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	**CLINICAL STUDY REPORT SYNOPSIS**

MK-0653A
Ezetimibe (+) Simvastatin, Tablets
Mixed Hyperlipidemia

PROTOCOL TITLE/NO.: A Study to Evaluate the Efficacy and Safety of Ezetimibe/Simvastatin and Fenofibrate Coadministration in Patients with Mixed Hyperlipidemia #071

INVESTIGATORS/STUDY CENTERS: Multicenter (68). 30 primary investigative sites in the United States, and 38 in Australia, Austria, Canada, Columbia, Costa Rica, France, Guatemala, Hungary, Israel, Mexico, Peru, Russia, Spain, Taiwan, and the United Kingdom.

PUBLICATION(S):

PRIMARY THERAPY PERIOD: 29-Nov-2004 to 28-Sep-2005 **CLINICAL PHASE:** III

DURATION OF TREATMENT: 12 week treatment period

OBJECTIVES: In patients with mixed hyperlipidemia (MHL), this study will evaluate: Primary: Low density lipoprotein cholesterol [LDL-C] lowering efficacy of ezetimibe/simvastatin 10/20 mg and fenofibrate 160 mg coadministration therapy compared to fenofibrate 160 mg. Secondary: (1) Lipid and lipoprotein altering effects (total cholesterol [TC], LDL-C, triglyceride [TG], non-high density lipoprotein cholesterol [non-HDL-C], high density lipoprotein cholesterol [HDL-C], very low density lipoprotein cholesterol [VLDL-C], very low density lipoprotein triglyceride [VLDL-TG], and apolipoprotein [Apo] B, Apo A-I) of ezetimibe/simvastatin 10/20 mg and fenofibrate 160 mg coadministration therapy compared to ezetimibe/simvastatin 10/20 mg; (2) Lipid and lipoprotein altering effects (TC, TG, non-HDL-C, HDL-C, VLDL-C, VLDL-TG, Apo B, Apo A-I) of ezetimibe/simvastatin 10/20 mg and fenofibrate 160 mg coadministration therapy compared to fenofibrate 160 mg; (3) Lipid and lipoprotein altering effects (TC, LDL-C, TG, non-HDL-C, HDL-C, VLDL-C, VLDL-TG, Apo B, Apo A-I) of ezetimibe/simvastatin 10/20 mg and fenofibrate 160 mg coadministration therapy compared to placebo; (4) The percentage of patients who attain their National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III target for LDL-C and non-HDL-C with coadministration of ezetimibe/simvastatin 10/20 mg and fenofibrate 160 mg compared to fenofibrate 160 mg; and (5) Safety and tolerability of ezetimibe/simvastatin 10/20 mg and fenofibrate 160 mg coadministration therapy.

STUDY DESIGN: This was a worldwide, multicenter, randomized, double-blind, placebo-controlled, parallel study. The study consisted of a 6-week washout for statins, niacin (>200 mg/day), and bile acid sequestrants and an 8-week washout for fibrates, followed by a 12-week active-treatment period and a poststudy follow-up contact. Lipid-lowering therapy naïve patients who did not require washout of concomitant therapy are required a minimum of 2-week diet stabilization period followed by a 2-week placebo/diet run-in period. Eligible patients with MHL were randomized in a 3:3:3:1 ratio to: (1) ezetimibe/simvastatin 10/20 mg and fenofibrate 160 mg, (2) ezetimibe/simvastatin 10/20 mg, (3) fenofibrate 160 mg, or (4) placebo. Patients were centrally randomized through an Interactive Voice Response System (IVRS). Patients were stratified according to the following baseline TG levels: >150 to ≤250 mg/dL and >250 to ≤500 mg/dL.

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SUBJECT/PATIENT DISPOSITION:

	Placebo	Ez/Simva 10/20 mg	Feno 160 mg	Ez/Simva 10/20 mg + Feno 160 mg	Total
RANDOMIZED:	60	184	184	183	611
Male (age range)	37 (21 to 72)	95 (28 to 77)	88 (31 to 78)	99 (31 to 77)	319 (21 to 78)
Female (age range)	23 (42 to 74)	89 (20 to 77)	96 (32 to 79)	84 (33 to 78)	292 (20 to 79)
COMPLETED:	57	170	172	170	569
DISCONTINUED:	3	14	12	13	42
Clinical adverse experience	1	6	6	7	20
Laboratory adverse experience	0	0	4	2	6
Other	2	8	2	4	16

