Original Research

A Multicenter, Randomized, Double-blind, Active-controlled, Factorial Design, Phase III Clinical Trial to Evaluate the Efficacy and Safety of Combination Therapy of Pitavastatin and Ezetimibe Versus Monotherapy of Pitavastatin in Patients With Primary Hypercholesterolemia

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ABSTRACT

Purpose: Pitavastatin is a unique lipophilic statin with moderate efficacy in lowering LDL-C levels by 30% to 50% with a tolerable safety profile. However, the efficacy of adding ezetimibe to pitavastatin in patients with dyslipidemia has not been well investigated. Therefore, the objective of this double-blind, multicenter, randomized, Phase III study was to compare the efficacy and safety of pitavastatin and ezetimibe combination therapy with those of pitavastatin monotherapy in Korean patients with primary hypercholesterolemia.

Methods: Korean men and women aged >19 and <80 years with primary hypercholesterolemia requiring medical treatment were included in this study. During the 8-week screening period, all patients were instructed to make therapeutic lifestyle changes. The screening period consisted of a 4-week washout period and a placebo run-in period (4–8 weeks). During treatment period I, patients were randomly assigned to receive 1 of 4 treatments: pitavastatin 2 mg plus ezetimibe 10 mg, pitavastatin 2 mg, pitavastatin 4 mg plus ezetimibe 10 mg, or pitavastatin 4 mg. The 8-week double-blind treatment period then commenced. Adverse events (AEs), clinical laboratory data, and vital signs were assessed in all patients.

Findings: The percentages in LDL-C from baseline after 8 weeks of double-blind treatment decreased significantly in the pooled pitavastatin/ezetimibe (–52.8% [11.2%]) and pooled pitavastatin (–37.1% [14.1%]) groups. Treatment with pitavastatin/ezetimibe resulted in a significantly greater LDL-C–lowering effect than that with pitavastatin (difference, –15.8 mg/dL; 95% CI, –18.7 to –12.9; $P < 0.001$). The precentages of achieving LDL-C goal in pooled pitavastatin/ezetimibe and pooled pitavastatin groups were 94.2% and 69.1%, respectively ($P < 0.001$). There were no significant differences in the incidence of overall AEs and adverse drug reactions. Serious AEs were comparable between the groups.

Implications: Pitavastatin and ezetimibe combinations effectively and safely decreased LDL-C levels by >50% in patients with dyslipidemia. The safety and tolerability of pitavastatin and ezetimibe combination therapy were comparable with those of pitavastatin monotherapy. ClinicalTrials.gov identifier: NCT04584736. (*Clin Ther.* 2022;44:1310–1325.)
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Key words: ezetimibe, hypercholesterolemia, pitavastatin.

INTRODUCTION

Statins have been shown to reduce the risk of cardiovascular events in primary and secondary outcomes.[1] Moreover, high-intensity statin therapy significantly lowers events in high-risk patients. However, high-intensity statins elevate abnormalities in liver function test results and creatine kinase levels and induce myopathy. In addition, a meta-analysis showed that high-intensity statin therapy could increase the risk of new-onset diabetes (NOD) in proportion to intensity.[2] Thus, a maximal tolerable statin dose is needed individually.

According to the 2018 American College of Cardiology/American Heart Association and the 2019 European Society of Cardiology guidelines for dyslipidemia, adding ezetimibe is reasonable if on a maximal statin and LDL-C levels are >70 mg/dL in high-risk patients.[3,4] Most available statins, including pravastatin, simvastatin, fluvastatin, pitavastatin, atorvastatin 10 to 20 mg, and rosuvastatin 5 to 10 mg, are indicated as

moderate-intensity statins. The previous IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) study showed that ezetimibe added to a moderate-intensity statin decreased LDL-C levels more and improved cardiovascular outcomes significantly.[5] Ezetimibe reduced cholesterol absorption from the intestine and reduced LDL-C levels by 19% to 23%.[6] In another study, adding ezetimibe to a statin was more effective at lowering LDL-C levels than escalating the statin dose.[7] Thus, use of a moderate-intensity statin plus ezetimibe could produce a high-intensity decrease in LDL-C levels (>50%).

In controlling dyslipidemia, pitavastatin is a unique lipophilic statin with moderate efficacy in decreasing LDL-C levels by 30% to 50% and with a favorable safety profile.[8,9] Pitavastatin is considered to be unrelated to NOD.[10] However, the efficacy of adding ezetimibe to pitavastatin in patients with dyslipidemia has not been well investigated. Therefore, the objective of this double-blind, multicenter, randomized, Phase III study was to compare the efficacy and safety of pitavastatin and ezetimibe combination therapy with those of pitavastatin monotherapy in Korean patients with primary hypercholesterolemia.

PARTICIPANTS AND METHODS

Study Patients

Korean men and women aged >19 and <80 years with primary hypercholesterolemia requiring medical treatment were included in this study. Patients who fulfilled the criteria of LDL-C levels ≤250 mg/dL and triglyceride (TG) levels <350 mg/dL were enrolled and started the run-in period with therapeutic lifestyle changes. After a >4-week run-in period, patients who fulfilled the following criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines were eligible for the treatment period: (1) patients with coronary artery disease or a 10-year cardiovascular disease (CVD) risk >20% with LDL-C levels ≥100 mg/dL (group I); (2) patients with ≥1 major risk factor and a 10-year CVD risk ≥10% but ≤20% with LDL-C levels ≥130 mg/dL (group IIA); (3) patients with ≥1 major risk factor and a 10-year CVD risk indicated by a Framingham risk score <10% with LDL-C levels ≥160 mg/dL (group IIB); and (4) patients with no other risk factors and LDL-C levels ≥160 mg/dL (group III).

A total of 422 patients were screened for inclusion in the study. Those (n = 139) who did not fulfill the inclusion criteria or meet any of the exclusion criteria were excluded. Eligible patients (N = 283) were included in the study from June 2019 through July 2020 (Figure 1) at 25 tertiary hospitals in the Republic of Korea. After treatment period I, a total of 176 patients (62.2%) entered treatment period II.

