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.

MK-0653A Prot. No. 808
Ezetimibe/Simvastatin (10mg/40mg) Compared to Doubling the Dose of Statin in Patients Hospitalized with a Coronary Event

2. Synopsis

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PROTOCOL TITLE/NO.: An Open-Label, Multicenter Study to Assess the Efficacy of Switching to a Combination Tablet Ezetimibe/Simvastatin 10mg/40mg, Compared to Doubling the Dose of Statin in Patients Hospitalized with a Coronary Event #808

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 [redacted].

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter (48 sites in 14 countries). A list of Primary Investigators can be found in [redacted]. The list includes only sites that received drug. Principal Author's Signature Page can be found in [redacted].

PUBLICATION(S): Found in [redacted].

PRIMARY THERAPY PERIOD: January 2005 to May 2007. Clean file declared on June 21, 2007.	**CLINICAL PHASE:** III

DURATION OF TREATMENT: Patients were screened and randomized into a 12-week treatment period at Visit 1, which extended through Visit 3 (Week 12).

OBJECTIVE(S):

PRIMARY OBJECTIVE: In patients taking a statin and admitted to hospital for investigation of a coronary event, to evaluate the efficacy of switching to ezetimibe/simvastatin (10mg/40mg) on discharge compared to doubling the statin dose as assessed by the low-density lipoprotein cholesterol (LDL-C) values achieved after 12 weeks of treatment.

SECONDARY OBJECTIVE: In patients taking a statin and admitted to hospital for investigation of a coronary event:

(1) To determine the effect of ezetimibe/simvastatin (10mg/40mg) compared to doubling the statin dose on total cholesterol (TC).

(2) To determine the effect of ezetimibe/simvastatin (10mg/40mg) compared to doubling the statin dose on triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, LDL-C/HDL-C ratio, TC/HDL-C ratio and apolipoprotein (apo) B.

(3) To evaluate the safety of ezetimibe/simvastatin (10mg/40mg) versus doubling the statin dose.

HYPOTHESES:

PRIMARY HYPOTHESIS: In patients taking a statin and admitted to hospital for investigation of a coronary event, the actual LDL-C achieved after 12 weeks of treatment is lower with ezetimibe/simvastatin (10mg/40mg) than with the admission dose of statin doubled.

SECONDARY HYPOTHESES: (1) In patients taking a statin and admitted to hospital for investigation of a coronary event, the actual total cholesterol achieved after 12 weeks of treatment is lower with ezetimibe/simvastatin (10mg/40mg) than with the admission dose of statin doubled.

(2) Ezetimibe/simvastatin (10mg/40mg) daily in patients admitted to hospital for investigation of a coronary event is generally well tolerated.

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STUDY DESIGN: Protocol 808 was a randomized, open-label comparative study to assess the efficacy on LDL-C of Ezetimibe/Simvastatin (10mg/40mg) compared to the admission dose of statin doubled in patients who were hospitalized for investigation of a coronary event. Consenting patients who met all eligibility criteria were randomized to a 12 week treatment period and were allocated to one of two open label treatment groups in a 1:1 ratio. Randomization was stratified according to statin/dose potency at the time of hospital admission; three strata were considered: low potency statin therapy, mid potency statin therapy and high potency statin therapy. Patients received either a combination tablet of ezetimibe/simvastatin (10mg/40mg) once daily for 12 weeks (Group 1) or had their admission dose of statin doubled (Group 2). A follow-up phone call or post-study visit (if necessary) was conducted 14 days after the final dose of study medication. The protocol can be found in [redacted]; [redacted], informed consent in [redacted], and sample case report forms in [redacted].

SUBJECT/PATIENT DISPOSITION:

Table 2-1 displays a summary of end of study status for all patients. Out of 213 randomized patients in the ezetimibe/simvastatin (10mg/40mg) group, 190 (89.2%) completed the study and 23 patients (10.8%) discontinued study therapy during treatment phase. Out of 211 randomized patients in the statin double dose group, 180 (85.3%) completed the study, with 31 patients (14.7%) discontinuing study therapy during the treatment phase.

