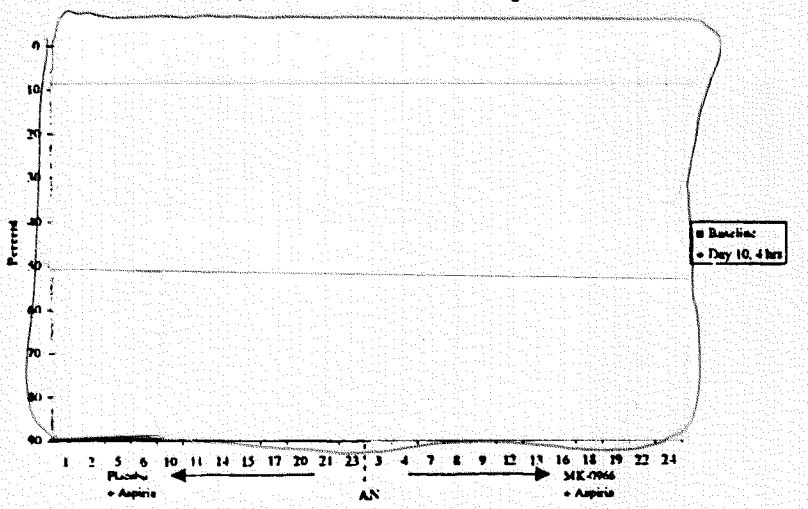
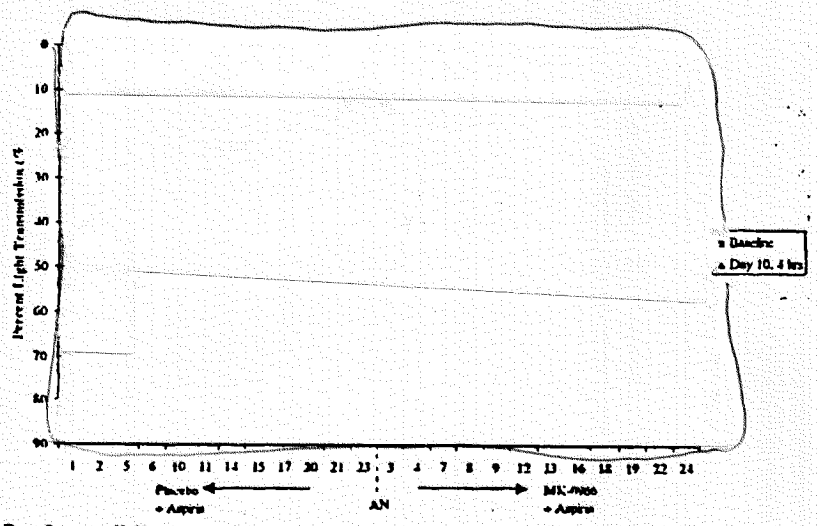
Platelet Aggregation Expressed as Percent Light Transmission for ANs 001 to 024 Using 1 mM of Arachidonic Acid as Agonist



Data Source: [2.2]

Sponsor's table

Platelet Aggregation Expressed as Percent Light Transmission for ANs 001 to 024 Using 1 µg/mL of Collagen as Agonist



Data Source: [2.2]

Sponsor's table

The pooled data indicate that the inhibition of platelet aggregation by aspirin using arachidonic acid or collagen agonists is not affected by coadministration of MK-0966.

Individual Patient Data: Platelet aggregation read as percent change in light transmission varied from patient to patient however consistent in all results is a marked decline in light transmission when baseline results are compared to Day 10 results. This result is consistent with the lack of effect of MK-0966 after10 days administration.

Primary Aggregation

Table 1. Platelet aggregation results expressed as percent light transmission (%) for subjects 001-024 using 1 mM of arachidonic acid as agonist on the primary aggregometer.

Allocation number	Day -1 (screening)	Day 1	Day 4	Day 10 (predose)	Day 10 (4 hr postdose)
001					
002					
003					
004					
005					
006					
007					
008					
009					
010					
011					
012					
013					
014					
015					
016					
017					
018					
019					
020					
021					
022					
023					
024					

Sponsor's table

Inhibition of primary aggregation is not affected by the coadministration of MK-0966 as is seen in the table above.

Secondary Aggregation

Table 3. Platelet aggregation results expressed as percent light transmission (%) for subjects 001-024 using 1 µg/ml of collagen as agonist on the primary aggregometer.

Allocation number	Day -1 (screening)	Day 1	Day 4	Day 10 (predose)	Day 10 (4 hr postdose)
001					
002					
003					
004					
005					
006					
007					
008					
009					
010					
011					
012					
013					
014					
015					
016					
017					
018					
019					
020					
021					
022					
023					
024					

Sponsor's table

Except for two patients (002 and 010), inhibition of secondary aggregation does not appear to be affected by the administration of MK-0966.

