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ORIGINAL RESEARCH

Efficacy and Safety of Single-Pill Combination of Rosuvastatin and Ezetimibe in Chinese Patients with Primary Hypercholesterolemia Inadequately Controlled by Statin Treatment (ROZEL): A Randomized, Double-Blind, Double Dummy, Active-Controlled Phase 3 Clinical Trial

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ABSTRACT

Introduction: Many patients with primary hypercholesterolemia do not achieve their plasma low-density lipoprotein cholesterol (LDL-C) goals with statin alone under a recommended dose of statin (e.g., 10 mg rosuvastatin) in China. The objective of this phase III study was to evaluate the efficacy and safety of a new single-pill combination (SPC) of rosuvastatin 10 mg/ezetimibe 10 mg (R10/E10) in this population.
Methods: This was a randomized, double-blind, double-dummy, active-controlled study in patients with primary hypercholesterolemia inadequately controlled with statin alone. The participants were randomized 1:1 to receive SPC R10/E10 or R10. The primary objective was to demonstrate the superiority of SPC R10/E10 vs. R10 in reducing the LDL-C levels after 8 weeks.
Results: This trial randomized 305 participants to SPC R10/E10 (n = 153) and R10 (n = 152). The superiority of SPC R10/E10 over R10 was demonstrated with the least square (LS) mean difference of percent change in LDL-C from baseline to week 8: − 13.85% (95% confidence interval [CI] − 20.15% to − 7.56%, $P < 0.0001$). The proportion of participants who achieved the LDL-C target (< 2.6 mmol/l) at week 8 was larger with SPC R10/E10 (n = 80, 54.1%) than with R10 (n = 42, 29.2%) (Odds ratio = 2.80, 95% CI 1.70 to 4.61, $P < 0.0001$). No unex-

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pected safety findings were reported.
Conclusion: The results suggest that SPC R10/E10 improve LDL-C reduction and goal achievement in Chinese patients with primary hypercholesterolemia not adequately controlled on statin therapy, without new safety findings.
Trial Registration: ClinicalTrials.gov (NCT04669041).

Keywords: Cardiovascular disease; Ezetimibe; Primary hypercholesterolemia; Rosuvastatin; Single-pill combination

Key Summary Points

Why carry out this study?

Many patients with primary hypercholesterolemia do not achieve their low-density lipoprotein cholesterol (LDL-C) goals with a recommended dose of statin (e.g., 10 mg rosuvastatin) in China.

Previous studies have demonstrated the synergistic lipid-lowering effect of ezetimibe and statins.

This phase III study was designed to compare the efficacy and safety of single-pill combination (SPC) of rosuvastatin 10 mg/ezetimibe 10 mg (R10/E10) vs. rosuvastatin 10 mg (R10) in Chinese patients with primary hypercholesterolemia inadequately controlled by statin alone.

What was learned from the study?

Compared with R10, SPC R10/E10 demonstrated superiority in LDL-C reduction without unexpected safety profile in patients with primary hypercholesterolemia who were not adequately controlled by statin therapy.

The SPC R10/E10 improved LDL-C target achievement without new safety findings in patients with primary hypercholesterolemia who were not adequately controlled by statin therapy.

INTRODUCTION

Over the past 20 years, as western lifestyle habits have become more prevalent in China, blood cholesterol levels in Chinese individuals have increased each year. The 2015 CANCDS (Chinese Adults Chronic Diseases and Nutrition Surveillance) results showed that the weighted means of total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) significantly increased linearly from 3.93, 1.12, and 2.12 mmol/l in 2002 to 4.63, 1.47, and 2.87 mmol/l in 2015, respectively [1]. In China, depending upon the patient populations and risk categories, only 3–39% of the patients with high LDL-C levels receive lipid-lowering therapies, of which only 13–65% achieve a relatively satisfactory level of control [2–6]. Hypercholesterolemia is a high-risk factor in the development of cardiovascular diseases (CVDs), and the risk of CVDs in patients with hypercholesterolemia is nearly doubled compared with healthy individuals [7]. It is estimated that the increase in serum cholesterol levels in the population will lead to an increase of approximately 9.2 million cardiovascular events in China from 2010 to 2030 according to CHD Policy Model-China [8]. Therefore, optimizing the treatment of hypercholesterolemia is imperative to reduce cardiovascular events and premature death [7].

Lipid-lowering therapies like statins decrease TC and LDL-C [9–11] and reduce the risk of CVD [12]. Among different available statins, rosuvastatin ranks first in decreasing LDL-C [13–15]. Although the cardiovascular benefits of statins have been extensively studied, current data suggest that some statins cause more adverse effects and that higher doses may be more harmful to patients [16]. Statin intolerance (e.g., liver dysfunction and myopathy) was more frequently reported in Chinese patients than in European patients [17], which might be attributed to the different statin pharmacokinetics between Asians and Caucasian, leading to higher plasma concentrations over time in Asians [18, 19]. Nevertheless, due to the limited effectiveness of low-moderate doses or

intolerance to high statin doses, combination therapy with a moderate dose of statins and non-statin drugs should be considered for Asians [20, 21].

Ezetimibe is a non-statin lipid-lowering drug that lowers LDL-C by preventing the intestinal absorption of cholesterol and has a synergistic lipid-lowering effect with statins [22, 23]. Ezetimibe monotherapy in patients with hypercholesterolemia reduces LDL-C by 15–22%, and adding ezetimibe to a previous statin therapy reduces LDL-C by a further 21–27% [24]. The European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) guidelines on dyslipidemia recommend the addition of ezetimibe to statin therapy for patients with dyslipidemia not adequately controlled with statin monotherapy [25]. While the combination of drugs can improve cholesterol level reduction, it also raises the issue of adherence. Fixed-dose single-pill combination (SPC) of statin and ezetimibe improves patients' drug adherence [26], and SPC reduces the possibility of missed medication or drug discontinuation by making the medication more convenient [27]. Nevertheless, there are few studies on the SPC of rosuvastatin 10 mg/ezetimibe 10 mg (R10/E10) in patients who are not adequately controlled by statin alone.

