**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

**CLINICAL STUDY REPORT SYNOPSIS**

MK-0524B, Extended-release Niacin/Laropiprant/Simvastatin Tablet, Primary Hypercholest-erolemia, Mixed Dyslipidemia

**PROTOCOL TITLE/NO.:**

A Phase III Multicenter, Double-Blind, Crossover Design Study to Evaluate Lipid-Altering Efficacy and Safety of 1 g/10 mg Extended-Release Niacin/Laropiprant/Simvastatin Combination Tablets in Patients with Primary Hypercholesterolemia or Mixed Dyslipidemia — #143-00

**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 109 active sites in 11 countries as follows (sites per country in parentheses): Chile (3), Germany (10), Hungary (3), Latvia (3), Lithuania (4), Mexico (5), Norway (3), Peru (2), Slovakia (6), United Kingdom (6), United States (64). A full listing of investigator sites and the number of patients enrolled at each site is provided in [16.2.4.1 Table 14.1.1] of the report.

**PUBLICATION(S):**
None

| **PRIMARY THERAPY PERIOD:** | **CLINICAL PHASE:** III |
|---|---|
| 14 Jun 2011 to 12 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 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).

**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/20 mg compared to extended-release

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niacin/laropiprant (ERN/LRPT) 2 g co-administered with simvastatin 20 mg.

**Secondary Objectives**

1. Evaluate the high-density lipoprotein cholesterol (HDL-C)-raising effects of ERN/LRPT/SIM 2 g/20 mg compared to ERN/LRPT 2 g co-administered with simvastatin 20 mg.
2. Evaluate the tolerability of ERN/LRPT/SIM.

Tertiary and exploratory efficacy and pharmacogenomic objectives were described in the protocol [16.1.1.1].

**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 (details in DURATION OF TREATMENT, above) and 2-week placebo run-in period, eligible patients were randomized in a 1:1 ratio on 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 I, patients took 1 tablet of ERN 1 g/LRPT 20 mg/ SIM 10 mg (designated as ERN/LPRT/SIM 1 g/10 mg); for Period II, patients took 2 tablets of ERN 1 g/LRPT 20 mg/SIM 10 mg; and for Period III, patients took 2 tablets of ERN 1 g/LRPT 20 mg (designated as ERN/LRPT 1 g) and 2 tablets of SIM 10 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 I, patients took 1 tablet of ERN/LRPT 1 g and 1 tablet of SIM 10 mg; for Period II, patients took 2 tablets of ERN/LRPT 1g and 2 tablets of SIM 10 mg; and for Period III, patients took 2 tablets of ERN/LRPT/SIM 1 g/10 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 treatment crossed over to the ERN/LRPT + SIM co-administration treatment and patients on co-administration treatment crossed over to the ERN/LRPT/SIM combination treatment for 8 weeks (Period III), for a total of 20 weeks of treatment.

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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 as a single tablet containing ERN 1 g, LRPT 20 mg, and SIM 10 mg (designated ERN/LRPT/SIM 1 g/10 mg).
  Note: ERN/LRPT/SIM 2 g/20 mg = 2 tablets of ERN/LRPT/SIM 1 g/10 mg
- 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 10 mg tablets.

Note: ERN/LRPT 2 g + SIM 20 mg = 2 tablets of ERN/LRPT 1 g and 2 tablets of SIM 10 mg.

Tablets of ERN/LRPT/SIM 1 g/10 mg and ERN/LRPT 1 g 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 Period I (4 weeks) (1 tablet of ERN/LRPT/SIM 1 g/10 mg and 1 tablet of SIM placebo or 1 tablet of ERN/LRPT 1 g and 1 tablet of SIM 10 mg). During Periods II and III (8 weeks each), patients took 4 tablets daily (2 tablets of ERN/LRPT/SIM 1 g/10 mg and 2 tablets of SIM placebo or 2 tablets of ERN/LRPT 1 g and 2 tablets of SIM 10 mg).

| Clinical Material: | Lot Numbers: |
|---|---|
| MK-0524A/B Placebo Tabs<br>MK-0524B Bilayer Tabs (ERN/LRPT/SIM 1 g/10 mg)<br>MK-0524A Bilayer Tabs (ERN/LRPT 1 g)<br>SIM Placebo Tab<br>SIM 10 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, historical and/or current lab values, and investigator's judgment.

