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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Supplementary materials

Supplementary Table S1. Full list of Ethical approvals

Names of the ethics committee	Approval number
Clinical Study Ethics Committee of Anzhen Hospital (Master)	2020-15
Medical Ethics Committee of Tianjin People's Hospital	2020-18
Ethics Committee of Affiliated Hospital of Xuzhou Medical University	XYFY2020-YL099-01
Affiliated Hospital of Guangdong Medical University Institutional Review Board Ethic Committee	PJ2020-055
Drug Clinical Trial Ethics Committee of Inner Mongolia Autonomous Region People's Hospital	YWLCSYLL-2020-022-01
Ethics Committee of Affiliated Hospital of Inner Mongolia Medical University	NO.SY (2020057)
Drug Clinical Trial Ethics Committee of The Third People's Hospital of Hubei Province	HBSDSRMYY-2020-A004-01
Drug/Device ClinicalTrial Ethics Committee of Siping Central People's Hospital	2020-Y-013-01
Clinical Trial Ethics Committee of Affiliated Hospital of Jiangsu University	2020-28
Drug Clinical Trial Ethics Committee of Jilin City Central Hospital	PJ-202004
Ethics Committee of Dalian Municipal Central Hospital	2020-050-01
Drug Clinical Trial Rthics Committee of Yueyang Central Hospital	2020-011
Medical Ethics Committee of Central Hospital Affiliated To Shandong First Medical University	2020-107-02
Medical Ethics Committee of Beijing Pinggu Hospital	2020-011-01
Medical Ethics Committee of the First Affiliated Hospital of Xi 'an Jiaotong University	2020-117
Medical Ethics Committee of the Second Affiliated Hospital of Bengbu Medical College	2020-08
Drug Clinical Trial Ethics Committee of East Hospital Affiliated To Tongji University	2020-068
Ethics Committee of Hainan General Hospital	2020-179
Clinical Trial Ethics Committee of Baotou Central Hospital	2020-YW-13
Ethics Committee of People's Hospital of Liaoning Province	2020-HS008
Clinical Trial Ethics Committee of Wuhan Puren Hospital	2020-004
Drug Clinical Trial Ethics Committee of Zibo Central Hospital	2020-013
Clinical Trial Ethics Committee of West China Hospital, Sichuan University	2020-71
Drug/Medical Device Clinical Trial Ethics Committee of Jilin Provincial People's Hospital	2020-Y-016-1

Ethics Committee of Union Hospital Affiliated to Tongji Medical College, Huazhong University of Science and Technology	2020-0324
Ethics Committee of the Third Xiangya Hospital, Central South University	20221
Ethics Committee of Tianjin Fourth Central Hospital	SZXLL-2020-H008
Clinical Trial Ethics Committee of the Second People's Hospital of Nanning	2020016
Clinical Trial Ethics Committee of Yanbian University Affiliated Hospital	2020-010-01
Ethics Committee of Chongqing People's Hospital	S 2020-017-01
Clinical Trial Ethics Committee of Lishui People's Hospital	2020-010-01
Clinical Trial Ethics Committee of Yuncheng Central Hospital of Shanxi Province	2020-YW-030
Clinical Trial Ethics Committee of Drug Clinical Trials, Zhuzhou Central Hospital	ZZCHGCPEC2020015-01
Ethics Committee of Drug/Medical Device Clinical Trials, General Hospital of Ningxia Medical University	2020-YW-127
Ethics Committee of North Jiangsu People's Hospital	2020041
Ethics Committee of the Second Affiliated Hospital of Nanjing Medical University	2020-YW-025-LP-01
Ethics Committee of China-Japan Friendship Hospital, Jilin University	2020-2020092301
Ethics Committee of Beijing Friendship Hospital affiliated to Capital Medical University	2020-P1-046-01
Ethics Committee of Shaanxi Provincial People's Hospital	2020-Y011
Ethics Committee of Liuzhou People's Hospital	2020-020-01

