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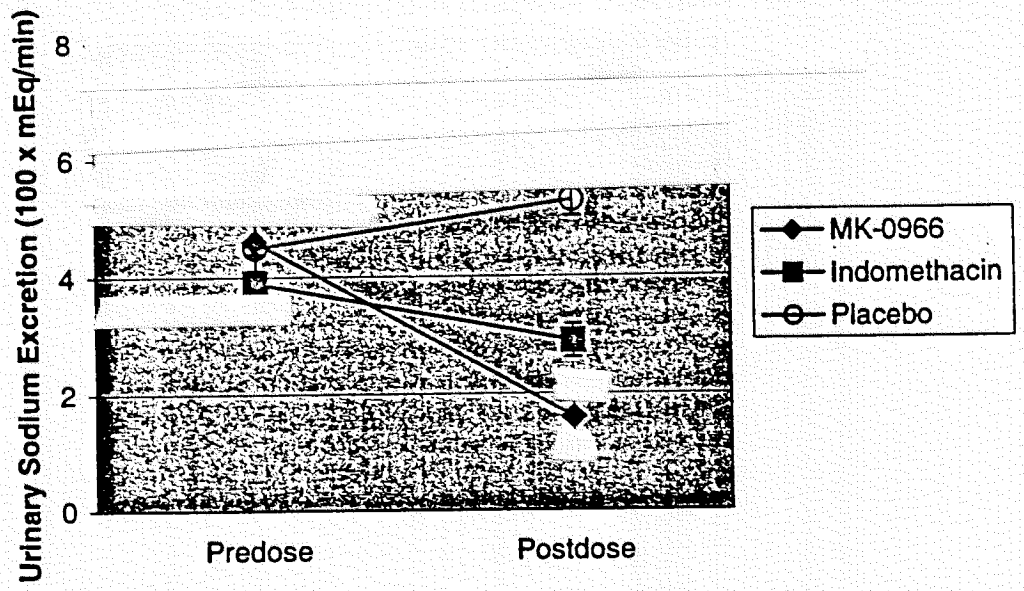
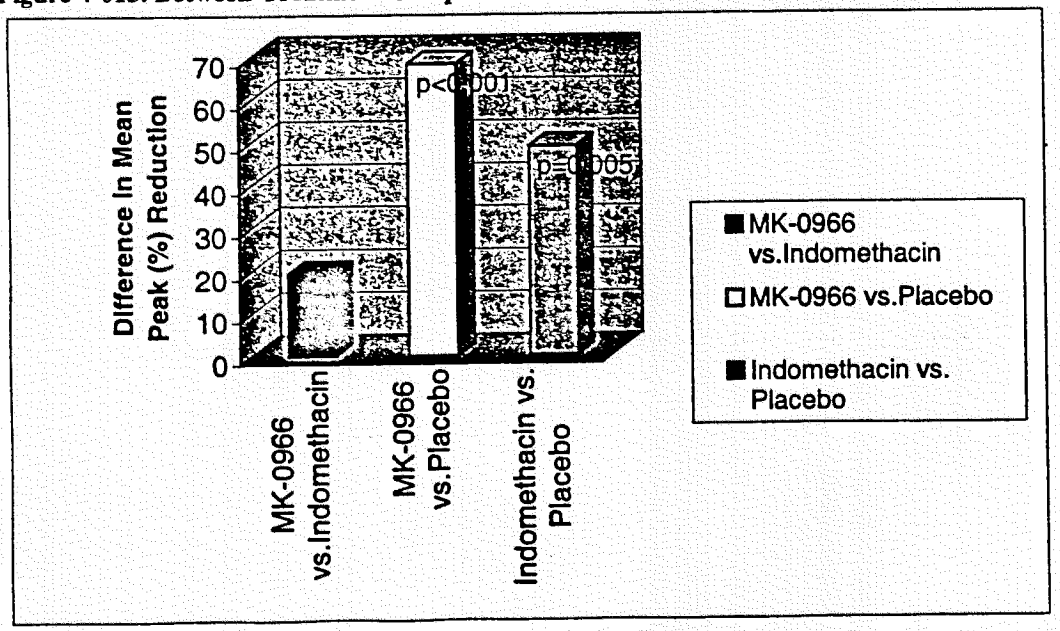
Figure 3-013. Mean (±SE) Pre- And Postdose Urinary Sodium Excretion



[Adapted from NDA 21-042, Vol. 1.105, Table 13, page 46. *denotes: p≤0.05.]

The between-treatment comparison on peak % reduction of urinary sodium excretion indicates that both MK-0966 and indomethacin albeit significantly different from placebo were not significantly different from each other (Figure 4-013).

Figure 4-013. Between-Treatment Comparison On Peak (%) Reduction Of Urinary Sodium Excretion



[Adapted from NDA 21-042, Vol. 1.105, Table 13, page 46.]

The mean baseline to postdose values for urinary potassium excretion was 6.1 to 2.8, 5.2 to 3.4, and 5.7 to 3.0 100 x mEq/min for the MK-0966, indomethacin, and placebo treatments, respectively. The mean percent within-treatment

reduction from baseline for urinary potassium excretion was statistically significant; 46.1, 30.0, and 39.5% for the MK-0966, indomethacin, and placebo treatments, respectively. The mean difference in peak percent reduction between the MK-0966 and placebo treatments was significant, with a 90% CI for the difference of (4.27, 18.30%). Other between-treatment differences were not significant[19].

SUMMARY/COMMENTS

Study protocol #013 compared the effects of single doses of 250 mg MK-0966, 75 mg indomethacin, and placebo on renal function in 15 generally healthy adult men and women, age 62 to 79 years old, on a low sodium diet (30 mEq/day). MK-0966 and indomethacin reduced (peak reduction) GFR by 62 and 48% more than placebo, respectively ($p<0.01$ for both MK-0966 and indomethacin versus placebo). Unlike placebo, MK-0966 and indomethacin treatments were associated with statistically significant reductions in urinary sodium excretion. The between-treatment comparison on peak % reduction of urinary sodium excretion indicates that both MK-0966 and indomethacin albeit significantly different from placebo were not significantly different from each other. Thus, MK-0966 effected qualitatively and quantitatively similar reductions in GFR and urinary sodium excretion as compared to indomethacin, and this effect on both variables was significantly different from placebo.

