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-0524B
laropiprant (+) niacin (+) simvastatin, Tablet
Hypercholesterolemia and Mixed Dyslipidemia

CLINICAL STUDY REPORT SYNOPSIS

PROTOCOL TITLE/NO.: A Multicenter, Randomized, Double-Blind, "Crossover" Design Study to Evaluate the Lipid-Altering Efficacy and Safety of MK-0524B Combination Tablet Compared to MK-0524A + Simvastatin Coadministration in Patients With Primary Hypercholesterolemia and Mixed Dyslipidemia	063
INVESTIGATORS/STUDY CENTERS: One hundred and eighty (180) primary investigative sites participated in this study. Seventy-six (76) of these sites were in the United States and 104 were international. The international sites were from 21 countries.	
PRIMARY THERAPY PERIOD: 07-Aug-2007 to 16-Jun-2008	**CLINICAL PHASE:** III
DURATION OF TREATMENT: 20-week double-blind treatment period preceded by a 2-week placebo run-in period.	

OBJECTIVES: Primary: In patients with primary hypercholesterolemia and mixed dyslipidemia, evaluate the LDL-C-lowering effects of ERN/LRPT/SIM (B16 formulation) 1.8 g/40 mg and 1.8 g/20 mg compared to ERN/LRPT 2 g coadministered with simvastatin 40 mg or 20 mg, respectively.

Secondary: In patients with primary hypercholesterolemia and mixed dyslipidemia, (1) evaluate the HDL-C-raising effects of ERN/LRPT/SIM 1.8 g/40 mg and 1.8 g/20 mg compared to ERN/LRPT 2 g coadministered with simvastatin 40 mg or 20 mg, respectively; (2) estimate the differences in percent change in LDL-C from baseline between ERN/LRPT/SIM 0.9 g/40 mg and ERN/LRPT 1 g coadministered 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 0.9 g/40 mg and ERN/LRPT 1 g coadministered with 40 mg of simvastatin, respectively, for 4 weeks; (4) evaluate the tolerability of ERN/LRPT/SIM.

Tertiary: In patients with primary hypercholesterolemia and mixed dyslipidemia, evaluate the effects of ERN/LRPT/SIM on triglycerides (TG), non-HDL-C, Total Cholesterol (TC), TC:HDL-C ratio, LDL-C:HDL-C ratio, apolipoprotein (Apo) B, and Apo A-I.

Note: The effect on triglycerides (TG), non-HDL-C, Total Cholesterol (TC), TC:HDL-C ratio, LDL-C:HDL-C ratio, apolipoprotein (Apo) B, and Apo A-I of ERN/LRPT/SIM 1.8 g/40 mg and 1.8 g/ 20 mg compared to ERN/LRPT 2 g coadministered with simvastatin 40 mg or simvastatin 20 mg, respectively, will be estimated.

STUDY DESIGN: This was a multicenter, double-blind, randomized, crossover study. Following a 6- to 8-week washout of lipid-lowering therapies (if needed) and a 2-week placebo run-in, eligible patients (~603/sequence) were randomized in a 1:1:1:1 ratio to one of the following 4 treatment arms for 4 weeks.

- ERN/LRPT/SIM 0.9 g/10 mg
- ERN/LRPT 1 g + simvastatin 10 mg
- ERN/LRPT/SIM 0.9 g/40 mg
- ERN/LRPT 1 g + simvastatin 40 mg

At Week 4 (Period I), treatment doses were increased in all treatment arms for an additional 8 weeks (Period II). At Week 12 (Period III), patients in the ERN/LRPT/SIM arms crossed over to the corresponding ERN/LRPT + simvastatin coadministration arms and patients in the coadministration arms crossed over to the corresponding ERN/LRPT/SIM arms. There were 7 scheduled clinic visits at

Weeks -2, 0 (Day 1), 4, 8, 12, 16, and 20. Patients who washed off of lipid lowering therapies required an additional Pre-screen Visit at Week -8 for fibrate washout or Week -6 for washout of statins and all other lipid modifying therapies. The final visit was conducted at Week 20, followed by a poststudy telephone contact 14 days after the last visit or last blinded treatment dose, whichever is the earliest. Patients who discontinued from the study prior to completion were contacted by telephone at their intended final visit study date (20 weeks from randomization) for cardiac related serious adverse experiences or death.

