The CSL112-2001 trial: Safety and tolerability of multiple doses of CSL112 (apolipoprotein A-I [human]), an intravenous formulation of plasma-derived apolipoprotein A-I, among subjects with moderate renal impairment after acute myocardial infarction

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Background CSL112 (apolipoprotein A-I [human]) is a plasma-derived apolipoprotein A-I developed for early reduction of cardiovascular risk following an acute myocardial infarction (AMI). The safety of CSL112 among AMI subjects with moderate, stage 3 chronic kidney disease (CKD) is unknown.

Methods CSL112_2001, a multicenter, placebo-controlled, parallel-group, double-blind, randomized phase 2 trial, enrolled patients with moderate CKD within 7 days following AMI. Enrollment was stratified on the basis of estimated glomerular filtration rate and presence of diabetes requiring treatment. Patients were randomized in a 2:1 ratio to receive 4 weekly infusions of CSL112 6 g or placebo. The co-primary safety end points were renal serious adverse events (SAEs) and *acute kidney injury*, defined as an increase ≥26.5 μmol/L in baseline serum creatinine for more than 24 hours, during the treatment period.

Results A total of 83 patients were randomized (55 CSL112 vs 28 placebo). No increase in renal SAEs was observed in the CSL112 group compared with placebo (CSL112 = 1 [1.9%], placebo = 4 [14.3%]). Similarly, no increase in acute kidney injury events was observed (CSL112 = 2 [4.0%], placebo = 4 [14.3%]). Rates of other SAEs were similar between groups. CSL112 administration resulted in increases in ApoA-I and cholesterol efflux similar to those observed in patients with AMI and normal renal function or stage 2 CKD enrolled in the ApoA-I Event Reducing in Ischemic Syndromes I trial.

Conclusions These results demonstrate the acceptable safety of the 6-g dose of CSL112 among AMI subjects with moderate stage 3 CKD and support inclusion of these patients in a phase 3 cardiovascular outcomes trial powered to assess efficacy. (Am Heart J 2019;208:81-90.)

Approximately 15% of patients with acute myocardial infarction (AMI) experience recurrent cardiovascular (CV) events within the following year despite receiving recommended medical therapy.[1,2] This residual risk is attributed, in part, to the persistence of CV risk factors.[3,4] In particular, patients with low high-density lipoprotein

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cholesterol (HDL-C) have a greater risk of ischemic events compared to those with normal or high HDL-C.[5-11] However, previous clinical trials of HDL-C–raising therapies failed to substantially reduce the risk of recurrent events among patients with coronary artery disease despite a significant increase in HDL-C concentrations.[12-15] This lack of effect has been largely attributed to the treatments having minimal impact on HDL function.[16] Subsequently, the "HDL hypothesis" has evolved, and the focus shifted from raising the concentration of HDL-C to improving the functionality of HDL.[17] The benefits of HDL are thought to be related to reverse cholesterol transport during which excess cholesterol is transported from the atherosclerotic plaque to the liver for degradation. This process, known as cholesterol efflux, is mediated by apolipoprotein A-I (ApoA-I), the dominant protein of HDL.[18-22] Cholesterol efflux capacity (CEC) has been strongly and inversely associated with the risk of ischemic events.[23,24]

CSL112 (apolipoprotein A-I [human]) is a human plasma-derived ApoA-I that raises plasma ApoA-I and increases the total and ATP-binding cassette A1 (ABCA1)–dependent cholesterol efflux capacity.[25-28] It is hypothesized that this elevation may be particularly important in the post-AMI phase, a time during which cholesterol efflux capacity is substantially impaired.[29,30] Potential hepatic safety concerns with a prior formulation of ApoA-I, attributed to the phosphatidylcholine content,[31,32] and theoretical renal safety concerns related to the sucrose stabilizer component of CSL112 were raised. However, the international, randomized, placebo-controlled, dose-ranging, phase 2b ApoA-I Event Reducing in Ischemic Syndromes I (AEGIS-I) trial demonstrated that 4 weekly intravenous (IV) infusions of lower-phosphatidylcholine– and low-sucrose–containing CSL112 were safe and not associated with either hepatotoxicity or renal toxicity among AMI patients with normal kidney function or mild renal impairment.[33] Rapid and substantial enhancement of CEC with CSL112 was also observed.