15.1.2 Protocol #065[20]: A Multicenter, Double-Blind, Placebo-Controlled Study To Evaluate And Compare The Effects Of Multiple Doses Of Mk-0966 And Indomethacin On Glomerular Filtration Rate And Other Parameters Of Renal Function

METHODS

This study had a double-blind, placebo-controlled, multicenter, double-dummy, and parallel-group design. The enrolled subjects were elderly volunteers with creatinine clearances of 30 to 80 ml/minute, who consumed 30 mEq sodium, 60 to 80 mEq potassium, 80 g protein diet for the duration of the study. On the eighth day on this diet (Day -1), subjects whose body weight had stabilized had a baseline measurement of glomerular filtration rate (GFR) taken. After GFR was measured, subjects received 6 days of either 12.5 mg MK-0966 once daily, 25 mg MK-0966 once daily, 50 mg indomethacin 3 times a day or placebo. Daily weight, urinary electrolytes, creatinine clearance, and vital signs (including orthostatic changes) were monitored. On the sixth day of drug administration (Day 6), GFR was reassessed. Urinary sodium and potassium excretion, creatinine clearance, and PRA were also measured before dosing and at specific intervals during the GFR procedure.

The objectives of the study included:

i. To compare the effects of 12.5 mg MK-0966 once daily, 25 mg MK-0966 once daily, 50 mg indomethacin 3 times a day, or placebo on mean percent change in minimum glomerular filtration rate (GFR).
ii. To compare the safety and tolerability of 6 days of 12.5 mg MK-0966 once daily, 25 mg MK-0966 once daily, 50 mg indomethacin 3 times a day, and placebo in subjects on a low-sodium diet.
iii. To compare the effects of 6 days of 12.5 mg MK-0966 once daily, 25 mg MK-0966 once daily, 50 mg indomethacin 3 times a day, or placebo on plasma renin activity (PRA), urinary sodium and potassium excretion, and creatinine clearance.

RESULTS

Demographics: Seventy-one subjects were randomized, 64% White, 33% Hispanic, and 3% Black. Sixty subjects (30 male and 30 female) completed the study. There were 7 discontinuations that occurred before receiving study drug and those subjects were not included in any analyses or evaluations (ANs 018, 022, 035, 036, 038, 044, 142); 2

[19] NDA 21-042, Volume 1.105, Reference P013, Table 14, page 48.
[20] NDA 21-042, Volume 1.178, Reference P065.

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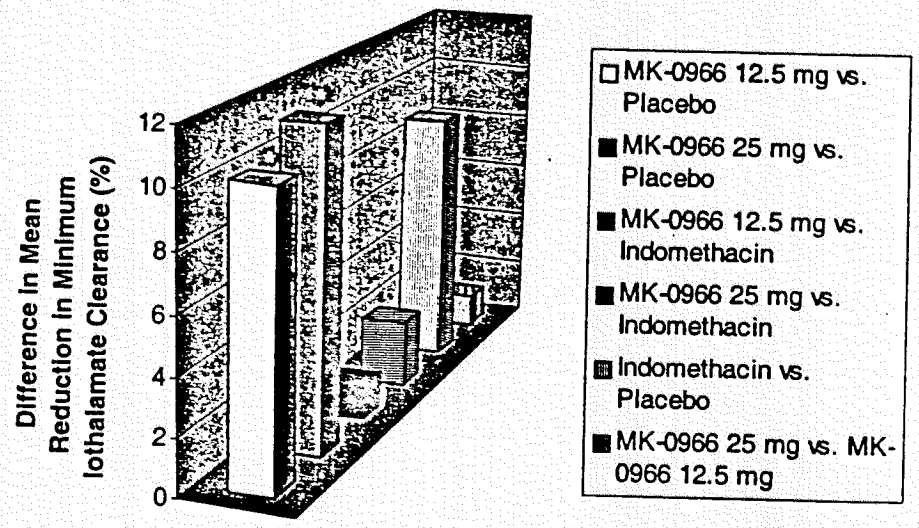
discontinued due to clinical adverse experiences (ANs 031 and 060 received MK-0966 12.5 mg). Two subjects (AN 045, MK-0966 25 mg, and AN 049, indomethacin) discontinued due to protocol violations[21].

Pharmacodynamics: Figure 1-065 outlines between treatment comparisons of the mean percent reduction (based on the adjusted means) in minimum iothalamate clearance. The primary hypothesis was based on the percent reduction in minimum iothalamate clearance associated with MK-0966 25 mg versus the percent reduction in placebo. In this regard, the only statistically significant differences demonstrated between treatment were those among MK-0966 12.5 mg or 25 mg and placebo.

Figure 1-065. Between Treatment Comparison For % Reduction In Minimum Iothalamate Clearance



[Adapted from NDA 21-042, Vol. 1.178, Table 13, page 52. *denotes: $p<0.05$. MK-0966 12.5 mg n=15; MK-0966 25 mg n=15; Indomethacin n=15; and Placebo n=15.]

Between treatment comparisons of the mean percent reduction (based on the adjusted means) in minimum creatinine clearance were directionally similar to those observed for iothalamate, however they did not achieve statistical significant[22].

The effects of the different treatments on urinary sodium and potassium excretion were also evaluated. The adjusted mean percent reductions on Day 6 from Day –1 for urinary sodium excretion were 9.40, 21.98, 12.06, and 7.04% for the placebo, MK-0966 12.5-mg, MK-0966 25-mg, and indomethacin treatments, respectively[23], and the difference between treatments was not significant. For urinary potassium excretion the adjusted mean percent reductions on Day 6 from Day -1 was 10.03, 10.31, 0.61, and -3.45% for placebo, MK-0966 12.5-mg, MK-0966 25-mg, and indomethacin treatments, respectively. None of the between treatment comparisons reach statistical significant[24].

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[21] According to the sponsor the subjects experienced collapsed veins on Day 6 and blood samples could not be obtained.
[22] NDA 21-042, Volume 1.178, Table 17, page 61.
[23] NDA 21-042, Volume 1.178, Table 19, page 64.
[24] NDA 21-042, Volume 1.178, Table 20, page 66.

