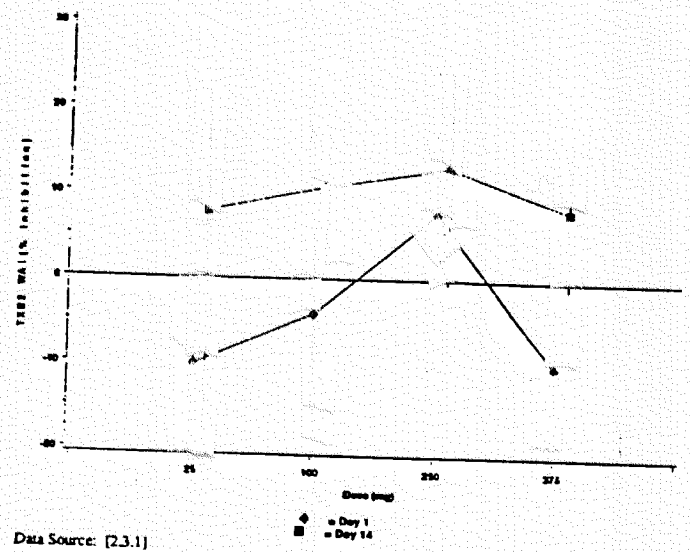
The pooled data from all patients suggest a consistent inhibition of COX-2 activity over time and across doses.

The effect of MK-0966 on TXB_2 is summarized in the following graph.

Effect of MK-0966 on TXB_2 WAI (%) on Days 1 and 14
Expressed as Difference From Placebo (Without AN 006)
(Mean ± 90% CI)



Data Source: [2.3.1]

Sponsor's graph

The pooled data in the graph above demonstrates less than a 15% inhibition of serum TXB_2 levels on day 14.

Individual Patient Data: Individuals in both the treatment and placebo groups demonstrated a decrease in serum TXB_2 levels at the sampling points. At those time points the decrease was greater for individuals in the treatment group compared to placebo. There appeared to be no dose response that accounted for that observation. No further conclusions can be drawn from the data.

Bleeding time: The pooled data are summarized in the following table and graph.

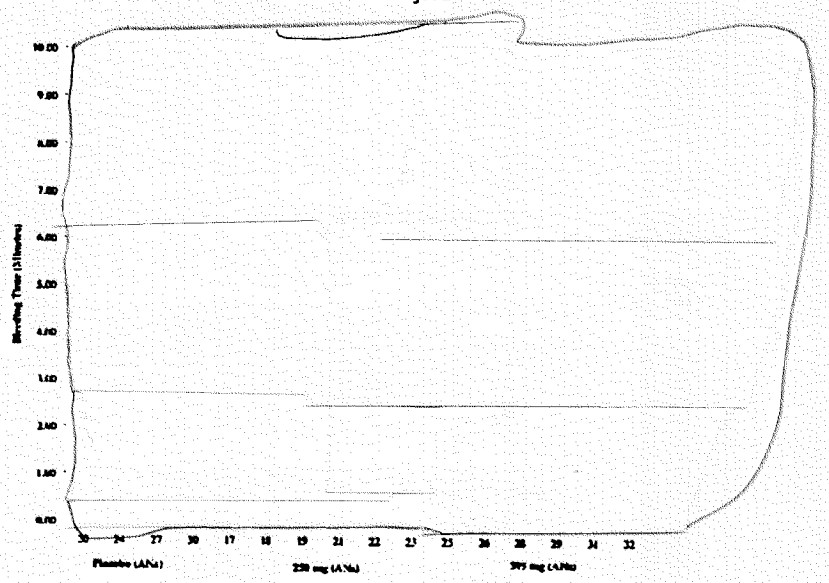
Summary Statistics for the Effect of MK-0966 on Mean Change From Baseline in Bleeding Time (Minutes)

Treatment Group (mg)	N	Mean	Median	Min, Max	Between-Subject SD	Change From Baseline p-Value
0	4	0.49	0.85		1.49	0.559
250	6	0.69	0.42		1.68	0.360
375	6	0.63	0.57		1.94	0.463

Data Source: [4.12]

Sponsor's table

Effect of Multiple Dose MK-0966 on Bleeding Time (Minutes)
in Individual Subjects



Data Source: [4.12]

