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A randomized study investigating the safety, tolerability, and pharmacokinetics of evinacumab, an ANGPTL3 inhibitor, in healthy Japanese and Caucasian subjects

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ABSTRACT

Background and aims: Evinacumab, an angiopoietin-like protein 3 monoclonal antibody, reduced low-density lipoprotein cholesterol (LDL-C) significantly in a Phase 2 study of patients with homozygous familial hypercholesterolemia. In this double-blind, placebo-controlled Phase 1 study, we compared safety, tolerability, pharmacokinetics, and pharmacodynamics of evinacumab between healthy Japanese and Caucasian adults.
Methods: Subjects with LDL-C ≥2.6 and <4.1 mmol/L were enrolled to one of four dose cohorts: evinacumab subcutaneous (SC) 300 mg single dose, SC 300 mg once weekly for eight doses, intravenous (IV) 5 mg/kg, or IV 15 mg/kg once every 4 weeks for two doses. Each cohort comprised 24 subjects (12 Japanese; 12 Caucasian), randomized (3:1) to receive evinacumab or placebo within each ethnic group with a 24-week follow-up.
Results: The safety profile of evinacumab (IV and SC) in both ethnicities was comparable with placebo, with no serious or severe treatment-emergent adverse events. Pharmacokinetic profiles were comparable between Japanese and Caucasian subjects across IV and SC groups. Mean calculated LDL-C decreased from baseline with both IV doses, beginning on day 3 up to week 8. Triglyceride changes observed with evinacumab IV were rapid (seen by day 2) and sustained up to week 8. Evinacumab SC doses also reduced LDL-C and triglyceride levels, although lower doses induced smaller changes. Evinacumab (IV and SC) reduced other lipids, including apolipoprotein B, *versus* placebo.
Conclusions: In both ethnicities, evinacumab (IV and SC) was generally well tolerated, exhibiting comparable pharmacokinetic profiles. Dose-related reductions in LDL-C and triglycerides were observed with evinacumab in both ethnic groups.

1. Introduction

Hypercholesterolemia is a major risk factor for atherosclerotic cardiovascular disease (ASCVD) [1]. Globally, cardiovascular disease (CVD) is the leading cause of mortality, placing a large socioeconomic burden on society [2,3]. Despite significant advances in the development of lipid-lowering medications, substantial CVD risk persists even when receiving currently recommended pharmacological therapies, particularly in patients with familial hypercholesterolemia (FH) [4,5]. Homozygous familial hypercholesterolemia (HoFH), a severe form of FH, is an ultra-rare, life-threatening, autosomal genetic disorder of lipid metabolism characterized by markedly elevated plasma levels of low-density lipoprotein cholesterol (LDL-C) from birth, tendon and skin xanthomas, and an exceedingly increased risk of ASCVD [5].

Plasma LDL-C levels are principally regulated by the number of low-density lipoprotein (LDL) receptors expressed at the surface of hepatocytes and are essential for the uptake and subsequent intracellular degradation of LDL [6]. FH is associated with mutations in several genes

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involved in the LDL catabolic pathway, including LDL receptor (*LDLR*), apolipoprotein B (*APOB*), proprotein convertase subtilisin/kexin type 9 (*PCSK9*), and LDL protein receptor adaptor 1 [5,7]. These mutations impair the liver's ability to remove LDL from the circulation, leading to elevated total and LDL-C concentrations [7,8]. Patients with HoFH most commonly have two pathogenic mutations in genes affecting LDLR function, one inherited from each parent [9]. Individuals with untreated HoFH are associated with plasma LDL-C levels >10.3 mmol/L (400 mg/dL) [10]. Patients with HoFH often require treatment with multiple lipid-lowering therapies, including lipoprotein apheresis, due to inadequate therapeutic responses achieved with statins and PCSK9 inhibitors, which are dependent on LDLR function [11].

In Japan there is an unmet need for more effective lipid-lowering therapies for patients with HoFH who respond inadequately to currently available drug therapies and/or lipoprotein apheresis [12]. The Japan Atherosclerosis Society recommends that, in the treatment of patients with HoFH, clinicians should set a management goal for LDL-C that is <2.6 mmol/L (100 mg/dL) in primary prevention and <1.8 mmol/L (70 mg/dL) in secondary prevention [13]. However, in HoFH patients, this goal is difficult to achieve even with the currently available treatment options [13]. Furthermore, although lipoprotein apheresis is widely performed in HoFH patients in Japan, it is still not enough to prevent the development of ASCVD [14].

Angiopoietin-like protein 3 (ANGPTL3) is a secreted glycoprotein predominately expressed in the liverthat plays a prominent role in the regulation of lipid metabolism by inhibiting lipoprotein lipase and endothelial lipase (EL) activity, thus increasing plasma levels of triglycerides, LDL-C, and high-density lipoprotein cholesterol (HDL-C) [15,16]. Genetic studies have shown that individuals with heterozygous loss-of-function variants of the *ANGPTL3* gene have a lipid phenotype of lower levels of LDL-C, triglycerides, and HDL-C, and a 41% lower risk of coronary artery disease, compared to those without mutations [17].

The mechanism for LDL-C reduction via inhibition of ANGPTL3 is independent of the LDLR [17–19]. A recent study in hyperlipidemic individuals and mice has identified a novel EL-dependent pathway that lowers LDL-C in the absence of LDLR [19]. More specifically, EL de-repression via inhibition of ANGPTL3 leads to extensive remodeling of very low-density lipoprotein (VLDL), and preferential removal of VLDL remnants from the circulation [19]. The LDL precursor pool becomes depleted and production of LDL particles is limited, which ultimately results in reduced plasma LDL-C [19].