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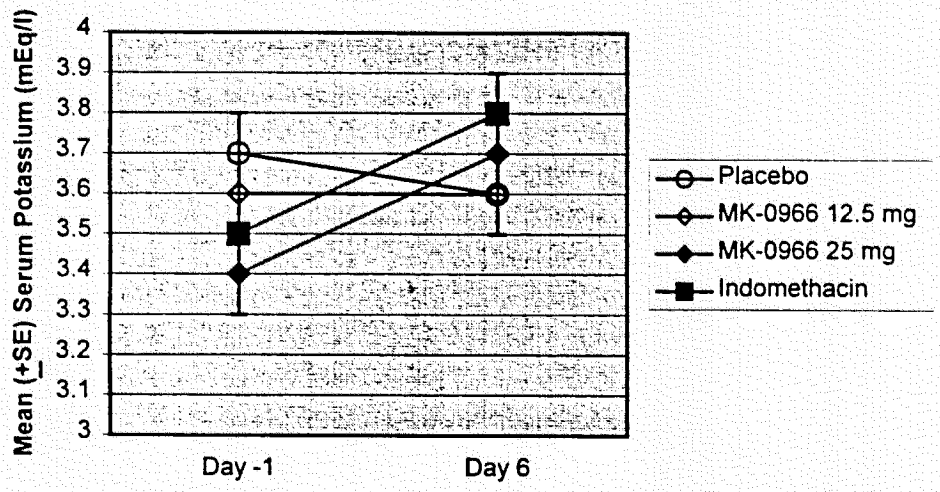
Changes over time in serum sodium as assessed by the adjusted mean percent reductions on Day 6 from Day -1 were negligible and not statistically significant[25]; -0.31, -0.10, -0.07, and 1.31% for placebo, MK-0966 12.5-mg, MK-0966 25-mg, and indomethacin treatments, respectively.

The mean Day -1 average values for serum potassium were 3.7, 3.6, 3.4, and 3.5 mEq/L for the placebo, MK-0966 12.5-mg, MK-0966 25-mg, and indomethacin treatments, respectively. The mean Day 6 average values were 3.6, 3.6, 3.7, and 3.8 mEq/L for the placebo, MK-0966 12.5-mg, MK-0966 25-mg, and indomethacin treatments, respectively. Thus, administration of MK-0966 25 mg/day and indomethacin (50 mg three times a day) were associated with increases in serum potassium, however these changes did not achieve statistical significance (Figure 2-065).

Figure 2-065. Mean (±SE) Serum Potassium On Day 6 From Day -1



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[Adapted from NDA 21-042, Vol. 1.178, Table 22, page 70. *denotes: $p<0.05$. MK-0966 12.5 mg n=15; MK-0966 25 mg n=15; Indomethacin n=15; and Placebo n=15.]

The adjusted mean percent changes in serum potassium on Day 6 from Day -1 were -1.26, 3.04, 6.80, 7.19% for placebo, MK-0966 12.5-mg, MK-0966 25-mg, and indomethacin treatments, respectively. Figure 3-065 illustrated the between treatment comparison for percent change in mean serum potassium[26].

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[25] NDA 21-042, Volume 1.178, Table 21, page 68.
[26] NDA 21-042, Vol. 1.178, Table 22, page 70.

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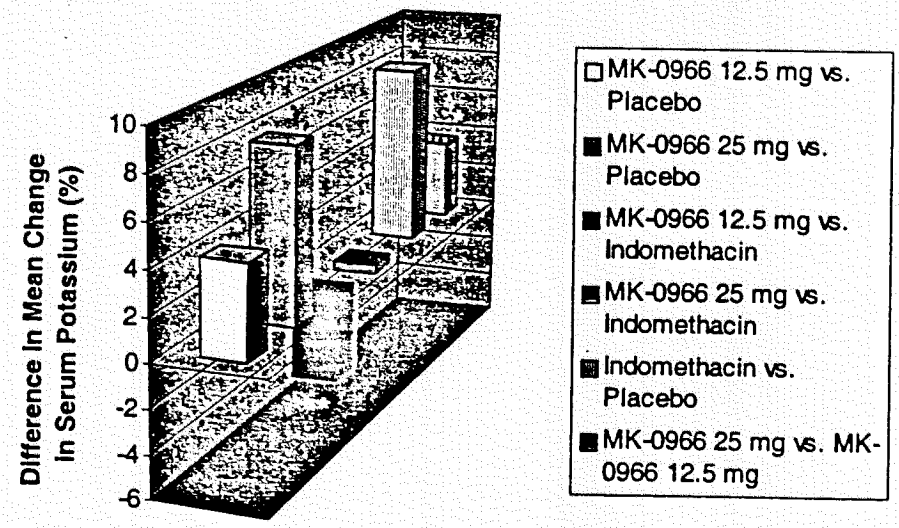
Figure 3-065. Between Treatment Comparison For % Change In Mean Serum Potassium



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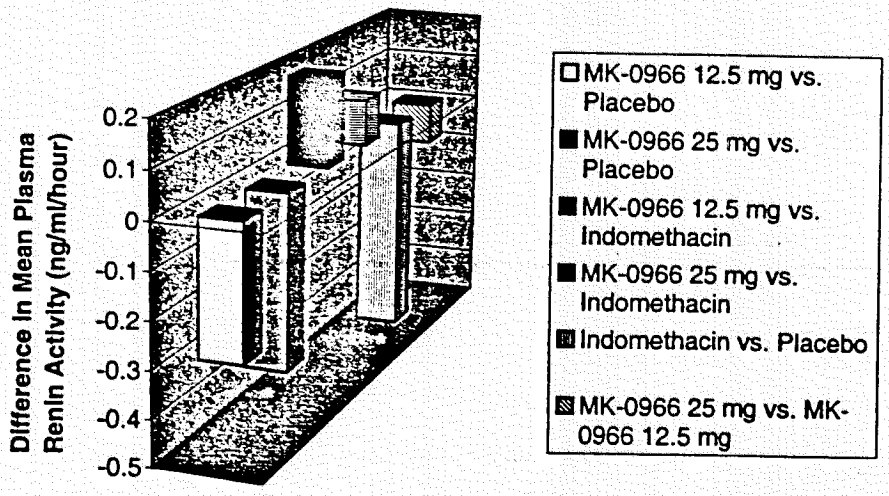
[Adapted from NDA 21-042, Vol. 1.178, Table 22, page 70. *denotes: p<0.05. MK-0966 12.5 mg n=15; MK-0966 25 mg n=15; Indomethacin n=15; and Placebo n=15.]

