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ARTICLE

Effect of CSL112 (apolipoprotein A-I [human]) on cholesterol efflux capacity in Japanese subjects: Findings from a phase I study and a cross-study comparison

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Abstract

CSL112 (apolipoprotein A-I [apoA-I, human]) is a novel drug in development to reduce the risk of recurrent cardiovascular events following acute myocardial infarction by increasing cholesterol efflux capacity (CEC). This phase I study aimed to compare the pharmacokinetics (PKs), pharmacodynamics (PDs), and safety of CSL112 in Japanese and White subjects. A total of 34 Japanese subjects were randomized to receive a single infusion of CSL112 (2, 4, or 6 g) or placebo and 18 White subjects were randomized to receive a single dose of 6 g CSL112 or placebo, followed by PK/PD assessment and adverse events monitoring. In addition, PK/PD parameters were compared across the CSL112 clinical development program. Plasma exposure of apoA-I increased in a dose-dependent but nonlinear manner in Japanese subjects receiving a single dose of CSL112. Mean baseline-corrected area under the curve from 0 to 72 h ($AUC_{0–72}$) increased from 840 to 6490 mg h/dl, in the 2 and 6 g cohorts, respectively, followed by dose-dependent increase of CEC. The plasma PK profile of apoA-I and increases in total and ATP binding cassette transporter A1 dependent CEC were comparable in Japanese and White subjects. The geometric mean ratio (Japanese:White) for plasma apoA-I $AUC_{0–72}$ and maximum plasma concentration (C_{max}) was 1.08 and 0.945, respectively. Cross-study comparison analysis demonstrated similar CSL112 exposure and CEC enhancement in Japanese and non-Japanese subjects (including patients with cardiovascular disease) and further confirmed consistent PKs/PDs of CSL112. This study suggests CSL112 acutely enhances CEC and is well-tolerated with no differences between Japanese and White subjects.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THIS TOPIC?

Cholesterol efflux, mediated by apolipoprotein A-I (apoA-I), removes excess cholesterol from atherosclerotic plaque and transports it to the liver for excretion;

impaired cholesterol efflux is associated with higher cardiovascular (CV) event rates. CSL112 (apoA-I, human) has been shown to enhance cholesterol efflux capacity and is being investigated as a novel therapy to reduce the risk of early recurrent CV events. Japanese ethnicity is known to confer differences in lipoprotein metabolism.

WHAT QUESTION DID THIS STUDY ADDRESS?

This ethno-bridging study characterized the pharmacokinetics (PKs), pharmacodynamics, safety and tolerability of CSL112 in healthy Japanese subjects compared with healthy White subjects to identify any ethnicity-based differences in cholesterol efflux capacity (CEC) and safety issues and determine the appropriate dose in Japanese subjects prior to inclusion in future or ongoing studies.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Japanese ethnicity confers no clinically relevant difference in CSL112 exposure and CEC compared to White populations and safety profiles were comparable between populations. This study supports the inclusion of Japanese subjects in an ongoing phase III study, investigating the impact of CSL112 on CV risk reduction post-myocardial infarction, with no dose adjustment needed.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

This study contributes to the discussion around PK differences between ethnic groups. It confirms similarity of apoA-I exposure and CEC responses in Japanese and White populations, which warrants further investigation of this novel treatment approach to reduce the risk of early recurrent CV events.

INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of annual mortality globally,[1,2] with recurrent myocardial infarctions (MIs) representing about a quarter of all MIs,[3] therefore placing an immense burden on healthcare systems. Data pooled from seven landmark trials in patients with high-risk acute coronary syndrome (ACS) showed that after an MI, 8.3% of patients developed a recurrent major adverse cardiovascular (CV) event (MACE, i.e., CV death, non-fatal MI, or stroke) within 1 year. Approximately 49% of all events occurred within the first 90 days; therefore, this is considered a high risk period for recurrent MACE.[4] Despite the incidence and mortality from CVD in Japan being one of the lowest globally,[5] CVD is the second leading cause of deaths (167.6 per 100,000 people) and acute myocardial infarction (AMI) accounted for >33,500 deaths in 2018.[6] In Japanese individuals, the mortality rate in the first 30 days following AMI ranges from ~10–18%,[7] and patients with recurrent MI were shown to have double the risk of all-cause mortality at 5 years.[8] Cumulative incidence of MACE after ACS in Japan was 6.4% and all-cause mortality was 6.3% at 2-year follow-up.[9] Overall, the risk of recurrent CV events remains high despite existing standard of care, thus representing an unmet clinical need for individuals with CVD.[8,10]

