CSL112 Enhances Cholesterol Efflux Equally in Patients with High and Low HDL Functionality

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Introduction

- The ability of high-density lipoprotein (HDL) to remove cholesterol from macrophages in atherosclerotic plaques is thought to underlie its inverse correlation with cardiovascular risk.
- CSL112 is a novel formulation of apolipoprotein A-I (apoA-I) purified from human plasma and reconstituted to form HDL particles suitable for infusion, which is currently in development for acute coronary syndrome (ACS).
- Two Phase 1 studies in healthy subjects and one Phase 2a study in patients with stable atherosclerotic disease have demonstrated favorable safety and pharmacokinetic (PK) behavior and strong elevation of cholesterol efflux capacity upon single or multiple infusions of CSL112.1-4
- The aim of the current study was to assess the influence of subject-specific HDL function, sometimes described as HDL dysfunction, on the pharmacodynamic effects of CSL112.

Methods

- Two Phase 1 studies of CSL112 have been conducted; single (SAD) and multiple ascending dose (MAD) studies.
  - In the SAD study (NCT01192661), healthy subjects were randomized to receive a single infusion of placebo or 5, 15, 40, 70, 105, 135 mg/kg CSL112.
  - In the MAD study (NCT01281774), healthy subjects were randomized to receive: placebo, 3.4 or 6.8 g of CSL112 once weekly (1W; 4 infusions); or placebo or 3.4 g CSL112 twice weekly (2W; 8 infusions) for 4 weeks.

Results

- In the Phase 2a study (NCT01499420), patients with stable atherosclerotic disease defined as a history of acute coronary syndrome (ACS), surgical revascularization or peripheral vascular disease were randomized to receive a single infusion of placebo or 1.7, 3.4 or 6.8 g of CSL112.
- Plasma and serum samples were obtained at multiple time-points allowing assessment of apoA-I, lipid profile and cholesterol efflux capacity in all three studies.
- PK and biomarker assessments
  - Plasma apoA-I and apolipoprotein B were measured by an immunometric turbidimetric method.
  - Serum total cholesterol efflux capacity was measured using the method described by de la Llera-Moya et al.5
  - HDL-VS was assessed by EUSIA using an anti-pre-pro HDL antibody (Sekiwa, Lexington, USA).
- Other lipid parameters were assessed by standard enzymatic methods.

Statistical analysis

- The specific cholesterol efflux activity of apoA-I (HDL function) is a measurement of the ability of HDL to remove cholesterol from macrophages in atherosclerotic lesions. FC in the HDL particle is then esterified by lecithin:cholesterol acyltransferase (LCAT) forming larger HDL particles (HDL2 and HDL3). HDL is also transferred to mature HDL via the APOC1 and SR-B1 transporters. Esterified HDL cholesterol is then transferred to the liver.
- Infusion of CSL112 increases both formation of HDL-3 (pre-β1 HDL) and cholesterol efflux capacity, predominantly via the APOC1 transporter.1-4

Specific apoA-I activity = cholesterol efflux capacity apoA-I concentration

How much cholesterol efflux is caused by one molecule of apoA-I?

Cholesterol removal from atherosclerotic plaque and its proposed removal by CSL112

Figure 1

- In reverse cholesterol transport, free cholesterol (FC) is transferred from cells to HDL-VS (pre-β1 HDL) via the ABCA1 transporter, which is abundant in plaque macrophages in atherosclerotic lesions. FC in the HDL particle is then esterified by lecithin:cholesterol acyltransferase (LCAT) forming larger HDL particles (HDL2 and HDL3). HDL is also transferred to mature HDL via the APOC1 and SR-B1 transporters. Esterified HDL cholesterol is then transferred to the liver.
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Cholesterol efflux capacity post infusion (2 h) to 24 hours

Figure 2

- An unpaired t-test was used to compare baseline levels of apoA-I, HDL-C, cholesterol efflux and HDL function between healthy subjects (Phase 1 studies) and patients (Phase 2a) post-hoc.
- Change in total cholesterol efflux (baseline-corrected area under the effect curve, AUCe,ic) was plotted against change in apoA-I (baseline-corrected area under the curve, AUCic,pre) and linear regression analysis was used to compare the relationship in healthy subjects (Phase 1 SAD and MAD combined) and patients (Phase 2a).
- Subjects were pooled from all three studies and stratified into tertiles by baseline HDL function. Linear regression analysis was used to test the effect of baseline HDL function cholesterol efflux for each tertile.

Limitations

- Study limitations which may potentially introduce bias include healthy subjects in the Phase 1 SAD study who were overweight or obese, patients receiving concurrent medication and the post-hoc nature of the analysis.

CSL112 enhances cholesterol efflux to a similar extent in healthy subjects and in patients with stable atherosclerotic disease

Figure 3

- Infusion of CSL112 caused a rapid increase in apoA-I, which peaked at the end of infusion (2 h) to 2-3 fold above baseline and remained elevated for up to 72 hours.
- Cholesterol efflux capacity peaked at the end of infusion (2 h) with CSL112 and was elevated 2-3 fold above baseline at high doses of CSL112.
- Data shown are from the Phase 2a study, effects were similar in healthy subjects (Phase 1).
- In infusion of CSL112

Conclusions

- "Specific cholesterol efflux activity" of apoA-I, a biomarker of HDL function, differenced more significantly between healthy and atherosclerotic populations than either apoA-I or cholesterol efflux alone.
- CSL112 caused strong and quantitatively similar elevation in cholesterol efflux regardless of baseline specific cholesterol efflux activity.
- These data suggest that CSL112 will effectively elevate cholesterol efflux in patients with impaired HDL functionality.
- Prospective studies are needed to confirm the utility of specific cholesterol efflux activity of apoA-I as a biomarker of CAD risk or a biomarker of therapeutic efficacy.

References

8. NCT01499420) by CSL Limited.
9. Presentation includes investigational uses of drugs.

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The ability of CSL112 to enhance cholesterol efflux capacity is not influenced by baseline HDL function

Figure 4

- In all three study populations a linear relationship was observed between individual baseline-corrected apoA-I exposure and baseline-corrected total cholesterol efflux.
- Concordant lines indicate equal elevation in efflux between healthy subjects and patients (p<0.01).

CSL112 may offer a novel means to rapidly remove cholesterol from plaque following an ACS event and rapidly reduce the occurrence of cardiovascular events.

Figure 5

- Cholesterol efflux capacity post infusion (2 h) to 24 hours increased in a dose-dependent manner following infusion of CSL112. Cholesterol efflux was similarly elevated between subjects in the highest and lowest tertiles of HDL functionality.

Figure 6


Disclosures

- Funding of the clinical trial (NCT01281774, NCT01281774, NCT01192661) by CSL Limited.
- All authors are employees of CSL Limited or CSL Behring.
- Presentation includes investigational uses of drugs.