Evinacumab is a fully human monoclonal antibody against ANGPTL3 that has been shown to reduce LDL-C, triglycerides, and non-HDL-C in healthy volunteers and patients with HoFH [11,17,20].

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E5 guidance document, entitled "Ethnic Factors in the Acceptability of Foreign Clinical Data", describes the use of bridging studies to aid in the extrapolation of foreign clinical data to a new region [21]. Consistent with the ICH E5 guidance, ethnic evaluation of the pharmacokinetics (PK) and safety of new drugs is required in Japan before joining global studies. Therefore, given the unmet medical need for additional therapeutic options for Japanese patients with HoFH, it is important to evaluate the impact of ethnicity on the safety, PK, and pharmacodynamics (PD) of evinacumab in order to enable development of this drug in Japanese patients. Thus, the objective of this study was to evaluate the safety, tolerability, PK, and PD of subcutaneous (SC) and intravenous (IV) doses of evinacumab in healthy Japanese (first-generation) and Caucasian subjects.

2. Patients and methods

2.1. Ethics

The study was conducted in accordance with the Declaration of Helsinki and the ICH Guidelines for Good Clinical Practice. An independent ethics committee approved the study protocol, informed consent form, and subject information. Written informed consent was obtained from each subject.

2.2. Study design and patients

This was a randomized, double-blind, placebo-controlled, single-center, Phase 1 study (NCT03146416) of evinacumab administered SC or IV to healthy first-generation Japanese and Caucasian subjects aged ≥18 and ≤ 55 years. 'First-generation Japanese' was defined as a population meeting all three of the following inclusion criteria: (1) born in Japan, (2) having both biological parents who are ethnic Japanese, and (3) following a Japanese lifestyle that has not significantly changed since leaving Japan, including having access to Japanese food and adhering to a Japanese diet. Caucasian subjects were required to be Caucasian, of European or Latin American descent, and adherent to a Western diet. All subjects were required to have modest elevations in LDL-C (≥2.6 but <4.1 mmol/L [≥100 but <160 mg/dL]) at screening. Subjects could have elevations in triglycerides (≥1.7 but <5.6 mmol/L [≥150 mg/dL but <500 mg/dL] measured after at least an 8-h fast) but this was not an inclusion requirement.

Key exclusion criteria included the use of any medication or nutritional supplement that altered serum lipids, including but not limited to statins, ezetimibe, fibrates, niacin, omega-3 fatty acids, and bile acid resins within 4 weeks (6 weeks for fibrates) prior to screening and for the duration of the study; the presence of significant concomitant illness; known allergy or sensitivity to monoclonal antibodies; and previous exposure to *anti*-ANGPTL3 antibodies. A full list of inclusion and exclusion criteria is detailed in Supplemental Table 1.

The total study population comprised 96 subjects (Japanese [n = 48]; Caucasian [n = 48]) at one study site in the United States. Subjects were enrolled into one of four dose cohorts, with each cohort comprising of 24 subjects (Japanese [n = 12]; Caucasian [n = 12]). Within each cohort, Japanese and Caucasian subjects were randomized to receive evinacumab or placebo in a 3:1 ratio (nine active: three placebo). To minimize between-group variability, Japanese and Caucasian subjects were group-matched to a target of an average age of ±10 years and an average body weight of ±20%.

Dosage regimens for each cohort were as follows: evinacumab 300 mg SC single dose (cohort 1), evinacumab 5 mg/kg IV once every 4 weeks [Q4W] for two doses (cohort 2), evinacumab 15 mg/kg IV Q4W for two doses (cohort 3), and evinacumab 300 mg SC once weekly [QW] for eight doses (cohort 4). Evinacumab was supplied as a lyophilized powder formulation for reconstitution in a sterile, single-use 20 mL glass vial for IV or SC administration. Each vial contained 287 mg of evinacumab. Placebo was supplied in matching vials.

The study comprised a screening period, a baseline visit, a treatment and follow-up period, and an end-of-study visit. Subjects underwent screening for study eligibility from day −21 to day −2. Eligible subjects were admitted to the clinic on day −1 for pre-dose procedures and remained overnight for 3 days (days −1, 1, and 2). On day 1 (baseline), subjects were randomized to evinacumab or placebo, remaining in clinic after study drug administration for safety observation and PK sampling. Subjects were discharged on day 3, returning to the clinic for regular safety and PK/PD assessments.

Following administration of study drug on day 1, subjects in cohort 1 did not receive additional doses of study drug. Subjects in cohorts 2 and 3 received a second IV infusion of study drug on day 29, and subjects in cohort 4 received a SC injection of study drug on days 8, 15, 22, 29, 36, 43, and 50 for a total of eight doses. After the last dose of study drug, subjects in all cohorts were to be followed for 24 weeks, with end-of-study visits on day 169 (week 24) for cohort 1 (SC), day 197 (week 28) for cohorts 2 and 3 (IV), and day 218 (week 31) for cohort 4 (SC). Cohort enrollment and dose escalation are detailed in Supplementary Text 1.

2.3. Outcome assessments

2.3.1. Primary endpoint

The primary endpoint was the incidence and severity of treatment-emergent adverse events (TEAEs). For SC and IV administration, the TEAE period was defined as the day from first dose of study drug to the end-of-study visit. TEAEs were defined as events that developed, worsened, or became serious during the TEAE period.

