
C. Michael Gibson, MS, MD
on behalf of the AEGIS-1 Investigators

Gibson et al. AHA 2016
Conflict of Interest Statement

Present Research/Grant Funding
- Angel Medical Corporation
- Bayer Corp.
- CSL, Inc.
- Ikaria, Inc.
- Janssen Pharmaceuticals
- Johnson & Johnson Corporation
- Portola Pharmaceuticals
- Stealth Peptides, Inc.
- St. Jude Medical

Peer to Peer Communications
- Eli Lilly and Company
- The Medicines Company

Royalties as a Contributor
- UpToDate in Cardiovascular Medicine

Consultant
(all with moderate support)
- Amarin Pharama
- Amgen
- Boston Clinical Research Institute
- Cardiovascular Research Foundation
- CSL Behring
- Eli Lilly and Company
- Gilead
- Novo Nordisk
- Pfizer
- Pharma Mar
- Roche Diagnostics
- St. Francis Hospital
- St. Jude Medical
- The Medicines Company
- Web MD

Consultant (with $0.00 monies received by Dr. Gibson)
- Bayer Corporation
- Janssen Pharmaceuticals
- Johnson & Johnson Corporation
- Ortho McNeil

Spouse:
- Employee of Boston Clin Res Institute with equity
• CSL112 is plasma-derived apolipoprotein A-I (apoA-I).

• ApoA-I is the primary functional component of high-density lipoprotein (HDL) and supports the rapid removal of cholesterol from plaque.

• Upon infusion, CSL112 produces an immediate and robust increase in cholesterol efflux capacity.

• Efflux is the first step of reverse cholesterol transport, the process by which HDL transports excess cholesterol to the liver for removal from the body.
Single 80 mg/kg Infusion of Reconstituted ApoA-I Reduced Human Femoral Plaque Lipid & Macrophage Size > 50% in 5-7 Days

Gibson et al. AHA 2016
Cholesterol Efflux From Macrophages

HDL
## Cholesterol Efflux is an Independent Predictor of Cardiovascular Risk

### HDL cholesterol

<table>
<thead>
<tr>
<th>Analysis Type</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted analysis</td>
<td>0.64 (0.40-1.03)</td>
</tr>
<tr>
<td>Analysis adjusted</td>
<td></td>
</tr>
<tr>
<td>For traditional risk factors</td>
<td>0.80 (0.47–1.37)</td>
</tr>
<tr>
<td>For traditional risk factors and HDL particle concentration</td>
<td>1.08 (0.59–1.99)</td>
</tr>
</tbody>
</table>

### Cholesterol efflux capacity

<table>
<thead>
<tr>
<th>Analysis Type</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted analysis</td>
<td>0.44 (0.27–0.73)</td>
</tr>
<tr>
<td>Analysis adjusted</td>
<td></td>
</tr>
<tr>
<td>For traditional risk factors</td>
<td>0.30 (0.18–0.50)</td>
</tr>
<tr>
<td>For traditional risk factors and HDL cholesterol</td>
<td>0.31 (0.18–0.52)</td>
</tr>
<tr>
<td>For traditional risk factors and HDL particle concentration</td>
<td>0.34 (0.20–0.56)</td>
</tr>
<tr>
<td>For traditional risk factors, HDL cholesterol, and HDL particle concentration</td>
<td>0.33 (0.19–0.55)</td>
</tr>
</tbody>
</table>
CSL112 can rapidly elevate cholesterol efflux capacity and may potentially reduce early recurrent cardiovascular events following ACS.
• CSL112 is apoA-I reconstituted into disc-shaped lipoproteins with phosphatidylcholine and stabilized with sucrose.

• An earlier formulation of apoA-I was associated with a dose-related elevation in transaminases related to its phosphatidylcholine content.

• A potential risk for acute kidney injury has been observed with other infusible agents that contain very high levels of sucrose.

