APPENDIX 4.17.1 (CONT.)

Patients Exceeding the Predefined Limits of Change Up to Week 18
Blood Chemistry and Hematology
Intention-to-Treat

Laboratory Test	Predefined Limit of Change	Treatment	Number†/ Total‡
Hematocrit (%)	Decrease ≥6.0	Placebo	2/184
		MK-0966 25 mg	12/187
		MK-0966 50 mg	20/182
		Ibuprofen 2400 mg	18/183
	Increase ≥20.0% and value >ULN	Placebo	0/184
		MK-0966 25 mg	1/187
		MK-0966 50 mg	0/182
		Ibuprofen 2400 mg	1/183
Hemoglobin (gm/dL)	Decrease ≥2.0	Placebo	1/184
		MK-0966 25 mg	6/187
		MK-0966 50 mg	11/182
		Ibuprofen 2400 mg	13/183
	Increase ≥20.0% and value >ULN	Placebo	0/184
		MK-0966 25 mg	0/187
		MK-0966 50 mg	0/182
		Ibuprofen 2400 mg	1/183

WBC count (10(3)/microl)	Decrease ≥20.0% and value <LLN	Placebo	16/184
		MK-0966 25 mg	28/187
		MK-0966 50 mg	26/182
		Ibuprofen 2400 mg	13/183
	Increase ≥20.0% and value >ULN	Placebo	4/184
		MK-0966 25 mg	3/187
		MK-0966 50 mg	8/182
		Ibuprofen 2400 mg	5/183

Patients Exceeding the Predefined Limits of Change Up to Week 18
Blood Chemistry and Hematology
Intention-to-Treat

Laboratory Test	Predefined Limit of Change	Treatment	Number†/ Total‡
Lymphocyte count (10(3)/microl)	Decrease ≥20.0% and value <LLN	Placebo	18/182
		MK-0966 25 mg	34/186
		MK-0966 50 mg	24/176
		Ibuprofen 2400 mg	21/181
	Increase ≥50.0% and value >ULN	Placebo	0/182
		MK-0966 25 mg	0/186
		MK-0966 50 mg	0/176
		Ibuprofen 2400 mg	0/181
Neutrophil count (10(3)/microl)	Decrease ≥20.0% and value <LLN	Placebo	8/182
		MK-0966 25 mg	5/186
		MK-0966 50 mg	4/176
		Ibuprofen 2400 mg	3/181
	Increase ≥50.0% and value >ULN	Placebo	5/182
		MK-0966 25 mg	2/186
		MK-0966 50 mg	8/176
		Ibuprofen 2400 mg	4/181

Patients Exceeding the Predefined Limits of Change Up to Week 18
Blood Chemistry and Hematology
Intention-to-Treat

Laboratory Test	Predefined Limit of Change	Treatment	Number†/ Total‡
Platelet count (10(3)/microl)	Decrease ≥25.0% and value <LLN	Placebo	4/184
		MK-0966 25 mg	1/187
		MK-0966 50 mg	10/182
		Ibuprofen 2400 mg	3/183
	Increase ≥50.0% and value >ULN	Placebo	0/184
		MK-0966 25 mg	1/187
		MK-0966 50 mg	1/182
		Ibuprofen 2400 mg	1/183

Sponsor's table

Sponsor's Analysis suggests that MK-0966 50 mg treatment group experienced a greater number of patients/percentage of patients had a decrease in hemoglobin and platelet counts compared to the 25 mg treatment group. Treatment with MK-0966 resulted in a greater number and percentage of patients experiencing a decrease in total white blood cell count and lymphocyte count compared to ibuprofen.

Selected Laboratory Adverse Events for Protocol 45

Event	Placebo (n=194)	MK-0966 25 mg (n=195)	MK-0966 50 mg (n=193)	Ibuprofen (n=193)
Hemoglobin	1	23	50	39

decreased				
Leukocytes decreased	7	11	10	7
Leukocytes increased**	1	5	1	2
Leukopenia	4	1	4	1
Lymphocytes decreased	0	1	1	0
Lymphocytopenia	0	1	0	0
Neutrophils increased	0	1	1	0
Partial Thromboplastin time increased	0	1	1	0
Platelets decreased	5	1	3	0

Reviewer's table form SAS transport files
** These increases were transient and not sustained.

More patients on the higher dose (50 mg) MK-0966 experienced a decrease in hemoglobin than the patients treated with the lower dose (25 mg) or Ibuprofen.

