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-0524A, Tablet Primary Hypercholesterolemia or Mixed Hyperlipidemia	**CLINICAL STUDY REPORT SYNOPSIS**	
PROTOCOL TITLE/NO.: A Worldwide, Multicenter, Double-Blind, Randomized, Parallel, Placebo-Controlled Study to Evaluate the Lipid-Altering Efficacy, Safety and Tolerability of MK-0524A in Patients With Primary Hypercholesterolemia or Mixed Hyperlipidemia		#020
INVESTIGATOR(S)/STUDY CENTER(S): One hundred and thirty-eight (138) sites participated: US: 79 sites; Europe: 44 sites (Austria – 2, Denmark – 5, Finland – 2, Germany – 8, Italy – 5, Norway – 6, Spain – 6, Sweden 8, Switzerland – 2). Remaining Countries: Australia – 2 sites; Canada – 4 sites; Israel – 3 sites; Mexico – 6 sites		
PRIMARY THERAPY PERIOD: 16-Jan-2006 to 07-Dec-2006	**CLINICAL PHASE:**	III
DURATION OF TREATMENT: 24-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, (1) evaluate the efficacy of MK-0524A 2g relative to placebo on plasma concentrations of low-density lipoprotein cholesterol (LDL-C), and (2) assess the effects of MK-0524A relative to ER-niacin on flushing during the acute dosing period when measured by maximum Global Flushing Severity Score (GFSS) categorized into none/mild, moderate, severe, extreme during the first week of treatment. Key Secondary: In patients with primary hypercholesterolemia or mixed hyperlipidemia, (1) evaluate the efficacy of MK-0524A 2g relative to placebo on plasma concentrations of HDL-C, triglycerides (TG), LDL-C:HDL-C ratio, non-HDL-C, Apo B, and Apo A-I; (2) assess the effects of MK-0524A relative to ER-niacin on flushing as measured by (a) number of days/week with moderate or greater GFSS (GFSS≥4) during weeks 2 to 24 (chronic dosing period), (b) maximum daily GFSS during the first week of treatment (acute dosing period), (c) maximum GFSS categorized as none, mild, moderate, severe or extreme during the first week of treatment (acute dosing period), (d) percentage of patients with maximum GFSS moderate or greater (GFSS ≥4) during the first week of treatment (acute dosing period), (e) percentage of patients with maximum GFSS severe or extreme (GFSS ≥7) during the first week of treatment (acute dosing period), (f) number of days/week with mild or greater GFSS (GFSS≥1) during weeks 2 to 24 (chronic dosing period); (3) assess the effects of MK-0524A relative to ER-niacin on percentage of patients who discontinue study treatment due to flushing; (4) evaluate the effects of MK-0524A relative to placebo on LDL-C, HDL-C, TG, LDL-C:HDL-C ratio, non-HDL-C, Apo B, and Apo A-I in patients not on concomitant statin therapy; (5) assess safety and tolerability of MK-0524A. Additional Secondary: In patients with primary hypercholesterolemia or mixed hyperlipidemia, evaluate the effects of MK-0524A relative to placebo on Lp(a), total cholesterol (TC), and TC:HDL-C ratio.		
STUDY DESIGN: Double-blind, randomized, parallel, and placebo-controlled. Patients were randomized to MK-0524A 1 g combination tablet (ER niacin 1 g /MK-0524 20 mg), ER niacin 1g or placebo in a 3:2:1 ratio. After 4 weeks of double-blind treatment, all doses were up-titrated, increasing the MK-0524A doses to 2 g/40 mg and ER niacin to 2 g. Patients remained on stable dose strengths for the remaining 20 weeks. Allocation was stratified by on-going statin use and study site. The endpoints related to flushing use the same endpoints that were validated in Phase II. The aggregate flushing experience of redness, warmth, tingling or itching were measured daily using an electronic diary incorporating a scale with response categories of None, Mild, Moderate, Severe and Extreme using the Flushing Symptom Questionnaire (FSQ). The categories are further refined with the Global Flushing Severity Score (GFSS), a numerical score with numbers 0 to 10 to allow for greater precision within the categories (None=0, Mild=1-3, Moderate=4-6, Severe=7-9, Extreme=10). Patients were asked to complete a Flushing Symptom Questionnaire (FSQ) daily to assess for flushing symptoms. In addition, patients who participated in the United States (US) completed an additional paper-based questionnaire assessing individual flushing symptoms at selected time points during the study.		