Finally, patients with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 who represent approximately one-third of acute coronary syndrome (ACS) patients were excluded from the AEGIS-I trial.[34,35] Thus, the renal safety of CSL112 among this population remains uncertain. Therefore, the aim of the CSL112_2001 phase 2 trial (URL: Clinicaltrials.gov, unique identifier: NCT02742103) was to evaluate the safety and tolerability of 4 weekly infusions of 6 g CSL112 among AMI patients with moderate chronic kidney disease (CKD).

Methods

Study design and population

The CSL112_2001 trial was an international phase 2, randomized, double-blind, placebo-controlled, parallel-group study intended to characterize the renal risk profile of CSL112 in AMI subjects with moderate renal impairment. Randomization occurred within 5 or 7 days (depending on geographic region) after first medical contact for an acute type 1 spontaneous myocardial infarction (MI), defined on the basis of the Third Universal Definition of MI.[36] Subjects were required to be older than 18 years and to have moderate stage 3 CKD, defined by an eGFR ≥30 and <60 mL/min/1.73 m^2, calculated with the Chronic Kidney Disease–Epidemiology Collaboration equation.[37] Major exclusion criteria included ongoing hemodynamic instability, planned coronary artery bypass graft surgery, evidence of active hepatobiliary disease, prior history of acute kidney injury (AKI) following previous exposure to IV contrast, current nephrotic range proteinuria, body weight <50 kg, and soy allergy or IgA deficiency. For subjects undergoing angiography, *stable renal function* (defined as an increase in serum creatinine <26.5 μmol/L from the precontrast administration value) was required at least 12 hours after IV contrast administration.

Study procedure

Participants were randomly assigned in a 2:1 ratio to receive 4 weekly IV infusions of 6 g CSL112 or placebo (0.9% sodium chloride solution administered as a 2-hour IV infusion). Randomization was stratified by eGFR according to stage of CKD (eGFR 30 to <45 mL/min/1.73 m^2 [stage 3b] or 45 to <60 mL/min/1.73 m^2 [stage 3a]) and by diabetes requiring any medication. At least one-third of randomized subjects were required to be stage 3b CKD (eGFR 30 to <45 mL/min/1.73 m^2). Infusions were administered 7 to 10 days apart, with all infusions administered within 30 days of randomization. The active treatment period was the time from initiation of the first infusion to day 29, whereas the safety follow-up period was 30 days from the end of the active treatment period (study day 60). Blood was collected to perform pharmacokinetic (PK) and pharmacodynamic (PD) assessments of the study drug. The PK and PD assessment methods in CSL112_2001 were similar to those previously described in the AEGIS-I trial.[33,38]

Co-primary end points

The co-primary end points were (1) renal serious adverse events (SAEs) and (2) treatment-emergent AKIs. *Renal SAE* was defined as any report of an SAE related to acute renal failure or renal tubular, cortical, or papillary necrosis occurring from the start of the first infusion through the end of the safety follow-up. *Treatment-emergent AKI* was defined as an absolute increase in serum creatinine ≥26.5 μmol/L from baseline during the active treatment period that is sustained upon repeat measurement occurring at least 24 hours after initial elevation. If no repeat value was obtained during the active treatment period, a single serum creatinine value that is increased ≥26.5 μmol/L was sufficient to fulfill the definition of AKI. All serum creatinine measures were

based on central laboratory values. An independent clinical events committee, blinded to treatment assignment, adjudicated renal SAEs for a confirmatory analysis.

Secondary and exploratory end points

Secondary end points included the occurrence of any treatment-emergent adverse event (TEAE) throughout the study. Secondary end points also included change from baseline in hepatic status (alanine aminotransferase >3× upper limit of normal or bilirubin >1.5× upper limit of normal) and change in serum creatinine (≥1.5, ≥2, or ≥3× baseline) that occurs during the active treatment period and that is sustained for ≥24 hours upon repeat measurement. The occurrence of binding antibodies specific to CSL112 or ApoA-I was also monitored for potential drug hypersensitivities. Rates of all grades of Bleeding Academic Research Consortium (BARC) bleeding were also assessed as a secondary safety end point because subjects were anticipated to be treated with dual-antiplatelet therapy after MI. Measured and baseline corrected plasma ApoA-I and phosphatidylcholine concentrations were assessed as secondary end points, and pharmacodynamic characteristics of CSL112, including changes in total, ABCA1-independent, and ABCA1-dependent cholesterol efflux measures (ex vivo), and lipid, and cardiovascular biomarkers were assessed as exploratory end points. Details regarding measurement of cholesterol efflux can be found in the supplemental appendix.