Sponsor's graph

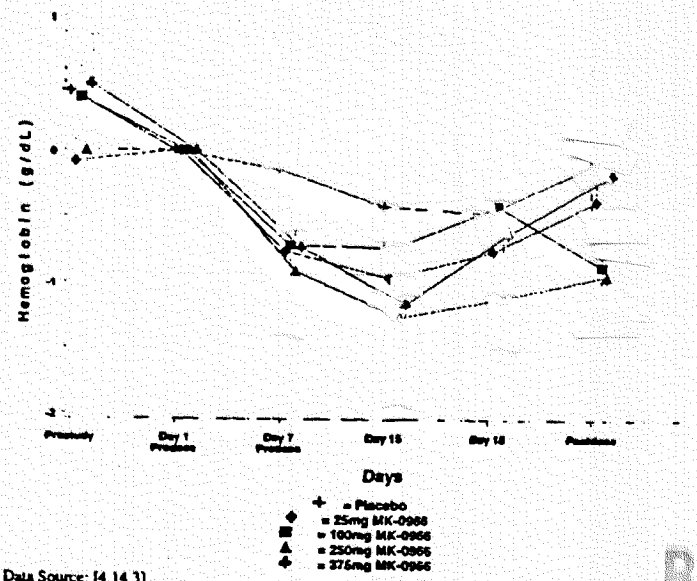
There was no significant change in bleeding times after multiple dose administration as demonstrated by the Day 14 data. Individual bleeding time data was reviewed in Appendix 4.12 and was consistent with the pooled data.

Clinical Adverse Events: No adverse hematological events were reported.

Changes in other Hematologic Parameters: Volunteers receiving MK-0966 appeared to experience a decrease in hemoglobin over the course of the study, which improved off study. The pooled data did not demonstrate a greater than 2 g/dL decrease. The decrease demonstrated here represents the effect of MK-0966 on repeated dosing. Below is a plot of the change from baseline hemoglobin for the dosage groups and post-dosing levels.

White blood cell count, platelet count, neutrophils, lymphocytes, and eosinophils did not appear to be affected by administration of MK-0966. A slight monocytosis and basophilia were observed in some volunteers receiving MK-0966 over time compared to those receiving placebo. A few individuals experienced an increased activated partial thromboplastin time (APTT) however no dose response effect could be observed.

Change From Baseline Hemoglobin (g/dL) Across Days by Treatment
(Mean Change ± 84% CI)



Data Source: [4.14.3]

Sponsor's table

Conclusion: Vioxx™ does not appear to affect bleeding time after multiple dose administration. This conclusion is evident when both the individual and pooled data are evaluated. Serum TXB_2 levels demonstrated significant individual variability. Pooled data also showed variable results. In general Vioxx™ has significant COX-2 inhibition without significant COX-1 inhibition. Individual patients may vary in their susceptibility to COX-1 inhibition by Vioxx™. The cause of the observed decrease in serum hemoglobin with repeated dosing in normal volunteers is unclear; however the lack of concurrent drop in white blood cell and platelet counts rules out marrow suppression.

Study Protocol P061

Objectives: To assess the inhibition of COX-1 activity by MK-0966, diclofenac, ibuprofen, naproxen, meloxicam and placebo based on serum TXB_2 level; to assess inhibition of COX-2 activity based on LPS-induced PGE_2; to assess urinary prostanoids, bleeding time, and ex-vivo platelet aggregation, and to monitor the safety and tolerability

Study Design: Partially blinded, randomized, parallel-group, placebo-controlled study

Subjects: Healthy females

Study Drug: Placebo, MK-0966 12.5 mg/d, MK-0966 25 mg/d, diclofenac 50 mg tid, ibuprofen 800 mg tid, naproxen 550mg bid, meloxicam 15 mg/d

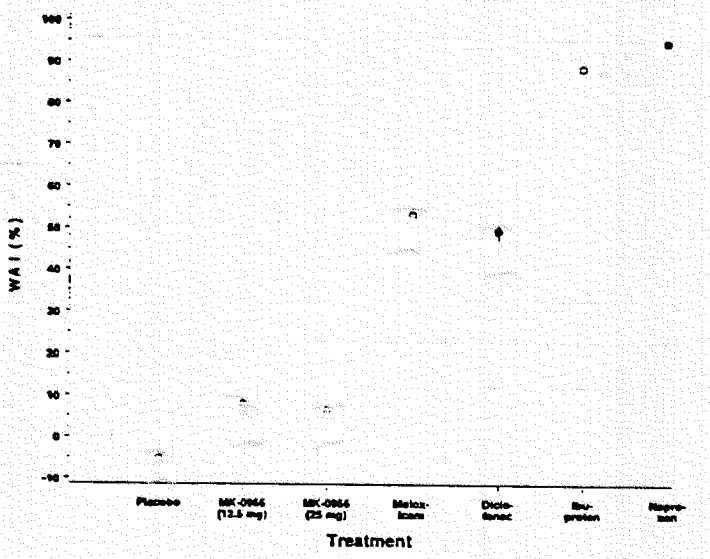
Study Plan: All treatments were administered for 5 full days plus a morning dose on day 6