The between treatment comparison for change in mean plasma renin activity (PRA) is depicted in Figure 4-065. When all the data were included, none of the between-treatment comparisons reached or approached significance (p≥0.103), although all active treatments showed numerically greater decreases than placebo with respect to the change in the average PRA.

Figure 4-065. Between Treatment Comparison For Change In Mean Plasma Renin Activity



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[Adapted from NDA 21-042, Vol. 1.178, Table 23, page 72. *denotes: p<0.05. MK-0966 12.5 mg n=15; MK-0966 25 mg n=15; Indomethacin n=15; and Placebo n=15.]

Safety: Urinary retention leading to drug study discontinuation was reported in a 31 years old white male receiving MK-0966 12.5 mg. Otherwise there were no clinical or laboratory adverse experiences related to the cardiovascular or renal systems reported by the investigators.

SUMMARY/COMMENTS

The effects of multiple doses of placebo, 50 mg indomethacin 3 times a day, 12.5 mg MK-0966 once a day, and 25 mg MK-0966 once a day on renal function were compared in 60 generally healthy adult men and women 65 to 80 years of age on a restricted sodium intake (30 mEq sodium/day). In comparison to placebo only MK-0966 (12.5 mg and 25 mg a day) effected a statistically significant reduction in GFR (assessed by the clearance of iothalamate). The reductions in urinary sodium excretion associated with MK-0966 treatment, both 12.5 mg and 25 mg, albeit they did not reach statistical significant they were numerically larger than placebo or indomethacin. Furthermore, MK-0966 25 mg/day and indomethacin 50 mg three times a day were associated with increases in serum potassium, which were significantly different from placebo and MK-0966 12.5 mg/day.

15.1.3 Protocol #023[27]: A Double-Blind, Placebo-Controlled, Parallel-Group Study To Evaluate And Compare The Effects Of L-748,731 (Mk–0966), Indomethacin, And Placebo On Urinary Sodium Excretion And Other Parameters Of Renal Function In Subjects Consuming A 200-Meq Sodium Diet

METHODS

This study had a double-blind, placebo-controlled, multicenter, double-dummy, and parallel-group design. Its objectives were:

i. To compare the effects of treatment with oral MK-0966 (50 mg daily), indomethacin (50 mg 3 times daily), or placebo on urinary sodium excretion over the initial 72 hours of treatment in subjects 60 to 80 years of age consuming a 200-mEq sodium diet.

ii. To compare the safety and tolerability of 2 weeks of treatment with oral MK-0966 (50 mg daily), oral indomethacin (50 mg 3 times daily), or placebo in subjects 60 to 80 years of age consuming a 200-mEq sodium diet.

Subjects randomized were healthy men and women between 60 and 80 years old having a body mass index ≤ 34 kg/m^2 and no history of hypersensitivity to iodine-containing contrast media or to iodine *per se*.

The primary end point was the change from baseline in total urinary sodium excretion over the first 72 hours of treatment. Other variables included change from baseline at other time points for urinary sodium excretion, and change from baseline for urinary potassium excretion, creatinine clearance, body weight, blood pressure, glomerular filtration rate (GFR) as assessed by iohexol clearance, urinary N-acetyl-beta glucosaminidase (NAG), urinary eicosanoids, 11-dehydro thromboxane B2 (serum TxB2), serum sodium, and potassium.

RESULTS

Demographics: Thirty-six subjects, 17 men age range 60 to 80 years old, and 19 women age range 58 to 79 years old were randomized into the study, and 34 completed the study. AN 112 discontinued at Day 12 because of anxiety which was considered a clinical adverse experience. AN 132 was lost to follow up following Day 14. Distribution of ethnic background of study participants was Black n=2, Hispanic n=6, and White n=28.

Pharmacodynamics: Figure 1-023 illustrates the least squares mean change from baseline for total urinary sodium excretion during the first 72 hours of treatment. MK-0966 and indomethacin significantly reduced urinary sodium excretion during the first 72 hours of treatment compared with baseline, and the mean change from baseline was significantly different from that of the placebo group. However, the mean changes for the MK-0966 and indomethacin groups were not significantly different from each other Figure 2-023.

[27] NDA 21-042, Volume 1.115, Reference P023.

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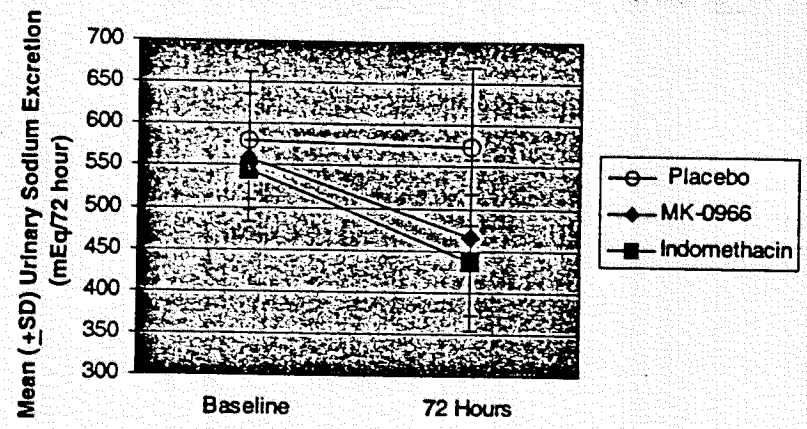
Figure 1-023. Mean (±SD) Baseline and 72 Hours Urinary Sodium Excretion