Table 2-1
Patient Disposition

	EZ/Simva 10/40mg (N=213)		Statin double dose (N=211)		Total (N=424)	
	n	(%)	n	(%)	n	(%)
Screening Failures					37	
Randomized	213		211		424	
Randomized and Treated	213	(100.0)	211	(100.0)	424	(100.0)
Completed the study	190	(89.2)	180	(85.3)	370	(87.3)
Discontinued from study	23	(10.8)	31	(14.7)	54	(12.7)
Clinical AE	12	(5.6)	13	(6.2)	25	(5.9)
Deviation from protocol	3	(1.4)	5	(2.4)	8	(1.9)
Lab AE	0	(0.0)	2	(0.9)	2	(0.5)
Patient lost to follow-up	1	(0.5)	2	(0.9)	3	(0.7)
Patient withdrew consent	4	(1.9)	5	(2.4)	9	(2.1)
Other	3	(1.4)	4	(1.9)	7	(1.6)

EZ/Simva = Ezetimibe/Simvastatin

Table 2-2 displays a summary of patient baseline characteristics by treatment group. Out of 424 randomized patients, 340 (80.2%) were male. Age, gender and race were well balanced between the treatment groups. Overall, the study population was primarily Caucasian (84.9%).

Table 2-2
Baseline Characteristics

	EZ/Simva 10/40 mg (N=213)		Statin double dose (N=211)		Total (N=424)	
	n	(%)	n	(%)	n	(%)
Gender						
Female	43	(20.2)	41	(19.4)	84	(19.8)
Male	170	(89.8)	170	(80.6)	340	(80.2)
Age						
64 and under	105	(49.3)	111	(52.6)	216	(50.9)
65 to 74	76	(35.7)	65	(30.8)	141	(33.3)
Over 74	32	(15.0)	35	(16.6)	67	(15.8)
Race						
Asian	24	(11.3)	24	(11.4)	48	(11.3)
Black	2	(0.9)	3	(1.4)	5	(1.2)
Caucasian	182	(85.4)	178	(84.4)	360	(84.9)
Other	5	(2.3)	6	(2.8)	11	(2.6)

EZ/Simva = Ezetimibe/Simvastatin

DOSAGE/FORMULATION NOS.: Eligible patients were allocated to one of two open label treatment groups in a 1:1 ratio. Patients either had their admission dose of statin doubled taken once daily for the 12 week treatment period, or received a combination tablet of ezetimibe/simvastatin (10mg/40mg) once daily for the 12 week treatment period.

DIAGNOSIS/INCLUSION CRITERIA: Men and women aged 18 years or older were enrolled. Patients were required to meet the following criteria:

- Patient was hospitalized for investigation of a coronary event, either unstable angina pectoris with electrocardiogram changes, increased troponin levels following myocardial infarction, or changes in creatine kinase-MB (CKMB) following myocardial infarction.
- Patient had taken a stable daily dose of one of the following medications for the 6 weeks immediately prior to enrollment in the study:
  atorvastatin or simvastatin 10 mg, 20 mg, 40 mg
  fluvastatin 20 mg, 40 mg
  lovastatin, pravastatin or rosuvastatin 10 mg or 20 mg

  Patients who had a change in dose or statin for a maximum of 3 days of dosing prior to randomization were also acceptable for inclusion.
- Patient had liver transaminases (ALT&AST) less than or equal to twice the upper limit of normal, with no active liver disease, and triglycerides < 4.00 mmol/l at Visit 1.

EVALUATION CRITERIA:

EFFICACY MEASUREMENTS: Primary variable: Actual follow-up LDL-C value at study endpoint after 12 weeks of treatment. An "endpoint" value for each patient was defined as the last post-baseline measurement during the 12-week open-label treatment period. Secondary variables: Follow-up value at study endpoint for TC, HDL-C, TG, non-HDL-C, LDL-C/HDL-C ratio, TC/HDL-C ratio and Apolipoprotein B.

SAFETY MEASUREMENTS: At Visit 1, clinical evaluation included physical examinations, vital signs (blood pressure, and pulse. Height and weight were recorded, if available), ECG and laboratory safety tests. Visit 2 and Visit 3 included clinical and laboratory safety evaluations, monitoring adverse events and discontinuations due to clinical and laboratory adverse events. Visit 4 is a follow up phone call to assess adverse experiences, or if necessary, repeat any safety laboratory tests.