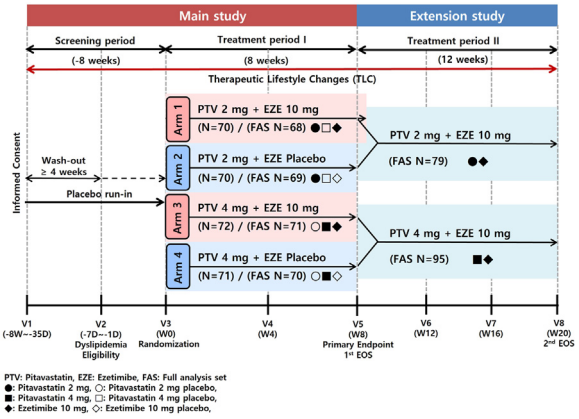


Figure 1. Study design. D = day; EOS = end of study; W = week; V = visit.

We excluded patients with uncontrolled hypertension (systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg), uncontrolled diabetes mellitus (glycated hemoglobin values ≥8% or fasting plasma glucose levels ≥160 mg/dL), or malignant arrhythmia. Patients with unstable angina pectoris, myocardial infarction, cerebrovascular disease, percutaneous coronary intervention, or coronary artery bypass graft surgery within the past 12 weeks were excluded, as were those with known histories of gallbladder diseases, active liver diseases, myopathy, or rhabdomyolysis. Patients were also excluded if they had a history of alcohol abuse within the past year, major psychiatric disorders, or malignancy within the past 5 years. Patients with biliary stenosis, thyroid dysfunction (thyroid-stimulating hormone levels ≥1.5 × upper limit of normal), elevated creatine kinase levels ≥2 × upper limits of normal, severe heart failure (New York Heart Association functional class III/IV), renal dysfunction (creatinine levels ≥2 × upper limits of normal), hepatic dysfunction (serum aspartate or alanine aminotransferase levels more than twice the upper limit of normal), or an elevated creatinine phosphokinase level more than twice the upper limit of normal were excluded. They were also

excluded if they had gastrointestinal disorders such as Crohn's disease or a history of gastrointestinal surgery. Women who were pregnant, breastfeeding, or of childbearing potential who were not on appropriate contraception were also excluded from the study. The use of other antilipidemic drugs, oral steroids, oral contraceptives, fish oil, cholestene, antipsychotics, phytosterol margarine, and cyclosporine was not permitted during the study. Patients with any condition that, in the investigator's opinion, would make their participation in this study unsafe or unsuitable were excluded.

Study Design

This trial was a multicenter, randomized, double-blind, active-controlled, factorial design, Phase III clinical trial conducted at 9 sites in the Republic of Korea. During the 8-week screening period, all patients were instructed to make therapeutic lifestyle changes. The screening period consisted of a 4-week washout period and a placebo run-in period (4–8 weeks). Patients were reevaluated at randomization during treatment period I to determine whether they were still eligible in terms of the inclusion and exclusion criteria. Patients were randomly assigned to receive 1 of 4 treatments (pitavastatin 2 mg plus ezetimibe 10 mg, pitavastatin 2 mg, pitavastatin 4 mg plus ezetimibe 10 mg, or pitavastatin 4 mg) and then commenced the 8-week double-blind treatment period. The principal investigators at each center enrolled and assigned the patients to the allocated intervention. Randomization was performed by using an interactive web response system in a 1:1:1:1 ratio using randomization code generated by SAS software version 9.1 (SAS Institute, Inc, Cary, NC, USA). All study personnel, including the investigators, study site personnel, participants, monitors, and central laboratory personnel, were blinded to the treatment allocation. Doses were not adjusted during the 8-week treatment period, and participants in all groups received 3 tablets once daily to maintain double-blinding. The experimental drugs were 2 pills of pitavastatin 2 mg and 4 mg, and 1 pill of ezetimibe 10 mg (**Figure 1**).

The pitavastatin plus ezetimibe group received one active tablet of pitavastatin from JW Pharma Co (Seoul, Republic of Korea); one placebo tablet of pitavastatin from JW Pharma Co; and one active tablet of ezetimibe from MSD Pharma Co (Seoul, Republic of Korea). The pitavastatin monotherapy group received one active tablet of pitavastatin from JW Pharma Co; one placebo tablet of pitavastatin from JW Pharma Co; and one placebo tablet of ezetimibe from JW Pharma Co. During treatment period II of the extension study, an additional 12 weeks followed to evaluate the efficacy and safety of the pitavastatin and ezetimibe combination therapy.

Ideally, participants were expected to have a medication adherence of at least 80% throughout the treatment period, and those with $<80\%$ or $>100\%$ were considered to have poor adherence. The institutional review board of each hospital approved the study. Written informed consent was obtained from all participants or their legal guardians before their inclusion in the study. All clinical investigations were conducted according to the principles of the Declaration of Helsinki.

End Points and Safety Assessment

The primary end point was to compare the efficacy of the pitavastatin and ezetimibe combination therapy with that of pitavastatin monotherapy in patients with primary hypercholesterolemia by comparing the mean percent change in LDL-C from baseline after 8 weeks of treatment. Secondary end points were: (1) the mean percent change from baseline in LDL-C levels after 4 weeks of treatment; (2) the mean changes from baseline in LDL-C levels after 4 and 8 weeks of treatment; (3) the mean percent change and mean changes from baseline after 4 and 8 weeks of treatment in total cholesterol (TC), TG, HDL-C, non–HDL-C, apolipoprotein (apo) B, apo A1, LDL-C/HDL-C, TC/HDL-C ratio, non–HDL-C/HDL-C ratio, and apo B/apo A1; and (4) high-sensitivity C-reactive protein (hs-CRP). The final secondary end point was a comparison of the LDL-C control rate, which was defined as the percentage of patients who achieved the target LDL-C according to their risk factors after 8 weeks of treatment.

