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 SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC. MK-0524B, MK-0524A + simvastatin, Tablet Mixed Hyperlipidemia	**CLINICAL STUDY REPORT SYNOPSIS**	
PROTOCOL TITLE/NO.: A Multicenter, Randomized, Double-Blind, Parallel Group, 12-Week Study to Evaluate the Efficacy and Safety of MK-0524B (Dosed as Coadministered MK-0524A and Simvastatin Tablets) Versus Atorvastatin in Patients With Mixed Hyperlipidemia		#024
INVESTIGATORS/STUDY CENTERS: Multicenter – A total of 265 sites randomized patients in the United States (210) and non-US (55): Chile-1, Colombia-9, Finland-2, Guatemala-2, Hong Kong-2, Lithuania-5, New Zealand-3, Panama-1, Peru-5, Poland-4, Spain-8, Sweden-9, and United Kingdom-4.		
PRIMARY THERAPY PERIOD: 14-Aug-2006 to 05-Aug-2010	**CLINICAL PHASE:** III	
DURATION OF TREATMENT: 12-week double blind treatment period preceded by a 3/5-week placebo run in period. MK-0524B was dosed as MK-0524A (ER niacin/laropiprant) coadministered with simvastatin tablets. ER niacin/laropiprant is referred to as ERN/LRPT for the remainder of this document.		
OBJECTIVES: In patients with mixed hyperlipidemia, to evaluate the effect of ERN/LRPT 2g + simvastatin 20 mg compared to atorvastatin 10 mg and ERN/LRPT 2g + simvastatin 40 mg compared to atorvastatin 20 mg, 40 mg and 80 mg after 12 weeks of treatment: Primary: the percent reduction from baseline in the LDL-C/HDL-C ratio Secondary: (1) the effect on increasing HDL-C; (2) the effect on decreasing TG; (3) the effect on decreasing non-HDL-C; (4) the effect on decreasing LDL-C; (5) the effect on Apo B, Apo A-I, lipoprotein and apolipoprotein ratios, Lp(a), and CRP; (6) the safety and tolerability of ERN/LRPT 2g + simvastatin.		
STUDY DESIGN: A multi-center, randomized, double-blind, 6 arm, parallel group study to evaluate the lipid altering efficacy and safety of the 2g/20 mg and 2g/40 mg doses of ERN/LRPT coadministered with simvastatin 20 mg and 40 mg compared with atorvastatin 10 mg, 20 mg, 40 mg and 80 mg in patients with mixed hyperlipidemia. The duration of the study was 16 weeks, comprised of a 4 week placebo run-in period and a 12 week active treatment period. Following the 4-week placebo run-in period, naïve patients or patients rendered naïve with appropriate prior lipid-lowering washout, and who met eligibility requirements, were randomized into the study in 2 phases: US and ex-US. During the first phase, 1780 US patients were randomized in equal ratio to one of six treatment groups. While the US phase was ongoing, results from other studies suggested that the 4 higher dose treatment arms (ERN/LRPT + simvastatin 40 mg, atorvastatin 20 mg, 40 mg, and 80 mg) were underpowered for selected comparisons. Therefore, during the second phase, 560 ex-US patients were randomized in equal ratio to these 4 higher dose groups. Overall, this procedure led to approximately 2:3:2:3:3:3 ratio for ERN/LRPT + simvastatin 20 mg, ERN/LRPT + simvastatin 40 mg, atorvastatin 10 mg, atorvastatin 20 mg, atorvastatin 40 mg and atorvastatin 80 mg. As a result, a total of 2,340 patients were randomized and stratified using Visit 2 LDL-C and TG levels to achieve balance across treatment groups in these parameters.		