SUBJECT/PATIENT DISPOSITION:

	MK-0524A	ER niacin	Placebo	TOTAL
SCREENING FAILURES:				1693
RANDOMIZED:	800	543	270	1613
Male (age range)	475 (21-83)	349 (23-85)	157 (33-84)	981 (21-85)
Female (age range)	325 (27-81)	194 (25-85)	113 (28-83)	632 (25-85)
PRE-TREATMENT	n=2	n=2	n=0	n=4
DISCONTINUED:	2	2	0	4
Clinical Adverse Experience	0	1	0	1
Flushing with Product	1	0	0	1
Other	1	1	0	2
TREATMENT	n=798	n=541	n=270	n=1609
COMPLETED:	570 (71.4%)	347 (64.1%)	239 (88.5%)	1156 (71.8%)
DISCONTINUED:	228 (28.6%)	194 (35.9%)	31 (11.5%)	453 (28.2%)
Clinical adverse experience	68 (8.5%)	36 (6.7%)	12 (4.4%)	116 (7.2%)
Flushing with product	81 (10.2%)	120 (22.2%)	2 (0.7%)	203 (12.6%)
Laboratory adverse experience	16 (2.0%)	3 (0.6%)	1 (0.4%)	20 (1.2%)
Other	63 (7.9%)	35 (6.5%)	16 (5.9%)	114 (7.1%)

DOSAGE/FORMULATION NOS.:

Dosing: Blinded treatment was provided as a bilayer combination tablet consisting of ER niacin 1 g/MK-0524 20 mg (MK-0524A), ER niacin 1 g alone, or a closely matching double-placebo. Placebo Run-In Period (4 weeks): Patients took 1 tablet in the evening with food. Treatment Period I (4 weeks): Patients took 1 tablet in the evening with food. Treatment Period II: (20 weeks): Patients took 2 tablets in the evening with food. Formulation: The formulation numbers used for MK-0524A are [redacted] The formulation number used for closely matching placebo was: [redacted]

DIAGNOSIS/INCLUSION CRITERIA:

Men and women ≥18 and ≤85 years of age with primary hypercholesterolemia or mixed hyperlipidemia were included if triglycerides (TG) were ≤350 mg/dL (3.95 mmol/L); alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were ≤ 1.5 x the upper limit of normal (ULN); and creatine kinase (CK) was ≤ 2 x ULN. Patients' glycemic statuses were determined prior to randomization. Investigators were instructed to determine a patient's glycemic status at baseline as normal, impaired, or diabetic based on medical history, lab evaluations, and clinical judgment. They were also responsible for decisions regarding the management of patients' glycemic status (lifestyle changes, modification of anti-diabetic treatment regimen).

Eligible patients met the criteria for one of the following 4 NCEP ATP III categorization of CHD risk:

1. On a statin and is high risk (CHD/CHD risk equivalent including diabetes) with an LDL-C <100 mg/dL (2.59 mmol/L);
2. On a statin and has multiple risk factors (≥2 RF) with an LDL-C <130 mg/dL (3.37 mmol/L);
3. On a statin and is low risk (0-1 RF) with an LDL-C ≥130 mg/dL and ≤190 mg/dL (3.37 and 4.92 mmol/L);
4. Not on a statin or other lipid-modifying therapy and is low risk (0-1 RF) according to NCEP ATP III criteria with an LDL-C ≥130 mg/dL and ≤190 mg/dL (3.37 and 4.92 mmol/L).