At Week -2, patients had to satisfy one of the following criteria:

1. Patients that 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 ≤ 190 mg/dL (≤ 4.91 mmol/L).

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2. Patients that were NOT high risk based on NCEP ATP III guidelines had to have LDL-C ≤ 240 mg/dL (≤ 6.21 mmol/L).

Patients not on lipid-modifying therapy (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 ERN/LRPT/SIM 2 g/20 mg and ERN/LRPT 2 g co-administered with SIM 20 mg and to estimate the LDL-C and HDL-C effects of ERN/LRPT/SIM 1 g/10 mg and ERN/LRPT 1 g co-administered with SIM 10 mg in patients with primary hypercholesterolemia or mixed dyslipidemia.

The primary endpoint was percent change from baseline at the end of the 8-week treatment period (Period II [Week 12] or Period III [Week 20]) in LDL-C. The secondary endpoint was percent change from baseline at the end of the 8-week treatment period in HDL-C. Tertiary endpoints included the following: a) percent change from baseline at the end of the 4-week treatment period (Period I) in LDL-C and HDL-C; b) percent change from baseline at the end of the 8-week treatment period in TG, non-HDL-C, total cholesterol (TC), Apolipoprotein (Apo) B, Apo A-I, TC:HDL-C ratio and LDL-C:HDL-C ratio; and c) percent change from baseline at the end of the 4-week Period I in TG, non-HDL-C, TC, Apo B, 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 (DILI) cases (defined as patients with AST/ALT [asparate aminotransferase/alanine aminotransferase] ≥ 3 x upper limit of normal [ULN], total bilirubin ≥ 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 serious adverse events [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 ANALYSIS:**

**Efficacy:** The planned efficacy analyses were described in detail in the protocol [16.1.1.1]. 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.

**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 adverse experiences 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, HbA1c diabetics) | | X | X |
| | SOCs, specific AEs (incidence ≥ 1% of patients in one of the treatment sequences) | | X | X |
| | Pre-defined limits of change | | 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:<br>• 1 to < 2 x ULN<br>• 2 to < 3 x ULN<br>• ≥ 3 x ULN<br>• ≥ 3 x ULN consecutive<br>• ≥ 5 x ULN<br>• ≥ 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; SOC = system organ class; ULN = upper limit of normal,
Note: 'AE' refers to both clinical and laboratory AEs.

Source: Table 3-4 of protocol [16.1.1]

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**PATIENT DISPOSITION:**

Patient disposition is summarized below. A total of 10 patients (0.9% of patients randomized) completed all three periods (I, II, and III) of the study. A total of 167 patients (14.7% 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 (72.1% in Periods I and II and 13.4% 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 | - | - | 1096 |
| Randomized | 577 | 562 | 1139 |
| Male | 232 (40.2) | 230 (40.9) | 462 (40.6) |
| Female | 345 (59.8) | 332 (59.1) | 677 (59.4) |
| **Periods I and II** (N, %) | | | |
| Completed | 84 (14.6) | 83 (14.8) | 167 (14.7) |
| Discontinued | 493 (85.4) | 479 (85.2) | 972 (85.3) |
| Adverse Event | 63 (10.9) | 43 (7.7) | 106 (9.3) |
| Lost to Follow-up | 3 (0.5) | 5 (0.9) | 8 (0.7) |
| Noncompliance with Study Drug | 1 (0.2) | 1 (0.2) | 2 (0.2) |
| Physician Decision | 2 (0.3) | 1 (0.2) | 3 (0.3) |
| Protocol Violation | 9 (1.6) | 10 (1.8) | 19 (1.7) |
| Study Terminated by Sponsor | 406 (70.4) | 415 (73.8) | 821 (72.1) |
| Withdrawal by Subject | 9 (1.6) | 4 (0.7) | 13 (1.1) |
| **Period III** (N, %) | | | |
| Completed | 6 (1.0) | 4 (0.7) | 10 (0.9) |
| Discontinued | 78 (13.5) | 79 (14.1) | 157 (13.8) |
| Adverse Event | 0 (0.0) | 2 (0.4) | 2 (0.2) |
| Lost to Follow-up | 1 (0.2) | 0 (0.0) | 1 (0.1) |
| Protocol Violation | 0 (0.0) | 1 (0.2) | 1 (0.1) |
| Study Terminated by Sponsor | 77 (13.3) | 76 (13.5) | 153 (13.4) |