Therefore, this double-blind, double-dummy, randomized, active-controlled, phase 3 clinical trial aimed to compare the efficacy and safety of the SPC R10/E10 vs. rosuvastatin 10 mg (R10) in Chinese patients with primary hypercholesterolemia inadequately controlled by statin alone.

METHODS

Study Design and Study Population

This study was a phase III double-blind, double-dummy, randomized, active-controlled, parallel clinical trial. The study was approved by ethics committees of all institutions (Supplementary Table S1) and conducted according to the tenets of the Declaration of Helsinki and the Good Clinical Practices. The master ethics committee at the main center (Beijing Anzhen Hospital) is Anzhen Hospital clinical study Ethic Committee (Approval number: 2020-02ID). All participants involved in this study provided written informed consent. The trial was registered with ClinicalTrials gov (NCT04669041).

The inclusion criteria for entering the study were (1) $\geq$ 18 years of age, (2) primary hypercholesterolemia, (3) male or female who is neither pregnant nor breastfeeding, (4) LDL-C levels inadequately controlled (> 2.6 mmol/l [100 mg/dl] and $\leq$ 4.9 mmol/l [190 mg/dl]) under a stable dose of R10 or equivalent dose of other statins for at least 4 weeks prior to the screening visit, without any other lipid-modifying therapy, and (5) signed the informed consent form.

The key exclusion criteria were (1) homozygous familial hypercholesterolemia, (2) LDL-C plasmapheresis treatment within 2 months prior to screening, (3) history of cardiac or cerebrovascular diseases or any related surgical intervention within 3 months, or (4) any clinically relevant endocrine disease affecting plasma lipids levels. A full list of the exclusion criteria is included in Supplementary Table S2.

This study comprised a 2-week screening period, a 4-week open-label run-in period, an 8-week randomized, double-blind period, and a 2-week safety follow-up period.

After screening, the eligible participants entered a 4-week open-label run-in period during which they were required to discontinue their ongoing lipid-lowering drug and receive oral R10 once daily. The participants who were not adequately controlled [LDL-C $\geq$ 2.6 mmol/l (100 mg/dl) and $\leq$ 4.9 mmol/l (190 mg/dl)] at the qualifying pre-randomization visits would enter the randomized, double-blind, double-dummy period. The participants were randomized 1:1 to receive one SPC R10/E10 tablet and one R10 placebo capsule daily or one R10 capsule and one SPC R10/E10 placebo tablet daily for 8 weeks, respectively. The participants were followed for safety for 2 weeks after the end of the double-blind period.

All participants were required to follow a stable diet (NCEP-ATPIII TLC diet or equivalent) throughout the trial and discouraged from drinking alcohol 48 h prior to each visit or performing strenuous exercise 24 h prior to each blood collection for clinical laboratory tests.

The randomization and the intervention allocation were performed through interactive response technology. Neither the investigators nor the participants knew the allocation. The R10 and corresponding placebo pills were packaged in identical capsules, while SPC R10/E10 and the corresponding placebo were provided as identical tablets.

Study Outcomes

The primary endpoint of this study was the percent change in LDL-C from baseline to week 8. The secondary endpoints included (1) the proportion of participants who achieved the target LDL-C level (< 2.6 mmol/l) at week 8, (2) the percent change in LDL-C from baseline to week 4, and (3) the percent changes in TC, TG, and high-density lipoprotein cholesterol (HDL-C) from baseline to weeks 4 and 8. The safety assessments included treatment-emergent adverse events (TEAEs), laboratory tests, and vital signs.

Participants attended the center seven times during the study: screening visit, run-in visit, qualifying visit, baseline visit (randomization, week 0), on-site visit (week 4), end of treatment visit (week 8), and end of study visit (week 10). LDL-C, TC, TG, and HDL-C levels were measured at the screening visit, the qualifying visit (except for TC), and at weeks 0, 4, and 8 during the double-blind period. The evaluation of adverse events (AEs), vital signs, and concomitant medication evaluation was conducted at all visits. Laboratory tests for safety assessments were performed at screening visit, baseline visit, week 8, and end of study visit if only in case of relevant abnormality at the end of treatment visit in the Investigator's opinion.

Statistical Analysis

A total of 148 participants per treatment arm (296 total) were required to achieve a power of 90% to detect a difference in percent change from baseline to week 8 in measured LDL-C between SPC R10/E10 and R10 using a two-sample *t*-test with a two-sided 5% α and assuming a common standard deviation (SD) of 20% and a 10% drop-out. Assuming drop-out rates of 55% in the run-in period, approximately 658 participants were planned to be included in the run-in period.

The primary efficacy analysis population was the modified intent-to-treat (mITT) population, defined as all randomized participants with an evaluable primary efficacy endpoint. The primary efficacy endpoint was considered evaluable when the baseline and at least week 4 or week 8 measured LDL-C values were available. The baseline was the last available measured LDL-C value obtained up to randomization (Supplementary Material S3). The safety population for the open-label run-in period included all participants who received at least one dose of R10. The safety population for the double-blind period included all randomized participants who received at least one dose of SPC R10/E10 or R10.