Results

Serum TBX_2

The serum TXB_2 Weighted Average Inhibition (WAI) and the Weighted Average Inhibition for LPS-induced$_2$ on day 6 of MK-0966 administration at various doses compared to placebo and NSAIDs are shown in the following graphs..

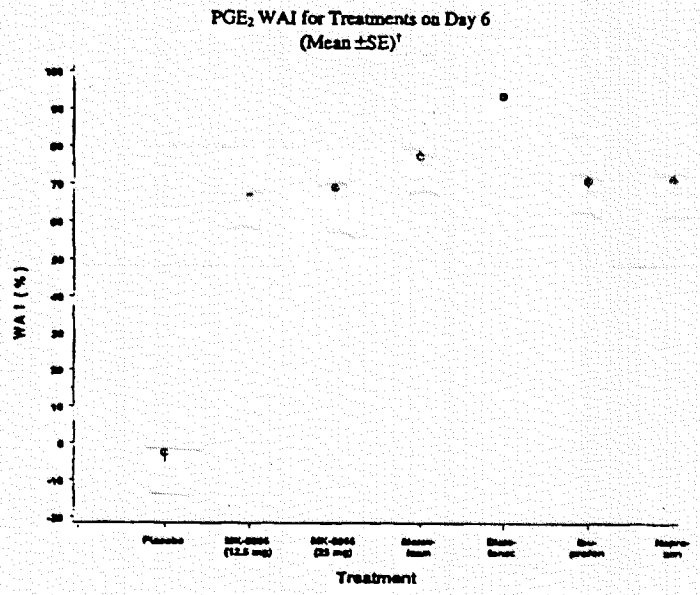
TXB_2 WAI (%) for Treatments on Day 6
(Mean ±SE)[1]



[1] The least square means and adjusted standard error from the ANCOVA model was back-transformed from log scale. Note that placebo, MK-0966 (12.5 mg), and MK-0966 (25 mg) means are from an ANCOVA model with only these treatments.

Data Source: [2.1]

Sponsor's graph



[1] The least square means and adjusted standard error from the ANCOVA model was back-transformed from log scale.

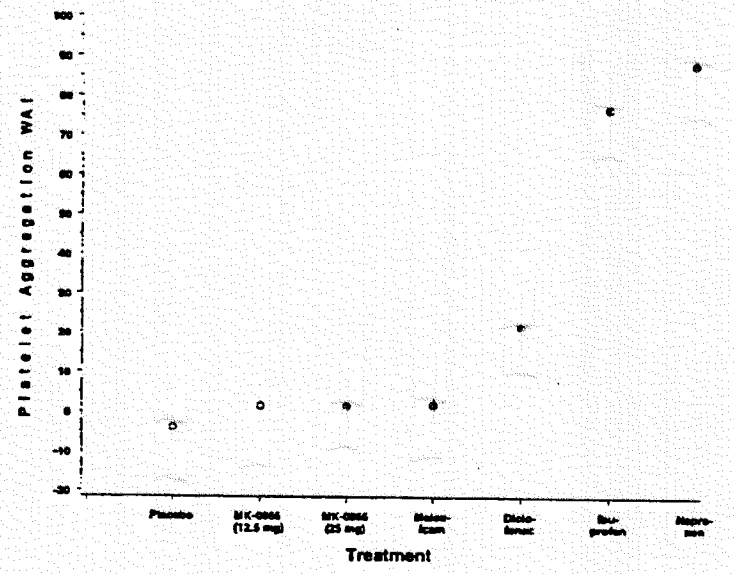
Sponsor's graph

Nonselective COX inhibitors caused a marked inhibition of serum TXB_2 while MK-0966 caused only a slight inhibition of serum TXB_2 when compared to placebo.

Both graphs shown above demonstrate MK-0966 selectivity of inhibition of COX-2 activity. MK-0966 has significant COX-2 inhibitory activity without significant COX-1 inhibitory activity. This contrasts with results seen with the relatively non-selective COX inhibitors (NSAIDs).