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STATISTICAL PLANNING AND ANALYSIS:

EFFICACY: The primary efficacy analysis was based on the "Full Analysis Set" (FAS) approach, including all patients who took at least one dose of study treatment and had at least one measurement after the start of open-label treatment. A patient must also have a baseline value to be included in the FAS population for analysis of covariance (with baseline value as covariate) as described below. Baseline value was defined as the last measurement in the baseline day range (through day 1). The primary variable (LDL-C value at endpoint) was assessed by an ANCOVA model including terms for treatment, study center, stratum (tertiles according to statin/dose potency) and baseline (continuous variable) as covariate. Study centers with less than 2 patients in one of the treatment groups were combined. The least-squares mean for each treatment between-treatment differences in LS means and 95% confidence intervals (95% CI) were estimated from the above ANCOVA model.

The consistency of the treatment effect over study centers and strata was evaluated. The secondary efficacy variables, the follow-up value at study endpoint for TC, HDL-C, TG, non-HDL-C, Apo-B, LDL-C/HDL-C ratio and TC/HDL-C ratio as well as the exploratory variable CRP, were assessed by the main effects ANCOVA model described above for the analysis of the primary variable. Due to the non-normal distribution associated with TG and CRP, a nonparametric evaluation using an ANCOVA model utilizing ranks with terms for treatment, center, stratum (tertiles according to statin/dose potency) and baseline (continuous variable) as covariate was performed for the follow-up TG and CRP value at study endpoint, treatment difference was estimated by the difference in medians utilizing Hodges-Lehmann estimate and corresponding 95% confidence intervals.

To allow a quantification of treatment effects in line with the widely-used concept of percent reduction, percent mean change from baseline (defined as [mean follow-up at endpoint/mean baseline - 1] x 100) were also reported.

SAFETY: Safety and tolerability were assessed by clinical and statistical review of all safety parameters including adverse experiences, laboratory values, and vital signs. The population for safety analyses is the "All Patients as Treated" (APaT) set including all randomized patients who took at least one dose of the open-label study medication. Three "Tiers" were used to classify and analyze adverse experience data. Tier I clinical and laboratory AEs include the following categories: (1) patients who experience at least 1 AE; (2) patients who experience a drug-related AE; (3) patients who experience ab serious AE; (4) patients who discontinued treatment due to an AE and (5) patients who experience an AE of specific interest. The AEs of specific interest included gastrointestinal related AEs; allergic reaction or rash AEs; gallbladder-related AEs; and hepatitis-related AEs. Tier II AEs included clinical and laboratory AEs by system organ class and specific AEs with an incidence 3% in one or both treatment groups; Tier III AEs were all other AEs. For Tier I AEs, comparison of ezetimibe/simvastatin (10mg/40mg) with admission statin dose doubled based on differences in proportions of patients with an event was performed using Fisher's exact test and confidence intervals for the between-group differences were computed using Wilson's Score method. For Tier II AEs, the difference in proportion of patients with the AE in the ezetimibe/simvastatin (10mg/40mg) versus admission statin dose doubled group was compared using 95% CIs. For Tier III AEs, individual adverse experiences were listed and summarized by frequency of occurrence; no statistical testing were performed for Tier III AEs and no confidence intervals were provided. Clinical safety and laboratory data were summarized with focused attention on clinically important elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and creatine kinase (CK). These elevations were compared between treatment groups using Fisher's exact test. The Statistical Analysis Plan is located in [redacted].

RESULTS:

The Statistical Report is located in [redacted].

EFFICACY:

Primary variable: The mean follow-up LDL-C was significantly lower for the ezetimibe/simvastatin (10mg/40mg) group than for the statin double dose group (p≤0.001). Mean follow-up values were 1.81 and 2.22 mmol/L in the ezetimibe/simvastatin (10mg/40mg) and statin double dose groups, respectively. The treatment difference in LS mean follow-up was -0.49 mmol/L, with a 95% CI of (-0.62, -0.35) . Results are summarized in Table 2-3.