2.3.2. Secondary endpoints

For all cohorts, the following PK parameters were determined for total evinacumab in serum following administration of the first dose: maximum serum concentration (C_{max}), C_{max} normalized by dose, and time to C_{max}. For the evinacumab 300 mg SC single-dose cohort, additional PK parameters included area under the concentration–time curve from time zero extrapolated to infinity (AUC_{inf}), apparent clearance for SC dose, AUC computed from time zero to the time of the last positive concentration (AUC_{last}), and AUC_{last} normalized by dose. Additional PK parameters that were determined for the evinacumab SC/IV multiple-dose cohorts only included AUC for a dosing interval (AUC_{tau}) and AUC_{tau} normalized by dose following the first dose. PD effects were assessed by analysis of fasting lipids over time and included calculated LDL-C (using the Friedewald formula), triglycerides, HDL-C, total cholesterol, non-HDL-C, lipoprotein(a) (Lp(a)), apolipoprotein (Apo) B, Apo A-1, and Apo C-3. The immunogenicity of evinacumab was determined by the potential emergence and titer of *anti*-evinacumab antibodies over time.

2.4. Statistical analysis

For this study, a statistical power analysis was not performed for sample size estimations. However, a sample size of 24 subjects for each cohort was considered adequate for descriptively characterizing the safety, tolerability, PK/PD, and immunogenicity of evinacumab. No formal statistical hypotheses were tested in this study. Description of the analysis sets is detailed in Supplementary Data 1.

Descriptive data for evinacumab dose regimens and placebo is displayed by ethnicity for each cohort. For each SC and IV treatment regimen, all placebo-treated subjects within each ethnic group were pooled for analysis. For continuous variables, descriptive statistics included the number of subjects (n), mean, median, standard deviation, first quartile, third quartile, minimum, and maximum. For categorical or ordinal variables, frequencies and percentages are presented by category. There was no formal comparison or testing between evinacumab and placebo, ethnic group, evinacumab doses, and route of administration (IV and SC).

3. Results

3.1. Patients

A total of 96 subjects (Japanese [n = 48]; Caucasian [n = 48]) were enrolled into the overall study, with 72 (Japanese [n = 36]; Caucasian [n = 36]) randomized to receive evinacumab (nine Japanese and nine Caucasian subjects in each of the IV and SC evinacumab treatment groups) and 24 randomized to receive placebo (six Japanese and six Caucasian subjects in each of the IV and SC placebo groups). All 96 randomized subjects (100%) received the study drug and were included in the safety and PD analysis set. The disposition of subjects is shown in Supplemental Fig. 1.

For subjects randomized to evinacumab IV, 86.1% (31/36) completed the end-of-study visit. Of those who did not, 8.3% (3/36) were lost to follow-up and 5.6% (2/36) withdrew consent; all subjects who discontinued were Caucasian. For subjects randomized to evinacumab SC, 91.7% (33/36) completed the end-of-study visit. Of those who did not, 2.8% (1/36) were lost to follow-up and 5.6% (2/36) withdrew consent; 5.6% (1/18) of subjects who discontinued were Japanese and 11.1% (2/18) were Caucasian.

In the evinacumab IV treatment groups, Japanese subjects were slightly older than Caucasian subjects (42.6 years *vs* 33.9 years, respectively). The majority (72.2%) of Japanese subjects were female, whilst the majority (77.8%) of Caucasian subjects were male. Japanese subjects had a lower mean body mass index (BMI) than Caucasian subjects (23.5 kg/m^2 *vs* 26.6 kg/m^2, respectively). Baseline lipids were comparable between Japanese and Caucasian subjects, except for higher triglycerides in Caucasian (1.5 mmol/L [132.0 mg/dL]) *versus* Japanese subjects (0.9 mmol/L [82.0 mg/dL]).

In the evinacumab SC treatment groups, baseline characteristics were similar between Japanese and Caucasian subjects, with the exception of BMI and the number of females. Baseline lipid parameters were generally comparable between Caucasian and Japanese subjects. Demographics, baseline characteristics, and lipid profiles are detailed in Table 1 and Supplemental Table 2 for the IV and SC treatment groups, respectively.

3.2. Safety

3.2.1. Evinacumab IV

The safety profile of the evinacumab treatment groups was comparable with that of placebo (Table 2). TEAEs occurred in six (50.0%) subjects in the combined placebo IV treatment group and in 15 (41.7%) subjects in the combined evinacumab IV treatment groups, with similar rates between the two evinacumab IV dose groups. Frequencies of TEAEs were similar between Japanese and Caucasian subjects in the 15 mg/kg IV Q4W dose group (33.3% and 44.4%) but were higher for Caucasian subjects (66.7%) than for Japanese subjects (22.2%) in the 5 mg/kg IV Q4W dose group (Table 2). Hypersensitivity adverse events (AEs) were experienced by one (16.7%) Caucasian subject in the combined IV placebo treatment group and one (11.1%) Caucasian subject in the evinacumab 15 mg/kg IV Q4W treatment group.

3.2.2. Evinacumab SC

TEAEs occurred in three (25.0%) subjects in the combined placebo SC treatment group and in 19 (52.8%) subjects in the combined evinacumab SC dose group, with more subjects experiencing TEAEs in the 300 mg QW group (77.8%) than in the 300 mg single-dose group (27.8%). The rate of TEAEs was similar between Japanese and Caucasian subjects in the 300 mg single-dose group (22.2% and 33.3%) but was higher for Caucasian subjects (88.9%) than for Japanese (66.7%) in the 300 mg QW group (Supplemental Table 3). Hypersensitivity AEs were reported at a higher frequency (27.8%) for evinacumab-treated subjects in the 300 mg QW group *versus* the 300 mg single-dose group (5.6%; Supplemental Table 3). Treatment-related TEAEs and injection-site reactions were reported by two (11.1%) and six (33.3%) subjects, respectively, only in the 300 mg QW group. No serious AEs (SAEs), severe TEAEs, TEAEs of special interest, TEAEs leading to study discontinuation, or TEAEs leading to death were observed in any SC or IV treatment groups. In both IV and SC groups, no positive *anti*-drug antibodies (ADAs) were detected from any subject or serum ADA sample.

