16.3 Osteoarthritis Studies
6-Months-to-86 Weeks Studies

16.3.1 Protocol #029-20/30: A Second/Third Double-Blind, Active-Comparator-Controlled Extension of a Placebo-Controlled Double-Blind Study to Assess Safety and Further Define the Clinically Effective Dose-Range of MK-0966 (L-748,731) in Patients With Osteoarthritis of the Knee or Hip

METHODS

Study design: multicenter (Fifty-one centers, United States), double-blind, active-comparator-controlled, parallel-group, extensions to MK-0966 Protocol 029-10 (First Extension). To be eligible for the Second Extension (Protocol 029-20) patients must have completed the 24-week First Extension. To be eligible for the Third Extension (Protocol 029-30) patients must have completed the 24-week Second Extension. Duration of treatment: Two consecutive treatment periods (24 weeks and 56 weeks) with 12.5, 25, and 50 mg MK-0966 orally once daily, and 50 mg diclofenac sodium orally, 3 times daily. The purpose of the Second and Third extensions was to further evaluate the safety profile of MK-0966 with a longer duration of continuous administration. Patients randomized into the study 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) or hip. Knee or hip OA was the patient's primary source of pain/disability. Patients must have completed the 6-week Base Study and the 24-week First Extension to be eligible for the Second Extension. Patients who completed the 24-week Second Extension were eligible for the 56-week Third Extension. Patients must have tolerated the study medication and been compliant with study procedures and medication in the Base Study and First Extension.

The primary therapy period extended from 31DEC96 to date unknown (study ongoing). This report presents the results of the Second and Third Extensions for all visits performed prior to 01APR98 (visit cutoff date). In-house case report form cutoff date was 25JUN98.

The objectives of the study were: (1) To evaluate the overall safety and tolerability of MK-0966 with once-daily administration for 2 consecutive extension periods (24 weeks and 56 weeks) following an initial 24-week extension period in patients with osteoarthritis (OA). (2) To monitor Pain Walking on a Flat Surface (WOMAC) and the Patient and Investigator Global Assessment of Disease Status with chronic administration of 12.5, 25, and 50 mg MK-0966 orally once daily and 50 mg diclofenac sodium orally 3 times daily to patients with OA.

The incidence of adverse experiences and the percent of patients outside the predefined limits of change for selected laboratory tests were tabulated. According to the sponsor, no formal statistical analyses were carried out because of the nonrandomized nature of the study (participation in these Extensions was optional for patients who completed the Base Study).

RESULTS

Demographics: Patients' baseline characteristics by treatment group are summarized Table 1-029C. Of the 286 randomized patients >70% were females >80% White with a mean age of 61.3 years.

Table 1-029C. Baseline Patient Characteristics by Treatment Group*

	MK-0966			Diclofenac
	12.5 mg N=63* n(%)	25 mg N=86 n(%)	50 mg N=75 n(%)	150 mg N=62 n(%)
Gender				
Female	44 (69.8)	67 (77.9)	60 (80.0)	44 (71.0)
Male	19 (30.2)	19 (22.1)	15 (20.0)	18 (29.0)
Age (years)				
Mean± SD	61.8±9.97	60.4±9.93	61.3±10.51	61.7±10.00

Table 1-029C. (Cont'd)

Race				
Asian	0 (0.0)	0 (0.0)	1 (1.3)	1 (1.6)
Black	6 (9.5)	5 (5.8)	4 (5.3)	4 (6.5)
Hispanic American	3 (4.8)	0 (0.0)	2 (2.7)	2 (3.2)
Native American	1 (1.6)	2 (2.3)	0 (0.0)	3 (4.8)
White	53 (84.1)	79 (91.9)	68 (90.7)	52 (83.9)

[Adapted from NDA 21-042, Vol. 1.121, Table 9, page 46. *Patients who entered the second extension.]

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

Deaths: No deaths were reported.

Other Serious Adverse Events: No patients in either the MK-0966 12.5 mg or diclofenac 150 mg groups had a serious clinical adverse experience related to Body as a Whole (i.e., edema), Cardiovascular (i.e., hypertension), Renal (i.e, serum creatinine increased, proteinuria) systems.

Table ?. Listing of Patients With Serious Clinical and Other Adverse Experiences Second and Third Extensions

AN	Gender	Race	Age	Day of Onset	Adverse Experience	Duration	Action Taken	Outcome
MK-0966 12.5 mg								
MK-0966 25 mg								
2515	F	White	51	429	Coronary vasospasm	2.00 days	PRx continued	Recovered
MK-0966 50 mg								
2281	F	White	62	230	Coronary artery occlusion	CONT	Discontinued PRx	Not recovered
Diclofenac 150 mg								

[Adapted from NDA 21-042, Vol. 1.121, Table 31, pages 96-99.]

Overall Profile of Dropouts: According to the sponsor, "there were 672 patients who were randomized into the Base Study and 467 (69.5%) of those patients continued into the First Extension. Of the 467 patients who participated in the First Extension, 341 (73%) completed the First Extension. Of the 341 who completed, 286 (83.9%) continued into the Second Extension. The percentage of patients who completed the First Extension and who continued into the Second Extension was similar among the treatment groups (Table 19). Six, 13, 8, and 5 patients in the 12.5-, 25-, and 50-mg MK-0966 and diclofenac groups, respectively, completed the Second Extension but did not elect to continue in the Third Extension (Table 20). Sixteen (25.4%), 20 (23.2%), 21 (28.0%), and 13 (21.0%) patients in the 12.5-, 25-, and 50-mg MK-0966, and diclofenac groups, respectively, discontinued due to adverse events, lack of efficacy or other reasons during participation in the Second and Third Extensions." There were no notable differences for the overall rate of discontinuation between the treatment groups (Table 2-029C).