SUBJECT/PATIENT DISPOSITION:

	ER niacin/laropiprant + Simvastatin 20 mg and 40 mg (pooled)	Atorvastatin 10, 20, 40 and 80 mg (pooled)	Total
SCREENING FAILURES:			9531
RANDOMIZED:	733[†]	1607	2340
Male (age range)	331 (20-79)	700 (20-80)	1031
Female (age range)	402 (21-80)	907 (22-81)	1309
COMPLETED:	545 (74.4%)	1409 (87.7%)	1954(83.5%)
DISCONTINUED:	187 (25.5)	198 (12.3 %)	385 (16.5%)
Clinical adverse experience	62 (8.5%)	73 (4.5%)	135 (57.7 %)
Laboratory adverse experience	6 (0.8%)	12 (0.7%)	18 (0.8%)
Pat. withdrew consent	31 (4.2%)	49 (3.0 %)	80 (3.4%)
Flushing with product	60 (8.2%)	7 (0.4%)	67 (2.9%)
Other	28 (3.8%)	63 (3.9 %)	91 (3.9%)

[†] One randomized patient discontinued the study prior to taking assigned study medication.

DOSAGE/FORMULATION NOS.: Atorvastatin was supplied and dosed as 10 mg, 20 mg, 40 mg and 80 mg tablets. MK-0524B was dosed as ERN/LRPT coadministered with simvastatin. ERN/LRPT tablets were supplied as 1000 mg ERN/20 mg LRPT. Simvastatin tablets were supplied as 10 mg, 20 mg and 40 mg. Patients were instructed to take study medication daily with food, in the evening or at bedtime. Patients took one placebo tablet daily during the 4-week placebo run-in period. During the blinded treatment period, patients took one tablet from each bottle (A, B, C and D) for 4 weeks. For the remaining 8 weeks of treatment, patients took 2 tablets from Bottle A, and 1 tablet from Bottles B, C and D (for a total of 5 tablets during the 8-week period). Section 9.4.2 has detailed information regarding formulation numbers.

DIAGNOSIS/INCLUSION CRITERIA: Men and women ≥18 and ≤80 years of age with mixed hyperlipidemia were eligible for randomization if they met LDL-C and TG criteria at Visit 2. All patients must have had TG levels ≥150 mg/dL ≤500 mg/dL (1.7-5.6 mmol/L).

Multiple or low risk patients on a lipid modifying therapy (LMT) were allowed to wash off their LMT and were eligible if they met the LDL-C requirements for their risk category. High, multiple or low risk patients not on an LMT were also eligible if they met the LDL-C requirements for their risk category.

Patients categorized as multiple risks (2 or more risk factors) had to have LDL-C ≥130 mg/dL and ≤160 mg/dL (3.4 and 4.1 mmol/L). Patients categorized as low risk (0-1 risk factor) had to have LDL-C ≥130 mg/dL and ≤190 mg/dL (3.4 and 5.0 mmol/L). Patients categorized as high risk (not on an LMT) had to have LDL-C ≥130 mg/dL and ≤160 mg/dL (3.4 and 4.1 mmol/L).

EVALUATION CRITERIA:

EFFICACY MEASUREMENTS: The primary efficacy parameter was the percent change from baseline in LDL-C/HDL-C ratio following 12 weeks of active treatment. In addition, LDL-C, HDL-C, TC, TG, non-HDL-C, Apo B, Apo A-1, lipoprotein and apolipoprotein ratios, Lp (a), and CRP were assessed in all patients.

SAFETY MEASUREMENTS: Clinical evaluation included physical examination, vital signs, and adverse experiences. Laboratory evaluations included ALT, AST, CK, serum glucose, and other general surveillance labs (hematology, chemistry, urinalysis, urine β-hCG). Pre-specified discontinuation was defined for confirmed consecutive elevations in the following laboratory 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. Serious cardiovascular events and any deaths occurring during the study and the protocol-specified follow-up period were subject to adjudication by an independent adjudication committee.

STATISTICAL PLANNING AND ANALYSIS:

