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 MK-0524 (+) niacin, Tablet Primary Hypercholesterolemia and Mixed Hyperlipidemia	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: A Worldwide, Multicenter, Double-Blind, Randomized, Parallel Study to Evaluate the Efficacy of MK-0524 to Improve Tolerability of Extended Release Niacin #023

INVESTIGATORS/STUDY CENTERS: Sixty-eight (68) sites participated: 43 in the United States, 3 in Austria, 7 in Germany, 6 in Italy, 5 in Norway, 4 in the United Kingdom

PRIMARY THERAPY PERIOD: 20-Jul-2006 to 19-Jan-2007 **CLINICAL PHASE:** III

DURATION OF TREATMENT: Ten weeks

OBJECTIVES: Primary: To demonstrate the efficacy of MK-0524 to protect against niacin-induced flushing in patients who resume therapy with either MK-0524A 2 g or ER niacin 2 g after a 5-day drug holiday from a stable dose of MK-0524A 2 g. This will be measured by the Maximum Global Flushing Severity Score (GFSS) categorized into none/mild, moderate, severe, extreme during the first 7 days following a 5-day drug holiday period. Secondary: (1) To demonstrate the efficacy of MK-0524 to protect against niacin-induced flushing in patients who resume therapy with either MK-0524A 2 g or ER niacin 2 g following a 5-day drug holiday from a stable dose of MK-0524A 2 g. This will be measured by (a) maximum GFSS during the first 7 days following a 5-day drug holiday period. (b) the percentage of patients with moderate or greater GFSS (GFSS $\geq$4) during the first 7 days following a 5-day drug holiday period. (c) percentage of patients with severe or extreme GFSS (GFSS $\geq$7) during the first 7 days following a 5-day drug holiday period. (2) To assess the safety and tolerability of MK-0524A. Exploratory: To assess flushing symptoms with MK-0524A versus ER niacin measured by: (a) The percentage of patients who discontinued study medication due to flushing during the first 7 days following a 5-day drug holiday period. (b) The number of days/week with moderate or greater Global Flushing Severity Score GFSS (GFSS $\geq$4) during the first 7 days following a 5-day drug holiday period. (c) Global Flushing Bothers Score (GFBS) based on flushing variables using the metrics and time points described for the GFSS-based variables. (d) Median duration of flushing episodes (minutes, as reported on the e-diary) during the first 7 days following a 5-day drug holiday period. (e) The percentage of patients with moderate or greater ($\geq$4) bothersome score because of difficulty sleeping due to flushing during the first 7 days following a 5-day drug holiday period.

STUDY DESIGN: This was a worldwide, multi-center, double-blind, randomized, parallel study. After an 8-week active run-in period on MK-0524A, patients continued in a 5:5:1 ratio to 1 of 3 treatment regimens: MK-0524A placebo for 5 days (drug holiday) followed by MK-0524A 2 g for an additional 7 days; MK-0524A placebo for 5 days (drug holiday) followed by ER niacin 2 g for an additional 7 days; MK-0524A 2 g for the remainder of the study (~2 weeks). 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 was 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 were further refined with the 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.

SUBJECT/PATIENT DISPOSITION:

Active Run-in Plus Drug Holiday

	MK-0524A 1g/ MK-0524A 2g/ Placebo
SCREENING FAILURES:	412
RANDOMIZED:	894
Male (age range)	363 (18-80)
Female (age range)	531 (18-80)
COMPLETED:	1
DISCONTINUED:	200
Clinical adverse experience	69
Flushing with product	68
Laboratory adverse experience	8
Other	55

Post-Holiday

	Placebo/ MK-0524A 2 g N=312	Placebo/ ER niacin 2 g N=325	MK-0524A 2g/ MK-0524A 2 g N=57	TOTAL
RANDOMIZED:	312 (19-70)	325 (21-70)	57 (22-71)	694 (19-71)
Male (age range)	190 (19-70)	196 (26-70)	38 (22-71)	424 (19-71)
Female (age range)	122 (27-70)	129 (21-70)	19 (34-68)	270 (21-70)
COMPLETED:	308	324	57	689
DISCONTINUED:	3	1	0	4
Flushing with product	2	1	0	3
Other	1	0	0	1

1 Active Run-In Plus Drug Holiday: Patients took MK-0524A 1 g for 4 weeks, then advanced to MK-0524A 2 g for 4 weeks, followed by Placebo or MK-0524A 2 g (10:1) for 5 days. Post Holiday: On Day 7 after Visit 5, patients took double-blinded study medication, MK-0524A 2 g, or ER niacin 2 g (5:6). 1:6 of the MK-0524A 2 g treated patients had never experienced a drug holiday and are classified by the treatment group MK-0524A 2 g/MK-0524A 2 g.