Description of Treatment Sequences:

Sequence 1 = ERN/LRPT/SIM 0.9 g/10 mg (B16 formulation) for 4 weeks (Period I) followed by ERN/LRPT/SIM 1.8 g/20 mg for 8 weeks (2 tablets 0.9-g/10-mg dosage strength) (Period II) followed by ERN/LRPT 2 g + Simvastatin 20 mg for 8 weeks (Period III).

Sequence 2 = ERN/LRPT 1 g + Simvastatin 10 mg for 4 weeks (Period I) followed by ERN/LRPT 2 g + Simvastatin 20 mg for 8 weeks (Period II) followed by ERN/LRPT/SIM 1.8 g/20 mg (2 tablets of the 0.9-g/10-mg dosage strength) for 8 weeks (Period III).

Sequence 3 = ERN/LRPT/SIM 0.9 g/40 mg (B16 formulation) for 4 weeks (Period I) followed by ERN/LRPT/SIM 1.8 g/40 mg for 8 weeks (2 tablets of B16 formulation – ERN/LRPT/SIM 0.9 g/20 mg) (Period II) followed by ERN/LRPT 2 g + Simvastatin 40 mg for 8 weeks (Period III).

Sequence 4 = ERN/LRPT 1 g + Simvastatin 40 mg for 4 weeks (Period I) followed by ERN/LRPT 2 g + Simvastatin 40 mg for 8 weeks (Period II) followed by ERN/LRPT/SIM 1.8 g/40 mg (2 tablets of the 0.9-g/20-mg dosage strength) for 8 weeks (Period III).

SUBJECT/PATIENT DISPOSITION:

Seq. 1 (ERN/LRPT/SIM 1.8 g/20 mg pre-crossover [Periods I & II] → ERN/LRPT 2 g + Simvastatin 20 mg post-crossover [Period III])

Seq. 2 (ERN/LRPT 2 g + Simvastatin 20 mg pre-crossover [Periods I & II] → ERN/LRPT/SIM 1.8 g/20 mg post-crossover [Period III])

	Seq. 1	Seq. 2	TOTAL
Screening Failures			910
Randomized	610	602	1212
Male (age range)	285 (20-79)	268 (19-84)	553 (19-84)
Female (age range)	325 (21-85)	334 (27-81)	659 (21-85)
Pre-crossover			
Discontinued	138 (22.6%)	162 (26.9%)	300 (24.8%)
Clinical AE	96 (15.7%)	99 (16.4%)	195 (16.1%)
Laboratory AE	0 (0.0%)	4 (0.7%)	4 (0.3%)
Other	42 (6.9%)	59 (9.8%)	101 (8.3%)
Post-crossover			
Entered	472 (77.4%)	440 (73.1%)	912 (75.2%)
Completed[†]	447 (94.7%)	419 ((95.2%)	866 (95.0%)
Discontinued	25 (5.3%)	21 (4.8%)	46 (5.0%)
Clinical AE	12 (2.5%)	13 (3.0%)	25 (2.7%)
Laboratory AE	3 (0.6%)	1 (0.2%)	4 (0.4%)
Other	10 (2.1%)	7 (1.6%)	17 (1.9%)

[†] Percentages relative to the number patients that entered the post-crossover period.

Seq. 3 (ERN/LRPT/SIM 1.8 g/40 mg pre-crossover [Periods I & II] → ERN/LRPT 2 g + simvastatin 40 mg post-crossover [Period III])

Seq. 4 (ERN/LRPT 2 g + Simvastatin 40 mg pre-crossover [Periods I & II] → ERN/LRPT/SIM 1.8 g/40 mg post-crossover [Period III])