Table 2-029C. Patient Accounting

	MK-0966			Diclofenac
	12.5 mg N=63* n(%)	25 mg N=86 n(%)	50 mg N=75 n(%)	150 mg N=62 n(%)
Patients Who Entered Third Extension	47 (74.6)	62 (72.1)	54 (72.0)	48 (77.4)
Continuing in Third Extension†	41 (65.1)	53 (61.6)	46 (61.3)	44 (71.0)
Discontinued‡	16 (25.4)	20 (23.2)	21 (28.0)	13 (21.0)
Clinical AE	4 (6.3)	3 (3.5)	9 (10.5)	1 (1.6)
Laboratory AE	0 (0.0)	3 (3.5)	0 (0.0)	2 (3.2)
Lack of efficacy	7 (11.1)	6 (7.0)	4 (5.3)	2 (3.2)
Lost to follow-up	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Patient discontinued	2 (3.2)	2 (2.3)	3 (4.0)	1 (1.6)
Patient moved	0 (0.0)	1 (1.2)	1 (1.3)	2 (3.2)

Table 2-029C. (Cont'd)

Patient withdrew consent	2 (3.2)	3 (3.5)	2 (2.7)	1 (1.6)
Protocol deviation	0 (0.0)	2 (2.3)	2 (2.7)	4 (6.4)
Patients Completed Second Extension	6 (9.5)	13 (15.1)	8 (10.7)	5 (8.1)

[Adapted from NDA 21-042, Vol. 1.121, Table 20, page 64. *Total Patients Who Entered Second Extension. †Patients continuing in the Third Extension at the 01APR98 cutoff. ‡Number represents any patient who discontinued in either the Second Extension or by the cutoff date of the Third Extension.]

Adverse Events Associated with Dropout: The listing of patients discontinued due to edema, cardiovascular or urogenital clinical adverse experiences are described in Table 3-029C. Administration of MK-0966 25 mg was associated with a patient's discontinuation due to hypertension (AN 2412).

Table 3-29C. Listing of Patients Discontinued Due to Clinical Adverse Experiences Second and Third Extensions

AN	Gender	Race	Age	Day of Onset	Adverse Experience	Duration	Day of Discontinuation	Action Taken	Outcome
MK-0966 12.5 mg									
MK-0966 25 mg									
2412	F	White	49	440	Hypertension	2.37 months	495	Discontinued PRx	Recovered
MK-0966 50 mg									
2281	F	White	62	230	Coronary artery occlusion	CONT	231	Discontinued PRx	Not recovered
Diclofenac 150 mg									

[Adapted from NDA 21-042, Vol. 1.121, Table 32, pages 103, 104.]

Dropouts for Laboratory Abnormalities: Table 4-029C provides the listing of patients who discontinued due to kidney-related laboratory adverse experiences second and third extensions. Two patients in the MK-0966 25 mg group were discontinued because BUN increased (4146) and serum creatinine increased (AN 2202).

Table 4-029C. Listing of Patients Discontinued Due to Laboratory Adverse Experiences Second and Third Extensions

AN	Gender	Race	Age	Day of Test	Adverse Experience	Value and Unit	Normal Range	Day of Discontinuation	Action Taken	Outcome
MK-0966 25 mg										
4146	F	White	74	372	BUN increased	36 mg/dL	4 to 24	376	Discontinued PRx	Recovered
2202	F	White	69	488	Serum creatinine increased	1.7 mg/dL	0.4 to 1.2	490	Discontinued PRx	Recovered

[Adapted from NDA 21-042, Vol. 1.121, Table 42, page 129.]

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 5-029C.

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

	MK-0966 12.5 mg (N=63) † n (%)	MK-0966 25 mg (N=86) n (%)	MK-0966 50 mg (N=75) n (%)	Diclofenac 150 mg (N=62) n (%)
Body as a Whole				
Edema	1 (1.6)	1 (1.2)	2 (2.7)	0 (0.0)
Lower extremity edema	1 (1.6)	3 (3.5)	2 (2.7)	1 (1.6)
Cardiovascular System				
Blood pressure increased	3 (4.8)	3 (3.5)	5 (6.7)	1 (1.6)
Hypertension	4 (6.3)	5 (5.8)	6 (8.0)	3 (4.8)

Table 5-029C. (Cont'd)

Irregular heartbeat	0 (0.0)	0 (0.0)	2 (2.7)	0 (0.0)
Palpitation	1 (1.6)	2 (2.3)	1 (1.3)	0 (0.0)
Urogenital System				
Prostatic disorder	0 (0.0)	0 (0.0)	2 (2.7)	1 (1.6)
Urinary incontinence	2 (3.2)	0 (0.0)	1 (1.3)	1 (1.6)
Urinary tract infection	4 (6.3)	5 (5.8)	5 (6.7)	1 (1.6)

[Adapted from NDA 21-042, Vol. 1.121, Table 29, pages 87-90. †N = number of patients who entered the Second Extension. As of the 01APR98 cutoff, 41, 53, 46, and 44 patients in the 12.5-, 25-, and 50-mg MK-0966, and diclofenac groups, respectively, remained the Third Extension. 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.]

Edema-type clinical adverse experiences[1] 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 in a dose-dependent manner with MK-0966 and at higher rates than with diclofenac. The incidence of hypertension-type[2] adverse experiences was also identified to be dose-dependent and to occur with a higher incidence with MK-0966 than with diclofenac.

Tables 6-029C and 7-029C summarize, by treatment group, hypertension- and edema-type adverse experiences, respectively.

