Non Pacing Pacemaker Like Devices for Heart Failure Therapy.

**Investigational Devices**

- Cardiac Contractility Modulation
  - Optimizer IV, Impulse Dynamics

- Baroreceptor Stimulation
  - Barostim, CVRx

**Freddy Abi-Samra MD**

- Research Support: Impulse Dynamics, CVRx
- Consultant: Impulse Dynamics
Cardiac Contractility Modulation (CCM™) OPTIMIZER IV System: An Investigational Treatment for Chronic Heart Failure

Heart Fix V Pivotal Trial

CAUTION – Investigational device. Limited by Federal (or United States) law to investigational use.
It has been known since the 1960’s that myocardial contractility could be modulated by electrically changing the amplitude and/or duration of membrane depolarization (action potential).

Evidence now shows that extracellular electric signals can also influence electrical properties, and thus mechanical strength, of heart muscle in a manner that can be applied clinically.
The Concept:
Cardiac Contractility Modulation (CCM)

Detect local activation

Apply electric signal during absolute refractory period

Delay | Duration | Amplitude
How could CCM Signals Effect Contractility?

1. Changes in action potential configuration influence calcium entry
2. Increased calcium entry can enhance calcium cycling and thence contractile strength
Questions:
1. Is AP influenced?
2. Is $[\text{Ca}^{2+}]_i$ influenced?
3. Is there $[\text{Ca}^{2+}]$ loading of SR?
Acute Hemodynamic Effects of CCM Signals in Patients with CHF
Acute CCM in CHF Patients:

dP/dt Increases Without Significant Change in MVO$_2$

Butter et al. 2004
Myocardial Oxygen Consumption

Adapted from: Nelson et al. 2000 & Butter et al. 2004
Heart failure

- Mechanical and neuro-hormonal stresses present in heart failure result in:
  - Protein dysfunction
  - Altered amounts and types of proteins present in the myocardium

- These effects have a progressive negative impact on LV function, induce apoptosis and drive ventricular dilation:
  - “LV Remodeling”
  - Stressed myocardial cells switch to fetal gene program

- Just like with beta blockers (Bristow, NEJM 2002), animal and clinical data indicate that CCM reverses the fetal gene program to the normal gene program
Sodium-Calcium Exchanger in CHF

1. Present on plasma membrane of myocytes
2. Is the main calcium extrusion system from the cytosol to the extracellular space
3. Its activity is increased in the failing heart
4. Its overexpression in CHF can:
   1. Lead to contractile systolic dysfunction if in forward mode due to depletion of SR calcium
   2. Lead to arrhythmogenesis and diastolic dysfunction if in reverse mode due to calcium overload. In reverse mode NCX compensates for reduced SERCA-2A activity.

Fetal Gene Program
Reversed by CCM in dog HF model

Imai JACC, 2007
Findings in human myocardial samples confirm findings in tissue from animal models.

Butter et al. JACC, 2008
Changes in Protein Expression Follow Changes in Gene Expression

Gene Expression of SERCA-2a (densitometric units)

- NL
- HF
- HF + CCM

Protein Expression of SERCA-2a (densitometric units)

- NL
- HF-Sham
- HF + CCM

P<0.05 vs. NL
P<0.05 vs. HF

Imai JACC, 2007
SERCa2a Expression is impacted **acutely** only in the region **near** where CCM signals are delivered.

Imai JACC, 2007
Improved regional cardiac function induces global improvement (3 months)

**SERCa2a** expression is normalized at sites both near to and remote from the site of CCM signal delivery by **3 months** of treatment.

Imai JACC, 2007
Improved regional cardiac function induces global improvement and reverse remodeling in patients

Yu et al., 2009 JACC Cardiovascular Imaging
The CCM™ mechanism of action has three steps

1. **Normalization of the activity of key regulatory proteins (Phosphorylation)** — Seconds
2. **Reversal of the Fetal Gene Program (Gene Expression)** — Hours
3. **Reverse Remodeling** — Months
CCM™ is a treatment for symptomatic Heart Failure with reduced EF

Heart Failure, Reduced EF, Symptomatic despite Optimal Medical Therapy

Wide QRS (Dyssynchrony)
- CRT

Normal QRS
- CRT not indicated
- CCM

Check manual for indications for use and contraindications
Electrode Placement
CCM™ signals are delivered by the Optimizer IVs™ System

Simple transcutaneous charging of the device at the patient’s home once a week

Graphic programmer for device interrogation and parameter setting at the physician’s office