Platelet Aggregation (Pooled data): Platelet aggregation as measured using arachidonic acid as agonist was not significantly inhibited by MK-0966. This result is contrasted with that seen with the more non-selective COX inhibitors (NSAIDs).

Platelet Aggregation WAI (%) for Treatments on Day 6 Using Arachidonic Acid as the Agonist (Amplitude)
(Mean ± SE)[†]



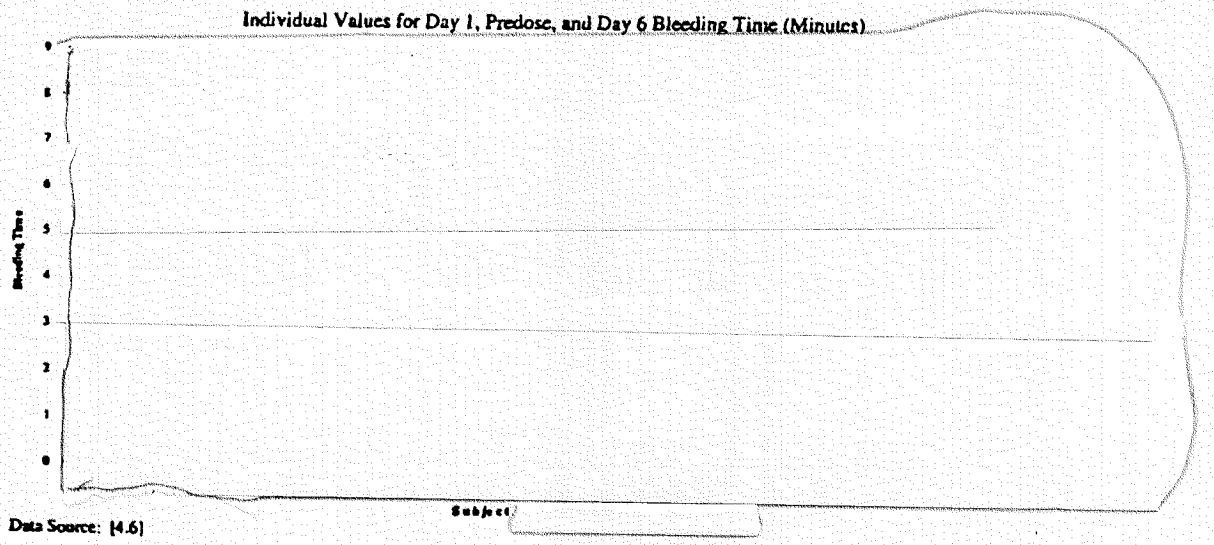
[†] The least square means and adjusted standard error from the ANCOVA model were used.

Data Source: [4.6]

Sponsor's graph

Effect of MK-0966 on Bleeding time: The results are summarized in the following table.

Individual Values for Day 1, Predose, and Day 6 Bleeding Time (Minutes)



Data Source: [4.6]

Sponsor's graph

While there may be some individual variation of bleeding times for MK-0966 from Day 0 to Day 6, the results were not consistent with a marked effect on bleeding time.

Urinary Prostanoids: 11-Dehydro Thromboxane B_2 (pg/mg): The results are shown in the corresponding tables.

Analysis of Change From Baseline on Day 6 (0- to 8-Hour Interval)
for Urinary 11-Dehydro TXB_2 (pg/mg Creatinine)

Treatment	N	Baseline Mean (SD)	Day 6 Mean (SD)	Mean Change (SD)	LSMean Change (SE)
Placebo	15	563.97 (119.62)	837.16 (579.22)	273.18 (563.90)	273.74 (92.39)†
MK-0966 (12.5 mg)	12	606.20 (230.55)	597.12 (162.85)	-9.07 (130.17)	16.23 (104.04)
MK-0966 (25 mg)	12	553.80 (138.69)	693.84 (401.22)	140.04 (390.64)	134.63 (103.33)
Meloxicam (15 mg)	12	479.59 (123.52)	423.02 (152.55)	-56.57 (235.20)	-105.50 (106.06)
Diclofenac (50 mg 3 times a day)	8	635.48 (232.68)	385.88 (71.32)	-249.60 (236.41)†	-207.10 (128.22)

Between-Treatment Comparison	Difference in LSMean	90% CI for Difference	p-Value
MK-0966 (12.5 mg) versus placebo	-257.5	(-486.2, -28.8)	0.070
MK-0966 (25 mg) versus placebo	-139.1	(-367.8, 89.6)	0.320
Meloxicam versus placebo	-379.2	(-607.9, 150.5)	0.009
Diclofenac versus placebo	-480.9	(-740.2, -221.6)	0.004

Effect	p-Value	Pooled SD for Change
Treatment	0.018	357.83
Baseline	0.047	

‡ ANCOVA within-treatment p-value ≤0.050.
† Univariate within-treatment p-value ≤0.050.