2 MK-0524A 1g/MK-0524A 2 g/Placebo: MK-0524A 1g for 4 weeks, followed by MK-0524A 2 g for 4 weeks, followed by placebo for 5 days (drug holiday). Placebo/MK-0524A 2 g: MK-0524A 2 g for 7 days following the drug holiday period. Placebo/ER niacin 2 g: ER niacin 2 g for 7 days following the drug holiday period. MK-0524A 2 g/MK-0524A 2 g: MK-0524A 2 g during the 5-day drug holiday (no drug holiday), followed by MK-0524A 2 g for 7 days.

3 One patient is listed as completed for the Active Run-in Plus Drug Holiday phase. This patient was incorrectly phased in the database based on tie-breaker rules. This patient took post-holiday treatment. Therefore, he is also counted in the number of patients who took drug during the post-holiday treatment period (N=312) but not in the number of patients who completed or discontinued during the post-holiday period.

DOSAGE/FORMULATION NOS.: 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 placebo.

Active Run-In Period: Beginning at Visit 2 (Week 0), patients were instructed to take 1 tablet/day of MK-0524A in the evenings with food. At Visit 3 (Week 4) and Visit 4 (Week 6), patients were instructed to take 2 tablets/day of MK-0524A in the evenings with food.

Treatment Period: Based upon the allocation schedule, beginning at Visit 5 (Week 8), patients were to take 2 tablets/day of MK-0524A, placebo/MK-0524A, or placebo/ER niacin for the remainder of study (2 weeks).

Formulation: The formulation numbers used for MK-0524A are [redacted]

DIAGNOSIS/INCLUSION CRITERIA: Men and women ≥18 and ≤70 years of age with primary hypercholesterolemia or mixed hyperlipidemia were included if triglycerides (TG) were ≤500 mg/dL (5.65 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 with evidence of ischemic cardiovascular disease and on a statin had low density lipoprotein cholesterol (LDL-C) <130 mg/dL (3.37 mmol/L), and non-diabetic patients with ≥2 risk factors had LDL<160 mg/dL (4.14 mmol/L). Patients' glycemic statuses were determined prior to randomization. Investigators were instructed to determine a patient's glycemic status 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).

EVALUATION CRITERIA:

Efficacy: Maximum GFSS categorized into none/mild, moderate, severe, and extreme during the first 7 days following a 5-day drug holiday period.

Safety: Clinical evaluations included medical history, physical examination, electrocardiogram (ECG), vital signs, weight, height, and adverse experiences. Laboratory evaluations included serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), creatine phosphokinase (CK), and fasting serum glucose levels (FSG). In addition, thyroid function and other laboratory assessments including hematology and urinalysis were performed. Prespecified discontinuation criteria were defined for confirmed consecutive elevations in the following lab parameters: CK, ALT, AST, and TG.

STATISTICAL PLANNING AND ANALYSIS: The primary endpoint of maximum GFSS categorized into none/mild, moderate, severe, extreme during the first 7 days following a 5-day drug holiday period was compared between the MK-0524A 2 g and ER niacin 2-g treatment groups using the Cochran-Mantel-Haenszel (CMH) test stratified by country. The MK-0524A 2 g/MK-0524A 2-g group was not included in the comparison. Other non binary, categorical exploratory endpoints were evaluated using the stratified CMH test specified above. Secondary and exploratory binary endpoints were evaluated using Fisher's exact test based on data from the MK-0524A 2 g/Placebo/MK-0524A 2 g and MK-0524A 2 g/Placebo/ER niacin 2-g arms only. Maximum GFSS during the first 7 days following a 5-day drug holiday period was analyzed using an analysis of variance model (ANOVA) with factors for treatment and country. Data from all 3 treatment groups were included in the model. Comparison of the MK-0524A 2 g/Placebo/MK-0524A 2-g treatment group with the MK-0524A 2 g/Placebo/ER niacin 2-g group was performed using an appropriate contrast from the ANOVA model. All significance tests were 2-tailed with α=0.05. A closed ordered testing procedure was applied to control the error across the primary and secondary hypotheses at the 0.05 level. First, the primary hypothesis was tested; if statistical significance was achieved at 0.05 level, the secondary hypotheses were tested sequentially in the order that they were specified. With 605 patients available for analysis, (275 patients in the MK-0524A 2 g/Placebo/MK-0524A 2-g group, and 275 patients in the MK-0524A 2 g/Placebo/ER niacin 2-g group), the study had 91% power to detect the difference in maximum GFSS during the first 7 days after a drug holiday categorized as none/mild moderate, severe, and extreme if the true percentages of patients in the categories none/mild, moderate, severe, and extreme were 54, 26, 17 and 4% respectively, in the MK-0524A 2 g/Placebo/ER niacin 2-g group and 64, 25, 11, and 0.4% in the MK-0524A 2 g/Placebo/MK-0524A 2-g group, respectively. These projected distributions were derived based on maximum GFSS during Week 1 categorized as none/mild, moderate, severe, and extreme observed in P011 by conservatively adjusting the differences between treatments. Based on 275 subjects in the MK-0524A 2 g/Placebo/MK-0524A 2 g and 275 subjects in the MK-0524A 2 g/Placebo/

ER niacin 2-g groups, the study had 90% power to detect a difference of 0.75 between the 2 groups in maximum GFSS during the first 7 days following a drug holiday.