• CSL112 contains low concentrations of both of these excipients.
Infusion of apoA-I (CSL112) in addition to standard of care in post MI subjects does not cause a clinically significant alteration in either liver or kidney function when compared to placebo.
Trial Leadership
Co-Chairs: C. Michael Gibson, Robert Harrington

Executive Committee
John Alexander, Pierluigi Tricoci, Philippe G. Steg, A. Michael Lincoff, John J.P. Kastelein, Roxana Mehran, Denise D’Andrea (Sponsor representative)

Data and Safety Monitoring Board
Douglas Weaver, Michel Bertrand, David Faxon, Bruce Molitoris, Jan Tijssen, David Waters, Irene Katzan, Andrew Muir

Clinical Operations
PERFUSE (Beth Israel Deaconess Medical Center) – Boston, Quintiles, Duke Clinical Research Institute - Durham NC

Clinical Event Committee
C5R at Cleveland Clinic; Venu Menon , Chair

Statistics
PERFUSE study group, Megan Yee, Purva Jain; Quintiles

Sponsor
CSL Behring
Patients > 18 years with spontaneous Type 1 MI within 7 days excluding CKD; CIN; ALT > 3x ULN; T bili > 1.5 x ULN; SBP < 100; LVEF <30; Killip CHF Class 3 or 4

Co-primary Endpoints (Safety): Clinically significant changes in hepatic and renal function
Secondary and Exploratory Endpoints: 1. Composite of CV death, nonfatal MI, ischemic stroke, and hospitalization for unstable angina; 2. Cholesterol efflux parameters

Low dose (2g CSL112) Q Wk x 4 (n = 419)
High Dose (6g CSL112) Q Wk x 4 (n = 421)
Placebo Q Wk x 4 (n = 418)

R

Stratification

Normal renal function
Mild renal impairment

eGFR ≥ 90
eGFR 60-90

All: Safety follow-up Day 112
Variable: Follow-up to 1 year
Country Leaders & Enrollment

16 Countries  188 Sites

POLAND (204)  BULGARIA (140)  DENMARK (28)  SPAIN (17)
J. Trebacz  N. Gotcheva  S. Jensen  A. Betriu

HUNGARY (202)  CZECH REPUBLIC (104)  CANADA (25)  UNITED KINGDOM (9)
B. Merkely  M. Solar  P. Armstrong  A. Gershlick

UNITED STATES (167)  GERMANY (86)  ITALY (22)  AUSTRIA (7)
P. Tricoci  C. Bode  G. Ambrosio  K. Huber

NETHERLANDS (145)  ISRAEL (81)  AUSTRALIA (18)  FRANCE (3)
J. Cornel  B. Lewis  P. Aylward  G. Montalescot

Gibson et al. AHA 2016
1401 Assessed for eligibility

1258 Randomized

Stratified by renal function
578 Normal renal function
680 Mild renal impairment

Lost to follow up
CSL112 High Dose (6g) - 1
CSL112 Low Dose (2g) - 0
Placebo - 0

Withdrawn Consent
CSL112 High Dose (6g) - 3
CSL112 Low Dose (2g) - 7
Placebo - 4

ITT Population
419 CSL112 Low Dose (2g)
195 Normal renal function
224 Mild renal impairment
421 CSL112 High Dose (6g)
192 Normal renal function
229 Mild renal impairment
418 Placebo
191 Normal renal function
227 Mild renal impairment

4 Did not receive study drug

Safety Population
415 CSL112 Low Dose (2g)
193 Normal renal function
222 Mild renal impairment
416 CSL112 High Dose (6g)
190 Normal renal function
226 Mild renal impairment
413 Placebo
189 Normal renal function
224 Mild renal impairment

143 Did not meet inclusion or exclusion criteria

191 Normal renal function
227 Mild renal impairment

Gibson et al. AHA 2016
## Baseline Characteristics

There were no statistical differences in baseline characteristics between the 3 study arms. Percentages are based on number of subjects with data.