Data Source: [2.1]

Sponsor's table

The difference of MK-0966 from placebo approached statistical significance for the 12.5 mg dose but not for the 25 mg dose. Meloxicam and diclofenac were both statistically different from placebo. This is consistent with the relatively selective inhibition of COX-2 for MK-0966.

Urinary 2,3-Dinor-6-Keto Prostaglandin $F_{1\alpha}$ (pg/mg Creatinine):.

Analysis of Change From Baseline on Day 6 (0- to 8-Hour Interval)
for Urinary 2,3-Dinor-6-Keto Prostaglandin $F_{1\alpha}$ (pg/mg Creatinine)

Treatment	N	Baseline Mean (SD)	Day 6 Mean (SD)	Mean Change (SD)	LSMean Change (SE)
Placebo	15	193.57 (60.17)	184.34 (69.53)	-9.23 (64.47)	-7.27 (10.91)
MK-0966 (12.5 mg)	12	176.93 (88.09)	94.34 (25.22)	-82.58 (76.16)†	-92.70 (12.24)‡
MK-0966 (25 mg)	12	205.98 (84.99)	97.27 (49.68)	-108.70 (77.76)†	-97.75 (12.25)†
Meloxicam (15 mg)	12	156.40 (49.24)	66.91 (27.85)	-89.49 (44.78)†	114.50 (12.50)†
Diclofenac (50 mg 3 times a day)	8	235.78 (76.06)	89.82 (28.07)	-146.00 (68.28)†	-113.40 (15.35)‡

Between-Treatment Comparison	Difference in LSMean	90% CI for Difference	p-Value
MK-0966 (12.5 mg) versus placebo	-85.4	(-112.4, -58.4)	<0.001
MK-0966 (25 mg) versus placebo	-90.5	(-117.5, -63.5)	<0.001
Meloxicam versus placebo	-107.2	(-134.2, -80.2)	<0.001
Diclofenac versus placebo	-106.1	(-136.7, -75.5)	<0.001

Effect	p-Value	Pooled SD for Change
Treatment	<0.001	42.23
Baseline	<0.001	

† Univariate within-treatment p-value ≤0.050.
‡ ANCOVA within-treatment p-value ≤0.050.

Data Source: [2.1]

Sponsor's table

All treatment groups demonstrated a statistically significant decrease in urinary 2,3-Dinor-6-Keto Prostaglandin $F_{1\alpha}$ excretion reflecting their ability to inhibit COX-2.

Urinary 6-Keto Prostaglandin $F_{1\alpha}$ (pg/mg Creatinine):

Analysis of Change From Baseline on Day 6 (0- to 8-Hour Interval)
for Urinary 6-Keto Prostaglandin $F_{1\alpha}$ (pg/mg Creatinine)

Treatment	N	Baseline Mean (SD)	Day 6 Mean (SD)	Mean Change (SD)	LSMean Change (SE)
Placebo	15	57.61 (18.71)	68.97 (32.84)	11.36 (28.40)	10.30 (5.57)
MK-0966 (12.5 mg)	12	54.53 (23.48)	29.12 (9.38)	-25.41 (17.29)†	-28.28 (6.24)‡
MK-0966 (25 mg)	12	63.88 (32.14)	41.61 (35.32)	-22.28 (30.79)†	-19.66 (6.24)‡
Meloxicam (15 mg)	12	52.93 (16.72)	24.44 (8.31)	-28.49 (16.83)†	-32.30 (6.26)†
Diclofenac (50 mg 3 times a day)	8	73.18 (41.32)	27.25 (7.83)	-45.93 (36.54)†	-37.85 (7.77)‡

Between-Treatment Comparison	Difference in LSMean	90% CI for Difference	p-Value
MK-0966 (12.5 mg) versus placebo	-38.6	(-52.4, -24.8)	<0.001
MK-0966 (25 mg) versus placebo	-30.0	(-43.7, -16.2)	0.001
Meloxicam versus placebo	-42.6	(-56.4, -28.8)	<0.001
Diclofenac versus placebo	-48.2	(-63.8, -32.5)	<0.001

Effect	p-Value	Pooled SD for Change
Treatment	<0.001	21.55
Baseline	<0.001	

‡ Univariate within-treatment p-value ≤0.050.
† ANCOVA within-treatment p-value ≤0.050.

