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CLINICAL STUDY REPORT
I. SYNOPSIS

MK-0653A
Ezetimibe/Simvastatin, One tablet administered orally each evening.
Type II Diabetes

PROTOCOL TITLE/NO.: A DOUBLE-BLIND, MULTICENTER STUDY TO ASSESS THE LDL-C LOWERING OF COMBINATION TABLETS EZETIMIBE/SIMVASTATIN (10MG/20MG) AND EZETIMIBE/SIMVASTATIN (10MG/40MG) COMPARED TO ATORVASTATIN 20MG IN PATIENTS WITH TYPE II DIABETES. #807-01-00

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter (84)

PUBLICATION(S):

PRIMARY THERAPY PERIOD: 23-Feb-2005 to 28-Sep-2005 | **CLINICAL PHASE:** III

DURATION OF TREATMENT: Following a 4-week baseline period, patients were randomized into a 6-week active treatment period.

OBJECTIVES: In patients already taking Atorvastatin 10 mg with Type II diabetes, where the investigator feels that further cholesterol lowering therapy is appropriate, Primary: to determine the additional LDL-C lowering achieved by switching to Ezetimibe/Simvastatin (10mg/40mg, 10mg/20mg) compared to double the dose of Atorvastatin (20mg). Secondary: (1) To determine the effect of Ezetimibe/Simvastatin (10mg/40mg, 10mg/20mg) compared to Atorvastatin 20mg on total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, LDL-C/HDL-C ratio, TC/HDL-C ratio and apolipoprotein (apo) B. (2) To further evaluate safety of Ezetimibe/Simvastatin (10mg/40mg, 10mg/20mg) compared to Atorvastatin 20mg.

STUDY DESIGN: Randomized, double-blind, parallel-group, 6-week, multicenter study. The duration of the study was approximately 12 weeks (4-week baseline period followed by a 6-week active treatment period and a follow-up phone call/visit two weeks after). Patients were randomized into a 6-week treatment period and were allocated to one of three blinded treatment groups in a 1:1:1 ratio. All lipid and lipoprotein measurements were blinded during the active treatment period of the study.

PATIENT DISPOSITION:

	EZ/Simva 10/20 mg	EZ/Simva 10/40 mg	Atorvastatin 20 mg	Total
SCREENING FAILURES:				171
RANDOMIZED:	220	222	219	661
Female (age range)	108 (28 to 86)	110 (41 to 83)	111 (33 to 82)	329 (28 to 86)
Male (age range)	112 (36 to 85)	112 (35 to 84)	108 (29 to 81)	332 (29 to 85)
COMPLETED:	217 (98.6)	215 (96.8)	216 (98.6)	648 (98.0)
DISCONTINUED:	3 (1.4)	7 (3.2)	3 (1.4)	13 (2.0)
Clinical adverse experience	3 (1.4)	7 (3.2)	2 (0.9)	12 (1.8)
Protocol deviation	0 (0.0)	0 (0.0)	1† (0.5)	1 (0.2)

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DOSAGE/FORMULATION NOS.: Medication was administered orally once daily each evening. Treatment period: One combination tablet of ezetimibe/simvastatin (10mg/20mg) plus a matching placebo for ezetimibe/simvastatin (10mg/40mg) and atorvastatin 20mg (group 1), or ezetimibe/simvastatin (10mg/40mg) plus a matching placebo for ezetimibe/simvastatin (10mg/20mg) and atorvastatin 20mg (group 2), or atorvastatin 20mg plus a matching placebo for ezetimibe/simvastatin (10mg/40mg) and ezetimibe/simvastatin (10mg/20mg) (group 3).

DIAGNOSIS/INCLUSION CRITERIA: Eligible patients were men and women of at least 18 years old, diagnosed with diabetes mellitus Type II, previously treated with atorvastatin 10 mg for at least 6 weeks prior to entry into the study and who completed the 4-week baseline period while on atorvastatin 10 mg daily. Patients had HbA1C ≤ 10.0%, a liver transaminases (ALT, AST) ≤ 50% above the upper limit of normal at screening Visit 1 (Week - 4), with no active liver disease, and/or creatine kinase (CK) ≤ 50% above the upper limit of normal. Additional criterion for Spain only was requested by the Spain Regulatory Authority; that is, patients had LDL-C levels of 100 mg/dL or higher at Visit 1 (Week - 4).

EVALUATION CRITERIA:

EFFICACY: Primary variable: Percentage change from baseline in LDL-C at study endpoint after 6 weeks of treatment. An "endpoint" value for each patient was defined as the last postbaseline measurement during the 6-week double-blind treatment period. Secondary variables: Percent changes from baseline to study endpoint in Total-C and HDL-C (key secondary), TG, non-HDL-C, LDL-C/HDL-C ratio, Total-C/HDL-C ratio and Apo B. Exploratory variables: Percent change from baseline to study endpoint in C-reactive protein (CRP) and percentage of patients reaching the LDL-C target of <2.5 mmol/L (100 mg/dL) at study endpoint.