Statistical analysis

The sample size was planned to meet regulatory requirements for treatment-emergent renal event characterization, and the study was not powered to detect differences between the treatment arms with regard to the co-primary end points. The intention-to-treat population included all randomized subjects. Safety analyses were performed in the *safety population*, defined as all randomized subjects who received at least a partial dose of study drug, and analyzed using the treatment the subject actually received. Two subjects did not have a baseline serum creatinine and were not included in the AKI analysis. For each co-primary end point, the Newcombe-Wilson score method was used to calculate 2-sided 95% CIs around the differences in rates (CSL112 minus placebo). Although not prespecified in the statistical analysis plan, Fisher exact *P* values were calculated to assess for differences in the rates for each co-primary end point between treatment arms. Descriptive summaries were performed for all PK and biomarker measures. All statistical analyses were performed using SAS version 9.4 by the PERFUSE Study Group (Percutaneous/Pharmacologic Endoluminal Revascularization For Unstable Syndromes Evaluation).

Study oversight

The Steering Committee (Supplemental Appendix) oversaw the design and conduct of the trial in collaboration with representatives of the study sponsor (CSL Behring). The study sponsor coordinated the data management. All renal SAEs and bleeding events were adjudicated by a blinded independent Clinical Events Committee. Safety reviews were performed by an independent Data and Safety Monitoring Board throughout the study duration. The corresponding author had full access to all the data in the study and is responsible for the final decision to submit for publication. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents. The study was in accordance with the Helsinki declaration and approved by institutional and national regulatory bodies and ethical committees. All subjects provided written informed consent prior to randomization. The study was funded by CSL Behring.

