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ORIGINAL RESEARCH ARTICLE

Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Alirocumab in Healthy Chinese Subjects: A Randomized, Double-Blind, Placebo-Controlled, Ascending Single-Dose Study

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Abstract

Background The addition of alirocumab (a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 [PCSK9]) to background statin therapy provides significant incremental low-density lipoprotein cholesterol (LDL-C) lowering and cardiovascular event risk reduction.

Objectives Our objectives were to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of single ascending doses of alirocumab in healthy Chinese subjects.

Methods In this double-blind, placebo-controlled, phase I study, 35 Chinese subjects (aged 21–45 years) with baseline LDL-C > 100 mg/dL (2.59 mmol/L) were randomized to receive a single 1 mL subcutaneous injection of alirocumab 75, 150, or 300 mg, or placebo, and followed up for ~ 12 weeks.

Results Treatment-emergent adverse events, most frequently nasal congestion and dry throat, were reported in three of seven or eight subjects in each alirocumab dose group (two of seven in the placebo group). One patient receiving alirocumab 300 mg had a mild local injection-site reaction. No alirocumab recipients demonstrated antidrug antibodies. Maximum alirocumab serum concentrations (6–34 mg/dL) occurred at a median of 3–7 days across the dose groups. Maximum mean LDL-C reductions from baseline were observed on days 8, 15, and 22 with alirocumab 75 (55.3%), 150 (63.7%), and 300 mg (73.7%), respectively. Mean free PCSK9 levels were reduced to below the lower limit of quantification within 4 h of dosing. Total cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B were reduced with alirocumab.

Conclusions In Chinese subjects, alirocumab 75, 150, and 300 mg was safe and well-tolerated. Pharmacokinetic/pharmacodynamic parameters, including clinically meaningful reductions in LDL-C and other lipids/lipoproteins, were consistent with data from Japanese and Western populations.

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Key Points

Data regarding the safety, tolerability, and pharmacokinetic and pharmacodynamic parameters of the proprotein convertase subtilisin/kexin type 9 monoclonal antibody alirocumab in Chinese subjects are limited.

In this double-blind, placebo-controlled, phase I study in 35 healthy Chinese subjects, alirocumab administered as a single ascending subcutaneous dose of 75, 150, or 300 mg was generally safe and well-tolerated.

The pharmacokinetic and pharmacodynamic parameters of alirocumab in healthy Chinese subjects were consistent with those reported for Japanese and Western populations, with pharmacodynamic data showing clinically meaningful reductions in low-density lipoprotein cholesterol and other lipids and lipoproteins.

1 Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality worldwide [1]. In China alone, cardiovascular disease accounts for about 3 million deaths annually [2]. Dyslipidemia, particularly increased levels of low-density lipoprotein cholesterol (LDL-C), is an important risk factor for ASCVD, and atherogenic lipid levels are reported to have gradually increased in the Chinese population over the last 30 years [3, 4].

Chinese guidelines for the management of dyslipidemia classify patients with clinical ASCVD as being at very high risk [3]. Despite statin therapy, LDL-C goal attainment is suboptimal in China, with almost 40% of treated patients with hyperlipidemia not achieving goal [5, 6]. Furthermore, an increase in statin intensity does not improve the lipid goal attainment rate [7], leaving statin-treated patients at residual cardiovascular risk.

For residual cardiovascular risk reduction, additional lipid-lowering therapies beyond statins may be required. The European [8] and US [9] guidelines recommend the addition of ezetimibe to maximally tolerated statin therapy for additional LDL-C lowering in high-risk and very high-risk patients, and, if LDL-C remains above target levels ($\geq$ 70 mg/dL [$\geq$ 1.8 mmol/L]), the addition of a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor may be considered. The protease PCSK9, first discovered in 2003 [10], has rapidly progressed from identification as a regulator of LDL-C receptor recycling to a key therapeutic target for LDL-C lowering and cardiovascular event risk reduction [11, 12]. Two PCSK9 inhibitors, alirocumab and evolocumab, both fully human monoclonal antibodies to PCSK9, are approved for clinical use in combination with statin/ezetimibe in the USA and Europe [13–15]. Evolocumab is also available in China [16], and alirocumab is currently undergoing regulatory review in this region.

Alirocumab provides significant additional reductions in LDL-C of up to 62%, relative to placebo, when added to background maximally tolerated statin therapy [17], as well as reductions in major adverse cardiovascular events [18]. However, data regarding the safety, pharmacokinetics, and pharmacodynamics of alirocumab in Chinese subjects are limited. For the first time, this study investigated the safety, tolerability, pharmacokinetics, and pharmacodynamics of alirocumab following subcutaneous administration of single ascending doses (75, 150, or 300 mg) in healthy Chinese subjects.

2 Methods

2.1 Study Design and Participants

This was a phase I, single-center, randomized, double-blind, placebo-controlled, ascending single-dose study of the safety, tolerability, pharmacokinetics, and pharmacodynamics of alirocumab following subcutaneous administration in healthy Chinese subjects (clinicaltrials.gov identifier: NCT02979015).

The study was conducted at the Peking University Third Hospital, Beijing, China, in accordance with recommendations of the 18th World Health Congress (Helsinki 1964) and all applicable amendments, and the International Conference on Harmonization guidelines for Good Clinical Practice (GCP). The protocol was approved by the relevant independent ethics committees. All participating subjects provided written informed consent.

Healthy male or female subjects (30 planned) aged between 21 and 45 years inclusive, with serum LDL-C > 100 mg/dL (2.59 mmoL/L) at screening, were eligible for enrollment. Exclusion criteria included a history/presence of clinically relevant disease (e.g., cardiovascular, pulmonary, hepatic, or renal) or signs of acute illness (for additional eligibility/exclusion criteria, see Supplementary Table 1).

The study comprised a screening period from 2 to 28 days prior to inclusion (days −28 to −2), a 5-day in-house period including 1 treatment day (days −1 to 4, with treatment on day 1), clinic visit days ± 2 days (days 8, 11, 15, 22, 29, 43, and 64), and an end of study (EOS) visit (day 85 ± 2 days). The total study duration for each subject, not including the screening period, was ~ 12 weeks; duration of follow-up was up to 113 days, including screening.

Subjects were randomized to one of three sequential ascending dose groups (each completed before initiating the next dose group) with ten subjects planned per group, eight to receive alirocumab and two to receive matching placebo: group 1, a single dose of alirocumab 75 mg (75 mg/mL × 1 mL) or placebo; group 2, a single dose of alirocumab 150 mg (150 mg/mL × 1 mL) or placebo; and group 3, a single dose of alirocumab 300 mg (2 × 150 mg/mL × 1 mL) or placebo. Each treatment was administered subcutaneously via prefilled pen in the abdomen on day 1 under fasting conditions. At the time of the discussion of the study design (16 October 2012), 75 and 150 mg were the therapeutic doses of alirocumab used in the worldwide phase III program (75 mg every 2 weeks [Q2W]/up to 150 mg Q2W). The highest dose of 300 mg was well-tolerated in previous studies [19, 20]; 75, 150, and 300 mg were therefore selected for this study to provide relevant data regarding the safety margin and dose proportionality. By the time of study initiation (29 November 2016), alirocumab 300 mg every 4 weeks had been investigated in the phase III program [21].