Hemoglobin

MK-0966 25 mg

Allocation number	Predose hemoglobin (g/dL)	Lowest hemoglobin (g/dL)	Day of lowest hemoglobin	Hemoglobin off study (g/dL)	Day of hemoglobin off study
536			76		105
549			141		182
20			144		170
38			171		185
15			172		185

Reviewer's table

Only one patient was found to have hemoccult positive stool to account for the observed drop in hemoglobin.

MK-0966 50 mg

Allocation number	Predose hemoglobin (g/dL)	Lowest hemoglobin (g/dL)	Day of lowest hemoglobin	Hemoglobin off study (g/dL)	Day of hemoglobin off study
635			71		101
190			160		181
204			89		10.8
573			85		181
531			148		184
544			92		184
238			22		183

Reviewer's table

Only patient 204 was found to have evidence of GI bleeding.

Leukocytes

Patient 536 experienced low leukocyte counts over the course of the trial. She had three WBC below 4 x 10^3/microL but none below 3.3 x 10^3/microL.

Patient 653 experiences low leukocyte counts to lowest levels of 3.1 x 10^3/microL throughout the course of the study. Review of her laboratory data however indicates that her baseline count was is 3.7 to 4.2 x 10^3/microL. .

Patient 188 experienced a low leukocyte count throughout most of the study however baseline values were not available.

Patient (allocation number 243) experienced a decrease in her leukocyte count throughout the course of the study. Although she was on multiple other medications, the improvement off MK-0966 suggests a positive dechallenge.

Patient 243.

Day	Leukocyte Count x 10^3/microL
-14	
2 (pretreatment)	
22	
45	
64	
85	
113	
141	
169	
181 ** off-study	

Platelets

Patient 827 experienced a significant drop in her platelet count and spontaneous improvement. The etiology of this patient's thrombocytopenia is unclear.

Patient 827

Day	Platelet count x 10^3/microL
-13	
1	
44	
65	
87	
113	
149	
173	
187	

An Active-Comparator- and Placebo-Controlled, Parallel-Group, 6-Week, Double-Blind Study Conducted Under In-House Blinding, to Assess the Efficacy, Safety, and Tolerability of MK-0966 in Patients Aged 80 and Over With Osteoarthritis of the Knee or Hip Extension

Clinical Adverse Events

In the MK 25 mg group, one patient (allocation number 1635) was taken off study for occult GI bleeding on day 33 and one patient (allocation number 1258) was taken off study for diverticulosis with GI bleed on day 86.

In the MK 12.5 mg group, one patient (allocation number 1021) was taken off study for a nose bleed on day 8.

Selected Clinical Adverse Events for Protocol 58

Event	Placebo (n=52)	MK-0966 12.5 mg (n=118)	MK-0966 25 mg (n=56)	Nabumetone (n=115)
Anemia	0	0	1	0
Bleeding Hemorrhoid	0	1	0	0
Contusion	0	1	0	4
Ecchymosis	0	1	0	0
Epistaxis	0	1	0	1
GI bleeding/rectal bleeding	0	0	1	1
Hematochezia	0	0	0	1
Subconjunctival Hemorrhage	0	0	0	1

Reviewer's table from SAS transport files

Changes in Hematologic Laboratory Parameters

Sponsor's Analysis

Appendix 4.34.2
Patients Exceeding the Predefined Limits of Change: Laboratory
(Intention-to-Treat Approach)
Base Study