Abbreviations: ER = extended release; ERN = extended-release niacin; LRPT = laropiprant.

† Sequence 1 = ERN/LRPT/SIM 1 g/10 mg for 4 weeks (Period I) followed by ERN/LRPT/SIM 2 g/20 mg for 8 weeks (Period II) followed by ERN/LRPT 2 g + SIM 20 mg for 8 weeks (Period III).

‡ Sequence 2 = ERN/LRPT 1 g + SIM 10 mg for 4 weeks (Period I) followed by ERN/LRPT 2 g + SIM 20 mg for 8 weeks (Period II) followed by ERN/LRPT/SIM 2 g/20 mg for 8 weeks (Period III).

ERN/LRPT 1 g = ER-niacin 1 g/laropiprant 20 mg

ERN/LRPT 2 g = 2 tablets of ER-niacin 1 g/laropiprant 20 mg

ERN/LRPT/SIM 1 g/10 mg = ER-niacin 1 g/laropiprant 20 mg/Simvastatin 10 mg (combination tablet)

ERN/LRPT/SIM 2 g/20mg = 2 tablets of ER-niacin 1 g/laropiprant 20 mg/Simvastatin 10 mg (combination tablet)

Source: [16.2.4.1 Table 14.1.7 and Table 14.1.8]

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**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.

**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, 269/567 patients (47.4%) in Sequence 1 and 257/554 patients (46.4%) in Sequence 2 had **at least one AE**. During the post-crossover period, 14/83 patients (16.9%) and 19/82 patients (23.2%), respectively, had at least one AE. The overall percentage of patients who experienced clinical AEs and laboratory AEs was similar between the two sequence groups. The system organ classes (SOCs) in which clinical AEs were most commonly reported (with an incidence of > 10% in either treatment sequence) pre-crossover included vascular disorders (15.9% in Sequence 1 and 13.9% in Sequence 2), skin and subcutaneous tissue disorders (15.7% in Sequence 1 and 11.2% in Sequence 2), and infections and infestations (10.8% in Sequence 1 and 8.7% in Sequence 2) [16.2.7.3 Table 14.3.10.1]. There were no SOCs in which AEs were reported with an incidence of > 10% in either treatment sequence post-crossover [16.2.7.3 Table 14.3.10.3]. The percentage of patients who experienced any AE by SOC was similar for both sequences groups during the pre-crossover and post-crossover treatment periods [16.2.7.3 Table 14.3.7.1 and Table 14.3.7.3].

Pre-crossover, the most common (> 5% of patients in either sequence group) treatment-emergent **clinical AEs** were flushing (13.9% in Sequence 1 and 13.4% in Sequence 2) and pruritus (6.9% in Sequence 1 and 5.2% in Sequence 2) [16.2.7.3 Table 14.3.10.1]. Post-crossover, there were no specific AEs in either sequence group that occured with ≥ 3% frequency; the AE that occured with the highest frequency was upper respiratory tract infection (2 patients [2.4%] in each sequence group) [16.2.7.3 Table 14.3.10.3]. There were no AEs in the pre-crossover or post-crossover periods that were considered statistically significantly different (difference in percentage between combination vs. co-administration as determined by 95% confidence intervals [CIs]) [16.2.7.3 Table 14.3.7.1 and Table 14.3.7.3].