✓ CE mark

An atrial lead used for sensing only

Two ventricular leads implanted in the RV septum, for sensing and delivery of CCM
CCM™ Clinical data

- >800 implants
- Patients with over 7 years of treatment
- 3 randomized studies showing significant impact on exercise tolerance and quality of life:
  - FIX-CHF-4 (n=168; randomized, double-blinded; EU)
  - FIX-HF-5 Feasibility (n=50, randomized, double-blinded; US)
  - FIX-HF-5 Pivotal (n=428; randomized; US)
- 3D Echocardiography study showing reverse LV remodeling within 3 months (Hong Kong Study)
- Subgroup analyses suggesting benefits in patients with heart failure and preserved ejection fraction (HFPEF)
Study included 50 patients implanted with CCM and randomized to CCM ON or OFF in a double blinded fashion.

Results favored CCM despite a sicker population in the treatment group (at baseline),
FixHF5 pivotal study
(215 pats with CCM implant vs 213 without, CHF III or IV, 1 yr F/up)
Overall Summary
(Differences between Treatment and Control)

Significant effects on peak VO2, MLWHFQ and NYHA
Positive trend in 6MW
FIX-HF-5 Results:
Comparison of Results in Different Patient Cohorts

△ VAT (ml/kg/min)

All Patients
EF 25-35, NYHA III
EF >=35

△ Peak VO₂ (ml/kg/min)

All Patients
EF 25-35, NYHA III
EF >=35
FIX-HF-5 Results:
Comparison of Results in Different Patient Cohorts

Graphs showing comparison of 6MW (meters) and MLWHFQ in different patient cohorts:
- All Patients
- EF 25-35, NYHA III
- EF >=35
Heart Fix C Trial– Ongoing IDE trial

- OPTIMIZER IV- CE mark approved
- 140 pats supplement to the heart Fix V pivotal trial
- CHF class III-IV, EF 25 to 45%
- CPX- Pk VO2 12-19 ml/kg/min
- 1:1 randomization
- Endpoints include CPX data (VO2 max, exercise tolerance, no AT), NYHA class, QOL, 6 min walk.
- Currently enrolling.
- Ochsner PI >> Freddy Abi-Samra 504 842 4145
Putting Things into Perspective

Wide QRS

Normal QRS

CCM effect comparable in magnitude to CRT in a different population

DVO2 (ml O₂/kg/min)
Putting Things Into Perspective: CRT vs CCM - Cross over trials

**6MW (meters)**

- **Baseline**
- **12 Wks ON**
- **24 Wks OFF**

**ΔMLWHFQ**

- **Baseline**
- **On**
- **Off**

Group 1

CCM
CRT (MUSTIC, single blind)
Barostim Therapy for Heart Failure
June, 2016
Fundamental Concept of BAROSTIM THERAPY in HF

Progressive autonomic imbalance… … Reduces patients’ functional capacity, quality of life and survival

Adapted from Robinson et al, 1966

Restoring autonomic balance improves patient outcomes

Cohn et al, 1984
Baroreflex Activation Therapy
The Baroreflex as a Therapeutic Target

Programmable Baroreceptor Activation

Brain

Autonomic Nervous System
- Reduced Sympathetic Activity
- Enhanced Parasympathetic Activity

Heart
- Heart rate
- Irritability

Vessels
- + Vasodilation
- - Stiffness
- + Venous capacitance

Kidneys
- + Diuresis
- + Natriuresis
- - RAAS activity

myocardial work and oxygen consumption
neurohormonal activation
arrhythmogenesis
excessive blood pressure
Effect of Baroreflex Activation in 21 Patients with Resistant Hypertension After Three Months of Therapy

Heart Rate Variability

Low Frequency

High Frequency

↓Sympathetic

↑Vagal

Wustmann et al, 2009
Modulation of Peripheral Sympathetic Nerve Activity

Heusser et al, 2010

68 yo awake female after 7 months of therapy
Effects on Arterial Stiffness

Aortic Pressure Waveform

Georgakopoulos et al, 2011
Pressure-Volume Loops in a Hypertensive (HFpEF) Patient

Hasenfuss et al, ESC 2011
5 Year Results in Resistant Hypertension

Bakris et al, 2014
The BAROSTIM NEO Technology Platform
First-in Man Study of Barostim in HFrEF

- 11 pats
- Class III
- Open Label
- Single center
- 6 months F/up
- >> longer walk
- > >less # meds
- Higher EF(4%)
- No change in HR,BP

Chronic baroreflex activation effects on sympathetic nerve traffic, baroreflex function, and cardiac haemodynamics in heart failure: a proof-of-concept study