Low levels of high-density lipoprotein cholesterol (HDL-C) have been previously associated with increased risk of atherosclerosis.[11,12] However, large-scale clinical trials aimed at raising HDL-C levels have not shown a reduced CV risk and as such have failed to demonstrate a clinical benefit.[13–17] The key atheroprotective mechanism of HDL is its role in reverse cholesterol transport, specifically by removing excess cholesterol from atherosclerotic plaques and transporting it to the liver for excretion.[18] A strong association between reduced cholesterol efflux capacity (CEC) and greater risk for CV events has been identified, independent of HDL-C levels.[19,20] Therefore, new therapies targeting CEC, to potentially reduce plaque burden and thus the risk of recurrent CV events, are being investigated.

Apolipoprotein A-I (apoA-I) is the key functional protein of HDL particles that mediates the cholesterol efflux from atherosclerotic plaques via ATP binding cassette transporter A1 (ABCA1).[21] A novel intravenous (i.v.) formulation, CSL112, has been developed containing human plasma-derived apoA-I formulated with phosphatidylcholine to form disc-shaped HDL particles.[22] The ability of CSL112 to promote CEC had previously been established both ex vivo and in human subjects across several clinical trials.[22–25] An ongoing phase III trial (AEGIS-II, NCT03473223) is investigating whether CSL112 can reduce the risk of MACE during the high risk, post-AMI 90-day period.[26]

Factors, such as Japanese ethnicity, are known to confer differences in lipoprotein metabolism; for example, individuals may have higher plasma levels of endogenous

HDL-C than individuals in the United States.[27] Therefore, the aim of this ethno-bridging phase I study was to characterize the pharmacokinetics (PKs), pharmacodynamics (PDs), safety, and tolerability of CSL112 in healthy Japanese subjects compared with healthy White subjects to identify any ethnicity-based safety issues and determine the appropriate dose in Japanese subjects prior to inclusion in future or ongoing studies.

METHODS

Ethics approval and consent

The clinical study protocol was approved by an independent ethics committee of the participating study site. The study was carried out in accordance with the International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines and written informed consent was obtained from all subjects prior to initiation of the study. This single-site study was conducted at Scientia Clinical Research, New South Wales, Australia, between May and September 2018.

Study design

This was a phase I, double-blind, randomized, placebo-controlled, sequential dose cohort study in healthy Japanese and White subjects. The primary end point of the study was to characterize the PK properties of CSL112 after a single i.v. infusion in healthy Japanese subjects and to compare these to healthy White subjects. Secondary end points included evaluation of the safety and tolerability of CSL112 after a single i.v. infusion and assessment of the effects of CSL112 on CEC in these subjects. An additional exploratory end point was to examine the effect of CSL112 dose and exposure on lipid and lipoprotein biomarkers in healthy Japanese participants.

Subjects were assigned to one of three dose cohorts (2, 4, or 6 g CSL112). Cohorts 1 and 2 comprised Japanese participants randomized 3:1 to receive either single infusion of CSL112 (2 or 4 g, respectively, $N = 6$ for each dose) or placebo ($N = 2$ for each cohort). Cohort 3 comprised Japanese and White subjects randomized 5:1 to receive either a single infusion of 6 g CSL112 ($N = 15$) or placebo ($N = 3$; Figure 1). White subjects were weight-matched to ±15% of the median weight of Japanese subjects in cohort 3. The study was divided into a screening period (days −21 to −2), followed by a 7-day mandatory in-house period, and a 23–30-day serology follow-up period, including nucleic acid testing for a virus panel and immunogenicity assessments.

Study population

The study enrolled healthy, male or female subjects of Japanese or White descent aged ≥20 to <55 years. Subjects with a body weight of ≥45 to ≤95 kg and a body mass index of ≥18.0 to ≤29.9 kg/m^2 that were determined to be healthy and hemodynamically stable by a comprehensive clinical assessment were included. Female subjects had to be postmenopausal or have a negative urine pregnancy test before randomization and had to be willing to use a method of contraception to avoid pregnancy during the study. The key exclusion criteria are listed in the Supplementary Materials.

