Original Research

Efficacy and Tolerability of Ezetimibe/Atorvastatin Fixed-dose Combination Versus Atorvastatin Monotherapy in Hypercholesterolemia: A Phase III, Randomized, Active-controlled Study in Chinese Patients

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ABSTRACT

Purpose: The 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors ("statins") and the cholesterol-lowering medication ezetimibe are widely used in the treatment of patients with high- and very high–risk atherosclerotic cardiovascular disease. This study compared the efficacy and tolerability of a fixed-dose combination (FDC) of ezetimibe/atorvastatin (EZ/AS) with those of escalating doses of atorvastatin monotherapy in Chinese patients with hypercholesterolemia uncontrolled with statin monotherapy.

Methods: This Phase III, 12-week, randomized, double-blind study included patients aged 18 to 80 years with hypercholesterolemia uncontrolled on atorvastatin 10 or 20 mg/d monotherapy. After a 5-week run-in period of treatment with atorvastatin 10 or 20 mg/d (cohorts A and B, respectively), or a bioequivalent dosage of another statin, patients were randomized in a 1:1 ratio within each cohort to receive EZ/AS 10/10 mg FDC (EZ10/AS10) or atorvastatin 20 mg (AS20), once daily (cohort A); or EZ/AS 10/20 mg FDC (EZ10/AS20) or atorvastatin 40 mg (AS40), once daily (cohort B). The primary end point was the percentage change from baseline in low-density lipoprotein cholesterol (LDL-C). Tolerability was also evaluated.

Findings: Of the 454 patients enrolled, 412 (90.7%) completed the study. The percentage change from baseline in LDL-C was statistically greater with EZ10/AS10 treatment (n = 88) compared with AS20 monotherapy (n = 89) (treatment difference, −19.5%; 95% CI, −26.7% to −12.3%; $P < 0.001$). The percentage change from baseline in LDL-C was statistically greater with EZ10/AS20 treatment (n = 137) compared with AS40 monotherapy (n = 140) (treatment difference, −15.9%; 95% CI, −21.0% to −10.7%; $P < 0.001$). The safety profile was comparable between the EZ/AS and atorvastatin groups in the two cohorts.

[#]Phase III Study Investigators are listed in the Acknowledgments.

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Implications: The LDL-C level at week 12 was significantly improved with both FDCs compared with escalated doses of atorvastatin (20 or 40 mg/d) in these Chinese patients with hypercholesterolemia uncontrolled on atorvastatin 10 or 20 mg/d. Both FDCs were well tolerated, with no new tolerability-related findings. Chinadrugtrials.org.cn identifier: CTR20190172; ClinicalTrials.gov identifier: NCT03768427 (*Clin Ther.* 2022;44:1282–1297.)

Key words: atorvastatin, China, ezetimibe, fixed-dose combination, hypercholesterolemia, LDL-C.

INTRODUCTION

Rapid economic development and an unhealthy lifestyle (eg, poor dietary choices, sedentary behavior, and smoking habits) irregular work and rest, high fat and cholesterol intake, decrease in physical activity have led to an exponential increase in serum cholesterol and triglyceride levels worldwide, including in the Chinese population.[1] In a nationwide, 4-year survey from China, the prevalence of dyslipidemia was changed from 2015 to 2019; specifically, hypercholesterolemia (from 1.6% to 5.8%), hypertriglyceridemia (from 5.7% to 15.0%), depressed high-density lipoprotein-cholesterol (from 18.8% to 24.9%), and elevated low-density lipoprotein cholesterol (LDL-C; from 1.3% to 7.2%).[2] In the China Patient-Centered Evaluative Assessment of Cardiac Events Million Persons Project study,[3] one third of the residents (33.8%) aged 35 to 75 years had been diagnosed with dyslipidemia that remained uncontrolled and untreated. Uncontrolled dyslipidemia is a major risk factor for atherosclerotic cardiovascular disease (CVD) and cerebrovascular disease.[4] Thus, there are emergent needs for addressing hypercholesterolemia and for identifying optimal therapeutic options that are both well tolerated and effective.

Statins, the competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase, are the recommended first-line therapy for patients with hypercholesterolemia.[5,6] In adults, the dose of a statin is generally increased to the maximal approved or tolerated dose used for achieving the recommended reduction in LDL-C level (by ≥50%).[7] Recent guidelines recommend up-titrating the statin dose to achieve specific LDL-C goals.[8,9] The 2013 and the updated 2018 American College of Cardiology/American Heart Association guidelines recommend the use of an intermediate to high statin dose in patients with hypercholesterolemia.[7,10] In a meta-analysis of data from large-scale, randomized studies, every 1.0-mmol/L (38.67-mg/dL)[11] reduction in LDL-C level with statin therapy was associated with a marked reduction in vascular disease–related mortality, with proportional risk reductions similar among men and women.[12]

However, there are two challenges with the use of statin monotherapy. First, a large subset of patients with hypercholesterolemia are at risk for CVD and fail to achieve sufficient lowering of LDL-C and other lipid parameters,[13–15] even with the maximal recommended statin dose.[16] Second, owing to their genetic disposition, the Asian population is more sensitive to statins: With the same doses of statins, the plasma drug concentration–time curve and the C_{max} in an Asian population were reported to be almost twofold those observed in a white population.[17,18] However, another study found no inter-racial variability.[19] This difference in pharmacokinetics is clinically relevant given that Chinese patients with coronary heart disease (CHD) do not have very high LDL-C levels (mean [SD], 2.93 [1.0] mmol/L), even high-risk patients (3.06 [1.08] mmol/L) and very high–risk patients (2.89 [0.97] mmol/L). Therefore, higher doses of statins might not be directly correlated with an improved therapeutic effect in this population.[20,21] In the Dyslipidemia International Study from China,[22] 45.2% of high-risk and 60.3% of very high–risk patients with dyslipidemia failed to achieve the target LDL-C level following aggressive treatment with a statin. Similar results were noted in other studies in which treatment with a high-dose statin was not associated with any additional benefit compared with an intermediate dose.[23–25]

Adverse events (AEs) associated with statins limit their use in clinical practice,[26,27] especially in patients in whom the concentration peaks sooner and intended doses are high. In the Chinese population, statin therapy has been shown to be associated with increased risks for new-onset diabetes[28] and liver dysfunction.[29] The AEs leading to treatment discontinuation or suboptimal adherence to statin therapy are hence a barrier in achieving LDL-C goals.