2.2 Safety Assessments

Safety was assessed by physical examination and monitoring of clinical laboratory and electrocardiogram (ECG) parameters, vital signs, and adverse events (AEs) spontaneously reported by the subject or observed by the investigator, including local tolerability/sensitivity reactions (further details are provided in the electronic supplementary material). Local tolerability parameters monitored included injection-site pain. Erythema or edema at the injection site were assessed qualitatively as mild, moderate, or severe.

AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA, version 20.1). Treatment-emergent AEs (TEAEs) were defined as those that occurred, worsened, or became serious during the period from alirocumab or placebo injection (day 1) until EOS (day 85 ± 2). A serious AE (SAE) was considered as any untoward medical occurrence/important event that at any dose resulted in death, was life threatening, required hospitalization, or resulted in significant disability/incapacity. TEAEs were listed by treatment group, primary system organ class (MedDRA order), and preferred term.

2.3 Pharmacokinetic and Antidrug Antibody Assessments

Blood samples for determination of alirocumab serum concentrations were collected before study drug administration and on days 1 (at 4 and 8 h), 2 (at 24 h), 3 (48 h), 4 (72 h), 8 (168 h), 11 (240 h), 15 (336 h), 22 (504 h), 29 (672 h), 43 (1008 h), 64 (1512 h), and 85 (2016 h) post-dose.

Total concentrations of alirocumab (free alirocumab and in PCSK9:alirocumab complexes) were determined in acid-treated human serum using a validated enzyme-linked immunosorbent assay (ELISA), with a lower limit of quantification (LLOQ) of 78 ng/mL (Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA) [22]. Free and total PCSK9 levels were determined by validated ELISA assay (Regeneron Pharmaceuticals, Inc.) [22]. The lower limits of detection for total and free PCSK9 were 156 ng/mL and 31.2 ng/mL, respectively. Antidrug antibodies (ADAs) to alirocumab were analyzed by the Regeneron Clinical Bioanalysis group using a validated, nonquantitative, titer-based bridging immunoassay [23].

Alirocumab serum pharmacokinetic parameters were calculated using noncompartmental analysis with validated software (pharmacokinetic data management system version 3 with Phoenix version 1.4). Calculated alirocumab pharmacokinetic parameters included maximum serum concentration (C_{max}); time to reach C_{max} (t_{max}); area under the serum concentration versus time curve (AUC) extrapolated from time zero to infinity (AUC_{∞}); AUC from time zero to day 15 ($AUC_{0–D14}$); AUC from time zero to day 29 ($AUC_{0–D28}$); AUC from time zero to time of last measurable concentration (AUC_{last}); the last concentration above the limit of quantification (C_{last}); time to C_{last}; apparent total body clearance (CL/*F*) from plasma; mean residence time; terminal elimination half-life ($t_{½z}$; alirocumab is a protein that is degraded to small peptides and amino acids so has a concentration-dependent clearance); and apparent distribution volume at steady state (V_{ss}/F).

2.4 Pharmacodynamic Assessments

Blood sampling for lipid/lipoprotein parameters, LDL-C, total cholesterol (TC), high-density lipoprotein (HDL-C), triglycerides, apolipoprotein (Apo) B, ApoA1, and lipoprotein a [Lp(a)] were performed in the morning under conditions of fasting (≥ 10 h) and no smoking (for further detail, see the electronic supplementary material).

The primary pharmacodynamic variables assessed were percent and absolute change from baseline in calculated LDL-C at each visit. LDL-C was calculated using the Friedewald formula [24]. Secondary pharmacodynamic variables assessed were percent and absolute change from baseline in TC, HDL-C, triglycerides, non-HDL-C, very low-density lipoprotein cholesterol (VLDL-C), ApoB, ApoA1, and Lp(a) at each visit.

2.5 Statistical Analysis

The sample size for this study was calculated based upon empirical considerations. We estimated that allocation of six subjects in the placebo groups and 24 in the active dose

groups would provide at least 90% power to detect a treatment difference of 30% (standard deviation 15%) versus placebo for percentage change from baseline in LDL-C, with a 5% significance level in a two-sided *t* test. There was no adjustment for multiplicity due to multiple comparisons.

The safety population included all randomized subjects exposed to study treatment, regardless of the amount of treatment administered. Safety data were analyzed by review of descriptive statistics and individual data for AEs, clinical laboratory values, vital signs, and ECG parameters. The immunogenicity of alirocumab was assessed by summarizing the number and percentage of subjects who tested positive or negative for ADAs. The pharmacokinetic population included all subjects with no important deviations related to alirocumab administration and who were considered to have sufficient and interpretable pharmacokinetic data; subjects who received only placebo were not included in this population. Alirocumab, free PCSK9, and total PCSK9 concentrations during the treatment period were summarized by treatment group and visit using descriptive statistics. No formal statistical comparisons were performed, and pharmacokinetic data are summarized descriptively. All subjects with no important deviations affecting pharmacodynamic evaluation, for whom some pharmacodynamic data were considered available, were included in the pharmacodynamic population.

3 Results

3.1 Baseline Subject Characteristics

Initially, 31 healthy subjects were randomized in the study. Four subjects (two each in the alirocumab 150 mg and alirocumab 300 mg groups) were noncompliant with GCP as they had used others' identification cards and were excluded from any of the analyses; these subjects were replaced. Overall, 31 subjects were randomized, treated, and analyzed: eight subjects in each of the alirocumab 75, 150, and 300 mg groups and seven subjects in the placebo group. One placebo recipient did not finish the study procedure because they experienced an SAE. The first subject was enrolled on 29 November 2016, and 31 subjects had completed the study treatment period by 27 November 2017. Figure 1 shows the flow of subjects through the study.

Baseline characteristics, including mean body mass index, were generally similar between the alirocumab and placebo groups (Table 1), except that the placebo group contained fewer males (42.9 vs. 83.3% across the alirocumab groups). Mean baseline LDL-C (111.8 mg/dL [2.89 mmol/L]) for all groups was similar between the alirocumab 75 (111.4 mg/dL [2.88 mmol/L]), 150 (109.8 mg/dL [2.84 mmol/L]), and 300 mg (111.8 mg/dL [2.89 mmol/L]) groups and placebo (114.8 mg/dL [2.97 mmol/L]).

Although none of the subjects took previous medications, some did take concomitant medications in response to AEs: one subject in the placebo group, two in the alirocumab 75 mg group, and three in the alirocumab 150 mg group.

