A Multicenter, Randomized Study Assessing the Efficacy of Left Ventricular Augmentation with Algisyl-LVR in the Treatment of Advanced Heart Failure Patients with Ischemic and Non-ischemic Cardiomyopathy: Interim Results of the AUGMENT-HF Study

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Funded by LoneStar Heart, Inc.
Douglas L. Mann

- Scientific Advisory Board - Lone Star Heart, miRagen therapeutics, Lilly Corporation
- Consultant – Bio Control Medical, Celgene, Cardioxyl, Medtronic, Juventas
- Grant Support – NIH
Background

• Therapeutic options are limited for patients with advanced heart failure who become refractory to conventional pharmacological therapies

• The injection of biomaterials into diseased myocardium has been shown to reduce myofiber stress, LV wall stress, restore LV geometry and improve LV function in animal models

• Algisyl-LVR™ is a medical device that consists of a proprietary alginate hydrogel that is injected into the midwall of the LV, where it remains as a permanent implant that is intended to reduce LV wall stress and prevent or reverse the progression of heart failure in patients who have dilated cardiomyopathy

• In a prior phase I pilot clinical study of Algisyl-LVR™ in patients with symptomatic heart failure undergoing CABG, significant improvements in cardiac function and reverse LV remodeling were observed within 3 months
LV Restoration & Laplace’s Law
The mechanism of the Algisyl-LVR™

\[
\sigma = \frac{P \times R}{2h}
\]

Dilated

Modified (LVR)

\[
\sigma = \frac{P \times R}{2h}
\]
LV Restoration with Algisyl- LVR™ Placement of Alginate Hydrogel
AUGMENT-HF Study Design

- AUGMENT-HF is a multicenter prospective phase II randomized clinical trial to evaluate the safety and potential efficacy of Algisyl-LVR™ in patients with advanced heart failure who remain symptomatic despite being treated with optimal medical and/or device therapy.

- A total of 76 patients will be randomized 1:1:
  - 38 patients receive the Algisyl-LVR implants
  - 38 receive optimal medical therapy

- 16 centers in Australia, Italy, Romania, Netherlands & Germany

- The primary safety objective is to estimate the 30 day mortality associated with the implantation of the Algisyl-LVR™ device.

- The primary efficacy objectives are to evaluate clinical outcomes of patients receiving Algisyl-LVR™ when compared to patients who are receiving optimal medical and/or device therapy:
  - Change in peak VO2 (6 months)
  - Six minute walk distance (6 months)
  - Change in KCCQ scores (at 6 months)
  - NYHA functional class (6 months)
AUGMENT-HF Study Design

- Patients will be evaluated prior to the procedure, during the immediate post operative period, and then at 30 days, 3, and 6 months. The efficacy phase of the study will end on a common date after a minimum of 6 months of follow-up for the last enrolled patient.
- The data analysis plan pre-specified an interim analysis of patient safety and efficacy of Algisyl-LVR™ after the first 30 patients were enrolled.
- Patients will be followed at the close of the trial at 12, 18 and 24 months to evaluate the long term safety of Algisyl-LVR™
- Inclusion criteria - patients with ischemic or non-ischemic DCM, EF ≤ 35%, Peak VO2 of 9.0 - 14.5 ml/kg/min, LVEDDi 30 to 40mm/m² (LVEDD/BSA), who remain symptomatic despite optimal evidence-based therapies for HF
- Exclusion criteria are typical for patients with advanced heart failure
- Blinded assessment for the key measures and outcomes by core laboratories
- A Clinical Events Committee adjudicates hospitalization, death and cardiac procedures
- An independent DSMB provides assessment of patient safety & study conduct
### AUGMENT-HF: Participating Centers

