RESEARCH

Cardiovascular Therapeutics

Lipid-Altering Efficacy of Ezetimibe/Simvastatin 10/20 mg Compared to Rosuvastatin 10 mg in High-Risk Patients with and without Type 2 Diabetes Mellitus Inadequately Controlled Despite Prior Statin Monotherapy

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SUMMARY

Aims: This *post hoc* analysis compared the effects of switching to ezetimibe/simvastatin 10/20 mg (EZE/SIMVA) or rosuvastatin 10 mg (ROSUVA) in uncontrolled high-risk hypercholesterolemic patients with/without type 2 diabetes mellitus (T2DM) despite statin monotherapy. **Methods:** Patients (n = 618) at high risk for coronary vascular disease with elevated LDL-C ≥100 and ≤190 mg/dL despite use of statins were randomized 1:1 to double-blind EZE/SIMVA 10/20 mg or ROSUVA 10 mg for 6 weeks. Patients were classified as having T2DM based on ≥1 of the following: diagnosis of T2DM, antidiabetic medication, or FPG ≥126 mg/dL. This analysis evaluated percent changes from baseline in lipids among patients with (n = 182) and without T2DM (n = 434). **Results:** EZE/SIMVA was more effective than ROSUVA at lowering LDL-C, TC, non-HDL-C, and apo B in the overall study population and within both subgroups. Numerically, greater between-treatment reductions in LDL-C, TC, non-HDL-C, and apo B were seen in patients with T2DM versus those without T2DM. A significant interaction ($P = 0.015$) was seen for LDL-C indicating that patients with T2DM achieved larger between-group reductions versus those without T2DM. **Conclusions:** Switching to EZE/SIMVA 10/20 mg versus ROSUVA 10 mg provided superior lipid reductions in patients with/without T2DM.

Introduction

Type 2 diabetes mellitus (T2DM) is associated with a 2- to 4-fold increased risk of coronary heart disease (CHD) compared with the general population [1]. Comprehensive medical management can reduce this risk through lifestyle modification and pharmacological intervention aimed at improving control of blood glucose, hypertension as well as the overall lipoprotein profile (i.e., lowering low-density lipoprotein cholesterol [LDL-C] and triglycerides [TG] and raising high-density lipoprotein cholesterol [HDL-C]) [2,3]. The American and European guidelines identify the primary goal of lipid-altering therapy as an LDL-C level <100 mg/dL in patients with

T2DM, with an optional target of <70 mg/dL in T2DM patients at very high risk for CHD, including those with both T2DM and a history of CHD [4–7].

Statins effectively reduce LDL-C and are currently the initial lipid-altering drug of choice [8,9]. Despite the proven association between elevated LDL-C levels and increased CHD risk in patients with and without T2DM, results suggest that apolipoprotein (apo) B and non-high-density lipoprotein cholesterol (non-HDL-C) levels may provide a more accurate assessment of future CHD risk [10–15]. To this end, the ADA and American College of Cardiology Foundation recently recommended non-HDL-C and apo B goals of <130 and <90 mg/dL, respectively, in T2DM patients with no other major risk factors, and non-HDL-C and apo B goals of <100 and <80 mg/dL, respectively, for T2DM patients plus one or more additional major risk factors [5].

Statin monotherapy has been demonstrated to improve CHD risk in patients with and without T2DM [8,9,16,17]; however, many patients fail to achieve recommended lipid/lipoprotein goals with statins alone and remain at increased risk of coronary events [18–21]. Therefore, combination lipid-lowering therapies may be warranted in high-risk patients with and without T2DM to achieve optimal targets. This *post hoc* exploratory analysis of data from a previously reported study compared the lipid/lipoprotein-altering effects of switching from a stable dose of statin monotherapy to the initial recommended starting doses of ezetimibe/simvastatin (EZE/SIMVA) 10/20 mg or rosuvastatin (ROSUVA) 10 mg monotherapy in high-risk hypercholesterolemic patients with and without T2DM who failed to reach LDL-C goal <100 mg/dL on statin therapy alone [22]. Rosuvastatin was selected as the comparator agent in this study because, according to the product label, the 10 mg dose provides comparable LDL-C reductions to that of ezetimibe/simvastatin 10/20 mg (i.e., approximately 52%). When the study protocol was written in 2006 both rosuvastatin 10 mg and ezetimibe/simvastatin 10/20 mg were usual recommended starting doses for higher potency statin monotherapy and combination therapy, respectively.

Materials and Methods

Patients and Study Design

This was a *post hoc* analysis of data from a previously reported multicenter, randomized, double-blind, active-controlled, 6-week, parallel group study (NCT00479713; Merck protocol number 809) that assessed the lipid-altering efficacy and safety profile of switching from a stable dose of statin monotherapy to EZE/SIMVA 10/20 mg or ROSUVA 10 mg daily for 6 weeks in high-risk hypercholesterolemic patients [22]. Patients were deemed to be of high cardiovascular risk if they met one or more of the following criteria: (1) history of CHD or established vascular atherosclerotic disease (i.e., peripheral vascular disease, ischemic stroke); (2) T2DM without a history of vascular disease and with high cardiovascular risk and/or at least 2 CHD risk factors per Framingham calculation; and (3) CHD risk >20% over 10 years as determined by the Framingham risk calculation. Following a 6-week open-label statin dose stabilization run-in phase, eligible patients with elevated LDL-C ≥100 and ≤160 mg/dL despite use of statins were stratified by study center and baseline statin dose/potency and randomized 1:1 to double-blind treatment with EZE/SIMVA 10/20 mg or ROSUVA 10 mg for 6 weeks. The protocol for the original study was approved by the institutional review board or ethics committee of each participating center and all patients provided written informed consent. All lipid and safety laboratory analyses were conducted at a central laboratory. Additional details of the study design and patient population have been reported [22].

Subgroup Analyses

Efficacy and safety analyses were conducted in the overall analysis population as well as patient subgroups defined by the presence and absence of T2DM. The overall analysis population consisted of all randomized patients with known T2DM status at baseline. Patients were included in the T2DM subgroup if they met one or more of the following criteria at baseline: previous diagnosis of T2DM; use of antihyperglycemic medication; or fasting plasma glucose value ≥126 mg/dL. The non-T2DM subgroup for this analysis consisted of all patients with known T2DM status at baseline excluding those patients with T2DM. Two patients were excluded from the analysis because their baseline T2DM status was unknown.

