Allocation number	Pre-drug hemoglobin (g/dL)	Lowest hemoglobin during study (g/dL)	Day of lowest hemoglobin	Duration in study
5377			142	182
5837			8	25

Reviewer's table

Leukocytes

One patient (allocation number 5589) on MK-0966 25 mg was also receiving another medication known to be associated with depression of white blood cell counts.

Another patient (allocation number 5064) had a sustained decrease in neutrophil count which approached but was not less than 1000/microL.

Platelets

One patient (allocation number 5204) had low platelets count on multiple occasions despite an initial normal count upon entering the trial. The low platelet counts were interspersed between normal counts.

Second six months

Clinical Adverse Events

No clinical hematologic adverse events resulted in a discontinuation from trial for any patient in the MK-0966 treatment group.

Selected Clinical Adverse Events Second Six Months of Protocol 34

Event	MK-0966 12.5 mg (n=169)	MK-0966 25 mg (n=183)	Diclofenac (n=174)
Anemia	0	0	2
Contusion	2	0	3
Fecal Occult Blood	0	0	2
Hematoma	2	0	2
Rectal Bleeding	0	0	1
Subconjunctival Hemorrhage	0	0	1

Reviewer's Table from SAS Transport files

Changes in hematologic Laboratory Parameters

Sponsor's Analysis

The sponsor combined the Predefined Limits of Change analysis for the extension phases of protocols 34 and 35. The data are listed in the analysis tables of protocol 35.

No patient was discontinued from the trial because of an adverse hematologic laboratory parameter.

Selected Laboratory Adverse Events Occurring During the Second Six Months of Protocol 34

Event	MK-0966 12.5 mg (n=169)	MK-0966 25 mg (n=183)	Diclofenac (n=174)

Hemoglobin decreased	0	3	1
Leukocytes decreased	0	0	1
Neutrophils decreased	0	2	2
Platelets decreased /thrombocytopenia	0	3	3

Reviewer's table

Hemoglobin
One patient (allocation number 5589) in the MK-0966 25 mg group had a sustained mild reduction in hemoglobin to 11.2 g/dL throughout the trial. No information exists about off study results.

Neutrophils
One patient (allocation number 5064) exhibits variability in neutrophil counts during the trial. During the course of the study this patient has several neutrophil counts under 1500/microL. At completion of the trial his neutrophil count had improved to 2000/microL.

Platelets
Patient 5332 experienced a decrease in his platelet counts over the course of this trial. During the first six months of trial he had on two occasions a small decrease in his platelet counts to the 130-140 x 10^3/microL from a normal baseline. In the second six months he experienced a further decline. The patient was on no other medications throughout the trial. No post-study platelet count is provided to assess recovery.

Day	Platelet count x 10^3/microL
233	
280	
287	

Protocol 35
An Active-Comparator-Controlled, Parallel-Group, 1 Year, Double-Blind Study, Conducted Under In-House Blinding Conditions, to Assess the Safety and Efficacy of MK-0966 Versus Diclofenac Sodium in Patients with Osteoarthritis of the Knee or Hip

Clinical Adverse Events

One patient (allocation number 7918) discontinues MK-0966 12.5 mg due to the development of hematuria on day 182.

Clinical Adverse Events for Protocol 35

Event	MK-0966 12.5mg (n=259)	MK-0966 25 mg (n=257)	Diclofenac (n=267)
Anemia	0	0	2
Black Stool	0	0	0
Blood Blister	0	1	0
Contusion	3	6	3

/ecchymosis			
Epistaxis	1	0	4
Hematochezia	0	1	2
Hematoptysis	1	0	0
Ophthalmologic Hemorrhage	0	1	0
Post-menopausal Bleeding	8	1	0
Rectal Bleeding	0	0	2
Subconjunctival Hemorrhage	0	0	1
Vitamin B_{12} deficiency	1	0	0

Reviewer's table from SAS transport files

Laboratory Adverse Events

Two patients were discontinued from the study due because of adverse hematologic laboratory parameters.

Patient (allocation number 7525) on MK-0966 25 mg experienced a decrease in hemoglobin of 1.1 g/dL from the baseline value of 11.8 g/dL during the study with stool hemoccult tests negative for occult blood. Two weeks off study drug her hemoglobin has improved to 11.4 g/dL.

Patient 7606 was discontinued from the study on day 14. This patient's serial hemoglobins are listed below.