The percent change from baseline in measured LDL-C at week 8 was analyzed in the mITT population using a mixed effect model with repeated measures (MMRM). This model provided least square (LS) mean estimates at week 8 for both groups and the differences of these estimates for the primary pairwise comparison with corresponding standard errors (SEs) and 95% confidence intervals (CIs). In the primary efficacy analysis, missing data were considered using the MMRM relied on the missing-at-random (MAR) assumption. The analysis of covariance (ANCOVA) assuming not-missing-at-random (NMAR) was performed as the sensitivity analysis with missing data at week 8 imputed by control-based multiple imputations.

A hierarchical testing procedure in a prioritized order was used to test the key secondary endpoints for the multiplicity consideration. The proportions of patients achieving the LDL-C target (< 2.6 mmol/l) at week 8 were analyzed by logistic regression adjusted on the baseline measured LDL-C value. The percent changes in LDL-C from baseline to week 4 and other lipid levels from baseline to week 4 and week 8 were expressed as least square mean for the continuous variables with a normal distribution (i.e., lipids other than TG) using the MMRM model as for the analysis of the primary endpoint, and

continuous variables with a nonnormal distribution (i.e., TG) were analyzed by robust regression adjusted for baseline TG. SAS 9.4 was used for statistical analysis. Two-sided *P* values < 0.05 were considered statistically significant.

RESULTS

Participant Disposition and Baseline Characteristics

This trial screened 834 patients with hypercholesterolemia; 322 patients (38.6%) were ineligible. Therefore, 512 participants were enrolled in the run-in period. Finally, 305 participants were randomized (153 participants in the SPC R10/E10 group and 152 in the R10 group). Among them, one (0.7%) participant in the R10/E10 group was randomized but not exposed to the double-blind intervention. The percentage of participants who discontinued the double-blind intervention was lower in the SPC R10/E10 group (six participants [3.9%]) than in the R10 group (nine participants [5.9%]). The most common reason for discontinuation was consent withdrawal (four [2.6%] in the SPC R10/E10 group and six [3.9%] in the R10 group). Two (1.3%) participants in the SPC R10/E10 group and one (0.7%) participant in the R10 group prematurely discontinued due to AEs (Fig. 1); the details of participant disposition are shown in Supplementary Table S4.

A total of 506 participants were included in the run-in safety population. Of the 153 randomized participants in the R10/E10 group and 152 randomized participants in the R10 group during the double-blind treatment period, 148 (96.7%) in the R10/E10 group and 144 (94.7%) in R10 group were included in the mITT population. The double-blind safety population included 152 participants in each study intervention group (Supplementary Table S5).

All randomized participants in both groups were Asian, the median age was 57 (range 25–80) years, 56.4% of the participants were female, and the average body mass index (BMI) was 25.11 ± 3.31 kg/m^2. The baseline characteristics were generally similar between the two treatment groups. All participants had primary hypercholesterolemia at baseline and received statin or xuezhikang treatment within 2 months prior to screening. The mean duration of hypercholesterolemia was 3.53 ± 4.36 years. The last statin treatment prior to screening was R10 ($n = 153$, 50.2%) or atorvastatin 20 mg ($n = 138$, 45.2%) (Table 1). Supplementary Tables S6 and S7 present the characteristics of the randomized population.

Primary Endpoint

The LS mean percent change in LDL-C from baseline to week 8 of the SPC R10/E10 group was − 21.98% (95% CI − 26.35%, − 17.60%), and that of the R10 group was − 8.12% (95% CI − 12.63%, − 3.61%). The LS mean difference in the percent changes in LDL-C of the SPC R10/E10 group over the R10 group was − 13.85% (95% CI − 20.15%, − 7.56%, $P < 0.0001$) (Fig. 2). The results of the sensitivity analysis with LS mean difference − 13.73% (95% CI − 20.01%, − 7.46%, $P < 0.0001$) are consistent with the primary analysis.

The analyses were performed on the primary endpoint across the subgroups of age, sex, baseline BMI, and diabetes mellitus. All results showed a consistent trend of greater percent change in LDL-C from baseline to week 8 in the SPC R10/E10 group than in the R10 group (Fig. 3). Supplementary Table S8 presents the percent changes in LDL-C for the mITT population.

Secondary Endpoints

Since statistical significance was reached for the primary efficacy endpoint, hierarchical testing was applied to the key secondary endpoints, as shown in Supplementary Tables S9. The statistical significance was demonstrated for the first five (out of eight) key secondary endpoints.

Statistical significance was not reached for the percent change in TG from baseline to Week 4. Consequently, the following two key secondary endpoints were not tested: percent changes in HDL-C from baseline to week 8 and percent changes in HDL-C from baseline to