	Seq. 3	Seq. 4	TOTAL
Randomized	597	605	1202
Male (age range)	284 (20-80)	289 (28-81)	573 (20-81)
Female (age range)	313 (22-85)	316 (25-81)	629 (22-85)
Pre-crossover			
Discontinued	157 (26.3%)	140 (23.1%)	297 (24.7%)
Clinical AE	98 (16.4%)	87 (14.4%)	185 (15.3%)
Laboratory AE	4 (0.7%)	4 (0.7%)	8 (0.7%)
Other	55 (9.2%)	49 (8.1%	104 (8.6%)
Post-crossover			
Entered	440 (73.7%)	465 (76.9%)	905 (74.7%)
Completed[†]	420 (95.5%)	447 (96.1%)	867 (95.8%)
Discontinued	20 (4.5%)	18 (3.9%)	38 (4.2%)
Clinical AE	12 (2.7%)	10 (2.2%)	22 (2.4%)
Laboratory AE	2 (0.5%)	2 (0.4%)	4 (0.4%)
Other	6 (1.3%)	6 (1.3%)	12 (1.3%)

[†] Percentages relative to the number patients that entered the post-crossover period.

DOSAGE/FORMULATION NOS.: Placebo Run-In Period: Beginning at Visit 1 (Week -2), all patients took 1 tablet/day from each bottle of placebo (placebo tablets for ERN/LRPT, ERN/LRPT/SIM, simvastatin 10 mg and simvastatin 40 mg) in the evenings with food. Treatment Period I (Weeks 1 to 4): At Visit 2 (Day 1), patients were randomized to one of 2 initiation doses of ERN/LRPT/SIM (0.9 g/ 10 mg or 0.9 g/40 mg) or to one of the corresponding initiation doses of ERN/LRPT coadministered with simvastatin (ERN/LRPT 1 g + simvastatin 10 mg or 40 mg) for 4 weeks. Patients took 1 tablet/day from each blinded treatment bottle. Treatment Period II (Weeks 5 to 12): At Visit 3 (Week 4), the dose from the large bottle (ERN/LRPT 1 g, ERN/LRPT/SIM 0.9 mg/10 mg, or ERN/LRPT/SIM 0.9 g/20 mg) was doubled. Patients took 2 tablets from the large bottle and continued taking 1 tablet from each of the two smaller bottles (simvastatin 10 mg, simvastatin 40 mg, or placebo) of blinded study therapy for 8 weeks. Treatment Period III (Weeks 12-20): At Visit 5 (Week 12), patients in the ERN/LRPT/SIM arms crossed over to the corresponding coadministration treatments and patients in the coadministration treatments crossed over to the corresponding ERN/LRPT/SIM treatments. Patients took 2 tablets from the large bottle and 1 tablet from each of the smaller bottles of blinded study therapy for 8 weeks. The formulation numbers used for ERN/LRPT placebo were [redacted] The formulation numbers used for simvastatin 10 mg and 40 mg were [redacted] The formulation numbers used for ERN/LRPT and ERN/LRPT/SIM were [redacted] The formulation numbers used for simvastatin 10 mg and 40 mg were [redacted]

DIAGNOSIS/INCLUSION CRITERIA: Male or female patients ≥18 and ≤85 years of age on the day of signing informed consent with hypercholesterolemia or mixed dyslipidemia based upon medical history, historic lipid values (within 6 months of screening), or as otherwise determined by the investigator through optional lipid measurements at the screening visit (Visit 1 or prior to the washout period). Patients taking niacin, statins, or fibrates had to have TG <500 mg/dL (5.65 mmol/L) at or

within 6 months of washout (Pre-screen visit). Patients naïve to lipid-modifying therapy (LMT) or who were taking a LMT other than niacin, statin, or fibrate had to have TG <600 mg/dL (6.78 mmol/L) at or within 6 months of screening (Visit 1 for naïve patients or Pre-screen visit for washout patients). Glycemic status of each patient had to be determined prior to randomization. The physician was required to make a determination based upon available records and clinical judgment whether a patient had normal, IFG or diabetic glycemic status.

