CUPID 2: A Phase 2b Trial Investigating the Efficacy and Safety of the Intracoronary Administration of AAV1/SERCA2a in Patients with Advanced Heart Failure

917 – Hot Line V – Heart Failure
Tuesday, 1 September 2015, 11:00-12:30, London, Main Auditorium
Presentation No. 7165

Barry Greenberg, MD
Distinguished Professor of Medicine
Director, Advanced Heart Failure Treatment Program
University of California, San Diego

On Behalf of the CUPID 2 Trial Investigators & Executive Steering Committee

ClinicalTrials.gov Identifier: NCT01643330
DECLARATION OF INTEREST

- Consulting/Royalties/Owner/ Stockholder of a healthcare company
Disclosures

The clinical study was funded by Celladon Corporation

Dr. Greenberg received financial support from Celladon Corporation
Executive Steering Committee
- Barry Greenberg, Chair
- Javed Butler
- G. Michael Felker
- Piotr Ponikowski
- Adriaan Voors

Data Monitoring Committee
- Jeff Borer, Chair
- Lloyd Fisher
- Alan Miller
- Ian Sarembock
- Karl Swedberg

Clinical Endpoints Committee
- Akshay Desai, Chair

National Coordinating Investigators
- Jozef Bartunek, Belgium
- Jens Kastrup, Denmark
- Veselin Mitrovic, Germany
- Péter Andréka, Hungary
- Adriaan Voors, The Netherlands
- Piotr Ponikowski, Poland
- Thomas Kahan, Sweden
- Alexander Lyon, UK
BACKGROUND
SERCA2a Deficiency is Central to the Progression of Heart Failure

SERCA2a: A Critical Enzyme
Responsible for Driving the Pumping Action of the Heart and Becomes Deficient in Patients with Heart Failure

Restoration in End-Stage Human Heart Cells
Can Restore Normal Contractility, Relaxation and Calcium Cycling

Rationale for CUPID 2

• Gene transfer with AAV1/SERC2a has been shown to improve cardiac performance and outcomes in a variety of experimental models.

• A Phase 1/Phase 2a study in heart failure patients (CUPID 1) suggested that AAV1/SERCA2a stabilized or improved several independent measures of patient wellbeing and cardiac function and that it was associated with a reduction in the recurrent heart failure event rate compared to a placebo-treated control population.

• CUPID 2 study was designed to confirm the beneficial effects of the percutaneous intra-coronary administration of AAV1/SERCA2a on clinical outcomes in patients with moderate to severe heart failure symptoms and reduced ejection fraction and to assess the safety of this approach.
METHODS – CUPID 2
# Main Inclusion and Exclusion Criteria

## Inclusion
- 18-80 years of age
- Diagnosis of NYHA Class II-IV chronic HF due to ischemic or non-ischemic cardiomyopathy
- LVEF ≥ 0.35
- Optimal tolerated stable medical therapy for ≥30 days
- Elevated natriuretic peptide or history of HF-related hospitalization within 6 months of enrollment
- <1:2 or equivocal anti-AAV1 neutralizing antibody

## Exclusion
- Hypertrophic, restrictive and obstructive cardiomyopathy; acute myocarditis; amyloidosis; discrete LV aneurysm
- Cardiac surgery, PCI, valvuoplasty or IV therapy for HF within 30 days prior to screening
- Surgically implanted LVAD
- Significant liver or renal impairment (>3x ULN; GFR ≤20 mL/min/1.73 m²)
- History of cancer within the past 5 years
- Active infection

AAV1/SERCA2a Administered Via Percutaneous Intracoronary Artery Perfusion

• One time antegrade epicardial coronary artery infusion over 10 minutes
• Infusion pump & commercially available guide or diagnostic catheters
• 60 mL divided into 1, 2 or 3 infusions depending on anatomy
• Nitroglycerin just prior to infusion (5 μg/min titrated up to MTD)
• Aim was to provide diffuse homogenous left ventricular exposure to AAV1/SERCA2a
Endpoints

