Table 7-064. MK-0966 $AUC_{(0-\infty\ hr)}$ (ng·hr/ml)

	Mean[a]±SD	p-Value[b]
Part 1: Hemodialysis initiated 48 hours postdose. n=6	6927±4393	0.269
Part 2: Hemodialysis initiated 4 hours postdose. n=6	6326±3663	

[Adapted from NDA 21-042, Volume 1.177, Table 23, page 52. [a]denotes: geometric mean±between-subject SD. [b]denotes: between-part p-Value.]

Table 8-064. MK-0966 C_{max} (ng/ml)

	Mean[a]±SD	p-Value[b]
Part 1: Hemodialysis initiated 48 hours postdose. n=6	395±144	0.014
Part 2: Hemodialysis initiated 4 hours postdose. n=6	325±111	

[Adapted from NDA 21-042, Volume 1.177, Table 25, page 54. [a]denotes: geometric mean±between-subject SD. [b]denotes: between-part p-Value.]

Table 9-064. MK-0966 T_{max} (hr)

	Mean±SD	p-Value[b]
Part 1: Hemodialysis initiated 48 hours postdose. n=6	3.2±?	0.642
Part 2: Hemodialysis initiated 4 hours postdose. n=6	4.6±?	

[Adapted from NDA 21-042, Volume 1.177, Table 27, page 55. [a]denotes: arithmetic mean. [b]denotes: between-part p-Value.]

Table 10-064. MK-0966 $T_{1/2}$ (hr)

	Mean±SD	p-Value[b]
Part 1: Hemodialysis initiated 48 hours postdose. n=6	12.1±4.7	0.055
Part 2: Hemodialysis initiated 4 hours postdose. n=6	13.3±4.7	

[Adapted from NDA 21-042, Volume 1.177, Table 28, page 55. [a]denotes: harmonic mean±between-subject SD (Jacknife standard deviation). [b]denotes: between-part p-Value.]

The dialysis clearance of MK-0966 was approximately 40 ml/min regardless of when the dialysis was initiated (48 or 4 hours postdose). Note that 1 patient (AN 3) had a calculated zero dialysis clearance, since in part 1 the concentrations of MK-0966 were all below the assay's limit of reliable quantification during the 3 hours of hemodialysis (Table 11-064).

Table 11-064. Dialysis Clearance (ml/min)

	Mean±SD	p-Value
Part 1: Hemodialysis initiated 48 hours postdose. n=6	38±21	?
Part 2: Hemodialysis initiated 4 hours postdose. n=6	45±7	

[Adapted from NDA 21-042, Volume 1.177, Table 29, page 56.]

Less than 6% of the 50-mg dose administered in part 1 or part 2 was recovered in the dialysate in all patients (Table 12-064).

Table 12-064. Recovery in Dialysate (% of Dose)

	Mean±SD	p-Value
Part 1: Hemodialysis initiated 48 hours postdose. n=6	0.5±0.4	?
Part 2: Hemodialysis initiated 4 hours postdose. n=6	4.0±1.2	

[Adapted from NDA 21-042, Volume 1.177, Table 30, page 57.]

Safety: There were no apparent safety issues in patients with end-stage renal disease undergoing hemodialysis who received single 50-mg doses of MK-0966.

SUMMARY/COMMENTS

This study was designed to determine the effect of renal insufficiency and hemodialysis on the pharmacokinetics of MK-0966 after a single oral dose of 50 mg. Comparisons of plasma pharmacokinetic parameters, i.e., $AUC_{(0\text{-}48\ hr)}$, $AUC_{(0-\infty\ hr)}$, C_{max}, T_{max}, $t_{1/2}$, and *in vitro* protein binding between patients with end-stage renal disease on hemodialysis and healthy volunteers, indicated that renal insufficiency has no notable effect on the pharmacokinetics of oral MK-0966. The dialysis clearance of MK-0966 was approximately 40 ml/min regardless of when the dialysis was initiated (48 or 4 hours postdose). The results of this study suggest that neither renal insufficiency, nor hemodialysis, do significantly affect the pharmacokinetics of MK-0966.

16.1 Osteoarthritis Studies
6-Weeks Studies

16.1.1 Protocol #010[1]: A Double-Blind, Placebo-Controlled Study To Evaluate Safety And Tolerability And Preliminarily Assess Clinical Efficacy Of MK-0966 In Patients With Osteoarthritis Of The Knee

METHODS

This was a multicenter (twenty-seven centers, United States), double-blind (with in-house blinding), randomized, placebo-controlled study. The duration of treatment was three- to 15-day nonsteroidal anti-inflammatory (NSAID) washout period, followed by 6-week treatment period with MK-0966 (25 or 125 mg) or placebo. Patients enrolled in the trial were healthy men or women of nonchildbearing potential ≥40 years old, with a clinical and radiologic diagnosis of OA of the knee (tibio-femoral joint).

The primary therapy period was from 06JUL95 to 08FEB96; the in-house case report form cutoff date was 27FEB96.