The primary efficacy objective was to assess the effects of treatment on the mean percentage change from baseline to study endpoint (i.e., last postbaseline measurement) in LDL-C. Other efficacy endpoints included percent change from baseline in total cholesterol (TC), TG, HDL-C, non-HDL-C, LDL-C/HDL-C ratio, TC/HDL-C ratio, apo B, and high-sensitivity C-reactive protein (hs-CRP). The percentage of patients achieving target LDL-C (<100 and <70 mg/dL), non-HDL-C (<130 and <100 mg/dL), and apo B goals (<90 and <80 mg/dL) at study endpoint were assessed.

Statistical Analyses

This subgroup analysis was performed on the full-analysis set population, which included all patients with known

T2DM status who received at least one dose of study medication, had a baseline efficacy measurement, and at least one postrandomization efficacy measurement. Missing data were imputed using the last observation carried forward method.

Continuous efficacy results for percent change from baseline in normally distributed parameters (i.e., LDL- C, TC, HDL-C, non-HDL-C, LDL-C/HDL-C ratio, TC/HDL-C ratio, and apo B) were analyzed using a parametric analysis of variance (ANOVA) model with terms for treatment, stratum, baseline efficacy variable (categorized based on quartiles), study center, T2DM status (with, without), and treatment-by-subgroup interaction. Least squares (LS) means and 95% confidence intervals (CIs) within each patient subgroup (i.e., T2DM/non-T2DM) using the above model (except the last two terms involving subgroup) were computed and used to quantify the differences between treatment groups.

Continuous efficacy results for percent change from baseline in nonnormally distributed parameters (i.e., TG and hs-CRP) were analyzed using an ANOVA model on ranks of these efficacy variables with terms for treatment, stratum, baseline efficacy variable (categorized based on quartiles), study center, T2DM status (with, without) and treatment-by-subgroup interaction. Differences between treatment groups were quantified as differences in medians and 95% CIs using Hodges–Lehmann estimates within each patient subgroup (i.e., T2DM/non-T2DM).

The percentages of patients achieving lipid/lipoprotein goals at study endpoint were analyzed using a logistic regression model with terms for treatment, stratum, baseline efficacy variable, T2DM status (with, without), and treatment-by-subgroup interaction. Odds ratio estimates and 95% CIs using the above model (except the last two terms involving subgroup) were computed and used to quantify the treatment effect within each patient subgroup (i.e., T2DM/non-T2DM).

Because of the exploratory nature of this analysis, no multiplicity adjustments were employed. Between-group differences and treatment-by-subgroup interaction tests with a P-value <0.050 were considered statistically significant.

The safety analysis was based on the all-patients-as-treated population of patients with known diabetes status who received ≥ 1 dose of study medication. Adverse experiences (AEs) were assessed throughout the study. The investigators determined the severity and relationship to study drug. Prespecified AEs of special interest included gastrointestinal-related AEs, gallbladder-related AEs, allergic reaction or rash AEs, hepatobiliary-related AEs, elevations in alanine aminotransferase and/or aspartate aminotransferase $\geq 3\times$ upper limit of normal (ULN), and creatine kinase elevations $\geq 10\times$ ULN with or without muscle symptoms.

Results

Patients

Of the 618 patients randomized to treatment in this study, a total of 616 had sufficient information to determine T2DM status at baseline with 313 patients in the EZE/SIMVA 10/20 mg group and 303 in the ROSUVA 10 mg group. Baseline demographic characteristics and baseline lipid values for the T2DM and non-T2DM subgroups are shown in Tables 1 and 2. Within each patient subgroup, baseline demographic and lipid/lipoprotein characteristics were generally well balanced across the EZE/SIMVA and ROSUVA groups. The T2DM ($n = 182$) and non-T2DM ($n = 434$) subgroups were similar in terms of age, race, gender, and smoking status at baseline. Patients with and without T2DM had generally similar lipid/lipoprotein profiles at baseline, except for the finding of slightly higher TG levels in patients with T2DM. A slightly higher proportion of patients with T2DM were taking low-potency statin monotherapy prior to enrollment in the study. Patients with T2DM had a higher body mass index at baseline compared with patients without T2DM. In addition, more patients in the T2DM subgroup had a medical history of hypertension; however, systolic and diastolic blood pressure levels were generally similar across the subgroups.

Effects of Treatment on Lipid/Lipoprotein Parameters and hs-CRP

The effects of EZE/SIMVA 10/20 mg and ROSUVA 10 mg on plasma concentrations of lipids, lipoproteins, and hs-CRP in T2DM and non-T2DM patients are summarized in Table 2. The results for the overall analysis population excluding the two patients with unknown T2DM status at baseline are provided for comparison. In the overall analysis population, switching from a stable dose of statin monotherapy to EZE/SIMVA 10/20 mg compared with ROSUVA 10 mg resulted in significantly greater between-group reductions from baseline in LDL-C (10.7%) (Figure 1), TC (7.2%), non-HDL-C (9.4%), apo B (8.1%) (Figure 2), LDL-C/HDL-C (9.6%), and TC/HDL-C (6.3%) at study endpoint (Table 2). A borderline significantly greater reduction from baseline in TG (Figure 3) was observed with EZE/SIMVA compared with ROSUVA therapy. Neither treatment produced significant within- or between-group reductions from baseline in hs-CRP (Table 2).