Edoardo Gronda1, Gino Seravalle2, Gianmaria Brambilla3, Giuseppe Costantino1, Andrea Casini1, Ali Alsheraei1, Eric G. Lovett4, Giuseppe Mancia2, and Guido Grassi1,2

1Cardiovascular Department, IRCCS Multimedica, Sette San Giovanni (Milan), Italy; 2Universita’ Milano-Bicocca, IRCCS Istituto Auxologico Italiano, Milan, Italy; 3Clinica Medica 3, Dipartimento di Scienze della Salute, Universita’ Milano-Bicocca, Milan, Italy; and 4CVRx, Inc., Minneapolis, MN, USA
Dose-dependent Reduction in Muscle Sympathetic Nerve Activity

Direct Microneurography Recordings of MSNA

Gronda et al, 2014
Reduced Hospitalization for Worsening Heart Failure

Gronda et al, 2014
Baroreflex Activation Therapy for the Treatment of Heart Failure with a Reduced Ejection Fraction

William Abraham, MD1, Michael Zile, MD2, Fred Weaver, MD3, Christian Butter, MD4, Anique Ducharme, MD5, Marcel Halbach, MD6, Didier Klug, MD7, Eric Lovett, PhD8, Jochen Müller-Ehmsen, MD9, Jill Schafer, MS10, Michele Senni, MD11, Vijay Swarup, MD12, Rolf Wachter, MD13, William Little, MD14;

on behalf of the BAT for HFrEF Study Group

1Division of Cardiovascular Medicine, The Ohio State University, Columbus, OH, USA; 2Medical University of South Carolina, Charleston, South Carolina; Ralph H. Johnson Department of Veterans Affairs Medical Center, Charleston, South Carolina, USA; 3Division of Vascular Surgery and Endovascular Therapy, Keck School of Medicine, University of Southern California, Los Angeles, California, USA; 4Department of Cardiology, Immanuel Heart Center Bernau, Medical School Brandenburg, Bernau, Germany; 5Montreal Heart Institute, University of Montréal, Montreal, Quebec, Canada; 6Department of Internal Medicine III, University Hospital of Cologne, Cologne, Germany; 7Department of Cardiology A, University Hospital, Lille, France; 8Department of Research, CVRx, Inc., Minneapolis, Minnesota, USA; 9Department of Medicine #, Asklepios Klinik Altona, Hamburg, Germany; 10Department of Statistics, NAMSA, Inc., Minneapolis, Minnesota, USA; 11Cardiovascular Department, Ospedale Papa Giovanni XXIII, Bergamo, Italy; 12Department of Electrophysiology, Arizona Heart Hospital, Phoenix, Arizona, USA; 13Clinic for Cardiology and Pneumology, University Medicine Göttingen and German Cardiovascular Research Center (DZHK), Göttingen, Germany; 14Division of Cardiology, University of Mississippi Medical Center, Jackson, Mississippi, USA
Concordance of Results Support BAT Efficacy in HFrEF (70 pats in each group)

<table>
<thead>
<tr>
<th></th>
<th>Difference</th>
<th>p value</th>
<th>Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA (% improved)</td>
<td>31</td>
<td>&lt; 0.01</td>
<td>BAT</td>
</tr>
<tr>
<td>MLWHF QoL Score (points)</td>
<td>20</td>
<td>&lt;0.001</td>
<td>BAT</td>
</tr>
<tr>
<td>6-MHW Distance (m)</td>
<td>58</td>
<td>&lt;0.01</td>
<td>BAT</td>
</tr>
<tr>
<td>NT-proBNP (pg/ml)*</td>
<td>342</td>
<td>0.02</td>
<td>BAT</td>
</tr>
<tr>
<td>LVEF (absolute %)</td>
<td>2.5</td>
<td>0.15</td>
<td>BAT</td>
</tr>
<tr>
<td>Hospitalization Days for Worsening HF (days/pt/yr)</td>
<td>6.4</td>
<td>0.05</td>
<td>BAT</td>
</tr>
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</table>