Clinical Adverse Events: No hematological adverse events leading to study discontinuation were reported. One patient in the placebo group experienced an ecchymosis.

Changes in other Hematology Parameters

Sixteen volunteers out of a total of 24 experienced a reduction in hemoglobin value at least once. Below is a table with the ranges of decrease or increase from pre-dose on Day 1 to predose on DAY 10 and whether or not off drug the volunteer improved their hemoglobin.

Change in Hemoglobin (g/dL) from predose DAY 1 to predose Day 10

	Decrease in Hemoglobin					Increase in Hemoglobin			
Group	-2.1 to −2.5	-1.6 to −2.0	-1.1 to −1.5	-0.6 to −1.0	-0.1 to −0.5	+0.0 to 0.5	0.6 to 1.0	1.1 to 1.5	Improved after off drug
MK-0966	1	3	2	2	1			1	Yes-7 No-3
Placebo			1	1	1		3		Yes-3 No-3

Reviewer's Table from data supplied in Laboratory Variations From the Normal Range (P063)

More patients in the MK-0966 group experienced a decrease in their hemoglobin from the predose values.
White blood cell count, platelet count, neutrophils, lymphocytes, monocytes, eosinophils, and basophils did not appear to be affected by administration of MK-0966.

Conclusion:
Study P063 showed that coadministration of MK-0966 with aspirin did not result in any significant change in platelet aggregation and serum TBX_2 over that observed with placebo plus aspirin. There appears to be a relatively mild decrease in hemoglobin with administration of MK-0966, which was not seen with placebo.

Review of the Hematologic Parameters data base (excluding cross-over studies) from the NDA Phase III Clinical Trials.

The protocol results reviewed are those for whom computerized datasets were provided and the study design was not crossover. All comments regarding the safety of the NDA data base in terms of hematologic laboratory parameters are limited by the predefined censoring of the data. Individual patient data had to achieve a certain threshold of change prior to being recognized as a laboratory adverse event.

Below is the table of predefined limits used for most protocols.

Definition of Predefined Limits of Change From Baseline

Parameter (Unit)	Definition[1]
Hematology	
Hematocrit (%)	Absolute decrease ≥6
	Increase ≥20% and >ULN
Hemoglobin (g/dL)	Absolute decrease ≥2
	Increase ≥20% and >ULN
Total WBC (x10^3/UL)	Decrease ≥20% and <LLN
	Increase ≥20% and >ULN
Lymphocyte count (x10^3/UL)	Decrease ≥20% and <LLN
	Increase ≥50% and >ULN
Neutrophil count (x10^3/UL)	Decrease ≥20% and <LLN
	Increase ≥50% and >ULN
Platelet count (x10^3/UL)	Decrease ≥25% and <LLN
	Increase ≥50% and >ULN

Sponsor's table

Depending on an individual patient's initial laboratory value, the predefined limits of change may exclude patients who experience a clinically significant decline. For example a patient with an initial hemoglobin of 10.7 would not be flagged until the patient dropped his hemoglobin to 8.7. Similar statements can be made for the predefined limits of change for the other blood parameters.

Patients with hematologic disorders were excluded and all trials except Protocol 58 excluded patients on aspirin, warfarin, and ticlopidine.

This review excludes patients with transient one-time decrease in hematologic parameter and spontaneous improvement to baseline.

Protocol 29
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 and Hip

Hematology Clinical Adverse Events

No clinical event from a hematological standpoint occurred requiring discontinuation of study treatment

Below is a list of clinical adverse events occurring during treatment or post-treatment. for Protocol 29

Event	Placebo (n=145)	MK-0966 5 mg (n= 149)	MK-0966 12.5 mg (n=144)	MK-0966 25 mg (n=137)	MK-0966 50 mg (n= 97)
Contusion	1	2	2	0	1
Epistaxis	1	0	0	0	0
Hemarthosis	0	1	0	0	0
Hematochezia	0	0	1	0	0
Gingival Hemorrhage	0	0	0	0	1
Rectal hemorrhage	0	1	0	0	0
Total number/ percentage	2/145 (1.4%)	4/149 (2.7%)	3/144 (2.1%)	0	2/97 (2.1%)

