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, Extended-release Niacin/Laropiprant/Simvastatin Tablet, Primary Hypercholest-erolemia, Mixed Dyslipidemia	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.:

A Phase III Multicenter, Double-Blind, Crossover Design Study to Evaluate Lipid-Altering Efficacy and Safety of Extended-Release Niacin/Laropiprant/Simvastatin Combination Tablet in Patients with Primary Hypercholesterolemia or Mixed Dyslipidemia — #118-00

PROTECTION OF HUMAN SUBJECTS:

This study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research. For study audit information see [16.1.8].

INVESTIGATOR(S)/STUDY CENTER(S):

A total of 102 sites in 17 countries as follows (sites per country in parentheses): Australia (5), Bulgaria (8), Canada (10), Chile (2), Colombia (1), Germany (5), Hong Kong (4), Hungary (5), Italy (3), Mexico (6), New Zealand (6), Peru (4), Poland (6), Romania (4), Singapore (1), Spain (4), United States (28)

PUBLICATION(S):

None

PRIMARY THERAPY PERIOD:	**CLINICAL PHASE:** III
15 Mar 2011 through 07 Dec 2011	

DURATION OF TREATMENT:

Participation in the study included a pre-screening/washout period (8 weeks for fibrates, or 6 weeks for other lipid-modifying therapies [LMTs], or a pre-screening visit 2 weeks prior to the placebo run-in period if not on LMTs), plus a 2-week placebo run-in period, plus 20 weeks on treatment (refer to DOSAGE, below), and a 2-week post-study follow-up period, for a total of up to 32 weeks. For patients who discontinued, the last contact was a phone call on the last intended final visit study date (20 weeks from randomization to assess for serious cardiovascular [CV] adverse events [AEs] or death).

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OBJECTIVE(S):

In patients with primary hypercholesterolemia or mixed dyslipidemia, after 8 weeks of treatment:

Primary Objective

Evaluate the low-density lipoprotein cholesterol (LDL-C)-lowering effects of extended-release niacin/laropiprant/simvastatin combination (ERN/LRPT/SIM) 2 g/40 mg compared to extended-release niacin/laropiprant (ERN/LRPT) 2 g co-administered with simvastatin 40 mg.

Secondary Objectives

1. Evaluate the high-density lipoprotein cholesterol (HDL-C)-raising effects of ERN/LRPT/SIM 2 g/40 mg compared to ERN/LRPT 2 g co-administered with simvastatin 40 mg.
2. Estimate the differences in percent change in LDL-C from baseline between ERN/LRPT/SIM 1 g/40 mg and ERN/LRPT 1 g co-administered with 40 mg of simvastatin, respectively, for 4 weeks.
3. Estimate the differences in percent change in HDL-C from baseline between ERN/LRPT/SIM 1 g/40 mg and ERN/LRPT 1 g co-administered with 40 mg of simvastatin, respectively, for 4 weeks.
4. Evaluate the tolerability of ERN/LRPT/SIM.

Exploratory efficacy and biomarker objectives were described in the protocol.

STUDY STATUS:

The decision to discontinue development of the ERN/LRPT/SIM formulation used in this study was based on subsequent results from a pharmacokinetic study showing that the combination tablet formulation of ERN/LRPT/SIM taken in this study was not bioequivalent to the co-administered ERN/LRPT and SIM tablet.

STUDY DESIGN:

This was a multicenter, double-blind, randomized, crossover study. Following the pre-screening/washout period (see DURATION OF TREATMENT, above) and 2-week placebo run-in period, eligible patients were randomized in a 1:1 ratio at Day 1 (Week 0) to one of two treatment sequences:

- Sequence 1 for which study drug was administered as extended-release niacin/laropiprant/simvastatin combination (ERN/LRPT/SIM) during Periods I and II for 12 weeks and extended-release niacin/laropiprant (ERN/LRPT) + simvastatin (SIM) during period III for 8 weeks. For Period 1, patients took 1 tablet of ERN 1 g/LRPT 20 mg/ SIM 40 mg (designated as ERN/LPRT/SIM 1 g/40 mg); for Period 2, patients took 2 tablets of ERN 1 g/LRPT 20 mg/SIM 20 mg (designated as ERN/LRPT/SIM 1 g/20 mg); and for Period 3, patients took 2 tablets of ERN 1 g/LRPT 20 mg (designated as ERN/LRPT 1 g) and 1 tablet of SIM 40 mg. For details, including placebo information to maintain the study drug blind, see the DOSAGE section below.
- Sequence 2 for which study drug was co-administered as extended-release niacin/laropiprant (ERN/LRPT) + simvastatin (SIM) (ERN/LRPT + SIM) during Periods I and II for 12 weeks and extended-release niacin/laropiprant/simvastatin combination (ERN/LRPT/SIM) during period III for 8 weeks. For Period 1, patients took 1 tablet of ERN/LRPT 1 g and 1 tablet of SIM 40 mg; for Period 2, patients took 2 tablets of ERN/LRPT 1g and 1 tablet of SIM 40 mg; and for Period 3, patients took 2

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tablets of ERN/LRPT/SIM 1 g/20 mg. For details, including placebo information to maintain the study drug blind, see the DOSAGE section below.

At Week 4 (the end of Period I), treatment doses of ERN/LRPT/SIM (Sequence 1) and ERN/LRPT and SIM (Sequence 2) were increased (details in DOSAGE, below) for an additional 8 weeks (Period II). At Week 12, patients on ERN/LRPT/SIM combination crossed over to the ERN/LRPT + SIM co-administration treatment and patients in the co-administration sequence crossed over to the ERN/LRPT/SIM combination treatment for 8 weeks (Period III), for a total of 20 weeks of treatment.

The final of 8 scheduled study visits was conducted at Week 20, followed by a post-study telephone contact 14 days after the last visit or last blinded treatment dose, whichever was latest. Patients who discontinued from the study prior to completion were contacted by telephone at their intended final study visit date (20 weeks from randomization) for serious CV AEs or death.

DOSAGE/FORMULATION NOs.:

- ERN/LRPT/SIM combination was provided in dose strengths as follows:
  - ERN 1 g, LRPT 20 mg, and SIM 40 mg (designated ERN/LRPT/SIM 1 g/40 mg); tablet.
  - ERN 1 g, LRPT 20 mg, and SIM 20 mg (designated ERN/LRPT/SIM 1 g/20 mg); tablet.
- ERN/LRPT was a fixed dose combination tablet containing ERN 1 g and laropiprant 20 mg (designated ERN/LRPT 1 g).
- SIM was supplied as 40 mg tablets.

Tablets of ERN/LRPT/SIM and ERN/LRPT were in the same image. Placebo was available in the image of ERN/LRPT/SIM and ERN/LRPT, and also in the image of SIM.

Following the 2-week placebo run-in period in which all patients took 2 placebo tablets daily (one in the image of ERN/LRPT/SIM and ERN/LRPT, and one in the image of SIM), eligible patients were randomized to one of two treatment sequences at Week 0 (on Day 1 of Period I) and took 2 tablets daily for 4 weeks (1 tablet of ERN/LRPT/SIM 1 g/40 mg and 1 tablet of SIM placebo or 1 tablet of ERN/LRPT 1 g and 1 tablet of SIM 40 mg) followed by 3 tablets daily for the next 16 weeks (2 tablets of ERN/LRPT/SIM 1 g/20 mg and 1 tablet of SIM placebo or 2 tablets of ERN/LRPT 1 g and 1 tablet of SIM 40 mg).

Clinical Material:	Lot Numbers:
MK-0524B Placebo Tabs MK-0524B Bilayer Tabs (ERN/LRPT/SIM 1g/40 mg) MK-0524B Bilayer Tabs (ERN/LRPT/SIM 1g/20 mg) MK-0524A Bilayer Tabs (ERN/LRPT 1g) SIM Placebo Tab SIM 40 mg	[redacted]

DIAGNOSIS/KEY INCLUSION CRITERIA:

Study participants included male and female patients who were ≥ 18 and ≤ 85 years of age on the day of signing informed consent, with primary hypercholesterolemia or mixed dyslipidemia based upon medical history,

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historical and/or current lab values, and investigator's judgment.