<table>
<thead>
<tr>
<th></th>
<th>Low Dose (2g) (N=419)</th>
<th>High Dose (6g) (N=421)</th>
<th>Placebo (N=418)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td>57.7 ± 10.1</td>
<td>59.2 ± 9.9</td>
<td>58.1 ± 10.6</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>80.4%</td>
<td>76.7%</td>
<td>81.6%</td>
</tr>
<tr>
<td>Mild renal impairment, %</td>
<td>47.9%</td>
<td>52.0%</td>
<td>50.7%</td>
</tr>
<tr>
<td>Current/former smoker, %</td>
<td>71.4%</td>
<td>69.4%</td>
<td>74.6%</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>24.8%</td>
<td>19.2%</td>
<td>22.7%</td>
</tr>
<tr>
<td>CHF, %</td>
<td>5.7%</td>
<td>2.6%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>64.2%</td>
<td>61.1%</td>
<td>57.4%</td>
</tr>
<tr>
<td>STEMI, %</td>
<td>59.7%</td>
<td>65.1%</td>
<td>60.1%</td>
</tr>
<tr>
<td>NSTEMI, %</td>
<td>40.3%</td>
<td>34.9%</td>
<td>40.0%</td>
</tr>
<tr>
<td>Time from First Medical Contact to First Dose (hrs), mean ± SD</td>
<td>103.5 ± 38.2</td>
<td>99.1 ± 41.9</td>
<td>101.8 ± 38.3</td>
</tr>
<tr>
<td>Time from Angiography to First Dose (hrs), mean ± SD</td>
<td>89.9 ± 38.7</td>
<td>89.9 ± 41.8</td>
<td>91.6 ± 39.9</td>
</tr>
</tbody>
</table>
Concomitant Therapy

There were no statistical differences in concomitant therapy between the 3 study arms. Percentages are based on number of subjects with data.

† Ezetimibe or PCSK9 Inhibitors

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Low Dose (2g) (N=419)</th>
<th>High Dose (6g) (N=421)</th>
<th>Placebo (N=418)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins, %</td>
<td>94.2%</td>
<td>90.1%</td>
<td>93.7%</td>
</tr>
<tr>
<td>Other lipid lowering agents†, %</td>
<td>3.4%</td>
<td>2.6%</td>
<td>3.2%</td>
</tr>
<tr>
<td>ACE Inhibitor/ARB, %</td>
<td>77.8%</td>
<td>78.1%</td>
<td>78.0%</td>
</tr>
<tr>
<td>Beta Blockers, %</td>
<td>80.2%</td>
<td>76.7%</td>
<td>77.7%</td>
</tr>
<tr>
<td>Aspirin, %</td>
<td>97.8%</td>
<td>94.7%</td>
<td>96.9%</td>
</tr>
<tr>
<td>Antiplatelet Agents, %</td>
<td>92.8%</td>
<td>95.0%</td>
<td>94.9%</td>
</tr>
<tr>
<td>Anticoagulants, %</td>
<td>8.2%</td>
<td>8.9%</td>
<td>10.2%</td>
</tr>
</tbody>
</table>

Gibson et al. AHA 2016
### Baseline Plasma and Lipid Values

There were no statistical differences in baseline lipid values between the 3 study arms. Percentages are based on number of subjects with data. HDL denotes high density lipoprotein, LDL low density lipoprotein.

<table>
<thead>
<tr>
<th></th>
<th>Low Dose (2g) (N=419)</th>
<th>High Dose (6g) (N=421)</th>
<th>Placebo (N=418)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoA-I mg/dL, Mean ± SD</td>
<td>124.6 ± 24.6</td>
<td>127.7 ± 25.2</td>
<td>126.1 ± 24.7</td>
</tr>
<tr>
<td>Apolipoprotein B mg/dL, Mean ± SD</td>
<td>90.8 ± 24.3</td>
<td>92.8 ± 25.3</td>
<td>91.9 ± 25.4</td>
</tr>
<tr>
<td>Total Cholesterol mg/dL, Mean ± SD</td>
<td>164.7 ± 39.3</td>
<td>169.3 ± 41.0</td>
<td>166.5 ± 41.6</td>
</tr>
<tr>
<td>HDL Cholesterol mg/dL, Mean ± SD</td>
<td>40.2 ± 11.0</td>
<td>41.6 ± 10.7</td>
<td>40.8 ± 11.0</td>
</tr>
<tr>
<td>Non-HDL Cholesterol mg/dL, Mean ± SD</td>
<td>124.2 ± 38.9</td>
<td>127.6 ± 40.4</td>
<td>125.8 ± 40.9</td>
</tr>
<tr>
<td>LDL Cholesterol mg/dL, Mean ± SD</td>
<td>92.1 ± 35.0</td>
<td>94.7 ± 34.9</td>
<td>92.1 ± 34.4</td>
</tr>
<tr>
<td>Triglycerides mg/dL, Mean ± SD</td>
<td>168.8 ± 99.5</td>
<td>168.0 ± 91.3</td>
<td>170.2 ± 95.1</td>
</tr>
</tbody>
</table>
# Co-primary Safety Endpoint Definitions