Table 1 Baseline characteristics for randomized patients with known T2DM status[a]

Characteristic	With T2DM N = 182		Without T2DM N = 434	
	EZE/SIMVA 10/20 mg N = 100	ROSUVA 10 mg N = 82	EZE/SIMVA 10/20 mg N = 213	ROSUVA 10 mg N = 221
Gender, n (%)				
Male	58 (58.0%)	45 (54.9%)	126 (59.2%)	139 (62.9%)
Age (yr)				
Mean ± SD	63.1 ± 8.6	64.5 ± 9.1	63.3 ± 10.4	62.6 ± 10.3
Race, n (%)				
White	100 (100.0%)	81 (98.8%)	213 (100.0%)	220 (99.5%)
Other	0	1 (1.2%)	0	1 (0.5%)
Body mass index (kg/m^2)				
Mean ± SD	30.7 ± 5.0	30.1 ± 5.1	26.9 ± 4.1	27.3 ± 4.2
FPG (mg/dL)				
Mean ± SD	130.8 ± 32.7	127.2 ± 38.6	95.1 ± 12.8	96.8 ± 11.0
Duration of hypercholesterolemia (yr)				
Mean ± SD	8.4 ± 5.9	10.1 ± 6.9	8.2 ± 5.5	8.9 ± 6.5
Current smoker, n (%)				
Yes	22 (22.0%)	25 (30.5%)	71 (33.3%)	70 (31.7%)
No[b]	78 (78.0%)	57 (69.5%)	142 (66.7%)	151 (68.3%)
Systolic blood pressure (mm Hg)				
Mean ± SD	133.0 ± 10.5	135.8 ± 11.7	132.7 ± 13.0	132.7 ± 12.4
Diastolic blood pressure (mm Hg)				
Mean ± SD	78.4 ± 6.3	80.5 ± 7.4	78.2 ± 7.5	77.8 ± 7.8
History of hypertension, n (%)				
Yes	79 (79.0%)	60 (73.2%)	124 (58.2%)	128 (57.9%)
No	21 (21.0%)	22 (26.8%)	89 (41.8%)	93 (42.1%)
History of CHD, n (%)				
Yes	36 (36.0%)	23 (28.0%)	155 (54.0%)	120 (54.3%)
No	64 (64.0%)	59 (72.0%)	98 (46.0%)	101 (45.7%)
History of PVD, n (%)				
Yes	4 (4.0%)	2 (2.4%)	24 (11.3%)	24 (10.9%)
No	96 (96.0%)	80 (97.6%)	189 (88.7%)	197 (89.1%)
Statin potency stratum, n (%)				
Low potency[c]	62 (62.0%)	54 (65.9%)	126 (59.2%)	125 (56.6%)
High potency[c]	38 (38.0%)	28 (34.1%)	87 (40.8%)	96 (43.4%)
Concomitant medications				
Drugs used in diabetes, n (%)				
Yes	73 (73.0%)	61 (74.4%)	0	0
No	27 (27.0%)	21 (25.6%)	213 (100%)	221 (100%)
Antithrombotic agents, n (%)				
Yes	10 (10.0%)	9 (11.0%)	51 (23.9%)	39 (17.6%)
No	90 (90.0%)	73 (89.0%)	162 (76.1%)	182 (82.4%)
Antihypertensive agents, n (%)				
Yes	84 (84.0%)	67 (81.7%)	160 (75.1%)	164 (74.2%)
No	16 (16.0%)	15 (18.3%)	53 (24.9%)	57 (25.8%)
Cardiac therapy, n (%)[d]				
Yes	12 (12.0%)	10 (12.2%)	38 (17.8%)	31 (14.0%)
No	88 (88.0%)	72 (87.8%)	175 (82.2%)	190 (86.0%)

CHD, coronary heart disease; EZE/SIMVA, ezetimibe/simvastatin combination tablet; FPG, fasting plasma glucose; PVD, peripheral vascular disease; ROSUVA, rosuvastatin; SD, standard deviation; T2DM, type 2 diabetes mellitus.

[a]Excludes two randomized patients with unknown diabetes status at baseline.

[b]Includes both ex-smokers and nonsmokers.

[c]Low-potency stratum: simvastatin 20 mg, pravastatin 40 mg, fluvastatin 80 mg, atorvastatin 10 mg; high-potency stratum: simvastatin 40 mg, atorvastatin 20 mg, rosuvastatin 5 mg.

[d]Includes cardiac glycosides, antiarrhythmics classes I and III, vasodilators used in cardiac disease and other cardiac preparations.

Table 2 Mean baseline values, percent changes from baseline and between-treatment differences for randomized patients with known T2DM status[a]

	Overall analysis Population with and without T2DM N = 616		With T2DM N = 182		Without T2DM N = 434	
	EZE/SIMVA 10/20 mg N = 313	ROSUVA 10 mg N = 303	EZE/SIMVA 10/20 mg N = 100	ROSUVA 10 mg N = 82	EZE/SIMVA 10/20 mg N = 213	ROSUVA 10 mg N = 221
LDL-C (mg/dL)[b]						
n	305	296	94	80	211	216
Baseline	123.6 ± 16.2	125.2 ± 16.7	123.3 ± 16.3	126.8 ± 15.9	123.7 ± 16.2	124.6 ± 17.0
% change from baseline	−27.7 (−30.3, −25.1)	−17.0 (−19.7, −14.3)	−30.3 (−36.2, −24.3)	−11.5 (−18.5, −4.5)	−26.5 (−29.6, −23.3)	−18.0 (−21.1, −15.0)
Difference vs. ROSUVA	−10.7 (−14.1, −7.3)**	–	−18.8 (−27.5, −10.1)	–	−8.4 (−12.3, −4.6)	–
P-value for interaction test	0.015	–	–	–	–	–
TC (mg/dL)[b]						
n	305	296	94	80	211	216
Baseline	207.4 ± 22.1	207.6 ± 23.0	207.9 ± 23.1	209.7 ± 22.6	207.2 ± 21.8	206.9 ± 23.2
% change from baseline	−17.6 (−19.4, −15.7)	−10.4 (−12.3, −8.5)	−18.3 (−22.3, −14.3)	−6.3 (−10.9, −1.6)	−17.0 (−19.2, −14.8)	−10.6 (−12.8, −8.4)
Difference vs. ROSUVA	−7.2 (−9.5, −4.8)**	–	−12.0 (−17.8, −6.3)	–	−6.4 (−9.1, −3.7)	–
P-value for interaction test	0.159	–	–	–	–	–
TG (mg/dL)[c]						
n	305	296	94	80	211	216
Baseline	131.0 ± 70.7	124.0 ± 72.6	153.0 ± 83.7	120.5 ± 80.9	119.0 ± 68.8	125.5 ± 67.0
% change from baseline	−11.0 (−15.3, −6.8)	−5.2 (−9.9, −0.9)	−12.7 (−19.6, −6.8)	−3.7 (−15.1, 3.0)	−10.3 (−15.6, −5.3)	−5.4 (−9.9, 0.0)
Difference vs. ROSUVA	−5.2 (−9.7, −0.4)*	–	−6.2 (−14.7, 2.3)	–	−4.7 (−10.3, 1.0)	–
P-value for interaction test	0.543	–	–	–	–	–
HDL-C (mg/dL)[b]						
n	305	296	94	80	211	216
Baseline	55.4 ± 14.2	55.0 ± 13.7	51.2 ± 12.3	55.0 ± 13.9	57.3 ± 14.6	55.0 ± 13.6
% change from baseline	2.1 (0.3, 3.9)	3.0 (1.2, 4.8)	1.0 (−2.7, 4.7)	2.4 (−1.9, 6.6)	1.2 (−1.1, 3.5)	3.1 (0.8, 5.4)
Difference vs. ROSUVA	−0.9 (−3.2, 1.4)	–	−1.3 (−6.4, 3.8)	–	−1.9 (−4.8, 1.0)	–
P-value for interaction test	0.546	–	–	–	–	–
Non-HDL-C (mg/dL)[b]						
n	305	296	94	80	211	216
Baseline	152.0 ± 21.2	152.7 ± 21.5	156.7 ± 23.2	154.7 ± 22.5	149.9 ± 20.0	151.9 ± 21.1
% change from baseline	−23.4 (−25.8, −21.0)	−14.0 (−16.5, −11.6)	−23.5 (−28.8, −18.1)	−7.9 (−14.1, −1.6)	−22.8 (−25.7, −19.8)	−14.8 (−17.6, −11.9)
Difference vs. ROSUVA	−9.4 (−12.5, −6.3)**	–	−15.6 (−23.1, −8.1)	–	−8.0 (−11.6, −4.4)	–
P-value for interaction test	0.132	–	–	–	–	–