Data from the full analysis set (FAS) population were used for the efficacy analysis. Blood samples were drawn from each patient after 12 hours of fasting. The lipid profiles and hs-CRP were analyzed at the central laboratory. Safety assessments included monitoring and recording adverse events (AEs), all laboratory tests (except lipid profiles), ECGs, vital signs (including body temperature, heart and pulse rates), consecutive hepatic dysfunction rate (serum aspartate or alanine aminotransferase levels $>3 \times$ the

upper limit of normal), and myopathy rate (creatinine phosphokinase level ≥10 × upper limits of normal). Data from a safety set population were used for the safety and follow-up period assessments.

AEs were classified with System Organ Class of Medical Dictionary for Regulatory Activities. Adverse drug reactions (ADRs) were defined as drug-related AEs and classified as definitely, possibly, unlikely, unrelated, or unassessable for the study drugs. ADRs unrelated to the study drugs were not considered study drug–related AEs. Laboratory AEs were assessed by comparing baseline laboratory values with those at follow-up. The AE severity was classified as mild for mild symptoms or signs not affecting daily activities, moderate for minor limitations in daily activities, and severe for marked limitations. The investigators at each center decided whether patients with ADRs should be withdrawn from the study.

Statistical Analysis

Data are expressed as the mean (SD) or median with interquartile range for the continuous variables, and the patient number and percentage for the categorical variables. Pearson's χ^2 test or Fisher's exact test was used to analyze the categorical variables. The Levene test was performed for testing normal distribution of the continuous variables, and then the independent two-sample *t* tests or Wilcoxon rank-sum test analyzed. The treatment effects on the primary and secondary end points were compared by using an ANCOVA, which included treatment and stratified factors according to the groups, with the relevant baseline value and NCEP ATP III criteria as a covariate. The control rates were analyzed by using the Cochran-Mantel-Haenszel test. The mean percent changes in LDL-C were analyzed with gatekeeping methods, in which pooled analysis with pitavastatin plus ezetimibe combination therapy versus pitavastatin monotherapy was performed first; pitavastatin 2 mg plus ezetimibe combination therapy versus pitavastatin 2 mg monotherapy, and pitavastatin 4 mg plus ezetimibe combination therapy versus pitavastatin 4 mg monotherapy followed.

The safety set included all the patients who received at least one dose of the double-blind study medication. The FAS included those patients who fulfilled safety set criteria and provided at least one end point measurement after randomization. This was a combination therapy study to verify the superiority of pitavastatin plus ezetimibe in terms of mean percent change in LDL-C (from baseline to week 8) over pitavastatin monotherapy. The overall statistical power of the whole hypothesis was set to 90%, and the two-sided significance level of each hypothesis was set to 5%. The study's sample size was determined based on the mean change in LDL-C estimation obtained in previous trials.[11] We assumed that the mean change in LDL-C after adding ezetimibe would be –9.0 (14.9) mm Hg. Required sample sizes were at least 59 patients per group. A total of 264 patients (66 for each of the 4 groups) were considered to meet the sample size cutoff under a dropout rate of 10% assumption. Two tailed *P* values <0.05 were considered statistically significant, and the SAS software was used for statistical analysis.

RESULTS

Patient Disposition and Baseline Characteristics

We randomly assigned 283 patients to receive pitavastatin 2 mg/ezetimibe 10 mg (n = 70), pitavastatin 2 mg (n = 70), pitavastatin 4 mg/ezetimibe 10 mg (n = 72), or pitavastatin 4 mg (n = 71) (Figure 1). Furthermore, 14 of the randomized patients dropped out, and the remaining 269 completed the treatment. Of the enrolled 283 patients, one patient did not take any of the study drugs; thus, 282 patients were analyzed for safety parameters. For efficacy parameters, 278 patients, excluding 4 whose lipid profile had not been measured during the trial, were analyzed as FAS. A total of 174 patients were analyzed for the study drugs' efficacy and 175 patients for safety during the extension study.

The demographic and baseline clinical characteristics of age, sex, body mass index, risk factors, or prior medications were similar in the 4 groups (Table 1). There were no significant differences between the groups in the baseline lipid profiles. More than three-quarters of the patients were at high risk, according to NCEP ATP III guidelines. Mean drug compliance for pitavastatin 2 mg/ezetimibe 10 mg, pitavastatin 2 mg, pitavastatin 4 mg/ezetimibe 10 mg, and pitavastatin 4 mg was 95.9% (5.7%), 96.5% (6.4%), 96.0% (4.6%), and 96.2% (5.0%), respectively. During the extension study, mean compliance for pitavastatin 2 mg/ezetimibe 10 mg and pitavastatin 4 mg/ezetimibe 10 mg was 95.5% (6.9%) and 96.1% (5.9%).

Table 1. Demographic and baseline clinical characteristics of study patients (full analysis set, FAS)