DOSAGE/FORMULATION NOS.: Each patient received 2 tablets per day consistent with their allocation. Patients received a combination of fenofibrate 160 mg or placebo to match fenofibrate 160 mg and ezetimibe/simvastatin 10/20 mg or placebo to match ezetimibe/simvastatin 10/20 mg. All dosage forms were tablets and the patient was instructed to dose orally with an evening meal. Study drug was supplied in kits containing 2 bottles, Bottle A and Bottle B for placebo run-in and Bottle C and Bottle D for treatment period. Bottle A contained placebo to match ezetimibe/simvastatin 10/20 mg and Bottle B contained placebo to match fenofibrate 160 mg. Bottle C contained ezetimibe/simvastatin 10/20 mg or placebo to match ezetimibe/simvastatin 10/20 mg, and Bottle D contained fenofibrate 160 mg or placebo to match fenofibrate 160 mg. The following formulation numbers were used:

Material	Formulation No.	Material	Formulation No.
Ezetimibe/simvastatin 10/20 mg Fenofibrate 160 mg	[redacted]	Ezetimibe/simvastatin 10/20 mg placebo Fenofibrate 160 mg placebo	[redacted]

DIAGNOSIS/INCLUSION CRITERIA: Men and women, 18 through 79 years of age diagnosed with MHL but without Coronary Heart Disease (CHD) or CHD-risk equivalent disease (other than diabetes mellitus) as defined by NCEP ATP III. After washout of previous lipid-lowering therapy (during diet stabilization/placebo run-in period), patients were eligible for randomization if LDL-C was 130 to 220 mg/dL (3.37 to 5.69 mmol/L), TG was 150 to 500 mg/dL (1.70 to 5.65 mmol/L), alanine aminotransferase (ALT)and aspartate aminotransferase (AST) were ≤ 1.5 x the upper limit of normal (ULN), and creatine kinase (CK) was ≤ 2 x ULN. Patients with diabetes were limited to an LDL-C entry range of 100 to 180 mg/dL (2.59 to 4.66 mmol/L).

EVALUATION CRITERIA:

EFFICACY: Primary Endpoint Parameter: Percent change from baseline to study endpoint in LDL-C. Secondary Endpoint Parameters: Percent change from baseline to study endpoint in following lipid measurements: TC, TG, non-HDL-C, HDL-C, VLDL-C, VLDL-TG, Apo B, Apo A-I.

SAFETY: Primary Endpoint: Clinical evaluation (physical examination, vital signs); adverse events; laboratory surveillance—ALT, AST, CK, serum creatinine, and other laboratory measurements (hematology, chemistry, urinalysis, beta-human chorionic gonadotropin [β-hCG]). Six areas of safety were pre-defined for inferential assessment; muscle effects, liver effects, rash/allergy, gastrointestinal, renal and gallbladder related terms. Prespecified discontinuation was defined for confirmed consecutive elevations in the following lab parameters: CK, ALT/AST, and serum creatinine. Prespecified discontinuation was also defined for confirmed consecutive elevations in TG.

STATISTICAL PLANNING AND ANALYSIS:

EFFICACY: The primary efficacy analysis was based upon the percent change in LDL-C from baseline to endpoint (defined as the last study treatment-period measurement regardless of whether patient was on or off study drug) after 12 weeks of treatment. An Analysis of Variance (ANOVA) model with terms for treatment and baseline TG stratum was used to compare treatment groups. The primary comparison of ezetimibe/simvastatin 10/20 mg and fenofibrate 160 mg coadministration therapy versus fenofibrate 160 mg monotherapy treatment groups was assessed using appropriate contrast statement from the above described ANOVA model.

SAFETY: Summary statistics and 95% confidence intervals (CI) were computed for changes from baseline in ALT, AST, CK, and creatinine by treatment groups. Inferential comparison utilizing Fisher's exact test was performed for the ezetimibe/simvastatin 10/20 mg and fenofibrate 160 mg versus the other 3 treatment groups with respect to the prespecified adverse experiences and proportions of patients exceeding predefined laboratory elevations in ALT, AST, CK, and creatinine.