3.2 Safety

Alirocumab was generally well-tolerated in the 31 healthy Chinese subjects included in the safety population. Overall, TEAEs were reported by three of eight, six of eight, and seven of eight subjects in the alirocumab 75, 150, and 300 mg groups, respectively, compared with two of seven in the placebo groups (Table 2). No single TEAE showed a clear dose-response relationship. No alirocumab recipients reported severe TEAEs or treatment-emergent SAEs. No deaths were reported during the study. One subject in the

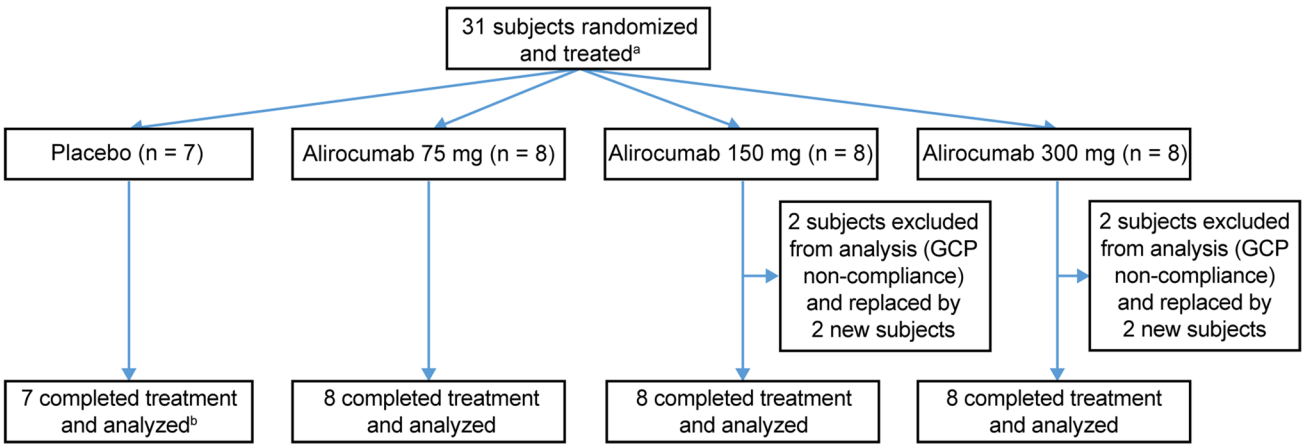

Fig. 1 Subject flow though the study. [a]A total of 35 subjects were enrolled: 31 were initially randomized, but four subjects were replaced because of non-compliance. [b]One treated subject did not finish the study visits because of a serious adverse event (acute appendicitis). *GCP* good clinical practice

Table 1 Baseline characteristics of healthy Chinese subjects

Characteristics	Alirocumab			Placebo ($n=7$)	All ($N=31$)
	75 mg ($n=8$)	150 mg ($n=8$)	300 mg ($n=8$)		
Age, years	30.3 ± 5.7	36.5 ± 5.8	36.0 ± 7.3	36.0 ± 8.9	34.6 ± 7.1
Male	8 (100.0)	7 (87.5)	5 (62.5)	3 (42.9)	23 (74.2)
Weight, kg	73.5 ± 11.9	74.2 ± 6.9	65.3 ± 8.9	62.3 ± 6.7	69.1 ± 9.9
Height, m	1.73 ± 0.06	1.71 ± 0.08	1.63 ± 0.04	1.57 ± 0.08	1.66 ± 0.09
BMI, kg/m^2	24.49 ± 2.9	25.6 ± 2.3	24.6 ± 2.8	25.4 ± 1.7	25.0 ± 2.4
Total PCSK9, ng/mL	353.3 ± 76.2	402.3 ± 102.4	435.5 ± 55.2	512.6 ± 124.1	423.1 ± 104.5
Free PCSK9, ng/mL	139.8 ± 38.9	149.9 ± 52.2	161.8 ± 32.8	199.9 ± 48.2	161.6 ± 47.0
LDL-C, mg/dL	111.4 ± 22.0	109.8 ± 29.0	111.8 ± 19.3	114.8 ± 22.8	111.8 ± 22.4
LDL-C, mmol/L	2.88 ± 0.57	2.84 ± 0.75	2.89 ± 0.50	2.97 ± 0.59	2.89 ± 0.58

Data are presented as mean ± standard deviation or *n* (%) unless otherwise indicated

BMI body mass index, *LDL-C* low-density lipoprotein cholesterol, *PCSK9* proprotein convertase subtilisin/kexin type 9

placebo group (14.3%) reported an SAE (acute appendicitis) during study treatment, which was not considered related to the study medication by the investigator. All TEAEs reported by subjects in the alirocumab groups were of mild or moderate intensity and resolved without sequelae.

The most frequently reported TEAEs by system organ class in the alirocumab and placebo groups were "infections and infestations," "respiratory, thoracic, and mediastinal disorders," and "gastrointestinal disorders" (Table 2), which were reported by a similar proportion of subjects in each group. Nasal congestion (three with alirocumab 300 mg and one with placebo) and dry throat (two with alirocumab 300 mg) were the most frequently reported TEAEs classified by preferred term. One subject receiving alirocumab 300 mg experienced a mild local injection-site reaction (erythema and itching on the right side of the injection site) on the day after study drug administration, which resolved spontaneously within 2 days.

There were no notable changes from baseline in vital signs, laboratory values, or ECG parameters, and no subjects showed potentially clinically significant abnormalities (PCSA) for liver or renal function parameters. Notably, no subjects had alanine transaminase or aspartate transaminase values > 3 × the upper limit of normal (ULN), alkaline phosphatase values > 1.5 × ULN, or total bilirubin values > 1.5 × ULN. Two subjects receiving alirocumab 150 mg had on-treatment PCSAs for biochemistry parameters. One subject with a baseline glucose of 5.5 mmol/L had a fasting glucose level above the ULN (7.2 mmol/L) on day 43, which returned to normal by the EOS visit. Another subject with baseline creatine phosphokinase (CPK) of 1.36 × ULN had a transient elevation to more than 3 × ULN on day 4. CPK levels remained elevated at day 7 (1.72 × ULN) and day 10 (1.48 × ULN), with a return to < 3 × ULN on day 15 (0.63 × ULN).

3.2.1 Immunogenicity

Across the three alirocumab dose groups, all subjects were ADA negative. A low ADA positive titer (60) was reported for one subject in the placebo group on a single occasion on day 85.

3.3 Pharmacokinetic Analysis

All subjects randomized to alirocumab 75, 150, and 300 mg were included in the pharmacokinetic population ($n=24$). Each of these subjects demonstrated measurable alirocumab levels; by contrast, no placebo recipients had detectable serum alirocumab levels. Figure 2 shows the mean serum alirocumab concentration versus time after single subcutaneous administration of alirocumab 75, 150, or 300 mg. C_{max} 6–34 mg/L was observed at a median of 3–7 days across the three dose groups, and AUC_{last} and AUC_{∞} were similar within each dose group (Table 3). The total variability (coefficient of variation) of C_{max}, AUC_{last}, and AUC_{∞} ranged from 30.0 to 53.5%, from 27.9 to 45.3%, and from 26.5 to 44.8%, respectively. Apparent CL/*F* decreased from 0.9 L/day following single subcutaneous administration of alirocumab 75 and 150 mg to 0.5 L/day with 300 mg; respective values for V_{ss}/F were 10, 12, and 7 L, respectively.