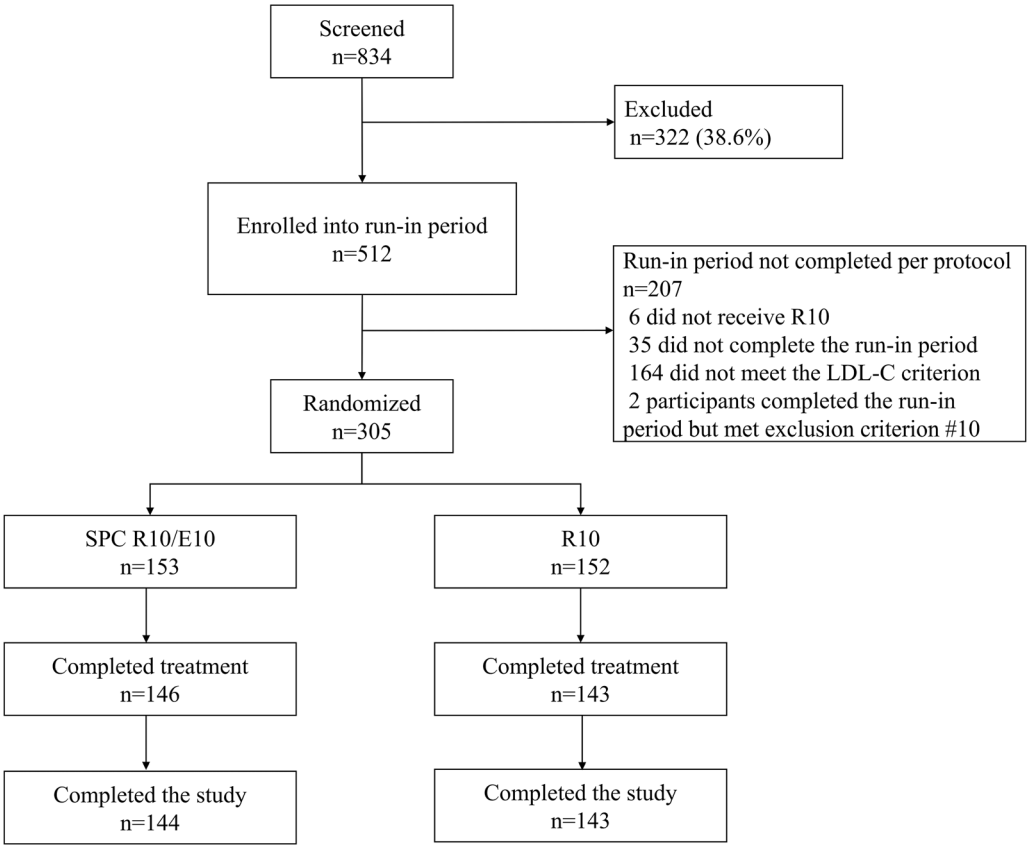

Fig. 1 Study flowchart. Completion of study, completion of follow-up period regardless of continuing the IMP; *E10* ezetimibe 10 mg, *IMP* investigational medicinal product, *R10* rosuvastatin 10 mg, *SPC* single-pill combination, *LDL-C* low-density lipoprotein cholesterol; exclusion criterion #10, any patient deemed unfit for participation by the investigators

week 4. The *P*-values for these two endpoints are presented for descriptive purposes only (Supplementary Table S9).

The proportion of participants achieving the LDL-C target at week 8 in the SPC R10/E10 group ($n = 80$, 54.1%) was significantly higher than in the R10 group ($n = 42$, 29.2%) (OR = 2.80, 95% CI 1.70, 4.61, $P < 0.0001$) (Fig. 4). The LS mean percent change in LDL-C from baseline to week 4 of the SPC R10/E10 group (− 22.90%, 95% CI − 26.86%, − 18.94%) was significantly higher than in the R10 group (− 8.50%, 95% CI − 12.51%, − 4.49%), with an LS mean difference of − 14.40% (95% CI − 20.04%, − 8.75%, $P < 0.0001$) (Fig. 2). The LS mean percent change in TC from baseline to week 4 between the SPC R10/E10 and R10 groups was significantly different (LS mean difference: − 10.22%, 95% CI − 13.98%, − 6.46%, $P < 0.0001$) and from baseline to week 8 (LS mean difference: − 9.77%, 95% CI − 13.70%, − 5.85%; $P < 0.0001$) (Fig. 5A). The percent changes in TG showed no significant difference at week 4 (adjusted mean percent change: − 5.21%, 95% CI − 12.17%, 1.74%, $P = 0.1420$) but were significant at week 8 (adjusted mean percent change: − 7.02%, 95% CI − 14.01%, − 0.04%, $P = 0.0488$) (Fig. 5B). There were increases in HDL-C from baseline to week 4 in the SPC R10/E10 group (LS mean percent change: 2.96%) and in the R10 group (LS mean percent change: 0.79%), with LS mean difference for the SPC R10/E10 group vs. R10 group of 2.17% (95% CI − 1.14% to 5.47%; $P = 0.1978$); a similar tendency was observed at week 8, with an LS mean difference for the SPC R10/E10

Table 1 Baseline characteristics

	SPC R10/E10 group (n = 153)	R10 group (n = 152)	Total (n = 305)
Age (years), mean (SD)	54.6 (11.9)	55.6 (11.6)	55.1 (11.8)
Sex (male), *n* (%)	64 (41.8)	69 (45.4)	133 (43.6)
Weight (kg), mean (SD)	67.4 (12.1)	67.3 (12.3)	67.4 (12.2)
BMI (kg/m^2), mean (SD)	25.169 (3.235)	25.051 (3.402)	25.110 (3.314)
BMI category, *n* (%)			
< 25	74 (48.4)	72 (47.4)	146 (47.9)
25–30	68 (44.4)	72 (47.4)	140 (45.9)
30–35	10 (6.5)	5 (3.3)	15 (4.9)
≥ 35	1 (0.7)	3 (2.0)	4 (1.3)
Duration of hypercholesterolemia (years), mean (SD)	3.40 (4.25)	3.66 (4.48)	3.53 (4.36)
Cardiovascular medical history, *n* (%)			
Hypertension	58 (37.9)	62 (40.8)	120 (39.3)
Diabetes mellitus	17 (11.1)	20 (13.2)	37 (12.1)
Myocardial infarction	11 (7.2)	11 (7.2)	22 (7.2)
Stroke	22 (14.4)	24 (15.8)	46 (15.1)
Peripheral artery disease	4 (2.6)	1 (0.7)	5 (1.6)
Heart failure	2 (1.3)	1 (0.7)	3 (1.0)
Last statin or xuezhikang treatment prior to screening, *n* (%)			
Rosuvastatin 10 mg	80 (52.3)	73 (48.0)	153 (50.2)
Atorvastatin 20 mg	65 (42.5)	73 (48.0)	138 (45.2)
Fluvastatin 80 mg	1 (0.7)	1 (0.7)	2 (0.7)
Pitavastatin 4 mg	0	2 (1.3)	2 (0.7)
Pravastatin 40 mg	5 (3.3)	3 (2.0)	8 (2.6)
Simvastatin 40 mg	1 (0.7)	0	1 (0.3)
Xuezhikang 1.2 g	1 (0.7)	0	1 (0.3)