The primary objectives of the study were: (1) To investigate the safety and tolerability of continuous administration of MK-0966 for 6 weeks to patients with osteoarthritis (OA) of the knee; (2) To investigate the effects of 125 mg MK-0966 orally once daily vs. placebo on the assessment of pain by patients with OA of the knee as reported on a general pain visual analogue scale (VAS) and on the Pain Subscale (WOMAC) after 2 weeks of treatment; (3) To investigate the effects of 25 mg MK-0966 orally once daily vs. placebo on the assessment of pain by patients with OA of the knee as reported on a general pain visual analog scale and on the Pain Subscale (WOMAC) after 2 weeks of treatment; (4) To investigate the effects of MK-0966 (25 or 125 mg) vs. placebo on the assessment of pain by patients with OA of the knee as reported on a general pain visual analog scale (VAS) and on the Pain Subscale (WOMAC) after 6 weeks of treatment; (5) To investigate the effects of MK-0966 vs. placebo on Patient and Investigator Global Assessment of Disease Status (VAS), Stiffness and Physical Disability Subscales (WOMAC), and Patient and Investigator Global Assessment of Response to Therapy after 2 and 6 weeks of treatment; (6) To compare the incidence of discontinuation of treatment, due to lack of efficacy, associated with MK-0966 vs. placebo; (7) To evaluate the use of acetaminophen (for rescue) medication during treatment with MK-0966 and placebo (Treatment Weeks 3 through 6); and (8) To assess the effect of 6 weeks administration of MK-0966 on body weight and serum creatinine.

The incidence of clinical and laboratory adverse experiences was analyzed using Fisher's exact test. Overall and pairwise treatment comparisons were performed.

RESULTS

Demographics: Of the 219 randomized patients, Placebo = 72, MK-0966 25 mg = 73 and MK-0966 125 mg = 74, 71% were females and 29% were males. Age ranged from 35 to 84 years. Ninety-four percent were white and 6% were of other origins. The average duration of OA was 11.9 years, and ranged from 2 to 64 years. No differences between treatment groups were noted for specific secondary diagnoses or prior therapies.

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

Deaths: No death was reported in this study.

Other Serious Adverse Events: Serious adverse experiences occurred in 3 of 219 patients (1.4%), all randomized to the 125-mg treatment group. However, none of these events were related to the cardiovascular or renal systems.

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[1] NDA 21-042, Vol. 1.101-1.103, Reference 010.

Overall Profile of Dropouts: Of the 219 patients randomized there were 31 (43.0%) and 26 (17.7%) patients who discontinued in the placebo and combined MK-0966 treatment groups, respectively (Table 1-010). The percent of patients who discontinued due to clinical adverse experience was numerically higher for MK-0966 compared with placebo.

Table 1-010. Patient Accounting

	Placebo	MK-0966	
	N=72 n (%)	25 mg N=73 n (%)	125 mg N=74 n (%)
DISCONTINUED:	31 (43.0)	9 (12.3)	17 (22.9)
Clinical adverse experience	6 (8.5)	4 (5.6)	10 (13.7)
Laboratory adverse experience	0 (0.0)	0 (0.0)	1 (1.4)
Deviation from protocol	3 (4.1)	1 (1.4)	2 (2.7)
Patient withdrew consent	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow up	0 (0.0)	0 (0.0)	1 (1.4)
Lack of efficacy	21 (29.6)	4 (5.6)*	1 (1.4)*
Other reasons†	1 (1.4)	0 (0.0)	2 (2.7)

[Adapted from NDA 21-042, Vol. 1.101, Table 19, page 80. * p<0.001 vs. placebo. †Includes reasons other than those listed.]

Adverse Events Associated with Dropout: Six (8.3%), 4 (5.5%), and 10 (13.5%) patients were discontinued from therapy in the placebo, 25-, and 125-mg groups, respectively, due to an adverse experience.

Of note, four patients (ANs 0053, 0059, 0102, 0044) were discontinued from the 125-mg treatment group due to edema-related adverse experiences (edema, upper extremity edema, lower extremity edema)[2].

A 74 years old patient (AN 1015) was discontinued because of a transient ischemic attack that lasted 8 hours; the patient recovered from the adverse event upon discontinuation.

Adverse Event Incidence Tables[3]*:* The incidence of Body as a Whole/Site Unspecified adverse experiences was significantly higher with the 125-mg group compared with the placebo group. This discrepancy was due in part to the increased incidence of edema-related (edema, lower extremity edema, upper extremity edema, fluid retention, Table 2-010). According to the sponsor, none of the 8 patients reporting edema-related adverse experiences, had a history of edema or had edema on the physical examination at the Screening Visit. Four patients in the 125-mg group reporting edema were discontinued from study therapy.

Table 2-010. Number (%) of Patients With Specific Edema-Related Adverse Experiences Regardless of Drug Relationship

	Placebo	MK-0966	
	N=72 n (%)	25 mg N=73 n (%)	125 mg N=74 n (%)
Lower extremity edema	0 (0.0)	2 (2.7)	5 (6.8)
Edema	0 (0.0)	0 (0.0)	2 (2.7)
Fluid retention	0 (0.0)	0 (0.0)	1 (1.4)
Upper extremity edema	0 (0.0)	1 (1.4)	1 (1.4)
ΣEdema	0 (0.0)	2 (2.7)	6 (8.1)*

[Adapted from NDA 21-042, Vol. 1.101, Table 44, page 138. ΣEdema = Lower extremity edema+Edema+Fluid retention+Upper extremity edema. * p=0.028 vs. placebo.]

[2] Adapted from NDA 21-042, Vol. 1.101, Table 43, pages 134-136.