Supplementary Table S2. Full list of exclusion criteria

Exclusion criteria
1) with homozygous familial hypercholesterolemia (FH)
2) received low-density lipoprotein cholesterol (LDL-C) plasmapheresis in the 2 months prior to the screening visit or planned to receive LDL-C apheresis
3) recently diagnosed (within 3 months prior to the screening visit) myocardial infarction(MI), unstable angina, myocardial revascularization (percutaneous coronary intervention[PCI], coronary artery bypass graft surgery [CABG]), transient ischemic attack (TIA), or stroke, carotid revascularization, endovascular procedure or surgical intervention for peripheral vascular disease.
4) planned to undergo scheduled PCI, CABG, carotid or peripheral revascularization during the study period
5) systolic blood pressure (SBP) >160 mmHg or diastolic blood pressure (DBP) >100 mmHg at study entry
6) history of congestive heart failure New York Heart Association (NYHA) class IIIb or IV within 12 months
7) any clinically relevant endocrine disease affecting blood lipids
8) uncontrolled or newly diagnosed diabetes mellitus at study entry [fasting blood glucose (FBG) >180 mg/dL or glycated hemoglobin (HbA1c) >9%]
9) history of cancer within 5 years, except treated basal cell or squamous cell skin cancer or in situ cervical cancer
10) any patient deemed unfit for participation by the investigators
11) known hypersensitivity reaction to statins or ezetimibe
12) current myopathy
13) history of statin-induced myopathy or rhabdomyolysis
14) current active liver disease
15) any contraindications to statins
16) not previously instructed on lipid-lowering drugs prior to the screening visit

17) systemic corticosteroids (unless used for adrenal/pituitary replacement therapy and with a stable dose for ≥6 weeks)

18) hormonal therapy or oral contraceptives, unless stable for ≥6 weeks

19) cyclosporine use

20) human immunodeficiency virus (HIV)-positive treated with protease inhibitors

21) received any investigational drugs within 1 month or five half-lives

22) fasting triglycerides (TG) >400 mg/dL, positive pregnancy test, serum Creatine Kinase (CK) >3 times the upper limit of normal value (ULN), hypo- or hyperthyroidism, estimated glomerular filtration rate <30 mL/min/1.73 m^2, or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the ULN

23) any patient institutionalized or imprisoned

24) impossible to randomize due to technical difficulties (e.g., homeless)