Therefore, the 2021 European Atherosclerosis Society Task Force recommends the combination of a

statin and a nonstatin agent (eg, ezetimibe) to intensify LDL-C lowering in patients who are at high or very high risk for CVD and who might fail to achieve the desired LDL-C goal with statin monotherapy.[30] The 2016 Guidelines for the Prevention and Treatment of Adult Dyslipidemia in China[4] also specify that high-intensity statin therapy is not suitable for use in the Asian/Chinese population, and that intermediate-intensity statin therapy might be more appropriate in the Chinese population.

Ezetimibe, a lipid-lowering drug, inhibits the absorption of exogenous (dietary) and endogenous (biliary) cholesterol from the small intestine by selectively binding to the Niemann–Pick C1-like 1 protein. Combination therapy with a statin and ezetimibe has been associated not only with a substantially lower LDL-C level but also an improved overall lipid profile compared with statin monotherapy.[14,31] These findings might be more marked with a greater or even doubled dose of the statin.[32] Ezetimibe, coadministered with any statin, irrespective of the dosage, has been associated with a consistently greater reduction in LDL-C through dual inhibition of cholesterol production and absorption.[32] Ezetimibe in combination with atorvastatin was associated with significantly greater reductions in LDL-C, total cholesterol, and triglycerides compared with an escalating dose of atorvastatin.[33] The combination of ezetimibe and a statin has been reported to be well tolerated in patients with hypercholesterolemia and has a tolerability profile comparable to that of statin monotherapy.[34]

Although the ezetimibe + statin combination therapy is widely used, the efficacy and tolerability of fixed-dose combinations (FDCs) in Chinese patients are yet to be established. The present study compared the efficacy and safety profiles of an FDC comprising ezetimibe + atorvastatin (EZ/AS) with those of escalating doses of atorvastatin in Chinese patients with hypercholesterolemia. The findings from this study will support the marketing authorization of the EZ/AS FDC in China.

PATIENTS AND METHODS

Study Design

This Phase III, 12-week, multicenter, randomized, double-blind (with in-house blinding), active-controlled, double-dummy, parallel-group study was conducted across 30 centers in China from May 27, 2019, to April 1, 2021 (see Supplemental Table I in the online version at doi:10.1016/j.clinthera.2022.08.013). The study comprised four periods (Figure 1): screening period (visit 1; 2 weeks), atorvastatin active run-in period (visits 2–3; 5 weeks), treatment period (visits 4–6; 12 weeks), and a post-treatment follow-up period (14 days, after the administration of the last dose). Following the active run-in period, patients with inadequately controlled hypercholesterolemia on treatment with atorvastatin ≤10 and ≤20 mg/d or a bioequivalent/lower dosage of another statin (simvastatin 10/20/40 mg/d, lovastatin 20/40/80 mg/d, pravastatin 20/40 mg/d, or fluvastatin 40/80 mg/d) were assigned to cohorts A and B, respectively. Patients

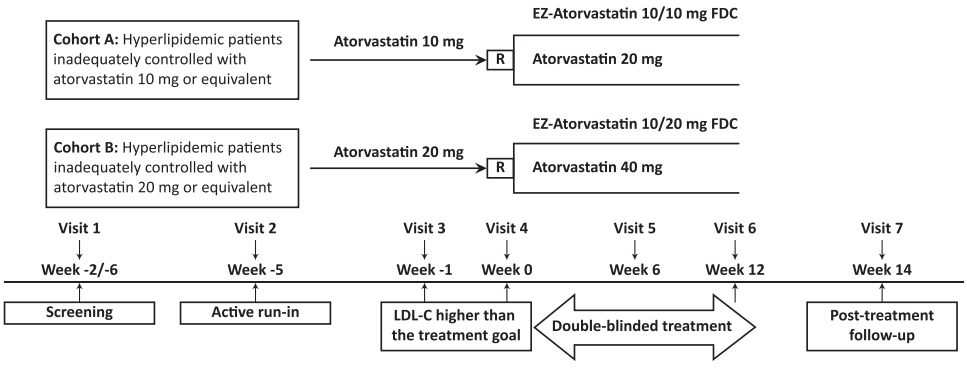

Figure 1. Study design. Cohort A = atorvastatin 10 mg/d during the run-in period; cohort B = atorvastatin 20 mg/d during the run-in period; EZ = ezetimibe; FDC = fixed-dose combination; LDL-C = low-density lipoprotein cholesterol; R = randomized.

in cohort A were randomized (1:1) to receive either EZ/AS 10/10 mg FDC (EZ10/AS10) or atorvastatin 20 mg (AS20), once daily. Patients in cohort B were randomized (1:1) to receive either EZ/AS 10/20 mg FDC (EZ10/AS20) or atorvastatin 40 mg (AS40), once daily (Figure 1). Central randomization was done using an interactive response technology system. CVD risk category was assigned according to the Guidelines for the Prevention and Treatment of Adult Dyslipidemia in China (2016)[4] based on demographic characteristics and clinical history including lipid profile. A double-dummy design was followed to ensure efficient blinding, considering the difference in appearance between the FDC and atorvastatin, and patients in both cohorts were given matching placebos. All study personnel, including the investigators, patients, sponsor personnel or delegates, were blinded to the treatment allocation throughout the study (in-house blinding). Doses were not adjusted during the 12-week treatment period.