Table 6-029C. Number (%) of Patients With Clinical Hypertension Adverse Experiences Second and Third Extensions

	MK-0966 12.5 mg (N=63)† n (%)	MK-0966 25 mg (N=86) n (%)	MK-0966 50 mg (N=75) n (%)	Diclofenac 150 mg (N=62) n (%)
Blood pressure increased	3 (4.8)	3 (3.5)	5 (6.7)	1 (1.6)
Hypertension	4 (6.3)	5 (5.8)	6 (8.0)	3 (4.8)
Labile hypertension	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
Systolic hypertension	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
ΣHypertension	**6 (9.5)**	**9 (10.5)**	**11 (14.7)**	**4 (6.5)**

[Adapted from NDA 21-042, Vol. 1.121, Tables 35, page 112. †N = number of patients who entered the Second Extension. As of the 01APR98 cutoff, 41, 53, 46, and 44 patients in the 12.5-, 25-, and 50-mg MK-0966, and diclofenac groups, respectively, remained the Third Extension. ΣHypertension = Blood pressure increased+Hypertension+Labile hypertension+Systolic hypertension 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.]

[1] 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.

[2] 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 7-029C. Number (%) of Patients With Clinical Edema Adverse Experiences Second and Third Extensions

	MK-0966 12.5 mg (N=63) † n (%)	MK-0966 25 mg (N=86) n (%)	MK-0966 50 mg (N=75) n (%)	Diclofenac 150 mg (N=62) n (%)
Edema	1 (1.6)	1 (1.2)	2 (2.7)	0 (0.0)
Fluid retention	1 (1.6)	0 (0.0)	1 (1.3)	0 (0.0)
Hand swelling	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
Lower extremity edema	1 (1.6)	3 (3.5)	2 (2.7)	1 (1.6)
Upper extremity edema	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
ΣEdema	2 (3.2)	5 (5.8)	5 (6.7)	1 (1.6)

[Adapted from NDA 21-042, Vol. 1.121, Tables 33, page 106. †N = number of patients who entered the Second Extension. As of the 01APR98 cutoff, 41, 53, 46, and 44 patients in the 12.5-, 25-, and 50-mg MK-0966, and diclofenac groups, respectively, remained the Third Extension. ΣEdema = Edema+Fluid retention+Hand swelling+Lower extremity edema+Upper extremity edema. 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.]

The number (%) of patients exceeding the predefined limits of change for systolic and diastolic blood pressure are summarized in Table 8-029C. As compared with diclofenac, MK-0966 50 mg administration was associated with higher percent of patients who exceeded the predefined limits of change for both diastolic and systolic blood pressure.

Table 8-029C. Patients Exceeding The Predefined Limits Of Change On Diastolic And Systolic Blood Pressure (Intention-To-Treat Analysis)

Vital Sign	Predefined Limit of Change	Treatment	Number†/Total‡(%)
Systolic blood pressure (mm Hg)	Increase >20 and value >140	MK-0966 12.5 mg	16/62 (25.8)
		MK-0966 25 mg	21/86 (24.4)
		MK-0966 50 mg	28/74 (37.8)
		Diclofenac 150 mg	16/62 (25.8)
Diastolic blood pressure (mm Hg)	Increase >15 and value >90	MK-0966 12.5 mg	2/62 (3.2)
		MK-0966 25 mg	8/86 (9.3)
		MK-0966 50 mg	11/74 (14.9)
		Diclofenac 150 mg	3/62 (4.8)

[Adapted from NDA 21-042, Vol. 1.121, Appendix 4.15, page 1507. †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 56 (19.8%) of 283 patients. Table 9-029C presents a summary of renal-related laboratory adverse experiences and the number (%) of patients with specific laboratory adverse experiences by laboratory test category. The few number of patients, regardless the treatment group, who had renal-related laboratory adverse experiences prevent one from reaching valid conclusions.

Table 9-029C. Number (%) of Patients With Specific Laboratory Adverse Experiences by Laboratory Test Category Second and Third Extensions

	MK-0966 12.5 mg (N=63) n (%)	MK-0966 25 mg (N=86) n (%)	MK-0966 50 mg (N=75) n (%)	Diclofenac 150 mg (N=62) n (%)
Serum creatinine increased	1/ 62 (1.6)	3/ 85 (3.5)	1/ 74 (1.4)	1/ 62 (1.6)
Blood urea nitrogen increased	1/ 62 (1.6)	6/ 85 (7.1)	0/ 74 (0.0)	1/ 62 (1.6)
Hypercalcemia	0/ 62 (0.0)	1/ 85 (1.2)	0/ 74 (0.0)	0/ 62 (0.0)
Hypocalcemia	0/ 62 (0.0)	0/ 85 (0.0)	1/ 74 (1.4)	1/ 62 (1.6)
Hyperkalemia	1/ 62 (1.6)	0/ 85 (0.0)	1/ 74 (1.4)	0/ 62 (0.0)
Hypokalemia	0/ 62 (0.0)	1/ 85 (1.2)	0/ 74 (0.0)	0/ 62 (0.0)
Hyponatremia	0/ 62 (0.0)	0/ 85 (0.0)	1/ 74 (1.4)	0/ 62 (0.0)
Uric acid increased	2/ 62 (3.2)	2/ 85 (2.4)	1/ 74 (1.4)	1/ 62 (1.6)
Proteinuria	0/ 62 (0.0)	3/ 85 (3.5)	1/ 74 (1.4)	1/ 62 (1.6)

[Adapted from NDA 21-042, Vol. 1.121, Table 40, pages 123-125.]

The analysis of laboratory data was also carried out based on between-treatment group comparisons of percent of patients exceeding predefined limits of change in blood chemistry (Table 10-029C). No statistically significant differences were noted. However, the MK-0966 50 mg group, as compared with the diclofenac group, had higher rates of occurrence for serum creatinine and potassium increase.