At Week -2, patients had to satisfy the following criteria: Patients who were high risk (coronary heart disease [CHD] or CHD risk equivalent based on National Cholesterol Education Program Adult Treatment Program III [NCEP ATP III] guidelines) had to have LDL-C ≤ 200 mg/dL (≤ 5.17 mmol/L). Patients who were NOT high risk based on NCEP ATP III guidelines had to have LDL-C ≤ 250 mg/dL (≤ 6.47 mmol/L). Patients not on LMT or on LMT other than niacin, statin, or fibrate had to have triglycerides (TG) < 600 mg/dL (< 6.77 mmol/L). Patients on niacin, statin, or fibrate had to have TG < 500 mg/dL (< 5.65 mmol/L).

Investigators established a baseline glycemic status for all patients (normal, impaired fasting glucose, or diabetes) before randomization.

EVALUATION CRITERIA:

Efficacy: The following efficacy endpoints were to be used to demonstrate clinically equivalent lipid modifying efficacy of the ERN/LRPT/SIM 2g/40 mg and ERN/LRPT 2g co-administered with SIM 40 mg and estimate the LDL-C and HDL-C effects of ERN/LRPT/SIM 1g/40 mg and ERN/LRPT 1g co-administered with SIM 40 mg in patients with primary hypercholesterolemia or mixed dyslipidemia.

The primary endpoint was percent change from baseline to the end of the 8-week treatment period in LDL-C. Secondary endpoints were a) percent change from baseline at the end of the 8-week treatment period in HDL-C, and b) percent change from baseline at the end of the 4-week treatment period (Period I) in LDL-C and HDL-C. Tertiary endpoints were a) percent change from baseline to the end of the 8-week treatment period in TG, non-HDL-C, total cholesterol (TC), TC:HDL-C ratio, LDL-C:HDL-C ratio, apolipoprotein (Apo) B, and Apo A-I, and b) percent change from baseline to the end of the 4-week Period I in TG, non-HDL-C, TC, ApoB, and Apo A-I.

Safety: Safety measurements included monitoring of AEs, clinical evaluation (including vital signs, body weight, and physical examination), and laboratory assessments. Selected serious CV events, any deaths, potential drug-induced liver injury cases (defined as patients with AST/ALT [asparate aminotransferase/alanine amintransferase] ≥ 3 x upper limit of normal [ULN], total billirubin ≥ 2 x ULN, and alkaline phosphatase [ALP] < 2 x ULN) and serious, non viral, drug-related hepatitis events (hepatitis, non-infective hepatitis, liver failure, jaundice, and asymptomatic elevated ALT reported as SAEs) in patients who received at least one dose of study drug, occurring during the study and the protocol-specified post-study follow-up period, were subject to adjudication by an independent CV or hepatic adjudication committee, respectively. Hepatitis-related AEs, new onset of diabetes, and confirmed adjudicated selected serious CV events were prespecified for inferential analysis.

Laboratory assessments included the following: ALT and AST, creatine kinase (CK), fasting serum glucose (FSG), and other general surveillance labs (hematology, chemistry, urinalysis, urine beta-human chorionic gonadotropin (β-hCG). Refer to Safety Analysis below for safety laboratory endpoints prespecified for inferential analysis.

STATISTICAL PLANNING AND SAFETY ANALYSIS:

Efficacy: The planned efficacy analyses were described in detail in the protocol. Since the study was terminated early due to the decision to discontinue the development of the ERN/LRPT/SIM formulation, no efficacy analysis is presented.

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Safety: The All Patients as Treated (APaT) population was used for the analysis of safety data in this study. The APaT population consisted of all randomized patients who received at least one dose of study treatment post randomization. Patients were included in the treatment sequence corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. No missing data imputations were done for safety parameters.

Due to confounding of the Period III AEs with the treatment received during Periods I and II, the primary approach to safety analysis was based on the experiences accumulated during Periods I and II combined, where the study followed a parallel design. In addition, a separate analysis of the AEs that occurred during Period III was provided.

The analysis of safety results followed a tiered approach (Table S1).