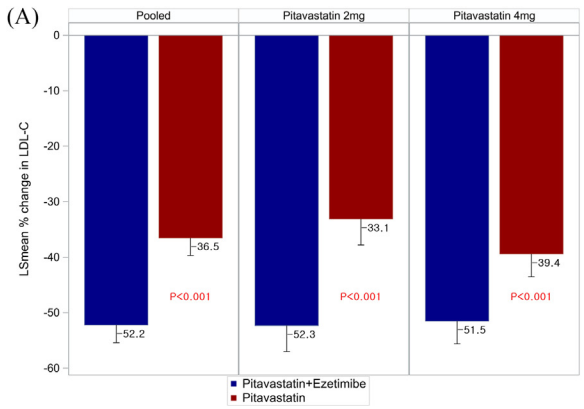
Variables		Pooled PTV+EZE (N=139)	PooledPTV (N=139)	PTV 2mg + EZE (N=68)	PTV 2mg (N=69)	PTV 4mg + EZE (N=71)	PTV 4mg (N=70)
Demographic							
Male, n (%)		96 (69.1%)	87 (62.6%)	49 (72.1%)	44 (63.8%)	47 (66.2%)	43 (61.4%)
	P-value	0.26		0.30		0.56	
Age, y ± SD		62.5 ± 9.5	63.5 ± 8.9	63.5 ± 9.9	64.1 ± 7.9	61.5 ± 9.1	62.9 ± 9.9
	Median	63.0	65.0	67.0	65.0	62.0	65.0
	Min∼Max	38.0∼79.0	31.0∼79.0	38.0∼78.0	46.0∼78.0	39.0∼79.0	31.0∼79.0
	P-value	0.42		0.79		0.20	
BMI, kg/m^2 ± SD		26.1 ± 3.1	25.6 ± 3.2	26.3 ± 3.1	25.9 ± 3.3	25.9 ± 3.1	25.4 ± 3.2
	Median	25.3	25.2	25.8	25.3	25.3	24.9
	Min∼Max	19.4∼37.5	18.3∼35.1	20.3∼37.4	18.3∼35.1	19.4∼37.5	19.4∼33.3
	P-value	0.20		0.50		0.30	
Risk factors							
Current smoking		28 (20.1%)	29 (20.9%)	16 (23.5%)	13 (18.8%)	12 (16.9%)	16 (22.9%)
	P-value	0.88		0.50		0.38	
Heavy drinking		69 (49.6%)	58 (41.7%)	36 (52.9%)	27 (39.1%)	33 (46.5%)	31 (44.3%)
	P-value	0.19		0.10		0.79	
Family history of premature		14 (10.1%)	18 (13.0%)	9 (13.2%)	10 (14.5%)	5 (7.0%)	8 (11.4%)
coronary heart disease	P-value	0.37		0.81		0.30	
Metabolic syndrome		62 (44.6%)	70 (50.4%)	28 (41.2%)	39 (56.5%)	34 (47.9%)	31 (44.3%)
	P-value	0.34		0.07		0.67	
Prior PCI or CABG		2 (1.4%)	1 (0.7%)	2 (2.9%)	1 (1.5%)	0 (0.00%)	0 (0.00%)
	P-value	0.99		0.62		NA	
Angina pectoris		70 (50.4%)	74 (53.2%)	29 (42.7%)	37 (53.6%)	41 (57.8%)	37 (52.9%)
	P-value	0.63		0.20		0.56	
Old myocardial infarction		28 (20.1%)	26 (18.7%)	17 (25.0%)	14 (20.3%)	11 (15.5%)	12 (17.1%)
	P-value	0.76		0.51		0.79	
Hypertension		89 (64.0%)	96 (69.1%)	47 (69.1%)	53 (76.8%)	42 (59.2%)	43 (61.4%)
	P-value	0.37		0.31		0.78	
Type II diabetes mellitus		18 (13.0%)	28 (20.1%)	10 (14.7%)	18 (26.1%)	8 (11.3%)	10 (14.3%)
	P-value	0.11		0.10		0.59	

(*continued on next page*)

Table 1. (*continued*)

Variables		Pooled PTV+EZE (N=139)	PooledPTV (N=139)	PTV 2mg + EZE (N=68)	PTV 2mg (N=69)	PTV 4mg + EZE (N=71)	PTV 4mg (N=70)
Prior medications, n (%)							
Prior anti-dyslipidemic agents		90 (64.8%)	97 (69.8%)	43 (63.2%)	50 (72.5%)	47 (66.2%)	47 (67.1%)
	P-value	0.37		0.25		0.91	
Beta blocking agents		44 (31.7%)	48 (34.5%)	21 (30.9%)	23 (33.3%)	23 (32.4%)	25 (35.7%)
	P-value	0.61		0.76		0.68	
Calcium channel blockers		28 (20.1%)	22 (15.8%)	16 (23.5%)	14 (20.3%)	12 (16.9%)	8 (11.4%)
	P-value	0.35		0.65		0.35	
thiazide		3 (2.2%)	3 (2.2%)	1 (1.5%)	2 (2.9%)	2 (2.8%)	1 (1.4%)
	P-value	1.00		1.00		1.00	
ACEi		6 (4.3%)	8 (5.8%)	3 (4.4%)	4 (5.8%)	3 (4.2%)	4 (5.7%)
	P-value	0.58		1.00		0.72	
ARB		33 (23.7%)	33 (23.7%)	12 (17.7%)	19 (27.5%)	21 (29.6%)	14 (20.0%)
	P-value	1.00		0.17		0.19	
Antithrombotic agents		81 (58.3%)	88 (63.3%)	38 (55.9%)	48 (69.6%)	43 (60.6%)	40 (57.1%)
	P-value	0.39		0.10		0.68	
Patients by CHD risk factor, n (%)							
Group I (CHD/CHD risk equivalents [10-y risk > 20%])		107 (77.0%)	109 (78.4%)	53 (77.9%)	54 (78.3%)	54 (76.1%)	55 (78.6%)
Group IIA (Risk factors ≥ 2 [10% ≤ 10-y risk ≤ 20%])		11 (7.9%)	10 (7.2%)	5 (7.4%)	5 (7.3%)	6 (8.5%)	5 (7.1%)
Group IIB (Risk factors ≥ 2 [10-y risk < 10%])		4 (2.9%)	4 (2.9%)	2 (2.9%)	2 (2.9%)	2 (2.8%)	2 (2.9%)
Group III (Risk factors 0 – 1)		17 (12.2%)	16 (11.5%)	8 (11.8%)	8 (11.6%)	9 (12.7%)	8 (11.4%)
	P-value	0.99		>0.99		>0.99	

PCI = percutaneous coronary intervention
CABG = coronary artery bypass grafting
ACEi = angiotensin-converting enzyme inhibitors
ARB = angiotensin receptor blocker
CHD = coronary heart disease
EZE = ezetimibe
PTV = pitavastatin