## Hepatic Safety:

- Increase in ALT > 3 x the upper limit of normal (ULN)
- OR
- Increase in total bilirubin > 2 x ULN

**Incidence in treatment group within pre-defined non-inferiority margin of 4%**

## Renal Safety:

- Increase in serum creatinine > 1.5 x baseline
- OR
- New requirement for renal replacement

**Incidence in treatment group within pre-defined non-inferiority margin of 5%**
Difference in Co-primary Safety Endpoints
Point Estimates and 95% Confidence Intervals

Hepatic Endpoint

2g v Placebo
4/415 (1.0%), p=0.12

6g v Placebo
2/416 (0.5%), p=0.50
0/413 (0.0%)

Renal Endpoint

2g v Placebo
0/415 (0.0%), p=0.50

6g v Placebo
3/416 (0.7%), p=0.62
1/413 (0.2%)

Gibson et al. AHA 2016
## AEGIS-I

### Treatment Emergent Adverse Events and Key Lab Values of Interest – Safety Population

<table>
<thead>
<tr>
<th></th>
<th>Low Dose (2g) (N=415)</th>
<th>High Dose (6g) (N=416)</th>
<th>Placebo (N=413)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>210 (50.6%)</td>
<td>214 (51.4%)</td>
<td>205 (49.6%)</td>
</tr>
<tr>
<td>Adverse event related to study drug</td>
<td>33 (8.0%)</td>
<td>33 (7.9%)</td>
<td>26 (6.3%)</td>
</tr>
<tr>
<td>Adverse events leading to death</td>
<td>3 (0.7%)</td>
<td>2 (0.5%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Adverse events leading to permanent discontinuation of study drug</td>
<td>11 (2.7%)</td>
<td>8 (1.9%)</td>
<td>9 (2.2%)</td>
</tr>
<tr>
<td>Any AE with CTCAE grade ≥3</td>
<td>77 (18.6%)</td>
<td>54 (13.0%)</td>
<td>65 (15.7%)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>66 (15.9%)</td>
<td>53 (12.7%)</td>
<td>54 (13.1%)</td>
</tr>
<tr>
<td>Serious related adverse events</td>
<td>1 (0.2%)</td>
<td>0 (0.0%)</td>
<td>2 (0.5%)</td>
</tr>
</tbody>
</table>

### On treatment worst case lab abnormalities

<table>
<thead>
<tr>
<th></th>
<th>Low Dose (2g)</th>
<th>High Dose (6g)</th>
<th>Placebo (N=413)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT &gt; 3 x ULN</td>
<td>7 (1.7%)</td>
<td>4 (1.0%)</td>
<td>8 (2.0%)</td>
</tr>
<tr>
<td>Total bilirubin &gt; 2 x ULN</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Serum Creatinine: Rises to &gt; ULN (&gt; 0.3 mg/dL from baseline)</td>
<td>13 (3.1%)</td>
<td>19 (4.6%)</td>
<td>16 (3.9%)</td>
</tr>
<tr>
<td>Serum Creatinine: &gt; 2-fold rise from baseline</td>
<td>0 (0.0%)</td>
<td>1 (0.2%)</td>
<td>2 (0.5%)</td>
</tr>
</tbody>
</table>
Time-to-First MACE
CV Death, Nonfatal MI, Ischemic Stroke, UA Hospitalization