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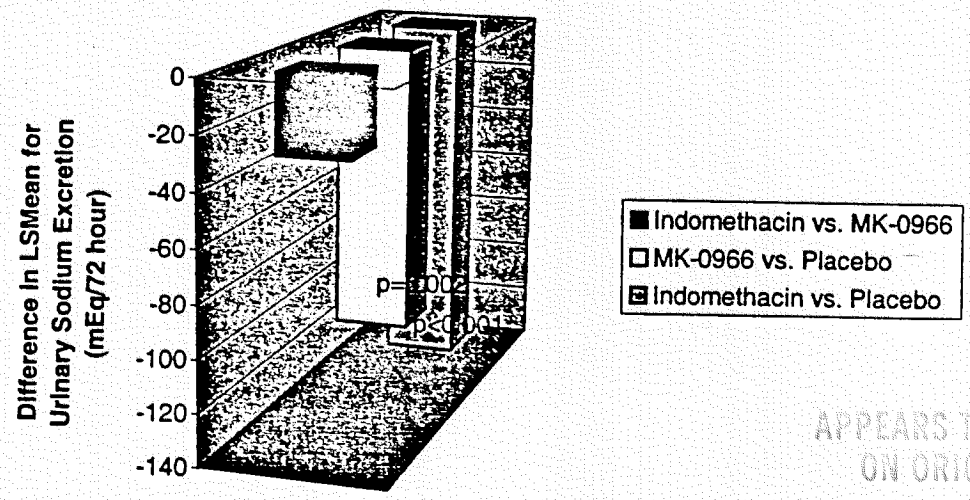
[Adapted from NDA 21-042, Vol. 1.115, Table 8, page 45. *denotes: p<0.05 vs. Baseline.]

Figure 2-023. Between-Treatment Comparison on Urinary Sodium Excretion



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[Adapted from NDA 21-042, Vol. 1.115, Table 8, page 45.]

The least square mean changes from baseline at Day 7 for urinary sodium excretion were all not significantly different from zero or between treatments[28]. The mean change from baseline at Day 14 for urinary sodium excretion for the indomethacin group was the only one significantly different from zero[29] however, all between-treatment differences in the mean change were not significant (Figure 3-023).

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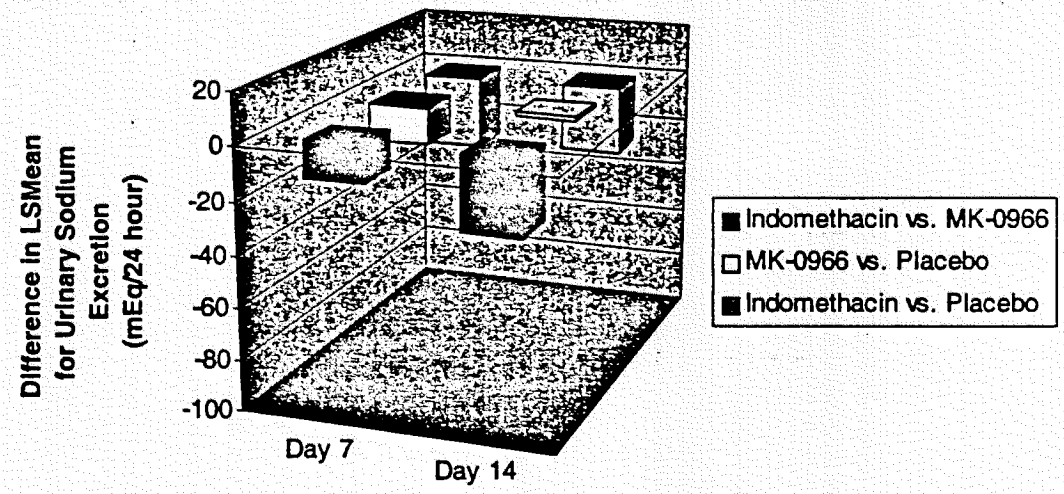
[28] NDA 21-042, Volume 1.115, Table 10, page 49.
[29] NDA 21-042, Volume 1.115, Table 10, page 49.

Figure 3-023. Between-Treatment Comparison on Urinary Sodium Excretion at Days 7 and 14



[Adapted from NDA 21-042, Vol. 1.115, Tables 9 & 10, pages 48 & 49.]

The mean change from baseline for total urinary potassium excretion during the first 72 hours of treatment was significantly different from zero only for the MK-0966 group (-9.79)[30]. The between-treatment differences in the mean change among the groups were not significant. At Day 7 the least squares mean change from baseline for urinary potassium excretion were all not significant within treatment and they were also not significantly different between treatments[31].

The least squares mean changes from baseline at Day 14 for urinary potassium excretion were all not significant within as well as between treatments[32].

At Day 14 the least squares mean change from baseline for creatinine clearance (24 hour) for the indomethacin group was significantly different from zero within treatment and it was significantly ($p=0.048$) different from that of the MK-0966 group (but not from placebo). However, the mean change for MK-0966 was not significant within treatment and was not significantly different from placebo[33]. Plotting of the mean (±SE) changes from baseline for creatinine clearance over time did not reveal a distinct pattern for any of the groups.

The least squares mean change from baseline at Day 14 for iohexol clearance was 0.38, 1.40, and -5.04 ml/min/1.73 m^2 for the placebo, MK-0966, and indomethacin groups, respectively. The mean change for the indomethacin group was significant within treatment ($p\leq 0.05$) and it was significantly different from those of the placebo ($p<0.014$) and MK-0966 ($p<0.004$) groups.

The least squares mean changes in systolic and diastolic blood pressure at Day 14 were not significant within and between treatments (Figure 4-023).