Laboratory Test	Predefined Limit of Change	Treatment	Number[1]/ Total[2] (%)	
WBC count (10(3)/microL)	Decrease ≥20.0% and Value <LLN	Placebo	4/52	(7.7)
		MK-0966 12.5 mg	4/118	(3.4)
		MK-0966 25 mg	2/54	(3.7)
		Nabumetone 1500 mg	9/114	(7.9)
	Increase ≥20.0% and Value >ULN	Placebo	3/52	(5.8)
		MK-0966 12.5 mg	4/118	(3.4)
		MK-0966 25 mg	2/54	(3.7)
		Nabumetone 1500 mg	0/114	(0.0)
Hematocrit (%)	Decrease ≥6.0	Placebo	0/52	(0.0)
		MK-0966 12.5 mg	0/118	(0.0)
		MK-0966 25 mg	0/54	(0.0)
		Nabumetone 1500 mg	0/114	(0.0)
	Increase ≥20.0% and Value > ULN	Placebo	0/52	(0.0)
		MK-0966 12.5 mg	0/118	(0.0)
		MK-0966 25 mg	0/54	(0.0)
		Nabumetone 1500 mg	0/114	(0.0)
Hemoglobin (gm/dL)	Decrease ≥2.0	Placebo	0/52	(0.0)
		MK-0966 12.5 mg	1/118	(0.8)
		MK-0966 25 mg	0/54	(0.0)
		Nabumetone 1500 mg	0/114	(0.0)
	Increase ≥20.0% and Value > ULN	Placebo	0/52	(0.0)
		MK-0966 12.5 mg	0/118	(0.0)
		MK-0966 25 mg	0/54	(0.0)
		Nabumetone 1500 mg	0/114	(0.0)
Lymphocyte count (10(3)/microL)	Decrease ≥20.0% and Value < LLN	Placebo	3/47	(6.4)
		MK-0966 12.5 mg	14/114	(12.3)
		MK-0966 25 mg	11/53	(20.8)
		Nabumetone 1500 mg	16/111	(14.4)
	Increase ≥50.0% and Value > ULN	Placebo	0/47	(0.0)
		MK-0966 12.5 mg	0/114	(0.0)
		MK-0966 25 mg	0/53	(0.0)
		Nabumetone 1500 mg	0/111	(0.0)
Neutrophil count (10(3)/microL)	Decrease ≥20.0% and Value < LLN	Placebo	1/47	(2.1)
		MK-0966 12.5 mg	0/114	(0.0)
		MK-0966 25 mg	0/53	(0.0)
		Nabumetone 1500 mg	0/111	(0.0)

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Appendix 4.34 .2 (Cont.)
Patients Exceeding the Predefined Limits of Change: Laboratory
(Intention-to-Treat Approach)
Base Study

Laboratory Test	Predefined Limit of Change	Treatment	Number[1]/ Total[2] (%)
Neutrophil count (10(3)/microL) (Cont.)	Increase ≥50.0% and Value > ULN	Placebo	1/47 (2.1)
		MK-0966 12.5 mg	2/114 (1.8)
		MK-0966 25 mg	1/53 (1.9)
		Nabumetone 1500 mg	3/111 (2.7)
Platelet count (10(3)/microL)	Decrease ≥25.0% and Value < LLN	Placebo	0/52 (0.0)
		MK-0966 12.5 mg	4/118 (3.4)
		MK-0966 25 mg	1/54 (1.9)
		Nabumetone 1500 mg	3/114 (2.6)
	Increase ≥50.0% and Value > ULN	Placebo	0/52 (0.0)
		MK-0966 12.5 mg	0/118 (0.0)
		MK-0966 25 mg	0/54 (0.0)
		Nabumetone 1500 mg	0/114 (0.0)

Sponsor's tables

In the Sponsor's Analysis treatment suggests that treatment with MK-0966 results in a greater percentage of patients experiencing a decrease in lymphocyte counts and platelet counts compared to Nabumetone or placebo.

Selected Laboratory Adverse Events
No patient discontinued from the trial for a hematologic laboratory parameter.

Laboratory Adverse Events for Protocol 58

Event	Placebo (n=52)	MK-0966 12.5 mg (n=118)	MK-0966 25 mg (n=56)	Nabumetone
Hemoglobin decreased	0	1	5	0
Leukocytes decreased	0	3	0	1
Platelets	0	5	1	1

Reviewer's table form SAS transport files

Hemoglobin
Below is a representative sampling of patients having decreases in hemoglobin while on study.

Changes in Hemoglobin Over the Study

Allocation number	Predose hemoglobin (g/dL)	Lowest hemoglobin (g/dL)	Day of lowest hemoglobin
1737			
1175			
1736*			

Reviewer's table
* This patient received MK-0966 12.5 mg, all others received MK-0966 25 mg.

Leukocytes

Patient 1345 experienced several low leukocyte counts over time on study to the lowest value of 3.1 x 10^3/microL and 3.7 x 10^3/microL. Causality to study drug is difficult to determine due to lack of baseline value.

Platelets

Patient 1013 experienced the following decrease in platelet count over the course of the study. The patient was not placed on any new medications during the trial.

Patient 1013

Day	Platelet count x 10^3/microL
-8	
1	
8	
15	
44	

The patient had an abnormal baseline platelet count which decreased further during study. This patient continues in the extension portion of the trial with this same pattern. (See this patient's results for Protocol 58-10.)