Pre-crossover, the most commonly reported **laboratory AEs** (occurring in at least 1% of patients in either treatment sequence), which was experienced by a similar percentage of patients in both sequence groups, was blood CK increased (0.7% vs. 1.1%) [16.2.7.3 Table 14.3.10.2]. Post-crossover, the most commonly reported specific AEs (occurring in at least 1% of patients in either treatment sequence), which appeared to occur with similar frequency in each treatment sequence, included blood CK increased (1 patient [1.2%] in each sequence group); liver function test abnormal (1 patient [1.2%] vs. no patients); and blood glucose increased, blood uric acid increased, and hepatic enzyme increased (no patients vs. 1 patient [1.2%] for each) [16.2.7.3 Table 14.3.10.4]. There was no significant difference in the occurence of these AEs between combination and co-administration treatment [16.2.7.3 Table 14.3.7.2 and Table 14.3.7.4].

Pre-crossover, **clinical SAEs** were reported for 11/567 patients (1.9%) in Sequence 1 and 5/554 patients (0.9%) in Sequence 2. The most frequent SAE experienced by patients in this study was flushing (3 patients: 1 [0.2%] in Sequence 1 and 2 [0.4%] in Sequence 2) [16.2.7.3 Table 14.3.11.1]; all other SAEs were experienced by 1 patient in one of the two sequence groups. A total of 4 SAEs (2 in each sequence group) were considered by the investigator to be related to study treatment (dizziness and flushing in Sequence 1 and 2 cases of flushing in Sequence 2) [16.2.7.3 Table 14.3.13.1]. Post-crossover,

no patients in Sequence 1 and 1/82 patients (1.2%) in Sequence 2 experienced a clinical SAE (breast cancer), which was not considered by the investigator to be related to study treatment [16.2.7.3 Table 14.3.11.3 and Table 14.3.13.3]. There were no **laboratory SAEs** pre-crossover or post-crossover in either treatment sequence [16.2.7.3 Table 14.3.11.2 and Table 14.3.11.4]. Listings for patients who experienced an SAE are provided in [16.2.7.3 Table 14.3.20.1 to Table 14.3.20.6] and patient narratives are in [16.2.7.2].

There were no **confirmed adjudicated CV** [16.2.7.3 Table 14.3.4.1 and Table 14.3.4.2] or **hepatitis-related AEs** in either sequence group.

There were no treatment-emergent **deaths** reported in this study [16.2.7.3 Table 14.3.16.1 to Table 14.3.16.4].

Pre-crossover, 62/567 patients (10.9%) in Sequence 1 and 41/554 patients (7.4%) in Sequence 2 **discontinued the study due to a clinical AE** [16.2.7.3 Table 14.3.14.1]. The most common clinical AEs leading to discontinuation of treatment for Sequences 1 and 2, respectively, (in at least 1% of patients in either treatment sequence) included flushing (1.6% vs. 1.8%), pruritus (1.4% vs. 0.7%), and rash (1.4% vs. 0.5%]). Post-crossover, no patients discontinued from Sequence 1, and 1/82 patients (1.2%) discontinued from Sequence 2 (breast cancer) [16.2.7.3 Table 14.3.14.3].

Pre-crossover, 1 patient (0.2%) in Sequence 1 **discontinued due to a laboratory AE** (blood CK increased) and 1 patient (0.2%) in Sequence 2 discontinued due to hepatic enzyme increased [16.2.7.3 Table 14.3.14.2]. Post-crossover, no patients discontinued from Sequence 1 or Sequence 2 due to a laboratory AE [16.2.7.3 Table 14.3.14.4].

Discontinuations due to drug-related clinical AEs [16.2.7.3 Table 14.3.15.1 and Table 14.3.15.3] had similar profiles as for all discontinuations due to clinical AEs. Discontinuations due to drug-related laboratory AEs [16.2.7.3 Table 14.3.15.2 and Table 14.3.15.4] had similar profiles as for all discontinuations due to laboratory AEs.