Date (day of study)	Hemoglobin (g/dL)
1/21/97 (-23)	
2/13/97 (1)	
2/19/97 (7)	
2/26/97 (14)	

Patient refused to come back for additional evaluation off study. This patient's results are difficult to interpret because of his day –23 result.

Changes in Hematologic Laboratory Parameters

Sponsor's Analysis

MK-0966 Prot. No. 035
Diclofenac OA Study—U.S.

APPENDIX 4.16

4.16.3: Predefined Limits of Change: Laboratory
(Intention-to-Treat Approach)

Treatment	Number/Total (%)	Pairwise Comparison p-value and 95% CI for Difference in Proportions
WBC count (10^{3}/microL):Decrease ≥20.0% and Value < LLN		
12.5 mg	35/257 (13.62%)	
25 mg	25/254 (9.84%)	
Diclofenac	43/266 (16.17%)	
12.5 mg vs. Diclofenac		0.462 (-8.64, 3.55)
25 mg vs. Diclofenac		0.037 (-12.07, -0.58)
25 mg vs. 12.5 mg		0.216 (-9.34, 1.79)
WBC count (10^{3}/microL):Increase ≥20.0% and Value > ULN		
12.5 mg	7/257 (2.72%)	
25 mg	4/254 (1.57%)	
Diclofenac	8/266 (3.01%)	
12.5 mg vs. Diclofenac		>0.999 (-3.14, 2.58)
25 mg vs. Diclofenac		0.384 (-3.99, 1.13)
25 mg vs. 12.5 mg		0.544 (-3.66, 1.36)
Hematocrit (%):Decrease ≥6.0		
12.5 mg	1/257 (0.39%)	
25 mg	2/254 (0.79%)	
Diclofenac	11/266 (4.14%)	
12.5 mg vs. Diclofenac		0.006 (-6.26, -1.24)
25 mg vs. Diclofenac		0.021 (-5.98, -0.72)
25 mg vs. 12.5 mg		0.622 (-0.93, 1.73)
Hematocrit (%):Increase ≥20.0% and Value > ULN		
12.5 mg	0/257 (0.00%)	
25 mg	1/254 (0.39%)	
Diclofenac	0/266 (0.00%)	
12.5 mg vs. Diclofenac		>0.999 (0.00, 0.00)
25 mg vs. Diclofenac		0.488 (-0.38, 1.16)
25 mg vs. 12.5 mg		0.497 (-0.38, 1.16)
Hemoglobin (g/dL):Decrease ≥2.0		
12.5 mg	7/257 (2.72%)	
25 mg	1/254 (0.39%)	
Diclofenac	18/266 (6.77%)	
12.5 mg vs. Diclofenac		0.039 (-7.66, -0.43)
25 mg vs. Diclofenac		<0.001 (-9.49, -3.26)
25 mg vs. 12.5 mg		0.068 (-4.46, -0.20)

MK-0966 Prot. No. 035
Diclofenac OA Study—U.S.

APPENDIX 4.16

4.16.3: Predefined Limits of Change: Laboratory (Intention-to-Treat Approach) (Cont.)

Treatment	Number/Total (%)	Pairwise Comparison p-value and 95% CI for Difference in Proportions
Hemoglobin (g/dL):Increase ≥20.0% and Value > ULN		
12.5 mg	0/257 (0.00%)	
25 mg	1/254 (0.39%)	
Diclofenac	0/266 (0.00%)	
12.5 mg vs. Diclofenac		>0.999 (0.00, 0.00)
25 mg vs. Diclofenac		0.488 (-0.38, 1.16)
25 mg vs. 12.5 mg		0.497 (-0.38, 1.16)
Lymphocyte count ($10^{[3]}$/microL):Decrease ≥20.0% and Value < LLN		
12.5 mg	31/253 (12.25%)	
25 mg	33/249 (13.25%)	
Diclofenac	38/264 (14.39%)	
12.5 mg vs. Diclofenac		0.519 (-7.99, 3.71)
25 mg vs. Diclofenac		0.798 (-7.11, 4.83)
25 mg vs. 12.5 mg		0.790 (-4.84, 6.84)
Lymphocyte count ($10^{[3]}$/microL):Increase ≥50.0% and Value > ULN		
12.5 mg	0/253 (0.00%)	
25 mg	1/249 (0.40%)	
Diclofenac	1/264 (0.38%)	
12.5 mg vs. Diclofenac		>0.999 (-1.12, 0.36)
25 mg vs. Diclofenac		>0.999 (-1.06, 1.10)
25 mg vs. 12.5 mg		0.496 (-0.38, 1.19)
Neutrophil count ($10^{[3]}$/microL):Decrease ≥20.0% and Value < LLN		
12.5 mg	5/253 (1.98%)	
25 mg	6/249 (2.41%)	
Diclofenac	8/264 (3.03%)	
12.5 mg vs. Diclofenac		0.577 (-3.74, 1.63)
25 mg vs. Diclofenac		0.789 (-3.43, 2.19)
25 mg vs. 12.5 mg		0.770 (-2.13, 3.00)
Neutrophil count ($10^{[3]}$/microL):Increase ≥50.0% and Value > ULN		
12.5 mg	7/253 (2.77%)	
25 mg	6/249 (2.41%)	
Diclofenac	8/264 (3.03%)	
12.5 mg vs. Diclofenac		>0.999 (-3.15, 2.63)
25 mg vs. Diclofenac		0.789 (-3.43, 2.19)
25 mg vs. 12.5 mg		>0.999 (-3.13, 2.42)