SAFETY: Clinical and laboratory adverse experiences, laboratory safety tests, vital signs.

STATISTICAL PLANNING AND ANALYSIS: The primary efficacy analysis was based on the All Patients Treated (APT) approach including all patients who received at least one dose of study treatment, had a measurement at baseline and at least one measurement after the start of treatment. The primary efficacy variable, the percentage reduction from baseline to study endpoint in LDL-C, was assessed by an analysis of variance (ANOVA) including terms for treatment and study center. Treatment comparisons were performed using appropriate contrasts, pairwise treatment differences were estimated by the difference in least-squares means from the ANOVA model and the 95% confidence interval (95% CI). The secondary efficacy variables, the percent changes from baseline to study endpoint in Total-C, HDL-C, TG, non-HDL-C, Apo-B, LDL-C/HDL-C ratio and Total-C/HDL-C ratio were assessed by the main effects ANOVA model described above for the analysis of the primary variable. Due to the non-normal distribution associated with TG, a nonparametric evaluation using an ANOVA model utilizing ranks with terms for treatment and center was performed for the percentage change from baseline in TG, pairwise treatment differences were estimated by the difference in medians utilizing Hodges-Lehmann estimate and corresponding 95% confidence intervals.

SAFETY: Fisher's exact test was performed to compare the ezetimibe/simvastatin (10mg/40mg) and ezetimibe/simvastatin (10mg/20mg) treatment groups to the atorvastatin 20 mg treatment group for incidences of prespecified adverse experiences and proportion of patients exceeding predefined clinically meaningful changes in ALT, AST, and CK.

RESULTS:

EFFICACY: The mean percentage reduction from baseline in LDL-C (primary variable) was significantly greater with ezetimibe/simvastatin (10mg/40mg) than atorvastatin 20 mg ($p \leq 0.001$). The treatment difference was 21.6% with a 95% CI of (16.7, 26.6). Ezetimibe/simvastatin (10mg/20mg) was also significantly better than atorvastatin 20 mg in the primary variable ($p \leq 0.001$, treatment difference 17.7% [95% CI: (12.6, 22.7)]). Ezetimibe/simvastatin (10mg/40mg) and Ezetimibe/simvastatin (10mg/20mg) were significantly better than atorvastatin 20 mg in the secondary variables, the percent change from baseline in Total-C (key secondary) ($p \leq 0.001$), non HDL-C ($p \leq 0.001$), Apo-B ($p \leq 0.001$), LDL-C/HDL-C ratio ($p \leq 0.001$) and Total-C/HDL-C ratio ($p \leq 0.001$). No significant difference was detected between ezetimibe/simvastatin (10mg/40mg, 10mg/20mg) and atorvastatin 20 mg for the percent change from baseline in HDL-C (key secondary) and TG.

Summary Results of Primary, Selected Secondary and Exploratory Efficacy Variables
(All Patients Treated Approach)

***Primary variable*:**

	Percent change from baseline to study endpoint		Comparison between Treatments (Ezetimibe/Simvastatin - Atorvastatin)		
Treatment group	Estimate†	95% CI	p-Value	Difference in Estimate	95% CI
Percent Change From Baseline in Low-Density Lipoprotein Cholesterol					
EZ/Simva 10/20 mg	-26.15	(-29.79, -22.51)	≤ 0.001	-17.66	(-22.69, -12.63)
EZ/Simva 10/40 mg	-30.13	(-33.75, -26.51)	≤ 0.001	-21.64	(-26.64, -16.65)
Atorvastatin 20 mg	-8.49	(-12.10, -4.88)	--	--	--

***Secondary variables*:**

	Percent change from baseline to study endpoint		Comparison between Treatments (Ezetimibe/Simvastatin - Atorvastatin)		
Treatment group	Estimate†	95% CI	p-Value	Difference in Estimate	95% CI
Percent Change From Baseline in Total Cholesterol					
EZ/Simva 10/20 mg	-14.15	(-16.47, -11.83)	≤ 0.001	-8.68	(-11.89, -5.47)
EZ/Simva 10/40 mg	-16.83	(-19.15, -14.51)	≤ 0.001	-11.36	(-14.57, -8.16)
Atorvastatin 20 mg	-5.47	(-7.80, -3.14)	--	--	--
Percent Change From Baseline in High-Density Lipoprotein Cholesterol					
EZ/Simva 10/20 mg	2.37	(0.53, 4.20)	0.569	0.74	(-1.81, 3.28)
EZ/Simva 10/40 mg	1.29	(-0.55, 3.13)	0.795	-0.34	(-2.87, 2.20)
Atorvastatin 20 mg	1.63	(-0.21, 3.47)	--	--	--
Percent Change From Baseline in Triglycerides					
EZ/Simva 10/20 mg	-9.72	(-14.30, -5.14)	0.279‡	-3.48§	(-8.61, 1.90)
EZ/Simva 10/40 mg	-8.40	(-13.47, -3.33)	0.117‡	-4.07§	(-9.84, 1.59)
Atorvastatin 20 mg	-5.46	(-10.12, -0.79)	--	--	--
Percent Change From Baseline in Non High-Density Lipoprotein Cholesterol					
EZ/Simva 10/20 mg	-20.91	(-24.12, -17.70)	≤ 0.001	-13.48	(-17.92, -9.04)
EZ/Simva 10/40 mg	-23.80	(-27.01, -20.59)	≤ 0.001	-16.37	(-20.80, -11.95)
Atorvastatin 20 mg	-7.43	(-10.64, -4.21)	--	--	--
Percent Change From Baseline in Apolipoprotein B					
EZ/Simva 10/20 mg	-14.93	(-17.60, -12.26)	≤ 0.001	-8.23	(-11.94, -4.52)
EZ/Simva 10/40 mg	-19.54	(-22.24, -16.84)	≤ 0.001	-12.84	(-16.57, -9.12)
Atorvastatin 20 mg	-6.70	(-9.40, -3.99)	--	--	--