**Primary Efficacy Endpoint:** Time to recurrent HF-related hospitalizations and ambulatory WHF in presence of terminal events (all-cause death, transplant, dMCS)

**Secondary Efficacy Endpoint:** Time to first terminal event (all-cause death, transplant, dMCS)

**Exploratory Endpoints:** NYHA class, NT-proBNP, 6MWT & KCCQ QOL

**Safety Endpoints:** Disposition, clinical events; AEs including procedure-related AEs; changes in medications, vital signs & weight, physical exam, 12-lead ECG, ICD & lab parameters; time to CV-related death

Sample Size Calculations

- Monte Carlo simulation performed using background rates and correlations similar to those observed in CUPID 1:
  - 186 recurrent events in 250 patients with a median follow-up time of 18 months
  - 80% power at the 0.05 two-sided significance level
  - To detect a recurrent event hazard ratio of 0.55 using a joint frailty model

CUPID 2 Study Design

PRE-SCREENING

DAYS PRIOR TO SCREENING

SCREENING, RANDOMIZATION & ENROLLMENT

DAYS PRIOR TO DAY 0

12-MONTH ACTIVE OBSERVATION PERIOD

MONTHS POST-INFUSION

LONG-TERM FOLLOW-UP

DAYS PRIOR TO SCREENING

N = 125

AAV1/SERCA2a
1 X 10^13 DRP

OBSERVE FOR 12 MONTHS

LONG-TERM FOLLOW-UP

PLACEBO

N = 125

OBSERVE FOR 12 MONTHS

LONG-TERM FOLLOW-UP
RESULTS
Patient Population Flowchart

Prescreened N=1558

Failed Screening, N=103
- I/E Criteria Not Met, n=77
- Withdrew Consent, n=11
- Worsening HF, n=4
- Death, n=4
- Comorbidity, n=4
- Other, n=3

Screened N=353

Randomized N=250

Allocated to AAV1/SERCA2a (ITT) N=123
- Not Treated, n=2
  - Worsening Renal Fx, n=1
  - Withdrew Consent, n=1
- Treated (mITT) n=121

Allocated to Placebo (ITT) N=127
- Not Treated, n=5
  - Transplant, n=1
  - Severe Aortic Stenosis, n=1
  - BiVentricular Pacer, n=1
  - URI Unresolving, n=1
  - Withdrew Consent, n=1
- Treated (mITT) n=122

Failed Prescreening, N=1205
- AAV1 NAb Positive, n=921
- I/E Criteria Not Met, n=159
- Withdrew Consent, n=95
- Lost to Follow-Up, n=7
- Noncompliance, n=7
- Worsening HF, n=6
- Death, n=4
- Comorbidity, n=4
- Other, n=2
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo N=122</th>
<th>AAV1/SERCA2a N=121</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), Mean (SD)</td>
<td>58.4 (12.26)</td>
<td>60.3 (9.77)</td>
</tr>
<tr>
<td>Sex, Male, n (%)</td>
<td>98 (80.3)</td>
<td>100 (82.6)</td>
</tr>
<tr>
<td>Race, White, n (%)</td>
<td>99 (81.1)</td>
<td>99 (81.8)</td>
</tr>
<tr>
<td>CAD, n (%)</td>
<td>67 (54.9)</td>
<td>68 (56.2)</td>
</tr>
<tr>
<td>6MWT (m), Mean (SD)</td>
<td>336.6 (71.29)</td>
<td>319.9 (91.47)</td>
</tr>
<tr>
<td>LVEF (%), Mean (SD)</td>
<td>24.0 (6.26)</td>
<td>23.0 (6.48)</td>
</tr>
<tr>
<td>NYHA Class, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>21 (17.2)</td>
<td>22 (18.2)</td>
</tr>
<tr>
<td>III</td>
<td>100 (82.0)</td>
<td>96 (79.3)</td>
</tr>
<tr>
<td>IV</td>
<td>1 (0.8)</td>
<td>3 (2.5)</td>
</tr>
<tr>
<td>KCCQ, Overall Score, Mean (SD)</td>
<td>59.2 (22.27)</td>
<td>58.4 (19.76)</td>
</tr>
<tr>
<td>NT-proBNP (pg.mL), Median (IQR)</td>
<td>1504 (849, 3031)</td>
<td>1754 (843.3, 3785)</td>
</tr>
</tbody>
</table>
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo N=122</th>
<th>AAV1/SERCA2a N=121</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF Etiology, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>63 (51.6)</td>
<td>62 (51.2)</td>
</tr>
<tr>
<td>Non-Ischemic</td>
<td>59 (48.4)</td>
<td>59 (48.8)</td>
</tr>
<tr>
<td>HF Optimized Regimen, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE/ARB</td>
<td>110 (90.2)</td>
<td>111 (91.7)</td>
</tr>
<tr>
<td>Aldosterone Antagonist</td>
<td>74 (60.7)</td>
<td>83 (68.6)</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>117 (95.9)</td>
<td>117 (96.7)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>109 (89.3)</td>
<td>111 (91.7)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>48 (39.3)</td>
<td>45 (37.2)</td>
</tr>
<tr>
<td>OAC/NOAC*</td>
<td>81 (66.4)</td>
<td>76 (62.8)</td>
</tr>
<tr>
<td>CRT, n (%)</td>
<td>39 (32)</td>
<td>53 (43.8)</td>
</tr>
<tr>
<td>ICD, n (%)</td>
<td>89 (73)</td>
<td>98 (81)</td>
</tr>
<tr>
<td>Diabetes Type 2, n (%)</td>
<td>49 (40.2)</td>
<td>59 (48.8)</td>
</tr>
</tbody>
</table>