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Table S1 Analysis Strategy for Key Safety Parameters

Safety Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	ALT and/or AST consecutive elevations ≥ 3 x ULN	X	X	X
	ALT and/or AST elevations ≥ 5 x ULN	X	X	X
	ALT and/or AST elevations ≥ 10 x ULN	X	X	X
	CK elevations ≥ 10 x ULN	X	X	X
	CK elevations ≥ 10 x ULN with muscle symptoms drug-related	X	X	X
	Hepatitis -related AE	X	X	X
	New onset of diabetes	X	X	X
	Confirmed adjudicated CV event	X	X	X
Tier 2	Any AE		X	X
	Any serious AE		X	X
	Any drug-related AE		X	X
	Any serious drug-related AE		X	X
	Any AE causing discontinuation from study		X	X
	Change from Baseline for ALT, AST, CK, FSG, hemoglobin A1c (HbA1c [diabetics])		X	X
	SOCs, specific AEs (incidence ≥ 1% of patients in one of the treatment sequences)		X	X
	PDLC		X	X
Tier 3	Specific AEs not in Tier 2			X
	Change from baseline lab results not in Tier 2 AEs			X
	ALT or AST elevation at: • 1 to < 2 x ULN • 2 to < 3 x ULN • ≥ 3 x ULN • ≥ 3 x ULN consecutive • ≥ 5 x ULN • ≥ 10 x ULN			X
	CK elevation at 3 to < 5 x ULN and 5 to < 10 x ULN			X

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; CK = creatine kinase; CV = cardiovascular; FSG = fasting serum glucose; HbA1c = hemoglobin A1c; PDLC = predefined limits of change; SOC = system organ class; ULN = upper limit of normal,
Note: 'AE' refers to both clinical and laboratory AEs.

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PATIENT DISPOSITION:

Patient disposition is summarized below. A total of 389 patients (39.8% of patients randomized) completed the study. An additional 65 patients (6.7% of patients randomized) completed only through Period II (Week 12) of the study. The majority of discontinuations from treatment were due to the early termination of the study (38.8% in Periods I and II and 4.5% in Period III).

	Sequence 1 ERN/LRPT/SIM → ERN/LRPT + SIM† n (%)	**Sequence 2 ERN/LRPT + SIM → ERN/LRPT/SIM‡ n (%)**	**Total n (%)**
Screening Failures	-	-	1032
Randomized	489	488	977
Male	259 (53.0)	230 (47.1)	489 (50.1)
Female	230 (47.0)	258 (52.9)	488 (49.9)
Periods I and II (N, %)			
Completed	232 (47.4)	222 (45.5)	454 (46.5)
Discontinued	257 (52.6)	266 (54.5)	523 (53.5)
Adverse Event	49 (10.0)	52 (10.7)	101 (10.3)
Lost to Follow-up	3 (0.6)	6 (1.2)	9 (0.9)
Noncompliance with Study Drug	1 (0.2)	1 (0.2)	2 (0.2)
Physician Decision	1 (0.2)	0 (0.0)	1 (0.1)
Protocol Violation	5 (1.0)	5 (1.0)	10 (1.0)
Study Terminated by Sponsor	187 (38.2)	192 (39.3)	379 (38.8)
Technical Problems	0 (0.0)	1 (0.2)	1 (0.1)
Withdrawal by Subject	11 (2.2)	9 (1.8)	20 (2.0)
Period III (N, %)			
Completed	199 (40.7)	190 (38.9)	389 (39.8)
Discontinued	33 (6.7)	32 (6.6)	65 (6.7)
Adverse Event	6 (1.2)	6 (1.2)	12 (1.2)
Lost to Follow-up	1 (0.2)	3 (0.6)	4 (0.4)
Study Terminated by Sponsor	23 (4.7)	21 (4.3)	44 (4.5)
Withdrawal by Subject	3 (0.6)	2 (0.4)	5 (0.5)

† Sequence 1 = ERN/LRPT/SIM 1 g/40 mg for 4 weeks (Period I) followed by ERN/LRPT/SIM 2 g/40 mg for 8 weeks (Period II) followed by ERN/LRPT 2 g + SIM 40 mg for 8 weeks (Period III).