3.3.1 Dose Proportionality

Comparison of the main pharmacokinetic parameters obtained with the lowest (75 mg) and highest (300 mg) doses showed that alirocumab exposure increased slightly more than expected from dose proportionality. In statistical assessment of dose proportionality (analysis of variance model estimated with 90% confidence interval [CI] for pairwise dose increases), the 4.00-fold increase in dose from 75 to

Table 2 Treatment-emergent adverse events

TEAE[a]	Alirocumab			Placebo ($n=7$)
	75 mg ($n=8$)	150 mg ($n=8$)	300 mg ($n=8$)	
TEAEs	3 (37.5)	6 (75.0)	7 (87.5)	2 (28.6)
Treatment-emergent SAEs	0	0	0	1 (14.3)[b]
TEAEs by system organ class, preferred term				
Any class	3 (37.5)	6 (75.0)	7 (87.5)	2 (28.6)
Infections and infestations	1 (12.5)	2 (25.0)	1 (12.5)	2 (28.6)
Folliculitis	0	0	1 (12.5)	0
Appendicitis	0	0	0	1 (14.3)
Tonsillitis	1 (12.5)	1 (12.5)	0	0
Upper respiratory tract infection	0	1 (12.5)	0	1 (14.3)
Psychiatric disorders	1 (12.5)	0	0	0
Insomnia	1 (12.5)	0	0	0
Respiratory, thoracic, and mediastinal disorders	0	2 (25.0)	3 (37.5)	1 (14.3)
Nasal congestion	0	0	3 (37.5)	1 (14.3)
Dry throat	0	0	2 (25.0)	0
Oropharyngeal pain	0	1 (12.5)	1 (12.5)	1 (14.3)
Rhinorrhea	0	1 (12.5)	0	0
Gastrointestinal disorders	2 (25.0)	2 (25.0)	1 (12.5)	1 (14.3)
Abdominal pain	1 (12.5)	0	1 (12.5)	1 (14.3)
Diarrhea	1 (12.5)	1 (12.5)	1 (12.5)	0
Enteritis	0	1 (12.5)	0	0
Mouth ulceration	1 (12.5)	0	0	0
Toothache	0	1 (12.5)	0	0
Hepatobiliary disorders	0	0	0	1 (14.3)
Hepatic steatosis	0	0	0	1 (14.3)
Skin and subcutaneous tissue disorders	0	3 (37.5)	2 (25.0)	0
Pruritus	0	1 (12.5)	1 (12.5)	0
Rash	0	1 (12.5)	1 (12.5)	0
Skin exfoliation	0	1 (12.5)	0	0
Musculoskeletal and connective tissue disorders	0	0	1 (12.5)	1 (14.3)
Back pain	0	0	1 (12.5)	0
Pain in extremity	0	0	0	1 (14.3)
General disorders and administration-site conditions	0	0	2 (25.0)	0
Asthenia	0	0	1 (12.5)	0
Injection-site reaction	0	0	1 (12.5)	0
Investigations	0	1 (12.5)	0	0
Blood creatine phosphokinase increased	0	1 (12.5)	0	0
Injury, poisoning, and procedural complications	0	0	1 (12.5)	0
Ligament sprain	0	0	1 (12.5)	0

Data are presented as *n* (%) unless otherwise indicated

SAE serious adverse event, *TEAE* treatment-emergent adverse event

[a]No TEAEs led to treatment discontinuation in any group as this was a single-dose study

[b]Subject did not finish the study procedure (did not complete the study visits) because of the SAE (acute appendicitis), which was not considered related to the investigational medicinal product by the investigator; the subject had a medical history of chronic appendicitis

300 mg resulted in a 5.38-fold (90% CI 3.84–7.55) increase in C_{max}, an 8.32-fold (90% CI 6.12–11.32) increase in AUC_{last}, and an 8.00-fold (90% CI 5.92–10.81) increase in AUC_{∞}. When comparing the exposure of the 75 and 150 mg dose groups, the point estimates for C_{max}, AUC_{last}, and AUC_{∞} were closer to an expected twofold increase (1.80, 2.17, and 2.10, respectively); for comparison of the 150 and 300 mg

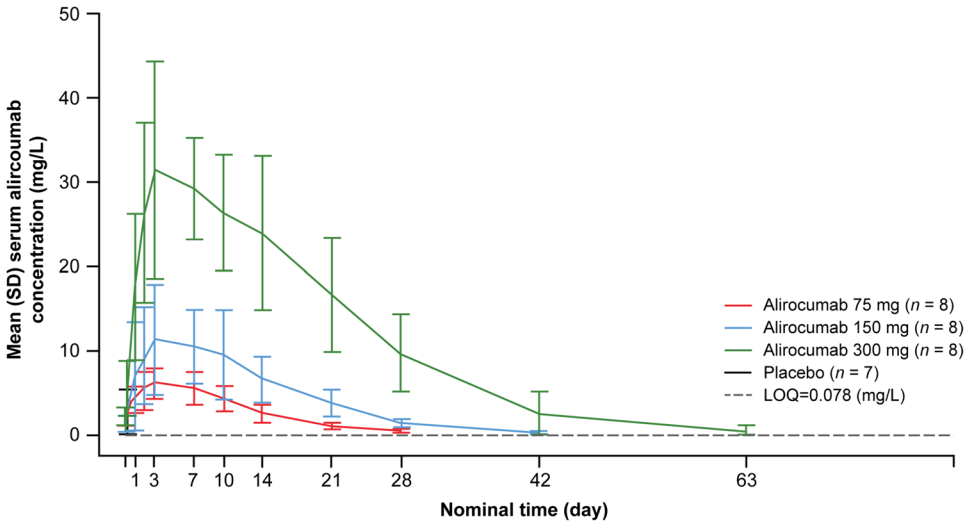

Fig. 2 Mean serum alirocumab concentration versus time profiles after single subcutaneous administration of alirocumab 75, 150, or 300 mg (linear scale). *LOQ* limit of quantification, *SD* standard deviation

Table 3 Pharmacokinetic parameters following subcutaneous administration of alirocumab 75, 150, or 300 mg in healthy Chinese subjects

Parameter	Alirocumab		
	75 mg ($n=8$)	150 mg ($n=8$)	300 mg ($n=8$)
C_{max}, mg/L	6.32 ± 1.90 (6.07) [30.0]	12.3 ± 6.60 (10.9) [53.5]	34.0 ± 10.6 (32.7) [31.2]
t_{max}, days[a]	3.00 (2.00–7.01)	5.00 (2.00–9.98)	6.99 (3.00–10.00)
AUC_{0-D14}, mg·day/L	64.4 ± 20.2 (61.8) [31.4]	126.0 ± 65.0 (114) [51.4]	365.0 ± 106.0 (353) [28.9]
AUC_{0-D28}, mg·day/L	83.2 ± 24.0 (80.3) [28.9]	181.0 ± 85.1 (165) [47.1]	598.0 ± 195.0 (574) [32.6]
AUC_{last}, mg·day/L	84.2 ± 23.5 (81.4) [27.9]	192.0 ± 87.1 (177) [45.3]	717.0 ± 288.0 (678) [40.2]
AUC_{∞}, mg·day/L	87.6 ± 23.2 (85.0) [26.5]	194.0 ± 86.8 (179) [44.8]	719.0 ± 288 (680) [40.0]
C_{last}, mg/dL	0.379 ± 0.255 (0.284) [67.3]	0.235 ± 0.066 (0.266) [27.9]	0.258 ± 0.215 (0.206) [83.2]
t_{last}, days[a]	28.06 (28.00–43.06)	42.02 (41.97–42.11)	63.00 (42.03–84.02)
$t_{½z}$, days	6.07 ± 1.55 (5.88) [25.5]	5.51 ± 0.789 (5.46) [14.3]	6.58 ± 1.22 (6.50) [18.5]
V_{ss}/F, L	9.78 ± 3.37 (9.27) [34.4]	11.5 ± 5.86 (10.3) [50.8]	6.96 ± 1.75 (6.75) [25.1]
MRT, days	10.6 ± 1.76 (10.5) [16.5]	12.3 ± 1.55 (12.3) [12.5]	15.4 ± 2.19 (15.3) [14.2]
CL/F, L/day	0.908 ± 0.224 (0.882) [24.7]	0.908 ± 0.378 (0.840) [41.6]	0.461 ± 0.134 (0.441) [29.1]

