRx	Not recovered
0912	M	White	77	8	Edema	7 day	9	Discontinued PRx	Recovered
0969	M	White	76	73	Dysuria	16 day	82	Discontinued PRx	Recovered

[Adapted from NDA 21-042, Vol. 1.156, Table 50, pages 200-203. †One patient (AN 0920, MK-0966 25 mg) was randomized and subsequently discontinued from the study due to a pretreatment adverse experience of lung malignant neoplasm that was confirmed after the patient had been randomized; this patient is not included in this listing. ‡CONT = Continuing at the time of the last follow-up visit. NA=Not applicable. Intensity ratings were not reported for type = other adverse experiences.]

Dropouts for Laboratory Abnormalities: The study's investigators due to laboratory adverse experiences discontinued four of 775 patients (0.5% crude rate)[19].

Noteworthy, AN 0536 (MK-0966 25 mg) was discontinued for a laboratory adverse experience of hyperkalemia. Two measurements of elevated potassium at routine visits were reported as laboratory adverse experiences for values of 5.6 and 5.1 on relative Days 85 and 91, respectively. The potassium level was within normal range at baseline (4.3 mEq(K)/L) and had slightly exceeded the upper limit of normal (5.0 mEq(K)/L) three times prior to the adverse experience report (values of 5.5, 5.2 and 5.3 mEq(K)/L after 43, 69, and 76 days of study therapy, respectively). The maximum change from the baseline value was 1.3 mEq(K)/L. No treatment was initiated for these small elevations and the level of potassium was normal (4.3 mEq(K)/L) at a follow-up visit after discontinuation of study medication. The investigator considered the elevation of serum potassium to be related to study therapy.

Adverse Event Incidence Tables: According to the sponsor, during the entire study, clinical adverse experiences were reported by 615 (79%-crude rate) of 775 randomized patients. Tables 5-045 and 6-045 summarized the number (%) of patients who had Cardiovascular, Urogenital or Body as a Whole/Site Unspecified clinical adverse experiences, at week 18 and entire study.

Tables 7-045 and 8-045 summarize the number (%) of patients with edema[20]- and hypertension[21]-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.

---

[19] NDA 21-042, Vol. 1.156, Table 58, page 250.

[20] 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.

[21] 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 5-045. Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence ≥2.0% in One or More Treatment Groups) by Body System Week 18

	Placebo N=194			MK-0966 25 mg N=195			MK-0966 50 mg N=193			Ibuprofen 2400 mg N=193		
	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§
Body As A Whole/Site Unspecified												
Lower extremity edema	3	1.2	1.5	7	3.7	3.6	8	4.7	4.1	7	4.2	3.6
Cardiovascular												
Hypertension	7	3.9	3.6	11	6.2	5.6	23	14.3*	11.9	7	3.9	3.6
Urogenital												
Dysuria	2	1.0	1.0	4	1.8	2.1	2	1.1	1.0	1	0.8	0.5
Urinary tract infection	9	5.2	4.6	4	2.4	2.1	8	4.7	4.1	4	3.0	2.1

[Adapted from NDA 21-042, Vol. 1.156, Table 44, pages 159-163. * 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 6-045. Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence ≥2.0% in One or More Treatment Groups) by Body System Entire Study

	Placebo N=194			MK-0966 25 mg N=195			MK-0966 50 mg N=193			Ibuprofen 2400 mg N=193		
	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§
Body As A Whole												
Lower extremity edema	3	--	1.5	8	4.4	4.1	9	6.3	4.7	7	4.2	3.6
Cardiovascular												
Bloodpressure increased	1	--	0.5	2	1.3	1.0	5	4.1	2.6	0	0.0	0.0
Hypertension	7	--	3.6	14	9.2	7.2	25	17.5	13.0	7	3.9	3.6
Urogenital												
Dysuria	2	--	1.0	5	3.2	2.6	2	1.1	1.0	2	3.1	1.0
Urinarytract infection	9	--	4.6	5	3.1	2.6	9	5.5	4.7	4	3.0	2.1

[Adapted from NDA 21-042, Vol. 1.156, Table 45, pages 164-168. * 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 7-045. Number (%) Of Patients Exceeding the Predefined Limits of Change–Laboratory Week 18 (Intention-to-Treat Approach)

Clinical Adverse Experience/ Laboratory Test	Treatment	Number‡/Total§	Life Table Rateϕ (%)	Crude Rate¶ (%)
ΣHypertension	Placebo	9/185	5.1	4.6
	MK0966 25 mg	12/183	6.8	6.2
	MK0966 50 mg	27/166	16.6*	14.0
	Ibuprofen 2400 mg	7/186	3.9	3.6
ΣEdema	Placebo	6/188	2.8	3.1
	MK0966 25 mg	11/184	5.9	5.6
	MK0966 50 mg	11/182	6.5	5.7
	Ibuprofen 2400 mg	9/184	5.7	4.7