Table 10-029C. Patients Exceeding The Predefined Limits Of Change Blood Chemistry (Intention-To-Treat Approach) Second And Third Extensions

Laboratory Test	Predefined Limits of Change	Treatment	Number‡/Total§ (%)
Serum creatinine (mg/dL)	Increase ≥0.5 and value >ULN	MK0966 12.5 mg	0/62 (0.0)
		MK0966 25 mg	4/83 (4.8)
		MK0966 50 mg	3/71 (4.2)
		Diclofenac 150 mg	1/61 (1.6)
Serum potassium (mEq(K)/L)	Increase ≥0.8 and value >ULN	MK0966 12.5 mg	1/62 (1.6)
		MK0966 25 mg	1/83 (1.2)
		MK0966 50 mg	3/71 (4.2)
		Diclofenac 150 mg	1/61 (1.6)
	Decrease ≥0.8 and value <LLN	MK0966 12.5 mg	2/62 (3.2)
		MK0966 25 mg	1/83 (1.2)
		MK0966 50 mg	0/71 (0.0)
		Diclofenac 150 mg	0/61 (0.0)
Serum uric acid (mg/dL)	Increase ≥50.0% and value >ULN	MK0966 12.5 mg	1/62 (1.6)
		MK0966 25 mg	2/83 (2.4)
		MK0966 50 mg	1/71 (1.4)
		Diclofenac 150 mg	0/61 (0.0)
Serum Calcium (mEq(Ca)/L)	Decrease ≥0.7 and value <LLN	MK0966 12.5 mg	1/62 (1.6)
		MK0966 25 mg	1/83 (1.2)
		MK0966 50 mg	1/71 (1.4)
		Diclofenac 150 mg	0/61 (0.0)
Serum Sodium (mEq(Na)/L)	Increase ≥0.8 and value >ULN	MK0966 12.5 mg	1/62 (1.6)
		MK0966 25 mg	3/83 (3.6)
		MK0966 50 mg	3/71 (4.2)
		Diclofenac 150 mg	1/61 (1.6)
	Decrease ≥0.8 and value <LLN	MK0966 12.5 mg	2/62 (3.2)
		MK0966 25 mg	1/83 (1.2)
		MK0966 50 mg	0/71 (0.0)
		Diclofenac 150 mg	0/61 (0.0)

[Adapted from NDA 21-042, Vol. 1.121, Appendix 4.15, pages 1510-1512. ULN = Upper limit of normal range. LLN = Lower limit of normal range. ‡Number of patients meeting the predefined limit criteria. §Total number of patients with valid values of the laboratory test.]

SUMMARY/COMMENTS

Study protocol #029-20/30 compared the effects of treatment with MK-0966 12.5 mg, 25mg and 50 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 purpose of the Second and Third extensions was to further evaluate the safety profile of MK-0966 with a longer duration of continuous administration.

The cardiovascular and renal safety profile of MK-0966 in this study is highlighted by edema- and hypertension-type adverse events. And MK-0966 at 50 mg caused increases in serum creatinine and potassium at higher rates than diclofenac.

One patient each in the MK-0966 25 mg group discontinued because BUN increased (AN 4146) and serum creatinine increased (AN 2202).

Administration of MK-0966 25 mg was associated with a patient's discontinuation due to hypertension (AN 2412).

16.3.2 Protocol # 034-02, and 035-02[3]: An Active-Comparator-Controlled, Parallel-Group, 1-Year, Double-Blind Study, And The First Double-Blind, Active-Comparator-Controlled Extension, To Assess The Safety And Efficacy Of MK-0966 Versus Diclofenac Sodium In Patients With OA Of The Knee Or Hip

METHODS

This was a multinational, multicenter (one hundred twelve centers worldwide including 69 in United States and 43 Multinational), double-blind (with in-house blinding for the first 6-month treatment period), active-comparator-controlled, and parallel group study. Patients underwent six months of treatment (a total of 1 year, including the first 6 months of the 1-year Base Studies) with MK-0966 12.5 or 25 mg once daily, or 50 mg diclofenac sodium 3 times daily.

The primary therapy period was, for the second 6 months of 1-Year Base Studies: Protocol 034-07OCT97 to 10MAY98; Protocol 035-14NOV97 to 10MAY98. The in-house case report form cutoff date for Protocol 034 was 01JUL98; for Protocol 035, 30JUN98.

Reviewer's Note: This report presents results for the second 6 months and the entire 12-month treatment period of the 1-Year Base Studies (Protocols 034 and 035).

The objectives of the second 6 months of 1-Year Base Studies were:

i. To demonstrate clinical efficacy of 25 mg MK-0966 comparable to diclofenac sodium in the treatment of osteoarthritis (OA) of the knee and hip primarily during a 12-week treatment period, secondarily to 6 months (results presented in the Clinical Study Reports for Protocols 034 and 035) and then to 1 year;
ii. To demonstrate the safety and tolerability of MK-0966 administration for a 1-year period;
iii. To explore the safety and clinical efficacy of MK-0966 administration in patients who regularly use acetaminophen/paracetamol for the treatment of OA of the knee or hip;
iv. To compare the clinical efficacy and safety of 12.5 mg versus 25 mg MK-0966 in the treatment of OA of the knee or hip;
v. To compare the clinical efficacy and safety of 12.5 mg of MK-0966 versus diclofenac sodium in the treatment of OA of the knee or hip;
vi. To evaluate radiographs of the study joint at baseline and 1 year of treatment with MK-0966 or diclofenac sodium; and

[3] NDA 21-042, Vol. 1.134-1.139, Reference P034C.

vii. To compare MK-0966 versus diclofenac sodium in the incidence of spontaneous adverse experiences which are consistent with NSAID use.