Table 2 continued

	Overall analysis Population with and without T2DM N = 616		With T2DM N = 182		Without T2DM N = 434	
	EZE/SIMVA 10/20 mg N = 313	ROSUVA 10 mg N = 303	EZE/SIMVA 10/20 mg N = 100	ROSUVA 10 mg N = 82	EZE/SIMVA 10/20 mg N = 213	ROSUVA 10 mg N = 221
LDL-C:HDL-C[b]						
n	305	296	94	80	211	216
Baseline	2.4 ± 0.6	2.4 ± 0.7	2.5 ± 0.6	2.5 ± 0.7	2.3 ± 0.6	2.4 ± 0.6
% change from baseline	−27.4 (−30.4, −24.4)	−17.8 (−20.9, −14.8)	−30.4 (−37.4, −23.4)	−12.0 (−20.2, −3.7)	−25.3 (−29.0, −21.7)	−18.7 (−22.3, −15.1)
Difference vs. ROSUVA	−9.6 (−13.5, −5.7)**	–	−18.4 (−28.3, −8.6)	–	−6.7 (−11.2, −2.1)	–
P-value for interaction test	0.027	–	–	–	–	–
TC:HDL-C[b]						
n	305	296	94	80	211	216
Baseline	3.9 ± 0.9	4.0 ± 0.9	4.2 ± 0.9	4.0 ± 1.0	3.8 ± 0.8	3.9 ± 0.9
% change from baseline	−17.8 (−19.9, −15.6)	−11.5 (−13.8, −9.3)	−17.6 (−22.7, −12.5)	−5.7 (−11.5, 0.2)	−16.4 (−19.1, −13.8)	−11.8 (−14.4, −9.2)
Difference vs. ROSUVA	−6.3 (−9.1, −3.4)**	–	−11.9 (−19.0, −4.9)	–	−4.7 (−7.9, −1.4)	–
P-value for interaction test	0.114	–	–	–	–	–
Apo B (mg/dL)[b]						
n	301	291	93	77	208	214
Baseline	119.4 ± 19.7	118.0 ± 20.6	123.0 ± 22.7	116.5 ± 21.3	117.8 ± 18.1	118.6 ± 20.4
% change from baseline	−17.9 (−20.0, −15.7)	−9.7 (−12.0, −7.5)	−17.9 (−22.9, −12.9)	−6.2 (−12.2, −0.3)	−17.3 (−20.0, −14.7)	−9.6 (−12.1, −7.0)
Difference vs. ROSUVA	−8.1 (−10.9, −5.3)**	–	−11.6 (−18.8, −4.5)	–	−7.8 (−11.0, −4.5)–	–
P-value for interaction test	0.472	–	–	–		–
hs-CRP (mg/L)[c]						
n	301	292	94	79	207	213
Baseline	1.6 ± 2.3	1.5 ± 2.4	2.3 ± 2.8	1.8 ± 3.0	1.4 ± 2.0	1.3 ± 2.2
% change from baseline	−8.3 (−16.7, 0.0)	0.0 (−7.1, 6.3)	−8.5 (−23.1, 1.0)	0.0 (−5.9, 18.9)	−8.3 (−16.7, 0.0)	0.0 (−11.1, 4.2)
Difference vs. ROSUVA	−6.5 (−16.7, 3.2)	–	−11.9 (−26.7, 5.2)	–	−4.8 (−16.8, 7.1)	–
P-value for interaction test	0.616	–	–	–	–	–

Apo, apolipoprotein; EZE/SIMVA, ezetimibe/simvastatin combination tablet; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LDL-C:HDL-C, ratio of LDL-C/HDL-C; ROSUVA, rosuvastatin; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TC:HDL-C, ratio of TC/HDL-C; TG, triglycerides.

[a]Excludes 2 randomized patients with unknown diabetes status at baseline.

[b]Baseline data are expressed as mean ± SD. Percent changes from baseline and differences vs. ROSUVA are expressed as LS mean (95% CI).

[c]Baseline data are expressed as median ± SD. Percent changes from baseline and differences vs. ROSUVA are expressed as median (95% CI).

*$p = 0.053$ vs. ROSUVA.