EVALUATION CRITERIA:

Efficacy: Co-Primary Endpoints: Percent change from baseline to the end of the 8-week treatment period with ERN/LRPT/SIM 1.8 g/20 mg (2 tablets of the 0.9-g/10-mg dosage strength) or ERN/LRPT 2 g + simvastatin 20 mg in LDL-C. Percent change from baseline to the end of the 8-week treatment period with ERN/LRPT/SIM 1.8 g/40 mg (2 tablets of the 0.9-g/20-mg dosage strength) or ERN/LRPT 2 g + simvastatin 40 mg in LDL-C. Secondary Endpoint: Percent change from baseline to the end of the 8-week treatment period with ERN/LRPT/SIM 1.8 g/20 mg or ERN/LRPT 2 g + simvastatin 20 mg in HDL-C. Percent change from baseline to the end of the 8-week treatment period with ERN/LRPT/SIM 1.8 g/40 mg or ERN/LRPT 2 g + simvastatin 40 mg in HDL-C. Percent change in LDL-C from baseline to week 4 for ERN/LRPT/SIM 0.9 g/40 mg and ERN/LRPT 1 g coadministered with 40 mg of simvastatin. Percent change in HDL-C from baseline to week 4 for ERN/LRPT/SIM 0.9 g/40 mg and ERN/LRPT 1 g coadministered with 40 mg of simvastatin. Tertiary Endpoints: Percent change from baseline following 8 weeks of treatment with either ERN/LRPT/SIM 1.8 g/20 mg or ERN/LRPT 2 g + simvastatin 20 mg in triglycerides (TG), non-HDL-C Total Cholesterol (TC), TC:HDL-C ratio, LDL-C:HDL-C ratio, apolipoprotein (Apo) B and Apo A-I. Percent change from baseline following 8 weeks of treatment with either ERN/LRPT/SIM 1.8 g/40 mg or ERN/LRPT 2 g + simvastatin 40 mg in triglycerides (TG), non-HDL-C Total Cholesterol (TC), TC:HDL-C ratio, LDL-C:HDL-C ratio, apolipoprotein (Apo) B and Apo A-I.

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

STATISTICAL PLANNING AND ANALYSIS:

Efficacy: To test the primary hypotheses, two separate analyses appropriate for a 2-period, 2-treatment crossover design were performed for the pair of sequences corresponding to the simvastatin dose of 20 mg (Sequences 1 and 2) and the pair of sequences corresponding to the simvastatin dose of 40 mg (Sequences 3 and 4). For each of the sequence pairs, the percent change from baseline to the end of the 8-week treatment period in LDL-C was analyzed using an analysis of variance (ANOVA) model with terms sequence, subject within sequence, period and treatment. The clinical equivalence of each sequence pair in LDL-C reduction was established if the 95% CI for the difference between these two treatments in percent change from baseline in LDL-C falls within ±3%. Following a closed ordered testing procedure, the secondary hypothesis of clinical equivalence in raising HDL-C would be tested using an ANOVA analysis similar to that described above and applied to the percent change in HDL-C from baseline to the end of the 8-week treatment period for each pair of sequences. The clinical equivalence of increasing HDL-C would be established if the 95% CI for the respective between-treatment difference in percent change from baseline in HDL-C fell within ±4%. In addition, the primary and secondary endpoint were analyzed using mixed model as a sensitivity analysis and using the per protocol population.

Two families of the hypotheses - one that includes the LDL-C and HDL-C equivalence hypotheses for the low dose of simvastatin, and another one that includes the LDL-C and HDL-C equivalence hypotheses for the high dose of simvastatin, were used in this study. Within each family a closed ordered testing procedure was applied to the LDL-C (primary) and HDL-C (secondary) hypothesis in the specified order. First, the LDL-C equivalence was to be tested; if that was met, the HDL-C equivalence was to be tested. The Type I error was controlled at 0.025 level within each family. The Type I error across the 2 primary hypotheses (as well as the overall Type I error across the two families) was controlled at 0.05.

The differences in percent change from baseline to the end of the 8-week treatment periods in other tertiary lipid parameters except for TG were estimated for each of the 2 crossovers separately based on ANOVA models similar to those used in primary analyses. The 95% CI for the differences is provided, but no equivalence boundaries were specified for the tertiary lipid endpoints.

The differences in percent change from baseline to the end of the 8-week treatment periods for TG were estimated using non-parametric methods.