[Adapted from NDA 21-042, Vol. 1.156, Tables 69 and 74, pages 293 and 303. ΣHypertension = Blood pressure increased, Hypertension, Hypertensive crisis. ΣEdema = Edema, Fluid retention, Hand swelling, Lower extremity edema, Peripheral edema, Upper extremity edema. *p≤0.05 vs. placebo. 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 8-045. Number (%) Of Patients Exceeding the Predefined Limits of Change–Laboratory Entire Study (Intention-to-Treat Approach)

Clinical Adverse Experience/ Laboratory Test	Treatment	Number‡/Total§	Life Table Rateϕ (%)	Crude Rate¶ (%)
ΣHypertension	Placebo	9/185	–	4.6
	MK0966 25 mg	16/179	10.5	8.2
	MK0966 50 mg	30/163	20.6	15.5
	Ibuprofen 2400 mg	7/186	3.9	3.6
ΣEdema	Placebo	6/188	–	3.1
	MK0966 25 mg	12/183	6.6	6.2
	MK0966 50 mg	13/180	8.9	6.7
	Ibuprofen 2400 mg	9/184	5.7	4.7

[Adapted from NDA 21-042, Vol. 1.156, Tables 70 and 75, pages 294 and 304. ΣHypertension = Blood pressure increased, Hypertension, Hypertensive crisis. ΣEdema = Edema, Fluid retention, Hand swelling, Lower extremity edema, Peripheral edema, Upper extremity edema. 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.]

The number (%) of patients exceeding the predefined limits of change for systolic and diastolic blood pressure, up to week 18 and for the entire study, are summarized in Tables 9-045 and 10-045, respectively. Statistically significant differences were noted for systolic blood pressure between MK-0966 and placebo. The incidence of systolic blood pressure with MK-0966 was dose-dependent, both at 18 weeks and for the entire study.

Table 9-045. Patients Exceeding the Predefined Limits of Change On Diastolic And Systolic Blood Pressure Up to Week 18 (Intention-to-Treat Analysis)

Vital Sign	Predefined Limit of Change	Treatment	Number†/ Total‡	Life Table Rate (%)§	Crude Rate (%)ϕ
Systolic blood pressure (mm Hg)	Increase >20 and value >140	Placebo	20/186	14.8	10.8
		MK0966 25 mg	36/191	20.9*	18.8
		MK0966 50 mg	45/184	27.3*	24.5
		Ibuprofen 2400 mg	26/185	16.8	14.1
Diastolic blood pressure (mm Hg)	Increase >15 and value >90	Placebo	10/186	6.5	5.4
		MK0966 25 mg	19/191	11.1	9.9
		MK0966 50 mg	17/184	10.9	9.2
		Ibuprofen 2400 mg	19/185	13.0*	10.3

[Adapted from NDA 21-042, Vol. 1.156, Table 59, page 260. *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. §Life-table rate = cumulative life-table rate, based on the probability that an event occurs by the time point. ϕCrude rate = number of

patients within the laboratory adverse experience category/number of patients with one or more laboratory tests postbaseline, as percent. A patient may be counted only once in a category; the same patient may appear in different categories.]

Table 10-045. Patients Exceeding the Predefined Limits of Change On Diastolic And Systolic Blood Pressure Entire Study (Intention-to-Treat Analysis)

Vital Sign	Predefined Limit of Change	Treatment	Number†/ Total‡	Life Table Rate (%)§	Crude Rate (%)ϕ
Systolic blood pressure (mm Hg)	Increase >20 and value >140	Placebo	20/186	--	10.8
		MK0966 25 mg	42/191	27.2	22.0
		MK0966 50 mg	53/184	36.3	28.8
		Ibuprofen 2400 mg	29/185	21.9	15.7
Diastolic blood pressure (mm Hg)	Increase >15 and value >90	Placebo	10/186	--	5.4
		MK0966 25 mg	23/191	15.3	12.0
		MK0966 50 mg	18/184	11.8	9.8
		Ibuprofen 2400 mg	20/185	14.1	10.8

[Adapted from NDA 21-042, Vol. 1.156, Table 60, page 261. †Number of patients meeting the predefined limit criteria. ‡Total number of patients with valid values of the laboratory or vital sign test. §Life-table rate = cumulative life-table rate, based on the probability that an event occurs by the time point. ϕCrude rate = number of patients within the laboratory adverse experience category/number of patients with one or more laboratory tests postbaseline, as percent. A patient may be counted only once in a category; the same patient may appear in different categories.]