APPENDIX 4.16

4.16.3: Predefined Limits of Change: Laboratory
(Intention-to-Treat Approach) (Cont.)

Treatment	Number/Total (%)	Pairwise Comparison p-value and 95% CI for Difference in Proportions
Platelet count ($10^{[3]}$/microL):Decrease ≥25.0% and Value < LLN		
12.5 mg	11/257 (4.28%)	
25 mg	8/253 (3.16%)	
Diclofenac	10/266 (3.76%)	
12.5 mg vs. Diclofenac		0.826 (-2.85, 3.89)
25 mg vs. Diclofenac		0.812 (-3.74, 2.55)
25 mg vs. 12.5 mg		0.641 (-4.40, 2.16)
Platelet count ($10^{[3]}$/microL):Increase ≥50.0% and Value > ULN		
12.5 mg	0/257 (0.00%)	
25 mg	1/253 (0.40%)	
Diclofenac	1/266 (0.38%)	
12.5 mg vs. Diclofenac		>0.999 (-1.11, 0.36)
25 mg vs. Diclofenac		>0.999 (-1.05, 1.09)
25 mg vs. 12.5 mg		0.496 (-0.38, 1.17)

Sponsor's table

Sponsor's Analysis does not demonstrate any trends for the MK-0966 treatment groups.

Selected Abnormal Hematologic Parameters

Selected Laboratory Adverse Events for Protocol 35

Event	MK-0966 12.5 mg (n=259)	MK-0966 25 mg (n=257)	Diclofenac (n=267)
Hematuria	1	2	1
Hemoglobin decreased	0	6	9
Leukocytes decreased	5	3	1
Platelets decreased	2	3	4
Reticulocytes decreased	0	0	1

Reviewer's table from SAS transport files

Leukocytes

One patient (allocation number 8217) experienced a progressive decrease in white blood cell count throughout the study. Review of his medication list did not suggest another drug as the cause for the observed effect. Below is the serial listing of his white cell counts.

Day	Leukocyte Count x 10^3 /microL
1	
15	
29	
68	
87	
136	

178

Two patients experienced a decrease in white blood cell count during treatment with MK-0966 25 mg. Both patients (7611 and 8161) were on multiple additional medications.

Platelets

One patient (7963) experienced a moderate reduction in platelet count. The data are shown in the following table.

This patient continued in the extension portion of the trial. All subsequent platelet counts remained in the 140.000 range.

Patient (allocation number 7963) platelet counts

Day	Platelet count x 10^3/microL
-15	
1	
15	
28	
56	
84	
133	
182	

Patient 7636 developed an abnormal platelet count six months into the study which remained low throughout the extension period. The patient was not on any new medications at the time of the decrease to 120 x 10^3/microL. Platelet counts remained decreased in the extension part of the study

Day	Platelet count x 10^3/microL
-8	
1	
13	
25	
53	
81	
130	
179	

Protocol 35-02, 35-10

An Active-Comparator-Controlled, Parallel-Group, 1-Year, Double-Blind Study, and the First Double-Blind Study Active-Comparator-Controlled Extension to Assess the Safety and Efficacy of MK-0966 Versus Diclofenac Sodium in Patients With OA of the Knee and Hip

This extension trial excluded patients with clinical adverse and laboratory adverse events occurring in the earlier portion of the trial (protocol 35).