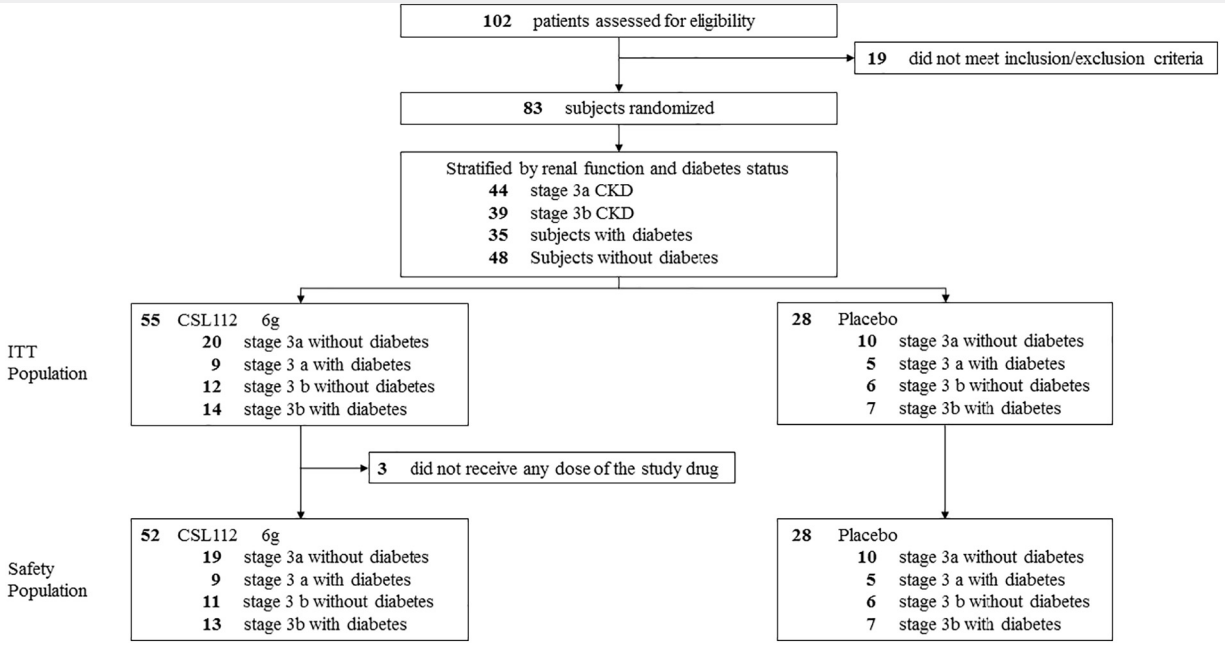
Results

From August 2016 through April 2017, a total of 83 subjects at 37 sites in 5 countries (Germany, Hungary, Israel, Netherlands, and United States) were randomized, of whom 80 (96.4%) received at least 1 dose of the study drug and 69 (83.1%) completed the study. A total of 21 (25.3%) subjects had stage 3b CKD (≥30 to <45 mL/min/1.73 m^2) with diabetes requiring medical treatment, 18 (21.7%) had stage 3b CKD (≥30 to <45 mL/min/1.73 m^2) without diabetes requiring medical treatment, 14 (16.9%) had stage 3a CKD (≥45 to <60 mL/min/1.73 m^2) with diabetes requiring medical treatment, and 30 (36.1%) had stage 3a CKD (≥45 to <60 mL/min/1.73 m^2) without diabetes requiring medical treatment (Figure 1). For the index event, 26.5% of subjects experienced ST-segment elevation MI and 73.5% experienced non–ST-segment elevation MI. The median duration from the index MI to first infusion was 3.2 days, and the median duration of follow-up was 62 days (interquartile range, 58-65 days). Subjects randomized into the CSL112 group were more likely to have chronic heart failure and to be treated with angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers. All other baseline characteristics were well balanced between the 2 treatment groups (Table I).

Co-primary safety end points

The co-primary safety end point of renal SAE occurred in 1 of 52 subjects (1.9%) in the CSL112 group and 4 of 28 subjects (14.3%) in the placebo group ($P = .048$). During the active treatment period, the co-primary safety end point of AKI (≥ 26.5 μmol/L increase in baseline serum creatinine for more than 24 hours) occurred in 2 of 50 subjects (4.0%) in the CSL112 group and 4 of 28 subjects (14.3%) in the placebo group ($P = .18$) (Table II). Comparisons of CSL112 and placebo were not different within each stratum of renal function and diabetes status (Supplemental Table I). Confirmatory analyses using adjudicated renal SAE events and local laboratory values for AKI events demonstrated similar results (Supplemental Table II).

Figure 1



Consolidated Standards of Reporting Trials diagram. *ITT,* intent-to-treat.

Secondary and exploratory end points

There were no study treatment-related fatal adverse events and no imbalances in treatment-related adverse events between treatment arms. The rate of all-cause mortality was similar across both treatment arms, with 2 deaths occurring in each arm (3.8% in the CSL112 arm vs 7.1% in the placebo arm). The overall rate of any serious TEAE was 27.5% and slightly higher among subjects in the placebo group (35.7%) compared with subjects in the CSL112 group (23.1%) (Table III). Subjects enrolled in the CSL112 group (13.5%) had a greater rate of TEAEs of heart failure compared with patients in the placebo group (7.1%). However, treatment-emergent SAEs of heart failure occurred at a similar frequency in the CSL112 (7.7%) and placebo (7.1%) groups. Rates of all grades of BARC bleeding events were low and comparable among the 2 treatment arms: 8 subjects (15.4%) in the CSL112 arm versus 5 subjects (17.9%) in the placebo group (Supplemental Table III). There were similar findings for serum creatinine change from baseline with CSL112 compared with placebo (Figure 2), and there were no clinically relevant elevations in bilirubin or alanine aminotransferase elevations with CSL112 compared with placebo. No antibodies to CSL112 or ApoA-I were detected in response to infusion, and no drug hypersensitivity reactions or infusion site reactions occurred.

Baseline plasma concentrations of ApoA-I, cardiovascular and lipid biomarkers, and CEC were comparable between the CSL112 treatment group and the placebo group (Supplemental Table IV). Infusion of CSL112 elevated ApoA-I 2-fold from baseline to the end of the first infusion (Table IV and Supplemental Figure 1) and was comparable between the 2 eGFR strata (data not shown). ApoA-I levels were returning to baseline by 24-48 hours after the first infusion. Before the fourth infusion, ApoA-I levels were similar to baseline, and elevations after the fourth infusion were comparable to elevations after the first infusion (Supplemental Figure 1). CSL112 infusion also led to an approximately 2-fold increase in total cholesterol efflux capacity, as well as an increase in ABCA1-independent and ABCA1-dependent cholesterol efflux capacity (Figure 3 and Table IV).