This study was conducted in compliance with local and/or national regulations (eg, International Council for Harmonisation Good Clinical Practice and in accordance with the ethics principles of the Declaration of Helsinki). The study protocol was approved by the institutional review board of each site, and written informed consent was obtained from all participants before commencing any study-specific procedure. The study is registered with chinadrugtrials.org.cn (CTR20190172) and ClinicalTrials.gov (NCT03768427).

Eligibility Criteria

Inclusion Criteria

Chinese men and women aged 18 to 80 years (inclusive) with documented hypercholesterolemia requiring medical treatment as per the Guidelines for the Prevention and Treatment of Adult Dyslipidemia in China (2016),[4] but with inadequately controlled or uncontrolled hypercholesterolemia, were eligible for participation in the study. Eligible patients were on a stable dose of atorvastatin 10 or 20 mg/d or a bioequivalent/lower dose of another statin for ≥4 weeks prior to visit 1. Eligible patients had ≥75% medication adherence during the atorvastatin run-in period. *Medication adherence*(in %) was calculated as [(total tablets provided) – (tablets remaining at visits 2–3)]/(total tablets provided) × 100. Eligible patients could have atherosclerotic CVD of low to moderate, high, or very high risk (LDL-C, 70–<100, 100–<160, or ≥160 mg/dL, respectively) at visit 3.

Exclusion Criteria

Patients with uncontrolled hypertriglyceridemia requiring drug intervention or with a fasting triglyceride level of ≥500 mg/dL, with active liver disease or liver aminotransferases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) of >2-fold the upper limit of normal, symptomatic New York Heart Association Class III-IV heart failure, endocrine or metabolic disease, and/or an estimated glomerular filtration rate of <30 mL/min/1.73 m^2 at visit 1 were excluded from the study. Patients who achieved treatment goal by visit 4 and those who had a creatine kinase level of >3-fold the upper limit of normal at visit 4 were excluded. Patients with a history of statin treatment at a dose bioequivalent to LDL-C–lowering effect greater than that of atorvastatin 20 mg/d, and those with a history of uncontrolled cardiac arrhythmia, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, and/or unstable angina or stroke within 12 weeks prior to visit 1 were also excluded. Patients with HIV^+ status; intestinal malabsorption; hypersensitivity or intolerance to ezetimibe, atorvastatin, or EZ/AS; and/or a history of gastrointestinal tract bypass surgery, cancer, psychiatric instability, and/or drug/alcohol abuse (>25 g/d) within the preceding 5 years were also excluded. The use of red yeast rice supplement, bile acid sequestrants, ezetimibe, fibrates or niacin (>200 mg/d), *PCSK9* inhibitors, antifungal drugs, warfarin, phytosterol margarines, herbal medicine, corticosteroids, fiber-based laxatives, macrolide, protease inhibitors, cyclosporine, cyclical hormones, and grapefruit or grapefruit juice (200 mL/d for >3 times per week) were not permitted during the study.

Study Objectives and End Points

The primary objective of the study was to compare the efficacy of the FDC at both dosages with that of atorvastatin monotherapy in patients with hypercholesterolemia previously uncontrolled with atorvastatin monotherapy. The primary efficacy end point was the percentage change in LDL-C level from baseline to week 12 in both cohorts. The lipid profiles were analyzed by a central laboratory (Q Squared Solutions Co., Ltd., Unit 302, Building 15B, Han's Enterprise Bay, BDA Beijing, China) to maintain

uniformity. The level of LDL-C was determined using the Friedewald method if the triglyceride level was ≤400 mg/dL and using β quantification ultracentrifugation if the triglyceride level was >400 mg/dL.

The secondary objective was to evaluate the tolerability of the FDC with 12-week use. Tolerability was assessed by the monitoring and recording of laboratory test values, vital sign measurements (heart rate and blood pressure), ECG, AEs, serious AEs (SAEs), AEs of interest (AEIs), discontinuation due to AEs/SAEs, and the causal relationship of AEs to the study drug. Physical examination including vital sign monitoring was done at each visit. Urine/serum β–human chorionic gonadotropin was measured at visits 1 and 4–6 if a urinary pregnancy test performed at the site was positive. A qualified local laboratory was also used to detect safety signals. A 12-lead ECG was performed and levels of free T4 and thyroid-stimulating hormone were measured at visit 1. Hematology and urinalysis were performed at visits 1, 3, and 6. Fasting basic blood chemistry was performed at visits 1 and 3–6. Local-laboratory results obtained within 4 weeks prior to visit 1 were used as reference for the screening of patients. After the 12-week treatment period, patients were followed up by phone for ≈14 days following the cessation of treatment, to identify SAEs.

Statistical Analysis

The efficacy analysis was conducted in the *full analysis set* (FAS), defined as all randomized patients who took at least one dose of the study treatment and who had data available from at least one observation of the respective end point (baseline or postbaseline) during the treatment period. The *safety set* included all randomized patients who received at least one dose of the study treatment. The percentage change in LDL-C from baseline to week 12 was evaluated using a constrained longitudinal data analysis model, separately for each cohort (ES/AS vs atorvastatin). The tolerability analysis followed a tiered approach. *P* values and 95% CIs for the prevalences of AEIs were derived using the Miettinen and Nurminen method. The primary hypothesis was that percentage change in LDL-C level from baseline to week 12 would be greater with EZ/AS versus atorvastatin monotherapy in each cohort. The overall success was determined by the success of the hypothesis in at least one cohort. The overall type I error rate over multiple treatment comparisons in the primary hypothesis was controlled using the Hochberg testing procedure.