EFFICACY: The primary hypothesis regarding the change from baseline in the LDL-C/HDL-C ratio was assessed by comparing the mean percent changes for ERN/LRPT 2 g + simvastatin 20 mg vs. atorvastatin 10 mg, ERN/LRPT 2g + simvastatin 40 mg vs. atorvastatin 20 mg, ERN/LRPT 2g + simvastatin 40 mg vs. atorvastatin 40 mg, and ERN/LRPT 2g + simvastatin 40 mg vs. atorvastatin 80 mg using a parametric analysis of covariance (ANCOVA) model with factors for baseline LDL-C stratum (≥130 mg/dL to <160 mg/dL and ≥160 mg/dL to ≤190 mg/dL), baseline triglyceride stratum (≥150 mg/dL to <250 mg/dL and ≥250 mg/dL to ≤500 mg/dL), baseline LDL-C/HDL-C, gender, cohort of patients (i.e. the 1st cohort or the 2nd cohort), and treatment group. Treatment group comparisons at Week 12 were performed using an appropriate linear contrast from the ANCOVA model. In addition, the least-squares mean (LS mean) for each treatment group and 95% confidence intervals (95% CI) was estimated from the above ANCOVA model. These ANCOVA analyses were based on patients from the FAS (Full-Analysis-Set); missing LDL-C/HDL-C data at Week 12 was imputed using carry forward (CF) of the last available post-titration visit value of LDL-C/HDL-C. The secondary hypotheses regarding the percent change from baseline in HDL-C, non-HDL-C, and LDL-C for the same dose comparisons were assessed in a similar way as the primary efficacy endpoint.

The comparison of treatment groups in TG was performed using a non-parametric ANCOVA model applied to Tukey's normalized ranks of the percent change from baseline; the model included terms for treatment, gender, cohort of patients (i.e. the 1st cohort or the 2nd cohort), baseline LDL-C stratum (≥130 mg/dL to <160 mg/dL and ≥160 mg/dL to ≤190 mg/dL), baseline triglyceride rank score as a covariate. 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.

To adjust for multiplicity, the following testing procedures were applied to primary and secondary hypotheses (1) the following testing order was established among primary and secondary efficacy endpoints: LDL-C/HDL-C, HDL-C, TG, non-HDL-C, and LDL-C; (2) within each of LDL-C/HDL-C, HDL-C, TG, and non-HDL-C endpoint, the closed ordered testing procedure was applied for four dose comparisons in the following order: ERN/LRPT 2g + simvastatin 20 mg vs. atorvastatin 10 mg, ERN/LRPT 2g + simvastatin 40 mg vs. atorvastatin 20 mg**,** ERN/LRPT 2g + simvastatin 40 mg vs. atorvastatin 40 mg, and ERN/LRPT 2g + simvastatin 40 mg vs. atorvastatin 80 mg. Thus, the Type I error was controlled at 0.05 level within each of these families; (3) for LDL-C endpoint, superiority of the top 2 comparisons were tested in the above order. Then non-inferiority followed by superiority was tested for the next two comparisons. Since the testing was not completely closed across the 2 higher dose comparisons given that both superiority of ERN/LRPT 2g + simvastatin 40 mg vs. atorvastatin 40 mg and non-inferiority of ERN/LRPT 2g + simvastatin 40 mg vs. atorvastatin 80 mg would be tested at α=0.05 (2-sided) simultaneously once non-inferiority ERN/LRPT 2g + simvastatin 40 mg vs. atorvastatin 40 mg was established, the overall type 1 error for LDL-C would not be strongly controlled at 2-sided 0.05 as with other key lipid endpoints. For LDL-C, the Type I error was strongly controlled at 0.05 level across the first two dose comparisons.

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 for 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 1% of patients in one or more of the combined groups), 95% CIs of the between treatment groups difference of incidence rates were provided. Statistical tests on safety parameters were compared in the pool of ERN/LRPT 2g + simvastatin 20 mg and ERN/LRPT 2g + simvastatin 40 mg groups vs. the pool of four atorvastatin groups. 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. P-values and 95% CIs of between-treatment differences in percentages were obtained using the Miettinen and Nurminen method. Vital signs and selected laboratory tests were also summarized.

RESULTS:

