This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

2. Synopsis

MERCK RESEARCH LABORATORIES MK-0524B, Tablet Primary Hypercholesterolemia or Mixed Hyperlipidemia	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: A Multicenter, Randomized, Double-Blind, "Factorial" Design Study to Evaluate the Lipid-Altering Efficacy and Safety of MK-0524B (dosed as coadministered MK-0524A and Simvastatin Tablets) in Patients With Primary Hypercholesterolemia or Mixed Hyperlipidemia #022

INVESTIGATOR(S)/STUDY CENTER(S): One hundred and eight (108) sites participated.
US: 56 sites
Non US: 52 sites (Brazil - 5, Canada - 4, Denmark - 3, France - 3, Hong Kong - 2, Lithuania - 9, Malaysia - 3, Netherlands - 2, Norway - 2, Peru - 3, Poland - 3, Sweden - 4, Taiwan - 3, and United Kingdom - 6.

PUBLICATION(S): No

PRIMARY THERAPY PERIOD: 17-May-2006 to 14-Jan-2007 **CLINICAL PHASE:** III

DURATION OF TREATMENT: 12-week double blind treatment period preceded by a 4-week placebo run in period.

OBJECTIVE(S): Primary: In patients with primary hypercholesterolemia or mixed hyperlipidemia, evaluate the low-density lipoprotein cholesterol (LDL-C) lowering efficacy of coadministered MK-0524A 2g + simvastatin (pooled across simvastatin doses of 20 and 40 mg) compared to MK-0524A 2g.

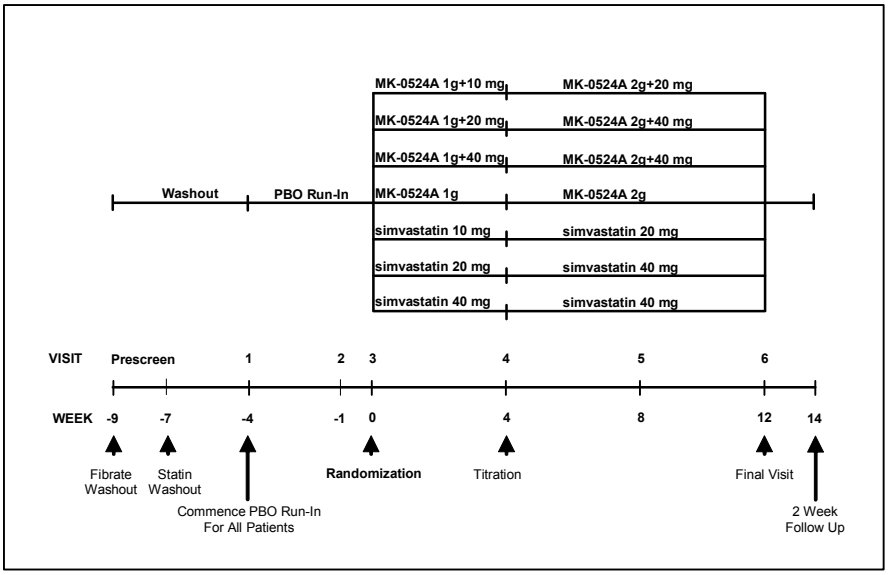
Key Secondary: In patients with primary hypercholesterolemia or mixed hyperlipidemia, evaluate (1) the effects of coadministered MK 0524A 2g + simvastatin (pooled across simvastatin doses of 20 and 40 mg) compared to simvastatin (pooled across doses of 20 and 40 mg) on high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), LDL-C, LDL-C:HDL-C ratio, non-HDL-C, Apolipoprotein B (Apo B), and Apolipoprotein A-I (Apo A-I); (2) the effects of coadministered MK-0524A 2g + simvastatin (pooled across simvastatin doses of 20 and 40 mg) compared to MK-0524A 2g on HDL-C, TG, LDL-C:HDL-C ratio, non-HDL-C, Apo B, and Apo A-I; (3) safety and tolerability of coadministered MK-0524A + simvastatin.