*OAC/NOAC, oral anticoagulants/novel oral anticoagulants*
CUPID 2: Primary Efficacy Endpoint Results
CUPID 2: Primary Efficacy Endpoint Results

Of the 232 recurrent events that qualified as primary endpoints, 128 were in the placebo group and 104 were in the AAV1/SERCA2a group.

Treatment with AAV1/SERCA2a failed to improve the rate of recurrent events (HR, 0.93; 95% confidence interval [CI] 0.53 to 1.65; p=0.81).
CUPID 2: Primary Efficacy Endpoint Results

Of the 232 recurrent events that qualified as primary endpoints, 128 were in the placebo group and 104 were in the AAV1/SERCA2a group.

Treatment with AAV1/SERCA2a failed to improve the rate of recurrent events (HR, 0.93; 95% confidence interval [CI] 0.53 to 1.65; p=0.81).
CUPID 2: Secondary Efficacy Endpoint Results

Of the 65 terminal events that qualified as secondary endpoints, 29 were in the placebo group and 36 were in the AAV1/SERCA2a group.

Treatment with AAV1/SERCA2a failed to improve time to first terminal event (HR, 1.27; 95% CI 0.72 to 2.24; p=0.40)
<table>
<thead>
<tr>
<th>Subgroup</th>
<th># Subjects</th>
<th>Recurrent Events HR (95% CI)</th>
<th>P value</th>
<th>Terminal Events HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>AAVI/SERCA2a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>127</td>
<td>123</td>
<td>0.92 (0.53, 1.62)</td>
<td>****</td>
<td>1.23 (0.71, 2.14)</td>
</tr>
<tr>
<td>ITT</td>
<td>122</td>
<td>121</td>
<td>0.93 (0.53, 1.65)</td>
<td>****</td>
<td>1.27 (0.72, 2.24)</td>
</tr>
<tr>
<td>Geography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>79</td>
<td>79</td>
<td>0.86 (0.42, 1.77)</td>
<td>0.72</td>
<td>0.81 (0.39, 1.67)</td>
</tr>
<tr>
<td>Ex-US</td>
<td>43</td>
<td>42</td>
<td>1.02 (0.49, 2.42)</td>
<td>****</td>
<td>3.25 (1.22, 8.65)</td>
</tr>
<tr>
<td>HF Etiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>63</td>
<td>62</td>
<td>1.13 (0.50, 2.57)</td>
<td>0.48</td>
<td>1.35 (0.60, 3.02)</td>
</tr>
<tr>
<td>Non-Ischemic</td>
<td>59</td>
<td>59</td>
<td>0.79 (0.36, 1.72)</td>
<td>****</td>
<td>1.22 (0.56, 2.67)</td>
</tr>
<tr>
<td>NYHA Class</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>21</td>
<td>22</td>
<td>0.93 (0.28, 3.14)</td>
<td>0.99</td>
<td>1.26 (0.28, 5.76)</td>
</tr>
<tr>
<td>III or IV</td>
<td>101</td>
<td>99</td>
<td>0.94 (0.50, 1.79)</td>