EVALUATION CRITERIA:

EFFICACY: Co-Primary Endpoints: Percent change from baseline across Weeks 12-24 in LDL-C. Maximum GFSS categorized as none/mild, moderate, severe or extreme during the first week of treatment. Secondary Endpoints: Percent change from baseline across Weeks 12-24 in following lipid measurements: HDL-C, TG, LDL-C:HDL-C ratio, non-HDL-C, Apo B, Apo A-I;. Number of days with moderate or greater GFSS (GFSS ≥4) during Weeks 2-24; maximum daily GFSS score during Week 1; maximum GFSS categorized as none, mild, moderate, severe, or extreme during Week 1; percent of patients with maximum GFSS moderate or greater (GFSS≥4) during Week 1; percent of patients discontinuing study medication due to flushing; ; percent of patients with maximum GFSS severe or extreme (GFSS≥7) during Week 1; number of days per week with mild or greater GFSS (GFSS≥1) during Weeks 2-24, and percent change from baseline across Weeks 12-24 in Lp(a), TC, and TC:HDL ratio;

SAFETY: Primary Parameters: Clinical evaluation (physical examination, vital signs); adverse events; laboratory surveillance—ALT, AST, CK, serum creatinine, fasting serum glucose, uric acid, amylase, LDH, phosphorus, platelet count, and prothrombin time, and other laboratory measurements (hematology, chemistry, urinalysis, beta-human chorionic gonadotropin [β-hCG]). Areas of safety were pre-defined for inferential assessment; muscle effects, liver effects, glycemic control, and adjudicated serious cardiovascular events. Pre-specified discontinuation was defined for confirmed consecutive elevations in the following lab parameters: CK, ALT/AST, and TG. Pre-specified discontinuation was also defined for patients who experienced hypersensitivity or severe intolerance to study therapy or who required continuous treatment with systemic corticosteroids.

STATISTICAL PLANNING AND ANALYSIS:

Efficacy: An analysis of variance (ANOVA) model was used to analyze the primary lipid endpoint of percent change from baseline in LDL-C across Weeks 12 to 24 (the time interval where the plateau of MK-0524A 2g lipid efficacy was expected to be achieved) The ANOVA model included factors for treatment (MK-0524A, ER niacin and placebo), country, gender and stratum defined by concomitant statin use. The primary lipid efficacy hypothesis regarding superiority of MK-0524A to placebo was assessed by testing the difference in least square (LS) means of MK-0524A versus placebo. The co-primary hypothesis of amelioration of flushing during the acute dosing period with MK-0524A relative to ER niacin was evaluated by maximum GFSS during the first week of treatment categorized as none/mild, moderate, severe or extreme using the Cochran-Mantel-Haenszel (CMH) test stratified by country.

The testing of key secondary lipid or flushing endpoints was conditional on the success of both primary endpoints. As both primary comparisons were statistically significant at α=0.05 level, therefore, 3 closed ordered testing procedures were applied separately to three families (lipids, flushing, and lipids in the naïve subset of patients) of key secondary hypotheses.

Key secondary lipid endpoints of percent change from baseline in HDL-C, LDL-C:HDL-C ratio, non-HDL-C, Apo B, Apo A-I were analyzed by the ANOVA model similar to the one used for the LDL-C analysis. Percent change from baseline in TG was analyzed using non-parametric methods based on medians.

The key secondary flushing hypothesis for the maintenance phase of therapy - the flushing endpoint of number of days per week with moderate or greater GFSS during Weeks 2 to 24 (with number of days categorized as 0, >0 and ≤1, >1 and ≤2, >2 and ≤3, >3 days per week), was assessed by the CMH test stratified by country. The other key flushing endpoint assessing flushing in the maintenance phase of therapy defined by number of days per week with mild or greater GFSS during Weeks 2 to 24 was analyzed similarly.

The key secondary flushing endpoint of maximum GFSS (as a numeric score on its 11-point scale) during Week 1 was analyzed by an ANOVA model with factors for treatment (MK-0524A and ER niacin) and country, where treatment effect was assessed by testing the difference in LS means of MK-0524A versus ER niacin. A logistic regression model with factors for treatment (MK-0524A and ER niacin) and region was used to assess the following key secondary flushing endpoints: percentage of patients with moderate or greater GFSS during Week 1, percentage of patients with severe or extreme GFSS during Week 1, and percentage of patients discontinued due to flushing. Treatment effect with MK-0524A relative to ER niacin was assessed by testing the odds ratio estimated from the logistic regression model for the binary key flushing endpoints.

