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-0653
Ezetimibe, 30 mg ezetimibe in 3 tablets
Homozygous Sitosterolemia

CLINICAL STUDY REPORT SYNOPSIS

PROTOCOL TITLE/NO.: Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Efficacy and Safety of Adding Ezetimibe 30 mg to an Ongoing Regimen of Ezetimibe 10 mg in Patients With Homozygous Sitosterolemia #062

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter (19). Twelve investigative sites in the United States and 7 in France, Germany, Netherlands, Norway, South African and United Kingdom [redacted]; [redacted]. Please see Table 2-1 for further information.

Table 2-1

Number of Patients Entered by Investigator and Treatment Group

Study Number	Investigator Name	EZ 10 mg + Placebo (N = 14)	EZ 40 mg (N = 13)	Total (N = 27)
[redacted]	[redacted]	1	0	1
		1	1	2
		0	3	3
		1	0	1
		0	1	1
		2	1	3
		1	0	1
		0	1	1
		1	1	2
		0	1	1
		2	0	2
		1	0	1
		1	0	1
		0	1	1
		1	0	1
		0	1	1
		1	0	1
		0	2	2
		1	0	1

Data Source: [redacted]

PUBLICATION(S): N/A

PRIMARY THERAPY PERIOD: 03-Nov-2004 to 29-Sep-2005 **CLINICAL PHASE:** III, V

DURATION OF TREATMENT: 26-week treatment period.

OBJECTIVE(S): In patients with sitosterolemia who have been taking ezetimibe 10 mg daily for at least 6 months prior to entry, this study was to compare the effects of adding ezetimibe 30 mg versus placebo to ongoing ezetimibe 10-mg treatment for 26 weeks on: **Primary**: plasma sitosterol concentration; **Secondary**: (1) plasma campesterol concentration; (2) change in size of Achilles tendon-thickness and non-Achilles xanthomas relative to baseline; and (3) the safety and tolerability of ezetimibe 40 mg in patients with sitosterolemia.

STUDY DESIGN: This was a worldwide, multicenter, double-blind, randomized, placebo-controlled, parallel study with a duration of approximately 27 weeks. It included a 1-week screening period, and a 26-week double-blind period. Patients had to have been taking ezetimibe 10 mg daily on an ongoing basis for at least 6 months prior to enrollment. There were 6 scheduled clinic visits at Weeks -1, 0 (Day 1), 4, 12, 24, and 26. Non-cholesterol sterols and lipids (for efficacy assessment) were measured on 2 separate determinations prior to randomization (Visits 1 and 2), and then at Visits 3, 5, and 6. Direct measurement of non-Achilles xanthoma were taken at Visit 1, and radiographs for Achilles tendon thickness were obtained at Visit 1 or 2 (baseline); both measurements were to be repeated at the final study visit. Patients were to receive open-label ezetimibe 10 mg for the duration of the study beginning at Week -1 (Visit 1), and were randomized at Day 1 (Visit 2) to receive either additional ezetimibe 30 mg or placebo for the 26-week double-blind period. The final visit was to be conducted at Week 26 (Visit 6), followed by a post-study telephone contact approximately 14 days after the last study visit to assess for potential serious adverse experiences [redacted].

SUBJECT/PATIENT DISPOSITION: Patient demographics and disposition data are summarized in below. Of the 27 patients who participated in the study, 2 discontinued and 25 completed.

SCREENING FAILURES:	0
RANDOMIZED:	27
Male (age range)	9 (34-61)
Female (age range)	18 (18-71)
COMPLETED:	25
DISCONTINUED:	2
Clinical adverse experience	2
Laboratory adverse experience	0
Other	0

Data Source: [redacted]

DOSAGE/FORMULATION NOS.: The duration of the study was approximately 27 weeks including a 1-week screening period (during which patients continued to take open-label ezetimibe 10 mg) and a 26-week double-blind period. During the 26-week double-blind period, patients continued to take 1 pill of open-label ezetimibe 10 mg concomitantly with 3 pills of blinded treatment of ezetimibe 10 mg or placebo for the duration of the study.