BMI body mass index, *R10* rosuvastatin 10 mg, *E10* ezetimibe 10 mg, *SD* standard deviation, *SPC* single-pill combination

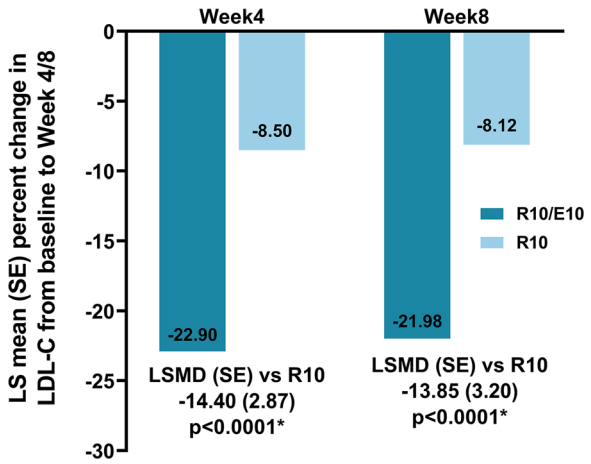

Fig. 2 Least square (LS) mean (SE) of percent changes in low-density lipoprotein cholesterol (LDL-C) from baseline to week 4 and week 8. *LDL-C* low-density lipoprotein cholesterol, *LS Mean* least square mean, *LSMD* least square mean differences, *SE* standard error, *R10* rosuvastatin 10 mg, *E10* ezetimibe 10 mg. The *P* value is followed by a * if statistically significant according to the fixed hierarchical approach used to ensure a strong control of the overall type-I error rate at the 0.05 level

group vs. the R10 group of 2.63% (95% CI − 0.63% to 5.89%; $P = 0.1131$) (Fig. 5C).

Safety

The mean duration of drug exposure during the double-blind period was similar in the two groups (SPC R10/E10 group: 56.1 days; R10 group: 55.2 days). The mean compliance was 99.20% in the SPC R10/E10 group and 98.63% in the R10 group during the double-blind period.

In the run-in period, the most common TEAEs were upper respiratory tract infections (1.0%). Only one AE of special interest (AESI, Supplementary Material S10) (elevated CK) was reported in the run-in period. One participant experienced the SAE of a transient ischemic attack, and another experienced two SAEs: a road traffic accident and a forearm fracture. In the run-in period, all treatment-emergent SAEs were irrelevant to the study drugs.

In the double-blind period, 44 participants (28.9%) in the SPC R10/E10 group and 35 participants (23.0%) in the R10 group reported at least one TEAE. The most common TEAEs are listed in Table 2. Ten (6.6%) participants from the SPC R10/E10 group and 15 (9.9%) from the R10 group reported treatment-related TEAEs. The most commonly reported TEAEs presented as high level terms (HLTs) were upper respiratory tract infections (4.6%), carbohydrate tolerance analyses (3.9%), and product administration errors and issues (2.6%) in the SPC R10/E10 group and hepatobiliary function diagnostic procedures (5.3%), upper respiratory tract infections (3.3%), and skeletal and cardiac muscle analyses (3.3%) in the R10 group. Only two (1.3%) participants experienced treatment-emergent AESI during the double-blind period in the R10 group, which was CK increase (CK > 3 × ULN), and it was related to double-blind investigational medical products (IMPs). Three participants (2.0%, corresponding AEs benign breast tumor, coronary sclerosis, and sudden cardiac death) in the SPC R10/E10 group and three in the R10 group (2.0%, corresponding AEs pneumonia, cerebral infarction, and unstable angina) experienced SAEs during the double-blind period. These SAEs were considered irrelevant to the double-blind IMPs.

Two participants in the SPC R10/E10 group (1.3%, corresponding AEs subacute thyroiditis and sudden cardiac death) and one in the R10 group (0.7%, corresponding AE elevated CK) experienced TEAEs leading to treatment discontinuation during the double-blind period. One participant in the SPC R10/E10 group (0.7%) died because of sudden cardiac death with unknown onset, which was considered unrelated to the IMP. No participant died during the run-in period.