RESULTS: All of the prespecified primary and secondary efficacy endpoints were significant in favor of MK-0524A ($p<0.01$ in all tests).

Compared with patients treated with ER niacin, patients treated with MK-0524A experienced significantly less flushing during the first seven days following a 5-day drug holiday as measured by the primary flushing endpoint of maximum GFSS categorized as none/mild, moderate, severe, extreme during the first 7 days following a 5-day drug holiday (results displayed below).

Maximum GFSS Categorized as None/Mild, Moderate, Severe, Extreme During the First 7 Days Following a 5-Day Drug Holiday

Treatment	None/Mild n (%)	Moderate n (%)	Severe n (%)	Extreme n (%)	Total N
Placebo/MK-0524A 2 g	217 (70.2)	62 (20.1)	26 (8.4)	4 (1.3)	309
Placebo/ER niacin 2 g	192 (59.1)	80 (24.6)	47 (14.5)	6 (1.8)	325
MK-0524A 2 g/MK-524A 2 g	47 (82.5)	8 (14.0)	1 (1.8)	1 (1.8)	57

Between-Group Comparison	p-Value[†]
MK-0524A vs. ER niacin following 5-day drug holiday	0.002

[†] p-Value based on Cochran-Mantel-Haenszel (CMH) test stratified by country.
Placebo/MK-0524A 2 g = 5-day drug holiday followed by 7 days of MK-0524A 2 g.
Placebo/ER niacin 2 g = 5-day drug holiday followed by 7 days of ER niacin 2 g.
MK-0524A 2 g/MK-0524A 2 g = No drug holiday followed by 7 days of MK-0524A 2 g.

Patients treated with MK-0524A experienced significantly less flushing during the first seven days following a 5-day drug holiday as measured by all key secondary flushing endpoints: the difference in LS means of maximum GFSS during the first seven days following a 5-day drug holiday was -0.6 (-1.0, -0.2) between Placebo/MK-0524A 2 g and Placebo/ER niacin 2 g (p=0.005); the percentage of patients with moderate or more GFSS during the first 7 days following a 5-day drug holiday was 29.8% with placebo/MK-0524A 2 g and 40.9% with Placebo/ER niacin 2 (p=0.004); the percentage of patients with severe or greater GFSS during the first seven days following a 5-day drug holiday was 9.7% with placebo/MK-0524A 2 g and 16.3% with Placebo/ER niacin 2 g (p=0.018).

SAFETY: Active Run-in Plus Drug Holiday Period: Of 894 patients in the safety analysis population (All-Patients-as-Treated) for the active run-in plus the drug holiday period, 22.4% discontinued the study. Approximately 7.7% discontinued due to clinical AEs (excluding those related to flushing), 7.6% discontinued due to flushing, and 0.9% discontinued due to laboratory AEs.

The numbers and percentages of patients with consecutive ≥3x ULN elevations (including presumed consecutive elevations) in ALT/AST were 3/864 (0.3%) during treatment with MK-0524A 1 g/ MK-0524A 2 g/5-day drug holiday. There were no patients with CK levels ≥10x ULN.

Post Holiday: Of 694 patients in the safety analysis population (All-Patients-as-Treated) for the post drug holiday period, 4 patients discontinued from the study during this period (3 (1.0%) and 1 (0.3%) in the placebo/MK-0524A 2 g and placebo/ER niacin 2-g groups, respectively). Of these, 2 patients in the placebo/MK-0524A 2-g group and 1 in the placebo/ER niacin 2 g group discontinued due to flushing. There were no discontinuations due to laboratory AEs during this period. The adverse event profile for the placebo/MK-0524A 2 g was generally similar to that of placebo/ER niacin 2 g. The numbers and percentages of patients with consecutives ≥3x ULN elevations (including presumed consecutive

elevations) in ALT/AST were 3/315 (1.0%) with placebo/MK-0524A 2 g, 2/325 (0.6%) with placebo/ER niacin 2 g and 0/57 (0%) with MK-0524 2 g/MK-0524 2 g, respectively. There was 1 (0.1%) hepatitis related AE during the post-holiday period, which was not considered to be related to study drug. Although randomized to the placebo/ER niacin treatment arm, prime therapy records revealed that the patient never dosed with active drug during the post-holiday treatment period. There was 1 (0.3%) patient with an asymptomatic rise in CK levels ≥10x ULN, that occurred in the placebo/ MK- 0524A 2-g group.

CONCLUSIONS: Efficacy: MK-0524A 2 g produced significantly less flushing than ER niacin 2 g during the first 7 days following a 5-day drug holiday period as measured by:

1) maximum GFSS categorized into none/mild, moderate, severe, or extreme
2) maximum GFSS
3) percentage of patients with moderate or greater GFSS (GFSS ≥4)
4) percentage of patients with severe or extreme GFSS (GFSS ≥7)

Safety: MK-0524A was well tolerated.

AUTHORS: [redacted]