The study planned to enroll 450 patients (cohort A, 180; cohort B, 270). The power calculation was conservative and based on the number of patients expected to have LDL-C data available from week 12. Assuming a dropout rate of 10%, 162 patients (81 per arm) in cohort A and 242 patients (121 per arm) in cohort B were available for the power calculation. The planned sample in cohort A had 93% power to demonstrate the efficacy of EZ10/AS10 over AS20 at a one-sided 2.5% α level. Similarly, the sample in cohort B had 95% power to demonstrate the efficacy of EZ10/AS20 over AS40 at a one-sided 2.5% α level. The overall power to succeed in at least one hypothesis was 99% at a 2.5% α level, with 88% power to succeed for both hypotheses. The power and sample sizes were determined based on the following assumptions (unpublished data on file from NCT01154036): the treatment differences in percentage changes from baseline in LDL-C at week 12 in cohorts A and B were 12.3% and 10.5%, respectively, and unconditional SDs were 22% and 23%. Analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Patient Disposition and Baseline Characteristics

A total of 1113 Chinese patients were screened, of whom 454 were included in the study. Of these 454 patients, 177 were assigned to cohort A and were administered the FDC (EZ10/AS10; n = 88) or AS20 (n = 89). A total of 277 patients were assigned to cohort B and were administered either the FDC (EZ10/AS20; n = 137) or AS40 (n = 140). Of the 454 patients included in the study, 42 (9.3%) discontinued, and 412 (90.7%) completed the treatment period (Figure 2). The most common reasons for discontinuation were consent withdrawal (n = 20, 4.4%) and AEs (n = 11, 2.4%). Of the 659 patients who were not included in study, 560 (85.0%) were screen failures and 69 (10.5%) withdrew consent. The three most common reasons for screen failure were: (1) not meeting the LDL-C level as per the inclusion criteria; (2) achieving the treatment goal with statin monotherapy; and (3) having endocrine or metabolic disease known to influence serum lipid or lipoprotein levels. The reasons for consent withdrawal included

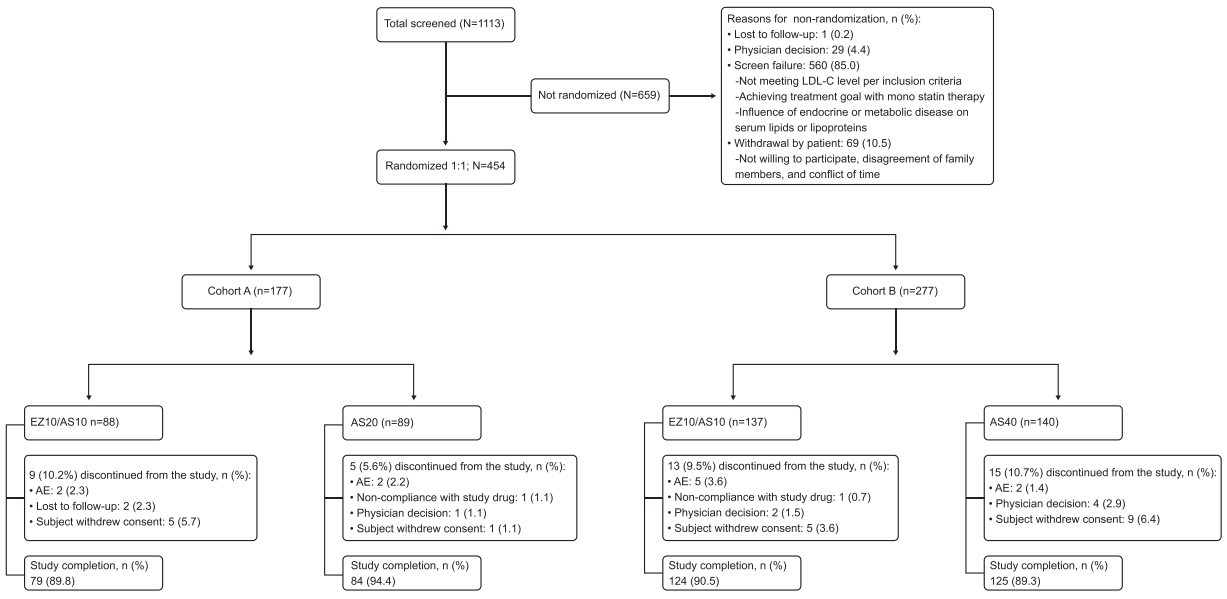

Figure 2. Patient disposition (full analysis set). AS20 = atorvastatin 20 mg; AS40 = atorvastatin 40 mg; cohort A = atorvastatin 10 mg/d during the run-in period; cohort B, atorvastatin 20 mg/d during the run-in period; EZ10/AS10 = ezetimibe/atorvastatin 10/10 mg; EZ10/AS20 = ezetimibe/atorvastatin 10/20 mg.

an unwillingness to participate, disagreement of family members, and conflict of time (Figure 2).

The baseline demographic and clinical characteristics were comparable between the treatment groups in both cohorts (Table I). The overall mean (SD) age of the patients was 60.9 (9.2) years, and 40.3% were aged ≥65 years. The majority of the patients (64.5%) were male, and most had very high–risk disease (89.2%). The baseline lipid profiles were comparable between the treatment groups (Table I).

Medication compliance was high (>96%) across the groups in both cohorts. Mean (SD) medication compliance rates were 98.4% (3.5%) in the EZ10/AS10 group and 98% (5.6%) in the AS20 group in cohort A, and 98.2% (5.9%) in the EZ10/AS20 group and 96.7% (8.6%) in the AS40 group in cohort B.