A total of 1200 evaluable patients were planned (600 with MK-0524A, 400 with ER niacin and 200 with placebo respectively) for the efficacy analyses. Assuming a standard deviation of 17%, it was expected that the study would have 95% (99%) power to detect a difference of 5.0% (6.0%) for percent change in LDL-C between MK-0524A and placebo. The study would have more than 99% power to detect a difference in percentage of patients with maximum GFSS during Week 1 categorized (none/mild, moderate, severe or extreme) between MK-0524A and ER niacin, if the true percentages of patients falling into these categories were 39%, 26%, 26%, 9% with ER niacin, and 63.5%, 25%, 11%, 0.5% with MK-0524A, respectively.

Safety: A multi-tiered approach was used in evaluating the safety and tolerability parameters in this study. Inferential comparisons utilizing Fisher's exact test was performed for the Tier 1 safety parameters (e.g., ALT/AST consecutive elevations≥3xULN, CK elevations≥10xULN, etc. as specified in the protocol). 95% confidence intervals based on Wilson's score method for between group differences were provided for the Tier 2 safety parameters, predefined limits of change parameters and confirmed cardiovascular events as specified in the protocol. For other adverse experiences, only counts and percentages were tabulated.

For patients without a diagnosis of diabetes at baseline, percentage of patients with a new diagnosis of diabetes or new diagnosis of impaired fasting serum glucose or other glucose related laboratory adverse experiences were tabulated for each treatment group; for patients with a diagnosis of diabetes at baseline, percentage of patients with worsening of existing diabetes or with an increase in dose or addition of new anti-diabetic medication were tabulated for each treatment group.

Summary statistics and 95% Confidence Intervals (CIs) were computed for change from baseline in glucose (in diabetic patients and separately in non-diabetic patients), HbA_{1c} (in diabetic patients), ALT, AST and CK. Summary of change from baseline over time were provided for the pre-specified laboratory (glucose, ALT, AST, CK, serum creatinine, fasting blood glucose, uric acid, amylase, LDH, phosphorous, platelet count, prothrombin time and vital signs parameters.

RESULTS:

Efficacy: All of the prespecified primary and secondary efficacy hypotheses were proven in favor of MK-0524A ($p<0.001$ in all tests).

Compared with placebo, MK-0524A demonstrated superior lipid efficacy in all primary and key secondary lipid endpoints. Results based on LS means (or medians) within treatment groups and the differences in LS means (or medians) between MK-0524A and placebo for the primary and key secondary lipid hypotheses are displayed in the table below.

Primary and Key Secondary Lipid Endpoints
LS Mean (95% CI) for Percent Change from Baseline across Weeks 12 to 24