‡ Sequence 2 = ERN/LRPT 1 g + SIM 40 mg for 4 weeks (Period I) followed by ERN/LRPT 2 g + SIM 40 mg for 8 weeks (Period II) followed by ERN/LRPT/SIM 2 g/40 mg for 8 weeks (Period III).

EFFICACY RESULTS: Not applicable. The study was terminated early due to the decision to discontinue the development of the ERN/LRPT/SIM formulation, no efficacy analysis is presented.

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SAFETY RESULTS:

Overall (clinical and laboratory **AEs** combined), the number of patients with at least one AE was comparable between treatment sequences. Throughout the course of the pre-crossover period, 244/486 patients (50.2%) in Sequence 1 and 249/486 patients (51.2%) in Sequence 2 had **at least one AE**. During the post-crossover period, 70/230 patients (30.4%) and 65/220 patients (29.5%), respectively, had at least one AE. The same was true for clinical AEs and laboratory AEs. The SOCs in which clinical AEs were most commonly reported (with an incidence of > 10% in either treatment sequence) pre-crossover included vascular disorders (19.3% in Sequence 1 and 17.3% in Sequence 2), skin and subcutaneous tissue disorders (16.3% in Sequence 1 and 15.4% in Sequence 2), and gastrointestinal disorders (8.8% in Sequence 1 and 10.9% in Sequence 2). Post-crossover, the incidence of infections and infestations appeared higher in Sequence 1 (9.6%) than in Sequence 2 (5.0%), as did musculoskeletal and connective tissue disorders (4.8% in Sequence 1 and 2.7% in Sequence 2); gastrointestinal disorders appeared higher in Sequence 2 (5.5%) than in Sequence 1 (1.7%).

Pre-crossover, the most commonly reported **clinical AEs**, in Sequence 1 and Sequence 2, respectively, were flushing (18.1% and 15.4%) and pruritus (8.6% and 6.8%). Post-crossover, the number of patients reporting specific clinical AEs was small. Only one specific clinical AE was reported by at least 4 patients (bronchitis: 4/230 patients in Sequence 1 [1.7%] compared to no patients in Sequence 2).

The incidence of arthralgia and gastroesophageal reflux disease appeared to be higher in the pre-crossover Sequence 1 (2.5% and 1.4%, respectively) than in Sequence 2 (0.6% and 0.2%, respectively); and the incidence of vomiting appeared to be more frequent in the pre-crossover Sequence 2 (2.3%) than in Sequence 1 (0.6%). Post-crossover, the incidence of diarrhea appeared to be higher in Sequence 2 (now on combination treatment) at 3.2% compared to 0.4% in Sequence 1.

Pre-crossover, the most commonly reported **laboratory AEs** included blood creatine phosphokinase increased (1.0% vs. 0.8%), blood glucose increased (1.2% vs. 1.2%), and blood uric acid increased (1.2% vs. 0.8%); the incidence was similar in Sequences 1 and 2, respectively. Post-crossover, the most commonly reported specific AEs appeared to occur with similar frequency in Sequences 1 and 2, respectively, and included ALT increased (1.3% vs. 0.9%), AST increased (1.3% vs. 0.9%), and blood glucose increased (1.3% vs. 1.4%).

Pre-crossover, **clinical SAEs** were reported for 6/486 patients (1.2%) in Sequence 1 and 9/486 patients (1.9%) in Sequence 2. Only 1 SAE in each sequence was considered by the investigator to be related to study treatment (chest pain in Sequence 1 and depression in Sequence 2). Post-crossover, clinical SAEs were reported for 1/230 patient (0.4%) in Sequence 1 and 5/220 patients (2.3%) in Sequence 2; none were considered to be drug-related. There were no **laboratory SAEs** pre-crossover or post-crossover in either treatment sequence.

There was one **confirmed adjudicated CV AE** in each sequence, both pre-crossover, and both considered by the investigator as not related to study drug (acute myocardial infarction in Sequence 1 and stress cardiomyopathy in Sequence 2), and none post-crossover.