DISCUSSION

This trial demonstrated the superiority of SPC R10/E10 over R10 in reducing LDL-C in Chinese patients with primary hypercholesterolemia inadequately controlled by statin. The results showed that SPC R10/E10 was significantly more effective in reducing LDL-C after 4 and 8 weeks compared with R10 monotherapy and allowed more participants to achieve the LDL-C

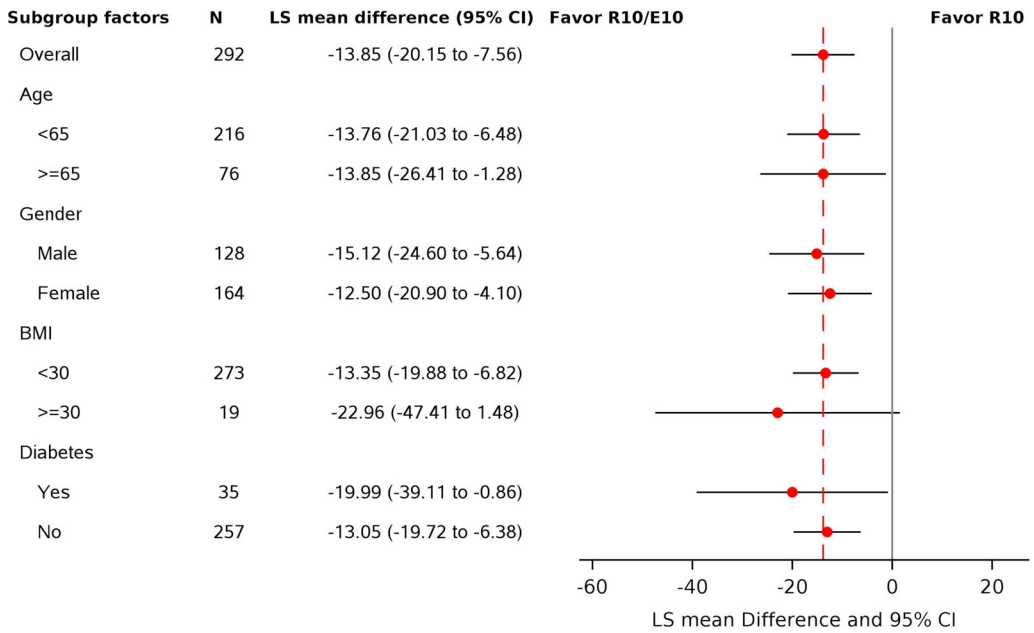

Fig. 3 Percent changes in low-density lipoprotein cholesterol (LDL-C) from baseline to week 8: subgroup analysis. *LDL-C* low-density lipoprotein cholesterol, *LS Mean* least square mean, *SE* standard error, *CI* confidence interval, *R10* rosuvastatin 10 mg, *E10* ezetimibe 10 mg, *BMI* body mass index

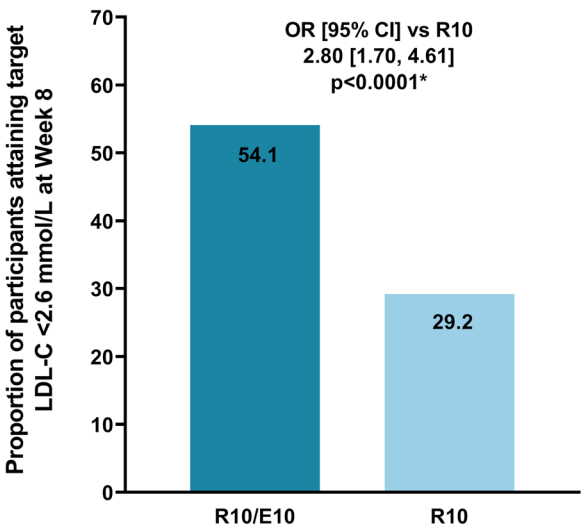

Fig. 4 The proportion of participants attaining target LDL-C < 2.6 mmol/l at week 8. *LDL-C* low-density lipoprotein cholesterol, *OR* odds ratio, *CI* confidence interval, *R10* rosuvastatin 10 mg, *E10* ezetimibe 10 mg. The *P* value is followed by a * if statistically significant according to the fixed hierarchical approach used to ensure a strong control of the overall type-I error rate at the 0.05 level

target at 8 weeks. In addition, SPC R10/E10 had a significant advantage in reducing TC after 4 and 8 weeks, and the reduction in TG after 8 weeks of SPC R10/E10 was statistically significant. SPC R10/E10 reduced TG after 4 weeks and increased HDL-C after 4 and 8 weeks, but the differences did not appear statistically significant. There were no unexpected safety findings or notable differences across treatment groups regarding the TEAEs.

The LDL-C reduction in patients with hypercholesterolemia of all R/E combinations were superior to R10 in the ROSETTE trial [28], supported by a similar clinical trial [29]. Furthermore, in patients with primary hypercholesterolemia inadequately controlled by statin, a better reduction in LDL-C level was achieved with R/E compared with R10 (− 27.7% vs. − 16.9%) in the IN-CROSS trial [30]. In the global RCT study of SPC R/E, SPC R40/E10 and SPC R20/E10 significantly reduced LDL-C than R40 in patients with hypercholesterolemia inadequately controlled by statin who were at very high risk of CVD [31]. Similarly, in the present trial, the percent changes in LDL-C of the SPC R10/E10 were significantly greater than