<table>
<thead>
<tr>
<th>Participating Center</th>
<th>Location</th>
<th>Principal Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policlinico Umberto I Rome</td>
<td>Rome, Italy</td>
<td>Prof. Fabio Miraldi</td>
</tr>
<tr>
<td>IRCCS Policlinico San Donato</td>
<td>San Donato, Italy</td>
<td>Dr. Enrico Pusineri</td>
</tr>
<tr>
<td>Instituto Scientifico Univ. San Raffaele</td>
<td>Milan, Italy</td>
<td>Dr. Ottavio Alfieri</td>
</tr>
<tr>
<td>IRCCS San Raffaele</td>
<td>Rome, Italy</td>
<td>Prof. Maurizio Volterrani</td>
</tr>
<tr>
<td>Azienda Ospedaliera di Padova</td>
<td>Padova, Italy</td>
<td>Dr. Gino Gerosa</td>
</tr>
<tr>
<td>Istituti Ospitalieri di Cremona</td>
<td>Cremona, Italy</td>
<td>Prof. Pirelli Salvatore</td>
</tr>
<tr>
<td>St. Antonius Ziekenhuis Nieuwegein</td>
<td>Nieuwegein, Netherlands</td>
<td>Dr. Benno Rensing</td>
</tr>
<tr>
<td>Heart Center at the Alfred</td>
<td>Melbourne, Australia</td>
<td>Dr. Anthony Dart</td>
</tr>
<tr>
<td>Military Hospital</td>
<td>Bucharest, Romania</td>
<td>Prof. Garbiel Cristian</td>
</tr>
<tr>
<td>Spitalul Clinic De Urgenta MAI</td>
<td>Bucharest, Romania</td>
<td>Dr. Dinu Dragomir</td>
</tr>
<tr>
<td>Clinica de Cardiologie Spitalul Clinic Urgenta</td>
<td>Bucharest, Romania</td>
<td>Dr. Sorin Stamate</td>
</tr>
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</table>

### Fall 2013 – Winter 2014

<table>
<thead>
<tr>
<th>Participating Center</th>
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<th>Principal Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herzzentrum Dresden Universitätsklinik</td>
<td>Dresden, Germany</td>
<td>Prof. Klaus Matschke</td>
</tr>
<tr>
<td>Universitätsklinikum Ulm</td>
<td>Ulm, Germany</td>
<td>Prof. Robert Bauernschmitt</td>
</tr>
<tr>
<td>Universität Schleswig-Holstein</td>
<td>Kiel, Germany</td>
<td>Prof. Norbert Frey</td>
</tr>
<tr>
<td>Charité - Universitätmedizin Berlin</td>
<td>Berlin, Germany</td>
<td>Prof. Carsten Tschöpe</td>
</tr>
<tr>
<td>Charité Campus Virchow</td>
<td>Berlin, Germany</td>
<td>Prof. Wilhelm Haverkamp</td>
</tr>
</tbody>
</table>
AUGMENT-HF Interim Analysis

pre-specified interim analysis: first 30 pts completing 3 mos

49 Patients Assessed for Eligibility

30 eligible patients randomized

19 excluded; did not meet inclusion criteria

15 Algisyl-LVR

1 withdrawn prior to implant

2 deaths in follow-up

3-month visit (N=12) 6-month visit (N=5)

15 control

1 death in follow-up

3-month visit (N=14) 6-month visit (N=5)
## AUGMENT-HF Interim Dataset
### Baseline Demographics (ITT)