Tables 11-045 and 12-045 number (%) of patients with specific laboratory adverse experiences by laboratory test category up to Week 18 and entire study.

MK-0966 50-mg treatment group had a significantly higher rate of increased **blood urea nitrogen** adverse experiences (6.0% up to Week 18, 6.8% for entire study; p=0.014). Compared to placebo (0.8% up to Week 18), there was a significantly higher rate of increased **serum creatinine** adverse experiences for the MK-0966 50-mg treatment group (3.8% up to Week 18, 8.5% for entire study; p=0.043). MK-0966 effected dose-dependent changes in BUN and serum creatinine increased.

Table 11-045. Number (%) of Patients With Specific Laboratory Adverse Experiences by Laboratory Test Category Week 18

	Placebo N=194			MK-0966 25 mg N=195			MK-0966 50 mg N=193			Ibuprofen 2400 mg N=193		
	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§
Serum creatinine increased	1/190	0.8	0.5	4/191	2.3	2.1	6/189	3.8*	3.2	3/190	1.9	1.6
BUN increased	2/190	1.4	1.1	3/191	1.7	1.6	10/189	6.0*	5.3	5/190	3.6	2.6
Bicarbonate decreased	0/190	0.0	0.0	1/191	0.6	0.5	0/189	0.0	0.0	0/190	0.0	0.0
Hyperkalemia	0/190	0.0	0.0	2/191	1.1	1.0	1/188	0.6	0.5	2/190	1.1	1.1
Hypocalcemia	2/190	1.3	1.1	0/191	0.0	0.0	1/189	0.5	0.5	0/190	0.0	0.0
Hypokalemia	0/190	0.0	0.0	0/191	0.0	0.0	2/188	1.4	1.1	0/190	0.0	0.0
Hyponatremia	0/190	0.0	0.0	0/191	0.0	0.0	1/189	0.6	0.5	0/190	0.0	0.0
Uric acid increased	1/190	0.6	0.5	0/191	0.0	0.0	1/189	0.5	0.5	1/190	0.8	0.5
Erythrocyturia	2/190	1.2	1.1	2/191	1.1	1.0	1/188	0.6	0.5	0/190	0.0	0.0
Glycosuria	0/190	0.0	0.0	0/191	0.0	0.0	1/188	0.6	0.5	1/190	1.0	0.5
Hematuria	3/190	1.7	1.6	4/191	2.1	2.1	1/188	0.7	0.5	1/190	0.7	0.5
Leukocyturia	7/175	3.9	4.0	4/177	2.3	2.3	3/173	1.9	1.7	1/181	0.5	0.6
Microalbuminuria	0/28	0.0	0.0	0/56	0.0	0.0	0/48	0.0	0.0	1/36	0.5	2.8
Proteinuria	2/190	1.2	1.1	2/191	1.1	1.0	2/188	1.1	1.1	3/190	2.2	1.6

[Adapted from NDA 21-042, Vol. 1.156, Table 54, pages 233-235. ‡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 12-045. Number (%) of Patients With Specific Laboratory Adverse Experiences by Laboratory Test Category Entire Study

	Placebo N=194			MK-0966 25 mg N=195			MK-0966 50 mg N=193			Ibuprofen 2400 mg N=193		
	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	0/190	-	0.0	1/191	0.6	0.5	1/189	1.6	0.5	0/190	0.0	0.0
BUN increased	2/190	-	1.1	4/191	2.4	2.1	11/189	6.8	5.8	7/190	7.0	3.7
Hyperkalemia	0/190	-	0.0	2/191	1.1	1.0	1/188	0.6	0.5	2/190	1.1	1.1
Hypocalcemia	2/190	-	1.1	0/191	0.0	0.0	2/189	2.1	1.1	0/190	0.0	0.0
Hypokalemia	0/190	-	0.0	0/191	0.0	0.0	2/188	1.4	1.1	0/190	0.0	0.0
Hyponatremia	0/190	-	0.0	0/191	0.0	0.0	1/189	0.6	0.5	0/190	0.0	0.0
Serum creatinine increased	1/190	-	0.5	4/191	2.3	2.1	9/189	8.5	4.8	3/190	1.9	1.6
Uric acid increased	1/190	-	0.5	0/191	0.0	0.0	2/189	2.1	1.1	1/190	0.8	0.5
Erythrocyturia	2/190	-	1.1	3/191	2.6	1.6	1/188	0.6	0.5	0/190	0.0	0.0
Glycosuria	0/190	-	0.0	1/191	0.7	0.5	1/188	0.6	0.5	1/190	1.0	0.5
Hematuria	3/190	-	1.6	4/191	2.1	2.1	1/188	0.7	0.5	1/190	0.7	0.5
Leukocyturia	7/175	-	4.0	5/177	3.0	2.8	3/173	1.9	1.7	1/181	0.5	0.6
Microalbuminuria	0/28	-	0.0	0/56	0.0	0.0	0/48	0.0	0.0	1/36	0.5	2.8
Proteinuria	2/190	-	1.1	2/191	1.1	1.0	3/188	2.7	1.6	3/190	2.2	1.6