Lipids Across Weeks 12 to 24	Entire Study Cohort			Statin Naïve Cohort		
	MK-0524A ($n^{\dagger}$=696)	Placebo ($n^{\dagger}$=257)	Difference vs. Placebo	MK-0524A 2g ($n^{\dagger}$=227)	Placebo ($n^{\dagger}$=85)	Difference vs. Placebo
LDL-C	-18.9 (-21.0, -16.8)	-0.5 (-3.3, 2.4)	-18.4 (-21.4, -15.4)	-20.8 (-24.6, -17.0)	-3.5 (-8.1, 1.2)	-17.4 (-21.5, -13.2)
HDL-C	18.8 (17.2, 20.4)	-1.2 (-3.4, 1.0)	20.0 (17.7, 22.3)	18.8 (15.1, 22.5)	-0.6 (-5.0, 3.9)	19.4 (15.4, 23.3)
Triglycerides (median)	-21.7 (-23.9, -19.5)	3.6 (-0.5, 7.6)	-25.8 (-29.5, -22.1)	-21.8 (-26.2, -17.5)	7.7 (-0.8, 16.2)	-27.8 (-34.9, -20.9)
LDL-C:HDL-C ratio	-28.9 (-31.3, -26.5)	2.3 (-1.0, 5.5)	-31.2 (-34.6, -27.8)	-31.1 (-35.6, -26.6)	-1.1 (-6.6, 4.3)	-30.0 (-34.9, -25.1)
Non HDL-C	-19.0 (-20.8, -17.2)	0.8 (-1.6, 3.3)	-19.8 (-22.4, -17.3)	-20.8 (-24.2, -17.4)	-1.5 (-5.6, 2.6)	-19.3 (-23.0, -15.6)
Apo B	-16.4 (-18.0, -14.7)	2.5 (0.2, 4.7)	-18.8 (-21.2, -16.5)	-18.4 (-21.8, -15.1)	1.2 (-2.9, 5.3)	-19.6 (-23.2, -16.0)
Apo A-1	11.2 (10.1, 12.4)	4.3 (2.7, 5.9)	6.9 (5.3, 8.6)	11.1 (8.6, 13.6)	4.7 (1.7, 7.8)	6.4 (3.7, 9.1)

† Sample size is based on the number of patients included in the analysis of the primary lipid endpoint (percent change from baseline across weeks 12 to 24 in LDL-C).
All comparisons of MK-0524A versus placebo were statistically significant ($p<0.001$).

Compared with patients treated with ER niacin, patients treated with MK-0524A experienced significantly less flushing during the initiation of therapy as measured by the co-primary flushing endpoint of maximum GFSS categorized as none/mild, moderate, severe, extreme during Week 1 (results displayed below.)

Maximum GFSS Categorized as None/Mild, Moderate, Severe, Extreme During Week 1

Treatment	None/Mild n (%)	Moderate n (%)	Severe n (%)	Extreme n (%)	Total N
MK-0524A	538 (68.9)	136 (17.4)	80 (10.2)	27 (3.5)	781
ER niacin	233 (44.0)	120 (22.7)	135 (25.5)	41 (7.8)	529
Placebo	246 (93.9)	15 (5.7)	1 (0.4)	0 (0.0)	262
Between-Group Comparison					p-Value†
MK-0524A vs ER niacin					<0.001
† p-Value based on Cochran-Mantel-Haenszel (CMH) test stratified by country.					

Patients treated with MK-0524A experienced significantly less flushing in the initiation of therapy as measured by all key secondary flushing endpoints specified for the initiation phase: the difference in LS means of maximum GFSS during Week 1 was -1.8 (-2.2, -1.5) between MK-0524A and ER niacin ($p<0.001$); the percentage of patients falling into categories of none, mild, moderate, severe, extreme for maximum GFSS during Week 1 was 41.1%, 27.8%, 17.4%, 10.2%, 3.5% with MK-0524A and 21.7%, 22.3%, 22.7%, 25.5%, 7.8% with ER niacin, respectively ($p<0.001$); the percentage of patients with moderate or greater GFSS during Week 1 was 31.1% with MK-0524A and 56.0% with ER niacin ($p<0.001$); the percentage of patients with severe or greater GFSS during Week 1 was 13.7% with MK-0524A and 33.3% with ER niacin ($p<0.001$).

Patients treated with MK-0524A experienced significantly less flushing during the maintenance phase of therapy as measured by number of days per week with moderate or greater GFSS (GFSS≥4) during Weeks 2 to 24 (results displayed in the table below). Results for number of days per week with mild or greater GFSS (GFSS≥1) during Weeks 2 to 24 was also statistically significant ($p<0.001$).