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

Zero (0%), 2 (2.7%) and 2 (2.7%) patients in the placebo, 25-, and 125-mg treatment groups, respectively, reported adverse experiences of hypertension and increased blood pressure (Table 3-010).

Table 3-010. Number (%) of Patients With Specific Increased Blood Pressure and Hypertension Adverse Experiences Regardless of Drug Relationship

	Placebo	MK-0966	
	N=72 n (%)	25 mg N=73 n (%)	125 mg N=74 n (%)
Increased blood pressure	0 (0.0)	1 (1.4)	1 (1.4)
Hypertension	0 (0.0)	1 (1.4)	1 (1.4)
ΣHypertension	0 (0.0)	2 (2.7)	2 (2.7)

[Adapted from NDA 21-042, Vol. 1.101, Table 45, page 140. ΣHypertension = hypertension+increased blood pressure.]

Analysis the of number (%) of patients exceeding the predefined limits of change in systolic blood pressure measurements revealed that a significantly greater percent of them in the 125-mg treatment group exceeded the predefined limit compared with the placebo ($p<0.001$) and 25-mg groups ($p=0.010$) (Table 4-010).

Table 4-010. 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	Placebo MK0966 25 mg MK0966 125 mg	5/71 (7.0) 10/72 (13.9) 24/73 (32.9)*ϕ
Diastolic blood pressure (mm Hg)	Increase >15 and value >90	Placebo MK0966 25 mg MK0966 125 mg	1/71 (1.4) 3/72 (4.2) 2/73 (2.7)

[Adapted from NDA 21-042, Vol. 1.101, Table 54, page 157. *$p<0.001$ vs. placebo. ϕ$p=0.010$ vs. 25 mg. †Number of patients meeting the predefined limit criteria. ‡Total number of patients with valid values of the laboratory or vital sign test.]

Laboratory Findings: The laboratory adverse experience profile is summarized in Table 5-010. No serious laboratory adverse experiences occurred.

Table 5-010. Number (%) of Patients With Specific Laboratory Adverse Experiences by Laboratory Test Category

	Placebo	MK-0966	
	N=72 n/N (%)	25 mg N=73 n/N (%)	125 mg N=74 n/N (%)
Hypercalcemia	0/72 (0.0)	1/73 (1.4)	0/74 (0.0)
Hypokalemia	1/71 (1.4)	0/73 (0.0)	0/74 (0.0)
Hyponatremia	0/72 (0.0)	0/73 (0.0)	1/74 (1.4)
Erythrocyturia	2/72 (2.8)	0/73 (0.0)	0/73 (0.0)
Leukocyturia	1/72 (1.4)	0/73 (0.0)	1/73 (1.4)
Proteinuria	0/72 (0.0)	0/73 (0.0)	1/73 (1.4)

[Adapted from NDA 21-042, Vol. 1.101, Table 50, pages 147 and 148. n/N = number of patients with laboratory adverse experience/number of patients for whom the laboratory test was recorded postbaseline.]

The number (%) of patients exceeding the predefined limits of change for creatinine, etc, are summarized Table 6-010. One patient in the MK0966 125 mg group developed increase in serum creatinine and two patients in the MK0966 25 mg group had an increase in serum potassium.

Table ?. Predefined Limits of Change: Laboratory (Intention-to-Treat Approach)

Laboratory Test	Predefined Limits of Change	Treatment	Number‡/Total§ (%)
Serum Calcium (mEq(Ca)/L)	Decrease >=0.7 and Value < LLN	Placebo	1 /71 (1.4)
		MK0966 25 mg	0 /73 (0.0)
		MK0966 125 mg	0 /73 (0.0)
Serum Creatinine (mg/dL)	Increase >=0.5 and Value > ULN	Placebo	0 /71 (0.0)
		MK0966 25 mg	0 /73 (0.0)
		MK0966 125 mg	1 /73 (1.4)
Serum Potassium (mEq(K)/L)	Decrease >=0.8 and Value < LLN	Placebo	1 /70 (1.4)
		MK0966 25 mg	0 /73 (0.0)
		MK0966 125 mg	0 /73 (0.0)
	Increase >=0.8 and Value > ULN	Placebo	0 /70 (0.0)
		MK0966 25 mg	2 /73 (2.7)
		MK0966 125 mg	0 /73 (0.0)
Serum Sodium (mEq(Na)/L)	Decrease >=8.0 and Value < LLN	Placebo	0 /71 (0.0)
		MK0966 25 mg	1 /73 (1.4)
		MK0966 125 mg	0 /73 (0.0)
Serum Uric Acid (mg/dL)	Increase >=50.0% and Value > ULN	Placebo	0 /71 (0.0)
		MK0966 25 mg	1 /73 (1.4)
		MK0966 125 mg	1 /73 (1.4)
Urine protein (mg/dL)	Increase ≥1*f*	Placebo	?
		MK0966 25 mg	
		MK0966 125 mg	

[Adapted from NDA 21-042, Vol. 1.101, APPENDIX 4.12, pages 1255 and 1256. ULN = Upper limit of normal range. LLN = Lower limit of normal range. ‡Number of patients meeting the predefined limit criteria. §Total number of patients with valid values of the laboratory or vital sign test. *f*Specification includes both character and numeric values. ?Information not available.]