Efficacy

In cohort A, the least squares (LS) mean percentage changes in LDL-C from baseline to week 12 were −24.8% and −5.3% in the EZ10/AS10 and AS20 groups, respectively. The lipid-lowering effect was statistically greater with EZ10/AS10 compared with AS20 monotherapy (treatment difference, −19.5%; 95% CI, −26.7% to −12.3%; $P < 0.001$). In cohort B, the LS mean percentage changes in LDL-C from baseline to week 12 were −24.6% and −8.7% in the EZ10/AS20 and atorvastatin 40 mg/d groups, respectively. Similar to in cohort A, the lipid-lowering effect was statistically greater with EZ10/AS20 compared with AS40 monotherapy in cohort B (treatment difference, −15.9%; 95% CI, −21.0% to −10.7%; $P < 0.001$) (Table II and Figure 3).

Sensitivity Analyses

Sensitivity analyses were performed to assess the robustness of the findings based on the results obtained from the constrained longitudinal data analysis of the primary end point. In the reference multiple-imputation analysis, treatment differences in the LS mean LDL-C values at week 12 between EZ/AS and AS were −14.8% (95% CI, −20.6% to −9.1%; $P < 0.001$) in cohort A and −13.2% (95% CI, −17.6% to −8.8%; $P < 0.001$) in cohort B. These findings support the primary-analysis results. Tipping point multiple-

Table I. Baseline demographic and clinical characteristics of the study patients (full analysis set).

Characteristic	Cohort A		Cohort B	
	EZ/AS 10/10 mg/d (n = 88)	Atorvastatin 20 mg/d (n = 89)	EZ/AS 10/20 mg/d (n = 137)	Atorvastatin 40 mg/d (n = 140)
Demographic				
Age, mean (SD), y	62.4 (7.4)	62.4 (8.5)	59.4 (9.3)	60.6 (10.3)
Male, no. (%)	45 (51.1)	51 (57.3)	103 (75.2)	94 (67.1)
BMI, mean (SD), kg/m^2	25.3 (3.2)	25.2 (3.5)	26.1 (3.7)	25.8 (3.3)
Asian race, no. (%)	88 (100)	89 (100)	137 (100)	140 (100)
Non-Hispanic or -Latino ethnicity, no. (%)	88 (100)	89 (100)	137 (100)	140 (100)
Clinical				
Medical history, no. (%)				
Dyslipidemia	62 (70.5)	59 (66.3)	92 (67.2)	98 (70.0)
Hypertension	58 (65.9)	63 (70.8)	91 (66.4)	93 (66.4)
Coronary artery disease	45 (51.1)	46 (51.7)	80 (58.4)	91 (65.0)
Lipid profile, mean (SD), mg/dL				
LDL-C	95.5 (24.6)	96.8 (25.9)	88.4 (21.9)	91.9 (24.9)
Total cholesterol, mg/dL	170.9 (28.1)	172.9 (28.2)	161.0 (25.8)	164.4 (28.3)
HDL-C, mg/dL	47.3 (12.5)	46.9 (11.5)	44.6 (10.1)	44.4 (10.0)
Non-HDL-C, mg/dL	123.6 (27.6)	126.0 (26.3)	116.4 (24.6)	120.0 (26.8)
Triglycerides, mg/dL	140.3 (59.2)	145.9 (60.7)	140.1 (63.4)	141.0 (63.2)
ApoB, mg/dL	95.5 (18.6)	97.2 (19.5)	91.8 (16.8)	93.8 (18.5)
Disease risk category, no. (%)				
Low	4 (4.5)	4 (4.5)	1 (0.7)	1 (0.7)
Intermediate	1 (1.1)	2 (2.2)	0 (0.0)	1 (0.7)
High risk	13 (14.8)	14 (15.7)	4 (2.9)	4 (2.9)
Very high	70 (79.5)	69 (77.5)	132 (96.4)	134 (95.7)

BMI = body mass index; cohort A = atorvastatin 10 mg/d during the run-in period; cohort B = atorvastatin 20 mg/d during the run-in period; EZ/AS = ezetimibe/atorvastatin; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol.

imputation analysis also confirmed the robustness of the primary results.

Tolerability

Of the 454 patients in the safety set, 202 (44.4%) experienced at least one AE after randomization. The most common AEs (≥2% patients in any treatment group) were elevated ALT (EZ10/AS10, 0% vs AS20, 0%; EZ10/AS20, 5.1% vs AS40, 1.4%), followed by elevated blood glucose (EZ10/AS10, 2.3% vs AS20, 2.2%; EZ10/AS20, 2.2% vs AS40, 5.0%) and urinary occult blood positivity (EZ10/AS10, 0% vs AS20, 0%; EZ10/AS20, 4.4% vs AS40, 0.7%). Overall, the AE profile was comparable between the EZ/AS and atorvastatin groups in each cohort. The prevalences of AEs, drug-related AEs, SAEs, and AEs leading to discontinuation were low and generally similar in patients receiving EZ/AS and atorvastatin in both cohorts. No drug-related deaths were reported during the study (Table III). In addition to the elevated liver enzymes (ALT and AST), the AEIs included myopathy (EZ10/AS20, 0.7% vs AS40, 0%) and elevated blood creatine phosphokinase (EZ10/AS10, 0% vs AS20, 1.1%; EZ10/AS20, 1.5% vs AS40, 0%). AEI of overdose (defined as any dose higher than the amount of study treatment taken beyond the

Table II. Low-density lipoprotein cholesterol levels before and after treatment with ezetimibe/atorvastatin (EZ/AS) combination therapy and atorvastatin monotherapy in patients with hypercholesterolemia (full analysis set).