25) alcohol abuse

26) dependent on the sponsor or investigator

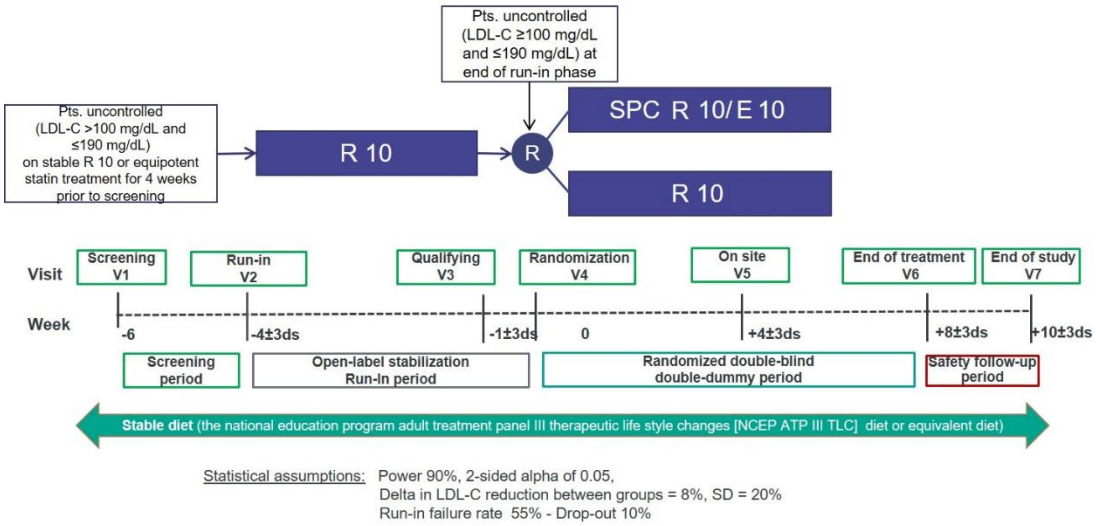
27) employees of the study site

28) any ethical conflict

29) sensitivity to any of the study interventions

Supplementary Material S3. Study design and visit windows of primary analysis

The baseline was the last available measured low-density lipoprotein cholesterol (LDL-C) value obtained up to randomization. The measured LDL-C at Week 4 and Week 8 was the LDL-C level obtained within the corresponding analysis window. The Week 4 analysis window was from Day 22 to Day 42 and Week 8 analysis window was from Day 43 to Day 70, with Day 1 as the day of randomization for participant during the double-blind period.



SPC: single-pill combination, R10: rosuvastatin 10 mg, E10: ezetimibe 10 mg

Supplementary Table S4. Participant disposition - Randomized population

n (%)	R10/E10 (N=153)	R10 (N=152)
Randomized and not exposed	1 (0.7)	0
Randomized and exposed	152 (99.3)	152 (100)
Completed the double-blind treatment period	146 (95.4)	143 (94.1)
Did not complete the double-blind treatment period	6 (3.9)	9 (5.9)
Reason for permanent double-blind intervention discontinuation		
Adverse event	2 (1.3)	1 (0.7)
Related to COVID19	0	0
Not related to COVID19	2 (1.3)	1 (0.7)
Lack of efficacy	0	0
Poor compliance to protocol	0	2 (1.3)
Progressive disease	0	0
Withdrawal by subject	4 (2.6)	6 (3.9)
Other***Error! Reference source not found.***	0	0
Reason for double-blind intervention withdrawal by subject		
Adverse event	0	0
Study procedure	0	0
Other***Error! Reference source not found.***	4 (2.6)	6 (3.9)
Related to COVID19	0	0
Not related to COVID19	4 (2.6)	6 (3.9)
Completed the study period	144 (94.1)	143 (94.1)
Did not complete the study period	9 (5.9)	9 (5.9)
Reason for study discontinuation		
Adverse event	2 (1.3)	1 (0.7)
Poor compliance to protocol	0	1 (0.7)

n (%)	R10/E10 (N=153)	R10 (N=152)
Site terminated by sponsor	0	0
Study terminated by sponsor	0	0
Withdrawal by subject	7 (4.6)	7 (4.6)
Other*Error! Reference source not found.*	0	0
Status at last contact		
Alive	152 (99.3)	152 (100)
Dead	1 (0.7)	0

COVID19: Corona Virus Disease 2019

a: Verbatim terms for these discontinuations are provided in the listing of participants with permanent double-blind intervention/study discontinuation.

Percentages are calculated using the number of participants randomized as denominator

Supplementary Table S5. Analysis populations

n (%)	**R10/E10**	**R10**	**All**
Run-in population	NA	NA	512
Run-in safety population	NA	NA	506
Randomized population	153 (100)	152 (100)	305 (100)
Modified Intent-to-Treat (mITT) population	148 (96.7)	144 (94.7)	292 (95.7)
Population without trial impact (disruption) due to COVID-19	148 (96.7)	142 (93.4)	290 (95.1)
Double-blind safety population	152	152	304

NA: Not applicable, R10: rosuvastatin 10 mg, E10: ezetimibe 10 mg, COVID19: Corona Virus Disease 2019

Note: For the double-blind safety population, participants are tabulated according to study intervention actually received (as treated)

For run-in population and run-in safety population, participants are tabulated according to all intervention group

For the other populations, participants are tabulated according to the study intervention allocated by randomization

Supplementary Table S6. Demographic and participant characteristics at baseline - Randomized population

