Follow-up of the CUPID Gene Therapy Studies

A Roadmap for Enhancement of Myocardial Metabolism and Viability

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Pathway to Heart Failure

- Injury / Damage

Coronary Disease
Myocardial Infarction
Familial/Genetic Hypertension
Pregnancy
Valvular
Alcohol Toxins

Mature
Dysfunctional
Dying
New

Fibroblasts
Extra-cellular Matrix
Blood vessel
Progenitors
Excitation-Contraction Coupling
Advanced Heart Failure Leads to a SERCA2a Deficiency Irrespective of the Underlying Cause of Heart Failure

Coronary Heart Disease (Atherosclerosis, Leading to MI)
Hypertension
Diabetes
Familial Genetic
Toxins, Infectious Agents, Congenital Mutations
Alcoholism and Drug Abuse
Pregnancy

Advanced Heart Failure
SERCA2a Deficiency
Targeting Calcium Cycling Abrogates Adverse Remodeling

- Cardiac injury
- Increased load
- Reduced systemic perfusion
- Activation of RAS, SNS, and cytokines
- Ischemia & energy depletion
- Altered gene expression
- Growth and remodeling
- Contractile Dysfunction
- Calcium Cycling Abnormalities
- SERCA2a Gene Transfer
- Apoptosis
- Cell death
GENE THERAPY

• Unmet needs using current therapies
• Advances in the understanding of the molecular basis of heart failure
• Cardiomyocyte-specific targets have emerged that are difficult to manipulate pharmacologically

VECTORS

• Increasingly efficient gene transfer technology
• Safe vectors
• Homogeneous transduction of the cardiomyocytes
• Long-term expression
• Cardiac specificity
• Effective and minimally invasive techniques of delivery
Targeting by Gene Therapy

- Choice of Vectors
- Modes of Delivery
- Immune Response
- Clinical Trials
Viral Vectors Used in Cardiovascular Application

- **Plasmid**
  - Diameter: --
  - Genome: DNA
  - Peak cardiac expression: 2–4 d
  - Expression duration: 2–4 w
  - Immune response: Mild

- **AAV**
  - Diameter: 20 nm
  - Genome: Single-stranded DNA
  - Peak cardiac expression: 2–4 w
  - Expression duration: Longterm
  - Immune response: Mild

- **Lentivirus**
  - Diameter: 90 nm
  - Genome: RNA
  - Peak cardiac expression: 4–6 d
  - Expression duration: Longterm
  - Immune response: Moderate

- **Adenovirus**
  - Diameter: 100 nm
  - Genome: Double-stranded DNA
  - Peak cardiac expression: 2–4 d
  - Expression duration: 1–4 w
  - Immune response: Robust
Recombinant AAV Vectors

- Major advance in gene transfer agents: safety issues of early generation vectors not observed with rAAV
- rAAV: Nonpathogenic: 90% of population exposed to wild-type AAV in adolescence (asymptomatic exposure)
- rAAV contains no viral genes and is non-integrating, non-mutagenic
- Safety established in >500 humans
- Results in long-term expression in man >4 yrs follow-up
AAV1.SERCA2a DNA: Vector Genome

- AAV1 is well suited for cardiac delivery
- High efficiency transduction of cardiac muscle
Calcium Up-Regulation by Percutaneous Administration of Gene Therapy In Cardiac Disease (CUPID Trial)

Intracoronary Administration of AAV1.SERCA2a in Class III/IV

Phase 1: Open-Label, Sequential Dose Escalation
1.4x10^{11}, 6x10^{11}, 3x10^{12}, 1x10^{13} drp N=12 (3:3:3:3)
CUPID 1: Phase 2a Study in Heart Failure Patients

Double-Blind, Randomized, Placebo Controlled Trial

AAV1.SERCA2a Administered on Top of Optimized Drug & Device Therapies

- N=8 Low 6 x 10^11 DRP
- N=8 Mid 3 x 10^12 DRP
- N=9 High 1 x 10^13 DRP
- N=14 Placebo

12 Months

- Observe 12 Months
- Weeks 1, 2, 3, 4, 5 & 6
- Months 2, 3, 6, 9 & 12

2 Years

- Long-Term Follow-Up
- Semi-Annual Phone Questionnaire

β-blockers, ACEARLB, Aldosterone Antagonists

Biventricular Pacemaker

ICD’s
CUPID Pre-Screen Anti-AAV1 Antibody Results

≈50% Heart Failure Patients Qualify

Percent by NAb Titer

N=509

- <1:2: 49% (n=244)
- 1:2: 7% (n=36)
- 1:4: 6% (n=30)
- 1:8: 7% (n=36)
- ≥1:16: 31% (n=160)
## Eligibility