The percent mean changes from baseline at study endpoint were -27.00% and -4.15% in the ezetimibe/simvastatin (10mg/40mg) and statin double dose groups, respectively.

Table 2-3
Analysis of Low-Density Lipoprotein Cholesterol (mmol/L) at Study Endpoint
After 12 Weeks of Treatment

		Baseline		Follow-up value			
Treatment	N	Mean	SD	Mean	SD	LS Mean†	95% CI for LS Mean
EZ/Simva 10/40 mg	201	2.48	0.78	1.81	0.69	1.74***	(1.64, 1.84)
Statin double dose	195	2.31	0.69	2.22	0.84	2.22***	(2.12, 2.33)
Between-Treatment Group Comparison				p-Value		Difference in LS Means	95% CI for Difference in LS Means
EZ/Simva 10/40 mg versus Statin double dose				≤ 0.001		-0.49	(-0.62, -0.35)
p-Value for the Effect							
Center				≤ 0.001			
Stratum				0.485			
Baseline LDL-Cholesterol				≤ 0.001			
Square Root of Mean Square Error (MSE) of Follow-up: 0.64							

† Within-treatment test of mean follow-up equal to 0: ***:p≤ 0.001, **:0.001<p≤ 0.010, *:0.010<p≤ 0.050.
CI = Confidence interval.
LS Mean = Least-squares mean - Model-derived mean adjusted for center, stratum and baseline LDL-C.
SD = Standard deviation.

Secondary variables:

(1) Key secondary - total cholesterol (TC): The mean follow-up TC was significantly lower for the ezetimibe/simvastatin (10mg/40mg) group than for the statin double dose group (p≤0.001). Mean follow-up values were 3.71 and 4.11 mmol/L in the ezetimibe/simvastatin (10mg/40mg) and statin double dose groups, respectively. Results are summarized in Table 2-4.

The percent mean changes from baseline at study endpoint were -14.60% and -1.70% in the ezetimibe/simvastatin (10mg/40mg) and the statin double dose groups, respectively

Table 2-4
Analysis of Total Cholesterol (mmol/L) at Study Endpoint After 12 Weeks of Treatment

		Baseline		Follow-up value			
Treatment	N	Mean	SD	Mean	SD	LS Mean†	95% CI for LS Mean
EZ/Simva 10/40 mg	201	4.35	0.91	3.71	0.83	3.64***	(3.52, 3.76)
Statin double dose	195	4.18	0.80	4.11	0.98	4.13***	(4.01, 4.25)
Between-Treatment Group Comparison				p-Value		Difference in LS Means	95% CI for Difference in LS Means
EZ/Simva 10/40 mg versus Statin double dose				≤ 0.001		-0.49	(-0.65, -0.33)
p-Value for the Effect							
Center				0.003			
Stratum				0.468			
Baseline Total-Cholesterol				≤ 0.001			
Square Root of Mean Square Error (MSE) of Follow-up: 0.75							

† Within-treatment test of mean follow-up equal to 0: ***:p≤ 0.001, **:0.001<p≤ 0.010, *:0.010<p≤ 0.050.
CI = Confidence interval.
LS Mean = Least-squares mean - Model-derived mean adjusted for center, stratum and baseline TC.
SD = Standard deviation.

(2)Other secondary variables: :

Triglycerides (TG): The median follow-up TG was not significantly different after treatment with ezetimibe/simvastatin (10mg/40mg) compared to statin double dose. Median follow-up values were 1.38 and 1.41 mmol/L in the ezetimibe/simvastatin (10mg/40mg) and statin double dose groups, respectively. Results are summarized in Table 2-5.