Other Secondary: In patients with primary hypercholesterolemia or mixed hyperlipidemia, assess the effects of coadministered MK-0524A + simvastatin on total cholesterol (TC), lipoprotein a (Lp(a)), TC:HDL-C ratio, C-reactive protein (CRP), Apolipoprotein C-III (Apo C-III), and lipid subfractions.

STUDY DESIGN: Double-blind, randomized, parallel-group study. Following a 6 - 8 week washout period of lipid-modifying therapies (if needed) and a concurrent 4-week placebo run-in, eligible patients were randomized to 1 of 7 treatment arms for 4 weeks in a 1:1:1:1:1:1:1 ratio. Treatment arms were the following:

- MK-0524A 1 g+10 mg/MK-0524A 2 g+20 mg
- MK-0524A 1 g+20 mg/MK-0524A 2 g+40 mg
- MK-0524A 1 g+40 mg/MK-0524A 2 g+40 mg
- MK-0524A 1 g/MK -0524A 2 g
- simvastatin 10 mg/simvastatin 20 mg
- simvastatin 20 mg/simvastatin 40 mg
- simvastatin 40 mg/simvastatin 40 mg

Statin/fibrate and other lipid modifying therapy naïve patients went directly to the placebo run-in if a fasting prescreen blood draw was not required. After 4 weeks of randomized treatment, doses were doubled in all treatment arms (with the exception of the simvastatin 40 mg group which remained unchanged, and the coadministered MK-0524A 1g + simvastatin 40 mg arm which was increased to MK-0524A 2g + simvastatin 40 mg) for an additional 8 weeks of treatment.



SUBJECT/PATIENT DISPOSITION:

	MK-0524A 2 g+20 and 40 mg (pooled)	MK-0524A 2g	Simvastatin 20 and 40 mg (pooled)	TOTAL
SCREENING FAILURES:				1904
RANDOMIZED:	610	195	593	1398
Male (age range)	265 (26-82)	82 (30-76)	268 (24-83)	615 (24-83)
Female (age range)	345 (24-84)	113 (24-79)	325 (20-85)	783 (20-85)
COMPLETED:	478 (78.4%)	143 (73.3%)	532 (89.7%)	1153 (82.5%)
DISCONTINUED:	132 (21.6%)	52 (26.7%)	61 (10.3%)	245 (17.5%)
Clinical adverse experience	72 (11.8%)	27 (13.8%)	29 (4.9%)	128 (9.2%)
Flushing with product	29 (4.8%)	17 (8.7%)	2 (0.3%)	48 (3.4%)
Laboratory adverse experience	0 (0.0%)	0 (0.0%)	3 (0.5%)	3 (0.2%)
Other	31 (5.1%)	8 (4.1%)	27 (4.6%)	66 (4.7%)

DOSAGE/FORMULATION NOS.:
MK-0524A or placebo was provided in bottles as bilayer combination tablets consisting of ER niacin 1g + MK-0524 20 mg (MK 0524A). Simvastatin or placebo was provided in blister packs as tablets consisting of simvastatin 10 mg, 20 mg, 40 mg, or a closely matching placebo. The dose of MK-0524 was fixed at 20 mg with ER niacin 1g and 40 mg with ER niacin 2g.

Placebo Run-In Period (4 weeks): Patients took 1 tablet daily in the evening or at bedtime, with food.
Treatment Period I (4 weeks): Patients took 1 tablet from the bottle and 1 tablet from each column from the blister card daily (3 tablets total from the blister card) in the evening or at bedtime, with food.
Treatment Period II (8 weeks): Patients took 2 tablets from the bottle and 1 tablet from each column from the blister card daily (3 tablets total from blister card) in the evening or at bedtime, with food.