**$p < 0.001$ vs. ROSUVA.

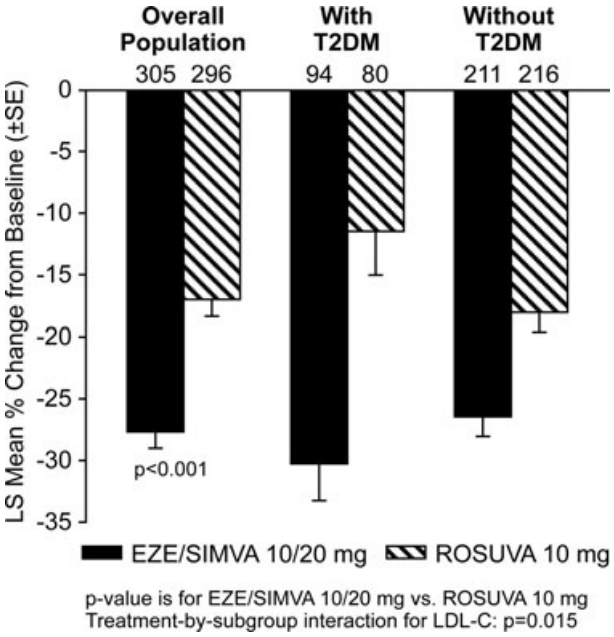

Figure 1 Least squares mean percent change from baseline in LDL-C for the overall analysis population and within patient subgroups defined by presence/absence of T2DM.

The treatment effects within each of the patient subgroups were consistent with those seen in the overall analysis population. Numerically, greater between-treatment reductions in LDL-C (18.8% vs. 8.4%, respectively) (Figure 1), TC (12.0% vs. 6.4%, respectively), non-HDL-C (15.6% vs. 8.0%, respectively), apo B (11.6% vs. 7.8%, respectively) (Figure 2), LDL-C/HDL-C (18.4% vs. 6.7%, respectively), and TC/HDL-C (11.9% vs. 4.7%, respectively) were seen in patients with T2DM compared with those without T2DM (Table 2). Significant treatment-by-subgroup interactions were seen for LDL-C ($P = 0.015$) and LDL-C/HDL-C ($P = 0.027$), indicating that patients with T2DM achieved significantly larger between-treatment differences compared with those without T2DM.

Lipid/Lipoprotein Goal Attainment

For the overall analysis population, a significantly higher percentage of patients achieved LDL-C (<100 and <70 mg/dL; $P < 0.001$ for both targets; Figure 4), non-HDL-C (<130 and <100 mg/dL; $P \leq 0.001$ for both values; Figure 5), and apo B (<90 and <80 mg/dL; $P \leq 0.005$ for both values; Figure 6) goals at study endpoint in the EZE/SIMVA group compared with the ROSUVA group. The LDL-C, non-HDL-C, and apo B goal attainment rates within each of the patient subgroups were generally consistent with those seen in the overall analysis population as demonstrated by the absence of significant treatment-by-subgroup interaction terms for all lipid/lipoprotein goals analyzed.

Safety and Tolerability

Treatment with EZE/SIMVA and ROSUVA was generally well tolerated in the overall population as well as in

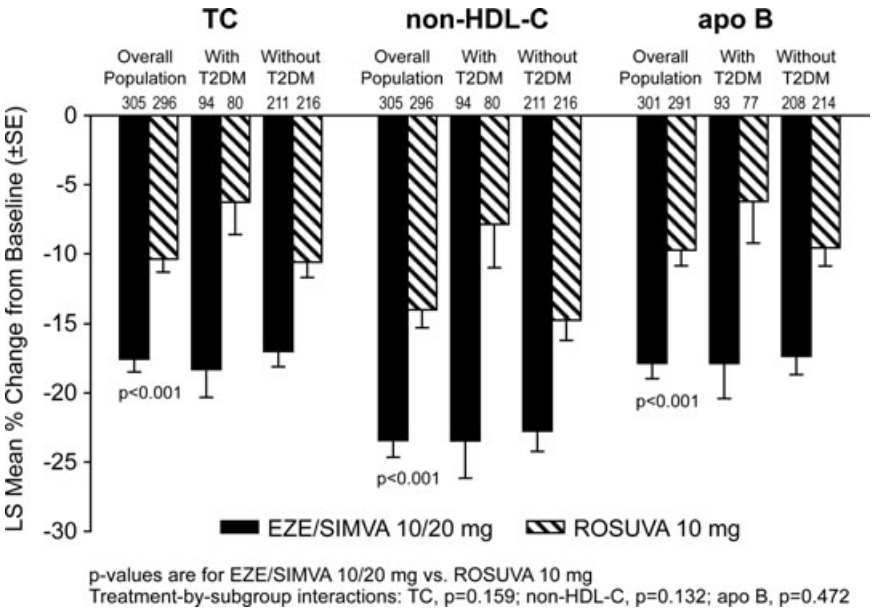

Figure 2 Least squares mean percent change from baseline in TC, non-HDL-C, and apo B for the overall analysis population and within patient subgroups defined by presence/absence of T2DM.

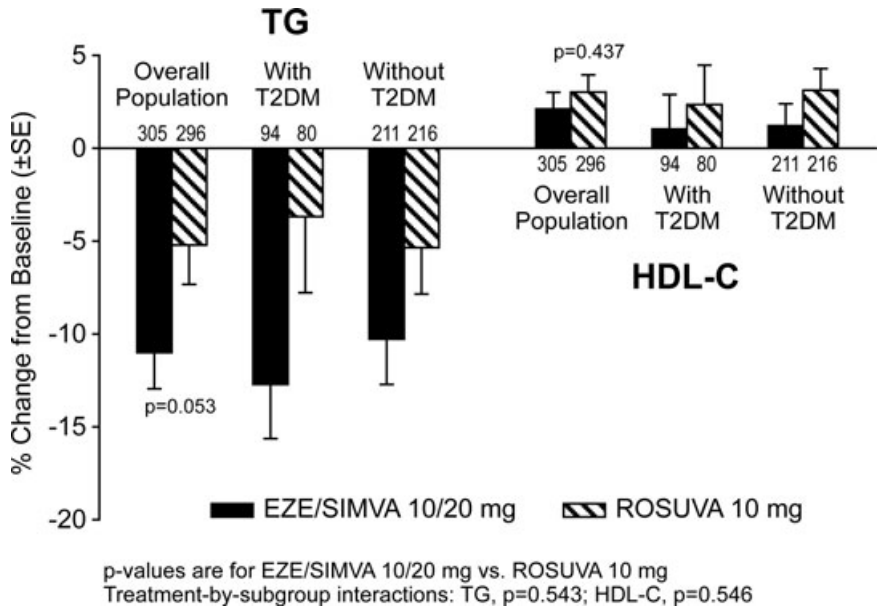

Figure 3 Median percent change from baseline in TG and least squares mean percent change from baseline in HDL-C for the overall analysis population and within patient subgroups defined by presence/absence of T2DM.