3.3. Pharmacokinetics

Mean concentrations (±standard deviation [SD]) of total evinacumab in serum over time for Japanese and Caucasian subjects are shown in Fig. 1. PK exposure parameters (AUC_{tau} and C_{max}) of evinacumab following first administration in the IV and SC dose cohorts are detailed in Supplemental Tables 4 and 5 Overall, serum evinacumab concentrations over time and PK exposure parameters were comparable between both ethnicities across IV and SC groups.

Table 1
Demographics, baseline characteristics, and lipid profile of subjects receiving IV regimens (safety analysis set).

	IV regimen							
	Placebo		Evinacumab 5 mg/kg Q4W		Evinacumab 15 mg/kg Q4W		Total evinacumab	
	Japanese (n = 6)	Caucasian (n = 6)	Japanese (n = 9)	Caucasian (n = 9)	Japanese (n = 9)	Caucasian (n = 9)	Japanese (n = 18)	Caucasian (n = 18)
Subject demographics								
Age, years, mean ± SD	42.0 ± 8.8	38.8 ± 7.8	43.9 ± 9.5	33.6 ± 6.3	41.2 ± 10.6	34.2 ± 10.0	42.6 ± 9.9	33.9 ± 8.1
Male, n (%)	5 (83.3)	4 (66.7)	1 (11.1)	7 (77.8)	4 (44.4)	7 (77.8)	5 (27.8)	14 (77.8)
Ethnicity, n (%)								
Hispanic or Latino	0	3 (50)	0	4 (44.4)	0	5 (55.6)	0	9 (50)
Not Hispanic or Latino	6 (100)	3 (50)	9 (100)	5 (55.6)	9 (100)	4 (44.4)	18 (100)	9 (50)
BMI, kg/m^2, mean ± SD	24.2 ± 3.5	26.0 ± 2.4	23.9 ± 3.1	25.1 ± 3.6	23.1 ± 2.8	28.0 ± 2.9	23.5 ± 2.9	26.6 ± 2.9
Baseline lipid profiles, median (min,max)								
Low-density lipoproteins								
LDL-C (calculated), mmol/L	3.1 (3,4)	3.3 (2,4)	3.1 (2,6)	3.1 (2,4)	2.8 (2,4)	3.6 (3,4)	3.1 (3,4)	3.3 (2,4)
Lipoprotein(a), mg/dL	63.0 (5.0,114.0)	17.0 (4.0,150.0)	34.0 (25.0,116.0)	12.0 (4.0,226.0)	19.0 (6.0,70.0)	32.0 (7.0,277.0)	29.0 (6.0,116.0)	21.0 (4.0,277.0)
Triglyceride-rich lipoproteins								
Triglycerides, mmol/L	1.1 (1,3)	1.4 (1,3)	0.9 (1,4)	1.5 (1,2)	0.9 (1,3)	1.6 (1,3)	1.1 (1,3)	1.4 (1,3)
Unfractionated non-HDL								
Non–HDL-C, mmol/L	3.8 (3,4)	3.8 (3,5)	3.4 (3,7)	3.8 (3,5)	3.1 (3,5)	4.3 (4,5)	3.8 (3,4)	3.8 (3,5)
Apo B, mg/dL	100.5 (82.0,114.0)	97.5 (79.0,122.0)	81.0 (67.0,164.0)	90.0 (75.0,114.0)	80.0 (72.0,130.0)	109.0 (89.0,132.0)	80.5 (67.0,164.0)	98.0 (75.0,132.0)
High-density lipoproteins								
HDL-C, mmol/L	1.4 (1,2)	1.0 (1,2)	1.5 (1,2)	1.1 (1,2)	1.5 (1,3)	1.0 (1,1)	1.4 (1,2)	1.0 (1,2)
Apo A-1, mg/dL	149.0 (124.0,176.0)	134.5 (115.0,162.0	142.0 (78.0,185.0)	124.0 (118.0,180.0)	157.0 (121.0,220.0)	142.0 (117.0,199.0)	156.0 (78.0,220.0)	131.0 (117.0,199.0)
Other								
Total cholesterol, mmol/L	5.3 (5,5)	5.1 (4,6)	5.1 (4,8)	5.0 (4,6)	5.0 (4,6)	5.2 (5,6)	5.3 (5,5)	5.1 (4,6)
Apo C-3, mg/dL	8.5 (5.0,9.0)	9.5 (6.0,12.0)	9.0 (3.0,17.0)	9.0 (5.0,14.0)	8.0 (5.0,18.0)	11.0 (7.0,17.0)	8.5 (3.0,18.0)	10.0 (5.0,17.0)

Apo: apolipoprotein; BMI: body mass index; HDL-C: high-density lipoprotein cholesterol; IV: intravenous; LDL-C: low-density lipoprotein cholesterol; Q4W: once every 4 weeks; SD: standard deviation.