Reviewer's table from SAS transport files

Changes in Hematologic Laboratory Parameters

Sponsor's Analysis

MK-0966 Prot. No. 029
Osteoarthritis Dose-Ranging Study

APPENDIX 4.21

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

	Treatment	Number/Total (%)	Pairwise comparison p-Value and 95% CI for (Treatment Group versus Placebo)†
Hematocrit			
Absolute Decrease ≥6%			
	Placebo	5 /132 (3.79%)	
	MK-0966 5 mg	4 /143 (2.80%)	---- (-5.22, 3.24)
	MK-0966 12.5 mg	7 /134 (5.22%)	---- (-3.54, 6.42)
	MK-0966 25 mg	9 /131 (6.87%)	---- (-2.34, 8.50)
	MK-0966 50 mg	9 /91 (9.89%)	---- (-0.84, 13.05)
Hematocrit			
Increase ≥20% and >ULN			
	Placebo	0 /132 (0.00%)	
	MK-0966 5 mg	0 /143 (0.00%)	
	MK-0966 12.5 mg	0 /134 (0.00%)	
	MK-0966 25 mg	0 /131 (0.00%)	
	MK-0966 50 mg	0 /91 (0.00%)	
Hemoglobin			
Absolute Decrease ≥2 g/dL			
	Placebo	1 /133 (0.75%)	
	MK-0966 5 mg	2 /143 (1.40%)	
	MK-0966 12.5 mg	1 /134 (0.75%)	
	MK-0966 25 mg	3 /134 (2.24%)	
	MK-0966 50 mg	1 /92 (1.09%)	
Hemoglobin (g/dL)			
Increase ≥20% and >ULN			
	Placebo	0 /133 (0.00%)	
	MK-0966 5 mg	0 /143 (0.00%)	
	MK-0966 12.5 mg	0 /134 (0.00%)	
	MK-0966 25 mg	0 /134 (0.00%)	
	MK-0966 50 mg	0 /92 (0.00%)	
Lymphocyte Count (10^3/microL)			
Decrease ≥20% and <LLN			
	Placebo	2 /132 (1.52%)	
	MK-0966 5 mg	1 /143 (0.70%)	
	MK-0966 12.5 mg	4 /134 (2.99%)	
	MK-0966 25 mg	2 /134 (1.49%)	
	MK-0966 50 mg	3 /92 (3.26%)	

MK-0966 Prot. No. 029
Osteoarthritis Dose-Ranging Study

APPENDIX 4.21

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

	Treatment	Number/Total (%)	Pairwise comparison p-Value and 95% CI for (Treatment Group versus Placebo)†
Lymphocyte Count (10^3/microL)			
Increase ≥50% and >ULN	Placebo	2 /132 (1.52%)	
	MK-0966 5 mg	2 /143 (1.40%)	
	MK-0966 12.5 mg	1 /134 (0.75%)	
	MK-0966 25 mg	0 /134 (0.00%)	
	MK-0966 50 mg	0 /92 (0.00%)	
Neutrophil Count (10^3/mL)			
Decrease ≥20% and <LLN	Placebo	44 /131 (33.59%)	
	MK-0966 5 mg	44 /143 (30.77%)	
	MK-0966 12.5 mg	44 /134 (32.84%)	
	MK-0966 25 mg	53 /134 (39.55%)	
	MK-0966 50 mg	28 /92 (30.43%)	
Neutrophil Count (10^3/mL)			
Increase ≥50% and >ULN	Placebo	0 /131 (0.00%)	
	MK-0966 5 mg	0 /143 (0.00%)	
	MK-0966 12.5 mg	0 /134 (0.00%)	
	MK-0966 25 mg	0 /134 (0.00%)	
	MK-0966 50 mg	0 /92 (0.00%)	
Platelet Count (10^3/mL)			
Decrease ≥25% and <LLN	Placebo	3 /132 (2.27%)	
	MK-0966 5 mg	7 /143 (4.90%)	
	MK-0966 12.5 mg	8 /134 (5.97%)	
	MK-0966 25 mg	6 /133 (4.51%)	
	MK-0966 50 mg	3 /91 (3.30%)	
Platelet Count (10^3/mL)			
Increase ≥50% and >ULN	Placebo	0 /132 (0.00%)	
	MK-0966 5 mg	0 /143 (0.00%)	
	MK-0966 12.5 mg	0 /134 (0.00%)	
	MK-0966 25 mg	0 /133 (0.00%)	
	MK-0966 50 mg	0 /91 (0.00%)	

Sponsor's tables

No dose response was observed for the predefined changes in laboratory paramenetrs from the sponsor's analyses of the hematologic parameters.