	SPC R10/E10 (N=153)	R10 (N=152)	All (N=305)
Age (years)			
Number	153	152	305
Mean (SD)	54.6 (11.9)	55.6 (11.6)	55.1 (11.8)
Median	57.0	57.0	57.0
Min ; Max	28 ; 74	25 ; 80	25 ; 80
Age group [n (%)]			
Number	153	152	305
From 18-64 years	114 (74.5)	112 (73.7)	226 (74.1)
65-74 years	39 (25.5)	34 (22.4)	73 (23.9)
75 years and over	0	6 (3.9)	6 (2.0)
Sex [n (%)]			
Number	153	152	305
Male	64 (41.8)	69 (45.4)	133 (43.6)
Female	89 (58.2)	83 (54.6)	172 (56.4)
Race [n (%)]			
Number	153	152	305
Asian	153 (100)	152 (100)	305 (100)
Ethnicity [n (%)]			
Number	153	152	305
Not Hispanic or Latino	153 (100)	152 (100)	305 (100)
Baseline Weight (kg)			
Number	153	152	305
Mean (SD)	67.4 (12.1)	67.3 (12.3)	67.4 (12.2)
Median	68.0	65.8	67.0
Min ; Max	40 ; 108	36 ; 114	36 ; 114

	SPC R10/E10 (N=153)	R10 (N=152)	All (N=305)
Baseline Weight by category (kg) [n (%)]			
Number	153	152	305
<50	9 (5.9)	7 (4.6)	16 (5.2)
50 to <100	142 (92.8)	143 (94.1)	285 (93.4)
≥100	2 (1.3)	2 (1.3)	4 (1.3)
Baseline BMI (kg/m2)			
Number	153	152	305
Mean (SD)	25.169 (3.235)	25.051 (3.402)	25.110 (3.314)
Median	25.060	25.085	25.080
Min ; Max	18.11 ; 37.64	14.12 ; 36.74	14.12 ; 37.64
Baseline BMI by category (kg/m2) [n (%)]			
Number	153	152	305
<18.5	1 (0.7)	2 (1.3)	3 (1.0)
18.5 to <25	73 (47.7)	70 (46.1)	143 (46.9)
25 to <30	68 (44.4)	72 (47.4)	140 (45.9)
30 to <35	10 (6.5)	5 (3.3)	15 (4.9)
≥35	1 (0.7)	3 (2.0)	4 (1.3)

SPC: single-pill combination, R10: rosuvastatin 10 mg, E10: ezetimibe 10 mg, BMI: body mass index, SD: Standard Deviation

The baseline values are defined as the values collected at the screening visit

Supplementary Table S7. Disease and therapy characteristics at baseline - Randomized population

	SPC R10/E10 (N=153)	R10 (N=152)	All (N=305)
Duration of hypercholesterolemia (years)			
Number	153	152	305
Mean (SD)	3.40 (4.25)	3.66 (4.48)	3.53 (4.36)
Median	1.72	2.12	2.08
Min ; Max	0.1 ; 22.7	0.0 ; 23.1	0.0 ; 23.1
Age of onset of hypercholesterolemia (years)			
Number	153	152	305
Mean (SD)	51.9 (11.7)	52.5 (11.0)	52.2 (11.3)
Median	55.0	54.0	54.0
Min ; Max	25 ; 73	24 ; 73	24 ; 73
Myocardial revascularization [n (%)]			
Number	153	152	305
Yes	14 (9.2)	20 (13.2)	34 (11.1)
No	139 (90.8)	132 (86.8)	271 (88.9)
Number of previous statins or Xuezhikang treatments within two months prior to screening [n (%)]			
Number	153	152	305
1	149 (97.4)	148 (97.4)	297 (97.4)
2	4 (2.6)	4 (2.6)	8 (2.6)

	SPC R10/E10 (N=153)	R10 (N=152)	All (N=305)
Duration of last statin or Xuezhikang treatment prior to screening (years)			
Number	153	152	305
Mean (SD)	1.30 (2.61)	1.25 (2.28)	1.28 (2.45)
Median	0.31	0.28	0.30
Min ; Max	0.1 ; 20.9	0.1 ; 13.3	0.1 ; 20.9
Last statin or Xuezhikang treatment prior to screening			
Number	153	152	305
Rosuvastatin 10 mg or equipotent statins	153 (100)	152 (100)	305 (100)
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)

SPC: single-pill combination, R10: rosuvastatin 10 mg, E10: ezetimibe 10 mg, SD: Standard Deviation