There were no **hepatic-related clinical AEs** reported during the study [16.2.7.3 Table 14.3.2.1 and Table 14.3.2.2]. No patient had ALT or AST $\geq$ 10 x ULN in either treatment sequence in either period (pre-crossover or post-crossover) [16.2.7.3 Table 14.3.5.1 and Table 14.3.5.2]. One patient in each sequence group had elevated ALT or AST $\geq$ 5 x ULN during Periods I/II and 1 patient in Sequence 2 during Period III. Six patients had consecutive ALT or AST values $\geq$3 x ULN (3 patients in Sequence 1 and 2 patients in Sequence 2 during Periods I/II and 1 patient in Sequence 2 during Period III). No significant differences in percentages between sequences were revealed in AST and/or ALT elevation categories. No patient met the potential DILI criteria (ALT or AST $\geq$ 3 x ULN, total bilirubin $\geq$ 2 x ULN, and ALP < 2 x ULN) at any time during the study [16.2.7.3 Table 14.3.50].

There were no clinically meaningful differences between treatment sequences in **skeletal muscle-related clinical AEs** [16.2.7.3 Table 14.3.7.1, Table 14.3.7.3, Table 14.3.10.1, and Table 14.3.10.3]. There were no cases of rhabdomyolysis or myopathies reported in this study. No CK laboratory AEs were reported as serious [16.2.7.3 Table 14.3.11.2 and Table 14.3.11.4]; one resulted in discontinuation from Sequence 1 pre-crossover [16.2.7.3 Table 14.3.14.2 and Table 14.3.14.4]. Pre-crossover, there were 2 patients (0.4%) in Sequence 1 and 1 patient (0.2%) in Sequence 2 with CK levels $\geq$ 10 x ULN, but none was associated with muscle symptoms [16.2.7.3 Table 14.3.6.1]. Post-crossover, 1 patient (1.2%) in Sequence 2 had CK levels $\geq$ 10 x ULN, but this patient did not experience any associated muscle symptoms [16.2.7.3 Table 14.3.6.2]. Among the various CK elevation categories, there were no

differences in between-sequence percentages pre-crossover or post-crossover.

There were 6 cases of **new onset of diabetes** (all based on pre-defined clinical AEs and none based on changes in anti-diabetic medication) during the study. All 6 cases were reported during the pre-crossover period (4 in Sequence 1 and 2 in Sequence 2) [16.2.7.3 Table 14.3.3.1 and Table 14.3.3.2]. Median change from baseline in FSG for Sequence 1 ranged from -0.5 to 4 mg/dL and for Sequence 2 ranged from -1.0 to 5 mg/dL. [16.2.7.3 Figure 14.3.58]. Only 1 patient in Sequence 2 had a hemoglobin A1c (HbA1c) value at Week 20 and, therefore, it is not possible to make any conclusions [16.2.7.3 Table 14.3.33].

There were no clinically meaningful differences between treatment sequences in predefined limits of changes (PDLCs) [16.2.7.3 Table 14.3.34.1, Table 14.3.34.2, Table 14.3.35.1, and Table 14.3.35.2] or vital signs [16.2.7.3 Table 14.3.26, Table 14.3.27, and Table 14.3.28].

Key safety outcomes are summarized in the table below.