Discussion

The CSL112_2001 trial was the first dedicated study in which CSL112 was administered to patients with moderate stage 3 CKD following an AMI. Infusions of 6 g CSL112, a plasma-derived ApoA-I, administered as 4 weekly infusions, were not associated with alterations in kidney function compared to placebo. CSL112 was also not associated with any serious or fatal treatment-related adverse events, providing consistent data on the safety and feasibility of the treatment in this specific population.

CKD is associated with poor short- and long-term outcomes among patients with ACS, as the risk of CV events and mortality is inversely related to the eGFR.[35] Despite an increased risk of adverse outcomes, patients

Table I. Demographics and baseline characteristics

	CSL112 (n = 55)	Placebo (n = 28)	*P* value
Age, mean ± SD, y	70.6 (10.95)	71.9 (10.12)	.60
Male sex, n (%)	37 (67.3%)	18 (64.3%)	.79
BMI, mean ± SD, kg/m^2	30.0 (5.30)	28.5 (4.68)	.21
Race, n (%)			.70
White	52 (94.5%)	28 (100.0%)	
Black	2 (3.6%)	0	
Asian	1 (1.8%)	0	
Renal function			
eGFR, mean ± SD, mL/min/1.73m^2	46.8 (9.70)	45.4 (9.99)	.54
eGFR, median (IQR), mL/min/1.73m^2	49.0 (38.53–55.10)	42.5 (37.71–53.91)	.46
CKD stage 3a, n (%)	29 (52.7%)	15 (53.6%)	.94
CKD stage 3b, n (%)	26 (47.3%)	13 (46.4%)	.94
Index event, n (%)			.45
STEMI	16 (29.1%)	6 (21.4%)	
NSTEMI	39 (70.9%)	22 (78.6%)	
Underwent angiography, n (%)	54 (98.2%)	26 (92.9%)	.41
Underwent PCI, n (%)	44 (80.0%)	21 (75.0%)	.60
Multivessel disease, n (%)	40 (72.7%)	22 (78.6%)	.56
Medical history, n (%)			
Prior coronary revascularization or surgery	25 (45.5%)	12 (42.9%)	.82
Previous MI	23 (41.8%)	12 (42.9)	.93
Cerebrovascular disease	9 (16.4%)	3 (10.7%)	.74
Peripheral arterial disease	10 (18.2%)	6 (21.4%)	.72
Hypertension	53 (96.4%)	24 (85.7%)	.17
Diabetes mellitus requiring treatment	23 (41.8%)	12 (42.9%)	.93
Dyslipidemia	36 (65.5%)	23 (82.1%)	.11
Previous heart failure	13 (23.6%)	2 (7.1%)	.06
Timing of first infusion from angiography, n (%)*			.73
12-<24 h	3 (5.9%)	2 (7.7%)	
24-<48 h	18 (35.3%)	7 (26.9%)	
≥48 h	30 (58.8%)	17 (65.4%)	
Medications			
Statins	47 (85.5%)	27 (96.4%)	.45
High intensity or dose	32 (58.2%)	17 (60.7%)	.82
Low/moderate intensity or dose	15 (27.3%)	10 (35.7%)	.43
Other lipid-lowering agents	3 (5.5%)	2 (7.1%)	.70
ACE inhibitor or ARB	44 (80.0%)	18 (64.3%)	.07
β-Blocker	43 (78.2%)	23 (82.1%)	.71
Aspirin	52 (94.5%)	27 (96.4%)	.21
Antiplatelet agents	50 (90.9%)	26 (92.9%)	.48
Oral antithrombotics	13 (23.6%)	9 (32.1%)	.52

Percentages were based on the total number of subjects in each treatment arm. The χ^2 test of independence or Fisher exact test if any expected cell count was less than 5 was used to calculate *P* values for categorical variables. Independent-samples *t* test and the rank sum test were used to calculate *P* values for parametric and nonparametric continuous variables. eGFR was calculated with the Chronic Kidney Disease–Epidemiology Collaboration equation.
BMI, body mass index; *ACE*, angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker.
* Percentages and *P* values were based on the total number of subjects with available data.