Reviewer's analysis of Selected Hematologic Adverse Events for Protocol 29

The following table summarizes the laboratory adverse events reported in study 29

Event	Placebo (n=145)	MK-0966 5 mg (n=149)	MK-0966 12.5 mg (n=144)	MK-0966 25 mg (n=137)	MK-0966 50 mg (n=97)
Anemia	0	0	0	1	0
Hematuria	0	1	0	0	1
Hemoglobin decreased	0	0	1	1	0
Leukocytes decreased	1	0	3	0	0
Neutrophils decreased	1	0	3	0	0
Platelets decreased	0	0	0	1	0

Reviewer's table from SAS transport files

Selected Laboratory Adverse Events Resulting in a Discontinuation From Trial

One patient (allocation number 2087), who received MK-0966 12.5 mg, was discontinued from the trial due to a decrease in her total leukocyte count and total neutrophil count. Her past medical history included a diagnosis of neutropenia in 1996. The patient experienced a decrease in her total leukocyte count to 3.11×10^3 and a decrease in her total neutrophil count to 1.04×10^3 on day 20 of treatment. This patient did recover her leukocyte and neutrophil count off study. No additional new medications were added on study. This patient had pre-existing leukopenia unrelated to study medication.

One patient (allocation number 4035), who received MK-0966 25 mg, experiences a mild pancytopenia while on study drug. The hemoglobin and platelet parameters are shown in the following table.

Day or date	Hemoglobin (g/dL)	Platelet count x 10^3/microL
-7	12.5	152
1	12.7	140
15	12.4	134
31	12.3	153
45 (12/19/96)	12.3	56***
12/23/96	11.9	64
12/31/96	10.9	82

Reviewer's table

***The patient was taken off drug at this time. The patient had also received a cephalosporin on day 17 because of an upper respiratory tract infection. The decrease in platelets appeared to improve after discontinuation of MK-0966.

Hemoglobin:

Several patients receiving MK-0966 experienced decreases in their hemoglobin levels while on study that were less than the pre-specified limits of change for censoring, namely $\geq$ 2 g/dL. The changes reported for these patients are shown in the following table. None of these patients had evidence of GI bleeding. The hemoglobin levels improved after discontinuation of study drug.

Hemoglobin Changes lower than the predefined limits of change (<2.0 g/dL)

Allocation Number	Dose	Day	Hemoglobin (g/dL)	Change (g/dL)
2281	MK-0966 12.5 mg	Baseline	13.4	
		4 weeks later	11.5	-1.9
2277	MK-0966 25 mg	Baseline	12.9	
		2 weeks later	11.9	-1.0
2141	MK-0966 25 mg	Baseline	11.1	
		4 weeks later	9.8	-1.3

Reviewer's table

Protocol 33
A Placebo- and Active-Comparator-Controlled, Paralled-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 and Hip

Clinical Adverse Events
No serious clinical adverse events resulted in withdrawal from a hematological standpoint.

Below is a list of selected clinical adverse events occurring during treatment or post-treatment

Selected Clinical Adverse Events for Protocol 33

Event	Placebo (n=69)	MK-0966 12.5 mg (n=219)	MK-0966 25 mg (n=227)	Ibuprofen 2400 mg (n=221)
Bruises Easily	0	0	0	1
Contusion	1	0	0	3
Epistaxis	0	0	1	1
GI bleed	0	0	0	1
Hematochezia	1	0	0	1
Hematoma	0	0	1	0
Postmenopausal bleeding	0	0	1	0
Retinal Hemorrhage	0	0	0	1
Subconjunct Hemorrhage	0	1	0	0

Reviewer's table from SAS transport files.

Selected Laboratory Adverse Events
No patient who received MK-0966 was discontinued from the study due to a laboratory adverse event.

Laboratory Adverse Events for Protocol 33

Event	Placebo (n=69)	MK-0966 12.5 mg (n=219)	MK-0966 25 mg (n=227)	Ibuprofen (n=221)
Hemoglobin decreased	1	0	7	5
Leukocytes decreased	0	0	4	0
Platelets decreased	0	0	0	0

Reviewer's table from SAS transport files

More hematologic adverse laboratory events occur with MK-0966 25 mg dose group than all other treatment groups.

Changes in Hematologic Laboratory Parameters

Sponsor's Analysis

MK-0966 Prot. No. 033
OA Placebo/Ibuprofen—U.S.