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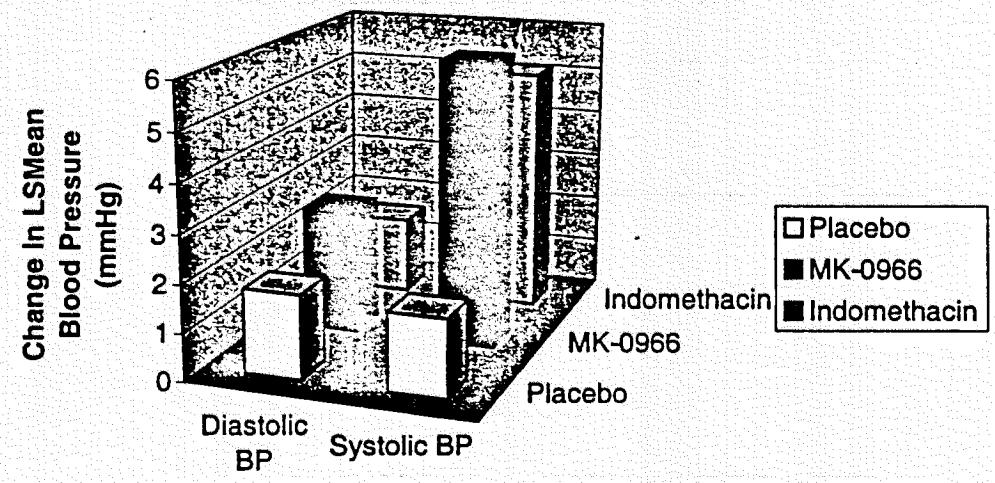
[30] NDA 21-042, Volume 1.115, Table 13, page 57.
[31] NDA 21-042, Volume 1.115, Table 14, page 59.
[32] NDA 21-042, Volume 1.115, Table 15, page 61.
[33] NDA 21-042, Volume 1.115, Table 18, page 67.

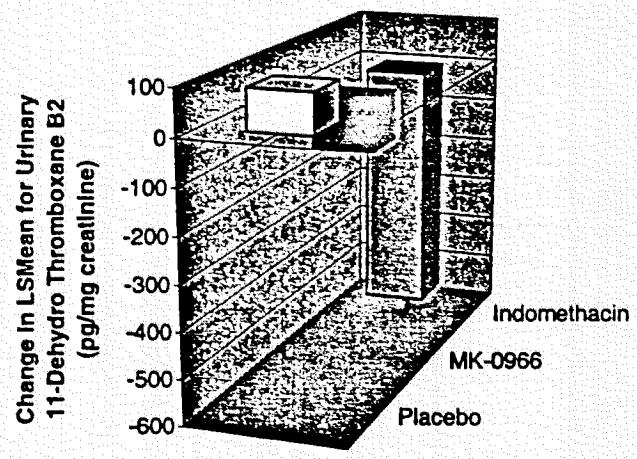
Figure 4-023. Change (Mean) From Baseline at Day 14 for Systolic and Diastolic Blood Pressure



[Adapted from NDA 21-042, Vol. 1.115, Tables 20 & 21, pages 71 & 73.]

Within and between treatment comparisons of the least squares mean change from baseline at Day 13 for urinary N-acetyl-beta glucosaminidase was all not significant. Results on urinary TxB_2 were not available at the time of the submission of the NDA. The least squares mean changes from baseline at Day 13 for urinary 11-dehydro thromboxane B2 are depicted in Figure 5-023. The mean change for the indomethacin group was significant within treatment and it was significantly different from those of the placebo and MK-0966 groups.

Figure 5-023. LSMean Change From Baseline at Day 13 for Urinary 11-Dehydro Thromboxane B_2



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[Adapted from NDA 21-042, Vol. 1.115, Tables 24, page 79. *denotes: $p \leq 0.05$ vs. Baseline.]

MK-0966 and indomethacin treatments effected significant reductions from baseline in urinary 6-keto-$PGF_{1\alpha}$ (Figure 6-023) and PGI-M (Figure 7-023), and the mean changes from baseline were significantly different from that of the

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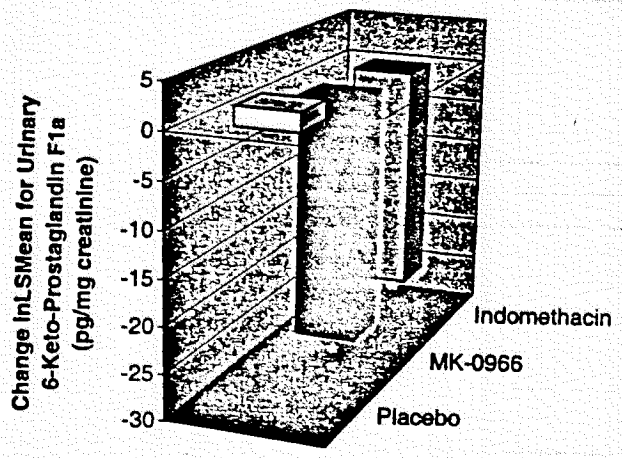
placebo group. However, the mean changes for the MK-0966 and indomethacin groups were not significantly different from each other[34].

Figure 6-023. LSMean Change From Baseline at Day 13 for Urinary 6-Keto-Prostaglandin $F_{1\alpha}$



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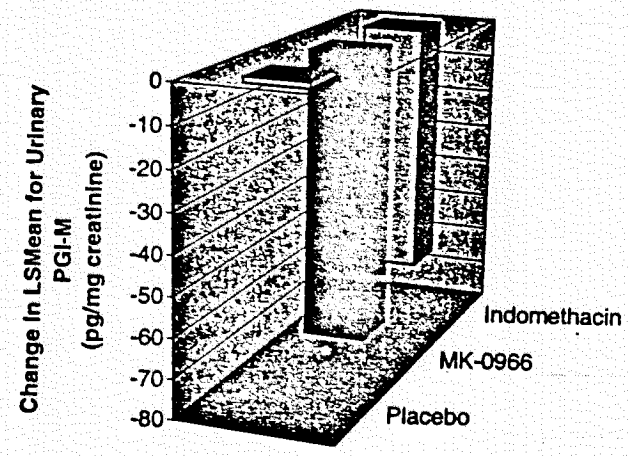
[Adapted from NDA 21-042, Vol. 1.115, Tables 25, page 82. *denotes: p≤0.05 vs. Baseline.]

Figure 7-023. LSMean Change From Baseline at Day 13 for Urinary PGI-M



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[Adapted from NDA 21-042, Vol. 1.115, Tables 26, page 84. *denotes: p≤0.05 vs. Baseline.]

Within and between treatment comparisons of the least squares mean changes from baseline at Day 14 for serum potassium were all not significant.