The following formulation numbers were utilized:

Material	Formulation
MK-0524A 1 g	[redacted]
MK-0524A 1 g placebo	
simvastatin 10 mg	
simvastatin 10 mg placebo	
simvastatin 20 mg	
simvastatin 20 mg placebo	
simvastatin 40 mg	
simvastatin 40 mg placebo	

DIAGNOSIS/INCLUSION CRITERIA:

Men and women ≥18 and ≤85 years of age with primary hypercholesterolemia or mixed hyperlipidemia were included if TG ≤350 mg/dL (3.95 mmol/L); alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were ≤ 1.5x the upper limit of normal (ULN); and creatine kinase (CK) was ≤ 2x ULN. High risk patients (CHD/CHD risk equivalent, including diabetes, per NCEP ATP III guidelines) were to be excluded. Patients' glycemic statuses were determined prior to randomization. Eligible patients met the criteria for one of the following 2 NCEP ATP III categorization of CHD risk:

1. 0-1 risk factor with LDL-C 130 to 190 mg/dL (3.37 to 4.92 mmol/L)
2. Multiple risk factors with LDL-C 130 to 160 mg/dL (3.37 to 4.14 mmol/L)

EVALUATION CRITERIA:

Efficacy: All laboratory efficacy measurements were performed using standardized methods. Fasting lipid/lipoprotein values were evaluated.

Safety: Clinical evaluation included physical examination, vital signs, electrocardiogram (ECG), adverse experiences, and patient interviews. Central laboratory evaluations included ALT, AST, CK, and fasting serum glucose levels (FSG). In addition, thyroid function and other laboratory assessments, including hematology and urinalysis were performed.

STATISTICAL PLANNING AND ANALYSIS:

EFFICACY: The primary hypothesis, comparing coadministered MK 0524A 2g + simvastatin (pooled across simvastatin doses of 20 and 40 mg) to MK-0524A 2g in percent change from baseline in LDL-C at Week 12 (Week 8 post-titration), was evaluated using an analysis of covariance (ANCOVA) model with the terms for treatment, gender, country, and baseline LDL-C as a covariate. The comparison was performed using the appropriate contrast from the ANCOVA model. The secondary hypotheses, comparing coadministered MK-0524A 2g + simvastatin (pooled across simvastatin doses of 20 and 40 mg) to simvastatin (pooled across simvastatin doses of 20 and 40 mg) in percent change from baseline in HDL-C, LDL-C, and Apo A-I at Week 12 were evaluated using an ANCOVA model similar to the one used for the analysis of the primary hypothesis, substituting the relevant baseline measurement as the covariate. The comparisons were performed using appropriate contrasts from the ANCOVA model. The secondary hypotheses, comparing coadministered MK 0524A 2g + simvastatin (pooled across simvastatin doses of 20 and 40 mg) to MK-0524A 2g in percent change from baseline in non-HDL-C and Apo B at Week 12 were evaluated using an ANCOVA similar to the one used in the analysis of the primary hypothesis.

The percent change from baseline in TG was analyzed by nonparametric methods. The ANCOVA model described above was applied to the Tukey's normalized ranks of the percent change from baseline in TG, while the Tukey's normalized ranks of baseline TG was used as a covariate. The comparison of MK 0524A 2g + simvastatin (pooled across simvastatin doses of 20 and 40 mg) with simvastatin (pooled across the simvastatin doses of 20 and 40 mg) were performed using the respective contrast from the ANCOVA model. The between-treatment group differences in medians were assessed using Hodges-Lehman estimates with the corresponding distribution-free 95% CI based on Wilcoxon's rank sum test.

A closed ordered testing procedure was applied to the primary and 6 key secondary hypotheses (in the order they are listed in) to adjust for multiplicity and to control the overall α level across these 6 tests at α=0.050.