APPENDIX 4.18

4.18.3: 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		
Placebo	3 /68 (4.41%)	
12.5 mg	12 /215 (5.58%)	
25 mg	15 /225 (6.67%)	
Ibuprofen	9 /219 (4.11%)	
25 mg vs. Ibuprofen		0.295 (-1.63, 6.74)
12.5 mg vs. Ibuprofen		0.510 (-2.57, 5.51)
25 mg vs. 12.5 mg		0.694 (-3.39, 5.56)
12.5 mg vs. Placebo		>0.999 (-4.60, 6.93)
25 mg vs. Placebo		0.773 (-3.61, 8.12)
Ibuprofen vs. Placebo		>0.999 (-5.85, 5.24)
WBC count (10[3]/microL):Increase >= 20.0% and Value > ULN		
Placebo	2 /68 (2.94%)	
12.5 mg	2 /215 (0.93%)	
25 mg	1 /225 (0.44%)	
Ibuprofen	4 /219 (1.83%)	
25 mg vs. Ibuprofen		0.210 (-3.36, 0.59)
12.5 mg vs. Ibuprofen		0.685 (-3.09, 1.29)
25 mg vs. 12.5 mg		0.616 (-2.04, 1.06)
12.5 mg vs. Placebo		0.245 (-6.23, 2.20)
25 mg vs. Placebo		0.136 (-6.61, 1.61)
Ibuprofen vs. Placebo		0.630 (-5.50, 3.28)
hematocrit (%):Decrease >= 6.0		
Placebo	2 /68 (2.94%)	
12.5 mg	2 /215 (0.93%)	
25 mg	3 /225 (1.33%)	
Ibuprofen	11 /219 (5.02%)	
25 mg vs. Ibuprofen		*0.030* (-6.95, -0.43)
12.5 mg vs. Ibuprofen		0.021 (-7.26, -0.93)
25 mg vs. 12.5 mg		>0.999 (-1.57, 2.38)
12.5 mg vs. Placebo		0.245 (-6.23, 2.20)
25 mg vs. Placebo		0.329 (-5.89, 2.68)
Ibuprofen vs. Placebo		0.740 (-2.87, 7.03)

MK-0966 Prot. No. 033
OA Placebo/Ibuprofen—U.S.

APPENDIX 4.18

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

Treatment	Number/Total (%)	Pairwise Comparison p-Value and 95% CI for Difference in Percentages
hematocrit (%):Increase >= 20.0% and Value > ULN		
Placebo	0 /68 (0.00%)	
12.5 mg	0 /215 (0.00%)	
25 mg	0 /225 (0.00%)	
Ibuprofen	0 /219 (0.00%)	
25 mg vs. Ibuprofen		>0.999 (0.00, 0.00)
12.5 mg vs. Ibuprofen		>0.999 (0.00, 0.00)
25 mg vs. 12.5 mg		>0.999 (0.00, 0.00)
12.5 mg vs. Placebo		>0.999 (0.00, 0.00)
25 mg vs. Placebo		>0.999 (0.00, 0.00)
Ibuprofen vs. Placebo		>0.999 (0.00, 0.00)
hemoglobin (gm/dL):Decrease >= 2.0		
Placebo	1 /68 (1.47%)	
12.5 mg	0 /215 (0.00%)	
25 mg	3 /225 (1.33%)	
Ibuprofen	5 /219 (2.28%)	
25 mg vs. Ibuprofen		0.499 (-3.43, 1.53)
12.5 mg vs. Ibuprofen		0.061 (-4.26, -0.30)
25 mg vs. 12.5 mg		0.249 (-0.17, 2.83)
12.5 mg vs. Placebo		0.240 (-4.33, 1.39)
25 mg vs. Placebo		>0.999 (-3.37, 3.09)
Ibuprofen vs. Placebo		>0.999 (-2.67, 4.29)
hemoglobin (gm/dL):Increase >= 20.0% and Value > ULN		
Placebo	0 /68 (0.00%)	
12.5 mg	0 /215 (0.00%)	
25 mg	0 /225 (0.00%)	
Ibuprofen	0 /219 (0.00%)	
25 mg vs. Ibuprofen		>0.999 (0.00, 0.00)
12.5 mg vs. Ibuprofen		>0.999 (0.00, 0.00)
25 mg vs. 12.5 mg		>0.999 (0.00, 0.00)
12.5 mg vs. Placebo		>0.999 (0.00, 0.00)
25 mg vs. Placebo		>0.999 (0.00, 0.00)
Ibuprofen vs. Placebo		>0.999 (0.00, 0.00)

MK-0966 Prot. No. 033
OA Placebo/Ibuprofen—U.S.