SUMMARY/COMMENTS

In this clinical trial where healthy men or women of nonchildbearing potential ≥40 years old with a clinical and radiologic diagnosis of OA of the knee were studied, the prominent safety features after only 6 weeks of treatment with MK-0966 were the development of hypertension and edema. These adverse events occurred in dose-related manner. Of note, edema-type adverse event was responsible for four-treatment discontinuation in the MK-125 mg group.

16.1.2 Protocol #029[4]: A Placebo-Controlled, Parallel-Group, Double-Blind Study To Assess Safety And Further Define The Clinically Effective Dose Range Of MK-0966 In Patients With Osteoarthritis Of The Knee Or Hip

METHODS

This study had a multicenter (sixty-four centers, United States), double-blind (with in-house blinding), randomized, placebo-controlled, parallel-group design; and randomized healthy men or women of nonchildbearing potential ≥40 years old, ≤127 kg, with a clinical and radiologic diagnosis of OA of the knee (tibio-femoral joint) or hip. The duration of treatment was three- to 12-day nonsteroidal anti-inflammatory drug (NSAID) washout period, followed by 6-week treatment period with MK-0966 (5, 12.5, 25 or 50 mg [knee only]) or placebo.

The primary therapy period was from 29APR96 to 15FEB97. In-house case report form cutoff date was 08MAY97.

[4] NDA 21-042, Vol. 1.118-1.120, Reference 029.

The objectives of the study were: (1) To demonstrate the clinical efficacy of MK-0966 in the treatment of osteoarthritis (OA) of the knee and hip, (2) To evaluate the overall safety and tolerability of MK-0966 with once-daily administration for a 6-week period, (3) To further define the clinically active dose range of MK-0966 in the treatment of OA, (4) To verify the consistency of therapeutic effect of MK-0966 on knee versus hip OA, (5) To evaluate and compare the effect of MK-0966 versus placebo on body weight, blood pressure, serum albumin, serum creatinine, and hemoglobin, and (6) To evaluate the response of the Medical Outcome Study 36-Item Short-Form Health Survey (SF-36) generic Quality-of-Life questionnaire in patients treated with MK-0966 and placebo.

Safety: Fisher's exact test was used to compare between-group incidence of adverse experiences and the percent of patients outside the predefined limits of change for selected laboratory tests. These were performed in step-down fashion from the highest to the lowest dose versus placebo and from the highest to lowest among active doses.

RESULTS

Demographics: Patients' baseline characteristics by treatment group are summarized Table 1-029. Seventy-one percent were women and 29% were men. Age ranged from 39 to 92 years. Eighty-nine percent were white and 11% were of other origins. Overall, there were no clinically meaningful differences between the treatment groups for any of these characteristics. Patients allocated to placebo, 5, and 12.5 mg tended to have greater incidences of digestive system secondary diagnoses. No other apparent differences between treatment groups were noted. There were no clinically meaningful differences between treatment groups in frequency or type of prior drug therapies.

Table 1-029. Baseline Patient Characteristics by Treatment Group

	Placebo	MK-0966			
	(N=145) n (%)	5 mg (N=149) n (%)	12.5 mg (N=144) n (%)	25 mg (N=137) n (%)	50 mg (N=97) n (%)
Gender					
Female	99 (68.3)	107 (71.8)	103 (71.5)	104 (75.9)	64 (66.0)
Male	46 (31.7)	42 (28.2)	41 (28.5)	33 (24.1)	33 (34.0)
Race					
Asian	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Black	8 (5.5)	10 (6.7)	11 (7.6)	10 (7.3)	6 (6.2)
Hispanic American	7 (4.8)	3 (2.0)	3 (2.1)	2 (1.5)	4 (4.1)
Native American	3 (2.1)	1 (0.7)	3 (2.1)	2 (1.5)	0 (0.0)
White	126 (86.9)	135 (90.6)	127 (88.2)	122 (89.1)	87 (89.7)
Age					
Mean±SD	61.4±10.79	61.2±9.11	61.4±10.50	63.0±9.88	61.3±10.99

[Adapted from NDA 21-042, Vol. 1.118, Table 13, pages 68 and 69.]

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

Deaths: No death was reported in this study.

Other Serious Clinical Adverse Experiences: Four of the six serious clinical adverse experiences were cardiovascular events (cerebrovascular accident, atrial fibrillation, unstable angina, and acute myocardial infarction) (Table 2-029). According to the sponsor, these serious adverse events occurred in patients with significant risk factors for cardiovascular disease.

Table 2-029. Listing of Patients With Serious Clinical Adverse Experiences

AN	Gender	Race	Age	Relative Day of Onset	Adverse Experience	Duration of AE	Action Taken	Outcome
Placebo								
MK-0966 5 mg								
MK-0966 12.5 mg								
4248	F	White	63	30	Cerebrovascular accident	4 days	Discontinued PRx†	Recovered
MK-0966 25 mg								
4069	M	White	75	40	Atrial fibrillation	4 days	Discontinued PRx	Recovered
4142	F	White	83	12	Unstable angina	1.7 months	Discontinued PRx	Recovered
4250	F	White	70	11	Acute myocardial infarction	4 days	Discontinued PRx	Recovered

[Adapted from NDA 21-042, Vol. 1.118, Table 52, page 192. †PRx = study medication.]