In the analysis of safety, 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 by treatment group for the second 6 months of the 1-year base studies are summarized in Table 1-34/35. Patients randomized were mainly White (~80%) females (>70%) with a mean of 61.9 years.

Table 1-34/35. Baseline Patient Characteristics by Treatment Group Second 6 Months of 1-Year Base Studies

	MK-0966 12.5 mg (N=352) n (%)	MK-0966 25 mg (N=349) n (%)	Diclofenac 150 mg (N=347) n (%)
Gender			
Female	260 (73.9)	248 (71.1)	264 (76.1)
Male	92 (26.1)	101 (28.9)	83 (23.9)
Race			
Asian	1 (0.3)	1 (0.3)	1 (0.3)
Polynesian	0 (0.0)	1 (0.3)	0 (0.0)
Hispanic American	43 (12.2)	45 (12.9)	41 (11.8)
Black	18 (5.1)	20 (5.7)	20 (5.8)
Multiracial	6 (1.7)	3 (0.9)	4 (1.2)
White	284 (80.7)	279 (79.9)	281 (81.0)
Age (mean±SD)	61.9 ±9.6	61.6 ±9.2	62.2 ±9.4
Prior NSAID Use			
Acetaminophen	32 (9.1)	29 (8.3)	36 (10.4)
NSAID	320 (90.9)	320 (91.7)	311 (89.6)

[Adapted from NDA 21-042, Vol. 1.134, Table 14, page 82.]

The % of patients with specific secondary diagnosis and prior therapies were well balanced among the groups. There were no apparent differences between treatment groups in frequency or type of concomitant drug therapies.

Safety[4]*:* 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.

The mean number of days on treatment in the second 6 months of Protocols 034 and 035 only were 168.8, 165.9, and 165.4 for patients in the 12.5-, 25-mg MK-0966, and diclofenac groups, respectively. Including the days in the first 6 months, the mean number of days on treatment for the second 6-month cohort was 351.1, 345.6, and 347.3 for 12.5, 25 mg MK-0966, and diclofenac, respectively.

[4] Clinical and laboratory adverse experience data are presented in 3 groups. According to the sponsor, the primary analysis of this Clinical Study Report is the second 6 months (Visits 8 to 12 and Poststudy) of the 1-year Base Studies (Protocols 034 and 035). Only adverse experiences that began in the second 6 months of the 1-year Base Studies are reported in this first group. The second group reports adverse experiences occurring at any time during the 1-year Base Studies. This analysis included all patients randomized (including patients who discontinued in the first 6 months of the 1-year Base Studies. Thus, this 1-year group will report the adverse experiences covered in the second 6 months plus all adverse experiences reported for the first 6 months. The third group is the Extension data for Protocols 034-10 and 035-10, because the rather small number of patients randomized in this extension the cardiovascular and renal safety data will not be anlyzed.

Deaths: There was one death (Second 6 Months of 1-Year Base Studies). AN 5761 (diclofenac), a 75-year-old female with a history of hypertension, was hospitalized after developing angina pectoris on Day 216. Visit 1 ECG revealed inferior and anterolateral ST segment depression. A coronary angiogram was performed which showed significant stenosis. A coronary artery bypass graft was performed. The patient then developed postoperative complications (9 days after the discontinuation of study treatment) which included bleeding, respiratory insufficiency, and heart failure, resulting in death.

Other Serious Adverse Events: Serious adverse experiences related to edema or the cardiovascular or urogenital systems are summarized in Table 2-034/35.

Blood pressure increased was reported as a serious adverse event in one patient (AN 5183) receiving MK-0966 12.5 mg.

Table 2-34/35. Listing of Patients With Serious Edema, Cardiovascular or Urogenital Adverse Experiences Second 6 Months of 1-Year Base Studies

AN	Gender	Race	Age	Day of Onset	Adverse Experience	Duration	Action Taken	Outcome
MK-0966 12.5 mg								
5183	F	Black	68	367	Blood pressure increased	3 days	PRx continued	Recovered
5788	F	White	46	327	Deep venous thrombosis	9 days	PRx continued	Recovered
5788	F	White	46	356	Phlebitis	18 days	PRx continued	Recovered
7961	F	White	66	360	Atrial fibrillation	2 days	PRx continued	Recovered
7631	F	White	52	303	Arterial occlusion	1.35 mos	Discontinued PRx	Recovered
8208	F	White	67	238	Cerebrovascular accident	Continuing	Interrupted PRx	Not recovered
8136	M	White	67	300	Atrial fibrillation	Continuing	Discontinued PRx	Not recovered
7942	M	Black	59	178	Congestive heart failure	Continuing	Discontinued PRx	Not recovered
8163	F	White	68	350	Chest pain	3 days	PRx continued	Recovered
7904	M	White	68	227	Urinary tract infection	5 days	Interrupted PRx	Recovered
8115	F	White	74	267	Deep venous thrombosis	8 days	Discontinued PRx	Recovered
MK-0966 25 mg								
5516	M	White	46	241	Urolithiasis	2 days	PRx continued	Recovered
7532	M	White	76	210	Coronary artery disease	10 days	PRx continued	Recovered
7593	F	White	43	221	Urolithiasis	22 days	Interrupted PRx	Recovered
8305	F	White	65	221	Deep venous thrombosis	1.51 mos	Discontinued PRx	Recovered
Diclofenac 150 mg								
5417	M	White	70	370	Urolithiasis	2 days	PRx continued	Recovered
5398	M	White	59	281	Angina pectoris	1 day	Interrupted PRx	Recovered
5324	F	Hisp	65	322	Urinary tract infection	11 days	Interrupted PRx	Recovered
5761	F	White	75	216	Angina pectoris	10 days	Discontinued PRx	Recovered
8119	M	White	48	352	Myocardial infarction	7 days	Discontinued PRx	Recovered
8125	M	White	63	246	Coronary artery disease	6 days	Discontinued PRx	Recovered
8126	F	White	64	212	Chest pain	4 days	PRx continued	Recovered
7916	F	White	67	357	Vascular insufficiency	Continuing	PRx continued	Not recovered

[Adapted from NDA 21-042, Vol. 1.134, Table 53, pages 178-182. PRx: denotes study medication.]