There were no treatment-emergent **deaths** reported in this study. However, 1 patient died of 'sudden cardiac death' during the Placebo Run-in Period and another patient died of "pulmonary embolism" during the Post-Reporting Period (which started at the latest of discontinuation date, completion date, or last dose date + 14 days); neither of these deaths were considered by the investigator to be drug-related.

Pre-crossover, 49 patients (10.1%) discontinued from Sequence 1 and 50 patients (10.3%) discontinued from Sequence 2 due to a **clinical AE**; the most common **clinical AEs leading to discontinuation of treatment** were pruritus (2.1% vs. 1.6%), flushing (1.9% vs. 1.9%), and rash (1.0% vs. 0.4%) in Sequences 1 and 2, respectively. Post-crossover, 1 patient (0.4%) discontinued from Sequence 1, and 6 patients (2.7%)

discontinued from Sequence 2 due to an AE; 1 patient in each sequence discontinued for rash; no other 2 patients discontinued for the same AE.

Pre-crossover, only one patient (from Sequence 2) discontinued from the study for a **laboratory AE** (hepatic enzyme increased). Post-crossover, 4 patients (2 patients with increased ALT and 2 patients with increased AST, all from Sequence 1) discontinued from the study for a laboratory AE.

Discontinuations due to drug-related clinical AEs had similar profiles as for all discontinuations due to clinical AEs. Discontinuations due to drug-related laboratory AEs had similar profiles as for all discontinuations due to laboratory AEs.

There were no **hepatic-related clinical AEs** reported during the study. No patient had ALT or AST $\geq$ 10 x upper limit of normal (ULN) in either treatment sequence in either period (pre-crossover or post-crossover). Four patients in Sequence 1 had elevated ALT or AST $\geq$ 5 x ULN, 2 patients during Periods I/II and 2 patients during Period III. Eight patients had consecutive ALT or AST values $\geq$3 x ULN (2 patients in Sequence 1 and 3 patients in Sequence 2 during Periods I/II and 3 patients in Sequence 1 during Period III). No significant differences in percentages between sequences were revealed in AST and/or ALT elevation categories or in median values of ALT or AST changes from baseline after 8 weeks of treatment. No patient met the potential drug-induced liver injury (DILI) (defined as patients with ALT or AST $\geq$ 3 x ULN, total bilirubin $\geq$ 2 x ULN, and ALP < 2 x ULN) at any time during the study.

There were no clinically meaningful differences between treatment sequences in **skeletal muscle-related clinical AEs**. There were no cases of rhabdomyolysis or myopathies reported in this study. No CK laboratory AEs were reported as serious. Pre-crossover, there were no patients in either treatment sequence with CK levels $\geq$ 10 x ULN; post-crossover, 2 patients in Sequence 1 had CK levels $\geq$ 10 x ULN but neither had associated muscle symptoms. However, the non-parametric analysis revealed a between-sequence difference in change from baseline in median CK (10.0 IU/L in Sequence 1, 6.5 IU/L in Sequence 2, difference of 3 IU/L, confidence interval (CI) [0.5, 5.5]).

There were 12 cases of **new onset of diabetes** (9 cases based on pre-defined clinical AEs and 3 based on changes in anti-diabetic medication) during the study. Median change from baseline in FSG rose steadily from baseline and peaked (at Week 8 for Sequence 2 [6 mg/dL] and Week 16 for Sequence 1 [6 mg/dL]), then fell at Week 20 to 3 mg/dL above baseline (both sequences). There was no difference between sequences in median change from baseline after 8 weeks of treatment in FSG between treatment sequences (median change from baseline was 4.0 mg/dL in both sequences). For HbA_{1c} values for patients who had diabetes at baseline, the mean change from baseline at Week 20 was similar for both sequence groups (an increase of 0.3% for Sequence 1 patients and an increase of 0.4% for Sequence 2 patients) and after 8 weeks of treatment (non-parametic analysis), the change in baseline was 0.2% in both sequence groups.

There were no clinically meaningful differences between treatment sequences in predefined limits of change (PDLC)s or vital signs.

Key safety outcomes are summarized in the table below.