Table 2-5
Non-Parametric Analysis of Follow-Up Triglycerides (mmol/L) at Study Endpoint After 12 Weeks of Treatment

		Baseline		Follow-up			
Treatment	N	Median	SD	Median†	SD	95% CI for Median	
EZ/Simva 10/40 mg	201	1.54	0.74	1.38***	0.78	(1.27, 1.49)	
Statin double dose	195	1.59	0.77	1.41***	0.80	(1.30, 1.53)	
Between-Treatment Group Comparison				p-Value	Difference in Medians‡	95% CI for Difference in Medians	
EZ/Simva 10/40 mg versus Statin double dose				0.550	-0.03	(-0.16, 0.07)	
p-Value for Effect							
Center				0.602			
Stratum				0.581			
Baseline Triglycerides				≤ 0.001			

† Non-parametric within-treatment test (Wilcoxon signed rank test) : ***:p≤ 0.001, **:0.001<p≤ 0.010, *:0.010<p≤ 0.050.
‡ The difference in medians was obtained by Hodges-Lehman estimation.
CI = Confidence interval.
SD = Standard deviation for median (calculated by [Q3-Q1]/1.075).
Q1 = 25th percentile; Q3 = 75th percentile.

High-density lipoprotein cholesterol (HDL-C): The mean follow-up HDL-C was not significantly different after treatment with ezetimibe/simvastatin (10mg/40mg) compared to statin double dose. Mean follow-up values were 1.20 and 1.15 mmol/L in the ezetimibe/simvastatin (10mg/40mg) and statin double dose groups, respectively. Results are summarized in Table 2-6.

Table 2-6
Analysis of High-Density Lipoprotein Cholesterol (mmol/L) at Study Endpoint
After 12 Weeks of Treatment

		Baseline		Follow-up value			
Treatment	N	Mean	SD	Mean	SD	LS Mean†	95% CI for LS Mean
EZ/Simva 10/40 mg	201	1.08	0.28	1.20	0.31	1.19***	(1.15, 1.22)
Statin double dose	195	1.07	0.27	1.15	0.30	1.15***	(1.12, 1.19)
Between-Treatment Group Comparison				p-Value		Difference in LS Means	95% CI for Difference in LS Means
EZ/Simva 10/40 mg versus Statin double dose				0.160		0.03	(-0.01, 0.08)
p-Value for the Effect							
Center				0.063			
Stratum				0.235			
Baseline HDL-Cholesterol				≤ 0.001			
Square Root of Mean Square Error (MSE) of Follow-up: 0.22							

† Within-treatment test of mean follow-up equal to 0: ***:p≤ 0.001, **:0.001<p≤ 0.010, *:0.010<p≤ 0.050.
CI = Confidence interval.
LS Mean = Least-squares mean - Model-derived mean adjusted for center, stratum and baseline HDL-C.
SD = Standard deviation.

Non HDL-C: The mean follow-up non HDL-C was significantly lower for the ezetimibe/simvastatin (10mg/40mg) group than for the statin double dose group (p≤0.001). Mean follow-up values were 2.52 and 2.96 mmol/L in the ezetimibe/simvastatin (10mg/40mg) and statin double dose groups, respectively. Results are summarized in Table 2-7.

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Table 2-7
Analysis of Non High-Density Lipoprotein Cholesterol (mmol/L) at Study Endpoint
After 12 Weeks of Treatment

		Baseline		Follow-up value			
Treatment	N	Mean	SD	Mean	SD	LS Mean†	95% CI for LS Mean
EZ/Simva 10/40 mg	201	3.27	0.84	2.52	0.80	2.44***	(2.33, 2.56)
Statin double dose	195	3.10	0.77	2.96	0.95	2.97***	(2.85, 3.09)
Between-Treatment Group Comparison				p-Value		Difference in LS Means	95% CI for Difference in LS Means
EZ/Simva 10/40 mg versus Statin double dose				≤ 0.001		-0.53	(-0.68, -0.37)
p-Value for the Effect							
Center				0.048			
Stratum				0.628			
Baseline Non HDL-Cholesterol				≤ 0.001			
Square Root of Mean Square Error (MSE) of Follow-up: 0.73							

† Within-treatment test of mean follow-up equal to 0: ***:p≤ 0.001, **:0.001<p≤ 0.010, *:0.010<p≤ 0.050.
CI = Confidence interval.
LS Mean = Least-squares mean - Model-derived mean adjusted for center, stratum and baseline non HDL-C.
SD = Standard deviation.