Clinical Adverse Events

No patient discontinued from this portion of the trial due to an adverse hematologic clinical event.

Clinical Adverse Events for the Second Six Months for Protocol 35

Event	MK-0966 12.5 mg (n=183)	MK-0966 25 mg (n=166)	Diclofenac (n=173)
Contusion	2	4	2
Epistaxis	0	1	1
Post-menopausal bleeding	1	0	2

Reviewer's table from SAS transport files

Changes in Hematologic Laboratory Parameters

Sponsor's Analysis

MK-0966 Prot. No. 034/035 and 034-10/035-10
Diclofenac Studies U.S./Multinational

APPENDIX 4.19

4.19.2 Predefined Limits of Change: Laboratory
(Intention-to-Treat Approach) (Cont.)

hematocrit (%):Increase >= 20.0% and Value > ULN		
12.5 mg	0 /350 (0.00%)	
25 mg	1 /349 (0.29%)	
Diclofenac	0 /344 (0.00%)	
12.5 mg vs. Diclofenac		>0.999 (0.00, 0.00)
25 mg vs. Diclofenac		>0.999 (-0.27, 0.85)
12.5 mg vs. 25 mg		0.499 (-0.85, 0.27)
hemoglobin (gm/dL):Decrease >= 2.0		
12.5 mg	8 /350 (2.29%)	
25 mg	13 /349 (3.72%)	
Diclofenac	22 /344 (6.40%)	
12.5 mg vs. Diclofenac		0.009 (-7.13, -1.09)
25 mg vs. Diclofenac		0.120 (-5.93, 0.59)
12.5 mg vs. 25 mg		0.279 (-3.97, 1.09)
hemoglobin (gm/dL):Increase >= 20.0% and Value > ULN		
12.5 mg	0 /350 (0.00%)	
25 mg	1 /349 (0.29%)	
Diclofenac	0 /344 (0.00%)	
12.5 mg vs. Diclofenac		>0.999 (0.00, 0.00)
25 mg vs. Diclofenac		>0.999 (-0.27, 0.85)
12.5 mg vs. 25 mg		0.499 (-0.85, 0.27)
lymphocyte count (10[3]/microL):Decrease >= 20.0% and Value < LLN		
12.5 mg	30 /342 (8.77%)	
25 mg	37 /346 (10.69%)	
Diclofenac	27 /340 (7.94%)	
12.5 mg vs. Diclofenac		0.782 (-3.32, 4.98)
25 mg vs. Diclofenac		0.238 (-1.59, 7.10)
12.5 mg vs. 25 mg		0.441 (-6.35, 2.50)

MK-0966 Prot. No. 034/035 and 034-10/035-10
Diclofenac Studies U.S./Multinational

APPENDIX 4.19

4.19.2 Predefined Limits of Change: Laboratory
(Intention-to-Treat Approach)

Treatment	Number/Total (%)	Pairwise Comparison p-value and 95% CI for Difference in Percentages
WBC count (10[3]/microL):Decrease >= 20.0% and Value < LLN		
12.5 mg	28 /350 (8.00%)	
25 mg	34 /349 (9.74%)	
Diclofenac	39 /344 (11.34%)	
12.5 mg vs. Diclofenac		0.158 (-7.73, 1.06)
25 mg vs. Diclofenac		0.537 (-6.17, 2.98)
12.5 mg vs. 25 mg		0.428 (-5.96, 2.47)
WBC count (10[3]/microL):Increase >= 20.0% and Value > ULN		
12.5 mg	12 /350 (3.43%)	
25 mg	8 /349 (2.29%)	
Diclofenac	12 /344 (3.49%)	
12.5 mg vs. Diclofenac		>0.999 (-2.78, 2.66)
25 mg vs. Diclofenac		0.373 (-3.69, 1.30)
12.5 mg vs. 25 mg		0.497 (-1.33, 3.61)
hematocrit (%):Decrease >= 6.0		
12.5 mg	7 /350 (2.00%)	
25 mg	11 /349 (3.15%)	
Diclofenac	19 /344 (5.52%)	
12.5 mg vs. Diclofenac		0.016 (-6.35, -0.70)
25 mg vs. Diclofenac		0.138 (-5.40, 0.66)
12.5 mg vs. 25 mg		0.353 (-3.50, 1.20)