Through Study Day 112
Low Dose CSL112 vs. Placebo
HR (95% CI) = 1.12 (0.58 – 2.16)
High Dose CSL112 vs. Placebo
HR (95% CI) = 0.81 (0.40 – 1.64)

Through End of Study
Low Dose CSL112 vs. Placebo
HR (95% CI) = 1.18 (0.67 – 2.05)
High Dose CSL112 vs. Placebo
HR (95% CI) = 1.02 (0.57 – 1.80)

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Low Dose CSL112 (2g)</th>
<th>Placebo</th>
<th>High Dose CSL112 (6g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSL112 2g</td>
<td>419 405 400 393 390 360</td>
<td>290 229 172 131 92 57 34 6 0</td>
<td>418 404 399 394 391 360</td>
</tr>
<tr>
<td>CSL112 6g</td>
<td>421 411 407 404 401 367</td>
<td>289 230 179 130 96 56 28 3 0</td>
<td>418 404 399 394 391 360</td>
</tr>
<tr>
<td>Placebo</td>
<td>418 404 399 394 391 360</td>
<td>283 220 171 123 84 53 24 2 0</td>
<td>418 404 399 394 391 360</td>
</tr>
</tbody>
</table>
Pre-Specified Exploratory MACE Endpoint
CV Death, Nonfatal MI, Stroke

Cumulative Incidence of MACE (%)

Through Study Day 112
Low Dose CSL112 vs. Placebo
HR (95% CI) = 0.60 (0.26 – 1.37)

High Dose CSL112 vs. Placebo
HR (95% CI) = 0.66 (0.30 – 1.46)

Through End of Study
Low Dose CSL112 vs. Placebo
HR (95% CI) = 0.93 (0.47 – 1.85)

High Dose CSL112 vs. Placebo
HR (95% CI) = 1.15 (0.60 – 2.20)

No. at risk
CSSL12 2g 419 409 407 403 400 371 298 233 176 134 93 58 35 6 0
CSSL12 6g 421 411 408 407 405 370 292 232 180 130 96 56 28 3 0
Placebo 418 406 401 396 393 364 287 226 174 125 85 54 25 2 0

Gibson et al. AHA 2016
### Individual Components of MACE Endpoint

<table>
<thead>
<tr>
<th>MACE Endpoint</th>
<th>Low Dose (2g) (N=419)</th>
<th>High Dose (6g) (N=421)</th>
<th>Placebo (N=418)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite 2° Endpoint</td>
<td>27 (6.4%)</td>
<td>24 (5.7%)</td>
<td>23 (5.5%)</td>
</tr>
<tr>
<td>CV death</td>
<td>2 (0.5%)</td>
<td>4 (1.0%)*</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>14 (3.3%)</td>
<td>13 (3.1%)</td>
<td>14 (3.3%)</td>
</tr>
<tr>
<td>Any strokes</td>
<td>0 (0.0%)</td>
<td>4 (1.0%)</td>
<td>3 (0.7%)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0 (0.0%)</td>
<td>3 (0.7%)</td>
<td>3 (0.7%)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0 (0.0%)</td>
<td>1 (0.2%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Hosp. for unstable angina</td>
<td>13 (3.1%)</td>
<td>6 (1.4%)</td>
<td>7 (1.7%)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>5 (1.2%)</td>
<td>4 (1.0%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Non-CV death</td>
<td>3 (0.7%)</td>
<td>0 (0.0%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>5 (1.2%)</td>
<td>4 (1.0%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>26 (6.2%)</td>
<td>17 (4.0%)</td>
<td>25 (6.0%)</td>
</tr>
</tbody>
</table>

*p = 0.048, not adjusted for multiplicity. Percentages proportion of patients with an event, not a KM estimate.

No events were classified as stroke indeterminate.
Fold Elevation in Cholesterol Efflux Capacity, ApoA-I and HDL after First Infusion of CSL112

Fold elevation at peak compared with baseline
All analyses were performed using patients with available data.

Gibson et al. AHA 2016
Summary

- Infusion of CSL112 following MI and contrast was well tolerated and does not significantly alter liver or kidney function.