EFFICACY: The primary efficacy hypothesis was met proving superiority of MK-0524B (dosed as ERN/LRPT coadministered with simvastatin) to atorvastatin after 12 weeks of treatment on decreasing the LDL-C/HDL-C ratio for pre-specified dose comparisons of ERN/LRPT 2g + simvastatin 20 mg vs. atorvastatin 10 mg, ERN/LRPT 2g + simvastatin 40 mg vs. atorvastatin 20 mg, ERN/LRPT 2g + simvastatin 40 mg vs. atorvastatin 40 mg, and ERN/LRPT 2g + simvastatin 40 mg vs. atorvastatin 80 mg. The secondary efficacy hypotheses were met for (1) superiority of ERN/LRPT 2g + simvastatin to atorvastatin after 12 weeks of treatment on increasing HDL-C and decreasing TG for the all above dose comparisons; and (2) superiority of ERN/LRPT 2g + simvastatin to atorvastatin after 12 weeks of treatment on decreasing non-HDL-C and decreasing LDL-C for the top 2 dose comparisons (i.e. ERN/LRPT 2g + simvastatin 20 mg vs. atorvastatin 10 mg and ERN/LRPT 2g + simvastatin 40 mg vs. atorvastatin 20 mg, respectively). The secondary efficacy hypotheses were not met for (1) superiority of ERN/LRPT 2g + simvastatin 40 mg vs atorvastatin after 12 weeks of treatment on decreasing non-HDL-C for the bottom 2 dose comparisons (i.e. ERN/LRPT 2g + simvastatin 40 mg vs. atorvastatin 40 mg and ERN/LRPT 2g + simvastatin 40 mg vs. atorvastatin 80 mg, respectively); and (2) non-inferiority of ERN/LRPT 2g + simvastatin 40 mg to atorvastatin after 12 weeks of treatment on decreasing LDL-C for the bottom 2 dose comparisons (i.e. ERN/LRPT 2g + simvastatin 40 mg vs. atorvastatin 40 mg and ERN/LRPT 2g + simvastatin 40 mg vs. atorvastatin 80 mg, respectively). 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 2-1.

Table 2-1

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)

	LDL-C/HDL-C	HDL-C	TG (median)	Non-HDL-C	LDL-C
Within Treatment					
ER niacin/laropiprant + Simvastatin 20 mg (n=255) †	-50.9 (-53.8, -47.9)	26.9 (24.7, 29.1)	-40.3 (-44.2,-36.5)	-40.4 (-42.9, -37.9)	-40.4 (-43.0, -37.7)
ER niacin/laropiprant + Simvastatin 40 mg (n=361) †	-53.0 (-55.4, -50.7)	26.6 (24.8, 28.4)	-42.0 (-45.7,-38.4)	-42.2 (-44.2, -40.2)	-42.8 (-44.9, -40.7)
Atorvastatin 10 mg (n=280) †	-37.6 (-40.5, -34.8)	7.0 (4.8, 9.1)	-21.9 (-25.0,-18.8)	-31.3 (-33.7, -28.9)	-33.6 (-36.1, -31.0)
Atorvastatin 20 mg (n=402) †	-42.2 (-44.5, -40.0)	5.3 (3.6, 7.0)	-23.8 (-26.5, -21.2)	-36.8 (-38.7,-34.9)	-39.8 (-41.8, -37.8)
Atorvastatin 40 mg (n=410) †	-47.9 (-50.1, -45.7)	4.5 (2.8, 6.2)	-30.4 (-32.8, -27.9)	-42.6 (-44.5,-40.7)	-45.6 (-47.6, -43.6)
Atorvastatin 80 mg (n=402) †	-48.8 (-51.1, -46.6)	3.6 (1.9, 5.3)	-33.8 (-36.4,-31.2)	-44.6 (-46.6, -42.7)	-47.5 (-49.5, -45.5)
Between Treatment					
ER niacin/laropiprant + Simvastatin 20 mg vs. Atorvastatin 10 mg	-13.2 (-16.8, -9.6)	19.9 (17.2, 22.6)	-17.3 (-21.2, -13.3)	-9.1 (-12.1, -6.0)	-6.8 (-10.2, -3.5)
ER niacin/laropiprant + Simvastatin 40 mg vs. Atorvastatin 20 mg	-10.8 (-13.8, -7.8)	21.3 (19.0, 23.6)	-15.5 (-19.1, -11.9)	-5.4 (-8.0, -2.9)	-3.0 (-5.8, -0.2)
ER niacin/laropiprant + Simvastatin 40 mg vs. Atorvastatin 40 mg	-5.1 (-8.1, -2.1)	22.1 (19.8, 24.4)	-10.3 (-13.7, -7.0)	0.4 (-2.2, 2.9)	2.8 (0.0, 5.6)
ER niacin/laropiprant + Simvastatin 40 mg vs. Atorvastatin 80 mg	-4.2 (-7.2, -1.2)	23.0 (20.7, 25.3)	-6.8 (-10.2, -3.4)	2.4 (-0.2, 5.0)	4.7 (2.0, 7.5)

† 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 (after Visit 4) value carry forward in LDL-C/HDL-C).