† The estimate is the least-squares mean from the parametric model for the primary and selected secondary variables, except for triglycerides where it is the median.
‡ Test based on non-parametric analysis using ANOVA on the rank transformation.
§ For triglycerides, the difference in medians was obtained by Hodges-Lehman estimation.
CI = Confidence interval.

SAFETY: Ezetimibe/simvastatin (10mg/40mg, 10mg/20mg) was generally well tolerated. There were no significant differences between ezetimibe/simvastatin (10mg/40mg, 10mg/20mg) and atorvastatin 20 mg in the proportion of patients with clinical adverse experiences (22.5%, 23.2% on ezetimibe/simvastatin (10mg/40mg, 10mg/20mg) versus 19.2% on atorvastatin 20 mg) or laboratory adverse experiences (4.5%, 4.5% on ezetimibe/simvastatin (10mg/40mg, 10mg/20mg) versus 3.7% on atorvastatin 20 mg). Specifically, there were no apparent differences in the ALT, AST, and CK findings. There was 1 patient (on ezetimibe/simvastatin (10mg/20mg)) with serious drug-related clinical adverse experiences leading to discontinuation, no patient had a serious drug-related laboratory adverse experiences. From patients who discontinued due to drug-related clinical adverse experiences, only 1 on ezetimibe/simvastatin (10mg/20mg) and 1 on ezetimibe/simvastatin (10mg/40mg) experienced Myalgia. Two patients died during the study (1 on ezetimibe/simvastatin (10mg/40mg) and 1 on atorvastatin 20 mg).

Clinical Adverse Experiences

	EZ/Simva 10/20 mg (N=220)		EZ/Simva 10/40 mg (N=222)		Atorvastatin 20 mg (N=219)	
	n	(%)	n	(%)	n	(%)
Number (%) of patients:						
With one or more adverse experiences	51	(23.2)	50	(22.5)	42	(19.2)
With drug-related† adverse experiences	13	(5.9)	9	(4.1)	11	(5.0)
With serious adverse experiences	1	(0.5)	1	(0.5)	5	(2.3)
With serious drug-related adverse experiences	1	(0.5)	0	(0.0)	0	(0.0)
Who died	0	(0.0)	1	(0.5)	1	(0.5)
Discontinued due to adverse experiences	3	(1.4)	7	(3.2)	2	(0.9)
Discontinued due to drug-related adverse experiences	3	(1.4)	4	(1.8)	0	(0.0)
Discontinued due to serious adverse experiences	1	(0.5)	1	(0.5)	1	(0.5)
Discontinued due to serious drug-related adverse experiences	1	(0.5)	0	(0.0)	0	(0.0)

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

Laboratory Adverse Experiences

	EZ/Simva 10/20 mg (N=220)		EZ/Simva 10/40 mg (N=222)		Atorvastatin 20 mg (N=219)	
	n	(%)	n	(%)	n	(%)
Number of patients with at least one laboratory test	220		222		219	
Number (%)† of patients:						
With one or more adverse experiences	10	(4.5)	10	(4.5)	8	(3.7)
With drug-related‡ adverse experiences	5	(2.3)	4	(1.8)	3	(1.4)
With serious adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)
With serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)
Who died	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to serious adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to serious drug-related adverse experiences	0	(0.0)	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: In patients already taking Atorvastatin 10 mg with Type II diabetes, where the investigator feels that further cholesterol lowering therapy is appropriate:

(1) The percentage reduction in LDL-C is greater with ezetimibe/simvastatin (10mg/40mg) and ezetimibe/simvastatin (10mg/20mg) than atorvastatin 20 mg following 6 weeks of treatment.

(2) The percentage reduction in Total-C is greater with ezetimibe/simvastatin (10mg/40mg) and ezetimibe/simvastatin (10mg/20mg) than atorvastatin 20 mg following 6 weeks of treatment.

(3) The study failed to show greater increase in HDL-C with ezetimibe/simvastatin (10mg/40mg, 10mg/20mg) compared to atorvastatin 20 mg.

(4) Ezetimibe/simvastatin (10mg/40mg, 10mg/20mg) daily is generally safe and well tolerated.

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ACKNOWLEDGEMENTS: [redacted]