MK-0966 Prot. No. 034/035 and 034-10/035-10
Diclofenac Studies U.S./Multinational

APPENDIX 4.19

4.19.2 Predefined Limits of Change: Laboratory
(Intention-to-Treat Approach) (Cont.)

lymphocyte count (10[3]/microL):Increase >= 50.0% and Value > ULN		
12.5 mg	0/342 (0.00%)	
25 mg	1/346 (0.29%)	
Diclofenac	2/340 (0.59%)	
12.5 mg vs. Diclofenac		0.248 (-1.40, 0.22)
25 mg vs. Diclofenac		0.621 (-1.29, 0.69)
12.5 mg vs. 25 mg		>0.999 (-0.85, 0.28)
neutrophil count (10[3]/microL):Decrease >= 20.0% and Value < LLN		
12.5 mg	7/342 (2.05%)	
25 mg	8/346 (2.31%)	
Diclofenac	6/340 (1.76%)	
12.5 mg vs. Diclofenac		>0.999 (-1.77, 2.33)
25 mg vs. Diclofenac		0.788 (-1.57, 2.66)
12.5 mg vs. 25 mg		>0.999 (-2.45, 1.92)
neutrophil count (10[3]/microL):Increase >= 50.0% and Value > ULN		
12.5 mg	6/342 (1.75%)	
25 mg	12/346 (3.47%)	
Diclofenac	6/340 (1.76%)	
12.5 mg vs. Diclofenac		>0.999 (-1.98, 1.96)
25 mg vs. Diclofenac		0.232 (-0.68, 4.09)
12.5 mg vs. 25 mg		0.232 (-4.09, 0.66)
platelet count (10[3]/microL):Decrease >= 25.0% and Value < LLN		
12.5 mg	12/350 (3.43%)	
25 mg	9/349 (2.58%)	
Diclofenac	7/344 (2.03%)	
12.5 mg vs. Diclofenac		0.353 (-1.03, 3.81)
25 mg vs. Diclofenac		0.801 (-1.69, 2.78)
12.5 mg vs. 25 mg		0.659 (-1.68, 3.38)

MK-0966 Prot. No. 034/035 and 034-10/035-10
Diclofenac Studies U.S./Multinational

APPENDIX 4.19

4.19.2 Predefined Limits of Change: Laboratory
(Intention-to-Treat Approach) (Cont.)

platelet count (10[3]/microL):Increase >= 50.0% and Value > ULN		
12.5 mg	0/350 (0.00%)	
25 mg	1/349 (0.29%)	
Diclofenac	0/344 (0.00%)	
12.5 mg vs. Diclofenac		>0.999 (0.00, 0.00)
25 mg vs. Diclofenac		>0.999 (-0.27, 0.85)
12.5 mg vs. 25 mg		0.499 (-0.85, 0.27)

Sponsor's tables

The Pre-defined Limits of Change Analysis suggests that a greater percentage of MK-0966 patients experienced a decrease in their lymphocyte, and platelet counts than patients on Diclofenac are.

Selected Laboratory Adverse Events

Discontinuation from study due to adverse hematological parameters.

Hemoglobin
Patient 7943 was eventually taken off study on day 338 because of decrease in hemoglobin. The patient was subsequently found to have GI bleeding a colon carcinoma.

Leukocytes
Patient 7958 was taken off study because of leukopenia on day 202. The patient's WBC improved off study as demonstrated below. This patient had demonstrated a similar pattern of WBC during the first portion of the trial.

Day	WBC count x 10^3
-15	
1	
184	
195	
202	
232	

Selected Laboratory Adverse Events for the Second Six Months of Protocol 35

Event	MK-0966 12.5 mg (n=183)	MK-0966 25 mg (n=166)	Diclofenac (n=173)
Hemoglobin decreased	3	3	6
Leukocytes decreased	1	2	1
Platelet decreased/ thrombocytopenia	8	2	0

Reviewer's table from SAS transport files

Hemoglobin
Patient (allocation number 8435). This patient's hemoglobin dropped during the first part of the study. He remained in the study with improvement of the hemoglobin parameters which subsequently remained normal.

Patient 8435 Day of Study	Hemoglobin (g/dL)
1	
183	
219	
232	
251	

Leukocytes
Patient 7611 experiences intermittent reduction in leukocyte count on several occasions during the first portion of the trial and during the continuation part of the study. The patient also had a mild decrease in platelet count on study (in the range of 140.000 cmm).