<table>
<thead>
<tr>
<th></th>
<th>ALL (n=30)</th>
<th>Algisyl-LVR (n=15)</th>
<th>Control (n=15)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>63.3 (9.1)</td>
<td>63.1</td>
<td>62.3</td>
<td>N.S.</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>24 (80%)</td>
<td>10 (67%)</td>
<td>14 (93%)</td>
<td>N.S</td>
</tr>
<tr>
<td><strong>Ethnicity (white)</strong></td>
<td>30 (100%)</td>
<td>15 (100%)</td>
<td>15 (100%)</td>
<td>N.S</td>
</tr>
<tr>
<td><strong>NYHA class II/III/IV</strong></td>
<td>(3)(23)(4)</td>
<td>(0)(13)(2)</td>
<td>(3)(10)(2)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Ischemic HF</strong></td>
<td>20 (67%)</td>
<td>10 (67%)</td>
<td>10 (67%)</td>
<td>N.S</td>
</tr>
<tr>
<td><strong>Non-Ischemic HF</strong></td>
<td>10 (33%)</td>
<td>5 (33%)</td>
<td>5 (33%)</td>
<td>N.S</td>
</tr>
<tr>
<td><strong>CRT</strong></td>
<td>13 (43%)</td>
<td>6 (40%)</td>
<td>7 (47%)</td>
<td>N.S</td>
</tr>
<tr>
<td><strong>LVEF (%)</strong></td>
<td>25.7</td>
<td>25.0</td>
<td>26.7</td>
<td>N.S</td>
</tr>
<tr>
<td><strong>LVEDD (cm)</strong></td>
<td>6.24</td>
<td>6.11</td>
<td>6.37</td>
<td>N.S</td>
</tr>
<tr>
<td><strong>Peak VO2 (ml/min/kg)</strong></td>
<td>12.2</td>
<td>12.3</td>
<td>12.0</td>
<td>N.S</td>
</tr>
<tr>
<td><strong>6 MWT (m)</strong></td>
<td>270</td>
<td>235</td>
<td>305</td>
<td>.013*</td>
</tr>
</tbody>
</table>
## AUGMENT-HF Interim Dataset
### Concomitant Medications

<table>
<thead>
<tr>
<th>Category</th>
<th>Algisyl-LVR (N=15)</th>
<th>Usual Care (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-thrombotics / Anti-platelet agents</td>
<td>14 (93.3%)</td>
<td>14 (93.3%)</td>
</tr>
<tr>
<td>Anti-platelet aggregation agents</td>
<td>12 (80.0%)</td>
<td>10 (66.7%)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>14 (93.3%)</td>
<td>13 (86.7%)</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>11 (73.3%)</td>
<td>5 (33.3%)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>13 (86.7%)</td>
<td>12 (80.0%)</td>
</tr>
<tr>
<td>ARB/ ACE</td>
<td>10 (66.7%)</td>
<td>11 (73.3%)</td>
</tr>
<tr>
<td>Lipid-lowering</td>
<td>10 (66.7%)</td>
<td>11 (73.3%)</td>
</tr>
</tbody>
</table>
### AUGMENT-HF Interim Dataset

#### Operative Procedure Metrics (n=14)

<table>
<thead>
<tr>
<th></th>
<th>Limited Anterior Thoracotomy</th>
<th>Algisyl-LVR (N=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean Anesthesia duration</strong> <em>(min-max)</em></td>
<td>190 ± 27 (150 - 240) min.</td>
<td></td>
</tr>
<tr>
<td><strong>Mean Procedure duration</strong> <em>(min-max)</em></td>
<td>78.6 ± 25.6 (50.0 - 135.0) min</td>
<td></td>
</tr>
<tr>
<td><strong>Mean ICU Length of Stay</strong></td>
<td>5.4 ± 10.9 days</td>
<td></td>
</tr>
<tr>
<td><strong>Mean Hospital Length of Stay</strong> <em>(min-max)</em></td>
<td>17.4 ± 14.9 (7.0 - 65.0) days</td>
<td></td>
</tr>
<tr>
<td><strong>Total number of implants/injections</strong> <em>(min-max)</em></td>
<td>15.8 ± 1.8 (11.0 - 18.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Total volume of implants</strong> <em>(mL)</em> <em>(min-max)</em></td>
<td>4.7 ± 0.6 (3.3 - 5.4) mL</td>
<td></td>
</tr>
</tbody>
</table>
Primary Safety End Point
Estimate of Algisyl-LVR device 30 day mortality