Variable	Cohort A		Cohort B	
	EZ/AS 10/10 mg/d (n = 88)	Atorvastatin 20 mg/d (n = 89)	EZ/AS 10/20 mg/d (n = 137)	Atorvastatin 40 mg/d (n = 140)
Baseline				
n	n = 88	n = 89	n = 137	n = 140
Mean (SD)	95.5 (24.6)	96.8 (25.9)	88.4 (21.9)	91.9 (24.9)
Week 12				
n	n = 67	n = 77	n = 114	n = 116
Mean (SD)	71.2 (25.7)	89.2 (25.6)	67.0 (23.1)	81.7 (23.1)
Percentage change				
n	n = 67	n = 77	n = 114	n = 116
Mean (SD)	–24.7 (24.9)	–5.3 (22.5)	–23.3 (23.1)	–9.1 (18.2)
LS mean (SE)*	–24.8 (2.7)	–5.3 (2.6)	–24.6 (1.9)	–8.7 (1.9)
(95% CI)	(–30.1 to –19.4)	(–10.4 to –0.3)	(–28.3 to –20.9)	(–12.4 to –5.1)
LS Mean Difference	–19.5		–15.9	
(95% CI; *P*)	(–26.7 to –12.3; <0.001)		(–21.0 to –10.7; <0.001)	

Cohort A = atorvastatin 10 mg/d during the run-in period; cohort B = atorvastatin 20 mg/d during the run-in period; EZ/AS = ezetimibe/atorvastatin; LS = least squares.

*LS mean; 95% CIs, and *P* values were obtained by fitting a constrained longitudinal model adjusting for time and the interaction of time by treatment as well as for time by baseline disease risk category, including all patients counted in the column labeled with *n*. A separate model was fit for each cohort.

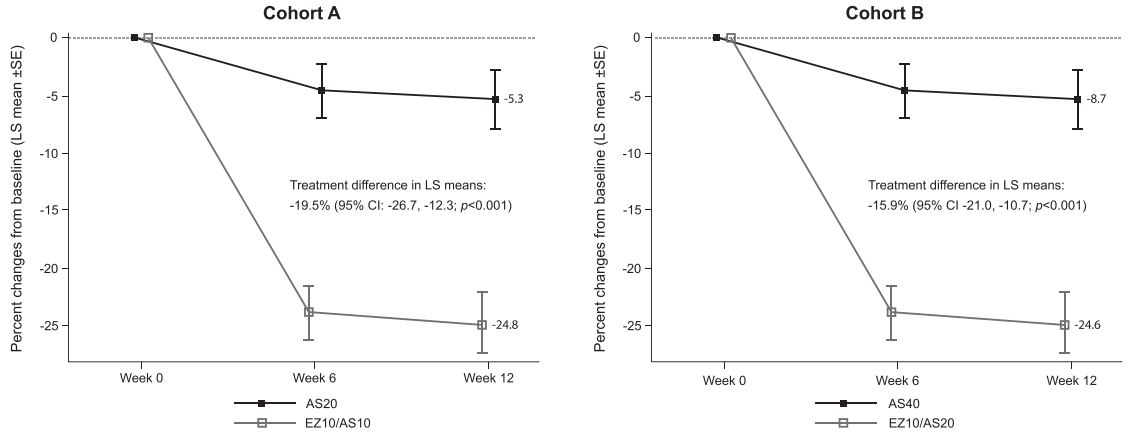

Figure 3. Least squares (LS) mean percentage changes in low-density lipoprotein cholesterol (LDL-C) level after 6 and 12 weeks of treatment with ezetimibe/atorvastatin (EZ/AS) or atorvastatin. AS20 = atorvastatin 20 mg; AS40 = atorvastatin 40 mg; cohort A = atorvastatin 10 mg/d during the run-in period; cohort B = atorvastatin 20 mg/d during the run-in period; EZ10/AS10 = ezetimibe/atorvastatin 10/10 mg; EZ10/AS20 = ezetimibe/atorvastatin 10/20 mg.

Table III. Adverse events (AEs), by preferred term, in the treated sets (all participants as treated). Data are given as number (%) of patients.

Variable	Cohort A		Cohort B	
	EZ/AS 10/10 mg/d (n = 88)	Atorvastatin 20 mg/d (n = 89)	EZ/AS 10/20 mg/d (n = 137)	Atorvastatin 40 mg/d (n = 140)
≥1 AE	28 (31.8)	31 (34.8)	76 (55.5)	67 (47.9)
No. of AEs	60 (68.2)	58 (65.2)	61 (44.5)	73 (52.1)
Treatment related*	7 (8.0)	7 (7.9)	22 (16.1)	17 (12.1)
Serious†	2 (2.3)	4 (4.5)	10 (7.3)	6 (4.3)
Discontinued due to AEs	2 (2.3)	2 (2.2)	4 (2.9)	3 (2.1)
Treatment related	0	2 (2.2)	2 (1.5)	1 (0.7)
Serious†	1 (1.1)	0	2 (1.5)	2 (1.4)
AEs occurring in ≥2% of patients				
Blood glucose increased	2 (2.3)	2 (2.2)	3 (2.2)	7 (5.0)
Hepatic function abnormal	2 (2.3)	2 (2.2)	3 (2.2)	5 (3.6)
Hyperuricemia	2 (2.3)	2 (2.2)	3 (2.2)	5 (3.6)
Urinary protein present	2 (2.3)	1 (1.1)	4 (2.9)	4 (2.9)
Cerebral infarction	2 (2.3)	1 (1.1)	1 (0.7)	0
Hypertension	2 (2.3)	0	2 (1.5)	2 (1.5)
Accidental overdose	1 (1.1)	3 (3.4)	5 (3.6)	4 (2.9)
Blood uric acid increased	1 (1.1)	3 (3.4)	2 (1.5)	2 (1.4)
Upper respiratory tract infection	1 (1.1)	1 (1.1)	5 (3.6)	4 (2.9)
Blood creatine phosphokinase increased	1 (1.1)	1 (1.1)	3 (2.2)	1 (0.7)
Urinary tract infection	1 (1.1)	1 (1.1)	0	3 (2.1)
Tinnitus	0	2 (2.2)	0	0
Vertigo	0	2 (2.2)	0	0
Hyperkalemia	0	1 (1.1)	4 (2.9)	3 (2.1)
T2DM	0	1 (1.1)	3 (2.2)	0
ALT increased	0	0	7 (5.1)	2 (1.4)
Urinary occult blood positive	0	0	6 (4.4)	1 (0.7)
AST and ALT increased	0	0	3 (2.2)	3 (2.1)
AST increased	0	0	3 (2.2)	1 (0.7)
Impaired fasting glucose	0	0	3 (2.2)	1 (0.7)
Myalgia	0	0	2 (1.5)	3 (2.1)
Urinary blood present	0	0	2 (1.5)	3 (2.1)
Chest pain	0	0	0	5 (3.6)
Carotid arteriosclerosis	0	0	0	3 (2.1)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; cohort A = atorvastatin 10 mg/d during the run-in period; cohort B = atorvastatin 20 mg/d during the run-in period; EZ/AS = ezetimibe/atorvastatin; T2DM = type 2 diabetes mellitus.