Study product, dose, and administration

The active component of CSL112 is apoA-I purified from human plasma.[22] The lyophilized product was

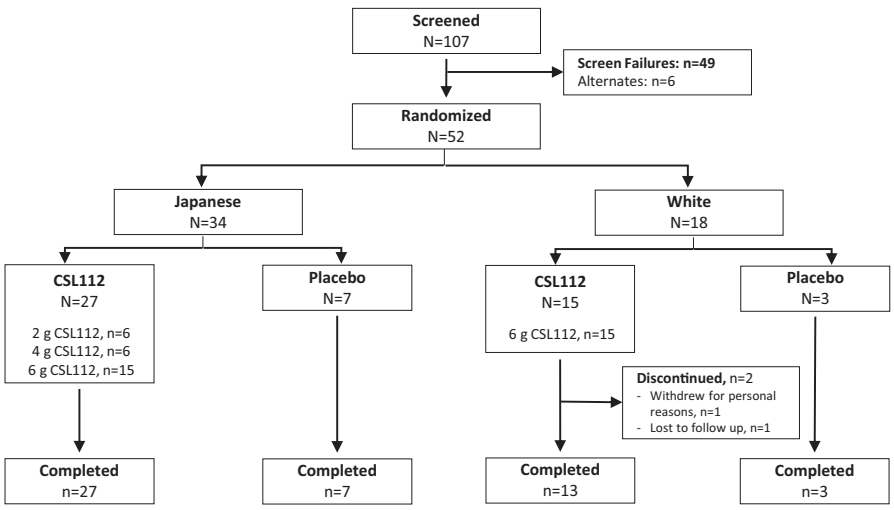

FIGURE 1 Study design overview. N = number of subjects; n = subset of N.

reconstituted with sterile water for injection and administered at a volume according to the assigned dose cohort (2, 4, or 6 g). The placebo treatment was 25% albumin solution diluted with 5% dextrose in water that was administered at an equivalent volume to CSL112 according to dose cohort. CSL112 or placebo was administered as a single 2 h i.v. infusion into a suitable peripheral or central vein.

Pharmacokinetics and pharmacodynamics of apoA-I

ApoA-I concentration was assessed by an immunonephelometric method run on Roche Modular P at a specialty lipid laboratory (Pacific Biomarkers). Details of PK bioanalyses have been described in detail previously.[24] The PK profile of CSL112 was characterized by measuring apoA-I plasma levels at given time points: on the day of admission to the study unit (day −1), prior to study product administration (to determine baseline endogenous levels), and at set times after the start of infusion up to 144 h. Primary PK parameters, including area under the concentration-time curve (AUC) from time 0 to 72 h (AUC_{0-72}), maximum concentration (C_{max}) up to 144 h after the start of CSL112 administration were calculated as previously described.[24]

Pharmacodynamics parameters were derived from serum CEC (total CEC, ABCA1-dependent and -independent) and were measured up to 144 h after the start of CSL112 administration. CEC assays were performed in apolipoprotein B (apoB)-depleted serum samples using J774 macrophages as previously described.[23,28] For calculation of baseline-corrected parameters, baseline values were based on concentration of analytes measured prior to study drug administration (day 1).

Safety evaluation

Treatment-emergent adverse events (TEAEs) were coded using Medical Dictionary for Regulatory Activities (MedDRA, version 21). The severity of each TEAE was assessed by the investigator. Adverse events (AEs) of special interest included hypersensitivity, potential hepatic injury, and acute kidney injury. Potential hepatic injury was defined as elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3.0×upper limit of normal (ULN) with concomitant elevated total bilirubin >2.0×ULN. Acute kidney injury was defined as any increase in serum creatinine concentration ≥0.3 mg/dl (26.5 μmol/L) from baseline during the mandatory in-house period. Clinically significant changes in laboratory tests or vital signs were recorded. Electrocardiogram values (including QT intervals, heart rate, QR intervals, and QRS) and their changes from baseline were recorded and categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant. The immunogenicity of CSL112 was determined by measurement of serum antibodies to CSL112 and to apoA-I.

Statistical analysis

The study sample size was not based on power calculations for statistical hypothesis testing and descriptive statistics were used to summarize the data. The baseline value for all analyses was the last recorded value before administration of study product.

Baseline-corrected apoA-I PK parameters were natural log-transformed, and 90% confidence intervals (CIs) for the mean differences in log-transformed AUC_{0-72} and C_{max} between Japanese and White subjects administered 6 g CSL112 were constructed based on a t-distribution using a pooled estimate of variance. The CIs were then exponentiated to form 90% CIs for the ratios for Japanese:White of the geometric means in the original scale.

Dose-proportionality of apoA-I was evaluated in Japanese subjects administered CSL112 using a power model and baseline-corrected C_{max}, AUC_{last}, and AUC_{0-72}. PK/PD parameters were derived by noncompartmental analysis. SAS version 9.3 was used to perform all data analyses.