Data are presented as mean ± standard deviation (geometric mean) [coefficient of variation %] unless otherwise specified

AUC area under the serum concentration versus time curve, AUC_{0-D14} AUC from time zero to day 15, AUC_{0-D28} AUC from time zero to day 29, AUC_{∞} AUC from time zero to infinity, AUC_{last} AUC from time zero to time of last measurable concentration, C_{last} last concentration above the limit of quantification, *CL/F* clearance relative to bioavailability (dose/AUC), C_{max} maximum serum concentration, *MRT* mean residence time, $t_{½Z}$ terminal elimination half-life, t_{last} time to C_{last}, t_{max} time to reach C_{max}, V_{ss}/F distribution volume at steady state (CL/F × MRT)

[a]Median (min–max)

dose groups, the point estimates were 3.00, 3.84, and 3.81, respectively.

3.4 Pharmacodynamic Analysis

3.4.1 LDL-C Lowering

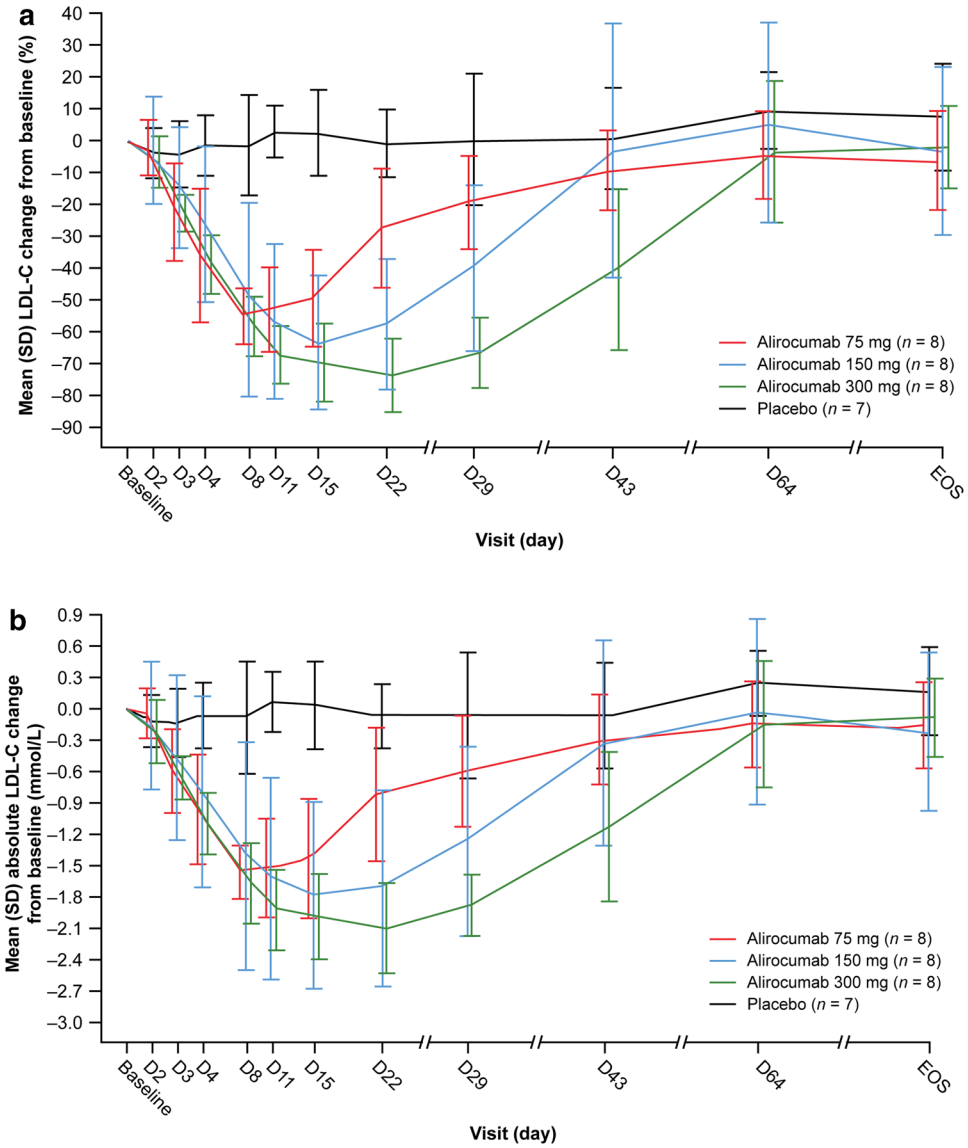

Fig. 3 Mean **a** percentage and **b** absolute change from baseline in LDL-C to EOS after single-dose alirocumab or placebo administration. Baseline = day 1 pre-dose assessment. *EOS* end of study, *LDL-C* low-density lipoprotein cholesterol, *SD* standard deviation

Among the three alirocumab groups, the first observed reduction in LDL-C relative to placebo with alirocumab 75, 150, and 300 mg was on days 3, 4, and 3, respectively, whereas the maximum mean reduction in LDL-C was observed on days 8 (55.3%), 15 (63.7%), and 22 (73.7%), respectively (Fig. 3a). The reduction in LDL-C with alirocumab 75, 150, and 300 mg was maintained until days 15, 29, and 43, respectively. By contrast, in the placebo group, LDL-C levels remained relatively unchanged from baseline to day 64 and EOS.

The maximum absolute changes in LDL-C with alirocumab 75, 150, and 300 mg were −60.8 (−1.57), −69.6 (−1.80), and −81.8 mg/dL (−2.11 mmol/L), respectively (Fig. 3b). Overall, the magnitude and duration of LDL-C reductions were positively associated with the alirocumab dose administered.

3.4.2 Free and Total PCSK9 Concentration

Figure 4a shows the mean free and total PCSK9 concentrations in serum versus time profiles after single subcutaneous administration of alirocumab 75, 150, and 300 mg. Mean baseline free PCSK9 concentrations were similar across the 75, 150, and 300 mg dose groups (140, 150, and 162 ng/mL, respectively). Mean free PCSK9 concentrations decreased below the LLOQ within 4 h post-dose and remained below the LLOQ for 10, 14, and 28 days after subcutaneous administration of alirocumab 75, 150, and 300 mg, respectively; these returned to baseline values on days 28, 42, and 63, respectively.