Platelets
Below are the results for patient allocation number 7963

Day	Platelet count x 10^3/microL
-15	
1	
28	
84	
182	
236	
365	
372	

The patient was not placed on any new medications during the trial.

Patient 7636 experienced a sustained drop in platelet counts lasting 140 days to values as low as 100,000/microL. However, this patient's platelet count recovered while on study.

Protocol 40
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

Clinical Adverse Events

No patient was discontinued from the trial due to an adverse clinical hematological event.

Selected Clinical Adverse Events for Protocol 40

Event	Placebo (n=74)	MK-0966 12.5 mg (n=244)	MK-0966 25 mg (n=242)	Ibuprofen 2400 mg (n=249)
Bruises easily/Contusion/ ecchymosis	0	2	2	3
Epistaxis	0	1	0	1
Genital bleeding	0	0	1	0
Gingival hemorrhage	0	0	1	0
Hematoma	0	1	0	0
Hypermenorrhea	0	0	1	0
Petechiae	0	0	1	0
Post-menopausal bleeding	0	1	0	0
Retinal Hemorrhage	0	0	0	1

Reviewer's table from SAS transport files

Changes in Hematologic Laboratory Parameters

Sponsor's Analysis

Table 58

Patients Exceeding the Predefined Limits of Change
Hematology Tests
(Intention-to-Treat Approach)

Laboratory Test	Predefined Limit of Change	Treatment	Number[1]/ Total[2] (%)
WBC count (10^3/microL)	Decrease ≥20.0% and value <LLN	Placebo	3/72 (4.2)
		MK-0966 12.5 mg	21/240 (8.8)
		MK-0966 25 mg	15/234 (6.4)
		Ibuprofen 2400 mg	19/245 (7.8)
	Increase ≥20.0% and value >ULN	Placebo	1/72 (1.4)
		MK-0966 12.5 mg	1/240 (0.4)
		MK-0966 25 mg	4/234 (1.7)
		Ibuprofen 2400 mg	1/245 (0.4)
Hematocrit (%)	Decrease ≥6.0	Placebo	0/72 (0.0)
		MK-0966 12.5 mg	2/240 (0.8)**
		MK-0966 25 mg	5/234 (2.1)**
		Ibuprofen 2400 mg	16/245 (6.5)
	Increase ≥20.0% and value >ULN	Placebo	0/72 (0.0)
		MK-0966 12.5 mg	0/240 (0.0)
		MK-0966 25 mg	0/234 (0.0)
		Ibuprofen 2400 mg	0/245 (0.0)

Table 58 (Cont.)

Patients Exceeding the Predefined Limits of Change
Hematology Tests
(Intention-to-Treat Approach)

Laboratory Test	Predefined Limit of Change	Treatment	Number[1]/ Total[2] (%)
Hemoglobin (gm/dL)	Decrease ≥2.0	Placebo	0/72 (0.0)
		MK-0966 12.5 mg	0/240 (0.0)**
		MK-0966 25 mg	1/234 (0.4)**
		Ibuprofen 2400 mg	9/245 (3.7)
	Increase ≥20.0% and value >ULN	Placebo	0/72 (0.0)
		MK-0966 12.5 mg	0/240 (0.0)
		MK-0966 25 mg	0/234 (0.0)
		Ibuprofen 2400 mg	0/245 (0.0)
Lymphocyte count (10^3/microL)	Decrease >20.0% and value <LLN	Placebo	2/70 (2.9)
		MK-0966 12.5 mg	14/231 (6.1)
		MK-0966 25 mg	15/227 (6.6)
		Ibuprofen 2400 mg	22/241 (9.1)
	Increase ≥50.0% and value >ULN	Placebo	0/70 (0.0)
		MK-0966 12.5 mg	0/231 (0.0)
		MK-0966 25 mg	0/227 (0.0)
		Ibuprofen 2400 mg	1/241 (0.4)
Neutrophil count (10^3/microL)	Decrease ≥20.0% and value <LLN	Placebo	2/70 (2.9)
		MK-0966 12.5 mg	4/231 (1.7)
		MK-0966 25 mg	2/227 (0.9)
		Ibuprofen 2400 mg	6/241 (2.5)
	Increase ≥50.0% and value >ULN	Placebo	2/70 (2.9)
		MK-0966 12.5 mg	3/231 (1.3)
		MK-0966 25 mg	2/227 (0.9)
		Ibuprofen 2400 mg	5/241 (2.1)
Platelet count (10^3/microL)	Decrease ≥25.0% and value <LLN	Placebo	2/72 (2.8)
		MK-0966 12.5 mg	3/240 (1.3)
		MK-0966 25 mg	4/234 (1.7)
		Ibuprofen 2400 mg	3/245 (1.2)
	Increase ≥50.0% and value >ULN	Placebo	0/72 (0.0)
		MK-0966 12.5 mg	0/240 (0.0)
		MK-0966 25 mg	0/234 (0.0)
		Ibuprofen 2400 mg	1/245 (0.4)