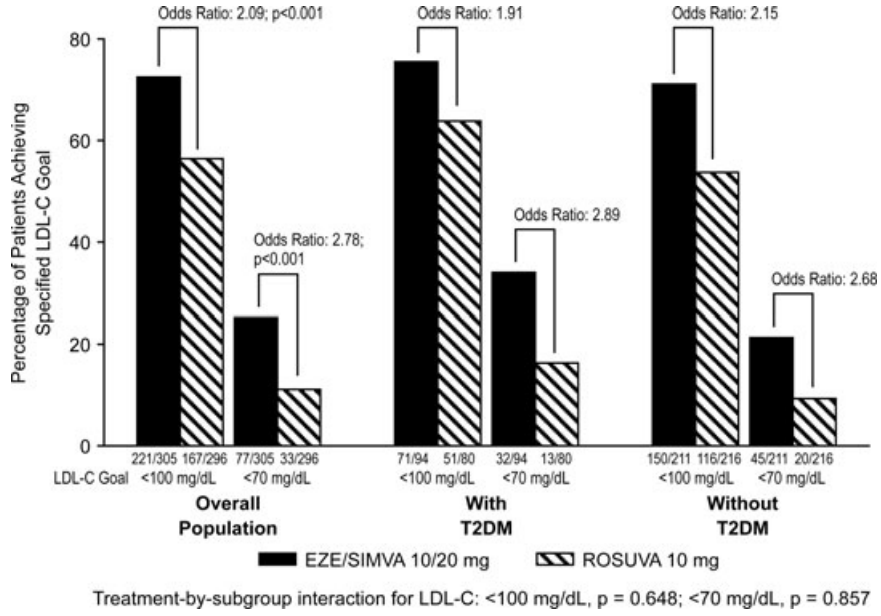

Figure 4 Percentages of patients who achieved LDL-C levels <100 and <70 mg/dL at study endpoint for the overall analysis population and within patient subgroups defined by presence/absence of T2DM.

patients with and without T2DM (Table 3). The incidences and types of clinical AEs were generally consistent across the patient subgroups and treatments, except for the finding of a ~2-fold increased incidence in overall clinical AEs in non-T2DM patients receiving ROSUVA. There were no meaningful differences between the two patient subgroups with respect to allergic adverse events or hepatitis-, gallbladder-, and gastrointestinal-related AEs. Presumed consecutive elevations in ALT and/or AST values ≥3× ULN were observed in two patients receiving EZE/SIMVA in the T2DM subgroup; such elevations were not seen in patients taking ROSUVA in the T2DM

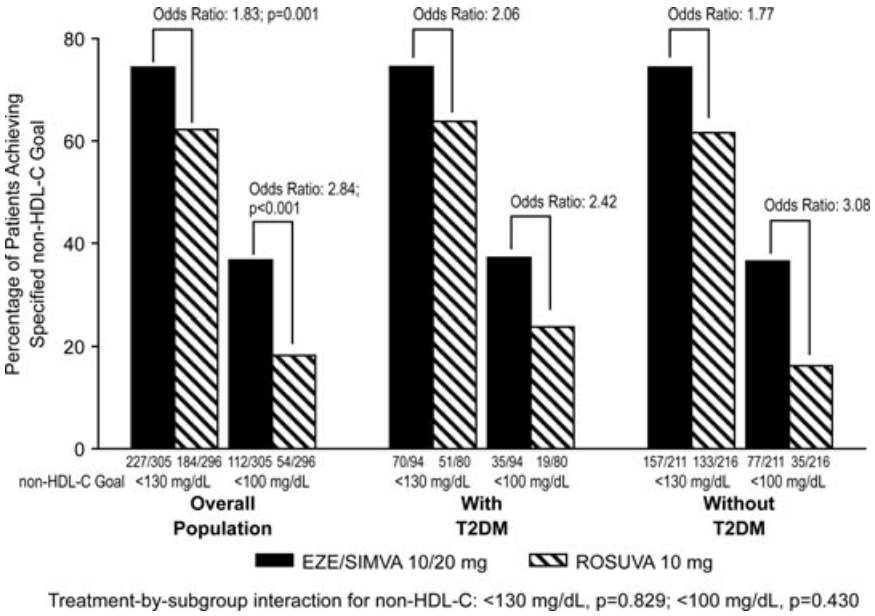

Figure 5 Percentages of patients who achieved non-HDL-C goals <130 and <100 mg/dL at study endpoint for the overall analysis population and within patient subgroups defined by presence/absence of T2DM.

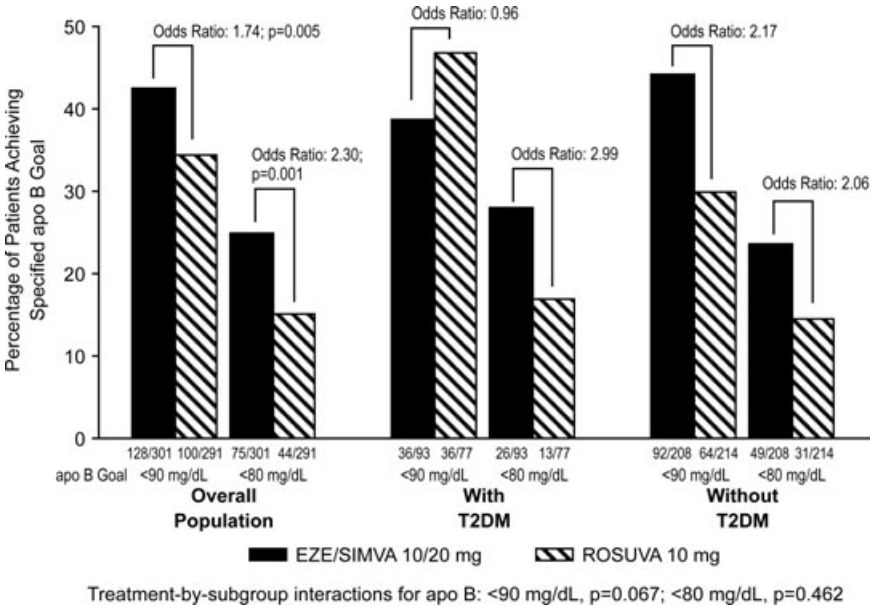

Figure 6 Percentage of patients who achieved apo B goals <90 and <80 mg/dL at study endpoint for the overall analysis population and within patient subgroups defined by presence/absence of T2DM.

subgroup or in the non-T2DM subgroup. There were no cases of hepatitis or jaundice. One patient with T2DM experienced a hepatobiliary-related adverse experience of cholangitis while taking EZE/SIMVA, which was considered not related to study medication by the investigator. There were no reports of creatine kinase elevations >10× ULN with any treatment in this study.