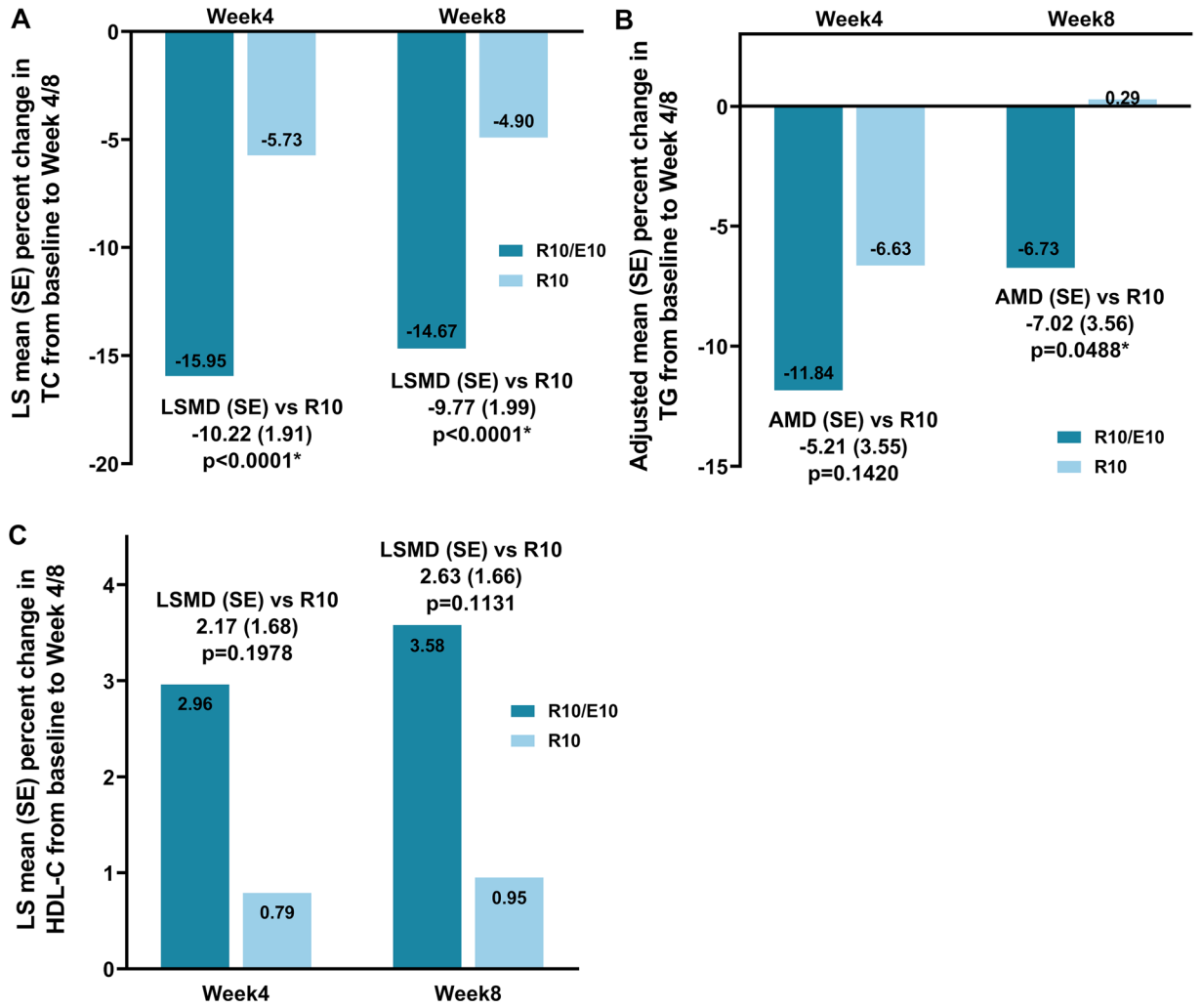

Fig. 5 The percent changes of TC (**a**) TG (**b**) and HDL-C (**c**) from baseline to week 4 and week 8. *LS Mean* least square mean, *LSMD* least square mean differences, *SE* standard error, *R10* rosuvastatin 10 mg, *E10* ezetimibe 10 mg, *TC* total cholesterol, *AMD* adjusted mean difference, *TG* triglyceride, *HDL-C* high-density lipoprotein cholesterol. The *P* value is followed by a * if statistically significant according to the fixed hierarchical approach used to ensure a strong control of the overall type-I error rate at the 0.05 level

in the R10 groups, with a difference of − 13.85%, showing a consistent efficacy with previous trials. Nevertheless, comparison with western trials must be performed cautiously since non-Asian patients can tolerate higher doses of statins than Asians [18, 19]. From these findings [28, 29, 31, 32], the SPC formulation of SPC R10/E10 could effectively lower LDL-C levels and might contribute to lightening the burden of cardiovascular events.

The achievement of the LDL-C target at week 8 was similar between the SPC R10/E10 (66.0%) and R20 (55.7%) groups at week 6 in the global trial [31]; the present study reported a significantly higher proportion of participants achieving the LDL-C target in the SPC R10/E10 group (54.1%) than in the R10 group (29.2%), similar to the R20 group in the global trial (55.7%) [31], and demonstrated in the I-ROSETTE trial (100% with R/E and 83.3% with rosuvastatin) [28]. Similar results were observed in the EXPLORER trial (R40/E10 94.0% vs. R40 79.1%) [33], MRS-ROSE trial (R/E 94.1% vs. rosuvastatin 86.3%) [34], Yang et al. trial [35]

Table 2 Treatment-emergent adverse events (TEAEs) during the double-blind period

n (%)	SPC R10/E10 (*n* = 152)	R10 (*n* = 152)
Any TEAEs	44 (28.9)	35 (23.0)
Treatment-related	10 (6.6)	15 (9.9)
Serious	3 (2.0)	3 (2.0)
Serious treatment-related	0	0
Death	1 (0.7)	0
Discontinuation due to TEAEs	2 (1.3)	1 (0.7)
Treatment-related	0	0
Serious	1 (0.7)	0
Serious treatment-related	0	0
TEAEs occurring ≥ 2% of patients (HLTs)		
Upper respiratory tract infections	7 (4.6)	5 (3.3)
Carbohydrate tolerance analyses	6 (3.9)	3 (2.0)
Product administration errors and issues	4 (2.6)	2 (1.3)
Hepatobiliary function diagnostic procedures	3 (2.0)	8 (5.3)
Skeletal and cardiac muscle analyses	1 (0.7)	5 (3.3)
Any AESI	0	2 (1.3)
Alanine aminotransferase increase > 3 × ULN	0	0
Creatine kinase increase > 3 × ULN	0	2 (1.3)
Pregnancy	0	0
Symptomatic overdose of study drug	0	0

TEAE treatment-emergent adverse event, *HLT* higher-level term, *AESI* adverse event of special interest, *ULN* upper limit of normal, *R10* rosuvastatin 10 mg, *E10* ezetimibe 10 mg, *SPC* single-pill combination

(R/E 87–95% vs. ezetimibe 64–87%), and Lee et al. trial [29] (R2.5/E10 100% vs. R2.5 47.6% and R5 65.2%).