SAFETY: A total of 2339 patients were assessed for safety. The clinical adverse experiences that occurred most frequently in the ERN/LRPT + simvastatin treatment groups, including those that were drug-related and those that led to discontinuation, were those typically associated with niacin and niacin containing compounds, specifically flushing and pruritus. The incidence of serious clinical adverse experiences was low and similar across the pooled treatment groups (1.5% in the ERN/LRPT + simvastatin treated group vs 1.1% in the atorvastatin treated group); none was drug-related. The occurrence of laboratory adverse experiences was similar across both pooled groups (5.2% in the ERN/LRPT + simvastatin pooled treatment group vs 5.9% in the atorvastatin pooled treatment group). Overall, the incidence of drug-related laboratory adverse experiences, including those that led to discontinuation, was also similar across both pooled treatment groups. Laboratory adverse experiences related to increases in blood glucose and uric acid, known side effects of niacin, occurred more frequently in the ERN/LRPT + simvastatin treated groups, whereas adverse experiences related to abnormal liver function (increased ALT, AST, GGT) occurred more frequently in the atorvastatin treated groups. There were no serious laboratory adverse experiences.

Safety parameters of special interest included those related to liver, muscle and glycemic control. For pre-defined hepatic-related clinical adverse experiences or elevations in transaminases, more atorvastatin treated patients than ERN/LRPT + simvastatin treated patients experienced elevations in ALT and/or AST to ≥3xULN (consecutive) [29/1577 patients (1.8%) vs 3/701 patients (0.4%), respectively] and to ≥ 5xULN [14/1577 (0.9%) vs 1/701 (0.1%), respectively]. ALT and/or AST ≥ 10-fold elevations occurred in 2/1577 patients (0.1%) in the atorvastatin group vs 0/701 patients in the ERN/LRPT + simvastatin group. A hepatitis-related clinical adverse experience of hepatomegaly (not drug-related) was reported for one patient treated with atorvastatin 80 mg. Two patients experienced elevated CK to ≥10xULN. One patient treated with ERN/LRPT + simvastatin 40 mg also experienced back muscle pain following intense physical exercise. These events were considered drug-related and thus, met the protocol definition of myopathy. One patient in the atorvastatin 80 mg treatment group experienced CK levels ≥ 10 x ULN without muscle symptoms. There were no cases of rhabdomyolysis in this study. For glycemic control, median FSG increased by 4.0 mg/dL in the ERN/LRPT + simvastatin pooled treatment group compared to 2.0 mg/dL in the atorvastatin pooled treatment group. New onset IFG, based on the report of a relevant adverse experience, was identified in 1/605 (0.2%) patient treated with ERN/LRPT + simvastatin and 1/1343 (0.1%) patient treated with atorvastatin. New onset diabetes, based on the report of a relevant adverse experience or addition of an anti-hyperglycemic medication, was identified in 6/703 (0.9%) and 3/1523 (0.2%) of patients treated with ERN/LRPT + simvastatin and atorvastatin, respectively.

CONCLUSIONS:

EFFICACY: In patients with mixed hyperlipidemia, relative to atorvastatin, ERN/LRPT + simvastatin produced:

1. Greater reductions in the LDL-C/HDL-C ratio for all pre-specified dose comparisons
2. Greater increases in HDL-C and Apo A-I for all pre-specified dose comparisons
3. Greater decreases in TG, Lp(a), and TC/HDL-C
4. Greater decreases in LDL-C, non-HDL, and Apo B at the 2 lower dose comparisons (ERN/LRPT + simvastatin 20 mg vs atorvastatin 10 mg and ERN/LRPT + simvastatin 40 mg vs atorvastatin 20 mg)

SAFETY: ERN/LRPT added to simvastatin 20 mg and 40 mg was generally well tolerated in this population.

AUTHORS:

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