Overall Profile of Dropouts: There were 34 (23.4%) and 73 (13.8%) patients who discontinued in the placebo and combined MK-0966 treatment groups, respectively (Table 3-029).

Table 3-029. Patient Accounting

	Placebo	MK-0966			
	(N=145) n (%)	5 mg (N=149) n (%)	12.5 mg (N=144) n (%)	25 mg (N=137) n (%)	50 mg† (N=97) n (%)
COMPLETED:	111 (76.6)	124 (83.2)	122 (84.7)	123 (89.8)	85 (87.6)
DISCONTINUED:	34 (23.4)	25 (16.8)	22 (15.3)	14 (10.2)	12 (12.4)
Clinical adverse experience	2 (1.4)	6 (4.0)	4 (2.8)	6 (4.4)	5 (5.2)
Laboratory adverse experience	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.7)	0 (0.0)
Deviation from protocol	0 (0.0)	1 (0.7)	1 (0.7)	0 (0.0)	3 (3.1)
Patient withdrew consent	0 (0.0)	3 (2.0)	1 (0.7)	1 (0.7)	0 (0.0)
Lost to follow-up	3 (2.1)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Lack of efficacy	28 (19.3)	15 (10.1)	12 (8.3)	6 (4.4)	3 (3.1)
Other reasons§	1 (0.7)	0 (0.0)	2 (1.4)	0 (0.0)	1 (1.0)

[Adapted from NDA 21-042, Vol. 1.118, Table 19, page 118. †Patients with OA of the hip did not receive 50 mg. § Includes reasons other than those listed.]

Adverse Events Associated with Dropout: Table 4-029 lists patients discontinued due to cardiovascular and renal adverse events. Of note, edema-related adverse experiences resulted in patient discontinuation one each in the MK-0966 12.5 mg and 50 mg groups (Table 4-029).

Table 4-029. 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									
2534	F	Hispanic	54	10	Urinary frequency	5 days	13	Discontinued PRx†	Recovered
MK-0966 5 mg									
MK-0966 12.5 mg									
2093	F	White	65	30	Lower extremity edema	6 days	31	Discontinued PRx	Recovered
4248	F	White	63	30	Cerebrovascular accident	4 days	32	Discontinued PRx	Recovered
MK-0966 25 mg									
4069	M	White	75	40	Atrial fibrillation	4 days	42	Discontinued PRx	Recovered
4142	F	White	83	12	Unstable angina	1.7 mos	13	Discontinued PRx	Recovered
4250	F	White	70	11	Acute myocardial infarction	4 days	14	Discontinued PRx	Recovered
MK-0966 50 mg									
2148	F	White	71	11	Lower extremity edema	4 days	11	Discontinued PRx	Recovered

[Adapted from NDA 21-042, Vol. 1.118, Table 53, pages 194 and 195. †PRx = Study medication.]

Adverse Events Incidence Tables: Clinical adverse experiences were reported by 358 (53%) of 672 randomized patients. The relevant cardiovascular- and renal-related adverse experiences are summarized by treatment group in Table 5-029. The duration of therapy was comparable between treatment groups. The mean number of days on treatment were 37, 38.6, 39.1, 40.3, and 39.2 for patients in the placebo, 5-, 12.5-, 25-, and 50-mg groups, respectively.

Because the terminology used by the investigators in reporting adverse events related to "fluid retention" or "hypertension" varied, they were incorporated by the sponsor into the following all-inclusive categories: Edema- and Hypertension-Type Adverse events. The incidence rates of edema- and hypertension-type adverse experiences are discussed below in detail.

Table 5-029. Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence ≥2.0% in One or More Treatment Groups) by Body System

	Placebo	MK-0966			
	(N=145) n (%)	5 mg (N=149) n (%)	12.5 mg (N=144) n (%)	25 mg (N=137) n (%)	50 mg (N=97) n (%)
Body as a Whole/Site Unspecified					
Edema	2 (1.4)	1 (0.7)	2 (1.4)	4 (2.9)	2 (2.1)
Fluid retention	1 (0.7)	0 (0.0)	0 (0.0)	3 (2.2)	1 (1.0)
Lower extremity edema	1 (0.7)	4 (2.7)	3 (2.1)	3 (2.2)	5 (5.2)*
Cardiovascular System					
Blood pressure increased	1 (0.7)	2 (1.3)	3 (2.1)	2 (1.5)	2 (2.1)
Urogenital System					
Urinary tract infection	5 (3.4)	2 (1.3)	3 (2.1)	4 (2.9)	2 (2.1)

[Adapted from NDA 21-042, Vol. 1.118, Table 50, pages 181 and 182. * $p<0.05$ vs. placebo. Although a patient may have had two or more clinical adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.]

Table 6-029 summarizes both the number and the percentage of patients with specific edema-related adverse experiences. MK-0966 treatment was associated with a dose-dependent incidence of edema-related adverse events. At any dose of MK-0966 there was a higher rate of occurrence for edema-related adverse experiences than in the placebo group.