RESULTS:

EFFICACY: Median percent changes from baseline to study endpoint in LDL-C were -15.7% and -45.8% in the fenofibrate 160 mg monotherapy and ezetimibe/simvastatin 10/20 mg and fenofibrate 160 mg coadministration therapy treatment groups, respectively. The difference in median percent change from baseline in LDL-C was -30.1% for coadministration therapy compared to fenofibrate monotherapy treatment group ($p<0.001$, 95% CI: -33.5%, -26.7%). There was no incremental benefit in LDL-C reduction in patients treated with coadministration therapy compared to patients treated with ezetimibe/simvastatin treatment. Ezetimibe/simvastatin and fenofibrate coadministration therapy was superior to both fenofibrate monotherapy and ezetimibe/simvastatin therapy with respect to median percent reduction from baseline in TG and non-HDL-C. Ezetimibe/simvastatin and fenofibrate coadministration therapy was superior to ezetimibe/simvastatin but not different from fenofibrate in HDL-C mean percent increase from baseline.

Summary of Key Efficacy Endpoints at Study Endpoint[†]
Percent Change From Baseline

	Median Percent Change From Baseline (%)			
	LDL-C[‡] (n)	Non-HDL-C[‡§] (n)	HDL-C[‖¶] (n)	TG[‡¶] (n)
Placebo	-3.5	-1.7	1.1	-3.1
EZ/Simva 10/20 mg	-47.1	-45.2	9.3	-28.6
Feno 160 mg	-15.7	-21.0	18.2	-41.3
EZ/Simva 10/20 mg + Feno 160 mg	-45.8	-50.5	18.7	-50.0

[†] Last available on-treatment measurement up to week 12.
[‡] The between-treatment difference for coadministration therapy versus fenofibrate monotherapy was significant ($p<0.001$).
[§] The between-treatment difference for coadministration therapy versus ezetimibe/simvastatin therapy was significant ($p=0.003$).
[‖] Least-squares mean percent change from baseline
[¶] The between-treatment difference for coadministration therapy versus ezetimibe/simvastatin therapy was significant ($p<0.001$).
n = Total number of patients in treatment group.
EZ/Simva 10/20 mg = ezetimibe/simvastatin 10/20 mg/day.
Feno 160 mg = fenofibrate 160 mg/day.
EZ/Simva 10/20 mg + Feno 160 mg = ezetimibe/simvastatin 10/20 mg coadministered with fenofibrate 160 mg/day.

SAFETY: The safety and tolerability of ezetimibe/simvastatin and fenofibrate coadministration therapy appeared to be similar to fenofibrate monotherapy, and there were no clinically or statistically meaningful differences in the clinical or laboratory adverse experiences assessed. There were 3 (1.6%) serious adverse events in the fenofibrate monotherapy treatment group and no serious adverse events were reported in the ezetimibe/simvastatin and fenofibrate coadministration therapy treatment group. Of those serious adverse events, 1 was considered drug related in the fenofibrate monotherapy treatment group. In the 6 predefined areas for the assessment of safety, the incidence of adverse experiences was comparable between the 3 active treatment groups. Specifically for muscle, there were no cases of myopathy or rhabdomyolysis or CK levels > 10 fold the ULN in either treatment group. For liver, no patients (0%) in the ezetimibe/simvastatin group, six (6) patients (3.3%) in the fenofibrate monotherapy treatment group and five (5) patients (2.8%) in the ezetimibe/simvastatin and fenofibrate coadministration treatment group sustained consecutive and ≥ 3 fold ULN elevations in ALT and/or AST. Six (6) of the 11 patients who experienced consecutive ≥ 3 fold ULN elevations in ALT and/or AST completed the treatment study, while the remaining 5 patients discontinued as a result of their elevations in liver enzymes. No patients experienced hepatic or gallbladder-related adverse experiences during the study.

CONCLUSIONS:

EFFICACY: This 12 week treatment study demonstrated that in patients with MHL, the coadministration of ezetimibe/simvastatin and fenofibrate produced: 1. incremental reductions in LDL-C compared with fenofibrate monotherapy 2. incremental increases in HDL-C compared with ezetimibe/simvastatin alone 3. incremental reductions in non-HDL-C compared with fenofibrate monotherapy 4. incremental reductions in TG compared with ezetimibe/simvastatin 5. no incremental reductions in LDL-C compared with ezetimibe/simvastatin alone.

SAFETY: The coadministration of ezetimibe/simvastatin and fenofibrate was well tolerated, without evidence of clinical adverse effects on liver function, muscle or creatinine levels, compared with fenofibrate monotherapy.

AUTHORS: [redacted]