* Determined by the investigator to have been related to the study treatment; MedDRA version 23.1 was used in the reporting of the AEs in this study.

† None of the serious events were considered as treatment related, and no deaths were reported.

treatment assignment that was not associated with clinical symptoms or abnormal laboratory results) was reported in 13 of 454 patients (2.9%). No other AEIs were reported during the study. No clinically meaningful findings or differences in changes from baseline in laboratory parameters or vital sign measurements between EZ/AS and atorvastatin groups were observed in either cohort. Summary of SAEs are presented in Table IV.

No patients died during the study. A patient in the EZ10/AS20 group with very high ASCVD risk at baseline died after follow-up period due to severe low cardiac output syndrome after aortic dissection surgery. The death was considered caused by the emergency cardiovascular event which is prone to occur in the elderly and related to some risk factors of ASCVD, such as hypertension and atherosclerosis. The SAE and subsequent death were not considered as study drug-related.

DISCUSSION

In this Phase III, randomized, active-controlled study in Chinese patients with hypercholesterolemia inadequately controlled with atorvastatin 10 or 20 mg/d monotherapy, the addition of ezetimibe to a statin was apparently more effective in reducing the LDL-C level as well as in achieving the treatment goal compared with atorvastatin monotherapy at two dosages (20 or 40 mg/d). The combination therapy was well tolerated at both dosage strengths. The overall

Table IV. Summary of serious adverse events experienced by ≥0% of patients by preferred-term in any one of the treatment groups in the treated set (all participants as treated).

Variables	Cohort A		Cohort B	
	EZ10/AS10 (n=88)	AS20 (n=89)	EZ10/AS20 (n=137)	AS40 (n=140)
Angina unstable	0 (0.0)	0 (0.0)	1 (0.7)	2 (1.4)
Atrioventricular block	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Cardiac failure	0 (0.0)	0 (0.0)	2 (1.5)	0 (0.0)
Vertigo	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)
Cataract	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Gastrointestinal hemorrhage	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)
Femur fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Subdural hemorrhage	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Type 2 diabetes mellitus	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Intervertebral disc protrusion	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Lumbar spinal stenosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Rheumatoid arthritis	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Colon adenoma	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Ovarian granulosa cell tumor	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Cerebral infarction	2 (2.3)	1 (1.1)	1 (0.7)	0 (0.0)
Dizziness	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)
Chronic kidney disease	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)
Aortic dissection	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)

All values are presented as n (%) unless otherwise stated.
* Determined by the investigator to be related to the drug; MedDRA version 23.1 was used in the reporting of this study.
AS20, atorvastatin 20 mg; AS40, atorvastatin 40 mg; Cohort A, atorvastatin 10 mg during the run-in period; Cohort B, atorvastatin 20 mg during the run-in period; EZ10/AS10 mg, ezetimibe 10/atorvastatin 10 mg; EZ10/AS20 mg, ezetimibe 10/atorvastatin 20 mg.

tolerability of the FDC was comparable to that of the well-established safety profiles of ezetimibe and atorvastatin, individually. Thus, both the primary and secondary objectives of the study were met.

The results of this study corroborated those from another randomized controlled study from China, in which patients (N = 98) with atherosclerotic CVD were included. In that study, the mean LDL-C level was significantly lower with combination therapy with a moderate atorvastatin dose (EZ10/AS20) than with an escalating dose of atorvastatin (AS40) (1.59 [0.44] vs 1.99 [0.56] mmol/L; $P = 0.001$).[35] Similar benefits were noted in another study that included patients with acute coronary syndrome who received combination therapy (EZ10/AS10) or an escalating dose of atorvastatin (AS40).[36] This benefit was noted in the patient population with coexisting acute coronary syndrome and type 2 diabetes mellitus (T2DM) who received combination therapy (EZ10/AS10 or atorvastatin, simvastatin, or pravastatin 20 mg/d) compared with statin monotherapy. The reduction in LDL-C level was significantly greater with combination therapy compared with an escalating dose of atorvastatin (50% vs 29%; $P < 0.001$).[37] Similar benefits were noted in another study that included patients with T2DM and CHD.[38] This is an important finding because many patients with T2DM have coexisting hypercholesterolemia.