Comparison with global clinical trial studies

A cross-study comparison was conducted to compare apoA-I PK parameters across five completed CSL112 clinical trials: the single ascending dose (SAD) and multiple ascending doses (MAD) phase I studies in healthy subjects,[23,24] a phase IIa study in subjects with stable atherothrombotic disease,[25,28] a phase IIb study in subjects with AMI,[29] and the above-mentioned phase I Japanese bridging study in healthy subjects. The dose-normalized and baseline-corrected PK parameters (C_{max}, AUC_{0-72}, and AUC_{last}) were compared by subgroups: healthy Japanese subjects, healthy White subject, patients with atherothrombosis and patients with AMI. Similarly, another cross-study comparison was conducted to compare dose-normalized and baseline-corrected parameters of CEC response (maximum response [R_{max}], area under the effect curve [$AUEC_{0-72}$] and $AUEC_{last}$) in healthy subjects from the Japanese bridging study and the phase I SAD study[23] and in subjects with AMI from the phase IIb study.[28] The

relationship of observed apoA-I concentration and level of CECs in Japanese subjects was also graphically compared with pooled data from all subjects included in four clinical trials (healthy subjects in the current study, healthy subjects and subjects with renal impairment (RI) in a phase I study,[30] subjects with AMI in a phase IIb study,[29] and subjects with AMI and RI in a phase II study[31]). Lastly, the maximum fold change in apoA-I plasma level and total and ABCA-1 dependent CEC from baseline after the first 6 g dose of CSL112 were compared between healthy Japanese and White subjects from this Japanese bridging study and AMI subjects from a phase IIb trial.

RESULTS

Study population

A total of 52 subjects, 34 (65.4%) Japanese and 18 (34.6%) White, were eligible and included in the analysis. Study population characteristics are summarized in Table 1. Japanese subjects were between 20 and 40 years of age, with no meaningful differences in the distributions of age and height across cohorts. All 34 Japanese subjects and 16 of the 18 White subjects completed the study; one subject withdrew for personal reasons and one was lost to follow-up.

Pharmacokinetics

Following administrations of a single dose of 2, 4, or 6 g of CSL112, plasma levels of apoA-I in Japanese subjects were rapidly and markedly increased in a dose-dependent manner (Figure 2a). The concentration of apoA-I in plasma peaked rapidly, with a median to reach the maximum concentration (T_{max}) of ~2 h. The concentration then decreased slowly over time in a biphasic manner. ApoA-I plasma levels above baseline were measurable through to 72 and 144 h after administration of 2 g and 4 g/6 g CSL112, respectively. The mean apoA-I plasma concentration-time profiles of Japanese and White subjects receiving 6 g CSL112 were comparable.

Noncompartmental PK analysis was conducted on baseline-corrected apoA-I concentration data and a summary of PK parameters is shown in Table 2. The PK parameters were similar in Japanese and White subjects that received 6 g CSL112. Dose proportionality was evaluated using baseline-corrected PK parameters and for the AUC_{0-72} of apoA-I, a dose-dependent but nonlinear relationship was observed in Japanese subjects increasing from 840 to 6490 mg h/dl, in the 2 and 6 g cohorts, respectively.