The sample size in this study was aimed to provide good power for primary lipid endpoints accounting for the multiplicity adjustment. With approximately 444 patients per sequence, the study will have power of approximately 95% (90%) for each of the two primary hypotheses assuming the absolute true difference of 1% (1.2%) in percent change from baseline in LDL-C between ERN/LRPT/SIM and ERN/LRPT co-administered with the respective dose of simvastatin and a SD of the within-patient difference of 16.5. The study will have power of >99% (96%) for each of the 2 secondary hypotheses assuming ≤1% (2%) difference in percent change from baseline in HDL-C between ERN/LRPT/SIM and ERN/LRPT co-administered with the respective dose of simvastatin and a SD of the within-patient difference of 15.6. The study will have power of at least 90% to prove both primary hypotheses as well as both secondary hypotheses assuming ≤1% difference in percent change from baseline in LDL-C and ≤1% difference in percent change from baseline in HDL-C between ERN/LRPT/SIM and ERN/LRPT co-administered with the respective dose of simvastatin.

Safety: A multi-tiered approach was used in evaluating the safety and tolerability parameters in this study. Analyses were performed based on adverse experience occurring during Periods I and II combined and Period III, separately. For Period I and II combined, pre-specified Tier 1 adverse experiences and/or safety parameters (e.g., Hepatitis-related adverse experiences, ALT/AST consecutive elevations ≥3xULN, CK elevations ≥10xULN with or without muscle symptoms, confirmed adjudicated CV events, new onset of diabetes or impaired fasting glucose, and worsening of diabetes, as specified in the protocol) were compared between Sequences 1 and 2 and, separately, between Sequences 3 and 4 using Fisher's exact test. The 95% confidence intervals based on Wilson's score method for between group differences were provided for the Tier 1 safety parameters and predefined limits of change parameters as specified in the protocol. For other adverse experiences, only counts and percentages were tabulated. For Period III, 95% confidence intervals based on Wilson's score method for between group differences were provided for the Tier 1 and 2 safety parameters and predefined limits of change parameters. For other adverse experiences, only counts and percentages were tabulated.

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

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

RESULTS:

Efficacy: The pre-specified primary and secondary efficacy hypotheses concerning ERN/LRPT/SIM at 1.8 g/40 mg (dosed as 2 tablets of the 0.9-g/20-mg dosage strength) were met demonstrating clinical equivalence of ERN/LRPT/SIM relative to ERN/LRPT, 2 g coadministered with simvastatin 40 mg, on lipid endpoints. The primary hypothesis concerning clinical equivalence of ERN/LRPT/SIM 1.8 g/ 20 mg (dosed as 2 tablets of the 0.9-g/10-mg dosage strength) relative to ERN/LRPT, 2 g coadministered with simvastatin 20 mg, in reducing LDL-C was not met. Although, 95% CI for ERN/LRPT/SIM 1.8 g/20 mg relative to ERN/LRPT, dosed at 2 g coadministered with simvastatin 20 mg, in increasing HDL-C resulted fell within the pre-specified equivalence bounds (±4%), under the ordered testing multiplicity paradigm, the hypothesis test is not considered statistically significant. The results based on LS means within treatment groups and the difference in LS means between ERN/LRPT/SIM relative to ERN/LRPT coadministered with simvastatin 20 mg and 40 mg are shown in tables below.

Primary and Secondary Lipid Endpoints
LS Mean (95% CI) for Percent Change From Baseline After 8 Weeks of Treatment
MK-0524B 1.8 g/40 mg or MK-0524A 2 g Coadministered With Simvastatin 40 mg

	LS Mean (95% CI) for Percent Change From Baseline After 8 Weeks of Treatment With:		Difference in LS Mean (95% CI)
	MK-0524B 1.8 g/ 40 mg (n=843)	MK-0524A 2 g Co-Administered With Simva 40 (n=843)	Combination vs. Coadministration
LDL-C	-48.9 (-49.7, -48.2)	-50.4 (-51.1, -49.7)	1.4 (0.4, 2.4)
HDL-C	27.7 (26.9, 28.4)	28.5 (27.8, 29.2)	-0.8 (-1.9, 0.2)

Primary and Secondary Lipid Endpoints
LS Mean (95% CI) for Percent Change From Baseline After 8 Weeks of Treatment
MK-0524B 1.8 g/20 mg or MK-0524A 2 g Co-administered With Simvastatin 20 mg