* Median
Response to Barostim in Non-CRT compared with CRT patients

<table>
<thead>
<tr>
<th>Measure</th>
<th>Estimate</th>
<th>P-value</th>
<th>Favors</th>
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</thead>
<tbody>
<tr>
<td>QoL Score</td>
<td>-12.31</td>
<td>0.040</td>
<td>Non-CRT</td>
</tr>
<tr>
<td>6MHWD (meters)</td>
<td>69.05</td>
<td>0.010</td>
<td>Non-CRT</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>-841.32</td>
<td>0.59</td>
<td>Non-CRT</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>5.51</td>
<td>0.022</td>
<td>Non-CRT</td>
</tr>
<tr>
<td># HF Hospitalization Days</td>
<td>-8.08</td>
<td>0.09</td>
<td>Non-CRT</td>
</tr>
</tbody>
</table>
Heart Failure Hospitalization Days

CHF days decreased by 6.3 in the overall group vs 8.9 in pats with narrow QRSd

6 Month Change from Baseline Days

Improvement

BAT

Control

p = 0.05

0.08
Key Inclusion Criteria:

- Left ventricular ejection fraction $\leq 35\%$
- NYHA Functional Classification of III
- On optimal, stable pharmacological therapy for at least 4 weeks prior to enrollment
- Not eligible for, or treated with CRT
- At elevated risk for clinical events (Recent HF hospitalization, elevated NT-proBNP)
Thank you
## Improved Hemodynamic Performance and Functional Capacity

Gronda et al, 2014

<table>
<thead>
<tr>
<th>Vital signs and medications</th>
<th>Baseline</th>
<th>Δ1 Month</th>
<th>Δ3 Months</th>
<th>Δ6 Months</th>
<th>ANOVA P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline: mean ± SD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Δ: mean ± SE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSNA (bursts/min)</td>
<td>45.1 ± 7.7</td>
<td>−8.7 ± 1.3&lt;sup&gt;§&lt;/sup&gt;</td>
<td>−12.5 ± 1.3&lt;sup&gt;§&lt;/sup&gt;</td>
<td>−13.8 ± 1.4&lt;sup&gt;§&lt;/sup&gt;</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MSNA (bursts/100 heartbeats)</td>
<td>67.6 ± 12.7</td>
<td>−13.1 ± 3.2&lt;sup&gt;§&lt;/sup&gt;</td>
<td>−19.5 ± 2.8&lt;sup&gt;§&lt;/sup&gt;</td>
<td>−22.5 ± 2.5&lt;sup&gt;§&lt;/sup&gt;</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Six minute walk distance (m)</td>
<td>304.4 ± 49.6</td>
<td>−</td>
<td>+49.7 ± 15.7&lt;sup&gt;†&lt;/sup&gt;</td>
<td>+51.1 ± 25.6</td>
<td>0.05</td>
</tr>
<tr>
<td>Minnesota Living with Heart Failure score</td>
<td>33.4 ± 29.8</td>
<td>−</td>
<td>−11.7 ± 4.4&lt;sup&gt;§&lt;/sup&gt;</td>
<td>−10.6 ± 3.8&lt;sup&gt;§&lt;/sup&gt;</td>
<td>0.007</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>118.5 ± 14.2</td>
<td>−8.5 ± 3.9</td>
<td>−0.3 ± 3.5</td>
<td>−1.2 ± 3.6</td>
<td>0.37</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>70.5 ± 9.3</td>
<td>−4.5 ± 3.0</td>
<td>+0.9 ± 2.8</td>
<td>−2.7 ± 2.2</td>
<td>0.51</td>
</tr>
<tr>
<td>Heart rate (b.p.m.)</td>
<td>72.3 ± 8.3</td>
<td>−2.6 ± 2.5</td>
<td>+0.2 ± 1.7</td>
<td>−0.5 ± 1.8</td>
<td>0.95</td>
</tr>
<tr>
<td>3D LV end-diastolic volume (mL)</td>
<td>168.6 ± 43.5</td>
<td>−</td>
<td>−11.3 ± 6.5</td>
<td>−8.7 ± 7.5</td>
<td>0.21</td>
</tr>
<tr>
<td>3D LV end-systolic volume (mL)</td>
<td>116.9 ± 40.9</td>
<td>−14.3 ± 5.5&lt;sup&gt;†&lt;/sup&gt;</td>
<td>−11.3 ± 5.6</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>3D LV ejection fraction (%)</td>
<td>32.0 ± 7.3</td>
<td>−</td>
<td>+4.3 ± 1.0&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>+3.6 ± 1.4&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>0.002</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>314.4 ± 306.9</td>
<td>−8.9 ± 40.2</td>
<td>+33.1 ± 112.3</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>Estimated GFR (mL/min/1.73 m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>65.1 ± 27.7</td>
<td>−</td>
<td>+2.1 ± 2.8</td>
<td>+5.7 ± 4.9</td>
<td>0.41</td>
</tr>
<tr>
<td>Body mass index (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>26.1 ± 4.6</td>
<td>−0.1 ± 0.1</td>
<td>+0.1 ± 0.2</td>
<td>−0.3 ± 0.3</td>
<td>0.55</td>
</tr>
<tr>
<td>Number of medications</td>
<td>4.5 ± 1.2</td>
<td>−0.4 ± 0.2&lt;sup&gt;§&lt;/sup&gt;</td>
<td>−0.4 ± 0.2&lt;sup&gt;§&lt;/sup&gt;</td>
<td>−0.3 ± 0.1</td>
<td>0.007</td>
</tr>
</tbody>
</table>
Physiology of Baroreflex Activation