Protocol 58-10

An Active-Comparator- and Placebo-Controlled, Parallel-Group, 6-Week, Double-Blind Study Conducted Under In-House Blinding, to Assess the Efficacy, Safety, and Tolerability of MK-0966 in Patients Aged 80 and Over With Osteoarthritis of the Knee or Hip Extension

This is an extension trial for Protocol 58.

Clinical Adverse Events

One patient (allocation number 1258) was discontinued from the trial after an adverse clinical event on MK25 mg. This patient experiences a diverticular bleed on Day 86.

Selected Clinical Adverse Events for Protocol 58-10

Event	MK-0966 12.5 mg (n=91)	MK-0966 25 mg (n=47)	Nabumetone (n=85)
Anemia	0	0	1
Contusion	3	0	0
Diverticular Bleed	0	1	0
Epistaxis	0	1	0
Hematochezia	1	0	0
Purpura senilis	1	0	0
Subconjunctival Bleed	0	1	0

Reviewer's table from SAS transport files

A greater percentage/ number of events are seen in the MK-0966 treatment groups.

Changes in Hematologic Laboratory Parameters

Sponsor's Analysis

Appendix 4.35.2
Patients Exceeding the Predefined Limits of Change
Laboratory Tests
(Intention-to-Treat Approach)
First Extension

Laboratory Test	Predefined Limit of Change	Treatment	Number[1]/ Total (%)[2]
WBC count (10^3/microL)	Decrease ≥20.0% and value <LLN	12.5 mg MK-0966	4/91 (4.4)
		25 mg MK-0966	3/47 (6.4)
		Nabumetone 1500 mg	6/85 (7.1)
Hematocrit (%)	Decrease ≥6.0	12.5 mg MK-0966	3/91 (3.3)
		25 mg MK-0966	1/47 (2.1)
		Nabumetone 1500 mg	1/85 (1.2)
Hemoglobin (gm/dL)	Decrease ≥2.0	12.5 mg MK-0966	3/91 (3.3)
		25 mg MK-0966	1/47 (2.1)
		Nabumetone 1500 mg	1/85 (1.2)
Lymphocyte count (10^3/microL)	Decrease ≥20.0% and value <LLN	12.5 mg MK-0966	8/84 (9.5)
		25 mg MK-0966	7/46 (15.2)
		Nabumetone 1500 mg	10/79 (12.7)
Neutrophil count (10^3/microL)	Decrease ≥20.0% and value <LLN	12.5 mg MK-0966	0/84 (0.0)
		25 mg MK-0966	0/46 (0.0)
		Nabumetone 1500 mg	0/79 (0.0)
Platelet count (10^3/microL)	Decrease ≥25.0% and value <LLN	12.5 mg MK-0966	1/91 (1.1)
		25 mg MK-0966	0/47 (0.0)
		Nabumetone 1500 mg	4/85 (4.7)

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

4.35.2 Patients Exceeding the Predefined Limits of Change
Laboratory Tests
(Intention-to-Treat Approach)
Extension

Laboratory Test	Predefined Limit of Change	Treatment	Number[1]/ Total (%)[2]
Platelet count (10^3/microL)	Decrease ≥25.0% and value <LLN	MK-0966 12.5 mg	1/91 (1.1)
		MK-0966 25 mg	0/47 (0.0)
		Nabumetone 1500 mg	4/85 (4.7)
	Increase≥50.0% and value >ULN	MK-0966 12.5 mg	0/91 (0.0)
		MK-0966 25 mg	0/47 (0.0)
		Nabumetone 1500 mg	0/85 (0.0)

Sponsor's table

Sponsor's Analysis suggests a greater percentage of MK-0966 patients experienced a decrease in hemoglobin over the course of the extension.

Discontinuation due to abnormal Hematologic Parameters

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

Selected Laboratory Adverse Events for Protocol 58-10

Event	MK-0966 12.5 mg (n=91)	MK-0966 25 mg (n=47)	Nabumetone (n=85)
Hemoglobin decreased	0	5	0
Leukocytes decreased	1	3	0
Platelets decreased	4	1	0

Reviewer's table from SAS transport files
A greater number of events are seen in the MK-0966 treatment groups.

Hemoglobin
Three patients experienced a decrease in hemoglobin over the course of the trial.

Patient 1737

Day	Hemoglobin (g/dL)
-7	
45	
64	
84	
98	
105	

Patient 1014 .

Day	Hemoglobin (g/dL)
-7	
15	
50	
57	
64	
85	
127	

Patient 1507.