3.4. Pharmacodynamic evaluation

3.4.1. LDL-C

Evinacumab treatment resulted in substantial reductions in LDL-C at all doses and routes of administrations compared with placebo (Fig. 2A). In the IV treatment groups, evinacumab lowered LDL-C in a dose-dependent manner. Mean calculated LDL-C decreased from baseline rapidly, beginning on day 3 and sustained up to week 8 of the follow-up period with mean percent changes from baseline of −18.2% and −33.6%, in the 5 mg/kg Q4W and 15 mg/kg Q4W IV dose groups, respectively. At week 8, the magnitude of LDL-C reduction was similar between Japanese and Caucasian for the 5 mg/kg group (−17.7% *vs* −18.9%, respectively); however, LDL-C reductions were higher in Caucasian than Japanese subjects for the 15 mg/kg group (−40.2% *vs* −28.6%, respectively). Changes with placebo were +4.9% (Japanese subjects) and +13.7% (Caucasian subjects; Fig. 2B and Supplemental Table 6). At week 4, LDL-C reductions were similar between Japanese and Caucasian subjects for the 15 mg/kg group (−37.9% *vs* −38.3%, respectively); changes with placebo were +8.7% (Japanese subjects) and +3.9% (Caucasian subjects). During the remainder of the follow-up period, LDL-C reductions tapered off, almost returning to baseline levels by the end of the study at week 28. In the SC treatment groups, the magnitude of LDL-C reduction was comparable between Japanese and Caucasian subjects at most timepoints and in both treatment groups (Fig. 2C and Supplemental Table 7).

3.4.2. Triglycerides

Relative to placebo, treatment with evinacumab resulted in significant reductions in triglycerides at all doses and routes of administrations (Fig. 3A). For IV doses, evinacumab reduced triglycerides rapidly in a dose-dependent manner, beginning on day 2 and sustained up to week 8. At week 4, the magnitude of triglyceride reductions (median percent change from baseline) was comparable between Japanese and Caucasian subjects for the 5 mg/kg group (−17.5% *vs* −15.0%, respectively) and 15 mg/kg group (−51.7% *vs* −59.8%, respectively); changes with placebo were +4.2% (Japanese subjects) and −7.0% (Caucasian subjects) (Fig. 3B and Supplemental Table 6). At week 8, triglyceride reductions were greater in Caucasian than Japanese subjects for the 5 mg/kg group (−32.5% *vs* −15.4%, respectively) and 15 mg/kg group (−63.1% *vs* −44.7%, respectively); changes with placebo were +43.3% (Japanese subjects) and +6.1% (Caucasian subjects; Fig. 3B; Supplemental Table 6). In the SC treatment groups, triglyceride reductions were mostly comparable between Japanese and Caucasian subjects in both treatment groups (Supplemental Fig. 3C and Supplemental Table 7).

3.4.3. Changes in other lipids

Japanese and Caucasian subjects receiving evinacumab IV or SC had greater reductions in mean non-HDL-C values *versus* placebo, sustained up to week 8 (Supplemental Tables 6 and 7). At week 8, in the 5 mg/kg group, the magnitude of non-HDL-C reduction was comparable between Japanese and Caucasian subjects (−17.0% *vs* −20.3%, respectively); in

Table 2
Summary of TEAEs by MedDRA preferred term in subjects receiving IV regimens (safety analysis set).

	IV regimen							
	Placebo		Evinacumab 5 mg/kg Q4W		Evinacumab 15 mg/kg Q4W		Total evinacumab	
	Japanese (*n* = 6)	Caucasian (*n* = 6)	Japanese (*n* = 9)	Caucasian (*n* = 9)	Japanese (*n* = 9)	Caucasian (*n* = 9)	Japanese (*n* = 18)	Caucasian (*n* = 18)
Number of TEAEs	8	5	3	9	7	8	10	17
Subjects with any TEAE, *n* (%)	3 (50.0)	3 (50.0)	2 (22.2)	6 (66.7)	3 (33.3)	4 (44.4)	5 (27.8)	10 (55.6)
Subjects with any serious TEAE, *n* (%)	0	0	0	0	0	0	0	0
Subjects with any severe TEAE, *n* (%)	0	0	0	0	0	0	0	0
Subjects with any treatment-related TEAE, *n* (%)	0	0	0	0	0	0	0	0
Subjects with any hypersensitivity reactions, *n* (%)	0	1 (16.7)	0	0	0	1 (11.1)	0	1 (5.6)
Subjects with at least one infusion-related reaction TEAE, *n* (%)	0	0	0	0	0	0	0	0
Subjects with any TEAE leading to treatment discontinuation, *n* (%)	0	0	0	0	0	0	0	0
Subjects with any TEAE leading to death, *n* (%)	0	0	0	0	0	0	0	0
Commonly occurring TEAEs by MedDRA preferred term[a]								
Nausea	1 (16.7)	0	0	0	1 (11.1)	0	1 (5.6)	0
Fatigue	1 (16.7)	0	0	0	1 (11.1)	0	1 (5.6)	0
Nasopharyngitis	0	1 (16.7)	0	1 (11.1)	0	0	0	1 (5.6)
Upper respiratory infection	1 (16.7)	0	2 (22.2)	2 (22.2)	0	0	2 (11.1)	2 (11.1)
Back pain	1 (16.7)	0	0	2 (22.2)	0	1 (11.1)	0	3 (16.7)
Headache	1 (16.7)	1 (16.7)	0	2 (22.2)	0	1 (11.1)	0	3 (16.7)
Tension headache	0	1 (16.7)	0	0	0	1 (11.1)	0	1 (5.6)

IV: intravenous; MedDRA: Medical Dictionary for Regulatory Activities; Q4W: once every 4 weeks; TEAE: treatment-emergent adverse event.
[a] TEAEs occurring in ≥2 patients in any group for each MedDRA preferred term.