with CKD are often treated less aggressively than patients with normal renal function. Reasons are multifactorial: the lack of dedicated randomized trials assessing therapeutic strategies added to the increased risk of bleeding and contrast-induced nephropathy associated with CKD may explain both the lower rate of evidence-based therapy and interventional strategy among these patients compared to those with normal renal function.[39-41] In a recent analysis of 49,491 ACS patients from the US-based National Cardiovascular Data Acute Coronary Treatment and Intervention Outcomes Network Registry, one-third of the population had stage 3 CKD.[34] Given the prevalence of CKD in patients with ACS coupled with the subsequent heightened risk of recurrent CV events in this population, identification of safe and effective therapy is critical.

Of interest, subjects in the CSL112_2001 trial had greater baseline CEC compared with the subjects randomized in the AEGIS-I trial (30). In fact, total cholesterol efflux was 13% higher and ABCA1-dependent cholesterol efflux was 35% higher in this analysis compared to AEGIS-I trial. This finding is consistent with the results of a phase 1 study comparing CSL112 PK and PD in healthy subjects and patients with moderate renal impairment.[42] However, the relative increases following infusion of CSL112 in total cholesterol efflux

Table II. Occurrence of the co-primary end points in the safety population

Co-primary end point treatment	Number of subjects with events n (%)	Rate difference between treatment groups: Difference in rates (CSL112 – placebo)	95% CI*	*P* value†
Renal SAEs				
CSL112 6 g (n = 52)	1 (1.9%)	–0.124	(–0.296 to –0.005)	.048
Placebo (n = 28)	4 (14.3%)			
AKI events				
CSL112 6 (n = 50)	2 (4.0%)	–0.103	(–0.277 to 0.025)	.18
Placebo (n = 28)	4 (14.3%)			

n (%) counts the number and percentage of subjects that experienced an event.
Two subjects in the CSL112 treatment arm were missing their baseline serum creatinine values and were not included in the AKI analysis.
* The 95% CIs of the difference in subject incidence rates are calculated using the Newcombe-Wilson score method intervals.
† *P* values were calculated using Fisher exact test. This analysis was completed post hoc and was not prespecified in the statistical analysis plan.

Table III. Rate of TEAEs in the safety population

	CSL112 6 g (n = 52)	Placebo (n = 28)	*P* value*
TEAE	38 (73.1%)	20 (71.4%)	.87
Study treatment-related TEAE	4 (7.7%)	1 (3.6%)	.65
Serious TEAE	12 (23.1%)	10 (35.7%)	.23
Study treatment-related serious TEAE	0	1 (3.6%)	.35
Fatal TEAE	2 (3.8)	2 (7.1)	.61
Study treatment-related fatal TEAE	0	0	–
TEAE with CTCAE grade ≥3	13 (25.0)	10 (35.7)	.31
Treatment emergent bleeding events	7 (13.5)	5 (17.9)	.74

CTCAE, common terminology criteria for adverse events.
CTCAE grade ≥3 include (grade 3) severe or medically significant, but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated, disabling, limiting self-care activities of daily living; (grade 4) life-threatening consequences, urgent intervention indicated; and (grade 5) death related to adverse event.
* *P* values were calculated using the χ^2 test of independence or Fisher exact test if any expected cell count was less than 5.

and ABCA1-dependent efflux were similar to those seen in AEGIS-I (Figure 3), suggesting that CSL112 has similar pharmacokinetic and pharmacodynamic effects in this population.[32] Of interest, the sustained elevations of ABCA1-dependent CEC observed at 24-48 hours after the first infusion may be related to the slower metabolism of pre-β1-HDL due to reduced LCAT in plasma[43] and ABCA1 in leukocytes of patients with CKD.[44]

Elevations in cholesterol efflux caused by CSL112 are transient and regress to baseline with clearance of ApoA-I.[25] It remains unknown whether these increases in CEC will affect clinical outcomes post-MI. However, the results of the CSL112_2001 study extend the renal safety findings of the large phase 2b AEGIS-I trial, which randomized 1,258 subjects with normal renal function or stage 2 CKD, by providing data on the safety profile of CSL112 in subjects with an eGFR between 30 and <60 mL/min/1.73 m^2. Therefore, these findings support the inclusion of subjects with moderate CKD in the planned AEGIS-II trial (NCT03473223), a large international phase 3, double-blind, randomized, placebo-controlled, parallel-group study designed to adequately evaluate the efficacy of CSL112, a human plasma-derived ApoA-I, for reducing the risk of major adverse cardiovascular events in patients with AMI.