Supplementary Table S8. Percent change in LDL-C from baseline to Week 4 and Week 8 using MMRM - mITT population

LDL-C	SPC R10/E10 (N=148)	R10 (N=144)
Double-blind baseline (mmol/L)		
Number	148	144
Mean (SD)	3.261 (0.724)	3.377 (0.713)
Median	3.235	3.300
Min ; Max	1.87 : 5.61	1.59 : 5.24
Week 4		
Percent change from baseline to Week 4 (%)		
LS Mean (SE)	-22.90 (2.01)	-8.50 (2.04)
95% CI	(-26.86 to -18.94)	(-12.51 to -4.49)
LS Mean difference (SE) vs. R10	-14.40 (2.87)	
95% CI	(-20.04 to -8.75)	
p-value	<0.0001*	
Week 8		
Percent change from baseline to Week 8 (%)		
LS Mean (SE)	-21.98 (2.22)	-8.12 (2.29)
95% CI	(-26.35 to -17.60)	(-12.63 to -3.61)
LS Mean difference (SE) vs. R10	-13.85 (3.20)	
95% CI	(-20.15 to -7.56)	
p-value	<0.0001*	

LDL-C: low-density lipoprotein cholesterol, SPC: single-pill combination, R10: rosuvastatin 10 mg, E10: ezetimibe 10 mg, LS: least square, MMRM: mixed-effect model with repeated measures, SD: Standard Deviation

LDL-C	SPC R10/E10 (N=148)	R10 (N=144)

Note: Least-squares (LS) Mean, standard error (SE), and the p-value is taken from the MMRM analysis. The model includes the fixed categorical effects of the intervention group, time point, intervention group-by-time point, and the continuous fixed covariates of baseline LDL-C value and baseline value-by-time point interaction.

MMRM model and baseline description run on participants with a baseline value and a post-baseline value in at least one of the analysis windows used in the model

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

Supplementary Table S9. Hierarchical testing strategy and results

Endpoint	Results	P-value
The proportion of participants reaching the LDL-C target at week 8	Estimate for odds-ratio vs. R10 of 2.80	<0.0001*
Percent change in LDL-C from baseline to week 4	LS mean difference vs. R10 of -14.40%	<0.0001*
Percent change in TC from baseline to week 8	LS mean difference vs. R10 of -9.77%	<0.0001*
Percent change in TC from baseline to week 4	LS mean difference vs. R10 of -10.22%	<0.0001*
Percent change in TG from baseline to week 8	Combined estimate for adjusted mean difference vs. R10 of -7.02%	0.0488*
Percent change in TG from baseline to week 4	Combined estimate for adjusted mean difference vs. R10 of -5.21%	0.1420
Percent change in HDL-C from baseline to week 8	LS mean difference vs. R10 of 2.63%	0.1131
Percent change in HDL-C from baseline to week 4	LS mean difference vs. R10 of 2.17%	0.1978

LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LS mean, Least-squares mean.

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

Supplementary Material S10. Adverse events of special interest (AESIs)

An adverse event (AE) of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

- Alaninetransaminase (ALT) >3 × upper limit of normal value (ULN)
- Increase in Creatine Kinase (CK) >3 × ULN.
- Pregnancy of a female subject entered in a study as well as pregnancy occurring in a female partner of a male subject entered in a study with investigational medicinal Product (IMP).
    i. It will be qualified as an SAE only if it fulfills one of the seriousness criteria
    ii. In the event of pregnancy in a female participant, IMP should be discontinued. If the pregnancy occurred in a female partner of a male subject included in the study it is not necessary to discontinue the IMP.
- Symptomatic overdose (serious or nonserious) with IMP.
    i. An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic pills count) and defined as at least twice the intended dose within the intended therapeutic interval, adjusted according to the tested drug. The patient should be monitored, and appropriate symptomatic treatment should be instituted, as needed. It will be recorded in the eCRF at "overdose" page.
    ii. The circumstances of the overdose (i.e., accidental or intentional) should be clearly specified in the verbatim, and the symptoms, if any, entered on separate AE/SAE (serious AE) forms.