Discussion

The purpose of the previously published study was to compare the lipid-altering efficacy and safety profile of switching from a stable dose of statin monotherapy to EZE/SIMVA 10/20 mg and ROSUVA 10 mg daily for 6 weeks in high-risk hypercholesterolemic patients who

Table 3 Summary of adverse events

	Number of patients (%)					
	Overall analysis population N = 615		With T2DM N = 181[a]		Without T2DM N = 434	
Adverse events	EZE/SIMVA 10/20 mg N = 312	ROSUVA 10 mg N = 303	EZE/SIMVA 10/20 mg N = 99	ROSUVA 10 mg N = 82	EZE/SIMVA 10/20 mg N = 213	ROSUVA 10 mg N = 221
With one or more clinical AEs	22 (7.1%)	34 (11.2%)	6 (6.1%)	4 (4.9%)	16 (7.5%)	30 (13.6%)
With treatment-related clinical AEs[b]	8 (2.8%)	10 (3.3%)	3 (3.0%)	0	5 (2.3%)	10 (4.5%)
With serious clinical AEs	3 (1.0%)	5 (1.7%)	2 (2.0%)	0	1 (0.5%)	5 (2.3%)
With serious treatment-related clinical AEs[b]	1 (0.3%)	1 (0.3%)	0	0	1 (0.5%)	1 (0.5%)
Death	1 (0.3%)[c]	0	1 (1.0%)[c]	0	0	0
Discontinued						
Clinical AEs	9 (2.9%)	6 (2.0%)	4 (4.0%)	1 (1.2%)	5 (2.3%)	5 (2.3%)
Treatment-related clinical AEs[b]	7 (2.2%)	3 (1.0%)	3 (3.0%)	0	4 (1.9%)	3 (1.4%)
Serious clinical AE	1 (0.3%)	1 (0.3%)	1 (1.0%)	0	0	1 (0.5%)
Serious treatment-related clinical AEs[b]	0	1 (0.3%)	0	0	0	1 (0.5%)
Hepatobiliary-related AEs	1/312 (0.3%)	0	1/99 (1.0%)	0	0	0
Gallbladder-related AEs	0	0	0	0	0	0
Gastrointestinal-related AEs	9/312 (2.9%)	7/303 (2.3%)	2/99 (2.0%)	1/82 (1.2%)	7/213 (3.3%)	6/221 (2.7%)
Allergic reaction or rash AEs	2/312 (0.6%)	2/303 (0.7%)	0	0	2/213 (0.9%)	2/221 (0.9%)
Consecutive ≥3× ULN elevations in ALT and/or AST[d]	2/302 (0.7%)	0	2/94 (2.1%)	0	0	0
CK ≥10× ULN[d]	0	0	0	0	0	0

AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; EZE/SIMVA, ezetimibe/simvastatin; ROSUVA, rosuvastatin; ULN, upper limit of normal.

[a]Excludes one randomized patient with T2DM from the EZE/SIMVA group who did not take at least one dose of postrandomization study medication.

[b]Determined by study investigator to be related to the drug.

[c]One death that occurred from a traumatic brain injury and subarachnoid hemorrhage was deemed not related to study drug by the investigator.

[d]Includes subjects with two consecutive measurements for ALT and/or AST ≥3× ULN and a single, last measurement ≥3× ULN or a measurement ≥3× ULN followed by a measurement <3× ULN that was taken more than 2 days after the last dose of study medication.

failed to reach their LDL-C goal <100 mg/dL while taking statin monotherapy [22]. This report describes the findings from a *post hoc* analysis comparing the lipid-altering efficacy and safety profile of EZE/SIMVA versus ROSUVA in patient subgroups defined by the presence or absence of T2DM.

Numerous studies have demonstrated the importance of aggressively lowering LDL-C levels in high-risk hypercholesterolemic patients [16,17,23–28]. Patients with T2DM are considered to be at high risk of coronary events even though these patients typically present with moderate to no elevations in plasma LDL-C levels [1,29,30]. Statin therapy significantly reduces the risk of cardiovascular events in patients with T2DM [9,17,31]. As a result, guidelines for the treatment of dyslipidemia in T2DM patients recommend lowering LDL-C below 100 mg/dL with an optional target of <70 mg/dL for T2DM patients at very high risk for CHD [4–7].

Despite the proven usefulness of LDL-C for assessing cardiovascular risk in patients with and without T2DM, this lipid parameter may not accurately reflect an individual patient's true atherosclerotic burden. The cholesterol content of LDL particles varies among individuals and is influenced by metabolic abnormalities such as insulin resistance and hyperglycemia [5]. Other lipoprotein parameters, such as non-HDL-C (a measure of the total concentration of cholesterol carried by all atherogenic particles) and apo B (a measure of the total number of atherogenic particles), may provide additional prognostic value regarding CHD risk in patients with T2DM [11–14]. Consequently, guidelines identify non-HDL-C and apo B as secondary targets of pharmacotherapy in patients with T2DM [5].

The results of this *post hoc* analysis demonstrate that switching from a stable dose of statin monotherapy to EZE/SIMVA 10/20 mg compared with ROSUVA 10 mg provided significantly greater improvements in LDL-C, TC, non-HDL-C, apo B, LDL-C/HDL-C, and TC/HDL-C in patients with and without T2DM. In general, numerically larger between-group reductions in these lipids/lipoprotein parameters were observed among patients with T2DM. For LDL-C and LDL-C/HDL-C, significant treatment-by-subgroup interactions were observed indicating that the magnitudes of the between-group reductions were significantly larger in patients with T2DM relative to those without T2DM. The lack of a significant treatment-by-subgroup interaction term for TG and HDL-C indicated that the treatment effects in the T2DM and non-T2DM subgroups were consistent with those observed in the overall analysis population [22].