Table 6-029. Number (%) of Patients With Specific Edema-Related Adverse Experiences

	Placebo	MK-0966			
	(N=145) n (%)	5 mg (N=149) n (%)	12.5 mg (N=144) n (%)	25 mg (N=137) n (%)	50 mg (N=97) n (%)
Lower Extremity Edema	1 (0.7)	4 (2.7)	3 (2.1)	3 (2.2)	5 (5.2)*
Edema	2 (1.4)	1 (0.7)	2 (1.4)	4 (2.9)	2 (2.1)
Fluid Retention	1 (0.7)	0 (0.0)	0 (0.0)	3 (2.2)	1 (1.0)
Upper Extremity Edema	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (1.0)
ΣEdema	4 (2.8)	5 (3.4)	5 (3.5)	11 (8.0)	9 (9.3)*

[Adapted from NDA 21-042, Vol. 1.118, Table 54, pages 196. * $p<0.05$ compared with placebo. ΣEdema = Lower Extremity Edema+Edema+Fluid Retention+Upper Extremity Edema.]

Table 7-029 summarizes both the number and the percentage of patients with specific hypertensive-related adverse experiences. MK-0966 treatment was associated with slightly higher rate of events than placebo.

Table 7-029. Number (%) of Patients With Specific Increased Blood Pressure and Hypertension Adverse Experiences Regardless of Drug Relationship

	Placebo (N=145) n (%)	MK-0966 5 mg (N=149) n (%)	MK-0966 12.5 mg (N=144) n (%)	MK-0966 25 mg (N=137) n (%)	MK-0966 50 mg† (N=97) n (%)
Increased blood pressure	1 (0.7)	2 (1.3)	3 (2.1)	2 (1.5)	2 (2.1)
Hypertension	1 (0.7)	1 (0.7)	1 (0.7)	1 (0.7)	0 (0.0)
ΣHypertension*	2 (1.4)	3 (2.0)	4 (2.8)	3 (2.2)	2 (2.1)

[Adapted from NDA 21-042, Vol. 1.118, Table 55, pages 197. *ΣHypertension = Increased blood pressure+ Hypertension.]

The number (%) of patients exceeding the predefined limits of change for blood pressure are summarized in Table 8-029. Patients receiving MK-0966 had almost a two-fold higher rate of systolic "hypertension" as compared with those treated with placebo.

Table 8-029. Number (%) of Patients Exceeding the Predefined Limits of Change Vital Sign Parameters (Intention-to-Treat Approach)

Vital Sign	Predefined Limit of Change	Treatment	Number†/Total‡
Systolic blood pressure (mm Hg)	Increase >20.0 and value >140.0	Placebo	10/142 (7.0)
		MK-0966 5 mg	19/148 (12.8)
		MK-0966 12.5 mg	20/143 (14.0)
		MK-0966 25 mg	19/135 (14.1)
		MK-0966 50 mg	11/97 (11.3)
Diastolic blood pressure (mm Hg)	Increase >15.0 and value >90.0	Placebo	5/142 (3.5)
		MK-0966 5 mg	3/148 (2.0)
		MK-0966 12.5 mg	3/143 (2.1)
		MK-0966 25 mg	3/135 (2.2)
		MK-0966 50 mg	3/97 (3.1)

[Adapted from NDA 21-042, Vol. 1.118, Table 66, pages 220. †Number of patients meeting the predefined limit criteria. ‡ Total number of patients with valid values of the laboratory or vital sign test.]

Laboratory Findings: Table 9-029 presents the number (%) of patients with specific laboratory adverse experiences by laboratory test category. Of note, hyperkalemia and serum creatinine increased developed only in patients receiving MK-0966.

Table 9-029. Number (%) of Patients With Specific Laboratory Adverse Experiences by Laboratory Test Category

Laboratory Test	Placebo (N=145) n/N (%)†	MK-0966 5 mg (N=149) n/N (%)	MK-0966 12.5 mg (N=144) n/N (%)	MK-0966 25 mg (N=137) n/N (%)	MK-0966 50 mg (N=97) n/N (%)
BUN increased	0/138 (0.0)	0/143 (0.0)	0/142 (0.0)	1/134 (0.7)	0/95 (0.0)
Hyperkalemia	0/137 (0.0)	0/142 (0.0)	0/142 (0.0)	0/134 (0.0)	3/95 (3.2)
Hypocalcemia	0/138 (0.0)	0/142 (0.0)	1/142 (0.7)	0/134 (0.0)	0/95 (0.0)
Hypokalemia	1/137 (0.7)	0/142 (0.0)	0/142 (0.0)	0/134 (0.0)	0/95 (0.0)
Hyponatremia	0/137 (0.0)	0/142 (0.0)	1/142 (0.7)	0/134 (0.0)	1/95 (1.1)
Serum creatinine increased	0/138 (0.0)	0/142 (0.0)	0/142 (0.0)	1/134 (0.7)	0/95 (0.0)
Uric acid increased	0/138 (0.0)	0/141 (0.0)	0/142 (0.0)	0/134 (0.0)	2/95 (2.1)
Hematuria	0/136 (0.0)	0/142 (0.0)	0/142 (0.0)	0/132 (0.0)	1/96 (1.0)
Leukocyturia	3/136 (2.2)	0/143 (0.0)	2/142 (1.4)	0/132 (0.0)	2/96 (2.1)
Proteinuria	1/131 (0.8)	0/134 (0.0)	2/135 (1.5)	0/123 (0.0)	1/91 (1.1)

[Adapted from NDA 21-042, Vol. 1.118, Table 61, pages 207-209. N = total number of patients per treatment group. †n/N (%) = number (%) of patients with laboratory adverse experience/number of patients with laboratory test postbaseline. 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.]