LDL-C/HDL-C ratio: The mean follow-up LDL-C/HDL-C ratio was significantly lower for the ezetimibe/simvastatin (10mg/40mg) group than for the statin double dose group (p≤0.001). Results are summarized in Table 2-8.

Table 2-8
Analysis of LDL Cholesterol/HDL Cholesterol Ratio at Study Endpoint
After 12 Weeks of Treatment

		Baseline		Follow-up value			
Treatment	N	Mean	SD	Mean	SD	LS Mean†	95% CI for LS Mean
EZ/Simva 10/40 mg	201	2.39	0.84	1.60	0.70	1.54***	(1.43, 1.64)
Statin double dose	195	2.27	0.84	2.03	0.93	2.02***	(1.91, 2.13)
Between-Treatment Group Comparison				p-Value		Difference in LS Means	95% CI for Difference in LS Means
EZ/Simva 10/40 mg versus Statin double dose				≤ 0.001		-0.48	(-0.62, -0.34)
p-Value for the Effect							
Center				0.018			
Stratum				0.910			
Baseline LDL-C/HDL-C Ratio				≤ 0.001			
Square Root of Mean Square Error (MSE) of Follow-up: 0.69							

† Within-treatment test of mean follow-up equal to 0: ***:p≤ 0.001, **:0.001<p≤ 0.010, *:0.010<p≤ 0.050.
CI = Confidence interval.
LS Mean = Least-squares mean - Model-derived mean adjusted for center, stratum and baseline LDL-C/HDL-C.
SD = Standard deviation.

TC/HDL-C ratio: The mean follow-up TC/HDL-C ratio was significantly lower for the ezetimibe/simvastatin (10mg/40mg) group than for the statin double dose group (p≤0.001). Results are summarized in Table 2-9.

Table 2-9
Analysis of Total Cholesterol/HDL Cholesterol Ratio at Study Endpoint
After 12 Weeks of Treatment

		Baseline		Follow-up value			
Treatment	N	Mean	SD	Mean	SD	LS Mean†	95% CI for LS Mean
EZ/Simva 10/40 mg	201	4.19	1.10	3.25	0.95	3.19***	(3.06, 3.33)
Statin double dose	195	4.08	1.10	3.74	1.16	3.72***	(3.58, 3.86)
Between-Treatment Group Comparison				p-Value		Difference in LS Means	95% CI for Difference in LS Means
EZ/Simva 10/40 mg versus Statin double dose				≤ 0.001		-0.53	(-0.71, -0.34)
p-Value for the Effect							
Center				0.196			
Stratum				0.985			
Baseline TC/HDL-C Ratio				≤ 0.001			
Square Root of Mean Square Error (MSE) of Follow-up: 0.87							

† Within-treatment test of mean follow-up equal to 0: ***:p≤ 0.001, **:0.001<p≤ 0.010, *:0.010<p≤ 0.050.
CI = Confidence interval.
LS Mean = Least-squares mean - Model-derived mean adjusted for center, stratum and baseline TC/HDL-C.
SD = Standard deviation.

Apolipoprotein (apo) B: The mean follow-up Apo-B was significantly lower for the ezetimibe/simvastatin (10mg/40mg) group than for the statin double dose group (p≤0.001). Results are summarized in Table 2-10.

Table 2-10
Analysis of Apolipoprotein B (g/L) at Study Endpoint
After 12 Weeks of Treatment

		Baseline		Follow-up value			
Treatment	N	Mean	SD	Mean	SD	LS Mean†	95% CI for LS Mean
EZ/Simva 10/40 mg	199	1.08	0.26	0.86	0.24	0.84***	(0.80, 0.87)
Statin double dose	193	1.04	0.23	0.97	0.28	0.98***	(0.94, 1.01)
Between-Treatment Group Comparison				p-Value		Difference in LS Means	95% CI for Difference in LS Means
EZ/Simva 10/40 mg versus Statin double dose				≤ 0.001		-0.14	(-0.18, -0.09)
p-Value for the Effect							
Center				0.062			
Stratum				0.222			
Baseline Apolipoprotein B				≤ 0.001			
Square Root of Mean Square Error (MSE) of Follow-up: 0.21							

† Within-treatment test of mean follow-up equal to 0: ***:p≤ 0.001, **:0.001<p≤ 0.010, *:0.010<p≤ 0.050.
CI = Confidence interval.
LS Mean = Least-squares mean - Model-derived mean adjusted for center, stratum and baseline Apo B.
SD = Standard deviation.