In addition, the decrease in TC levels was significantly greater in the SPC R10/E10 group than in the R10 group. The HDL-C levels showed non-statistically significant numerical increases. The TG levels were significantly decreased at week 8 only (the decrease at week 4 was not statistically significant). The results could be explained by the fact that ezetimibe can affect the TG levels significantly under relatively long treatment time. The mechanism of action on TG decrease with ezetimibe is probably based on promoting the expression of PPARγ protein (a lipid storage promoting protein) and downregulating the expression of PPARα and β proteins (lipid mobilization promoting proteins), thereby promoting TG storage [36]. Similar results were also reported in previous studies [29, 31]. In a similar global trial, the decrease in TC was greater in the R/E group than in the rosuvastatin group in very-high-risk participants, while the difference in the changes in TG were not statistically significant [31]. In I-ROSETTE, compared with R, SPC R/E led to higher decreases in TC, but a numeric decrease in TG and an increase in HDL-C were not statistically significant [28]. Similar results were reported by Lee et al. [29]. A previous study showed that the SPC R/E had a more significant impact on the cholesterol levels of patients with diabetes [34], but another study of a non-fixed dose combination of a statin with E10 showed no difference in LDL-C reduction with or without diabetes [37]. The subgroup analysis of this study showed that the combination had a better absolute numerical efficacy in patients with diabetes. Moreover, the benefits of the R + E combination therapy for patients with diabetes still need more trials for a further validation.

Ezetimibe is not metabolized by cytochromes, and the risk of interactions with other drugs is greatly reduced [22]. A global RCT study of SPC R/E proved the safety of the SPC of high-dose statin (R20) and E10, and there were no new AE signals [31]. In this study, compared with R10, the SPC R10/E10 formulation showed no new AE signals, similar to the previous trials.

The difference in the rate of AE-related discontinuation between the SPC R10/E10 group and the R10 group was similar (1.3% vs. 0.7%). Whether SPC R10/E10 therapy has a higher safety benefit than single-drug rosuvastatin therapy needs to be validated by future clinical trials. Still, this study suggests a good safety of the SPC R10/E10 formulation.

A previous study of the adherence to a SPC lipid-lowering therapy showed that compared with patients with a multi-pill combination (MPC) therapy; those with SPC were 32% more likely to adhere to treatment [38]. In a retrospective study, compared with patients with dual-pill combination therapy of statin plus E, those with the SPC therapy were 87% more likely to have a high medication adherence (the study defined adherence as low, intermediate, and high based on < 25%, 25–75%, and > 75% of proportion of days covered) [39]. SPC was also associated with a higher 1-year adherence rate (SPC: 84.9%; MDC: 76%; HR = 0.62, 95% CI 0.55–0.72) [40]. SPC has several advantages over multi-pill combination (MPC), such as convenience, high adherence, reduced production cost, and reduced possibility of missed or incorrect medication [38–40].

This study had limitations. As per the study design, this study was only performed in Chinese participants, and whether the results can be generalized to other Asian populations remains unknown. Second, additional studies are necessary in the future to define the exact patient populations who could benefit from the SPC R10/E10, including patients with high-risk or very high-risk factors. Finally, the R10 dose was selected in the present study for the following reasons: Some studies showed that the rate of statin exposure in Asians (in Japan, China, and Southeast Asia) is twice that in Caucasians [18, 19]; the guidelines recommend that Chinese patients with hypercholesterolemia adopt low- or moderate-dose R10 as conventional therapy [21]. Thus, the number of Chinese patients receiving R20 therapy is relatively small. Therefore, R10 will be a reasonable choice as the control group with less risk and better enrollment for Chinese participants. Whether R20 could be a better choice might be determined in future studies in China.

CONCLUSION

The SPC R10/E10 improves the LDL-C reduction with a favorable safety profile in participants with primary hypercholesterolemia not adequately controlled on statin therapy in China, compared with R10. Improving LDL-C target achievement in Chinese individuals without adequate control of statin therapy might reduce the burden of cardiovascular disease in China. Overall, the study demonstrated the superiority of SPC R10/E10 over R10 in LDL-C reduction after 8 weeks of treatment without unexpected safety findings.

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Data Availability. All data generated or analyzed during this study are included in this published article and supplementary information files.

Declarations

Conflict of Interest. Min Wang, Shifang Mei, Genevieve Garon, and Yanzhen Wu are employees of Sanofi, and may hold shares and/or stock options in the company' for the Sanofi employees. Qiaoli Su, Ying Liu, Guogang

Zhang, Li Xu, Qiang Lv and Changsheng Ma all have no conflict of interests.

Ethical Approval. The study was approved by ethics committees of all institutions (Supplementary Table S1) and conducted according to the tenets of the Declaration of Helsinki and the Good Clinical Practices. The master ethics committee at the main center (Beijing Anzhen Hospital) is Anzhen Hospital clinical study Ethic Committee (Approval number: 2020-02ID). All participants involved in this study provided written informed consent.

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