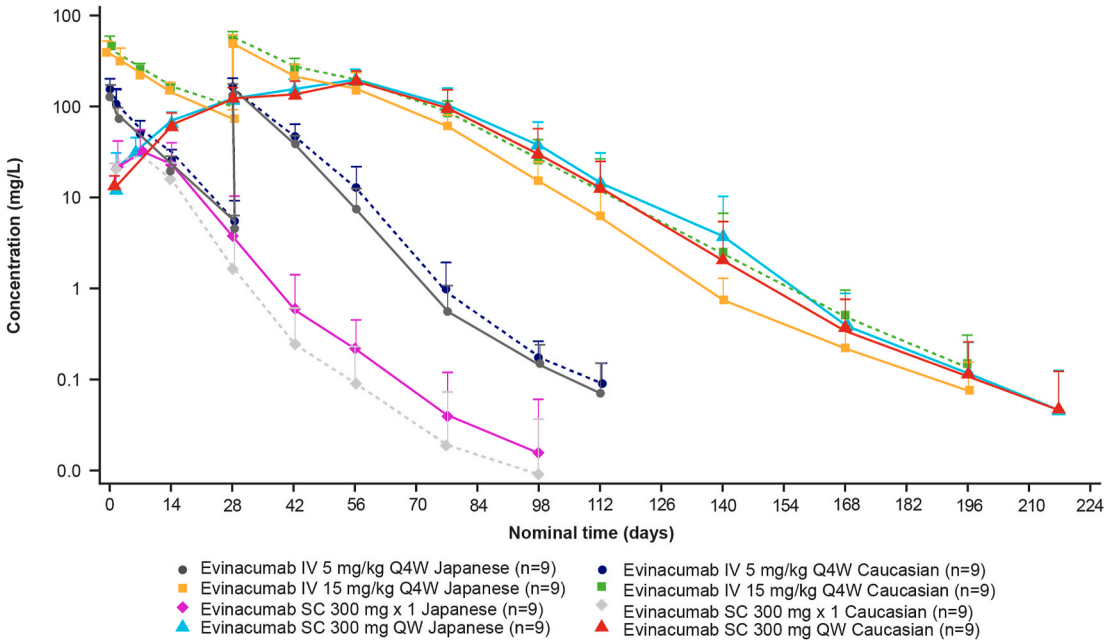

Fig. 1. Mean (±SD) log-scaled concentrations of total evinacumab in serum by nominal time and treatment group in Japanese and Caucasian subjects.
IV: intravenous; N: number of subjects; Q4W: once every 4 weeks; QW: once weekly; SC: subcutaneous; SD: standard deviation.

the 15 mg/kg group, non-HDL-C reduction was greater in Caucasian than Japanese subjects (−44.2% *vs* −30.4%, respectively); changes with placebo were +5.0% (Japanese subjects) and +5.1% (Caucasian subjects). At week 4, non-HDL-C reductions were similar between Japanese and Caucasian subjects for the 5 mg/kg group (−9.8% *vs* −15.4%, respectively) and 15 mg/kg group (−39.6% *vs* −42.9%, respectively); changes with placebo were +7.8% (Japanese subjects) and −2.1% (Caucasian subjects).

For subjects receiving evinacumab IV, Japanese and Caucasian subjects had greater reductions in mean HDL-C *versus* placebo (Supplemental Table 6). At week 8, in the 5 mg/kg Q4W IV group, the magnitude of HDL-C reduction was comparable between Japanese and Caucasian subjects (−6.0% *vs* −4.0%, respectively); in the 15 mg/kg Q4W group, HDL-C reduction was greater in Caucasian than Japanese subjects (−23.8% *vs* −12.6%, respectively). For subjects receiving evinacumab SC, both ethnicities had comparable reductions in HDL-C that were greater compared with placebo (Supplemental Table 7).

Compared with placebo, evinacumab IV and SC doses resulted in

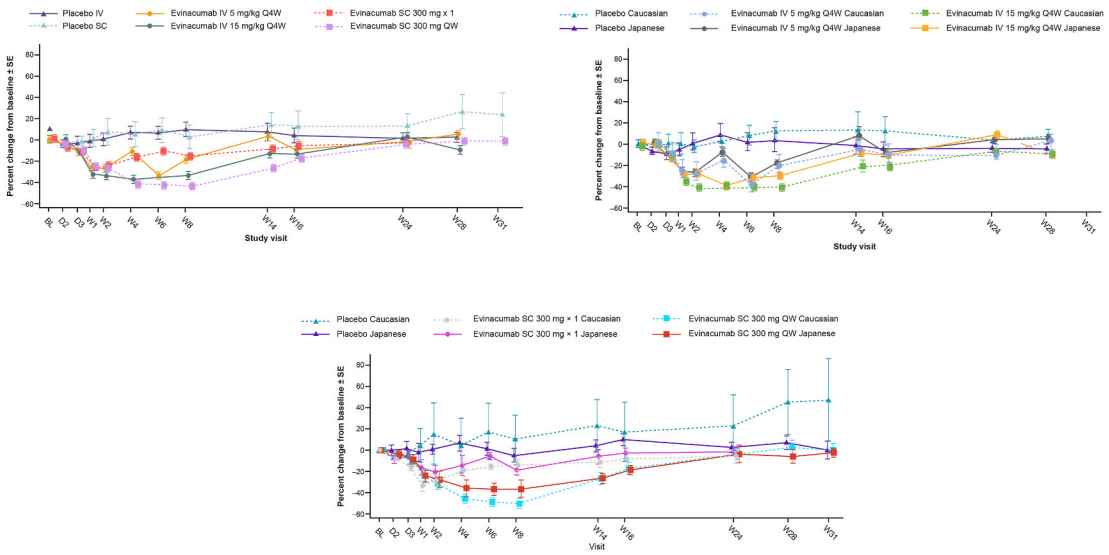

Fig. 2. Mean percent change (±SD) from baseline in calculated LDL-C for (A) all subjects receiving IV and SC regimens and (B) by ethnic group for subjects receiving IV regimens or (C) SC regimens (PD analysis set).
BL: baseline; D: day; IV, intravenous; LDL-C: low-density lipoprotein cholesterol; PD: pharmacodynamic; Q4W: once every 4 weeks; QW: once weekly; SC: subcutaneous; SD: standard deviation; SE: standard error; W: week.