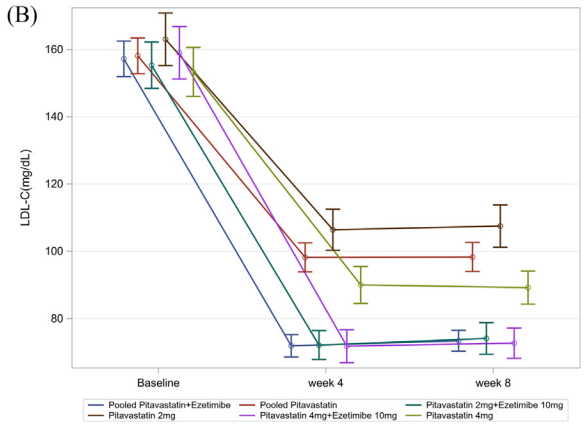
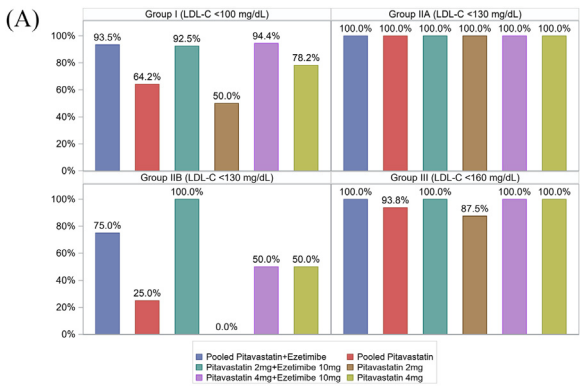


Figure 2. (A) Percent changes in mean LDL-C levels at 8 weeks. (B) Forest plot with mean changes in LDL-C levels between groups. LS = least squares.



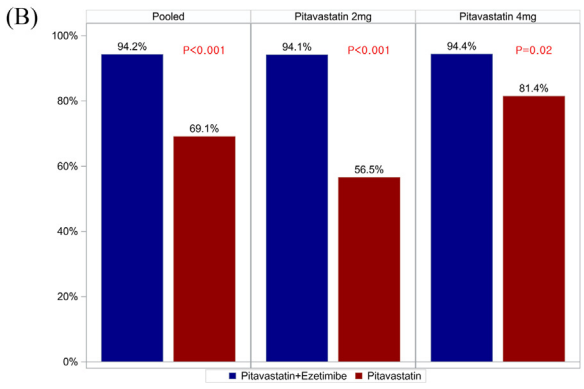


Figure 3. (A) Overall control rates of LDL-C target. (B) Control rates according to National Cholesterol Education Program Adult Treatment Panel III guidelines. Percent changes in mean LDL-C levels at 4 and 8 weeks.

Efficacy

The LDL-C percentages from baseline after 8 weeks of double-blind treatment decreased significantly in the pooled pitavastatin/ezetimibe group (–52.2% [1.6%]), the pooled pitavastatin group (–36.5% [1.6%]), the pitavastatin 2 mg/ezetimibe 10 mg group (–52.3% [2.4%]), the pitavastatin 2 mg group (–33.1% [2.4%]), the pitavastatin 4 mg/ezetimibe 10 mg group (–51.5% [2.1%]), and the pitavastatin 4 mg group (–39.4% [2.1%]) (Table 2, Figure 2**A**). Treatment with pitavastatin/ezetimibe resulted in a statistically greater LDL-C–lowering effect than treatment with pitavastatin (difference, –15.8 mg/dL; 95% CI, –18.7 to –12.9; $P < 0.001$). The LDL-C change from baseline to 8 weeks was –82.6 (2.5) mg/dL and –58.0 (2.5) mg/dL in the pooled pitavastatin/ezetimibe group and pooled pitavastatin group, respectively ($P < 0.001$) (Table 2, Figure 2**B**).

Overall rates of achieving the LDL-C target were significantly higher in the pitavastatin/ezetimibe combination group than in the pitavastatin monotherapy (Table 3, Figure 3). The pooled pitavastatin/ezetimibe and pooled pitavastatin groups achieved 94.2% and 69.1%, respectively (least squares mean difference, 24.9%; 95% CI, 16.5–33.3; $P < 0.001$). According to the ATP III guideline targeting LDL-C levels <100 mg/dL, the pitavastatin/ezetimibe combination group showed superior efficacy to pitavastatin monotherapy in high-risk patients.

The percent changes in mean LDL-C levels at 4 weeks compared with baseline values were –53.0% (1.6%) versus –35.8% (1.6%) in the pooled

Table 2. The mean percentage change and mean changes from baseline after 4 weeks and 8 weeks treatment in LDL-C

Variables		Pooled PTV+EZE (N=139)	PooledPTV (N=139)	PTV2+EZE10 (N=68)	PTV2 (N=69)	PTV4+EZE10 (N=71)	PTV4 (N=70)
LDL-C at baseline	Mean ± Std	157.2 ± 31.6	158.1 ± 32.3	155.3 ± 29.2	163.0 ± 33.5	159.0 ± 33.8	153.3 ± 30.6
	Median	154.0	155.0	152.0	159.0	156.0	152.0
	Min∼Max	100.0∼236.0	102.0∼244.0	101.0∼224.0	104.0∼244.0	100.0∼236.0	102.0∼240.0
LDL-C at after 4-week follow-up	Mean ± Std	72.0 ± 19.2	98.2 ± 25.1	72.1 ± 17.4	106.4 ± 24.8	71.8 ± 20.8	90.1 ± 22.7
	Median	68.0	94.0	71.0	105.0	67.0	87.0
	Min∼Max	37.0∼174.0	55.0∼195.0	37.0∼106.0	55.0∼166.0	43.0∼174.0	58.0∼195.0
LDL-C at after 8-week follow-up	Mean ± Std	73.4 ± 19.4	98.3 ± 25.5	74.1 ± 19.7	107.5 ± 26.7	72.7 ± 19.3	89.2 ± 20.6
	Median	70.0	95.0	72.0	102.0	68.0	85.5
	Min∼Max	36.0∼157.0	43.0∼168.0	41.0∼134.0	54.0∼168.0	36.0∼157.0	43.0∼134.0
Change of LDL-C from baseline at week 4	Mean ± Std	-86.0 ± 25.7	-58.6 ± 27.4	-85.0 ± 23.7	-54.6 ± 27.5	-86.9 ± 27.5	-62.6 ± 27.0
	Median	-87.0	-57.0	-89.0	-53.0	-87.0	-58.5
	Min∼Max	-151.0∼-27.0	-149.0∼24.0	-142.0∼-30.0	-124.0∼9.0	-151.0∼-27.0	-149.0∼24.0
	P-value (within)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
ANCOVA	LSmean ± SE	-83.2 ± 2.5	-56.6 ± 2.5	-87.5 ± 3.4	-54.7 ± 3.5	-78.3 ± 3.3	-58.1 ± 3.3
	LSmean difference (95% C.I.)	-26.6 (-31.1, -22.2)	.	-32.8 (-39.2, -26.4)	.	-20.2 (-26.3, -14.2)	.
	P-value (ANCOVA)	<0.001	.	<0.001	.	<0.001	.
Percentage change of LDL-C from baseline at week 4	Mean ± Std	-54.0 ± 10.3	-36.6 ± 14.1	-53.7 ± 10.3	-33.0 ± 14.1	-54.2 ± 10.4	-40.2 ± 13.3
	Median	-54.7	-39.4	-54.6	-35.1	-54.9	-43.0
	Min∼Max	-72.0∼-13.9	-62.1∼20.3	-72.0∼-24.0	-61.4∼6.8	-69.5∼-13.9	-62.1∼20.3
	P-value (within)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