<table>
<thead>
<tr>
<th><strong>Main Inclusion Criteria</strong></th>
<th><strong>Main Exclusion Criteria</strong></th>
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</thead>
<tbody>
<tr>
<td>- Age 18-75 years old</td>
<td>- Anti-AAV1 neutralizing antibody titer (NAb) ≥1:2</td>
</tr>
<tr>
<td>- NYHA Class III/IV</td>
<td>- Clinically significant MI within 6 months</td>
</tr>
<tr>
<td>- Ischemic or non-ischemic cardiomyopathy</td>
<td>- Likely need for HF-related surgery within next 6 months</td>
</tr>
<tr>
<td>- Maximal oxygen consumption ($V_{O_2}^{max}$) of ≤20 mL/kg/min</td>
<td>- Expected survival &lt;1 years</td>
</tr>
<tr>
<td>- Left ventricular ejection fraction ≤35%</td>
<td>- Based on investigator’s clinical judgment of HF and co-morbid conditions</td>
</tr>
<tr>
<td>- ICD implanted</td>
<td></td>
</tr>
<tr>
<td>- If indicated, biventricular pacemaker implanted for &gt;6 months</td>
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</tbody>
</table>
| - Stable, optimized HF regimen for 30 days, except for diuretics | }
Administration via Percutaneous Intracoronary Artery Infusion

- Gene delivery to viable myocardium
  - Dominance and coronary artery anatomy from angiography determines infusion scenario

- Antegrade epicardial coronary artery infusion over 10 minutes
  - 60 mL divided into 1, 2 or 3 infusions depending on anatomy
  - Delivered via commercially available angiographic injection system & guide or diagnostic catheters
## Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Subjects N=39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>60.5 (11.5)</td>
</tr>
<tr>
<td>Sex, n</td>
<td>34 Male</td>
</tr>
<tr>
<td>Race, n</td>
<td>34 White</td>
</tr>
<tr>
<td>HF Etiology, n (%)</td>
<td></td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>19 (48.7)</td>
</tr>
<tr>
<td>Idiopathic cardiomyopathy</td>
<td>14 (35.9)</td>
</tr>
<tr>
<td>Hypertensive cardiomyopathy*</td>
<td>4 (10.3)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (7.7)</td>
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</tbody>
</table>
## Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Subjects N=39</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>6MWT</strong>, m, mean (SD)</td>
<td>343 (124)</td>
</tr>
<tr>
<td><strong>VO₂max</strong>, mL/kg/min, mean (SD)</td>
<td>13.9 (3.9)</td>
</tr>
<tr>
<td><strong>LVEF</strong>, %, mean (SD)</td>
<td>25 (7)</td>
</tr>
<tr>
<td><strong>LVESV</strong>, mL, mean (SD)</td>
<td>202 (91)</td>
</tr>
<tr>
<td><strong>NYHA Class III</strong>, n (%)</td>
<td>39 (100)</td>
</tr>
<tr>
<td><strong>MLWHFQ</strong>, mean (SD)</td>
<td>46 (22)</td>
</tr>
<tr>
<td><strong>NT-proBNP</strong>, pg/mL, mean (SD)</td>
<td>2932 (3028)</td>
</tr>
<tr>
<td><strong>Creatinine</strong>, mg/dL, mean (SD)</td>
<td>1.34 (0.53)</td>
</tr>
</tbody>
</table>
12 Months Follow up following AAV1.SERCA2a Injection: Cumulative Clinical Event Rates Adjusted for Competing Risk of Terminal Events
AAV1.SERCA2a Improved in a Number of Biological Parameters vs. Placebo

<table>
<thead>
<tr>
<th>Efficacy Domain</th>
<th>AAV1.SERCA2a</th>
<th>Placebo / Optimized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality Of Life Questionnaire</td>
<td>↑↑</td>
<td>↓</td>
</tr>
<tr>
<td>Functional</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Minute Walk Test</td>
<td>←→</td>
<td>↓↓↓↓</td>
</tr>
<tr>
<td>VO₂max</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biomarker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>←→</td>
<td>↓↓↓↓</td>
</tr>
<tr>
<td>Remodeling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection Fraction</td>
<td>←→</td>
<td>↓↓</td>
</tr>
<tr>
<td>End Systolic Volume</td>
<td>↑</td>
<td>↓↓</td>
</tr>
</tbody>
</table>