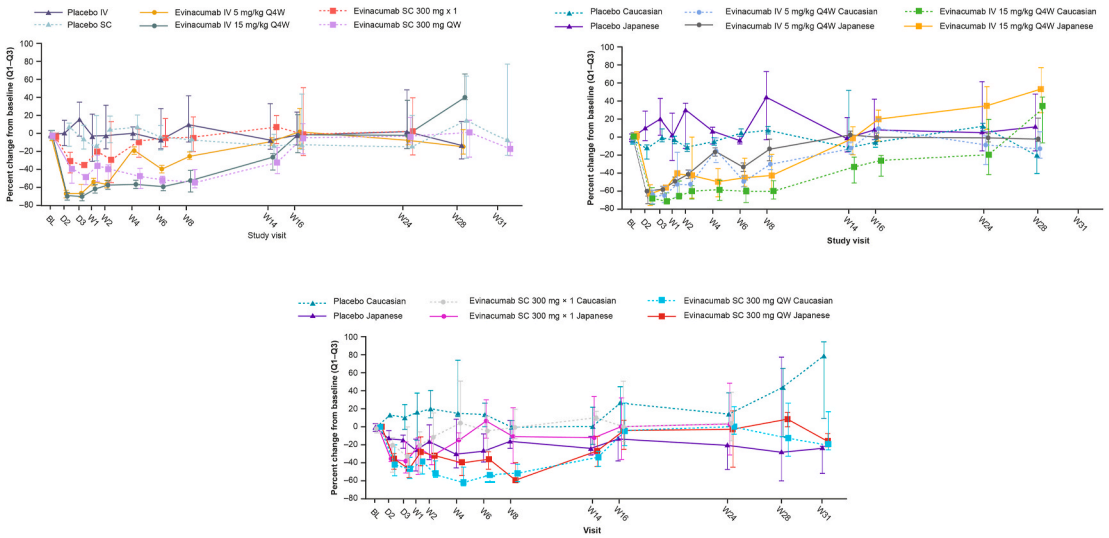

Fig. 3. Median percent change (±SD) from baseline in triglycerides for (A) all subjects receiving IV and SC regimens and (B) by ethnic group for subjects receiving IV regimens or (C) SC regimens (PD analysis set).
BL: baseline; D: day; IV: intravenous; LDL-C: low-density lipoprotein cholesterol; PD: pharmacodynamic; Q1: first quartile; Q3: third quartile; Q4W: once every 4 weeks; QW: once weekly; SC: subcutaneous; SD: standard deviation; W: week.

greater mean reductions in total cholesterol Apo B, Apo A-1, and Apo C-3 for Japanese and Caucasian subjects (Supplemental Tables 6 and 7). In evinacumab IV and SC treatment groups, there was no appreciable pattern in median Lp(a) values relative to placebo (Supplemental Tables 6 and 7).

4. Discussion

In this Phase 1 study of healthy Japanese and Caucasian subjects with modest LDL-C elevations (≥2.6 but <4.1 mmol/L [≥100 but <160 mg/dL]), IV and SC doses of evinacumab were well tolerated, up to and including the highest doses administered (IV 15 mg Q4W and SC 300 mg QW). The safety profile of evinacumab in Japanese and Caucasian groups was comparable with placebo, with no SAEs, severe TEAEs, TEAEs of special interest, TEAEs leading to study discontinuation, or TEAEs leading to death in any treatment group. PK and PD profiles of evinacumab, IV and SC, were similar between Japanese and Caucasian subjects, thus indicating that alternative dosage regimens based on ethnicity are not required.

In Japanese and Caucasian subjects, treatment with evinacumab produced substantial reductions in calculated LDL-C and triglycerides at all doses and routes of administrations compared with placebo. For the IV route of administration, evinacumab lowered LDL-C and triglyceride levels in a dose-dependent manner. At week 8, LDL-C reductions with the 15 mg/kg dose were greater among Caucasian than Japanese subjects, but this was not seen for other time points or the 5 mg/kg dose. At week 4, triglyceride reductions were comparable for both ethnicities in the 5 and 15 mg/kg doses; however, at week 8, triglyceride reductions were greater in Caucasian subjects than Japanese subjects for both IV doses. The magnitude of LDL-C and triglyceride reductions varied

between route of administration and dose, most likely due to a higher SD in the small numbers of subjects (including placebo treatment groups).

Compared with placebo, sustained reductions with IV and SC doses of evinacumab were additionally observed in non-HDL-C, Apo B, total cholesterol, and Apo C-3 levels. HDL-C levels and Apo A-1 levels were also reduced, although the clinical significance of this is unclear. Whilst Lp(a) reductions were demonstrated for some dose groups in Japanese and Caucasian subjects relative to placebo, there was no appreciable pattern. Moreover, the wide range of Lp(a) reductions between patients limits interpretation due to small subject numbers. Conflicting results pertaining to Lp(a) have been reported in two previous studies. In patients with mixed dyslipidemia there was no reduction in Lp(a) following evinacumab treatment [22]. Conversely, in a study comprising nine patients with HoFH, a median reduction in Lp(a) was observed, although a reduction in Lp(a) was not seen in all patients [11].