Formulation numbers for the study medications were as follows:

- Open-label ezetimibe 10 mg: [redacted]
- Ezetimibe 10 mg: [redacted]
- Placebo: [redacted]

DIAGNOSIS/INCLUSION CRITERIA: Male and female patients with homozygous sitosterolemia, who were at least 18 years of age, and who had a history of plasma sitosterol concentration >5 mg/dL. Patients in an ongoing Sitosterolemia Extension Study, as well as new patients with sitosterolemia, were eligible for participation in this study. All patients had to be on a stable treatment regimen which included ezetimibe 10 mg/day for at least the preceding 6 months.

EVALUATION CRITERIA:

EFFICACY MEASUREMENTS: Plasma concentrations of sitosterol, campesterol, lathosterol, desmosterol, total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C); radiographic assessment of Achilles tendon thickness and direct measurements of non-Achilles xanthomas.

SAFETY MEASUREMENTS: Clinical evaluation (physical examination, vital signs); electrocardiogram (ECG); alanine transaminase (ALT), aspartate transaminase (AST), and creatine phosphokinase (CPK); other laboratory assessments including hematology, blood chemistry, beta-human chorionic gonadotropin [β-hCG]) and urinalysis; patient monitoring for adverse experiences.

STATISTICAL PLANNING AND ANALYSIS: The primary efficacy endpoint was the percent change from baseline (average of Week -1 and Day 1) to study endpoint (average of Week 24 and Week 26) in plasma sitosterol. A one-way parametric analysis of variance (ANOVA) model with terms for treatment was used to estimate the least-squares mean (LS mean) for each treatment, between-treatment difference, and 95% confidence intervals (95% CI). The primary hypothesis, evaluation of the effect of adding ezetimibe 30 mg versus placebo to ongoing treatment with ezetimibe 10 mg on the percent change in plasma sitosterol concentration relative to baseline after 26 weeks of treatment was evaluated using the above model. Similar analyses were performed on additional endpoints like plasma campesterol, lathosterol and LDL sterols.

RESULTS:

Efficacy: The study failed to show evidence of a difference between ezetimibe 30 mg/day and placebo added to a background therapy of ezetimibe 10 mg/day on plasma sitosterol concentrations. The between-group comparison was not statistically significant (median difference and 95% CIs: 9.6% [-4.1, 18.3]). Similar results were seen for plasma campesterol. There was no effect on the Achilles tendon thickness. Please see Table 2-2.

Table 2-2

Nonparametric Analysis of Percent Change From Baseline
All-Patients-Treated Approach

	EZ 10 mg + Placebo N = 14	EZ 40 mg N = 13
Sitosterol		
Percent Change From Baseline at Study Endpoint		
Median (95% CI)	-10.0 (-21.6, 1.5)	3.3 (-5.9, 12.5)
Difference: EZ 10 mg + Placebo versus EZ 40 mg		
Median† (95% CI)† p-Value‡	9.6 (-4.1, 18.3) 0.180	
Campesterol		
Percent Change From Baseline at Study Endpoint		
Median (95% CI)	-9.7 (-19.1, -0.3)	-0.5 (-11.6, 10.7)
Difference: EZ 10 mg + Placebo versus EZ 40 mg		
Median† (95% CI)† p-Value‡	7.6 (-8.5, 20.7) 0.359	
† Hodges-Lehmann estimate of the median difference between treatments with a corresponding distribution-free CI based on Wilcoxon's rank sum test. ‡ p-Value from ANCOVA model based on Tukey's normalized ranks.		

Data Source: [redacted]

Safety: No deaths occurred in this study. A total of 8 (57.1%) patients were reported to have adverse experiences in the ezetimibe 10-mg group and 10 (76.9%) patients were reported to have adverse experiences in the ezetimibe 40-mg group. Please see Table 2-3. Overall, there was no pattern suggestive of a meaningful difference between the treatement groups in the occurrence of adverse events. The most common adverse events reported in the ezetimibe 10-mg group were in the category of musculoskeletal disorders (4 patients; 28.6%). In the ezetimibe 40-mg group the most common adverse events were in the category of gastrointestinal disorders (4 patients; 30.8%). Please see Table 2-5.