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	Sequence 1 ERN/LRPT/SIM → ERN/LRPT + SIM† n (%)	Sequence 2 ERN/LRPT + SIM → ERN/LRPT/SIM‡ n (%)	Total n (%)
Periods I and II (N [patients], %)			
Entered (Treated), All Patients as Treated Population	486	486	972
Completed	232 (47.4)	222 (45.5)	454 (46.5)
Discontinued	257 (52.6)	266 (54.5)	523 (53.5)
≥ 1 **AE**	244 (50.2)	249 (51.2)	493 (50.7)
Discontinued Due to AE	49 (10.1)	51 (10.5)	100 (10.3)
≥ 1 Drug-related AE	167 (34.4)	167 (34.4)	334 (34.4)
Discontinued Due to Drug-related AE	40 (8.2)	42 (8.6)	82 (8.4)
SAE	6 (1.2)	9 (1.9)	15 (1.5)
≥ 1 Drug-related SAE	1 (0.2)	1 (0.2)	2 (0.2)
Discontinued Due to an SAE	3 (0.6)	4 (0.8)	7 (0.7)
Discontinued Due to Drug-related SAE	1 (0.2)	1 (0.2)	2 (0.2)
≥ 1 **Clinical** AE	238 (49.0)	241 (49.6)	479 (49.3)
Discontinued Due to Clinical AE	49 (10.1)	50 (10.3)	99 (10.2)
≥ 1 Drug-related Clinical AE	159 (32.7)	159 (32.7)	318 (32.7)
Discontinued Due to Drug-related Clinical AE	40 (8.2)	41 (8.4)	81 (8.3)
≥ 1 Clinical SAE	6 (1.2)	9 (1.9)	15 (1.5)
≥ 1 Drug-related Clinical SAE	1 (0.2)	1 (0.2)	2 (0.2)
Discontinued Due to Clinical SAE	3 (0.6)	4 (0.8)	7 (0.7)
Discontinued Due to Drug-related Clinical SAE	1 (0.2)	1 (0.2)	2 (0.2)
≥ 1 **Laboratory** AE	19 (3.9)	21 (4.3)	40 (4.1)
Discontinued Due to Laboratory AE	0 (0.0)	1 (0.2)	1 (0.1)
≥ 1 Drug-related Laboratory AE	14 (2.9)	11 (2.3)	25 (2.6)
Discontinued Due to Drug-related Laboratory AE	0 (0.0)	1 (0.2)	1 (0.1)
≥ 1 Laboratory SAE	0 (0.0)	0 (0.0)	0 (0.0)
≥ 1 Drug-related Laboratory SAE	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued Due to Laboratory SAE	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued Due to Drug-related Laboratory SAE	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)
ALT and/or AST:			
≥ 3 x ULN (Consecutive)	2 (0.4)	3 (0.6)	5 (0.5)
≥ 5 x ULN	1 (0.2)	2 (0.4)	3 (0.3)
≥ 10 x ULN	0 (0.0)	0 (0.0)	0 (0.0)
Potential DILI cases[a]	0 (0.0)	0 (0.0)	0 (0.0)
≥ 1 Hepatic-related AE	0 (0.0)	0 (0.0)	0 (0.0)
New onset Diabetes	5 (1.0)	2 (0.4)	7 (0.7)

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC
MK-0524B, Extended-release Niacin/Laropiprant/Simvastatin Tablet, Primary Hypercholesterolemia, Mixed Dyslipidemia