| | **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 | 567 | 554 | 1121 |
| ≥ 1 **AE** | 269 (47.4) | 257 (46.4) | 526 (46.9) |
| Discontinued Due to AE | 63 (11.1) | 42 (7.6) | 105 (9.4) |
| ≥ 1 Drug-related AE | 172 (30.3) | 149 (26.9) | 321 (28.6) |
| Discontinued Due to Drug-related AE | 56 (9.9) | 36 (6.5) | 92 (8.2) |
| ≥ 1 SAE | 11 (1.9) | 5 (0.9) | 16 (1.4) |
| ≥ 1 Drug-related SAE | 2 (0.4) | 2 (0.4) | 4 (0.4) |
| Discontinued Due to an SAE | 3 (0.5) | 2 (0.4) | 5 (0.4) |
| Discontinued Due to Drug-related SAE | 1 (0.2) | 2 (0.4) | 3 (0.3) |
| ≥ 1 **Clinical** AE | 265 (46.7) | 252 (45.5) | 517 (46.1) |
| Discontinued Due to Clinical AE | 62 (10.9) | 41 (7.4) | 103 (9.2) |
| ≥ 1 Drug-related Clinical AE | 170 (30.0) | 145 (26.2) | 315 (28.1) |
| Discontinued Due to Drug-related Clinical AE | 55 (9.7) | 35 (6.3) | 90 (8.0) |
| ≥ 1 Clinical SAE | 11 (1.9) | 5 (0.9) | 16 (1.4) |
| ≥ 1 Drug-related Clinical SAE | 2 (0.4) | 2 (0.4) | 4 (0.4) |
| Discontinued Due to Clinical SAE | 3 (0.5) | 2 (0.4) | 5 (0.4) |

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**CLINICAL STUDY REPORT SYNOPSIS**

MK-0524B, Extended-release Niacin/Laropiprant/Simvastatin Tablet, Primary Hypercholesterolemia, Mixed Dyslipidemia

| | **Sequence 1 ERN/LRPT/SIM → ERN/LRPT+SIM† n (%)** | **Sequence 2 ERN/LRPT+SIM → ERN/LRPT/SIM‡ n (%)** | **Total n (%)** |
|---|---|---|---|
| Discontinued Due to Drug-related Clinical SAE | 1 (0.2) | 2 (0.4) | 3 (0.3) |
| ≥ 1 **Laboratory** AE | 14 (2.5) | 11 (2.0) | 25 (2.2) |
| Discontinued Due to Laboratory AE | 1 (0.2) | 1 (0.2) | 2 (0.2) |
| ≥ 1 Drug-related Laboratory AE | 4 (0.7) | 6 (1.1) | 10 (0.9) |
| Discontinued Due to Drug-related Laboratory AE | 1 (0.2) | 1 (0.2) | 2 (0.2) |
| ≥ 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) | 3 (0.5) | 2 (0.4) | 5 (0.4) |
| ≥ 5 x ULN | 1 (0.2) | 1 (0.2) | 2 (0.2) |
| ≥ 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 | 4 (0.7) | 2 (0.4) | 6 (0.5) |
| CK ≥ 10 x ULN[b] | 2 (0.4) | 1 (0.2) | 3 (0.3) |
| **Period III** (N [patients], %) | | | |
| Entered (Treated)[c] | 83 | 82 | 165 |
| ≥ 1 **AE** | 14 (16.9) | 19 (23.2) | 33 (20.0) |
| Discontinued Due to AE | 0 (0.0) | 1 (1.2) | 1 (0.6) |
| ≥ 1 Drug-related AE | 4 (4.8) | 1 (1.2) | 5 (3.0) |
| Discontinued Due to Drug-related AE | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ≥ 1 SAE | 0 (0.0) | 1 (1.2) | 1 (0.6) |
| ≥ 1 Drug-related SAE | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Discontinued Due to SAE | 0 (0.0) | 1 (1.2) | 1 (0.6) |
| Discontinued Due to Drug-related SAE | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ≥ 1 **Clinical** AE | 14 (16.9) | 16 (19.5) | 30 (18.2) |
| Discontinued Due to Clinical AE | 0 (0.0) | 1 (1.2) | 1 (0.6) |
| ≥ 1 Drug-related Clinical AE | 3 (3.6) | 0 (0.0) | 3 (1.8) |

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**CLINICAL STUDY REPORT SYNOPSIS**