[1] Number of patients meeting the predefined limit criteria.
[2] Total number of patients with valid values of the laboratory or vital sign test.
** p≤0.05 vs. ibuprofen.
ULN = Upper limit of normal range. LLN = Lower limit of normal range.

Data Source: [4.27]

Sponsor's table

Review of the data does not suggest a particular trend for MK-0966 compared to ibuprofen.

No patient was discontinued from the trial due to an abnormal hematological parameter.

Selected Laboratory Adverse Events for Protocol 40

Event	Placebo (n=74)	MK-0966 12.5 mg (n=244)	MK-0966 25 mg (n=242)	Ibuprofen (n=249)
Hemoglobin decreased	0	4	2	9
Leukocytes decreased	0	1	1	2
Lymphocytopenia	0	0	1	1
Platelets decreased	0	2	0	2

Reviewer's table form SAS transport files

Hemoglobin

None of the patients listed below were found to have experienced a bleeding event to account for the decrease in hemoglobin.

Below is a representative sampling of the decrease in hemoglobin seen on study. In addition, patient 8959 experienced a mild decrease in hemoglobin over the course of the study.

Change in Hemoglobin over the Course of the Study

Allocation number	Predose hemoglobin (g/dL)	Lowest hemoglobin (g/dL)	Day of lowest hemoglobin	Post study hemoglobin (g/dL)	Day of post study hemoglobin
8863	[redacted]	[redacted]	45	[redacted]	52
9312			43		54
9592			29		50

Reviewer's table

Leukocytes and Platelets

No patient experienced a sustained drop in leukocytes or platelet counts.

Protocol 44

A Multicenter, Randomized, Parallel-Group, Active- and Placebo-Controlled, Double-Blind Study, Conducted Under In-House Blinding Conditions to Determine the Incidence of Gastrointestinal Ulceration After 12 Weeks of Treatment With MK-0966, Ibuprofen, or Placebo With a Twelve Week Continuation Period

Clinical Adverse Events

No patient was discontinued from the trial due to an abnormal hematologic clinical event.

Selected Clinical Adverse Events for Protocol 44

Event	Placebo(n=177)	MK-0966 25 mg (n=195)	MK-0966 50 mg (n=186)	Ibuprofen (n=184)

Anemia	0	2	0	2
Black Stool/Melena	0	1	0	2
/Ecchymosis/Hematoma	1	2	4	4
Fecal Occult Blood	0	0	3	1
Gastrointestinal Bleeding	0	1	1	2
Hematochezia	2	1	1	0
Pancytopenia	0	0	1	0
Rectal Bleeding	0	1	1	0
Subconjunctival Hemorrhage	0	1	0	0
Uterine/Vaginal Hemorrhage	0	1	1	1

Reviewer's table from SAS transport files

Laboratory Adverse Events

Sponsor's Analysis

MK-0966 Prot. No. 044
Multicenter OA Endoscopy Study

Appendix 4.17.1

Patients Exceeding the Predefined Limits of Change
(Intention-to-Treat Approach) - Laboratory
Week 18

Laboratory Test	Predefined Limits of Change	Treatment	Number†/ Total‡
Hematocrit (%)	Decrease ≥6.0	Placebo	1/162
		MK-0966 25 mg	4/188
		MK-0966 50 mg	9/178
		Ibuprofen 2400 mg	18/170
	Increase ≥20.0% and Value >ULN	Placebo	0/162
		MK-0966 25 mg	1/188
		MK-0966 50 mg	1/178
		Ibuprofen 2400 mg	0/170
Hemoglobin (gm/dL)	Decrease ≥2.0	Placebo	3/162
		MK-0966 25 mg	3/188
		MK-0966 50 mg	9/178
		Ibuprofen 2400 mg	11/170
	Increase ≥20.0% and Value >ULN	Placebo	1/162
		MK-0966 25 mg	0/188
		MK-0966 50 mg	1/178
		Ibuprofen 2400 mg	0/170
WBC count (10(3)/microL)	Decrease>=20.0% and Value<LLN	Placebo	18/162
		MK0966 25 mg	20/188
		MK0966 50 mg	23/178
		Ibuprofen	10/170
	Increase >=20.0% and Value >ULN	Placebo	3/162
		MK0966 25 mg	3/188
		MK0966 50 mg	1/178
		Ibuprofen	2/170