Studies in other populations have demonstrated a similar benefit. In Japanese patients with hypercholesterolemia, the lipid-lowering effect was significantly greater with combination therapy (EZ10/AS10) than an escalating dose of monotherapy with AS20 or a switch to rosuvastatin 2.5 mg/d (both, $P < 0.0001$).[39] Similar results were observed in other randomized controlled trials from Japan in which LDL-C lowering was greater with combination therapy compared with atorvastatin monotherapy.[40,41] Studies in other populations also replicate these findings.[42,43]

Elderly people constitute another vulnerable population in which the efficacy and tolerability of combination therapy have been studied. In a 12-week, randomized study in patients aged ≥65 years at high or very high risk for CHD, with or without atherosclerotic vascular disease, patients received EZ10/AS10 or atorvastatin monotherapy (AS20 for 6 weeks, uptitrated to AS40 for 6 weeks). LDL-C lowering was greater with EZ10/AS10 than with the escalating dose of atorvastatin monotherapy (60.5% vs 49.7%; odds ratio = 1.55).[44] Significantly higher mean reductions in LDL-C of ≥15% were noted with a comparable or greater atorvastatin dose with the addition of ezetimibe (ie, EZ10/AS20 vs AS40,[45] EZ10/AS40 vs AS80,[33] or EZ10/AS40 vs simvastatin 40 mg[46]). Similar results were noted in another study that compared EZ10/AS10 with an escalating dose of AS20 monotherapy; therein, liver dysfunction was observed to be minimal with combination therapy.[47]

In the Vytorin Versus Atorvastatin study,[14] the decrease in LDL-C was 9% greater with EZ10/AS40 compared with AS40 monotherapy in patients with hypercholesterolemia and established CHD or CHD risk equivalent. Two recent meta-analyses of data from 11 studies underlined the efficacy of combination therapy (EZ10/AS10) in lowering LDL-C compared with an escalating dose of atorvastatin monotherapy (AS20).[32,33] Another meta-analysis also demonstrated significantly improved LDL-C, non–high-density lipoprotein cholesterol, and total cholesterol levels with combination therapy (EZ10/AS20) compared with an escalating dose of atorvastatin monotherapy (AS40) in patients with high cardiovascular risk (all, $P < 0.001$).[48]

These findings together provide strong scientific evidence that the addition of ezetimibe to atorvastatin may be useful in achieving significant improvement in LDL-C level in Chinese patients with hypercholesterolemia. These findings call for an FDC of ezetimibe and a statin that may improve medication adherence and tolerability while reducing pill burden in patients compared with free combinations of lipid-lowering therapy. In a large-scale observational study (N = 256,012) conducted for ~7 years, the likelihood of adherence was higher with an EZ/simvastatin FDC (odds ratio = 1.84; 95% CI, 1.72–1.86) or an EZ/rosuvastatin FDC (odds ratio = 2.47; 95% CI, 2.31–2.65) compared with free combinations.[49] In a retrospective analysis in patients (n = 311,242) with a high cardiovascular risk, the reduction in LDL-C was significantly higher in patients treated with FDC of ezetimibe + a statin in comparison to those administered free combinations (mean reduction, 28.4% vs 19.4%; $P < 0.0001$). Consequently, a larger percentage of patients achieved the target LDL-C level of <70 mg/dL (31.5% vs 21.0%).[50] In the present study, >96% of patients with hypercholesterolemia were compliant with the FDC of EZ/AS, which

seems to be clinically important. Thus, the FDC of ezetimibe + a statin may be an option useful for improving compliance without increasing the complexity of treatment.

In the tolerability analysis in the present study, the combination therapy (EZ/AS) was well tolerated in Chinese patients with hypercholesterolemia and was comparable to the well-established AE profiles of ezetimibe and atorvastatin. Overall, there were low prevalences of AEs with both treatments. The 12-week tolerability results from the present study are commensurate with the tolerability findings from other studies of the EZ/AS combination.[27,33] In addition, no serious drug-related AEs, including death, were observed. Possibly, the low doses in the EZ/AS combination contributed to the low prevalence of AEs.

Overall, the results from the present study are encouraging and in line with relevant recommendations and guidelines. Escalating the statin dose might not always correlate with efficacy, and it also limits the treatment options in patients with statin intolerance. Therefore, a combination of ezetimibe with a low to moderate statin dose seems to be a better option in terms of efficacy, without a compromise in tolerability; moreover, combination therapy also provides the physician and patient room for dose adjustments (eg, dose escalation if a low dose of statin is not efficient for achieving the treatment goal). These results also support the earlier finding that moderate-intensity statin therapy will yield better outcomes by reducing the LDL-C in Chinese patients with hypercholesterolemia, with an acceptable safety profile.

CONCLUSIONS

In this study, LDL-C levels were significantly improved with the FDCs of EZ10/AS10 and EZ10/AS20 versus escalating doses of atorvastatin (ie, AS20 and AS40) at week 12. These results may implicate clinical relevance of the atherosclerotic end points in the long term. Overall, the FDCs of EZ10/AS10 and EZ10/AS20 were well tolerated in these Chinese patients with hypercholesterolemia during the 12-week treatment period, with no new safety concerns. Further studies are required to evaluate the long-term clinical outcomes and tolerability of combination therapy (EZ/AS) for lowering LDL-C levels in patients with hypercholesterolemia.

DECLARATIONS

Xinru Ren is an employee of Merck Sharp & Dohme. The authors have indicated that they have no other conflicts of interest with regard to the content of this article.

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AUTHOR CONTRIBUTIONS

Drs. Juying Qian, Zhanquan Li, Xuelian Zhang, Jiyan Chen, Chunhua Ding, Ping Yang, and Junbo Ge were the principal investigators in this study and were also involved in conceiving, designing, or planning the study. Yan Liu and Dr. Miao Shi were involved in conceiving, designing, or planning the study, provided substantive suggestions, and performed data interpretation. Xinru Ren was the statistical lead and was primarily involved in statistical analyses and data interpretation. All of the authors contributed to the data interpretation, development, editing, and review of the manuscript; confirm that they have read the journal's position on issues involved in ethical publication; and affirm that this report is consistent with those guidelines.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinthera.2022.08.013.

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