The enhanced efficacy of EZE/SIMVA versus ROSUVA in reducing LDL-C, non-HDL-C, and apo B resulted in higher percentages of patients with and without T2DM achieving recommended goals. Significantly greater proportions of patients in the overall analysis population achieved target LDL-C, non-HDL-C, and apo B levels with EZE/SIMVA than with ROSUVA. No significant treatment-by-subgroup interactions were observed for any of the lipid/lipoprotein goals examined, indicating that the goal attainment rates in the two patient subgroups were consistent with those seen in the overall analysis population. Numerically, higher percentages of patients with and without T2DM achieved target LDL-C, non-HDL-C, and apo B levels (<80 mg/dL) with EZE/SIMVA compared with ROSUVA. The only exception was in the T2DM subgroup, which demonstrated a numerically higher percentage of patients achieving apo B levels <90 mg/dL with ROSUVA relative to EZE/SIMVA. This finding was surprising because EZE/SIMVA was shown to be more effective at lowering plasma concentrations of apo B in both T2DM and non-T2DM patients. Upon further exploration, the numerically lower apo B <90 mg/dL goal attainment rate in T2DM patients taking EZE/SIMVA versus ROSUVA appeared to be due to an anomaly in the distributions of study end apo B values seen in the two treatment groups. There were a large number of T2DM patients in the ROSUVA group compared with the EZE/SIMVA group with apo B values falling within the 80–90 mg/dL range. In addition, there was a slight imbalance in the baseline apo B values across the two treatment groups (i.e., 123.0 mg/dL in the EZE/SIMVA group vs. 116.5 mg/dL in the ROSUVA group). However, the lack of a significant treatment-by-subgroup interaction indicates that the apo B <90 mg/dL goal attainment rates in the T2DM and non-T2DM patients were not significantly different from those seen in the overall analysis population.

The explanation behind the enhanced LDL-C-lowering effect of EZE/SIMVA relative to ROSUVA seen in patients with T2DM is not conclusively known. Increasing evidence suggests that patients with T2DM exhibit defects in the formation and assembly of chylomicrons leading to abnormal chylomicron composition, which may influence the atherogenic potential of LDL and HDL particles through the lipoprotein cascade. A significant increase in the expression of duodenal Niemann-Pick C1-like 1 (NPC1-L1) mRNA has been demonstrated in patients with T2DM relative to nondiabetic patients [32]. Furthermore, a significant correlation between chylomicron cholesterol and NPC1-L1 mRNA has been demonstrated in patients with T2DM [32]. However, it is not possible to determine the quantity of chylomicron cholesterol derived from increased *de novo* synthesis of cholesterol in the cell, cholesterol re-absorbed from the bile or dietary cholesterol. Because NPC1-L1 protein is the confirmed molecular target of ezetimibe therapy, the

increased levels of NPC1-L1 seen in T2DM patients suggests that these patients may particularly benefit from the addition of ezetimibe to a statin compared with nondiabetic patients who exhibit lower NPC1-L1 expression levels [33].

T2DM with insulin resistance is associated with increased cholesterol synthesis and decreased cholesterol absorption [34,35]. Nevertheless, several studies have shown that CHD patients with T2DM and CHD patients with increased prevalence of diabetes and metabolic syndrome exhibit increased cholesterol absorption and decreased cholesterol synthesis [36,37]. Thus, shifts in the balance of whole body cholesterol homeostasis may predispose individuals to the development of CVD [37]. Among T2DM patients, as in normal population, large inter-individual variabilities exist in individual cholesterol synthesis and absorption rates. However, the absolute synthesis and dietary absorption of cholesterol are significantly interrelated in patients with T2DM [38].

Another possible explanation for the enhanced efficacy of EZE/SIMVA versus ROSUVA seen in patients with T2DM may be the study design, which excluded patients who reached their LDL-C goals while taking statin therapy. Usually, in T2DM, the baseline LDL-C level before statin therapy is only moderately elevated [31]. So the population of T2DM patients enrolled in this study may be more enriched in subjects who are poor responders to statin therapy compared with the population of patients without T2DM.

The overall safety and tolerability profile of EZE/SIMVA was similar to that seen with ROSUVA in patients with and without T2DM. There was no evidence of a clinically meaningful difference in the incidences of adverse experiences, including those related to muscle or liver toxicity, in T2DM and non-T2DM patients taking EZE/SIMVA versus ROSUVA.

Conclusions

This *post hoc* exploratory analysis demonstrated that switching from statin monotherapy to EZE/SIMVA 10/20 mg compared with ROSUVA 10 mg provided greater reductions in LDL-C, TC, non-HDL-C, and apo B in patients with and without T2DM. The enhanced efficacy of EZE/SIMVA versus ROSUVA allowed greater proportions of patients with and without T2DM to achieve recommended LDL-C, non-HDL-C, and apo B goals. Patients with T2DM achieved larger between-group reductions in LDL-C compared with non-T2DM patients (favoring EZE/SIMVA versus ROSUVA) resulting in higher LDL-C goal attainment rates. Both EZE/SIMVA and ROSUVA were generally well tolerated with a similar safety and tolerability profile in T2DM and non-T2DM patients. Taken together, the results of the present analysis demonstrate that EZE/SIMVA is a generally well-tolerated and effective therapy for T2DM and non-T2DM patients who require further LDL-C lowering to reach optimal lipid and lipoprotein goals. Future studies are needed to assess the possible benefit of EZE/SIMVA on cardiovascular outcomes.

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Author Contributions

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Data collection: Averna, Johnson-Levonas, Missault, Viigimaa
Data analysis/interpretation: Averna, Brudi, Farnier, Johnson-Levonas, Missault, Shah, Dong, Viigimaa, Vaverkova
Drafting/revising manuscript: Averna, Brudi, Farnier, Johnson-Levonas, Missault, Shah, Dong, Viigimaa, Vaverkova
Approval of final version: Averna, Brudi, Farnier, Johnson-Levonas, Missault, Shah, Dong, Viigimaa, Vaverkova

Conflict of Interest

The authors declare no conflict of interests.

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