* Circulation. 2011 Jul 19;124(3):304-313. Double arrows indicate that change from baseline at 6 months (primary endpoint) reached prespecified criteria for a clinically meaningful change.
Clinical Events over 3 years

Months

1
6
12
18
24
30
36

Placebo

AAV1.SERCA2a Low

AAV1.SERCA2a Mid

AAV1.SERCA2a High

WHF ▲  MI ▲  LVAD ●  Transplant ■  Chronic Inotrope ○  Death ■  NAb* ●
3-Year Follow-up following AAV1.SERCA2a Delivery

Survival Probability

Days

AAV1/SERCA2a, p = 0.11

PLACEBO

Survival Probability

Days

0.00

900

990

1080
Reduction in Hospitalizations – 3 year follow-up

1 Year HR(95% CI) = 0.12, 88% Risk Reduction, p = 0.003

3 Year HR(95% CI) = 0.24, 76% Risk Reduction, p = 0.02
AAV1/SERCA2a qPCR Biomarker Results Consistent with High-Dose Subjects Improvement

<table>
<thead>
<tr>
<th>STUDY PHASE</th>
<th>Treatment Group</th>
<th>Time Point</th>
<th>AAV1/SERCA2a Copies DNA/µg Total DNA*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 2</td>
<td>Placebo</td>
<td>Month 2</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Month 10</td>
<td>Negative (all)</td>
</tr>
<tr>
<td>Phase 2</td>
<td>Placebo</td>
<td>Month 7</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Month 10</td>
<td>Negative (all)</td>
</tr>
<tr>
<td>Phase 1</td>
<td>AAV1.SERCA2a Very Low-dose</td>
<td>Month 8</td>
<td>Negative (all tissues)</td>
</tr>
<tr>
<td>Phase 1</td>
<td>AAV1.SERCA2a Mid-dose</td>
<td>Month 1</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Month 21</td>
<td>Negative (all)</td>
</tr>
<tr>
<td>Phase 2</td>
<td>AAV1.SERCA2a Mid-dose</td>
<td>Month 5</td>
<td>Negative (all)</td>
</tr>
<tr>
<td>Phase 2</td>
<td>AAV1.SERCA2a Mid-dose</td>
<td>Month 10</td>
<td>Negative (all)</td>
</tr>
<tr>
<td>Phase 2</td>
<td>AAV1.SERCA2a Mid-dose</td>
<td>Month 11</td>
<td>Negative</td>
</tr>
<tr>
<td>Phase 1</td>
<td>AAV1.SERCA2a High-dose</td>
<td>Month 18</td>
<td>&gt;20 to &lt;200 Copies</td>
</tr>
<tr>
<td>Phase 2</td>
<td>AAV1.SERCA2a High-dose</td>
<td>Month 11</td>
<td>&gt;20 to &lt;200 Copies</td>
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<tr>
<td></td>
<td></td>
<td>Month 23</td>
<td>561 Copies (AS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>365 Copies (PS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;20 to &lt;200 Copies (AW and PLW)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>230 Copies (LVAC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>250 Copies (RVAC)</td>
</tr>
<tr>
<td>Phase 1</td>
<td>AAV1.SERCA2a High-dose</td>
<td>Month 31</td>
<td>&gt;20 to &lt;200 Copies</td>
</tr>
<tr>
<td>Phase 2</td>
<td>AAV1.SERCA2a High-dose</td>
<td>Month 22</td>
<td>&gt;20 to &lt;200 Copies (AS, PS and AW)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>223 Copies (PW)</td>
</tr>
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</table>
CUPID: AAV1.SERCA2a Demonstrated an Excellent Safety Profile

Safety Through 3 Years of Long Term Follow-Up

- **NO INCREASE** in Adverse Events, Disease-Related Events or Laboratory Abnormalities in Any of the AAV1.SERCA2A-Treated Subjects
- **NO INDICATION** of an Increase in Any New Occurrences or Exacerbation of Pre-Existing Clinical Conditions or Prior Disorders or Other Unexpected Illnesses Associated with AAV1.SERCA2a Administration

Deaths Through 3 Years of Long Term Follow-Up

- **13 Deaths in Phase 2 Trial**
  - 6 in Placebo
  - 3 in Low Dose
  - 3 in Mid Dose
  - 1 in High Dose (Occurred at Month 21)
CUPID SUMMARY

• In this phase 2a study of patients with advanced HF, AAV1.SERCA2a was found to be safe and associated with benefit in the following:
  – Clinical outcomes
  – Symptoms
  – Functional Status
  – Biomarkers
  – Cardiac Structure