APPENDIX 4.18

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

Treatment	Number/Total (%)	Pairwise Comparison p-Value and 95% CI for Difference in Percentages
lymphocyte count (10[3]/microL):Decrease >= 20.0% and Value < LLN		
Placebo	5 /67 (7.46%)	
12.5 mg	14 /214 (6.54%)	
25 mg	19 /224 (8.48%)	
Ibuprofen	16 /214 (7.48%)	
25 mg vs. Ibuprofen		0.728 (-4.07, 6.08)
12.5 mg vs. Ibuprofen		0.850 (-5.77, 3.90)
25 mg vs. 12.5 mg		0.474 (-2.99, 6.87)
12.5 mg vs. Placebo		0.783 (-8.03, 6.19)
25 mg vs. Placebo		>0.999 (-6.25, 8.29)
Ibuprofen vs. Placebo		>0.999 (-7.20, 7.23)
lymphocyte count (10[3]/microL):Increase >= 50.0% and Value > ULN		
Placebo	0 /67 (0.00%)	
12.5 mg	0 /214 (0.00%)	
25 mg	0 /224 (0.00%)	
Ibuprofen	0 /214 (0.00%)	
25 mg vs. Ibuprofen		>0.999 (0.00, 0.00)
12.5 mg vs. Ibuprofen		>0.999 (0.00, 0.00)
25 mg vs. 12.5 mg		>0.999 (0.00, 0.00)
12.5 mg vs. Placebo		>0.999 (0.00, 0.00)
25 mg vs. Placebo		>0.999 (0.00, 0.00)
Ibuprofen vs. Placebo		>0.999 (0.00, 0.00)
neutrophil count (10[3]/microL):Decrease >= 20.0% and Value < LLN		
Placebo	0 /67 (0.00%)	
12.5 mg	0 /214 (0.00%)	
25 mg	4 /224 (1.79%)	
Ibuprofen	2 /214 (0.93%)	
25 mg vs. Ibuprofen		0.686 (-1.31, 3.01)
12.5 mg vs. Ibuprofen		0.499 (-2.22, 0.35)
25 mg vs. 12.5 mg		0.124 (0.05, 3.52)
12.5 mg vs. Placebo		>0.999 (0.00, 0.00)
25 mg vs. Placebo		0.577 (0.05, 3.52)
Ibuprofen vs. Placebo		>0.999 (-0.35, 2.22)

MK-0966 Prot. No. 033
OA Placebo/Ibuprofen—U.S.

APPENDIX 4.18

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

Treatment	Number/Total (%)	Pairwise Comparison p-Value and 95% CI for Difference in Percentages
neutrophil count (10[3]/microL):Increase >= 50.0% and Value > ULN		
Placebo	2 /67 (2.99%)	
12.5 mg	2 /214 (0.93%)	
25 mg	3 /224 (1.34%)	
Ibuprofen	2 /214 (0.93%)	
25 mg vs. Ibuprofen		>0.999 (-1.58, 2.39)
12.5 mg vs. Ibuprofen		>0.999 (-1.82, 1.82)
25 mg vs. 12.5 mg		>0.999 (-1.58, 2.39)
12.5 mg vs. Placebo		0.242 (-6.32, 2.22)
25 mg vs. Placebo		0.325 (-5.99, 2.70)
Ibuprofen vs. Placebo		0.242 (-6.32, 2.22)
platelet count (10[3]/microL):Decrease >= 25.0% and Value < LLN		
Placebo	1 /68 (1.47%)	
12.5 mg	1 /214 (0.47%)	
25 mg	3 /224 (1.34%)	
Ibuprofen	0 /218 (0.00%)	
25 mg vs. Ibuprofen		0.248 (-0.17, 2.84)
12.5 mg vs. Ibuprofen		0.495 (-0.45, 1.38)
25 mg vs. 12.5 mg		0.624 (-0.89, 2.63)
12.5 mg vs. Placebo		0.425 (-4.01, 2.00)
25 mg vs. Placebo		>0.999 (-3.36, 3.10)
Ibuprofen vs. Placebo		0.238 (-4.33, 1.39)
platelet count (10[3]/microL):Increase >= 50.0% and Value > ULN		
Placebo	0 /68 (0.00%)	
12.5 mg	0 /214 (0.00%)	
25 mg	0 /224 (0.00%)	
Ibuprofen	0 /218 (0.00%)	
25 mg vs. Ibuprofen		>0.999 (0.00, 0.00)
12.5 mg vs. Ibuprofen		>0.999 (0.00, 0.00)
25 mg vs. 12.5 mg		>0.999 (0.00, 0.00)
12.5 mg vs. Placebo		>0.999 (0.00, 0.00)
25 mg vs. Placebo		>0.999 (0.00, 0.00)
Ibuprofen vs. Placebo		>0.999 (0.00, 0.00)

Sponsor's tables

Using the Predefined Limits of Change Analysis, the MK-0966 treatment groups suggested a greater percentage of patients with a decrease in total white blood cell count compared to ibuprofen and placebo. The hemoglobin change was similat to placebo or Ibuprofen. The changes in platelet counts were similar to placebo.