<td>****</td>
<td>1.30 (0.70, 2.42)</td>
</tr>
<tr>
<td>Years of Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65</td>
<td>82</td>
<td>76</td>
<td>0.73 (0.36, 1.48)</td>
<td>0.16</td>
<td>1.29 (0.66, 2.52)</td>
</tr>
<tr>
<td>≥ 65</td>
<td>40</td>
<td>45</td>
<td>1.75 (0.65, 4.74)</td>
<td>****</td>
<td>1.30 (0.44, 3.81)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>98</td>
<td>100</td>
<td>1.01 (0.54, 1.89)</td>
<td>0.47</td>
<td>1.38 (0.75, 2.55)</td>
</tr>
<tr>
<td>Female</td>
<td>24</td>
<td>21</td>
<td>0.60 (0.16, 2.35)</td>
<td>****</td>
<td>0.68 (0.13, 3.49)</td>
</tr>
<tr>
<td>Diabetic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>73</td>
<td>62</td>
<td>1.59 (0.69, 3.65)</td>
<td>0.09</td>
<td>2.70 (1.04, 7.04)</td>
</tr>
<tr>
<td>Yes</td>
<td>49</td>
<td>59</td>
<td>0.57 (0.27, 1.22)</td>
<td>****</td>
<td>0.69 (0.33, 1.44)</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; Median</td>
<td>66</td>
<td>56</td>
<td>0.62 (0.25, 1.57)</td>
<td>0.33</td>
<td>1.21 (0.51, 2.87)</td>
</tr>
<tr>
<td>≥ Median</td>
<td>56</td>
<td>65</td>
<td>1.08 (0.54, 2.16)</td>
<td>****</td>
<td>1.26 (0.60, 2.64)</td>
</tr>
<tr>
<td>LVEF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; Median</td>
<td>53</td>
<td>60</td>
<td>0.75 (0.36, 1.55)</td>
<td>0.40</td>
<td>1.18 (0.57, 2.43)</td>
</tr>
<tr>
<td>≥ Median</td>
<td>69</td>
<td>60</td>
<td>1.19 (0.49, 2.85)</td>
<td>****</td>
<td>1.19 (0.49, 2.90)</td>
</tr>
<tr>
<td>ICD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>33</td>
<td>23</td>
<td>0.39 (0.10, 1.49)</td>
<td>0.15</td>
<td>1.28 (0.28, 5.84)</td>
</tr>
<tr>
<td>Yes</td>
<td>89</td>
<td>98</td>
<td>1.03 (0.55, 1.93)</td>
<td>****</td>
<td>1.27 (0.69, 2.34)</td>
</tr>
<tr>
<td>Risk Factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>14</td>
<td>15</td>
<td>0.44 (0.07, 2.68)</td>
<td>0.42</td>
<td>0.39 (0.03, 5.43)</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>41</td>
<td>45</td>
<td>1.95 (0.76, 5.05)</td>
<td>0.22</td>
<td>2.55 (0.93, 6.81)</td>
</tr>
<tr>
<td>HF Hospitalization</td>
<td>30</td>
<td>25</td>
<td>0.31 (0.07, 1.46)</td>
<td>0.09</td>
<td>1.08 (0.28, 4.23)</td>
</tr>
<tr>
<td>Both</td>
<td>29</td>
<td>31</td>
<td>1.05 (0.50, 2.22)</td>
<td>****</td>
<td>1.19 (0.43, 3.04)</td>
</tr>
</tbody>
</table>
Exploratory Efficacy Endpoints