MK-0524B, Extended-release Niacin/Laropiprant/Simvastatin Tablet, Primary Hypercholesterolemia, Mixed Dyslipidemia

| | **Sequence 1 ERN/LRPT/SIM → ERN/LRPT+SIM† n (%)** | **Sequence 2 ERN/LRPT+SIM → ERN/LRPT/SIM‡ n (%)** | **Total n (%)** |
|---|---|---|---|
| Discontinued Due to Drug-related Clinical AE | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ≥ 1 Clinical SAE | 0 (0.0) | 1 (1.2) | 1 (0.6) |
| ≥ 1 Drug-related Clinical SAE | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Discontinued Due to Clinical SAE | 0 (0.0) | 1 (1.2) | 1 (0.6) |
| Discontinued Due to Drug-related Clinical SAE | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ≥ 1 **Laboratory** AE | 2 (2.4) | 3 (3.7) | 5 (3.0) |
| Discontinued Due to Laboratory AE | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ≥ 1 Drug-related Laboratory AE | 1 (1.2) | 1 (1.2) | 2 (1.2) |
| Discontinued Due to Drug-related Laboratory AE | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ≥ 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) | 0 (0.0) | 1 (1.2) | 1 (0.6) |
| ≥ 5 x ULN | 0 (0.0) | 1 (1.2) | 1 (0.6) |
| ≥ 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 | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| CK ≥ 10 x ULN[b] | 0 (0.0) | 1 (1.2) | 1 (0.6) |

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; DILI = drug-induced liver injury; ER = extended release; 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. None of these cases had associated muscle symptoms.
c. Percentages relative to the number of patients who entered and were treated in Period III.

† Sequence 1 = ERN/LRPT/SIM 1 g/10 mg for 4 weeks (Period I) followed by ERN/LRPT/SIM 2 g/20 mg for 8 weeks (Period II) followed by ERN/LRPT 2 g + SIM 20 mg for 8 weeks (Period III).

‡ Sequence 2 = ERN/LRPT 1 g + SIM 10 mg for 4 weeks (Period I) followed by ERN/LRPT 2 g + SIM 20 mg for 8 weeks (Period II) followed by ERN/LRPT/SIM 2 g/20 mg for 8 weeks (Period III).

ERN/LRPT 1 g = ER-niacin 1 g/laropiprant 20 mg

ERN/LRPT 2 g = 2 tablets of ER-niacin 1 g/laropiprant 20 mg

ERN/LRPT/SIM 1 g/10 mg = ER-niacin 1 g/laropiprant 20 mg/Simvastatin 10 mg (combination tablet)

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MK-0524B, Extended-release Niacin/Laropiprant/Simvastatin Tablet, Primary Hypercholesterolemia, Mixed Dyslipidemia

ERN/LRPT/SIM 2 g/20mg = 2 tablets of ER-niacin 1 g/laropiprant 20 mg/Simvastatin 10 mg (combination tablet)

Source: For Periods I and II, disposition [16.2.4.1 Table 14.1.7], AEs, [16.2.7.3 Table 14.3.8.1], clinical AEs [16.2.7.3 Table 14.3.8.3], laboratory AEs [16.2.7.3 Table 14.3.8.5], death [16.2.7.3 Table 14.3.8.1], ALT/AST [16.2.7.3 Table 14.3.5.1], DILI [16.2.7.3 Table 14.3.50], hepatic-related AE [16.2.7.3 Table 14.3.2.1], new onset diabetes [16.2.7.3 Table 14.3.3.1], and CK [16.2.7.3 Table 14.3.6.1]; for Period III, disposition [16.2.4.1 Table 14.1.7] and for Entered (Treated) [16.2.7.3 Table 14.3.8.2], AEs, [16.2.7.3 Table 14.3.8.2], clinical AEs [16.2.7.3 Table 14.3.8.4], laboratory AEs [16.2.7.3 Table 14.3.8.6], death [16.2.7.3 Table 14.3.8.2], ALT/AST [16.2.7.3 Table 14.3.5.2], DILI [16.2.7.3 Table 14.3.50], hepatic-related AE [16.2.7.3 Table 14.3.2.2], new onset diabetes [16.2.7.3 Table 14.3.3.2], and CK [16.2.7.3 Table 14.3.6.2]

**CONCLUSIONS:**

Overall, combination (ERN/LRPT/SIM 2 g/20 mg) and co-administration (ERN/LRPT 2 g + SIM 20 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.

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