Data Source: [2.1]

Sponsor's table

Significant inhibition of 6-Keto Prostaglandin $F_{1\alpha}$ excretion occurred with all treatment groups when compared to placebo.

Urinary PGE_2

Analysis of Change From Baseline on Day 6 (0- to 8-Hour Interval)
for Urinary PGE_2 (pg/mg Creatinine)

Treatment	N	Baseline Mean (SD)	Day 6 Mean (SD)	Mean Change (SD)	LSMean Change (SE)
Placebo	15	249.72 (106.56)	214.76 (93.29)	-34.96 (86.52)	-33.0 (18.1)
MK-0966 (12.5 mg)	12	201.97 (88.49)	113.80 (59.35)	-88.17 (63.05)†	-106.0 (20.5)‡
MK-0966 (25 mg)	12	281.00 (164.32)	181.36 (144.45)	-99.64 (102.54)†	-84.7 (20.4)†
Meloxicam (15 mg)	12	208.44 (97.68)	119.50 (84.15)	-88.95 (91.32)†	-104.1 (20.4)‡
Diclofenac (50 mg 3 times a day)	8	301.43 (143.16)	173.61 (94.11)	-127.80 (75.88)†	-104.4 (25.2)‡

Between-Treatment Comparison	Difference in LSMean	90% CI for Difference	p-Value
MK-0966 (12.5 mg) versus placebo	-73.0	(-117.8, -28.3)	0.010
MK-0966 (25 mg) versus placebo	-51.7	(-96.4, -6.9)	0.063
Meloxicam versus placebo	-71.1	(-115.9, -26.4)	0.012
Diclofenac versus placebo	-71.4	(-122.1, -20.6)	0.025

Effect	p-Value	Pooled SD for Change
Treatment	0.041	70.02
Baseline	<0.001	

‡ Univariate within-treatment p-value ≤0.050.
† ANCOVA within-treatment p-value ≤0.050.

Data Source: [2.1]

Sponsor's table

The mean change from placebo was statistically significant for all treatment groups except MK-0966 25 mg dose where it approached statistically significance.

Clinical Adverse Events: The clinical adverse events were not more frequent with MK-09666. The adverse events reported in the study are summarized in the following table.

Patient #	Treatment	Study Day	Duration	Intensity	Event
049	MK-0966 (25 mg)	4	23 days	Mild	Bruising on both thighs
019	Naproxen sodium	2	19 days	Mild	Bruises on left knee and lower leg
070	MK-0966 (12.5 mg)	3	3 days	Mild	Spotting
056	Meloxicam	7	6 hours	Mild	Vaginal Bleeding
056	Meloxicam	9	11 days	Mild	Spotting
054	Ibuprofen	9	2 days	Mild	Vaginal blood loss

Other Hematologic parameters: All patients experienced a decrease in hemoglobin. White blood cell count, platelet count and neutrophil count did not appear to be affected by administration of MK-0966.

Conclusion: Individual bleeding times were not affected by the administration of MK-0966. Individual platelet aggregation by arachidonic acid and collagen were not affected by the administration of MK-0966. Vioxx™ does not appear to affect bleeding time.

Urinary TXB_2 levels with MK-0966 12.5 mg dosage group approached statistical significance compared to placebo while those levels in the 25 mg dosage group did not.
Laboratory data demonstrated a mild decrease in hemoglobin for all treatment groups. No further conclusions can be drawn form this data.

Study Protocol P063

Objectives: To assess the effect of low dose aspirin on serum TXB_2 and platelet aggregation, assess the effect of MK-0966 on the aspirin-induced inhibition of serum TXB_2 and platelet aggregation, confirm lack of effect of MK-0966 on serum TXB_2 and platelet aggregation, confirm the safety and tolerability of concomitant therapy with 50 mg MK-0966 and low dose (81 mg) aspirin

Study Design: Double-blind, randomized, placebo-controlled, parallel-group study of two treatment groups in which subjects received double-blind tablets of either 50mg of MK-0966 or matching placebo for 10 days. All patients were given open-label once daily aspirin 81 mg beginning on day 4 through day 10.