Prior to single subcutaneous administration of alirocumab 75, 150, and 300 mg on day 1, mean total PCSK9 levels were similar across the groups (353, 402, and 435 ng/mL, respectively). After alirocumab single-dose administration, mean

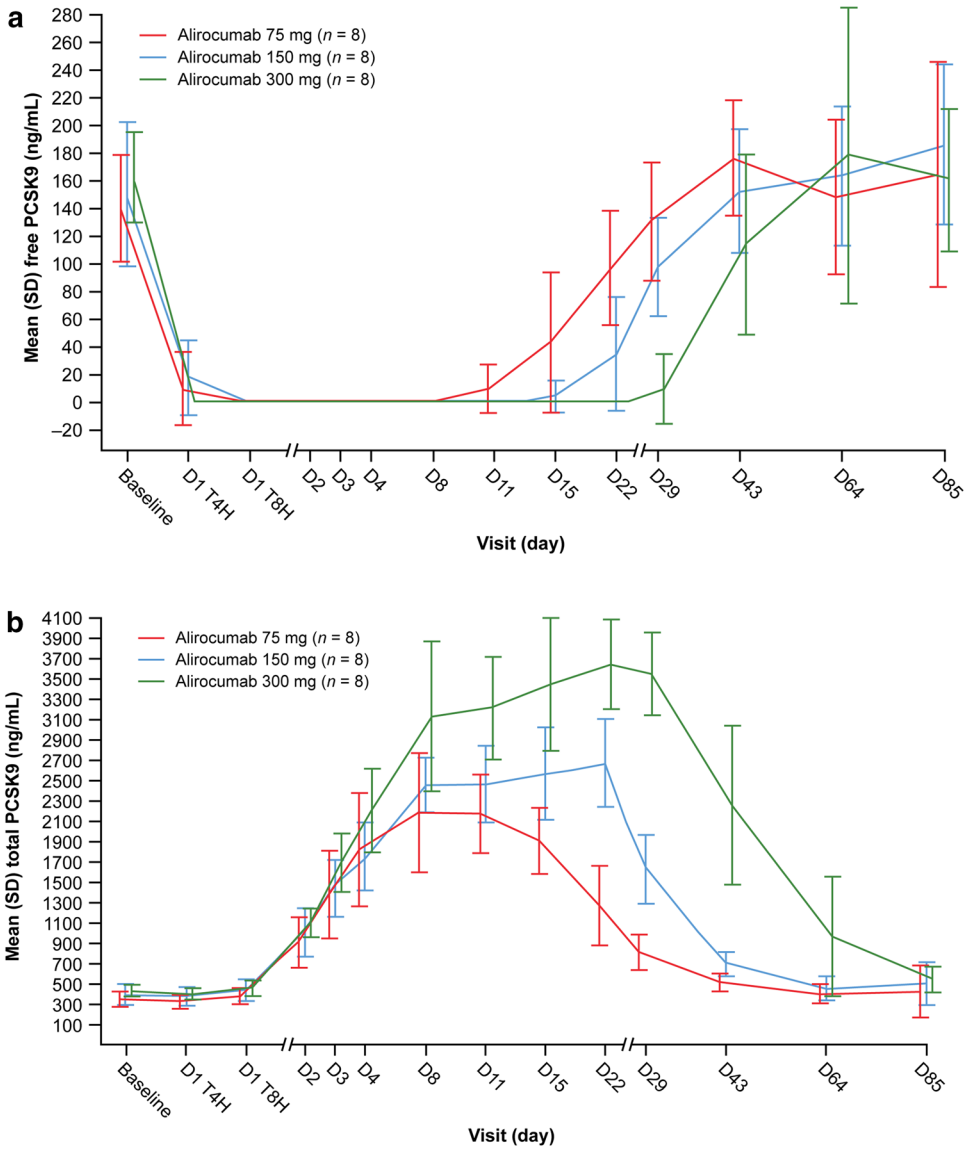

Fig. 4 Mean **a** free and **b** total PCSK9 concentrations in serum over time after single subcutaneous administration of alirocumab 75, 150, or 300 mg. Baseline = day 1 pre-dose assessment. *PCSK9* proprotein convertase subtilisin/kexin type 9, *SD* standard deviation

total PCSK9 concentrations increased from days 3 to 7 and reached a plateau that was maintained to days 14, 24, and 28 with alirocumab 75, 150, and 300 mg, respectively; plateau levels were higher in the higher dose groups (Fig. 4b). Mean total PCSK9 levels returned to baseline values from days 42 (75 mg) to 84 (300 mg).

3.4.3 Relationship Between Alirocumab, PCSK9, and LDL-C Levels

Figure 5 shows the relationships between alirocumab, free PCSK9, and percentage change in LDL-C levels over time following subcutaneous administration of alirocumab 75, 150, and 300 mg.

3.4.4 Other Lipid/Lipoprotein Lowering

In the three alirocumab groups, reductions were also observed in levels of TC, non-HDL-C, and ApoB, with the maximum reductions seen between days 8 and 22 (Fig. 6). Although there were no significant changes in HDL-C, triglycerides, VLDL-C, ApoA1, and Lp(a), trends were observed for increases in HDL-C and ApoA1 and decreases in triglycerides, VLDL-C, and Lp(a); these lipid/lipoprotein parameters remained unchanged in the placebo group.

4 Discussion

In this first study of alirocumab in healthy Chinese subjects with LDL-C > 100 mg/dL (2.59 mmol/L), subcutaneous administration of single alirocumab doses (75, 150,