	LS Mean (95% CI) for Percent Change From Baseline After 8 Weeks of Treatment With:		Difference in LS Mean (95% CI)
	MK-0524B 1.8 g/ 20 mg (n=844)	MK-0524A 2 g Co-Administered With Simva 20 (n=844)	Combination vs. Co-administration
LDL-C	-44.6 (-45.3, -43.8)	-46.9 (-47.7, -46.2)	2.4 (1.3, 3.4)
HDL-C	27.4 (26.5, 28.2)	27.6 (26.7, 28.4)	-0.2 (-1.4, 1.0)

In patients with primary hypercholesterolemia or mixed hyperlipidemia, the estimate of the between treatment difference in percent change from baseline at Week 4 in LDL-C following treatment with ERN/LRPT/SIM 0.9 g/40 mg relative to ERN/LRPT 1 g coadministered with simvastatin 40 mg was 3.7% with a 95% CI of (1.2%, 6.1%), this suggested that ERN/LRPT/SIM is less efficacious than corresponding coadministered dosage strengths in lowering LDL-C. The estimated difference in HDL-C between the 2 groups was 0.2% with a 95% CI of (-1.9%, 2.3%).

SAFETY: The safety profile and incidence of clinical and laboratory adverse experiences was similar across Sequences 1 and 2 and across Sequences 3 and 4 including those that were drug-related, serious or led to discontinuation. Across the study, the clinical and laboratory drug-related adverse experiences that occurred more frequently in the treatment groups were those typically associated with niacin and niacin-containing products, specifically clinical adverse experiences related to paraesthesia, flushing, rash, pruritus, and gastrointestinal upset, and laboratory adverse experiences related to elevations in liver transaminases (ALT, AST), fasting blood glucose, uric acid, and creatine kinase. Other common clinical adverse experiences that also occurred at a high incidence were headache and nasopharyngitis. Throughout the course of the pre-crossover treatment period, there were 3 (0.5%) serious adverse events in Sequence 1 and 6 (1.0%) in Sequence 2; 12 (2.0%) patients had a serious clinical adverse experience in Sequence 3 and 9 (1.5%) patients had a serious clinical adverse experiences in Sequence 4. For the post-crossover period, 4 (0.8%) and 2 (0.5%) patients had a serious clinical adverse experience in Sequences 1 and 2, respectively and 5 (1.1%) and 3 (0.6%) patients had a serious clinical adverse experiences in Sequences 3 and 4, respectively.

Of the 44 patients who had serious adverse experiences, 3 were determined by the investigator to be drug-related (erythema nodosum, drug eruption, and nausea and vomiting). There were no deaths reported in this study. In the pre-defined areas for the assessment of safety the incidence of adverse experiences was comparable among the 4 treatment groups. Specifically for muscle, there were no cases of myopathy or rhabdomyolysis. There were 5 patients with CK levels ≥10 x ULN but none had associated muscle symptoms; 2 (0.4%) patients in Sequence 1 (ERN/LRPT 2 g + simvastatin 20 mg, post-crossover); 2 (0.4%) patients in Sequence 3 (ERN/LRPT/SIM 1.8 g/40 mg, pre-crossover) and 1 (0.2%) patient in Sequence 4 (ERN/LRPT 2 g + simvastatin 40 mg, pre-crossover).

For liver, 24 patients (1.0%) sustained consecutive and ≥3 fold ULN elevations in ALT and/or AST:

- 2 (0.3%) patients in Sequence 1 and 3 (0.5%) patients in Sequence 2 during the pre-crossover period
- 3 (0.6%) patients in Sequence 1 and 4 (0.9%) patients in Sequence 2 during the post-crossover period
- 4 (0.7%) patients in Sequence 3 and 6 (1.0%) patients in Sequence 4 during the pre-crossover period
- 1 (0.2%) patients in Sequence 3 and 1 (0.2%) patient in Sequence 4 during the post-crossover period