Overall Profile of Dropouts: Three hundred and ten (88.1%), 300 (85.9%), and 299 (86.2%) patients continued in the trial from 12.5-mg, 25-mg MK-0966, and diclofenac groups, respectively. A total of one hundred and thirty nine patients were discontinued due to clinical adverse experiences. The percents of patients who discontinued therapy due to clinical adverse experiences were 11.9, 14.0, and 13.8% in the 12.5-mg, 25-mg MK-0966, and diclofenac groups, respectively (Table 3-34/35). The rates of discontinuation in the MK-0966 groups were similar to the diclofenac group.

Table 3-34/35. Patient Accounting Second 6 Months of 1-Year Base Studies

Number (%) of patients:	MK-0966 12.5 mg (N=490) n (%)	MK-0966 25 mg (N=489) n (%)	Diclofenac 150 mg (N=498) n (%)
COMPLETED 1-YEAR BASE STUDIES:	310 (88.1)	300 (85.9)	299 (86.2)
DISCONTINUED (After the first 6 months but before the end of 1 year):	42 (11.9)	49 (14.0)	48 (13.8)
Clinical adverse experiences	10 (2.8)	16 (4.6)	15 (4.3)
Laboratory adverse experiences	0 (0.0)	1 (0.3)	0 (0.0)
Protocol deviation	8 (22.7)	9 (2.6)	6 (1.7)
Patient withdrew consent	9 (2.6)	7 (2.0)	4 (1.2)
Lost to follow-up	3 (0.9)	0 (0.0)	1 (0.3)
Lack of efficacy	8 (2.3)*	13 (3.7)	19 (5.5)
Other reasons‡	4 (1.1)	4 (1.5)	3 (0.9)

[Adapted from NDA 21-042, Vol. 1.134, Table 23, page 102. *p=0.031 vs. diclofenac. All patients were >39 years of age when randomized. ‡Includes reasons other than those listed.]

The incidence of discontinuations due to clinical adverse experiences and serious adverse experiences were comparable between the active-treatment groups Table 4-34/35.

Table 4-34/35. Summary Of Clinical Adverse Experience Summary Entire 1-Year Base Studies All Patients Randomized

Number (%) of patients:	MK-0966 12.5 mg (N=490) n (%)	MK-0966 25 mg (N=489) n (%)	Diclofenac 150 mg (N=498) n (%)
who died	1 (0.2)	0 (0.0)	6 (1.2)
with one or more adverse experiences	407 (83.1)	396 (81.0)	415 (83.3)
with serious adverse experiences	49 (10.0)	42 (8.6)	59 (11.8)
discontinued due to adverse experiences	57 (11.6)	54 (11.0)	72 (14.5)
discontinued due to serious adverse experiences	2 (0.4)	2 (0.4)	2 (0.4)

[Adapted from NDA 21-042, Vol. 1.134, Table 42, page 150. 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.]

Adverse Events Associated with Dropout: The listing of patients discontinued due to edema, cardiovascular or urogenital clinical adverse experiences are described in Table 5-34/35.

MK-0966 25 mg resulted in three patients' discontinuation due to hypertension (ANs 5760, 5766, 7958).

Table 5-34/35. Listing Of Patients Discontinued Due To Clinical Edema, Cardiovascular Or Urogenital Adverse Experiences Second 6 Months Of 1-Year Base Studies

AN	Gender	Race	Age	Day of Onset	Adverse Experience	Duration	Day of Discontinu -ation	Action Taken	Outcome
MK-0966 12.5mg									
7631	F	White	52	303	Arterial occlusion	1.35 mos	337	Discontinued PRx	Recovered
8136	M	White	67	300	Atrial fibrillation	Continuing	309	Discontinued PRx	Not recovered
7942	M	Black	59	178	Congestive heart failure	Continuing	229	Discontinued PRx	Not recovered
8115	F	White	74	267	Deep venous thrombosis	8 days	267	Discontinued PRx	Recovered
MK-0966 25mg									
5760	F	White	63	354	Hypertension	Continuing	356	Discontinued PRx	Not recovered
5766	F	White	67	238	Hypertension	Continuing	326	Discontinued PRx	Not recovered
7958	F	White	71	232	Hypertension	15 days	232	Discontinued PRx	Recovered
8095	M	White	66	240	Cerebrovascular accident	1.18 mos	283	Discontinued PRx	Recovered
8091	M	White	67	234	Myocardial infarction	1 day	237	Discontinued PRx	Recovered
8305	F	White	65	221	Deep venous thrombosis	1.51 mos	232	Discontinued PRx	Recovered
Diclofenac 150 mg									
5729	F	White	58	216	Urinary tract infection	Continuing	227	Discontinued PRx	Not recovered
5761	F	White	75	216	Angina pectoris	10 days	216	Discontinued PRx	Recovered
8119	M	White	48	352	Myocardial infarction	7 days	352	Discontinued PRx	Recovered
8125	M	White	63	246	Coronary artery disease	6 days	248	Discontinued PRx	Recovered

[Adapted from NDA 21-042, Vol. 1.132, Table 57, pages 191-193.]