- CSL112 elevates cholesterol efflux capacity in a dose dependent fashion.

- Assessment of the efficacy of CSL112 will require further evaluation in an adequately powered phase 3 trial.
Back Up Slides
Days from Randomization Until Death

Gibson et al. AHA 2016
Limitations in Interpreting Efficacy Data

- The number of MACE events overall was low (n=74)
- The number of subjects with complete follow-up through one year was very low 89/1258
- The statistical power to assess the secondary MACE endpoint was very low, approximately 8.4%
- Calculated p-values were not adjusted for the multiplicity of 32 efficacy comparisons.
- No clustering of death in proximity to the CSL112 infusion
- Indeterminant causes of death were included as cardiovascular death.
- Isolated difference in mortality inconsistent with the overall similarity in MACE rates.
## MDCO-216 Compared to CSL 112

<table>
<thead>
<tr>
<th></th>
<th><strong>apoA-1 Milano</strong></th>
<th><strong>CSL 112</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protein</strong></td>
<td>Milano mutant sequence which results in dimeric rather than monomeric apoA-I</td>
<td>Non mutated apoA-1</td>
</tr>
<tr>
<td><strong>Lipid Component</strong></td>
<td>1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine</td>
<td>Phosphatidylcholine</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>20 mg/kg (ie 1.6 gm for a typical 80 KG person)</td>
<td>2 gm or 6 gm</td>
</tr>
</tbody>
</table>

Gibson et al. AHA 2016
Proposed Mechanism of Remodeling

Unstable fusion product

L-HDL\text{rem} \rightarrow \text{CSL112} \rightarrow \text{HDL} \rightarrow \text{L-HDL}_{\text{rem}} \rightarrow \text{S-HDL}_{\text{rem}}

Lipid-poor apoA-1

Unstable fusion product

L-HDL\text{rem} \rightarrow \text{CSL112} \rightarrow \text{HDL} \rightarrow \text{L-HDL}_{\text{rem}} \rightarrow \text{S-HDL}_{\text{rem}}

Particle remodelling

A

B

Didichenko et al. AHA 2016
Remodeling Induced by CSL112 Leads to an Increase in HDL functionality

<table>
<thead>
<tr>
<th>Atheroprotective Function:</th>
<th>HDL</th>
<th>Products of HDL remodeling</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CSL12</td>
<td>HDL3</td>
</tr>
<tr>
<td>ABCA1-dependent Cholesterol Efflux</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Anti-oxidant</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

Consequences of Remodeling

• CSL112 spontaneously interacts with endogenous HDL to yield small remodeled HDL species with high efflux capacity.

• Remodeling causes a dramatic increase in lipid-poor apoA-I, a product that maximally supports ABCA1-dependent efflux.

• The lipid-poor apoA-I formed during remodeling derives from both CSL112 and HDL.

• CSL112 makes existing HDL more active in cholesterol efflux.
IVUS Sample Sizes

- GLAGOV trial enrolled 954 patients yielding 90% power to demonstrate a plaque atheroma volume (PAV) difference of 0.706 with 25% of patients anticipated to not have adequate pre and post IVUS assessments.

- MILANO-PILOT to have 90% power to demonstrate a PAV difference of 1.06 (observed in the Nissen et al study in JAMA 2003) would have required a study of 427 patients.

- With 120 patients (as studied), assuming NO missing data or patient dropout, it is estimated that the power is only 51%.
Basis for Planning a Phase III Outcomes Study

- There was hypothesis generating data associating improved cholesterol efflux with improved outcomes, and this observation was prospectively validated in the Dallas Heart Study.
- Likewise, the observation that CSL 112 improves cholesterol efflux has been prospectively validated in multiple independent studies.
- Planning for an adequately powered Phase 3 is now underway to test the hypothesis that improvements in cholesterol efflux by CSL 112 will in turn be associated with improved clinical outcomes.
Two Hypotheses Prospectively Validated Third to be Tested in Phase III

CSL 112 Improves Cholesterol Efflux

Improved Cholesterol Efflux

Improved Clinical Outcomes