Some patients experienced unexplained decrease in hemoglobin values of less than 2.0 g/dL over time on study with no evidence of bleeding. The changes in hemoglobin levels for two patients are shown below.

Selected Changes In Hemoglobin Over the Study for Protocol 33

Allocation Number	Dose	Day	Hemoglobin (g/dL)	Change (g/dL)
6815	MK-0966 25 mg	Baseline	14.6	
		6 weeks later	13.3	-1.3
6472	MK-0966 25 mg	Baseline	11.5	
		6 weeks later	10.1	-1.4

Reviewer's table

Leukocytes

Two patients treated with MK-0966 25 mg experienced intermittent decrease in white blood cell during the course of the study (patient allocation numbers 6815 and 7045). Their lowest total white blood cell counts were 3.2×10^3 (7045) and 3.6×10^3 (6815).

Platelets

No sustained platelet count abnormalities were reported in any treatment group.

Protocols 34, 34-02, and 34-10

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

Protocol 34 includes the first six months of therapy and the other two protocols, 34-02 and 34-10, include the later six month extensions of the trial. Patients only entered the extension portion of the trial if they did not experience either a clinical or laboratory adverse event during the first part of the study.

First six months of study

Clinical Adverse Events

Two patients were discontinued from the trial for adverse hematological clinical events. The patients are listed below, both patients received 12.5 mg MK-0966.

Clinical Adverse Events Resulting in a Discontinuation of Trial

Allocation Number	Adverse Event	Day of Onset	Duration of Adverse event (days)	Intensity
5307	GI bleed	85	3	Mild
5221	Melena	62	4	Moderate

Reviewer's table

Other clinical events not resulting in discontinuation of treatment that were reported during treatment or post-treatment are shown in the following table.

Clinical Adverse Events for the first six months for Protocol 34

Event	MK-0966 12.5 mg (n=231)	MK-0966 25 mg (n=232)	Diclofenac (n=230)
Black Stool	0	1	0
Bleeding hemorrhoid	1	0	0
Bloody diarrhea/occult blood/melena	3	0	1
Contusion/ Hematoma	6	2	1
Gastritis	3	1	1
GI bleed/ rectal bleed	2	0	2
Hematochezia	1	1	1
Hemolytic anemia	1*	0	0
Post-menopausal bleeding	1	0	0
Retinal hemorrhage	1	0	0
Subconjunctival hemorrhage	0	1	0
Subdural hematoma	2	0	0

Reviewer's table from SAS transport files

*This patient (allocation number 5392) had a hemoglobin level of 11.2 g/dL with elevated serum LDH of 429 mg/dL and reduced haptoglobin to 12mg/mL on day 164. The patient was on additional medication known to be associated with the development of hemolytic anemia. The patient continued on study and entered the extension portion of this trial. No further episodes of hemolysis were reported.

Laboratory Adverse Events

No patient was discontinued for an adverse hematological laboratory event.

Changes in Hematologic Laboratory Parameters

Sponsor's Analysis
MK-0966 Prot. No. 034
Diclofenac OA Study—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 Proportions
WBC Count (10^3/microL):Decrease ≥20.0% and Value < LLN		
12.5 mg	32 /229 (13.97%)	
25 mg	38 /229 (16.59%)	
Diclofenac	26 /229 (11.35%)	
12.5 mg vs. Diclofenac		0.483 (-3.47, 8.71)
25 mg vs. Diclofenac		0.138 (-1.09, 11.57)
25 mg vs. 12.5 mg		0.516 (-3.97, 9.21)
WBC count (10^3/microL):Increase ≥20.0% and Value > ULN		
12.5 mg	6 /229 (2.62%)	
25 mg	10 /229 (4.37%)	
Diclofenac	8 /229 (3.49%)	
12.5 mg vs. Diclofenac		0.787 (-4.03, 2.28)
25 mg vs. Diclofenac		0.811 (-2.68, 4.43)
25 mg vs. 12.5 mg		0.446 (-1.61, 5.11)
Hematocrit (%):Decrease ≥6.0		
12.5 mg	2 /229 (0.87%)	
25 mg	3 /229 (1.31%)	
Diclofenac	7 /229 (3.06%)	
12.5 mg vs. Diclofenac		0.175 (-4.72, 0.35)
25 mg vs. Diclofenac		0.338 (-4.42, 0.93)
25 mg vs. 12.5 mg		>0.999 (-1.47, 2.34)
Hematocrit (%):Increase ≥20.0% and Value > ULN		
12.5 mg	0 /229 (0.00%)	
25 mg	0 /229 (0.00%)	
Diclofenac	0 /229 (0.00%)	
12.5 mg vs. Diclofenac		>0.999 (0.00, 0.00)
25 mg vs. Diclofenac		>0.999 (0.00, 0.00)
25 mg vs. 12.5 mg		>0.999 (0.00, 0.00)