TABLE 1 Baseline characteristics of study population

	Cohort 1 (2 g) Japanese		Cohort 2 (4 g) Japanese		Cohort 3 (6 g) Japanese		Cohort 3 (6 g) White		Total Japanese	
Mean (SD)*	CSL112 (*N* = 6)	Placebo (*N* = 2)	CSL112 (*N* = 6)	Placebo (*N* = 2)	CSL112 (*N* = 15)	Placebo (*N* = 3)	CSL112 (*N* = 15)	Placebo (*N* = 3)	CSL112 (*N* = 27)	Placebo (*N* = 7)
Age, years	30.6 (4.22)	25.1 (0.08)	26.5 (3.94)	33.5 (9.33)	27.7 (5.37)	24.0 (1.88)	27.0 (4.91)	25.3 (5.13)	28.0 (4.90)	27.0 (5.95)
Sex, *N* (%) male	4 (66.7)	1 (50.0)	4 (66.7)	0	8 (53.3)	0	4 (26.7)	2 (66.7)	16 (59.3)	1 (14.3)
Body weight, kg	64.1 (7.09)	60.3 (4.88)	66.6 (7.10)	63.6 (2.19)	60.9 (6.91)	51.4 (2.41)	59.9 (3.35)	62.9 (2.02)	62.9 (7.12)	57.3 (6.23)
BMI, kg/m^2	21.7 (1.20)	21.0 (1.79)	23.6 (2.46)	24.8 (0.35)	21.9 (2.29)	21.2 (1.12)	21.3 (1.44)	21.7 (1.57)	22.2 (2.20)	22.1 (2.04)
ApoA-I, mg/dl	165.3 (15.64)	NC	133.7 (8.57)	NC	144.5 (20.88)	NC	134.4 (22.64)	NC	146.7 (20.44)	NC
Total CEC (% Efflux/4 h)	9.858 (1.8145)	10.175 (0.1061)	7.718 (1.2125)	7.115 (0.3606)	9.490 (1.5278)	11.347 (1.4877)	9.028 (1.9483)	9.310 (0.4200)	9.178 (1.6815)	9.803 (2.0994)
ABCA1-dependent CEC (% Efflux/4 h)	1.703 (1.2325)	2.560 (0.2404)	0.865 (1.0041)	0.510 (0.5940)	0.999 (0.8444)	2.120 (1.9195)	1.145 (1.0241)	1.843 (1.1344)	1.126 (0.9859)	1.786 (1.4473)

Abbreviations: ABCA1, ATP binding cassette transporter A1; apoA-I, apolipoprotein A-I; BMI, body mass index; CEC, cholesterol efflux capacity; *N*, number of subjects; NC, not calculated; SD, standard deviation.

*Unless stated otherwise.

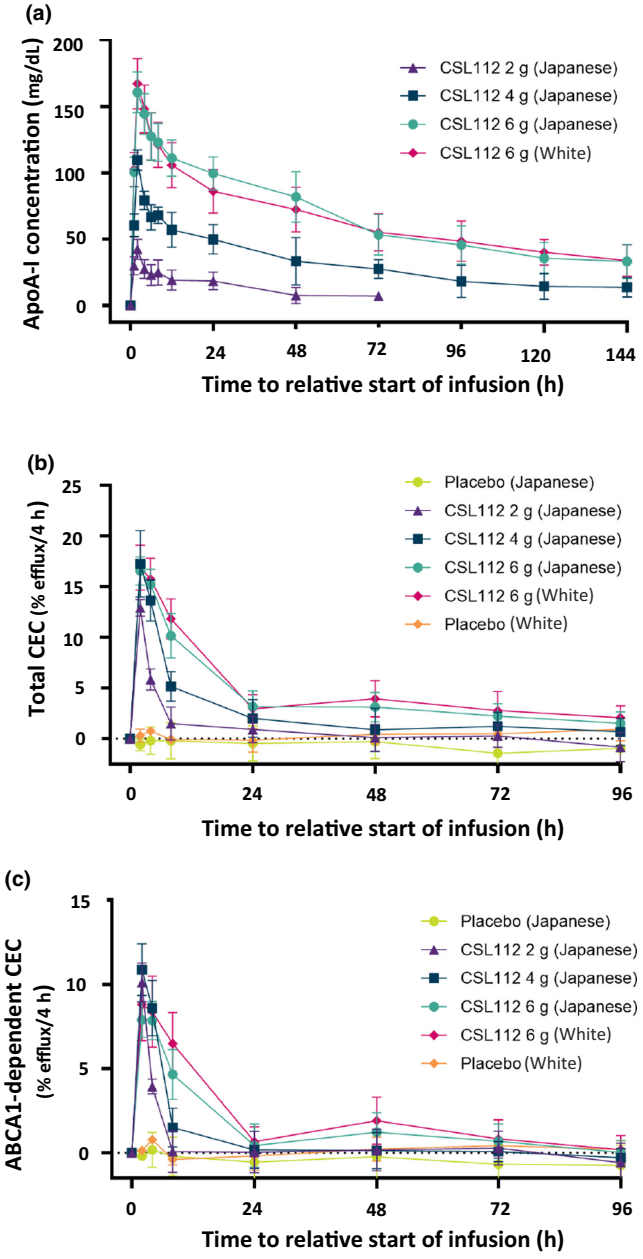

FIGURE 2 Mean baseline-corrected plasma concentration of apoA-I (a) and total (b) and ABCA1-dependent (c) CEC by treatment cohort and ethnicity. Data are presented as arithmetic mean and standard deviations. ABCA1, ATP binding cassette transporter A1; CEC, cholesterol efflux capacity.