Number (%) of patients exceeding the predefined limits of change for laboratory chemistry is described in Table 10-029. As was the case for laboratory adverse experiences, only patients in the MK-0966 groups developed abnormally high values for serum creatinine and potassium. None of the patients exceeded the predefined limit of change for urine protein.

Table 10-029. Number (%) of Patients Exceeding the Predefined Limits of Change: Laboratory Chemistry (Intention-to-Treat Approach)

	Predefined Limits of Change	Treatment	Number/Total (%)
Serum creatinine (mg/dL)	Increase >= 0.5 and Value > ULN	Placebo	0 /134 (0.00%)
		MK-0966 5 mg	0 /141 (0.00%)
		MK-0966 12.5 mg	2 /134 (1.49%)
		MK-0966 25 mg	1 /134 (0.75%)
		MK-0966 50 mg	1 /92 (1.09%)
Serum potassium (mEq(K)/L)	Decrease >= 0.8 and Value < LLN	Placebo	1 /133 (0.75%)
		MK-0966 5 mg	1 /141 (0.71%)
		MK-0966 12.5 mg	1 /133 (0.75%)
		MK-0966 25 mg	4 /134 (2.99%)
		MK-0966 50 mg	0 /92 (0.00%)
	Increase >= 0.8 and Value > ULN	Placebo	0 /133 (0.00%)
		MK-0966 5 mg	1 /141 (0.71%)
		MK-0966 12.5 mg	1 /133 (0.75%)
		MK-0966 25 mg	1 /134 (0.75%)
		MK-0966 50 mg	3 /92 (3.26%)
Serum uric acid (mg/dL)	Increase >= 50.0% and Value > ULN	Placebo	0 /134 (0.00%)
		MK-0966 5 mg	1 /140 (0.71%)
		MK-0966 12.5 mg	1 /136 (0.74%)
		MK-0966 25 mg	0 /134 (0.00%)
		MK-0966 50 mg	0 /92 (0.00%)

[Adapted from NDA 21-042, Vol. 1.120, APPENDIX 4.21, pages 1677 and 1679.]

SUMMARY/COMMENTS

In this clinical trial where healthy men or women ≥40 years old with a clinical and radiologic diagnosis of OA of the knee or hip were studied, the noticeable cardiovascular and renal safety features after only 6 weeks of treatment with MK-0966 were the development of hypertension and edema, and hyperkalemia and serum creatinine increased. Two patients receiving MK-0966, 12.5 mg and 50 mg, were discontinued from the trial because as judged by the investigators they developed clinically significant edema.

16.1.3 Protocol #033[5]: A Placebo- and Active-Comparator-Controlled, Parallel-Group, 6-Week, Double-Blind Study, Conducted Under In-House Blinding Conditions, to Assess the Safety and Efficacy of MK-0966 Versus Ibuprofen in Patients With Osteoarthritis of the Knee or Hip

METHODS

The design of this study was double-blind (with in-house blinding), placebo and active comparator controlled, parallel group, and multicenter (Sixty-two centers, United States). The study enrolled 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. Three- to 15-day nonsteroidal anti-inflammatory drug

[5] NDA 21-042, Vol. 1.129-1.132, Reference 033.

(NSAID) washout period, followed by a 6-week treatment period with 12.5 mg MK-0966 once daily, 25 mg MK-0966 once daily, 800 mg ibuprofen 3 times daily, or placebo.

The primary therapy period was from 14APR97 to 18NOV97. The in-house case report form cutoff date was 11MAR98.

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

According to the sponsor, 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: Baseline patient characteristics are summarized by treatment group in Table 1-033. Of the 736 randomized patients, Placebo = 69, MK-0966 12.5 mg = 219, MK-0966 25 mg = 227, and Ibuprofen 2400 mg = 221, >71% were females and <29% were males. The mean age was similar among the groups, ~ 60 years. The great majority of patients were white. The average duration of OA and the percentage distribution of specific secondary diagnoses or prior therapies were similar among the groups.

Table 1-033. Baseline Patient Characteristics by Treatment Group

	Placebo (N=69) n (%)	MK-0966 12.5 mg (N=219) n (%)	MK-0966 25 mg (N=227) n (%)	Ibuprofen 2400 mg (N=221) n (%)
Gender				
Female	56 (81.2)	167 (76.3)	162 (71.4)	163 (73.8)
Male	13 (18.8)	52 (23.7)	65 (28.6)	58 (26.2)
Race				
Asian	1 (1.4)	2 (0.9)	1 (0.4)	0 (0.0)
Black	2 (2.9)	27 (12.3)	16 (7.0)	8 (3.6)
Eurasian	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
European	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Hispanic American	0 (0.0)	1 (0.5)	3 (1.3)	3 (1.4)
Indian	1 (1.4)	0 (0.0)	0 (0.0)	1 (0.5)
Native American	2 (2.9)	3 (1.4)	3 (1.3)	1 (0.5)
White	63 (91.3)	186 (84.9)	203 (89.4)	207 (93.7)
Age				
Mean SD	61.8±10.6	59.8±10.5	61.9±10.4	61.1±9.8
Prior NSAID Use				
Acetaminophen	9 (13.0)	21 (9.6)	20 (8.8)	22 (10.0)
NSAID	60 (87.0)	198 (90.4)	207 (91.2)	199 (90.1)

[Adapted from NDA 21-042, Vol. 1.129, Tables 12 and 13, pages 69 and 70.]