Limitations

The small sample size, limited number of participating centers and countries, and highly selective population limit the generalizability of this study. Additionally, this phase 2 safety study was not designed to assess efficacy. As with many phase 2 studies, this trial was undertaken primarily to assess safety, tolerability, pharmacokinetics, and pharmacodynamics.

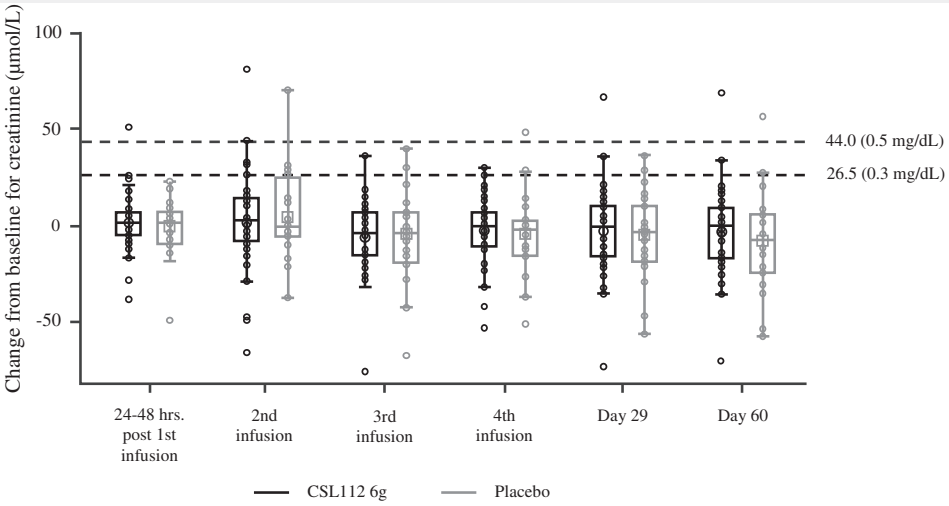
Conclusion

CSL112 was not associated with alterations in kidney function or other serious safety concerns among AMI subjects with moderate CKD. These results demonstrate the acceptable safety of the 6-g dose of CSL112 among AMI subjects with moderate CKD and support inclusion of these subjects in an adequately powered phase 3 clinical trial.

Sources of funding

This study was funded by the sponsor, CSL Behring LLC.

Figure 2



Change in serum creatinine level from baseline by treatment arm is displayed. The first infusion occurred on study day 1, 24-48 hours post the first infusion occurred on study day 2 or 3, second infusion occurred on study day 8, third infusion occurred on study day 15, and fourth infusion occurred on study day 22. Day 29 occurs approximately a week after the fourth infusion and marks the end of the active treatment period. Day 60 marks the end of the 30-day safety follow-up period.

Table IV. Fold elevation of ApoA-I and CEC after the first infusion

	Arithmetic mean ± SD	Fold elevation*
ApoA-I (mg/dL)		
CLS112	239.1 ± 37.7	2.10
Placebo	108.8 ± 24.6	0.96
Total CEC (%efflux/4 h)		
CLS112	22.3 ± 3.71	2.33
Placebo	9.5 ± 2.84	0.96
ABCA1-independent CEC (%efflux/4 h)		
CLS112	12.5 ± 2.44	2.01
Placebo	6.1 ± 2.01	0.98
ABCA1-dependent CEC (%efflux/4 h)		
CLS112	9.8 ± 2.52	3.17
Placebo	3.5 ± 2.38	0.92

*Fold elevation compared with baseline, calculated as geometric mean of the individual patient ratios.