(*continued on next page*)

Table 2. (*continued*)

Variables		Pooled PTV+EZE (N=139)	PooledPTV (N=139)	PTV2+EZE10 (N=68)	PTV2 (N=69)	PTV4+EZE10 (N=71)	PTV4 (N=70)
ANCOVA	LSmean ± SE	-53.0 ± 1.6	-35.8 ± 1.6	-54.9 ± 2.3	-33.7 ± 2.3	-50.8 ± 2.1	-37.6 ± 2.1
	LSmean difference (95% C.I.)	-17.2 (-20.1, -14.3)	.	-21.2 (-25.4, -17.0)	.	-13.3 (-17.2, -9.4)	.
	P-value (ANCOVA)	<0.001	.	<0.001	.	<0.001	.
Change of LDL-C from baseline at week 8	Mean ± Std	-83.8 ± 26.8	-59.8 ± 27.9	-81.2 ± 26.5	-55.5 ± 26.2	-86.3 ± 27.1	-64.1 ± 29.0
	Median	-84.0	-59.0	-81.5	-57.0	-87.0	-61.5
	Min∼Max	-149.0∼-4.0	-183.0∼20.0	-142.0∼-4.0	-125.0∼20.0	-149.0∼-15.0	-183.0∼8.0
	P-value (within)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
ANCOVA	LSmean ± SE	-82.6 ± 2.5	-58.0 ± 2.5	-83.6 ± 3.6	-53.5 ± 3.7	-80.1 ± 3.2	-61.9 ± 3.2
	LSmean difference (95% C.I.)	-24.5 (-29.0, -20.0)	.	-30.1 (-36.8, -23.5)	.	-18.2 (-23.8, -12.5)	.
	P-value (ANCOVA)	<0.001	.	<0.001	.	<0.001	.
Percentage change of LDL-C from baseline at week 8	Mean ± Std	-52.8 ± 11.2	-37.1 ± 14.1	-51.8 ± 12.2	-33.3 ± 13.8	-53.7 ± 10.0	-40.8 ± 13.6
	Median	-54.5	-38.2	-53.3	-33.0	-55.7	-43.0
	Min∼Max	-72.7∼-2.9	-76.3∼15.0	-72.7∼-2.9	-61.9∼15.0	-72.3∼-8.7	-76.3∼6.8
	P-value (within)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
ANCOVA	LSmean ± SE	-52.2 ± 1.6	-36.5 ± 1.6	-52.3 ± 2.4	-33.1 ± 2.4	-51.5 ± 2.1	-39.4 ± 2.1
	LSmean difference (95% C.I.)	-15.8 (-18.7, -12.9)	.	-19.2 (-23.6, -14.9)	.	-12.1 (-15.9, -8.4)	.
	P-value (ANCOVA)	<0.001	.	<0.001	.	<0.001	.

EZE = ezetimibe
LDL-C = Low-density lipoprotein-cholesterol
PTV = pitavastatin

Table 3. Rate of achievement of low-density lipoprotein (LDL-C) cholesterol target

Variables		Pooled PTV+EZE (N=139)	Pooled PTV (N=139)	PTV 2mg + EZE (N=68)	PTV 2mg (N=69)	PTV 4mg + EZE (N=71)	PTV 4mg (N=70)
Total number of patients achieving LDL-C goal, n (%)	P-value	131 (94.2%) <0.001	96 (69.1%) .	64 (94.1%) <0.001	39 (56.5%) .	67 (94.4%) 0.02	57 (81.4%) .
Patients by CHD risk factors, n (%)							
Group I (CHD/CHD risk equivalents [10-y risk > 20%])	LDL-C <100mg/dL	100 (93.5%)	70 (64.2%)	49 (92.5%)	27 (50.0%)	51 (94.4%)	43 (78.2%)
	Total	107	109	53	54	54	55
	P-value	<0.001	.	<0.001	.	0.01	.
Group IIA (Risk factors ≥ 2 [10% ≤ 10-y risk ≤ 20%])	LDL-C <130mg/dL	11 (100.0%)	10 (100.0%)	5 (100.0%)	5 (100.0%)	6 (100.0%)	5 (100.0%)
	Total	11	10	5	5	6	5
	P-value	NA	.	NA	.	NA	.
Group IIB (Risk factors ≥ 2 [10-y risk < 10%])	LDL-C <130mg/dL	3 (75.0%)	1 (25.0%)	2 (100.0%)	0 (0.0%)	1 (50.0%)	1 (50.0%)
	Total	4	4	2	2	2	2
	P-value	0.49	.	0.33	.	>0.99	.
Group III (Risk factors 0 – 1)	LDL-C <160mg/dL	17 (100.0%)	15 (93.8%)	8 (100.0%)	7 (87.5%)	9 (100.0%)	8 (100.0%)
	Total	17	16	8	8	9	8
	P-value	0.48	.	>0.99	.	–	.