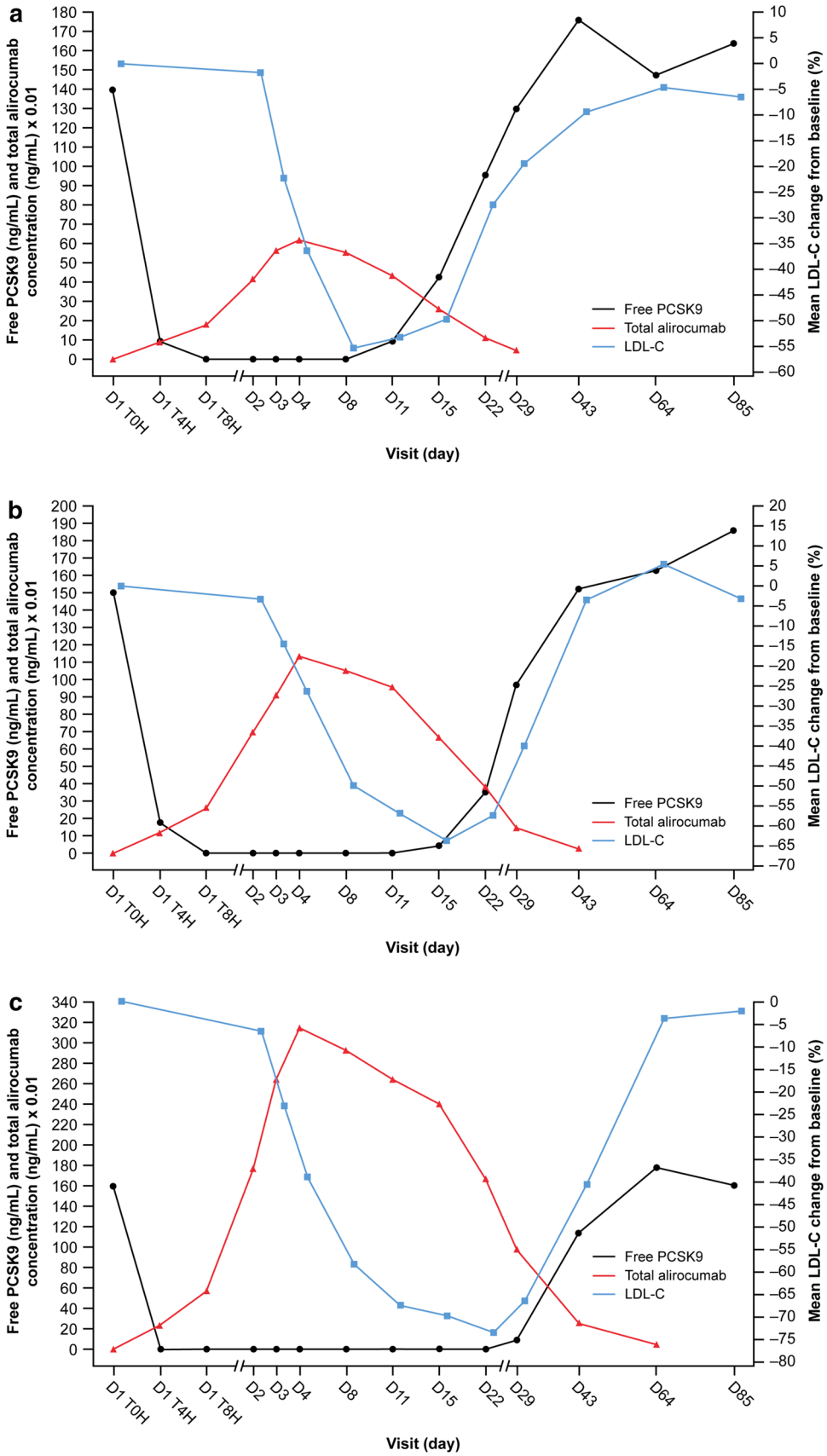

Fig. 5 Relationship between alirocumab, free PCSK9, and mean percentage change in LDL-C levels following single-dose subcutaneous administration of alirocumab **a** 75, **b** 150, and **c** 300 mg. Baseline = day 1 pre-dose assessment. *LDL-C* low-density lipoprotein cholesterol, *PCSK9* proprotein convertase subtilisin/kexin type 9

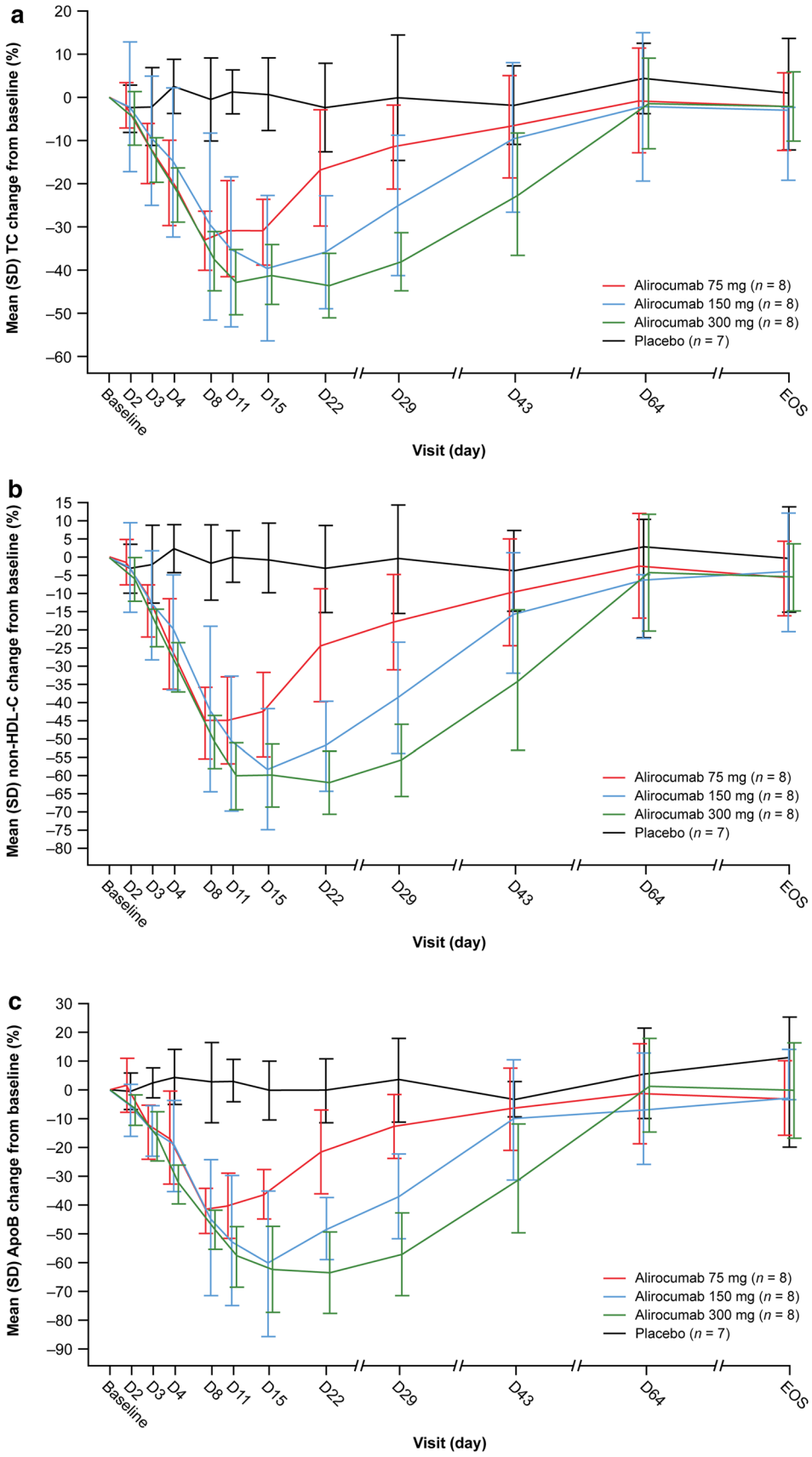

Fig. 6 Mean change (%) from baseline (day 1) to EOS in **a** TC, **b** non-HDL-C, and **c** ApoB after subcutaneous single-dose alirocumab or placebo administration. Baseline = day 1 pre-dose assessment. *Apo* apolipoprotein, *EOS* end of study, *non-HDL-C* non-high-density lipoprotein cholesterol, *SD* standard deviation, *TC* total cholesterol

or 300 mg) were generally well-tolerated, and the pharmacokinetics and pharmacodynamics shown in this population, including effects on PCSK9 and LDL-C, were generally consistent with those reported in studies in the overall predominantly non-Asian population of the alirocumab clinical trial program [22, 25–28] and in phase I studies in healthy subjects of mixed ethnicity [29] and healthy Japanese men [30].