Safety: Nine subjects (6 women, 3 men) had 19 clinical adverse experiences, none of which were serious. No renal- and/or cardiovascular related adverse experiences in clinical or laboratory safety tests were observed. No clinically significant deviations were observed for electrocardiogram, heart rate, or systolic or diastolic blood pressure across varying time points.

[34] NDA 21-042, Volume 1.115, Table 25, page 82.

SUMMARY/COMMENTS

Study protocol #023 was a 2-week, double-blind, parallel-group study of renal function which demonstrated that MK-0966 50 mg daily was associated with a sodium-retaining effect in healthy elderly subjects maintained on a high-salt diet (200 mEq sodium/day). This effect of MK-0966, a specific COX-2 inhibitor, was not significantly different from that of indomethacin, a dual COX-1/COX-2 inhibitor. Only indomethacin reduced the creatinine and iohexol clearances, and the excretion of urinary 11-dehydro thromboxane B2. However, MK-0966 and indomethacin were associated with significant reductions at Day 13 in the excretion of urinary urinary 6-keto-$PGF_{1\alpha}$ and PGI-M. No renal- and/or cardiovascular related adverse experiences in clinical or laboratory safety tests were observed.

15.2 Pharmacodynamic Interaction Studies

15.2.1 Protocol #054[35]: A Double-Blind, Placebo-Controlled, Randomized, Crossover Study Of The Effects Of Mk-0966, Indomethacin And Placebo On The Antihypertensive Response To Benazepril In Patients With Mild-To-Moderate Hypertension

METHODS

This study had a multicenter (six investigators at 6 U.S. sites) double-blind, placebo-controlled, balanced, 3-period, crossover, clinical design comparing the antihypertensive activity of a stable dose of an angiotensin-converting enzyme (ACE) inhibitor, benazepril 10, 20, 30 or 40 mg once daily, coadministered with 25 mg MK-0966 daily, 75 mg indomethacin daily, or placebo in patients with mild-to-moderate hypertension. All patients were individually stabilized (diastolic blood pressure [DBP] ≤100 mm Hg) on once-daily benazepril prior to entering the 3-period crossover portion of the trial. They remained on the same dose of benazepril throughout the 12 weeks of the study. Each 4-week treatment period, consisting of coadministration with MK-0966, indomethacin, or placebo, followed the previous period with a 1-week washout interval. End points were monitored on the last day (Day 28) of each 4-week treatment period.

The patient population studied consisted of healthy males or females between 18 and 65 years with mild-to-moderate hypertension (diastolic BP of 95 to 115 mm Hg off all antihypertensive medication).

The primary therapy period was from 26JUL97 to 04FEB98. The in-house case report form cutoff date was 30APR98.

The main objectives were:

i. To determine the influence of MK-0966, indomethacin sustained-release formulation (hereafter referred to as indomethacin), and placebo on blood pressure in patients with mild-to-moderate hypertension treated with benazepril,
ii. To compare the safety and tolerability of MK-0966, indomethacin and placebo coadministered with benazepril, and
iii. To evaluate the influence of treatments on serum electrolyte concentrations, most notably, potassium.

Laboratory evaluations (serum electrolytes, serum creatinine, total protein, and liver function tests) and heart rate and body weight were evaluated for evidence of adverse effects.

RESULTS

Demographics: Twenty-seven 27 men, age 29 to 64 years old, and 14 females, age 44 to 65 years old, were randomized into the study. Six patients were Hispanic, 1 Asian, 1 Black and the remainders were White. These patients' primary active disease was hypertension. Of the forty-one patients randomized, 36 completed the study[36].

[35] NDA 21-042, Vol. 1.166-1.167, Reference 054.

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24-Hour Mean ABPM Measurements: 24-hour mean DBP values of 85.7, 84.9, and 83.8 mm Hg were observed following MK-0966, indomethacin, and placebo treatments, respectively (Table 1-054). There was no overall treatment effect in the ANOVA model (p=0.124).

Table 1-054. Between-Treatment Comparisons for 24-Hour Mean DBP (mm Hg)

Treatment	N	Mean	Difference From Placebo		Difference From Indomethacin	
			Mean	90% CI	Mean	90% CI
24-Hour Mean DBP						
MK-0966	36	85.7	1.9	(0.3, 3.6)	0.8	(-0.9, 2.4)
Indomethacin	36	84.9	1.1	(-0.5, 2.8)	-	-
Placebo	36	83.8	-	-	-	-
Posterior probability (true mean of MK-0966 minus placebo <5 mm Hg) = 0.999.						
Root mean square error (RMSE) = 4.2, overall treatment p-value = 0.124.						

[Adapted from NDA 21-042, Vol. 1.166, Table 10, page 44.]

Table 2-054 summarizes the 24-hour mean SBP and MAP.

Table 2-054. 24-Hour Mean SBP and MAP (mm Hg)

Treatment	N	Mean	SE
24-Hour Mean SBP			
Baseline	36	133.2	2.0
MK-0966 25 mg	36	139.9	2.2
Indomethacin 75 mg	36	137.4	2.2
Placebo	36	135.4	2.2
24-Hour Mean MAP			
Baseline	36	98.8	1.3
MK-0966 25 mg	36	103.8	1.5
Indomethacin 75 mg	36	102.4	1.6
Placebo	36	101.0	1.5

[Adapted from NDA 21-042, Vol. 1.166, Table 11, page 46.]

For 24-hour mean SBP, the mean difference (90% CI) for MK-0966 versus placebo (MK-0966 minus placebo) was 4.5 (2.2, 6.8) mm Hg and for indomethacin versus placebo (indomethacin minus placebo) was 2.0 (-0.3, 4.4) mm Hg (Table 3-054).

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[36] Five patients (ANs 012, 013, 015, 028, and 029) were discontinued from the study. AN 012 discontinued after completing 4 weeks of indomethacin treatment due to repeated ABPM failures. The rest of the patients were discontinued because of clinical or laboratories adverse events.