Adverse Event Incidence Tables: The number (%) of patients who had Cardiovascular, Urogenital and Body as a Whole/Site Unspecified clinical adverse experiences are presented in Table 6-34/35. The most frequent clinical adverse experiences in the 1-year Base Studies were edema and hypertenson. The incidence of these adverse events in the MK-0966 groups was higher as compared with diclofenac.

Table 6-34/35. Number (%) Of Patients With Specific Clinical Adverse Experiences (Incidence ≥2.0% In One Or More Treatment Groups) By Body System Entire 1-Year Base Studies All Patients Randomized

Number (%) of patients:	MK-0966 12.5 mg (N=490) n (%)	MK-0966 25 mg (N=489) n (%)	Diclofenac 150 mg (N=498) n (%)
Body as a Whole/Site Unspecified			
Lower extremity edema	30 (6.1)	24 (4.9)	20 (4.0)
Cardiovascular System			
Blood pressure increased	7 (1.4)	9 (1.8)	10 (2.0)
Hypertension	33 (6.7)	37 (7.6)	24 (4.8)
Urogenital System			
Urinary tract infection	33 (6.7)	27 (5.5)	34 (6.8)

[Adapted from NDA 21-042, Vol. 1.134, Table 48, page 150.]

Edema-type clinical adverse experiences[5] 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. Similarly, hypertension-type[6] clinical adverse experiences were identified also to occur with a higher incidence with MK-0966 than with diclofenac.

Tables 7-34/35 and 8-34/35 summarize, by treatment group, edema- and hypertension-type adverse experiences, respectively. MK-0966 treatment, at any dose, was associated with higher rates of edema-type adverse experiences than diclofenac, and the incidence of this adverse event with MK-0966 was dose-dependent.

Table 7-34/35. Number (%) of Patients With Specific Edema-Type Adverse Experiences by Body System for the Entire 1-Year Base Studies All Randomized Patients

	MK-0966 12.5 mg (N=490) n (%)	MK-0966 25 mg (N=489) n (%)	Diclofenac 150 mg (N=498) n (%)
Edema	5 (1.0)	9 (1.8)	5 (1.0)
Hand swelling	4 (0.8)	2 (0.4)	2 (0.4)
Lower extremity edema	30 (6.1)	24 (4.9)	20 (4.0)
Peripheral edema	1 (0.2)	7 (1.4)	3 (0.6)
ΣEdema	**39 (8.0)**	**45 (9.2)**	**29 (5.8)**

[Adapted from NDA 21-042, Vol. 1.134, Table 83, page 262. ΣEdema = Edema+Hand swelling+Lower extremity edema+Peripheral edema.]

The rate of occurrence of hypertension-type adverse experiences with MK-0966 treatment, at any dose, was higher than with diclofenac. MK-0966 effected dose-dependent changes in the incidence of this adverse event.

---

[5] 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.

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

Table 8-34/35. Number (%) of Patients With Specific Hypertensive-Type Adverse Experiences Entire 1-Year Base Studies All Randomized Patients

	MK-0966 12.5 mg (N=490) n (%)	MK-0966 25 mg (N=489) n (%)	Diclofenac 150 mg (N=498) n (%)
Blood pressure increased	7 (1.4)	9 (1.8)	10 (2.0)
Borderline hypertension	0 (0.0)	0 (0.0)	1 (0.2)
Hypertension	33 (6.7)	37 (7.6)	24 (4.8)
ΣHypertension	**41 (8.4)**	**46 (9.4)**	**32 (6.4)**

[Adapted from NDA 21-042, Vol. 1.134, Table 87, page 266. ΣHypertension = Blood pressure increased+Borderline hypertension+Hypertension.]

Table 9-34/35 reports additional clinical information on patients with hypertension-type adverse experiences, Noteworthy, more 25 mg MK-0966 patients had an associated edema-related adverse experience compared to diclofenac.

Table 9-34/35. Summary Of Number (%) Of Patients With Specified Increased Blood Pressure† And Hypertension Adverse Experiences Entire 1-Year Base Studies All Randomized Patients

	MK-0966 12.5 mg (N=490) n/N (%)	MK-0966 25 mg (N=489) n/N (%)	Diclofenac 150 mg (N=498) n/N (%)
Total	**41 (8.4)**	**46 (9.4)**	**32 (6.4)**
Number (%) of Patients:			
with a history of hypertension	27 (65.9)	23 (50.0)	20 (62.5)
taking antihypertensives at Visit 1	22 (53.7)	21 (45.7)	18 (56.5)
change in antihypertensive medication ‡			
with a history of hypertension	16 of 27 (39.0)	16 of 23 (34.8)	15 of 20 (46.9)
without a history of hypertension	10 of 14 (24.4)	18 of 23 (39.1)	8 of 12 (25.0)
adverse experience rated severe §	1 (2.4)	0 (0.0)	0 (0.0)
discontinued for adverse experience	1 (2.4)	4 (8.7)	1 (3.1)
with an edema-related adverse experience	5 (12.2)	8 (17.4)	2 (6.3)
exceeding blood pressure predefined limits of change¶	9 (22.0)	10 (21.7)	7 (21.9)

[Adapted from NDA 21-042, Vol. 1.134, Table 88, page 267. †Includes all patients as delineated in Table 8-34/35. ‡Represents either a change in dose and/or initiation of antihypertensive therapy. §Defined as incapacitating, with inability to work or do usual activity. ¶A 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 who exceeded the predefined limits of change for blood pressure 2 or more times (i.e., at 2 or more visits) for the entire 1-year Base Studies are summarized in Table 10-34/35.