The geometric mean ratio (Japanese:White) for baseline-corrected plasma apoA-I AUC_{0-72} and C_{max} was 1.08 (90% CI: 0.99, 1.18) and 0.945 (90% CI: 0.90, 1.00), respectively.

Pharmacodynamics

Rapid and robust dose-dependent increases in total and ABCA1-dependent CEC were observed after CSL112 administration in Japanese subjects (Figure 2b,c). The effect of 6 g CSL112 administration on total and ABCA1-dependent CEC was similar for Japanese and White subjects (Table S1). After 6 g infusion of CSL112, total CEC was increased by a median of 2.74-fold in Japanese and 2.92-fold in the White subjects, whereas ABCA1-dependent CEC increased by a median of 7.29-fold in Japanese and 8.36-fold in White subjects. Total and ABCA1-dependent CEC peaked rapidly after CSL112 administration, with a median T_{max} of ~2 h for all CSL112 doses. The total CEC then decreased and returned to baseline by 24 h after administration of 2 g and over a longer period after administration of 4 or 6 g CSL112, extending to 96 h. The ABCA1-dependent CEC decreased and returned to baseline by 8 or 24 h after administration of 2 or 4 g CSL112, respectively, and after 96 h in the 6 g CSL112 cohort.

Dose-dependent increases for preß1-HDL, and for all measures of HDL-C (total, unesterified, and esterified) were observed after CSL112 administration in Japanese subjects. The effects of 6 g CSL112 administration were similar for Japanese and White subjects (data not shown). CSL112 administration did not increase plasma concentrations of non-HDL-C, apoB, LDL-cholesterol, or triglyceride in either Japanese or White subjects (data not shown).

Safety

All subjects were treatment compliant and were administered the planned dose and were therefore included in the safety analysis. There were no differences in the frequency and type of TEAEs reported in Japanese subjects receiving a single dose of 2, 4, or 6 g CSL112 or placebo. Overall, 22 (42.3%) of the 52 subjects enrolled in the study had 37 TEAEs, including 16 subjects (38.1%) who received CSL112 and six (60.0%) who received placebo. The most common reported AEs were infections, upper respiratory tract infection ($n = 8$), and oropharyngeal pain ($n = 5$), none of which were related to study treatment; an overview of the number of reported AEs across each cohort is presented in Table 3. All TEAEs were described to be mild or moderate in intensity and only two White subjects had TEAEs related to study treatment (4 TEAEs total), including mild hypersensitivity that resolved without treatment. Hypersensitivity (3 events in 3 subjects) was the only AE of special interest reported during the study. All three instances were nonserious events of rash, one of which was assessed as related to study treatment and all of which resolved without treatment. No serious AEs were reported during the study and no subjects had acute kidney injury or

TABLE 2 Baseline-corrected plasma PK parameters of CSL112

Mean (SD)*	Cohort 1 (2 g)	Cohort 2 (4 g)	Cohort 3 (6 g)	
	Japanese ($N = 6$)	Japanese ($N = 6$)	Japanese ($N = 15$)	White ($N = 15$)
C_{max} (mg/dl)	42.3 (7.45)	110 (7.66)	161 (15.4)	169 (14.7)
T_{max} (h)	2.02 (2.00, 2.03)	2.00 (2.00, 2.00)	2.00 (2.00, 2.07)	2.00 (4.00, 2.00)
AUC_{0-24} (mg h/dl)	506 (164)	1469 (169)	2734 (269)	2620 (326)
AUC_{0-72} (mg h/dl)	840 (444)	3106 (775)	6490 (953)	6024 (859)
AUC_{last} (mg h/dl)	737 (409)	4131 (1599)	9460 (1730)	8993 (1824)
$t_{½}$ (h)	17.3 (10.7)[a]	66.6 (60.2)	68.0 (15.7)	76.4 (26.1)
CL (L/h)	0.341 (0.306)[a]	0.135 (0.065)[b]	0.064 (0.010)[c]	0.062 (0.009)[c]
V_Z (L)	5.37 (0.369)[a]	4.83 (0.765)[b]	4.21 (0.260)[b]	4.07 (0.779)[c]

Abbreviations: AUC, area under the concentration-time curve; AUC_{0-72}, AUC from 0 to 72 h; AUC_{last}, AUC from 0 to the last quantifiable concentration; CL, clearance; C_{max}, maximum concentration; h, hour; PK, pharmacokinetics; SD, standard deviation; $t_{½}$, terminal half-life; T_{max}, time to reach maximum concentration; V_Z, volume of distribution.