Day	Hemoglobin (g/dL)
-7	
1	
50	
64	
87	
129	

Platelets
Patient 1013 experienced low platelets in the first part of the trial fails and remained thrombocytopenic during the extension part of the study.

Patient 1013

Day	Platelet count x 10^3/microL
52	
65	
85	
128	
168	
211	

Patient 1073 experienced a decrease in platelets over the course of the extension trial. The patient was not started on any new medications during the trial.

Patient 1073.

Day	Platelet count x 10^3/microL
49	
64	
83	
127	
169	

Conclusions

Phase I Data

MK-0966 appeared to exert a primarily selective COX-2 inhibitory effect. Tests of platelet function (serum and urine TXB_2, platelet aggregation, and bleeding time) from protocols 002, 005, 0061, and 0063 did not appear to be affected by the administration of MK-0966. Howevwe, there were suggestions from individual and pooled data that there may be some individual inhibition of COX-1 activity.

Healthy volunteers in two multiple dose trials experienced a drop in hemoglobin from predose levels with the majority experiencing less than a 2g/dL change. The drop in hemoglobin in these volunteers could not be attributed to GI blood loss. The isolated reduction in hemoglobin and hematocrit and its occurrence following short periods of drug administration seem to rule out marrow suppression. Aside from occult blood loss, hemodilution and blood sampling may account for the hemoglobin changes seen in normal volunteers.
No further conclusions could be drawn for any of the other hematological parameters because of study design and limited patient population.

Phase III Data

No trend for decreased safety or increase in major bleeding events with MK-0966 was observed for the adverse events reported in the clinical trials.

No hematological adverse events were reported that were clinically relevant. No patient was withdrawn due to clinical adverse events, however three patients were discontinued from the study due to decreases in white blood cell and platelets. It must be noted, however, that the safety assessment of the NDA database in terms of laboratory parameters is significantly limited by the censoring of the data. Individual patient data had to achieve a certain threshold of change prior to being recognized as a laboratory adverse event.

Platelet Count
Fourteen patients experienced a drop in platelets that was not self-limited or followed by spontaneous recovery.

One patient (allocation number 4035/protocol 29) was discontinued from the trial because of a marked thrombocytopenia (platelet count of 56 x 10^3/microL). His platelet counts improved off MK-0966. No explanation or other known etiology (e.g. medication effect) can be found as the cause of the decrease in the platelet count.

Three patients experience a mild decrease in platelet counts during the trial and did not demonstrate recovery within the study or post-study. Review of their medication, prior medical conditions, and on treatment diagnoses did not provide another etiology for the observed drop. These patients are listed below.

Protocol number	Allocation number	Lowest Platelet count
34	5332	
35	7963	
58	1073	

Reviewer's table

Three additional patients experienced a decrease in platelet counts. Review of their medications, medical history and on treatment medical problems provided other possible causes for the observed decline.

Other patients experienced intermittent decreases in their platelet counts. No further interpretation can be drawn from the data presented.

The number of patients with unexplained decreases in platelet counts is small and the etiology of the decrease remains unexplained.

Leukocytes
All elevations of leukocyte count during the trials were transient and usually reflected an infectious etiology.

Twenty-two patients experienced a decrease in leukocyte or neutrophil counts during the study that was not self-limited or followed by spontaneous recovery.

Two patients were taken off drug because of a decrease in leukocyte counts during the trial. Both of these patients had other possible causes for the leukopenia.

Two patients experienced a sustained decrease in their leukocyte counts. Review of their medication, prior medical conditions, and on treatment diagnoses do not provide another etiology for the observed drop. These patients are listed below.

Protocol number	Allocation number	Lowest leukocyte count
35	8217	
45	243	

Reviewer's table

One patient (allocation number 5589/protocol 34) was on another medication known to be associated with depression of leukocyte count.

All other patients had either an intermittent pattern of decrease or other confounding issues such as a low leukocyte count at baseline. No further conclusions could be drawn from their data.

The number of patients with unexplained decreases in leukocyte counts is small and the etiology of such decrease remains unclear.

Hemoglobin

Although a small number of patients on trial experienced a decline in hemoglobin on trial, this effect may not be fully appreciated because of the predefined limits of change required for the censoring of data. The specified protocol analysis for hemoglobin only flagged those patients whose change in hemoglobin levels was greater than 2 g/dL. The clinical significance of a cut-off of 2 g/dL depends on the initial hemoglobin level. .