CHD = coronary heart disease
EZE = ezetimibe
LDL-C = Low-density lipoprotein-cholesterol
PTV = pitavastatin
NA = not available

pitavastatin/ezetimibe and pooled pitavastatin groups, respectively (Table 2). The LDL-C change from baseline to 4 weeks was –83.2 (2.5) mg/dL and –56.6 (2.5) mg/dL in the pooled pitavastatin/ezetimibe and pooled pitavastatin groups ($P < 0.001$). TC levels were significantly decreased after 8 weeks of treatment in the pooled pitavastatin/ezetimibe group versus pooled pitavastatin(–36.2% [1.3%] vs –25.7% [1.3%]; $P < 0.001$) (see **Supplemental Table I** in the online version at doi:10.1016/j.clinthera.2022.09.001). The pooled pitavastatin/ezetimibe group also showed a modest decrease in TG level compared with pooled pitavastatin (–18.0% [4.5%] vs –14.4% [4.5%]; $P = 0.39$) (see **Supplemental Table II** in the online version at doi:10.1016/j.clinthera.2022.09.001). Moreover, HDL-C was comparable between the pooled pitavastatin/ezetimibe and the pooled pitavastatin groups (7.4% [1.8%] vs 6.2% [1.8%]; $P = 0.49$) (see **Supplemental Table III** in the online version at doi:10.1016/j.clinthera.2022.09.001). The percent changes in non–HDL-C, apo B, LDL-C/HDL-C, TC/HDL-C, non–HDL/HDL-C ratio, and apo B/apo A-I were significantly greater with the pooled pitavastatin/ezetimibe group than with pooled pitavastatin, excluding apo A-I (see **Supplemental Tables IV–IX** in the online version at doi:10.1016/j.clinthera.2022.09.001). The changes in hs-CRP levels after 4 and 8 weeks were similar between the pooled pitavastatin/ezetimibe and pooled pitavastatin groups (see **Supplemental Table X** in the online version at doi:10.1016/j.clinthera.2022.09.001). After the extension study, LDL-C percent changes and target-achieving rates were consistently comparable between groups.

Safety

Of the 282 patients in the safety analysis set, 14 (5.0%) experienced at least one ADR after treatment (Table 4). The most common ADR was peripheral edema. There were no significant differences in the overall incidence of AEs, ADRs, and serious AEs. Laboratory findings, including liver function tests and creatinine kinase, were comparable between the 2 groups. Three patients dropped out because of AEs. Reported AEs after the extension study were comparable between groups.

DISCUSSION

This clinical trial compared the efficacy and safety of pitavastatin and ezetimibe combination therapy with those of pitavastatin monotherapy in patients with primary hypercholesterolemia. In this double-blind, multicenter, randomized, Phase III study, combination therapy with pitavastatin and ezetimibe significantly decreased LDL-C levels compared with pitavastatin monotherapy without increasing the overall AEs. Furthermore, achievements in the target LDL-C rates according to the NCEP ATP III guidelines were also significantly higher in the pitavastatin/ezetimibe group than with pitavastatin monotherapy during the 8-week follow-up.

Dyslipidemia is an established risk factor for cardiovascular diseases, whose prevalence is gradually increasing with age.[12] Nearly 85% of patients with diabetes and 70% of patients with hypertension had dyslipidemia simultaneously. Anti-dyslipidemia therapy could reduce 20% to 50% of cardiovascular death, myocardial infarction, coronary revascularization, and stroke in these patients.[13] It is well established that, in terms of LDL-C, "lower is better." Therefore, current guidelines highlight statins and nonstatins used in achieving the desired LDL-C according to each patient's risks.[4] However, in the real world of clinical practice, only 60% of patients with dyslipidemia are treated, and 20% are adequately controlled.[12] Statin discontinuation rates were reported to be up to 50% due to statin-related events. Although most rechallenged patients could tolerate statins, an individualized approach would be needed to improve adherence, reduce AEs, and reach the LDL-C target.[14] Recent research comparing moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy showed that combination therapy was noninferior to monotherapy, and discontinuation or dose reduction of study medication due to intolerance was significantly low in the combination therapy group.[15] In high-risk Korean patients with relatively low baseline LDL-C levels of ~120 mg/dL, the percent reduction in LDL-C from baseline was 18.7% in the pitavastatin 1 mg group and 28% in the pitavastatin 4 mg group, with no increase in NOD risks.[10] In addition, there was no significant increase in fasting blood glucose levels, glycated hemoglobin values, or NOD with pitavastatin compared with the control group.[16] However, other statins with a high dose increased the risk of NOD compared with moderate-dose statin therapy.[17] Although pitavastatin 2 mg effectively decreased LDL-C by 33% and pitavastatin 4 mg by

Table 4. Summary of adverse events (AEs) and frequency of drug-related adverse events in treated set