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SAFETY:

Ezetimibe/simvastatin (10mg/40mg) was generally well tolerated. The safety profiles of ezetimibe/simvastatin (10mg/40mg) and statin double dose were generally comparable. There were no significant differences between ezetimibe/simvastatin (10mg/40mg) and statin double dose treatment groups with respect to consecutive elevation ≥3xULN in alanine (ALT) and/or aspartate (AST) aminotransferase (ALT: 1.0% vs. 1.5% respectively, AST: 0 vs. 0 % respectively). No significant difference was found between treatment groups with respect to allergic reaction or rash (6.6% in both groups) or gastrointestinal-related (7.0% and 11.8%, respectively) adverse events. No elevations in creatine kinase ≥3xULN or gall bladder-related adverse events were observed. No instances of hepatitis were observed, and no significant difference was seen in hepatitis-related adverse events between the ezetimibe/simvastatin (10mg/40mg) (2.6%) and statin double dose (3.4%) treatment groups. No significant differences were seen between treatment groups in the proportion of patients with clinical adverse experiences, drug-related adverse experiences, serious adverse experiences or adverse experiences leading to discontinuation. Clinical adverse experiences are summarized in Table 2-11, and laboratory adverse experiences are summarized in Table 2-12.

Table 2-11
Clinical Adverse Experience Summary

	EZ/Simva 10/40 mg (N=213)		Statin double dose (N=211)	
	n	(%)	n	(%)
Number (%) of patients:				
With one or more adverse experiences	102	(47.9)	96	(45.5)
With drug-related† adverse experiences	18	(8.5)	17	(8.1)
With serious adverse experiences	44	(20.7)	42	(19.9)
With serious drug-related adverse experiences	4	(1.9)	4	(1.9)
Who died	4	(1.9)	4	(1.9)
Discontinued due to adverse experiences	12	(5.6)	13	(6.2)
Discontinued due to drug-related adverse experiences	8	(3.8)	5	(2.4)
Discontinued due to serious adverse experiences	6	(2.8)	8	(3.8)
Discontinued due to serious drug-related adverse experiences	2	(0.9)	2	(0.9)

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

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MK-0653A
ezetimibe (+) simvastatin, Tablet
Hypercholesterolemia

CLINICAL STUDY REPORT
SYNOPSIS
-11-

Table 2-12
Laboratory Adverse Experience Summary

	EZ/Simva 10/40 mg (N=213)		Statin double dose (N=211)	
	n	(%)	n	(%)
Number of patients with at least one laboratory test	204		203	
Number (%)[†] of patients:				
With one or more adverse experiences	10	(4.9)	13	(6.4)
With drug-related[‡] adverse experiences	3	(1.5)	6	(3.0)
With serious adverse experiences	0	(0.0)	0	(0.0)
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	(1.0)
Discontinued due to drug-related adverse experiences	0	(0.0)	1	(0.5)
Discontinued due to serious adverse experiences	0	(0.0)	0	(0.0)
Discontinued due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)

[†] The percent = number of patients within the laboratory adverse experience category *100 / number of patients with one or more laboratory test.
[‡] Determined by the investigator to be possibly, probably or definitely drug related.

CONCLUSIONS:

PRIMARY: In patients taking a statin and admitted to hospital for investigation of a coronary event, the actual LDL-C achieved after 12 weeks of treatment is lower with ezetimibe/simvastatin (10mg/40mg) than with the admission dose of statin doubled (p≤0.001).

SECONDARY: In patients taking a statin and admitted to hospital for investigation of a coronary event, the actual total cholesterol achieved after 12 weeks of treatment is lower with ezetimibe/simvastatin (10mg/40mg) than with the admission dose of statin doubled (p≤0.001).

Ezetimibe/simvastatin (10mg/40mg) daily in patients admitted to hospital for investigation of a coronary event is generally safe and well tolerated.

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