MK-0966 Prot. No. 044
Multicenter OA Endoscopy Study

Laboratory Test	Predefined Limits of Change	Treatment	Number†/ Total‡
Lymphocyte count (10(3)/microL)	Decrease>=20.0% and Value<LLN	Placebo	11/158
		MK0966 25 mg	19/185
		MK0966 50 mg	18/174
		Ibuprofen	18/169
	Increase >-50.0% and Value >ULN	Placebo	0/158
		MK0966 25 mg	0/185
		MK0966 50 mg	1/174
		Ibuprofen	0/169
Neutrophil count (10(3)/microL)	Decrease>=20.0% and Value<LLN	Placebo	8/158
		MK0966 25 mg	5/185
		MK0966 50 mg	3/174
		Ibuprofen	3/169
	Increase >-50.0% and Value >ULN	Placebo	4/158
		MK0966 25 mg	1/185
		MK0966 50 mg	3/174
		Ibuprofen	2/169
Platelet count (10(3)/microL)	Decrease>=25.0% and Value<LLN	Placebo	5/162
		MK0966 25 mg	6/188
		MK0966 50 mg	7/178
		Ibuprofen	2/170
	Increase >-50.0% and Value >ULN	Placebo	0/162
		MK0966 25 mg	0/188
		MK0966 50 mg	1/178
		Ibuprofen	0/170

Sponsor's table

The Sponsor's Analysis demonstrates a greater percentage of patients treated with MK-0966 experienced a decrease in total white blood cell counts than Ibuprofen.

Study discontinuation due to Hematologic Parameters

No patient was discontinued from the trial due to an abnormal hematologic parameter.

Selected Laboratory Adverse Events for Protocol 44

Event	Placebo (n=177)	MK-0966 25 mg (n=195)	MK-0966 50 mg (n=186)	Ibuprofen (n=184)
Hemoglobin decreased	3	4	3	1
Leukocytes decreased	9	4	2	2
Platelets decreased	6	3	1	2

Reviewer's table from SAS transport files

Several patients in this trial experienced a slight decrease in more than one laboratory parameter. However, the data were variable and not consistent with any pattern.

Patient 5618 experiences moderate leukopenia during the course of the study. The patient was not started on any new medications during the course of the study. His lowest leukocyte count was 2.9 x 10^3/microL.

Protocol 45

A Multicenter, Randomized, Parallel-Group, Active- and Placebo-Controlled, Double-Blind Study, Conducted Under In-House Blinding Conditions, to Determine the Incidence of Gastrointestinal Ulceration After 12 Weeks of Treatment With MK-0966, Ibuprofen, or Placebo With a Twelve Week Extension

Clinical Adverse Events

One patient (allocation number 0414) on MK-0966 50 mg was discontinued after development of an anorectal hemorrhage.

Selected Clinical Adverse Events for Protocol 45

Event	Placebo (n=194)	MK-0966 25 mg (n=195)	MK-0966 50 mg (n=193)	Ibuprofen (n=193)
Anemia	1	0	3	1
Black Stool/Melena	1	1	0	2
Contusion/Ecchymosis/ Hematoma	6	6	3	4
Epistaxis	1	0	1	0
Gastric Hemorrhage	0	0	1	1
Hematochezia	1	0	0	0
Hemorrhage	1	0	1	1
Hemorrhoidal bleeding	1	1	0	0
Hypermenorrhea/Metrorrhagia	0	3	1	0
Macroscopic Hematuria	0	0	0	1
Petechiae	1	3	7	5
Rectal bleeding		1	4	1
Subconjunctival Hemorrhage	0	2	0	0
Vaginal Hemorrhage/spotting	1	1	0	0

Reviewer's table from SAS transport files

Laboratory Adverse Events

Sponsor's Analysis