Number of patients reporting AE, n (%)		Pooled PTV+EZE (N=142)	PooledPTV (N=140)	PTV 2mg + EZE (N=70)	PTV 2mg (N=69)	PTV 4mg + EZE (N=72)	PTV 4mg (N=71)
Number of AEs		28 (19.7%)	25 (17.9%)	13 (18.6%)	10 (14.5%)	15 (20.8%)	15 (21.1%)
	P-value	0.69	.	0.52	.	0.97	
Number of drug-related AEs		5 (3.5%)	9 (6.4%)	2 (2.9%)	3 (4.4%)	3 (4.2%)	6 (8.5%)
	P-value	0.26	.	0.68	.	0.33	
Serious AEs		1 (0.7%)	2 (1.4%)	1 (1.4%)	1 (1.5%)	0 (0.0%)	1 (1.4%)
	P-value	0.62	.	1.00	.	0.50	
SADR		0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	P-value	NA	.	NA	.	NA	.
Severity	**Total**	**35 (53.9%)**	**30 (46.2%)**	**16 (51.6%)**	**15 (48.4%)**	**19 (55.9%)**	**15 (44.1%)**
Mild		31 (88.6%)	24 (80.0%)	14 (87.5%)	13 (86.7%)	17 (89.5%)	11 (73.3%)
Moderate		4 (11.4%)	5 (16.7%)	2 (12.5%)	2 (13.3%)	2 (10.5%)	3 (20.0%)
Severe		0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)
Action taken with IP	**Total**	**35 (53.9%)**	**30 (46.2%)**	**16 (51.6%)**	**15 (48.4%)**	**19 (55.9%)**	**15 (44.1%)**
Maintenance dose		34 (97.1%)	28 (93.3%)	15 (93.8%)	15 (100.0%)	19 (100.0%)	13 (86.7%)
Permanent dechallenge		1 (2.9%)	2 (6.7%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	2 (13.3%)
AEs according to system organ class							
Musculoskeletal and connective tissue disorders		3 (2.1%)	6 (4.3%)	2 (2.9%)	2 (2.9%)	1 (1.4%)	4 (5.6%)
Arthralgia		2 (1.4%)	3 (2.1%)	1 (1.4%)	2 (2.9%)	1 (1.4%)	1 (1.4%)
Myopathy		0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders		7 (4.9%)	2 (1.4%)	4 (5.7%)	1 (1.5%)	3 (4.2%)	1 (1.4%)
Dyspnoea exertional		3 (2.1%)	0 (0.0%)	2 (2.9%)	0 (0.0%)	1 (1.4%)	0 (0.0%)
Cough		1 (0.7%)	1 (0.7%)	0 (0.0%)	1 (1.5%)	1 (1.49%)	1 (0.0%)

(*continued on next page*)

Table 4. (*continued*)

Number of patients reporting AE, n (%)	Pooled PTV+EZE (N=142)	PooledPTV (N=140)	PTV 2mg + EZE (N=70)	PTV 2mg (N=69)	PTV 4mg + EZE (N=72)	PTV 4mg (N=71)
Nervous system disorders	2 (1.4%)	5 (3.6%)	0 (0.0%)	3 (4.4%)	2 (2.8%)	2 (2.8%)
Headache	1 (0.7%)	3 (2.1%)	0 (0.0%)	2 (2.9%)	1 (1.4%)	1 (1.4%)
Dizziness	1 (0.7%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (1.4%)
Gastrointestinal disorders	3 (2.1%)	4 (2.9%)	0 (0.0%)	3 (4.4%)	3 (4.2%)	1 (1.4%)
Constipation	0 (0.0%)	2 (1.4%)	0 (0.0%)	2 (2.9%)	0 (0.0%)	0 (0.0%)
Nausea	1 (0.7%)	1 (0.7%)	0 (0.0%)	0(0.0%)	1 (1.4%)	1 (1.4%)
Infections and infestations	3 (2.1%)	4 (2.9%)	2 (2.9%)	1 (1.5%)	1 (1.4%)	3 (4.2%)
Viral upper respiratory tract infection	1 (0.7%)	3 (2.1%)	1 (1.4%)	1 (1.5%)	0 (0.0%)	2 (2.8%)
General disorders and administration site conditions	3 (2.1%)	1 (0.7%)	2 (2.9%)	0 (0.0%)	1 (1.4%)	1 (1.4%)
Oedema peripheral	2 (1.4%)	0 (0.0%)	2 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Investigations	2 (1.4%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	2 (2.8%)	1 (1.4%)
Elevated liver function tests	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
Skin and subcutaneous tissue disorders	1 (0.7%)	2 (1.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	2 (2.8%)
Pruritis	1 (0.7%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Psychiatric disorders	2 (1.4%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (1.4%)	0 (0.0%)
Insomnia	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)
Anxiety	1 (0.7%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

AE = adverse event
ADR = adverse drug reaction
EZE = ezetimibe
PTV = pitavastatin
NA = not available

39% in this study, the achieving rates of the LDL-C target were generally low. Therefore, dose escalation and the addition of nonstatin therapy after starting moderate-intensity statin, such as pitavastatin, can be a reasonable option.

Ezetimibe is the nonstatin agent most commonly used to reach the LDL-C target. It lowers LDL-C levels by 13% to 20% and has a low incidence of side effects.[6] Addition of ezetimibe to moderate-intensity statin therapy in very-high-risk patients significantly lowered adverse cardiovascular events.[5] Another nonstatin agent is proprotein convertase subtilisin kexin type 9 inhibitors. These inhibitors can be initiated in patients on a maximally tolerated statin with ezetimibe or those on maximally tolerated statin alone. However, excluding ezetimibe would expose more patients to the inconvenience of antibody therapy and overall high cost. In this study, addition of ezetimibe to pitavastatin also decreased LDL-C levels up to 20% more. Pitavastatin with ezetimibe exhibited high-intensity lowering of LDL-C levels by >50%, and nearly 100% of patients reached their LDL-C target in this study.

Although ~20% of patients experienced AEs, combination therapy with pitavastatin and ezetimibe was generally well tolerated in this trial. In the Japanese long-term prospective postmarketing surveillance LIVES (Livalo Effectiveness and Safety) study, pitavastatin reduced LDL-C levels up to 30%, and only 10.4% of pitavastatin-treated patients reported AEs.[18] Increases in blood creatine phosphokinase (2.7%), alanine aminotransferase (1.8%), myalgia (1.1%), aspartate aminotransferase (1.5%), and gamma-glutamyltransferase (1.0%) levels were the most common AEs. Drug-related AEs were comparable with the previous study. There is only one case of severe AE due to osteoarthritis, but there were no severe drug-related AEs. In addition, adding ezetimibe to pitavastatin did not increase AEs such as myopathy or gastrointestinal problems in our study. Consequently, pitavastatin and ezetimibe combination therapy showed promising efficacy in lowering LDL-C levels in patients with dyslipidemia, with a good safety profile and tolerability.

CONCLUSIONS

Pitavastatin and ezetimibe combination effectively and safely decreased LDL-C levels by >50% in patients with dyslipidemia. The safety and tolerability of pitavastatin and ezetimibe combination therapy were comparable with those of pitavastatin monotherapy.

DECLARATION OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinthera.2022.09.001.

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