SAFETY: Safety and tolerability were assessed by a statistical and clinical review of all safety parameters, including adverse experiences, laboratory values, and vital signs. Statistical tests were performed and the 95% CI and p-values were displayed on the Tier 1 AEs and/or tolerability parameters (prespecified safety parameters of interest). For Tier 2 events (that includes, among other categories of AEs, individual AEs that occurred in at least 2% of patients in one or more of the groups), 95% CIs of the between treatment groups difference of incidence rates were provided. For all other clinical and laboratory AEs, events were listed and summarized by frequency of occurrence, only the counts and percentages were tabulated by treatment group. The between-group pairwise comparisons were performed using Fisher's Exact test. Ninety-five percent CIs of between-treatment differences in percentages were derived using Wilson's score method. Vital signs and selected laboratory tests were also summarized.

RESULTS:

EFFICACY:

All of the pre-specified primary and secondary efficacy hypotheses covered by multiplicity were met proving superiority of MK-0524A 2g+simvastatin (pooled across simvastatin doses of 20 and 40). A summary for the magnitude of treatment effect expressed in LS means (or medians) for the primary and key secondary lipid endpoints are provided in Table 1. The comparisons covered by multiplicity (Bold in the table) are all significant with p-values <0.001. The lipid parameters are listed in the order consistent with multiplicity strategy.

Summary of LS Mean (95% CI) for Percent Change from Baseline at Week 12 in the Primary and Key Secondary Lipid Endpoints
Full-Analysis-Set

Lipids Endpoints	MK-0524A +Simvastatin ($n^{\dagger}$=520)	MK-0524A ($n^{\dagger}$=160)	Simvastatin ($n^{\dagger}$=565)	MK-0524A+ Simvastatin vs. MK-0524 A	MK-0524A+ Simvastatin vs. Simvastatin
LDL-C	-47.9 (-50.0, -45.8)	-17.0 (-20.3, -13.6)	-37.0 (-39.1, -35.0)	**-30.9 (-34.4, -27.3)**	**-10.8 (-13.2, -8.4)**
HDL-C	27.5 (25.8, 29.2)	23.4 (20.7, 26.2)	6.0 (4.3, 7.6)	4.1 (1.2, 6.9)	**21.5 (19.6, 23.5)**
Triglycerides (TG, median)	-33.3 (-36.1, -30.6)	-21.6 (-27.1, -16.1)	-14.7 (-17.1, -12.3)	-10.8 (-15.4, -6.2)	**-18.7 (-21.6, -15.8)**
Non HDL-C	-45.8 (-47.7, -43.9)	-18.1 (-21.1, -15.0)	-33.4 (-35.3, -31.6)	**-27.7 (-31.0, -24.5)**	-12.4 (-14.6, -10.2)
Apo B	-41.0 (-42.8, -39.1)	-17.1 (-20.2, -14.1)	-28.8 (-30.6, -27.0)	**-23.8 (-27.0, -20.6)**	-12.2 (-14.3, -10.1)
Apo A-I	8.6 (7.1, 10.0)	8.2 (5.9, 10.6)	2.3 (0.9, 3.7)	0.3 (-2.1, 2.8)	**6.3 (4.6, 7.9)**
LDL-C:HDL-C Ratio	-57.1 (-59.4, -54.8)	-31.2 (-34.9, -27.6)	-39.8 (-42.0, -37.6)	-25.9 (-29.8, -22.0)	-17.3 (-19.9, -14.7)

MK-0524A+Simvastatin = MK-0524A 2 g+simvastatin all doses pooled; Simvastatin = simvastatin all doses pooled.
† Sample size is based on the number of patients included in the analysis of the primary lipid endpoint (percent change from baseline at Week 12 with last post-titration (Period II, after Visit 4) value carry forward in LDL-C).