Subjects: Healthy non-smoking, 24 males and females of non-child bearing potential, within 30% of ideal weight, aged 18 to 38

Study Drug: 50 mg MK-0966 tablets, placebo tablets 81 mg aspirin

Study Plan: MK-0966 50 mg tablets or placebo tablets taken once daily starting on Day 1 and continued through Day 10. Serum TXB_2 and platelet aggregation performed 72 hours prior to first dose on Day 1, predose Day 1, prior to first aspirin dose day 4, prior to MK-0966 dose on Day 10, and 4 hours post dose of MK-0966 on Day 10.

Results

Pooled Data from all subjects

Below is a table with summary statistics of the pooled data from all subjects.

Summary Statistics of TXB_2 Percent Inhibition From Baseline by Time Point

Day	Time (Hours)	Treatment	N	Mean	Median	Min, Max	Between-Subject SD		
Baseline (ng/mL)									
1	0	MK-0966	12	302.83	259.90	205.30, 621.20	128.54	.	.
		Placebo	12	250.31	239.65	142.10, 448.90	83.36	.	.
Day	Time (Hours)	Treatment	N	Mean[1]	Median[1]	Min, Max[1]	Between-Subject SD[1]	Within-Group p-Value[1]	Within-Group 90% CI
Inhibition From Baseline (%)									
4	0	MK-0966	12	6.79	-1.99	-20.55, 45.20	26.19	0.373	(-6.77, 18.62)
		Placebo	12	-4.94	-9.89	-20.50, 13.07	10.30	0.133	(-10.70, 0.51)
Inhibition From Baseline (%)									
10	0	MK-0966 + Aspirin[4]	12	97.22	96.70	94.91, 99.31	65.65	<0.001	(96.09, 98.02)
		Aspirin	12	96.99	97.00	95.20, 98.38	35.80	<0.001	(96.38, 97.50)
Inhibition From Baseline (%)									
10	4	MK-0966 + Aspirin[4]	12	98.37	97.87	96.60, 99.69	78.98	<0.001	(97.55, 98.92)
		Aspirin	12	98.36	98.02	95.75, 99.64	67.64	<0.001	(97.67, 98.84)

[1] Back-transformed from the log scale.
[2] SD on the log scale * 100.
[3] Within-group p-value versus no inhibition.
[4] Note that concomitant therapy with aspirin began on Day 4.

Data Source: 12.1]

Sponsor's table

The pooled data indicate that administration of MK-0966 tablets did not affect the serum TXB_2 results taken on Day 4. The coadministration of MK-0966 tablets with aspirin did not affect the expected outcome of nearly complete inhibition of serum TXB_2. These results suggest no significant interaction of MK-0966 with aspirin in terms of serum TXB_2 levels over this period of time.

The Individual Patient Data are shown in the following table.

Serum TXB2

Treatment Group: Placebo/Aspirin

AN	Day/Time	TXB2 ng/ml	% change from Day 1
01	predtudy	197.5	
01	1	162.7	
01	4	180.3	10.8%
01	10/predose	6.4	-96.0%
01	10/4hrs	4.2	-97.4%
02	predtudy	251.5	
02	1	249.5	
02	4	236.1	-5.4%
02	10/predose	7.4	-97.0%
02	10/4hrs	4.9	-98.0%
05	predtudy	201.1	
05	1	229.8	
05	4	261.8	13.9%
05	10/predose	9.1	-96.0%
05	10/4hrs	5.3	-97.7%
06	predtudy	424.1	
06	1	339.6	
06	4	372.3	9.6%
06	10/predose	7.5	-97.8%
06	10/4hrs	5.1	-98.5%
10	predtudy	199.6	
10	1	225.1	
10	4	212.0	-5.8%
10	10/predose	6.0	-97.3%
10	10/4hrs	4.6	-98.0%
11	predtudy	249.7	
11	1	210.8	
11	4	232.2	10.1%
11	10/predose	5.6	-97.3%
11	10/4hrs	3.5	-98.3%

baseline = Day1 (boxed number)

% Change = $\frac{\text{(predose TXB2 - baseline TXB2)}}{\text{baseline TXB2}} \times 100$