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

Clinical adverse experiences were reported by 413 (56%) of 736 randomized patients. The clinical adverse experience profile is summarized by treatment group in Table 2-033. The duration of therapy was comparable between treatment groups. The mean number of days on treatment were 36.2, 39.4, 40.0, 37.7, for patients in the placebo, 12.5-, 25-mg MK-0966, and ibuprofen groups, respectively.

Table 2-033. Clinical Adverse Experience Summary

	Placebo	MK-0966		Ibuprofen
		12.5 mg	25 mg	2400 mg
	(N=69)	(N=219)	(N=227)	(N=221)
	n (%)	n (%)	n (%)	n (%)
Number (%) of patients:				
with one or more adverse experiences	38 (55.1)	114 (52.1)	136 (59.9)	125 (56.6)
with serious adverse experiences	3 (4.3)	3 (1.4)	4 (1.8)	4 (1.8)
who died	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
discontinued due to adverse experiences	4 (5.8)	12 (5.5)	15 (6.6)	8 (3.6)

[Adapted from NDA 21-042, Vol. 1.129, Table 39, page 142. 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.]

Deaths: No death was reported in this study.

Other Serious Clinical Adverse Experiences: Serious clinical adverse experiences were reported as follows: placebo = 3, MK-0966 12.5 mg = 3, MK-0966 25 mg = 4, and Ibuprofen 2400 mg = 4 (Table 3-033). Cardiovascular events were the most common type of all adverse experiences. None of the serious adverse experiences reported were in the category of edema- or hypertension-type.

Table 3-033. Listing of Patients With Serious Clinical Adverse Experiences

AN	Gender	Race	Age	Relative Day of Onset	Adverse Experience	Duration of AE	Action Taken	Outcome
Placebo								
6384	M	White	63	25	Cerebrovascular accident	3.75 months	Discontinued PRx†	Recovered
6371	F	White	71	43	Atrial fibrillation	4 days	No action with test drug‡	Recovered
MK-0966 12.5 mg								
6388	F	White	63	12	Coronary artery disease	Continuing	Discontinued PRx	Not recovered§
MK-0966 25 mg								
6998	F	White	78	19	Atrial arrhythmia	4 days	Discontinued PRx	Recovered
7023	F	White	69	2	Unstable angina	6 days	Discontinued PRx	Recovered
7223	F	White	62	28	Chest pain	15 hours	Interrupted PRx	Recovered
6750	F	White	72	42	Cerebrovascular accident	3 days	PRx continued	Recovered
Ibuprofen 2400 mg								
7223	F	White	62	28	Chest pain	15 hours	Interrupted PRx	Recovered
6750	F	White	72	42	Cerebrovascular accident	3 days	PRx continued	Recovered

[Adapted from NDA 21-042, Vol. 1.129, Table 43, pages 153 and 154. †PRx = Study medication. ‡No action with test drug = Patient had already completed the study by the onset of the experience. §Not recovered = Adverse experience was continuing at last follow up.]

Overall Profile of Dropouts: Of the 736 randomized patients at the Flare/Randomization Visit, 625 (84.9%) completed the 6-week treatment period (Table 4-033). There were 19 (27.5%), 33 (15.1%), 27 (11.9%), and 32 (14.5%) patients who discontinued in the placebo, 12.5-, 25-mg MK-0966, and ibuprofen treatment groups, respectively. According to the sponsor, the discontinuation rate was significantly higher ($p<0.05$) in the placebo group compared with each MK-0966 group and ibuprofen primarily due to those discontinuing because of lack of efficacy.

Table 4-033. Patient Accounting

	Placebo	MK-0966		Ibuprofen
		12.5 mg	25 mg	2400 mg
	(N=69)	(N=219)	(N=227)	(N=221)
	n (%)	n (%)	n (%)	n (%)
COMPLETED:	50 (72.5)	186 (84.9)	200 (88.1)	189 (85.5)
DISCONTINUED:	19 (27.5)*	33 (15.1)	27 (11.9)	32 (14.5)
Clinical adverse experience	4 (5.8)	12 (5.5)	15 (6.6)	8 (3.6)
Laboratory adverse experience	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Deviation from protocol	0 (0.0)	1 (0.5)	1 (0.4)	0 (0.0)
Patient withdrew consent	2 (2.9)	1 (0.5)	2 (0.9)	2 (0.9)
Lost to follow up	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Lack of efficacy	13 (18.8)*	17 (7.8)	9 (4.0)	19 (8.6)
Other reasons ‡	0 (0.0)	1 (0.5)	0 (0.0)	2 (0.9)

[Adapted from NDA 21-042, Vol. 1.129, Table 19, page 88. * $p<0.05$ vs. MK-0966 and ibuprofen. ‡ Includes reasons other than those listed.]

Adverse Events Associated with Dropout: Table 5-033 lists patients discontinued due to cardiovascular and renal adverse events.

Of note, edema-related adverse experiences resulted in patient discontinuation; three patients in the MK-0966 12.5 mg group, and one patient in the MK-0966 25 mg group (Table 5-033). None of the patients in the Ibuprofen group were discontinued due to the aforementioned reasons.