In the case of the study patients, occult bleeding, frequently missed, may have been the main cause for drop in hemoglobin. There was no evidence of hemolysis and marrow suppression seems unlikely because of the pattern of decrease observed, the temporal occurrence, and lack of concomitant involvement of WBC or platelets.

Recommendations

The number of Vioxx™ patients who experienced abnormalities of hematologic parameters was not significantly greater than was seen with other NSAIDS or, at times, with placebo. Nevertheless, three patients were taken off study because of abnormal hematologic parameters.

The true incidence of borderline abnormalities is undetermined because the cut off for reporting laboratory values may have limited their detection.

Additional hematologic safety data should be obtained in a large simple clinical trial. Laboratory data (CBC) should be obtained at the beginning of the trial, for patient discontinued for adverse event, and at the end of trial. Data from such a study will provide additional safety assessment of Vioxx™ needed in view of the anticipated widespread and prolonged usage of the drug.

/S/

Ann Farrell, M.D.

/S/

cc:
NDA 20-042
NDA 20-052
HFD-550/
HFD-550/PM Consult File
HFD-180/Consult File
HFD-180/LTalarico
HFD-180/AFarrell
f/t 4/6/99 jgw
C/N200420AF

/S/ 4-7-99

Table 2-064. MK-0966 $AUC_{(0-\infty\ hr)}$ (ng·hr/ml) Hemodialysis Patients versus Healthy Volunteers

	Dose	Mean[a]	p-Value[b]
Part 1: Hemodialysis initiated 48 hours postdose. n=6	50 mg	7228	0.178
Healthy Volunteers. n=47	25-50 mg	8678	

[Adapted from NDA 21-042, Volume 1.177, Table 15, page 44. [a]denotes: adjusted mean. [b]denotes: between-population p-Value.]

Table 3-064. MK-0966 C_{max} (ng/ml) Hemodialysis Patients versus Healthy Volunteers

	Dose	Mean[a]	p-Value[b]
Part 1: Hemodialysis initiated 48 hours postdose. n=6	50 mg	405	0.301
Healthy Volunteers. n=47	25-50 mg	461	

[Adapted from NDA 21-042, Volume 1.177, Table 17, page 47. [a]denotes: adjusted mean. [b]denotes: between-population p-Value.]

Table 4-064. MK-0966 T_{max} (hr) Hemodialysis Patients versus Healthy Volunteers

	Dose	Median	p-Value[b]
Part 1: Hemodialysis initiated 48 hours postdose. n=6	50 mg	3.0	0.797
Healthy Volunteers. n=47	25-50 mg	3.0	

[Adapted from NDA 21-042, Volume 1.177, Table 19, page 49. [b]denotes: between-population p-Value.]

Table 5-064. MK-0966 $T_{1/2}$ (hr) Hemodialysis Patients versus Healthy Volunteers

	Dose	Mean[a]	p-Value[b]
Part 1: Hemodialysis initiated 48 hours postdose. n=6	50 mg	12.5	0.403
Healthy Volunteers. n=47	25-50 mg	11.3	

[Adapted from NDA 21-042, Volume 1.177, Table 21, page 51. [a]denotes: adjusted mean. [b]denotes: between-population p-Value.]

Table 6-064. *In Vitro* Protein Binding of ^{14}C-MK-0966 (%)

Concentration	Mean[a]±SD
50 mg/ml	85.9±5.2
100 mg/ml	86.5±4.5
500 mg/ml	85.4±4.8
Overall*	85.9±4.8

[Adapted from NDA 21-042, Volume 1.177, Table 22, page 51. [a]denotes: arithmetic mean±between-subject SD. *Averaged over the 3 concentration levels per patient.]

The effect of hemodialysis on MK-0966 pharmacokinetics was also examined in this study. Cmax values were slightly lower for the 4 hours postdose hemodialysis treatment, the AUC and other parameters were similar between treatments Tables 7-064 to10-064. According to the sponsor: "the ~18% reduction in Cmax would not be anticipated to have a clinically important influence on therapeutic response" and "the low recovery of MK-0966 in the dialysate (~4% of dose when dialysis was initiated just 4 hours postdose) supports the conclusion that hemodialysis has little effect on the plasma pharmacokinetics of MK-0966."

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

SUMMARY/COMMENTS

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

16.1 Osteoarthritis Studies
6-Weeks Studies

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

METHODS

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

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

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

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

RESULTS

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

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

Deaths: No death was reported in this study.

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

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

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

Table 1-010. Patient Accounting

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

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

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

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

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

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

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

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

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

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

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