Disclosures

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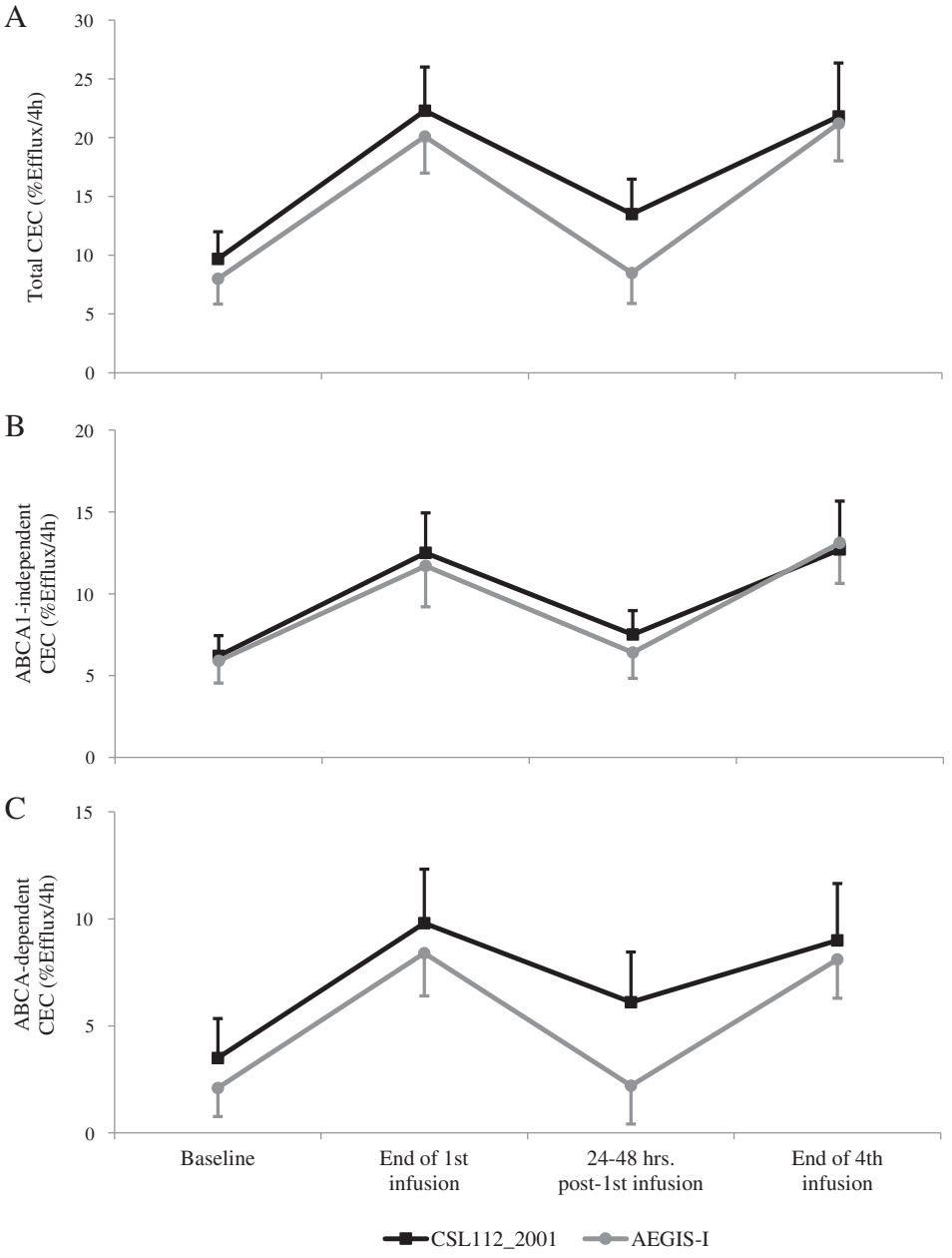
Figure 3



CEC in subjects receiving CSL112 6 g is displayed. **A**, The change in total CEC. **B**, The change in ABCA1-independent CEC. **C**, The change in ABCA1-dependent CEC. End of the first infusion occurred on study day 1, 24 to 48 hours after the first infusion occurred on study day 2 or 3, and end of the fourth infusion occurred on study day 22. Total and ABCA1-independent cholesterol efflux was measured after incubation of apolipoprotein B–depleted serum in vitro with macrophages preloaded with radiolabeled cholesterol (3H-cholesterol), with and without cyclic AMP induction, respectively. ABCA1-dependent cholesterol efflux was calculated as the difference between total cholesterol efflux and ABCA1-independent cholesterol efflux.Lines displayed between time points on the graph are meant as a visual aid and do not indicate increases in decreases in CEC are linear.

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Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2018.11.008.

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