Number of Days Per Week with GFSS ≥ 4 During Weeks 2 Through 24 Partitioned into 5 Categories

	Number of Days per Week with GFSS ≥ 4					
Treatment	0 n (%)	>0 and ≤ 1 n (%)	>1 and ≤ 2 n (%)	>2 and ≤ 3 n (%)	>3 n (%)	Total N
MK-0524A	347 (45.5)	314 (41.2)	45 (5.9)	20 (2.6)	37 (4.8)	763
ER niacin	120 (23.6)	241 (47.4)	64 (12.6)	36 (7.1)	47 (9.3)	508
Placebo	203 (75.7)	58 (21.6)	3 (1.1)	1 (0.4)	3 (1.1)	268
Between-Group Comparison						p-Value[†]
MK-0524A vs ER niacin						<0.001
[†] p-Value based on Cochran-Mantel-Haenszel (CMH) test stratified by country.						

The percentage of patients that discontinued due to flushing were 10.2% with MK-0524A and 22.2% with ER niacin ($p<0.001$).

SAFETY: Other than adverse experiences and discontinuations due to flushing which occurred more frequently in the ER niacin group, MK-0524A given as monotherapy or when added to on-going statin therapy had a safety profile similar to ER niacin 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 active treatment groups than in placebo 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 liver transaminases (ALT, AST), fasting blood glucose, uric acid, and creatine kinase. There were 37 (4.6%) serious adverse events in the MK-0524A treatment group, 18 (3.3%) in the ER niacin treatment group, and 9 (3.3%) in the placebo treatment group. Of those serious adverse events, 5 were considered drug-related: 4 in the MK-0524A treatment group and 1 in ER niacin treatment group. In the pre-defined areas for the assessment of safety, the incidence of adverse experiences was comparable between the 2 active treatment groups. Specifically for muscle, there were no cases of myopathy or rhabdomyolysis in either the MK-0524A or ER niacin treatment group. There were 3 (0.4%) patients with CK levels > 10 fold the ULN in the MK-0524A group. None of the patients with CK levels >10x ULN had concurrent muscle symptoms. For liver, 11 patients (1.4%) in the MK-0524A group, 5 patients (1.0%) in the ER niacin treatment group, and no patients (0%) in the placebo

group sustained consecutive and ≥3 fold ULN elevations in ALT and/or AST. No patients experienced hepatitis-related adverse experiences during the study. For glycemic control, FBG increased by 4 mg/dL in the MK-0524A and ER niacin groups compared to 0.5 mg/dL in the placebo group. Among diabetic patients, HbA1c was unchanged in placebo-treated patients and was increased by 0.2% and 0.1% in the MK-0524A and ER niacin groups, respectively. Patients on anti-diabetic therapies were allowed to manage their hyperglycemia through ongoing modifications of their anti-diabetic regimens during the course of treatment.

CONCLUSIONS:

EFFICACY: This 24 week study demonstrated that in patients with primary hypercholesterolemia or mixed hyperlipidemia, treatment with MK-0524A (administered as monotherapy or added to on-going statin use):

(1) Produced superior lipid-altering efficacy relative to placebo for LDL-C (co-primary endpoint), HDL-C, triglycerides (TG), LDL-C:HDL-C ratio, non-HDL-C, Apo B, and Apo A-I in the whole population and in the subgroup of patients not on concomitant statin therapy

(2) Produced significantly less flushing relative to ER-niacin during the initiation of therapy (Week 1) as measured by (a) maximum Global Flushing Severity Score (GFSS) categorized into none/mild, moderate, severe, extreme (co-primary endpoint); (b) maximum daily GFSS; (c) maximum GFSS categorized as none, mild, moderate, severe or extreme; (d) percentage of patients with maximum GFSS moderate or greater (GFSS ≥4); (e) percentage of patients with maximum GFSS severe or extreme (GFSS ≥7)

(3) Produced significantly less flushing relative to ER niacin during the maintenance phase of therapy (Weeks 2 to 24) as measured by (a) number of days/week with moderate or greater GFSS (GFSS≥4); (b) number of days/week with mild or greater GFSS (GFSS≥1)

(4) Resulted in fewer patients discontinuing due to flushing relative to ER niacin

SAFETY: MK-0524A given as monotherapy or added to on-going statin therapy was well tolerated. MK-0524A was associated with fewer flushing-related AEs and discontinuations, but otherwise, had a similar safety profile to that of ER niacin.

AUTHORS:

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