Pooled safety data from 14 phase II and III randomized trials showed a higher incidence of injection-site reactions in subjects receiving alirocumab than in controls [31]. In this study, on the day after alirocumab administration, a local injection-site reaction of mild intensity was reported for one recipient of alirocumab 300 mg, which spontaneously resolved within 2 days. Very low rates of immunogenicity have been reported in clinical trials of alirocumab. An immunogenicity analysis of patient data ($n = 4747$) pooled from ten phase III alirocumab trials found no association between the occurrence of ADAs (5.1%) and the efficacy and safety of alirocumab, although injection-site reactions (mostly mild) were more frequent among patients with treatment-emergent ADAs than those without (11.6 vs. 5.9%) [23]. All subjects who received alirocumab in the current study were ADA negative.

Consistent with the pharmacokinetics of alirocumab 75–300 mg in other populations [13, 22, 29], after single subcutaneous doses of alirocumab 75, 150, or 300 mg in healthy Chinese subjects, alirocumab C_{max} occurred at a median of 3–7 days with generally low-to-moderate subject variability. Additionally, following single-dose subcutaneous administration of alirocumab 75 mg in this healthy cohort, C_{max}, $t_{max,}$ AUC_{∞}, and V_{ss}/F were 6.32 mg/L, 3.00 days, 87.6 mg·day/L, and 9.78 L, respectively, similar to the data previously reported for a healthy cohort comprising various ethnicities (8.18 mg/L, 2.96 days, 129 mg·day/L, and 7.28 L, respectively) [29].

After subcutaneous administration of single-dose alirocumab 75, 150, and 300 mg, LDL-C levels were reduced from baseline from as early as day 3, with maximum mean reductions on days 8 (55.3%), 15 (63.7%), and 22 (73.7%), respectively. These percentage reductions are consistent with those reported in a pooled analysis of phase III alirocumab trials in patients with hypercholesterolemia receiving maximally tolerated background statin therapy in which, at week 12, LDL-C was reduced by 44.5–49.2% with alirocumab 75 mg Q2W and by 62.6% with alirocumab 150 mg Q2W [32]. Additionally, the reductions were similar to those in data reported in a phase III study that investigated alirocumab 300 mg every 4 weeks on maximally tolerated background statin therapy: at week 12, LDL-C was reduced by 55.3% [21]. In most clinical laboratories, LDL-C is not directly measured but is instead estimated using the Friedewald equation [24], which has limitations, particularly when LDL-C levels are low and triglyceride levels are elevated (> 400 mg/dL); however, this was not the case in our study. As shown in previous phase I trials [25], the magnitude and duration of LDL-C reduction were positively associated with the alirocumab dose administered and showed an inverse association with the observed increase in total PCSK9 levels, which reached a plateau from days 3 to 7 that persisted up to day 28 (300 mg). Consistent with the target-mediated clearance of monoclonal antibodies [33], by binding to PCSK9, the apparent CL/*F* of alirocumab was reduced at the highest dose administered.

It has previously been shown that alirocumab has two elimination phases [34]: at low concentrations, elimination is predominately through saturable binding to PCSK9, whereas at higher concentrations, elimination is predominantly through a linear non-saturable proteolytic pathway [13]. At higher alirocumab doses, when alirocumab has bound all free PCSK9 and there is excess antibody (target saturation) [27], most of the total PSCK9 is in the biologically inert bound complex. With the elimination of the PCSK9–alirocumab complex being slow relative to formation, the concentration of total PCSK9 plateaus, indicating target saturation. Generally, the magnitude and duration of reduction in LDL-C is positively related to the alirocumab dose administered.

A population pharmacokinetic analysis of 2799 healthy volunteers or patients with hypercholesterolemia who received intravenous or subcutaneous alirocumab showed that age, bodyweight, creatinine clearance, sex, and race had no significant influence on the pharmacokinetic parameters of alirocumab; therefore, no dose adjustments are recommended for these populations [13, 27]. Furthermore, no meaningful difference in exposure was found between healthy Japanese and Caucasian subjects following single-dose subcutaneous administration of alirocumab 100–300 mg [35]. A recent study that qualified a population pharmacokinetic model for alirocumab in the Chinese population, including data from the present Chinese cohort, showed that alirocumab exposure parameters (C_{max} and $AUC_{0–D14}$) were similar to those reported in Caucasian/Black populations and non-Chinese Asian patients [36]. The population pharmacokinetic modeling further supports the notion that the same alirocumab doses used globally are applicable to the Chinese population.

Administration of alirocumab led to reductions in LDL-C and in other atherogenic lipids/lipoproteins (TC, non-HDL-C, and ApoB), peaking between days 8 and 22. Although no significant changes in HDL-C, triglycerides, VLDL-C, ApoA1, or Lp(a) levels were seen in this study, trends for increases in HDL-C and ApoA1 and decreases in triglycerides, VLDL-C, and Lp(a) were noted. Notably, alirocumab has been shown to reduce Lp(a) levels [25, 37, 38]: in a pooled analysis of ten alirocumab phase III trials, alirocumab 75/150 mg Q2W significantly reduced Lp(a) levels

from baseline to week 24 by up to 29% [38]. Alirocumab was administered as a single dose in this study, which may explain the minor effect on levels of Lp(a) and other lipids/lipoproteins.

The present study has several limitations. The upper age limit for study inclusion (45 years) precluded recruitment of older adults, and fewer female ($n=8$ [25.8%]) than male ($n=23$ [74.2%]) subjects were enrolled. Additionally, only healthy subjects, rather than those with prior ASCVD, were assessed; hence, studies in patients with ASCVD in China are required to evaluate the effects of alirocumab in this patient population. Results from the completed ODYSSEY EAST study, which investigated the efficacy and safety of alirocumab versus ezetimibe on background statin therapy in patients with hypercholesterolemia at high cardiovascular risk ($n=615$) in China, India, and Thailand, showed that, consistent with previous ODYSSEY studies, alirocumab significantly reduced LDL-C versus ezetimibe in patients at high cardiovascular risk from Asia and was generally well-tolerated [39].

5 Conclusions

Single-dose subcutaneous administration of alirocumab 75, 150, or 300 mg was generally safe and well-tolerated in healthy Chinese subjects. The pharmacokinetic and pharmacodynamic parameters of alirocumab, including clinically meaningful reductions in LDL-C and other lipids/lipoproteins, are consistent with those in data from Japanese [30] and Western populations [25, 29], suggesting that the alirocumab dosages used worldwide are applicable in the Chinese population.

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Compliance with Ethical Standards

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Conflict of interest HL, YW, ZY, SZ, and XX are employees of the Peking University Third Hospital. MS, OV, YWW, MTB-D and JL are employees of and shareholders in Sanofi. YZ is an employee of and shareholder in Regeneron Pharmaceuticals, Inc.

Ethical approval All procedures performed in the study participants were in accordance with the ethical standards of the independent ethics committee and with the 1964 Helsinki declaration and its later amendments.

Informed consent All participants provided written informed consent. No identifying information for individual subjects is included in this article.

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