Serum TXB2

Treatment Group: Placebo/Aspirin

AN	Day/Time	TXB2 ng/ml	% change from Day 1
13	predtudy	237.4	
13	1	247.2	
13	4	290.2	17.4%
13	10/predose	8.5	-96.6%
13	10/4hrs	6.1	-97.5%
15	predtudy	307.3	
15	1	294.8	
15	4	333.3	13.1%
15	10/predose	11.0	-96.3%
15	10/4hrs	7.5	-97.5%
17	predtudy	129.5	
17	1	181.2	
17	4	172.6	-4.7%
17	10/predose	8.7	-95.2%
17	10/4hrs	7.7	-95.8%
20	predtudy	121.4	
20	1	142.1	
20	4	143.2	0.8%
20	10/predose	4.3	-97.0%
20	10/4hrs	3.2 *	-97.7%
21	predtudy	223.1	
21	1	252.4	
21	4	219.4	-13.1%
21	10/predose	4.0	-98.4%
21	10/4hrs	3.2 *	-98.7%
23	predtudy	419.1	
23	1	448.9	
23	4	518.6	15.5%
23	10/predose	8.0	-98.2%
23	10/4hrs	3.2 *	-99.3%

baseline = Day1 (boxed number)

% Change = $\frac{\text{(predose TXB2 - baseline TXB2)}}{\text{baseline TXB2}} \times 100$

* LLORQ = 3.2 ng/ml

Sponsor's table

Listed above are the control results. There is variability in the percent change in serum TXB_2 levels from Day 1 to Day 4. This corresponds to 4 days of placebo administration.

Serum TXB2

Treatment Group: MK-0966/Aspirin

AN	Day/Time	TXB2 ng/ml		% change from Day 1
03	predstudy	302.4		
03	1	275.0		
03	4	254.6		-7.4%
03	10/predose	14.0		-94.9%
03	10/4hrs	3.2	*	-98.8%
04	predstudy	258.7		
04	1	241.6		
04	4	266.9		10.5%
04	10/predose	11.7		-95.1%
04	10/4hrs	6.2		-97.4%
07	predstudy	406.7		
07	1	512.6		
07	4	306.8		-40.1%
07	10/predose	4.6		-99.1%
07	10/4hrs	3.2	*	-99.4%
08	predstudy	185.6		
08	1	233.1		
08	4	281.0		20.5%
08	10/predose	3.2	*	-98.6%
08	10/4hrs	3.2	*	-98.6%
09	predstudy	338.2		
09	1	304.0		
09	4	166.6		-45.2%
09	10/predose	9.5		-96.8%
09	10/4hrs	5.6		-98.2%
12	predstudy	165.7		
12	1	232.8		
12	4	255.3		9.6%
12	10/predose	9.3		-96.0%
12	10/4hrs	7.5		-96.8%

baseline = Day1 (boxed number)

% Change = (postdose TXB2 - baseline TXB2) / baseline TXB2 x 100

* LLOQ = 3.2 ng/ml

Serum TXB2

Treatment Group: MK-0966/Aspirin

AN	Day/Time	TXB2 ng/ml	% change from Day 1
14	predstudy	333.8	
14	1	266.6	
14	4	321.5	20.5%
14	10 predose	12.8	-95.2%
14	10/4hrs	6.5	-97.6%
16	predstudy	243.1	
16	1	215.0	
16	4	244.9	13.9%
16	10/predose	10.4	-95.2%
16	10/4hrs	7.3	-96.6%
18	predstudy	188.0	
18	1	205.3	
18	4	204.8	-0.2%
18	10/predose	9.2	-95.5%
18	10/4hrs	6.2	-97.0%
19	predstudy	267.0	
19	1	273.6	
19	4	285.3	4.3%
19	10/predose	7.6	-97.2%
19	10/4hrs	4.2	-98.4%
22	predstudy	579.1	
22	1	621.2	
22	4	573.7	-7.6%
22	10/predose	16.7	-97.3%
22	10/4hrs	8.6	-98.6%
24	predstudy	284.7	
24	1	272.6	
24	4	205.9	-24.5%
24	10/predose	5.5	-98.0%
24	10/4hrs	9.1	-96.6%

baseline = Day1 (boxed number)

% Change = (postdose TXB2 - baseline TXB2) / baseline TXB2 x 100

Sponsor's table

Listed above are results from the MK-0966 comparison groups where MK-0966 was administered for the first 4 days and then coadministered with aspirin for the remainder of the study. Variability in TXB_2 values was observed.

Platelet Aggregation Studies:

Primary Platelet Aggregation studies were performed with arachidonic acid. Secondary platelet aggregation studies were performed with collagen.
Platelet aggregation expressed as a percentage of light transmission was plotted for before (baseline) and after administration of MK-0966.

The Graph of Pooled data results is shown below.