30 day mortality

<table>
<thead>
<tr>
<th>Algisyl-LVR (N=14)</th>
<th>Total # of events</th>
<th># Pts with event (% of Pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 day mortality</td>
<td>0</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>30 day morbidity - Serious adverse events within 30 days of the surgical implant procedure</td>
<td>5</td>
<td>3 (21.4%)</td>
</tr>
</tbody>
</table>

**Overall mortality in the interim data set**

- Algisyl-LVR Group: 2 patients died > 30 days post-operatively
  - Drug resistant Klebsiella Pneumonia – 66 days post-procedure
  - Critical illness 2° to Sepsis – 49 days post-procedure
- Usual Care Group: 1 patient
  - Worsening Heart Failure – 39 days post-randomization
AUGMENT-HF
Six Minute Walk Distance by Visit

**Algisyl-LVR**
- Baseline (n=30): 235
- 3 Month (n=23): 328
- 6 Month (n=10): 345

**Controls**
- 305 (n=23)
- 295 (n=10)
- 277 (n=10)

*P = 0.008
*P = 0.03
P = NS
AUGMENT-HF
Six Minute Walk Distance – change from baseline

3 Months (n=23)

\[ \text{Algisyl-LVR} \]
\[ \text{Control} \]

\[ 100.0 \]

\[ *P = 0.02 \]

\[ -4.3 \]

6 Months (n=10)

\[ \text{Algisyl-LVR} \]
\[ \text{Control} \]

\[ 140.0 \]

\[ P = 0.06 \]

\[ -30.2 \]
AUGMENT-HF
NYHA Functional Class by Visit

*P = 0.002
*P < 0.0001
P = 0.446

Algisyl-LVR
BL (n=30) 3 MO (n=23) 6 MO (n=10)
3.1 2.3 1.8

Controls
2.9 2.8 3.0
AUGMENT-HF
NYHA Functional Class– change from baseline

Change from Baseline at 3 Mo (n=23)

-0.8
-0.1

*P = 0.001

Change from Baseline at 6 Mo (n=10)

-1.3

*P = 0.001

-0.1

Algisyl-LVR
Controls
AUGMENT-HF
KCCQ Overall Summary Score

*P = 0.017
*P = 0.01
P = NS

![Bar Chart]

- **Algisyl-LVR**
  - Baseline (n=30): 39.2
  - 3 Month (n=23): 58.6
  - 6 Month (n=10): 68.3

- **Controls**
  - Baseline (n=30): 56.5
  - 3 Month (n=23): 65.2
  - 6 Month (n=10): 69.8
AUGMENT-HF
KCCQ - Overall Summary Score change from baseline

3 Months (n=23)

- Algisyl-LVR: 20.0
- Control: 5.7

P = 0.10

6 Months (n=10)

- Algisyl-LVR: 34.8
- Control: 3.5

P = 0.03
AUGMENT-HF
Clinical Composite of Peak VO2 at 3 Months

Usual Care Group
- Improved: 50%
- Unchanged: 8%
- Worsened: 0%

Algisyl-LVR Group
- Improved: 30%
- Unchanged: 40%
- Worsened: 30%

- Improved is an increase of 1.0 ml/min/kg or more
- Unchanged is a change of -0.99 to +0.99 ml/min/kg
- Worsened a decrease of 1.0 ml/min/kg or more
Interim results of the AUGMENT-HF trial show that Algisyl-LVR™ is safe, with an acceptable 30 day post-operative morbidity and mortality.

The interim efficacy analysis suggests that the Algisyl-LVR™ leads to improvements in quality of life and functional capacity in comparison to patients who are treated with optimal medical management alone.

These interim results should be viewed as provisional given the small number of patients and the short follow-up time.

These studies provide proof-of-concept for LV reconstruction with Algisyl-LVR™ as a potential novel new therapy for patients with advanced heart failure.