SAFETY:

Other than adverse experiences and discontinuations due to flushing, which occurred more frequently in the MK-0524A 2 g + 20 and 40 mg (pooled) and the MK-0524A 2 g alone treatment groups, MK-0524A 2 g coadministered with simvastatin had a safety profile similar to MK-0524A and simvastatin 20 and 40 mg (pooled) with respect to the incidence of adverse experiences including those that were drug-related, serious or led to discontinuation.

The clinical and laboratory drug-related adverse experiences that occurred more frequently in the MK-0524A 2 g+20 and 40 mg (pooled) and MK-0524 treatment groups than in simvastatin 20 and 40 mg (pooled) treated patients were those typically associated with niacin and niacin-containing products, specifically clinical adverse experiences related to flushing and gastrointestinal upset, and laboratory adverse experiences related to elevations in fasting blood glucose, and uric acid. Serious clinical adverse experiences were reported in 7 (1.1%), 5 (2.6%), and 5 (0.8%) of patients in the MK-0524A 2 g+20 and 40 mg (pooled), MK-0524A 2 g, and simvastatin 20 and 40 mg (pooled) treatment groups, respectively. Of those serious adverse events, 3 were considered to be related to study drug (1 per treatment group).

In the predefined areas for the assessment of safety, the incidence of adverse experiences was comparable between the 3 treatment groups. Specifically for muscle, there were no cases of myopathy or rhabdomyolysis in this study. There were 0 (0.0%) patients in the MK-0524A 2 g + simvastatin (pooled), 1 (0.5%) in the MK-0524A, and 2 (0.3%) patients in the simvastatin (pooled) treatment groups with CK levels ≥ 10xULN. One patient had a ≥10-fold CK elevation with muscle symptoms in the MK-0524A 2 g group which was not considered to be related to study drug. Two patients had ≥10-fold CK elevations without muscle symptoms in the simvastatin 10mg/simvastatin 20mg treatment group; one elevation was considered to be study drug related and the other was not. For liver, 2 patients (0.3%) in the MK-0524A 2 g + 20 and 40 mg (pooled) group, 1 (0.5%) in the MK 0524A group, and 6 (1.0%) in the simvastatin 20 and 40 mg (pooled) had consecutive ≥3x ULN elevations in ALT and/or AST. One patient in the MK-0524A 1 g + 20 mg/MK-0524A 2 g + 40 mg group reported a hepatitis adverse experience (0.5%) which was deemed not to be drug related by the investigator. Adverse experiences related to glycemic control were reported by 2 (0.3%) patients in the MK-0524A 2 g + 20 and 40 mg (pooled) group, 1 (0.5%) patient in the MK-0524A 2 g group, and 2 (0.3%) patients in the simvastatin 20 and 40 mg (pooled) group. Of these, one report of impaired fasting glucose in the MK-0524A 2 g + 20 and 40 mg (pooled) group was considered to be drug-related. For glycemic control, there was a median increase in FBG of 4.0 mg/dL in the MK-0524A 2 g + simvastatin (pooled) and MK-0524A groups and of 1.0 mg/dL in the simvastatin (pooled) group.

CONCLUSIONS:

In patients with primary hypercholesterolemia or mixed hyperlipidemia, MK-0524B 2 g (coadministered as MK-0524A 2 g + simvastatin 20 and 40 mg, pooled) produced:

(1) greater reductions in LDL-C than MK-0524A 2 g,
(2) greater increases in HDL-C than simvastatin 20 and 40 mg (pooled),
(3) greater reductions in triglycerides than simvastatin 20 and 40 mg (pooled),
(4) greater reductions in non-HDL-C than MK-0524A 2 g,
(5) greater reductions in LDL-C than simvastatin 20 and 40 mg (pooled),
(6) greater reductions in Apo B than MK-0524A 2 g, and
(7) greater increase in Apo A-I than simvastatin 20 and 40 mg (pooled).

MK-0524B (coadministered as MK-0524A + simvastatin) was generally well-tolerated.

AUTHORS: (CRS) (Statistician) (Clinical Monitor)

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