MK-0966 Prot. No. 034
Diclofenac OA Study—Multinational

APPENDIX 4.19

4.19.2: 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 (gm/dL):Decrease ≥2.0		
12.5 mg	1 /229 (0.44%)	
25 mg	2 /229 (0.87%)	
Diclofenac	11 /229 (4.80%)	
12.5 mg vs. Diclofenac		0.006 (-7.27, -1.47)
25 mg vs. Diclofenac		0.021 (-6.95, -0.91)
25 mg vs. 12.5 mg		>0.999 (-1.04, 1.91)
Hemoglobin (gm/dL):Increase ≥20.0% and Value > ULN		
12.5 mg	0 /229 (0.00%)	
25 mg	0 /229 (0.00%)	
Diclofenac	0 /229 (0.00%)	
12.5 mg vs. Diclofenac		>0.999 (0.00, 0.00)
25 mg vs. Diclofenac		>0.999 (0.00, 0.00)
25 mg vs. 12.5 mg		>0.999 (0.00, 0.00)
Lymphocyte Count (10^3/microL):Decrease ≥20.0% and Value < LLN		
12.5 mg	26 /225 (11.56%)	
25 mg	32 /228 (14.04%)	
Diclofenac	26 /224 (11.61%)	
12.5 mg vs. Diclofenac		>0.999 (-5.97, 5.87)
25 mg vs. Diclofenac		0.483 (-3.73, 8.59)
25 mg vs. 12.5 mg		0.483 (-3.67, 8.63)
Lymphocyte Count (10^3/microL):Increase ≥50.0% and Value > ULN		
12.5 mg	1 /225 (0.44%)	
25 mg	0 /228 (0.00%)	
Diclofenac	1 /224 (0.45%)	
12.5 mg vs. Diclofenac		>0.999 (-1.23, 1.23)
25 mg vs. Diclofenac		0.496 (-1.32, 0.43)
25 mg vs. 12.5 mg		0.497 (-1.31, 0.42)

APPENDIX 4.19

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

Treatment	Number/Total (%)	Pairwise Comparison p-Value and 95% CI for Difference in Proportions
Neutrophil count (10^3/microL):Decrease ≥20.0% and Value < LLN		
12.5 mg	9 /225 (4.00%)	
25 mg	6 /228 (2.63%)	
Diclofenac	5 /224 (2.23%)	
12.5 mg vs. Diclofenac		0.416 (-1.44, 4.98)
25 mg vs. Diclofenac		>0.999 (-2.44, 3.24)
25 mg vs. 12.5 mg		0.444 (-4.67, 1.93)
Neutrophil Count (10^3/microL):Increase ≥50.0% and Value > ULN		
12.5 mg	8 /225 (3.56%)	
25 mg	8 /228 (3.51%)	
Diclofenac	9 /224 (4.02%)	
12.5 mg vs. Diclofenac		0.811 (-3.99, 3.07)
25 mg vs. Diclofenac		0.810 (-4.02, 3.00)
25 mg vs. 12.5 mg		>0.999 (-3.45, 3.35)
Platelet Count (10^3/microL):Decrease ≥25.0% and Value < LLN		
12.5 mg	6 /229 (2.62%)	
25 mg	7 /229 (3.06%)	
Diclofenac	9 /229 (3.93%)	
12.5 mg vs. Diclofenac		0.601 (-4.57, 1.95)
25 mg vs. Diclofenac		0.800 (-4.24, 2.49)
25 mg vs. 12.5 mg		>0.999 (-2.60, 3.48)
Platelet Count (10^3/microL):Increase ≥50.0% and Value > ULN		
12.5 mg	0 /229 (0.00%)	
25 mg	1 /229 (0.44%)	
Diclofenac	1 /229 (0.44%)	
12.5 mg vs. Diclofenac		>0.999 (-1.29, 0.42)
25 mg vs. Diclofenac		>0.999 (-1.21, 1.21)
25 mg vs. 12.5 mg		>0.999 (-0.42, 1.29)

Sponsor's table

A greater percentage of patients in the MK-0966 treatment groups experienced a decrease in total white blood cell, neutrophil, and lymphocyte counts compared to Diclofenac.

Selected abnormalities of hematologic parameters

Hemoglobin

Two patients experienced a sustained drop in hemoglobin greater than 1 g/dL over the course of the study without evidence of blood loss. Patient 5377 was diagnosed with breast carcinoma on study day 24.

Representative Sampling of Changes in Hemoglobin for Protocol 34