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Table 3-054. Between-Treatment Comparisons for 24-Hour Mean SBP and MAP (mm Hg)

Treatment	N	Mean	Difference From Placebo		Difference From Indomethacin	
			Mean	90%CI	Mean	90% CI
24-Hour Mean SBP						
MK-0966	36	139.9	4.5	(2.2, 6.8)	2.5	(0.1, 4.7)
Indomethacin	36	137.4	2.0	(-0.3, 4.4)	-	-
Placebo	36	135.4	-	-	-	-
RMSE = 5.9, overall treatment p-value = 0.006.						
24-Hour Mean MAP						
MK-0966	36	103.8	2.8	(1.0, 4.6)	1.4	(-0.5, 3.1)
Indomethacin	36	102.4	1.4	(-0.4, 3.2)	-	-
Placebo	36	101.0	-	-	-	-
RMSE = 4.6, overall treatment p-value = 0.033.						

[Adapted from NDA 21-042, Vol. 1.166, Table 12, page 47.]

Safety: Twenty-three patients reported a total of 61 clinical adverse experiences (14 on MK-0966 25 mg; 29 on indomethacin 75 mg; 18 on placebo). Of these, there was 1 episode of nocturia while on placebo), and 1 incident of mid-chest pain while on MK-0966 25 mg.

A total of 44 laboratory adverse experiences were reported in 9 patients including the following: two events of increased serum creatinine, 1.4 mg/dL and 1.4 mg/dL for AN 016 (normal range, 0.8 to 1.2 mg/dL); one event of increased potassium, 5.2 mEq/L for AN 016 (normal range, 3.6 to 4.8 mEq/L) (Table 4-054).

Table 4-054. Postrandomization Laboratory Adverse Experiences

AN	Adverse Experience	Treatment	Value	Normal Range	Onset	Action Taken
009	Increased potassium	MK-0966	5.9 mEq/L	3.6 to 4.8 mEq/L	Period 2	None
014	Increased potassium	MK-0966	5.8 mEq/L	3.6 to 4.8 mEq/L	Period 3	None
016	Increased creatinine	MK-0966	1.4 mg/dL	0.8 to 1.2 mg/dL	Period 2	None
	Increased potassium	Placebo	5.20 mEq/L	3.6 to 4.8 mEq/L	Period 3	None
	Increased creatinine	Placebo	1.4 mg/dL	0.8 to 1.2 mg/dL	Period 3	None

[Adapted from NDA 21-042, Vol. 1.166, Table 18, page 69.]

SUMMARY/COMMENTS

NSAIDs are known to attenuate the antihypertensive effects of ACE inhibitors, β-blockers and diuretics, the present trial only examined ACE inhibitors. The primary objective of this study was to determine the influence of MK-0966 on blood pressure in patients with mild-to-moderate hypertension treated with the commonly used ACE inhibitor, benazepril. Similarly to indomethacin, MK-0966 attenuated the antihypertensive efficacy of the ACE inhibitor benazepril. MK-0966 and indomethacin were associated with mean (90% CI) increases (relative to placebo) in 24-hour mean SBP of 4.5 (2.2, 6.8) and 2.0 (-0.3, 4.4) mm Hg, respectively, and increases in the 24-hour mean MAP of 2.8 (1.0, 4.6) and 1.4 (-0.4, 3.2) mm Hg, respectively. Of note, two events of increased serum creatinine, and one event of increased potassium were reported.

15.3 Pharmacokinetic Studies

15.3.1 Protocol #064[37]: An Open-Label, Three-Part, Oral Study To Investigate The Pharmacokinetics, Safety, And Tolerability Of Mk-0966 In Patients With Renal Insufficiency

METHODS

This was an open-label, 2 parts study in 6 patients on hemodialysis (creatinine clearance <5 ml/min/1.73 m^2). The study consisted of two single-dose treatments of 50 mg MK-0966 separated by a washout interval of at least 28 days. During part 1 the patients took the study drug 24 hours after their previous hemodialysis and 48 hours before their next hemodialysis. The 48-hour hemodialysis was initiated immediately following the 48-hour blood draw. Plasma samples were collected at specified times before and after drug intake and every half-hour during hemodialysis, and the dialysate was collected for a 1-minute interval every half-hour for MK-0966 assay. Each hemodialysis session lasted 3 hours. Part 2 consisted of the same 6 patients on hemodialysis from part 1. These patients took the study drug 4 hours prior to the their normally scheduled hemodialysis. Their subsequent hemodialysis was initiated immediately following the 4-hour blood draw. Plasma samples were collected at specified times before and after drug intake and every hour during hemodialysis, and the dialysate was collected for MK-0966 assay. There was a period of ≥1 month between parts 1 and 2[38].

This study was designed to determine the effect of renal insufficiency and hemodialysis on the plasma pharmacokinetics of MK-0966 after a single oral dose of 50 mg. The main objectives of the study were:

i. To evaluate the safety and tolerability of MK-0966 in patients with renal insufficiency.
ii. To determine the effect of renal dysfunction on the plasma pharmacokinetics of MK-0966 after a single oral dose of 50 mg.
iii. To determine the effects of hemodialysis on the plasma pharmacokinetics of MK-0966 after a single oral dose of 50 mg.

RESULTS

Demographics: Four men and 2 women with end-stage renal disease on hemodialysis were randomized, 3 were White, 2 Black, and 1 Hispanic.

Pharmacokinetics: Comparisons of plasma pharmacokinetic parameters, i.e., $AUC_{(0\text{-}48\ hr)}$, $AUC_{(0-\infty\ hr)}$, 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[39] (Tables 1-064 to 6-064).

Table 1-064. MK-0966 $AUC_{(0\text{-}48\ hr)}$ (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	6501	0.096
Healthy Volunteers. n=47	25-50 mg	8008	

[Adapted from NDA 21-042, Volume 1.177, Table 13, page 41. [a]denotes: adjusted mean. [b]denotes: between-population p-Value.]

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[37] NDA 21-042, Volume 1.177, Reference P064.

[38] Because the MK-0966 clearance in hemodialysis patients in Part 1 was not significantly different from that seen in normal control subjects, Part 3 in patients with advanced renal disease 5 to 30 mL/min/1.73 m^2, was determined to be unnecessary and was not carried out.

[39] NDA 21-042, Volume 1.177, Reference P064, pages 39-51.

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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 (%)

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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."

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