Table 2-3

Clinical Adverse Experience Summary

	EZ 10 mg + Placebo (N = 14)		EZ 40 mg (N = 13)	
	n	(%)	n	(%)
Number (%) of patients:				
With one or more adverse experiences	8	(57.1)	10	(76.9)
With no adverse experience	6	(42.9)	3	(23.1)
With drug-related adverse experiences†	3	(21.4)	4	(30.8)
With serious adverse experiences	0	(0.0)	2	(15.4)
With serious drug-related adverse experiences	0	(0.0)	0	(0.0)
Who died	0	(0.0)	0	(0.0)
Discontinued due to adverse experiences	0	(0.0)	2	(15.4)
Discontinued due to drug-related adverse experiences	0	(0.0)	1	(7.7)
Discontinued due to serious adverse experiences	0	(0.0)	1	(7.7)
Discontinued due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)

† Determined by the investigator to be possibly, probably or definitely drug related.

Data Source: [redacted]

Drug-related adverse events (deemed by the investigator(s) to be "possibly" study drug related) were reported in 3 (21.4%) patients in the ezetimibe 10-mg group and in 4 (30.8) patients in the ezetimibe 40-mg group. None of the treatment-related adverse events were considered serious adverse events. Among the reported specific drug-related clinical adverse experiences, abdominal distension, abdominal pain, and headache were the only events for which there was more than 1 patient (2 each) in the ezetimibe 40-mg treatment group; for the ezetimibe 10-mg group, there were no specific adverse events that occurred in more than 1 patient. Please see Table 2-4.

Table 2-4

Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence >0% in One or More Treatment Groups) by System Organ Class by System Organ Class—Drug Related

	EZ 10 mg + Placebo (N = 14)		EZ 40 mg (N = 13)	
	n	(%)	n	(%)
Patients With One Or More Adverse Experiences	3	(21.4)	4	(30.8)
Patients With No Adverse Experience	11	(78.6)	9	(69.2)
Gastrointestinal Disorders	0	(0.0)	2	(15.4)
Abdominal Distension	0	(0.0)	2	(15.4)
Abdominal Pain	0	(0.0)	2	(15.4)
General Disorders And Administration Site Conditions	1	(7.1)	1	(7.7)
Fatigue	1	(7.1)	1	(7.7)
Musculoskeletal And Connective Tissue Disorders	2	(14.3)	1	(7.7)
Arthralgia	1	(7.1)	0	(0.0)
Myalgia	1	(7.1)	1	(7.7)
Pain In Extremity	1	(7.1)	0	(0.0)
Nervous System Disorders	1	(7.1)	2	(15.4)
Dizziness	1	(7.1)	0	(0.0)
Headache	0	(0.0)	2	(15.4)
Respiratory, Thoracic And Mediastinal Disorders	0	(0.0)	1	(7.7)
Pharyngolaryngeal Pain	0	(0.0)	1	(7.7)
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.				

Data Source: [redacted]

Table 2-5

Number (%) of Patients With Specific Clinical Adverse Experiences
(Incidence >0% in One or More Treatment Groups)
by System Organ Class

	EZ 10 mg + Placebo (N = 14)		EZ 40 mg (N = 13)	
	n	(%)	n	(%)
Patients With One Or More Adverse Experiences	8	(57.1)	10	(76.9)
Patients With No Adverse Experience	6	(42.9)	3	(23.1)
Eye Disorders	0	(0.0)	1	(7.7)
Amblyopia	0	(0.0)	1	(7.7)
Gastrointestinal Disorders	1	(7.1)	4	(30.8)
Abdominal Distension	0	(0.0)	2	(15.4)
Abdominal Pain	0	(0.0)	2	(15.4)
Constipation	0	(0.0)	1	(7.7)
Diarrhoea	1	(7.1)	0	(0.0)
Flatulence	0	(0.0)	1	(7.7)
General Disorders And Administration Site Conditions	1	(7.1)	2	(15.4)
Fatigue	1	(7.1)	1	(7.7)
Oedema Peripheral	0	(0.0)	1	(7.7)
Infections And Infestations	2	(14.3)	3	(23.1)
Device Related Infection	1	(7.1)	0	(0.0)
Herpes Ophthalmic	1	(7.1)	0	(0.0)
Influenza	1	(7.1)	1	(7.7)
Nasopharyngitis	0	(0.0)	1	(7.7)
Sinusitis	0	(0.0)	1	(7.7)
Injury, Poisoning And Procedural Complications	0	(0.0)	1	(7.7)
Accidental Overdose	0	(0.0)	1	(7.7)
Musculoskeletal And Connective Tissue Disorders	4	(28.6)	3	(23.1)
Arthralgia	2	(14.3)	1	(7.7)
Back Pain	0	(0.0)	1	(7.7)
Bursitis	1	(7.1)	0	(0.0)
Musculoskeletal Discomfort	0	(0.0)	1	(7.7)
Myalgia	1	(7.1)	1	(7.7)
Pain In Extremity	1	(7.1)	0	(0.0)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	0	(0.0)	1	(7.7)
Multiple Myeloma	0	(0.0)	1	(7.7)