Table 10-34/35. Patients Exceeding The Predefined Limits Of Change On Diastolic And Systolic Blood Pressure Entire 1-Year Base Studies (Intention-To-Treat Analysis)

Vital Sign	Predefined Limit of Change	Treatment	Number†/Total‡(%)
Systolic blood pressure (mm Hg)	Increase >20 and value >140	MK-0966 12.5 mg	46/469 (9.8)
		MK-0966 25 mg	50/460 (10.9)
		Diclofenac 150 mg	47/479 (9.8)
Diastolic blood pressure (mm Hg)	Increase >15 and value >90	MK-0966 12.5 mg	10/469 (2.1)
		MK-0966 25 mg	14/460 (3.0)
		Diclofenac 150 mg	9/479 (1.9)

[Adapted from NDA 21-042, Vol. 1.134, Table 80, page 257. †Number of patients meeting the predefined limit criteria. ‡Total number of patients with valid values of vital sign test.]

Laboratory Findings: Tables 11-34/35 and 12-34/35 present a summary of laboratory adverse experiences and the number (%) of patients with specific laboratory adverse experiences by laboratory test category,

respectively. Patients receiving diclofenac had more laboratory adverse experiences than those treated with MK-0966.

Table 11-34/35. Laboratory Adverse Experience Summary Entire 1-Year OA Studies All Randomized Patients

	MK-0966 12.5 mg (N=490) n (%)	MK-0966 25 mg (N=489) n (%)	Diclofenac 150 mg (N=498) n (%)
Number of patients with at least one laboratory test postbaseline	486	484	496
Number (%) of patients:			
With one or more adverse experiences	75 (15.4)	94 (19.4)	142 (28.6)
Discontinued due to adverse experiences	1 (0.2)	4 (0.8)	24 (4.8)

[Adapted from NDA 21-042, Vol. 1.134, Table 66, page 207.]

Serum creatinine increased, hyperkalemia, and proteinuria were laboratory adverse experiences that occurred in a dose-dependent manner with MK-0966.

Table 12-34/35. Number (%) of Patients With Specific Laboratory Adverse Experiences by Laboratory Test Category Entire 1-Year Base Studies All Patients Randomized

	MK-0966 12.5 mg (N=490) n/N (%)	MK-0966 25 mg (N=489) n/N (%)	Diclofenac 150 mg (N=498) n/N (%)
Blood urea nitrogen increased	4/486 (0.8)	16/483 (3.3)	11/496 (2.2)
Serum creatinine increased	7/486 (1.4)	12/483 (2.5)	13/496 (2.6)
Hyperkalemia	1/486 (0.2)	5/483 (1.0)	3/496 (0.6)
Hyperuricemia	0/486 (0.0)	1/483 (0.2)	2/496 (0.4)
Hypocalcemia	1/486 (0.2)	0/483 (0.0)	0/496 (0.0)
Hypokalemia	3/486 (0.6)	3/483 (0.6)	3/496 (0.6)
Hyponatremia	0/486 (0.0)	2/483 (0.4)	0/496 (0.0)
Uric acid increased	1/486 (0.2)	8/483 (1.7)	3/496 (0.6)
Albuminuria	3/486 (0.6)	1/484 (0.2)	1/495 (0.2)
Glycosuria	6/486 (1.2)	1/484 (0.2)	6/495 (1.2)
Hematuria	3/434 (0.7)	3/433 (0.7)	4/430 (0.9)
Microalbuminuria	0/103 (0.0)	1/120 (0.8)	0/113 (0.0)
Proteinuria	13/486 (2.7)	19/484 (3.9)	17/495 (3.4)

[Adapted from NDA 21-042, Vol. 1.134, Table 69, pages 212-214.]

The analysis of laboratory data was also carried out based on between-treatment group comparisons of percent of patients exceeding predefined limits of change in blood chemistry for the second 6 months of 1-year base studies[7] (Table 13-34/35).

[7] Data on the entire 1-year base studies were not available for review.

Table 13-34/35. Patients Exceeding the Predefined Limits of Change: Laboratory Second 6 Months of 1-Year Base Studies (Intention-to-Treat Analysis)

Laboratory Test	Predefined Limits of Change	Treatment	Number†/Total‡(%)
Serum creatinine (mg/dL)	Increase≥0.5% and Value>ULN	MK0966 12.5 mg MK0966 25 mg Diclofenac 150 mg	3/350 (0.86) 3/349 (0.86) 2/344 (0.58)
Serum potassium (mEq(K)/L)	Increase ≥8.0 and value >ULN	MK0966 12.5 mg MK0966 25 mg Diclofenac 150 mg	16/350 (4.57) 26/349 (7.45) 18/344 (5.23)
Urine protein (mg/dL)	Increase ≥1*f*	MK0966 12.5 mg MK0966 25 mg Diclofenac 150 mg	57/350 (16.29) 55/349 (15.76) 45/344 (13.20)

[Adapted from NDA 21-042, Vol. 1.134, Appendix 4.19, pages 2462-2465. †Number of patients meeting the predefined limit criteria. ‡Total number of patients with valid values of vital sign test. *f*Specification includes both character and numeric values.]

SUMMARY/COMMENTS

Study protocol #034-02, and 035-02 compared the effects of treatment with MK-0966 12.5 mg, 25mg and 50 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 purpose of the second 6 months extension was to further evaluate the safety profile of MK-0966 with a longer duration of continuous administration.

The cardiovascular and renal safety profile of MK-0966 in the Entire 1-Year Base Studies is highlighted by edema- and hypertension-type, serum creatinine increased, hyperkalemia, and proteinuria adverse events.

MK-0966 25 mg resulted in three patients' discontinuation due to hypertension (ANs 5760, 5766, 7958).