• At three years:
  – Persistent of SERCA2a gene for up to 31 months post gene transfer
  – Clinical improvements still present in the high dose group
International Phase 2b/3 Trial  
\( N=250, \, 2\text{-Arm} \)

**PATIENT POPULATION**
- 18-80 years of age, inclusive
- Chronic systolic HF
- Ischemic or dilated cardiomyopathy
- EF \( \leq 35\%
- NYHA Class III or IV
- Maximal, optimized HF regimen
- AAV NAb titer negative

<table>
<thead>
<tr>
<th>Startup 6m</th>
<th>Enrollment 16 mos</th>
<th>Conduct 12 mos</th>
<th>Follow-Up 12 mos</th>
<th>Close-Out</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**AAV1.SERCA2a 1x10^{13} DRP, N=125**

Sample Size/Power:
N=125 per treatment group with 186 recurrent events provides:
83% power, 0.05 two-sided significance level, to detect at least a 45% risk reduction (HR=0.55)

All Subjects Followed Quarterly for Clinical Events Until:
Last enrolled subject completes 12 months of observation AND 186 adjudicated HF-related hospitalizations have occurred

**Placebo, N=125**

**Long-Term Follow-Up**
All subjects followed quarterly for clinical events until:
- Last enrolled subject completes 12 months of observation
  - AND
- 186 adjudicated HF-related hospitalizations have occurred

Subjects undergoing LVAD or transplant on-study will continue to be followed until death or end-of-study.

**Primary Endpoint:** Time-to-recurrent hospitalization for heart failure in presence of terminal events (all-cause death, transplant, LVAD)

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

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

**Safety:** AEs including procedure-related AEs; changes in conmeds, VS, PE, ICD & lab parameters; time-to-CV-related death

60 centers in Belgium, Denmark, Germany, Hungary, Israel, Netherlands, Poland, Sweden, UK & US
Baseline Characteristics Well Matched Between CUPID 1 vs. CUPID 2

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CUPID 1 (N = 39)</th>
<th>CUPID 2 (N = 250)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic HF</td>
<td>49%</td>
<td>48%</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>2268 ± 2209</td>
<td>2834 ± 4137</td>
</tr>
<tr>
<td>LV-Ejection Fraction</td>
<td>25% ± 7</td>
<td>23% ± 6</td>
</tr>
<tr>
<td>6-Minute Walk Test (m)</td>
<td>345 ± 119</td>
<td>326 ± 81</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>61 ± 11</td>
<td>59 ± 11</td>
</tr>
<tr>
<td>Male</td>
<td>87%</td>
<td>82%</td>
</tr>
<tr>
<td>NYHA III or IV</td>
<td>100%</td>
<td>84%</td>
</tr>
<tr>
<td>White</td>
<td>90%</td>
<td>82%</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>92%</td>
<td>93%</td>
</tr>
<tr>
<td>ACE/ARB</td>
<td>92%</td>
<td>88%</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>46%</td>
<td>59%</td>
</tr>
<tr>
<td>Diuretic</td>
<td>92%</td>
<td>92%</td>
</tr>
</tbody>
</table>
AAV1-CMV-Serca2a \textbf{GENe} Therapy in patients with advanced \textbf{Heart Failure} : AGENT-HF Clinical trial
PI: Jean Sebastien Hulot MD, PhD

Objectives:
- Define changes in ventricular volume & size after SERCA2a gene transfer
- Changes in Myocardial perfusion
LVAD Trial

Patients undergoing LVAD insertion as destination-therapy or bridge to transplant receive AAV1.SERCA2a at least one month after VAD placement $10^{13}$ drp (8 patients Nab neg. and 8 patients Nab pos.) and saline (8 patients).

(Harefield/Papworth, UK, PIs: Drs. Alex Lyon, Sian Harding)
Other Trials with AAV1.SERCA2a

• Patients undergoing AV-Fistula Surgery – Phase 2 to start in Q4 2015
• Patients with pulmonary arterial hypertension
• Patients with Preserved Ejection Fraction Heart Failure
• Patients with ventricular arrhythmias and ICD for secondary prevention
Translation of SERCA2a as a Target to Clinical Trials

- Biology of Heart Failure
- Vector Development
- Gene/Cell Delivery
- Preclinical Studies
- Lead Optimization
- Target Validation
- Imaging Modalities
- Genomics/Proteomics
- Animal Models
- Discovery
- Target Identification

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TRIAL
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Thank you for your attention