*Unless stated otherwise; median (minimum, maximum); [a]$n = 5$; [b]$n = 3$; [c]$n = 4$.

potential hepatic injury. The safety profile of 6 g CSL112 was comparable between Japanese and White subjects, with no clinically significant changes in hepatic or renal function. Mean and median ALT, AST, and serum creatinine concentrations were similar in Japanese subjects across the dose cohorts, and between Japanese and White subjects administered 6 g CSL112 over time. No subject had a serum ALT or AST concentration that met protocol defined criteria for clinical significance (i.e., concentration >3.0 × ULN sustained for ≥24 h). Two subjects had electrocardiogram values shift from normal at baseline to abnormal during the in-house period; none of these changes were clinically significant nor were associated with any TEAEs. No subject developed anti-apoA-I antibodies after CSL112 administration.

Comparison across CSL112 global clinical trials

Cross-study comparison of the CSL112 PK characteristics across the clinical development program confirmed that the baseline-corrected, dose-normalized exposures (C_{max} and AUC) of apoA-I were similar across four study populations (Japanese healthy volunteers, White healthy volunteers, patients with atherothrombotic disease, and patients with AMI; Figure S1A).

Similarly, cross-study comparison of CSL112 PD showed that dose-normalized baseline corrected CEC (total and ABCA1-dependent CEC) was comparable between Japanese subjects, White subjects, and patients with AMI (Figure S1B). In general, the similar distribution range and pattern of PK and PD in those subpopulations suggest no effect of ethnicity and health status on apoA-I exposure and CEC. The correlation between apoA-I concentration versus total or ABCA1-dependent CEC stratified by ethnicity (i.e., Japanese vs. non-Japanese population) is shown in Figure S2. Overall, these data demonstrate that Japanese subjects treated with 6 g CSL112 have similar CEC compared to non-Japanese subjects from the global clinical program. Although within the distribution of the overall cross study population, the ABCA1-dependent cholesterol efflux response in the Japanese subgroups appears slightly lower (or "right shifted") compared to the rest of the population. This is in large part due to the higher baseline apoA-I levels in this study of healthy volunteers (both Japanese and White) compared with the largest study in this comparison (i.e., phase IIb study in patients with AMI).[29]

Finally, infusion of 6 g CSL112 resulted in similar fold elevation of apoA-I in Japanese and White subjects and patients with AMI (median 2.08, 2.33, and 2.08-fold increase, respectively). Total CEC is increased by a median of 2.74, 2.92 and 2.55-fold in Japanese, White subjects, and patients with AMI, respectively. Lastly, ABCA1-dependent CEC increased by a median of 7.29-fold in Japanese subjects, 8.36-fold in White subjects, and 3.84-fold in patients with AMI (Figure S3). These results demonstrate similar elevation of ABCA1-dependent cholesterol efflux capacity between White and Japanese subjects, although the median values are lower in patients with AMI, likely due to assay variability when comparing across studies. However, there is significant overlap in the value range.

In summary, the cross-study comparison analysis demonstrated similar exposure of CSL112 in Japanese

TABLE 3 Adverse events overview

Parameter, *N* (%)	Cohort 1 (2 g) Japanese		Cohort 2 (4 g) Japanese		Cohort 3 (6 g) Japanese		Cohort 3 (6 g) White		Total Japanese	
	CSL112 (*N* = 6)	Placebo (*N* = 2)	CSL112 (*N* = 6)	Placebo (*N* = 2)	CSL112 (*N* = 15)	Placebo (*N* = 3)	CSL112 (*N* = 15)	Placebo (*N* = 3)	CSL112 (*N* = 27)	Placebo (*N* = 7)
AEs	1 (16.7)	1 (50.0)	4 (66.7)	2 (100.0)	2 (13.3)	0	10 (66.7)	3 (100.0)	7 (25.9)	3 (42.9)
TEAEs	1 (16.7)	1 (50.0)	4 (66.7)	2 (100.0)	2 (13.3)	0	9 (60.0)	3 (100.0)	7 (25.9)	3 (42.9)
Related TEAEs	0	0	0	0	0	0	2 (13.3)	0	0	0
TEAEs of special interest										
Hypersensitivity	0	0	1 (16.7)	0	0	0	1 (6.7)	1 (33.3)	1 (3.7)	0

Abbreviations: AE, adverse event; *N*, number of subjects; TEAEs, treatment-emergent adverse events.

and non-Japanese subjects (including patients with CVD) and similar total and ABCA1-dependent cholesterol efflux response in Japanese and non-Japanese subjects at all dose levels. These results also demonstrate that PKs and PDs of CSL112 are similar between healthy Japanese subjects and non-Japanese subjects from this and previous global studies.