Compared to placebo, treatment with AAV1/SERCA2a had no significant effect on change from baseline in:

- NYHA Functional Class
- Percentage of patients who improved > 1 NYHA Functional Class
- Distance walked over 6 minutes
- KCCQ overall score
- NT-proBNP levels
SAFETY
CV-Related Death: Safety Population

HR (95% CI) = 1.28 (0.69, 2.39)
p-value = 0.43

At Risk (n)
Placebo: 122 122 122 119 118 116 113 97 79 61 52 30 20 6
MYDICAR: 121 120 117 117 113 109 109 95 73 60 50 26 19 5

*Subjects who died from other than cardiovascular-related causes were censored at their death dates.
## Adjudicated Clinical Events: Safety Population

<table>
<thead>
<tr>
<th>Clinical Event</th>
<th>Placebo (N=122) n (Rate)</th>
<th>AAV1/SERCA2a (N=121) n (Rate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All clinical events</td>
<td>262 (147)</td>
<td>190 (111)</td>
</tr>
<tr>
<td>All-cause hospitalizations</td>
<td>240 (135)</td>
<td>172 (100)</td>
</tr>
<tr>
<td>HF-related hospitalizations</td>
<td>121 (67.9)</td>
<td>99 (57.7)</td>
</tr>
<tr>
<td>Ambulatory WHF</td>
<td>7 (4.0)</td>
<td>8 (4.8)</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>5 (2.8)</td>
<td>3 (1.7)</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>3 (1.7)</td>
<td>5 (2.9)</td>
</tr>
<tr>
<td>Heart transplant</td>
<td>4 (2.2)</td>
<td>7 (4.1)</td>
</tr>
<tr>
<td>Durable MCSD implant</td>
<td>8 (4.5)</td>
<td>7 (4.1)</td>
</tr>
<tr>
<td>Deaths</td>
<td>20 (11.2)</td>
<td>25 (14.6)</td>
</tr>
<tr>
<td>Non-cardiovascular</td>
<td>2 (1.1)</td>
<td>3 (1.7)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>18 (10.1)</td>
<td>22 (12.8)</td>
</tr>
</tbody>
</table>

Note: Rate per 100 patient-years of observation
CUPID 2: Safety

- The only treatment-emergent SAEs occurring in ≥2% of either treatment group was that placebo patients had a higher rate of ICD insertion than AAV1/SERCA2a patients (4.9% versus 0%; p=0.03)
- The only significant change in hematology, blood chemistries, cardiac enzymes, LFTs was a greater number of SERCA2a patients with BUN >ULN at 3 months (without change in creatinine or eGFR)
- No evidence of any cell-mediated immune response; a single positive ELISPOT result in a placebo patient
- No clinically meaningful changes in vital signs, ECG parameters (including QT duration), or arrhythmias on ICD interrogation
- No significant differences between study groups in change in medical therapy during the course of CUPID 2
CUPID 2: Summary

- Treatment of patients with moderate-severe heart failure with AAV1/SERCA2a did not significantly reduce the likelihood of either recurrent hospitalizations (primary end-point) or terminal events (secondary end-point).
- There was no evidence of improvement for these endpoints in any predefined or exploratory subgroup.
- There were no beneficial effects on exploratory efficacy endpoints.
- No safety concerns emerged.
CUPID 2: Conclusions

CUPID 2 failed to support the hypothesis that AAV1/SERCA2a at the dose used has clinical benefits in patients with moderate to severe heart failure and reduced ejection fraction
What Can We Learn From the Results of CUPID 2

• Exploring questions regarding outcomes:
  
  - Did it turn out to be the wrong target patient population? Was the study design optimal? Were the end-points appropriate?
  
  - Was it the target (i.e., can we conclude that correction of SERCA2a by gene therapy doesn’t improve heart failure outcomes)?
  
  - Was there adequate drug delivery to the cardiac myocytes? (a complex challenge with gene therapy)