CLINICAL STUDY REPORT SYNOPSIS

	Sequence 1 ERN/LRPT/SIM → ERN/LRPT + SIM† n (%)	Sequence 2 ERN/LRPT + SIM → ERN/LRPT/SIM‡ n (%)	Total n (%)
CK ≥ 10 x ULN	0 (0.0)	0 (0.0)	0 (0.0)
Period III (N [patients], %)			
Entered (Treated)[b]	230	220	450
Completed	199 (86.5)	190 (86.4)	389 (86.4)
Discontinued	33 (14.3)	32 (14.5)	65 (14.4)
≥ 1 **AE**	70 (30.4)	65 (29.5)	135 (30.0)
Discontinued Due to AE	5 (2.2)	6 (2.7)	11 (2.4)
≥ 1 Drug-related AE	20 (8.7)	18 (8.2)	38 (8.4)
Discontinued Due to Drug-related AE	4 (1.7)	4 (1.8)	8 (1.8)
≥ 1 SAE	1 (0.4)	5 (2.3)	6 (1.3)
≥ 1 Drug-related SAE	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued Due to SAE	0 (0.0)	2 (0.9)	2 (0.4)
Discontinued Due to Drug-related SAE	0 (0.0)	0 (0.0)	0 (0.0)
≥ 1 **Clinical** AE	64 (27.8)	60 (27.3)	124 (27.6)
Discontinued Due to Clinical AE	1 (0.4)	6 (2.7)	7 (1.6)
≥ 1 Drug-related Clinical AE	15 (6.5)	15 (6.8)	30 (6.7)
Discontinued Due to Drug-related Clinical AE	1 (0.4)	4 (1.8)	5 (1.1)
≥ 1 Clinical SAE	1 (0.4)	5 (2.3)	6 (1.3)
≥ 1 Drug-related Clinical SAE	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued Due to Clinical SAE	0 (0.0)	2 (0.9)	2 (0.4)
Discontinued Due to Drug-related Clinical SAE	0 (0.0)	0 (0.0)	0 (0.0)
≥ 1 **Laboratory** AE	14 (6.1)	7 (3.2)	21 (4.7)
Discontinued Due to Laboratory AE	4 (1.7)	0 (0.0)	4 (0.9)
≥ 1 Drug-related Laboratory AE	8 (3.5)	4 (1.8)	12 (2.7)
Discontinued Due to Drug-related Laboratory AE	3 (1.3)	0 (0.0)	3 (0.7)
≥ 1 Laboratory SAE	0 (0.0)	0 (0.0)	0 (0.0)
≥ 1 Drug-related Laboratory SAE	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued Due to Laboratory SAE	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued Due to Drug-related Laboratory SAE	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)
ALT and/or AST:			
≥ 3 x ULN[a]	3 (1.3)	0 (0.0)	3 (0.7)
≥ 5 x ULN	2 (0.9)	0 (0.0)	2 (0.4)
≥ 10 x ULN	0 (0.0)	0 (0.0)	0 (0.0)
Potential DILI cases[a]	0 (0.0)	0 (0.0)	0 (0.0)
≥ 1 Hepatic-related AE	0 (0.0)	0 (0.0)	0 (0.0)
New onset Diabetes	3 (1.3)	2 (0.9)	5 (1.1)

CK ≥ 10 x ULN[c]	2 (0.9)	0 (0.0)	2 (0.4)

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; DILI = drug-induced liver injury; ERN = extended-release niacin; LRPT = laropiprant; SAE = serious adverse event; SIM = simvastatin; ULN = upper limit of normal.

a. Met Drug-induced Liver Injury (DILI): ALT or AST ≥ 3 x ULN, total bilirubin ≥ 2 x ULN, and ALP < 2 x ULN).
b. Percentages relative to the number of patients who entered Period III.
c. None of these cases had associated muscle symptoms.

† Sequence 1 = ERN/LRPT/SIM 1 g/40 mg for 4 weeks (Period I) followed by ERN/LRPT/SIM 2 g/40 mg for 8 weeks (Period II) followed by ERN/LRPT 2 g + SIM 40 mg for 8 weeks (Period III).

‡ Sequence 2 = ERN/LRPT 1 g + SIM 40 mg for 4 weeks (Period I) followed by ERN/LRPT 2 g + SIM 40 mg for 8 weeks (Period II) followed by ERN/LRPT/SIM 2 g/40 mg for 8 weeks (Period III).

CONCLUSIONS:

Overall, combination (ERN/LRPT/SIM 2 g/40 mg) and co-administration (ERN/LRPT 2 g + SIM 40 mg) treatments were generally well tolerated and tolerated similarly in both treatment sequences, pre-crossover and post-crossover, up until the early termination of the study.

AUTHORS: (Medical Writer) (Statistician) (Clin. Monitor)

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