In addition, 2 patients experienced hepatic-related clinical adverse experiences. One patient experienced hepatomegaly during the pre-crossover period in Sequence 1 (ERN/LRPT/SIM 1.8 g/20 mg) and 1 patient developed jaundice during the pre-crossover period of Sequence 4 (ERN/LRPT 2 g + simvastatin 40 mg). Both events were considered non-serious, 1 was considered possibly study-drug-related (jaundice), and 1 patient discontinued. For glycemic control, at Week 4 (pre-crossover), median increases in FSG peaked at 5 mg/dL and 6 mg/dL in the ERN/LRPT/SIM 1.8 g/20 mg and ERN/LRPT 2 g + simvastatin 20 mg, respectively, and remained steady throughout the pre-crossover period. For ERN/LRPT/SIM 1.8 g/40 mg and ERN/LRPT 2 g + simvastatin 40 mg, median increases in FSG at Week 4 were 5 mg/dL and 6 mg/dL, respectively. Median changes from baseline in FSG at Week 20 (post-crossover) were similar in magnitude. There were no clinically meaningful differences across the corresponding treatment groups. Among diabetic patients, mean HbA_{1c} increased by 0.4% and 0.3% for the ERN/LRPT/SIM 1.8 g/20 mg and ERN/LRPT 2 g + simvastatin 20-mg treatment groups, respectively, and by 0.3% for both the ERN/LRPT/SIM 1.8 g/40 mg and ERN/LRPT 1.8 g + simvastatin 40-mg treatment groups. Patients on anti-diabetic therapies were allowed to manage their hyperglycemia through ongoing modifications of their anti-diabetic regimens during the course of treatment.

CONCLUSIONS:

EFFICACY: In patients with primary hypercholesterolemia or mixed hyperlipidemia, ERN/LRPT/SIM (Formulation #B16) 1.8 g/40 mg (dosed as two 0.9-g/20-mg tablets), compared to ERN/LRPT, at a maintenance dose of 2 g coadministered with simvastatin 40 mg, after 8 weeks of treatment, produced:

(1) Reductions in LDL-C that met pre-specified boundaries (±3%) for demonstrating equivalence between ERN/LRPT/SIM and comparable doses of coadministered ERN/LRPT and simvastatin.

(2) Elevations in HDL-C that met pre-specified boundaries (±4%) for demonstrating equivalence between ERN/LRPT/SIM and comparable doses of coadministered ERN/LRPT and simvastatin.

In patients with primary hypercholesterolemia or mixed hyperlipidemia, ERN/LRPT/SIM (Formulation #B16) 1.8 g/20 mg (dosed as two 0.9-g/10-mg tablets) compared to ERN/LRPT, at a maintenance dose of 2 g coadministered with simvastatin 20 mg, after 8 weeks of treatment, produced:

(1) Reductions in LDL-C that did not meet the pre-specified boundaries (±3%) for demonstrating equivalence between ERN/LRPT/SIM and comparable doses of coadministered ERN/LRPT and simvastatin.

- the upper boundary of the 95% confidence interval for the between treatment group difference in LS Means was 3.4%; thus, non-similarity resulted from only a 0.4% breach of the upper bound of 3%.

(2) Elevations in HDL-C that met pre-specified boundaries (±4%) for demonstrating equivalence between ERN/LRPT/SIM and comparable doses of coadministered ERN/LRPT and simvastatin.

In patients with primary hypercholesterolemia or mixed hyperlipidemia, analysis of the estimation hypothesis of the efficacy of ERN/LRPT/SIM 0.9 g/40 mg and of ERN/LRPT 1 g coadministered with simvastatin 40 mg using the FAS population resulted in a between-group difference (for the percent change from baseline after 4 weeks of treatment) in LS Means (95% CI) that suggested that ERN/LRPT/SIM is less efficacious than corresponding coadministered dosage strengths in lowering LDL-C, but ERN/LRPT/SIM is equally efficacious in raising HDL-C.

SAFETY: The different dosage strengths of ERN/LRPT/SIM were generally well-tolerated and had safety profiles similar to the corresponding coadministration of ERN/LRPT + simvastatin. There was no meaningful increase with ERN/LRPT/SIM administration (versus coadministration therapy) in adverse events that reflect muscle and liver function, as well as glycemic control.

AUTHORS: [redacted]