[Adapted from NDA 21-042, Vol. 1.156, Table 55, pages 236-239. ‡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 13-045 and 14-045. In keeping with the pattern observed for serum creatinine increased adverse events, Mk-0966 was associated with dose-dependent changes in serum creatinine. MK-0966 administration resulted in dose-dependent increases in serum potassium.

Table 13-045. Number (%) Of Patients Exceeding the Predefined Limits of Change–Laboratory Or Clinical Hypertension-Type Or Edema-Type Adverse Experiences Week 18 (Intention-to-Treat Approach)

Clinical Adverse Experience/ Laboratory Test	Treatment	Number‡/Total§	Life Table Rateϕ (%)	Crude Rate¶ (%)
Serum creatinine (mg/dL) Increase ≥0.5 and Value > ULN	Placebo	0/84	0.0	0.0
	MK-0966 25 mg	1/188	0.6	0.5
	MK-0966 50 mg	3/182	2.2	1.6
	Ibuprofen 2400 mg	1/183	0.7	0.5
Serum potassium (mEq(K)/L) Increase ≥0.8 and Value >ULN	Placebo	4/184	2.3	2.2
	MK0966 25 mg	16/188	9.0*	8.5
	MK0966 50 mg	21/182	13.6*	11.5
	Ibuprofen 2400 mg	7/183	4.9	3.8
Urine protein (mg/dL) Increase ≥1*f*	Placebo	20/183	15.0	10.9
	MK0966 25 mg	34/188	19.9	18.1
	MK0966 50 mg	26/182	16.6	14.3
	Ibuprofen 2400 mg	17/183	13.7	9.3

[Adapted from NDA 21-042, Vol. 1.156, Tables 62 and 67, pages 272 and 289. *p≤0.05 vs. placebo. ‡Number of patients meeting the predefined limit criteria. §Total number of patients with valid values of the laboratory. 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. A patient may be counted only once in a category; the same patient may appear in different categories.]

Table 14-045. Number (%) Of Patients Exceeding the Predefined Limits of Change–Laboratory Or Clinical Hypertension-Type Or Edema-Type Adverse Experiences Entire Study (Intention-to-Treat Approach)

Clinical Adverse Experience/ Laboratory Test	Treatment	Number‡/Total§	Life Table Rateϕ (%)	Crude Rate¶ (%)
Serum creatinine (mg/dL) Increase ≥0.5 and value >ULN	Placebo	0/184	--	(0.0)
	MK-0966 25 mg	1/188	0.6	(0.5)
	MK-0966 50 mg	3/182	2.2	(1.6)
	Ibuprofen 2400 mg	1/183	0.7	(0.5)
Serum potassium (mEq(K)/L) Increase ≥0.8 and Value >ULN	Placebo	4/184	--	2.2
	MK0966 25 mg	21/188	12.7	11.2
	MK0966 50 mg	26/182	19.3	14.3
	Ibuprofen 2400 mg	11/183	13.3	6.0
Urine protein (mg/dL) Increase ≥1*f*	Placebo	21/183	--	11.5
	MK0966 25 mg	45/188	36.6	23.9
	MK0966 50 mg	32/182	26.9	17.6
	Ibuprofen 2400 mg	22/183	21.0	12.0

[Adapted from NDA 21-042, Vol. 1.156, Tables 63 and 68, pages 273 and 290. ‡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. A patient may be counted only once in a category; the same patient may appear in different categories.]

SUMMARY/COMMENTS

Study protocol #045 compared the effects of 6 months treatment with MK-0966 25 mg and 50 mg with 2400 mg of ibuprofen, in adult men and women, ≥40 years old, with clinical and radiographic diagnosis of OA of the knee or hip.

Edema- and hypertension-type, and serum creatinine increased were the salient adverse events that outlined the cardiovascular and renal safety profile of MK-0966 in this study.

Two patients (ANs 0099 and 0413) receiving MK-0966 25 mg were discontinued from the trial because of edema-type adverse events. Hypertension resulted in two withdrawals (ANs 0121 and 1006) from the MK-0966 50 mg group. A patient (AN 0536) receiving MK-0966 25 mg was discontinued for a laboratory adverse experience of hyperkalemia.