The PD evaluation and safety results of evinacumab observed in this study are consistent with results demonstrated previously in a Phase 1 (NCT01749878) and Phase 2 study (NCT02265952) [11,17]. Moreover, this study confirms that evinacumab doses (IV and SC) used for the Caucasian population are similarly appropriate for Japanese patients. The effects of ethnicity on PK and PD characteristics have been assessed for other monoclonal antibodies which, similar to this study, demonstrate that modification of dose regimens is not necessary for Asian subjects [23–25]. Using pooled data from five Phase 1 trials, population PK/PD modeling determined there was no significant differences in PK exposures, or PD differences on LDL-C reduction, between healthy Caucasian and Asian subjects following the administration of evolocumab [23]. Moreover, population PK analysis of alirocumab in healthy volunteers or hypercholesterolemic subjects determined that ethnicity (Asian, Black, and Caucasian populations) had no significant impact on steady-state PK exposures [25].

Body weight may have an influence on the PK of evinacumab, with lower body weight subjects having greater exposure than heavier subjects, following administration of the same fixed dose, and an opposite trend can be observed following administration of dose normalized to body weight. In a PK/PD study of alirocumab in Japanese and non-Japanese patients with high CVD risk, body weight was a significant covariate affecting the PK of alirocumab in Japanese patients [24]. However, when PK exposures were normalized for body weight, no difference was observed between Japanese and non-Japanese populations [24]. In our study, potential evinacumab exposure differences as a result of weight differences were minimized by ensuring that Japanese and Caucasian subjects were group-matched to an average body weight of ±20%, and administering a weight-normalized dose.

Our study evaluated both IV and SC routes of administration for evinacumab. Although IV administration is more invasive, dosing is less frequent (Q4W) and, as it will be administered in a healthcare setting, patient adherence to treatment can be monitored. Conversely, SC administration may be more convenient for patients as they can self-administer at home, although dosing is more frequent (QW). In this study, the 300 mg SC evinacumab dose was effective in both Caucasian and Japanese subjects in reducing LDL-C and triglycerides. Consequently, the 300 mg SC dose is being further evaluated in Phase 2 studies (NCT03175367).

Although evinacumab demonstrated reductions in lipid parameters, with no associated drug toxicity concerns, the study was limited by its small sample size, short study duration, and a study population restricted to healthy volunteers with modestly raised LDL-C. An imbalance in sex between ethnic groups was additionally noted, and thus subanalysis by sex was not feasible. No statistical analysis was planned for this study. The variability of the sampling distribution was due to the small sample size of each group and likely the reason for the numerical differences in PD and safety results observed between the Japanese and Caucasian populations.

The PD evaluation and safety results observed in this study helped inform the subsequent Phase 3, randomized, placebo-controlled study (NCT03399786) evaluating efficacy and safety of evinacumab in patients with HoFH ($n = 65$) [20]. After 24 weeks of treatment, evinacumab demonstrated a significant 47.1% reduction in LDL-C *versus* a 1.9% increase with placebo, resulting in a between-group least squares mean difference of −49.0% ($p < 0.0001$). These Phase 3 results indicate that evinacumab is a potentially viable treatment option for those with severely elevated lipid parameters despite multiple lipid-lowering drugs. Future studies may also look to evaluate the potential effects of ethnicity, sex, and other subgroups on evinacumab efficacy.

Clinicaltrials.gov identifier

NCT03146416.

Conflicts of interest

Mariko Harada-Shiba reports honoraria from Astellas, Amgen, Sanofi, Merck Sharp & Dohme (MSD), Boehringer Ingelheim, AstraZeneca, and Medicine Company; and research grants from Aegerion, Astellas, Amgen, Kaneka, Sanofi, and MSD.

Shazia Ali, Evelyn Gasparino, Vladimir Son, Yi Zhang, and Robert Pordy are employees of and shareholders in Regeneron Pharmaceuticals, Inc.

Daniel A Gipe was an employee of and shareholder in Regeneron Pharmaceuticals, Inc.

Alberico L. Catapano reports honoraria, lecture fees, or research grants from Akcea, Aegerion Amgen, AstraZeneca, Eli Lilly, Genzyme, Kowa, Mediolanum, Menarini, Merck, Recordati, Regeneron Pharmaceuticals, Inc., Sanofi, and Sigma Tau.

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This study was funded by Regeneron Pharmaceuticals, Inc. The sponsor was involved in the study design, collection, analysis and interpretation of data, as well as data checking of information provided in the manuscript. The authors had unrestricted access to study data and were responsible for all content and editorial decisions.

Author contributions

Shazia Ali, Daniel A. Gipe, Evelyn Gasparino, Vladimir Son, Yi Zhang, and Robert Pordy contributed to the concept or study design. Mariko Harada-Shiba and Alberico L. Catapano were investigators who contributed to the data acquisition. Mariko Harada-Shiba, Shazia Ali, Daniel A. Gipe, Evelyn Gasparino, Vladimir Son, Yi Zhang, Robert Pordy, and Alberico L. Catapano contributed to the analysis and interpretation of the data. Mariko Harada-Shiba, Shazia Ali, Evelyn Gasparino, Vladimir Son, Yi Zhang, Robert Pordy, and Alberico L. Catapano critically reviewed and edited the manuscript. All authors approved the final version.

Data sharing

Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan) that support the methods and findings reported in this manuscript. Individual anonymized participant data will be considered for sharing once the product and indication has been approved by major health authorities (e.g., FDA, EMA, PMDA, etc), if there is legal authority to share the data and there is not a reasonable likelihood of participant re-identification. Submit requests to https://vivli.org/.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2020.10.013.

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