DISCUSSION

This study investigated and compared the PK and PD properties, safety, and tolerability of CSL112 in healthy Japanese and White subjects. A single i.v. infusion of CSL112 produced a dose-proportional increase in plasma apoA-I in Japanese subjects and PK parameters were similar between the Japanese and White cohorts. These results are consistent with dose-dependent increases in plasma exposure of apoA-I observed in other completed clinical studies of CSL112 that enrolled predominantly White healthy subjects,[23,24] as well as in non-Japanese patients with underlying CVD, such as atherosclerosis.[25]

This study also assessed the effect of CSL112 on CEC, the first step in reverse cholesterol transport. The positive correlation between apoA-I concentration and total CEC in non-Japanese subjects has been demonstrated in previous studies.[23,25,28] The current study confirmed a consistent CEC response in healthy Japanese and White subjects. The cross-study comparison analysis with the global cohort demonstrated similar responses in Japanese and non-Japanese subjects at all investigated dose levels. Importantly, the degree of ABCA1-dependent CEC was increased to a larger extent than total CEC, consistent with prior data, demonstrating that infusion of CSL112 leads to the formation of highly functional small, lipid poor apoA-I, also known as preβ1-HDL, which preferentially increases ABCA1-dependent cholesterol efflux.[23]

CSL112 was previously shown to be well-tolerated in healthy subjects, those with underlying CVD, and patients with varying degrees of baseline renal function ranging from normal to moderately impaired.[23,25,29,31] The current study demonstrates a comparable safety profile between Japanese and White subjects receiving a 6 g CSL112 dose.

A fixed dose of 6 g CSL112 was selected as the treatment dose with maximum efficacy for the global phase III AEGIS-II trial based on previous PK/PD model-based analysis that demonstrated a desired elevation in CEC, irrespective of body weight, sex, and ethnicity.[32] In Japanese subjects, known differences

in lipoprotein metabolism (i.e., higher plasma levels of endogenous HDL-C than individuals in the United States),[27] do not appear to have an impact on CEC. Moreover, ex vivo CEC has been found to correlate with MACE end points independently of HDL-C levels both in Japanese and non-Japanese patients.[33,34] The key factor accounting for the higher HDL-C levels in Japanese population is genetic mutation in cholesteryl ester transfer protein (CETP) that regulates HDL-C levels in plasma.[27,35] CETP plays a pivotal role in transfer of cholesteryl ester from HDL to apoB containing LDL particles and thus does not affect ABCA-1 dependent CEC.[27,36] Furthermore, ethnic differences in PKs are often a consequence of genetic differences in hepatic cytochrome P450 (CYP450)-mediated drug metabolism.[37] CSL112 is a macromolecular complex and as such does not enter cells and is not metabolized by the intracellularly located CYP450 enzymes. Consequently, this study confirmed the expected safety and dosing regimen for CSL112 in Japanese subjects with no adjustments needed.

The potential limitations of this study include a relatively small sample size and that this was a single dose study while the regimen that is being evaluated in the phase III outcomes trial is a multiple dose regimen. However, the sample size was deemed sufficient to assess the PKs/PDs of CSL112, and importantly the reported findings were consistent with previously published studies assessing CSL112 across different populations. It remains unclear whether factors other than CEC are associated with MACE end points in the Japanese population. Furthermore, slight regional variations in the standard of care for patients with CVD may also influence the final results.[38]

Despite regional and ethnic differences, the rate of recurrent MACE in patients suffering from an AMI remains high.[4,7] This unmet medical need exists also in post-MI population of Japanese patients. Data from this ethnobridging study demonstrate that administration of CSL112 increases CEC in Japanese subjects, similarly to that observed in other populations. Future studies should focus on exploring the potential benefit of CSL112 to reduce the risk of recurrent CV outcomes in the high risk 90-day period. The findings of this phase I study thus support the inclusion of Japanese subjects in an ongoing phase III study, AEGIS-II, investigating the impact of CSL112 on CV risk reduction post-MI.

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript. B.Z., S.G., R.C., J.F., P.D., J.A., and M.T. designed the research. S.G., R.C., D.D., P.D., J.A., and C.M.G. performed the research. B.Z., S.G., R.C., J.F., D.D., J.A., M.T., and J.R. analyzed the data.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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