Table 2-5 (Cont.)

Number (%) of Patients With Specific Clinical Adverse Experiences
(Incidence >0% in One or More Treatment Groups)
by System Organ Class

	EZ 10 mg + Placebo (N = 14)		EZ 40 mg (N = 13)	
	n	(%)	n	(%)
Nervous System Disorders	2	(14.3)	2	(15.4)
Dizziness	1	(7.1)	0	(0.0)
Headache	1	(7.1)	2	(15.4)
Paraesthesia	0	(0.0)	1	(7.7)
Psychiatric Disorders	1	(7.1)	0	(0.0)
Insomnia	1	(7.1)	0	(0.0)
Reproductive System And Breast Disorders	0	(0.0)	3	(23.1)
Breast Mass	0	(0.0)	1	(7.7)
Breast Pain	0	(0.0)	1	(7.7)
Oligomenorrhoea	0	(0.0)	1	(7.7)
Respiratory, Thoracic And Mediastinal Disorders	0	(0.0)	1	(7.7)
Pharyngolaryngeal Pain	0	(0.0)	1	(7.7)
Vascular Disorders	2	(14.3)	0	(0.0)
Hypertension	2	(14.3)	0	(0.0)
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.				

Data Source: [redacted]

There were 2 patients in the ezetimibe 40 mg who experienced serious clinical adverse experiences. Please see Table 2-6.

[redacted] The investigator reported multiple mylenoma as not related to study therapy. [redacted] The patient continued the study and the investigator reported the overdose as not related to study medication.

Table 2-6

Clinical Adverse Experiences
Listing of Patients With Serious

[redacted]

Data Source: [redacted]

Two patients discontinued the study. [redacted] Please see Table 2-7.

Table 2-7

Clinical Adverse Experiences
Listing of Patients Discontinued Due to

[redacted]

Data Source: [redacted]

There was one report of a laboratory adverse experience of reticulocyte count decreased in the ezetimibe 10-mg group. Please see Table 2-8.

A summary of details concerning all adverse experiences can be found in [redacted].

Table 2-8

Number (%) of Patients With Specific Laboratory Adverse Experiences
(Incidence >0% in One or More Treatment Groups)
by Laboratory Test Category

	EZ 10 mg + Placebo (N=14)		EZ 40 mg (N=13)	
	n/m	(%)	n/m	(%)
Patients with one or more adverse experiences	1/14	(7.1)	0/13	(0.0)
Patients with no adverse experiences	13/14	(92.9)	13/13	(100.0)
Hematology Laboratory Test	**1/14**	**(7.1)**	**0/13**	**(0.0)**
Reticulocyte Count Decreased	1/14	(7.1)	0/13	(0.0)

† Indicates there was no associated laboratory test or there were no patients for whom the laboratory test was recorded postbaseline.
n/m = number of patients with laboratory adverse experiences/number of patients for whom the laboratory test was recorded postbaseline.
Although a patient may have had 2 or more laboratory adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.

Data Source: [redacted]

CONCLUSIONS: The results of this study indicate that treatment with ezetimibe 40 mg/day as compared to treatment with ezetimibe 10 mg/day resulted in:

- No significant change from baseline in plasma sitosterol.
- No significant change from baseline in plasma campesterol.
- No significant change from baseline in LDL-C from baseline.

Ezetimibe 40 mg/day was generally safe and well-tolerated compared with ezetimibe 10 mg/ day.

AUTHORS: [redacted]