Adapted from Floras, J Am Coll Cardiol 2009
Key Inclusion Criteria:
- Left ventricular ejection fraction ≤35%
- NYHA Functional Classification of III
- On optimal, stable pharmacological therapy for at least 4 weeks prior to enrollment
- Not eligible for, or treated with CRT
- At elevated risk for clinical events (Recent HF hospitalization, elevated NT-proBNP)
Mechanism of Action
Company Background

- A private, Minneapolis-based medical device company
  - Founded in 2001
  - 65 employees worldwide
- Developed Baroreflex Activation Therapy (Barostim) to treat patients with chronic heart failure or resistant hypertension
- Treated >1,100 patients to date in Europe and the U.S.
- The BAROSTIM NEO is the second generation system

<table>
<thead>
<tr>
<th></th>
<th>Europe</th>
<th>U.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Failure</td>
<td>2014</td>
<td>Phase II RCT completed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase III RCT in progress (EAP)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2011</td>
<td>Phase III RCT FDA-approved</td>
</tr>
</tbody>
</table>
Therapy is Tailored to Individual Patient Need

63 yo awake female

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>1 Volt</th>
<th>2 Volts</th>
<th>3 Volts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate</td>
<td>71</td>
<td>56</td>
<td>58</td>
<td>50</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>210 / 96</td>
<td>168 / 73</td>
<td>156 / 72</td>
<td>144 / 66</td>
</tr>
</tbody>
</table>

CVRx data on file

≈ 4 min
Baroreflex Activation Therapy (BAT) ≠ Vagus Nerve Stimulation (VNS)

<table>
<thead>
<tr>
<th></th>
<th>Barostim</th>
<th>VNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nerve Pathway Targeted</td>
<td>Specific: Carotid Sinus Nerve</td>
<td>Non-specific: Vagus Nerve</td>
</tr>
<tr>
<td>Side Effects</td>
<td>Sparse</td>
<td>Frequent</td>
</tr>
<tr>
<td>Target</td>
<td>Central Nervous System</td>
<td>Heart</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Integrated</td>
<td>Site-specific</td>
</tr>
<tr>
<td>Autonomic Effects</td>
<td>Sympathetic + Parasympathetic</td>
<td>Parasympathetic</td>
</tr>
<tr>
<td>Phase II RCT results in HF</td>
<td>Positive (HOPE-HF)</td>
<td>Negative (NECTAR-HF)</td>
</tr>
<tr>
<td>Phase III RCT results in HF</td>
<td>BeAT-HF set to commence</td>
<td>Negative (NOVATE-HF)</td>
</tr>
</tbody>
</table>

Effects on Cardiac Contractility
- Barostim: Neutral
- VNS: Negative

![Graph comparing Barostim and VNS effects on LV Pressure and LV Volume](image)

Technology
Platform
Placement Procedure
Programming

• Achieve maximum efficacy by:
  • Maximizing therapeutic dose
  • Maintaining patient comfort and safety

• A standardized approach using:
  • Pulse amplitude
  • Pulse width
  • Frequency
Transparent to Patient Lifestyle

- Fully Implantable
- Personalized Therapy
- No Adherence Required
- Targeted and reversible
## Clinical Evidence Development in Heart Failure

<table>
<thead>
<tr>
<th>Phase</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Rationale</strong></td>
<td>Georgakopoulos et al, J Cardiac Fail 2012</td>
</tr>
<tr>
<td></td>
<td>Sabbah et al, Curr Cardiol Rep 2012</td>
</tr>
<tr>
<td></td>
<td>Halbach et al, Curr Heart Fail Rep 2016</td>
</tr>
<tr>
<td><strong>Preclinical</strong></td>
<td>Zucker et al, Hypertension 2007</td>
</tr>
<tr>
<td></td>
<td>Sabbah et al, Circ Heart Failure 2011</td>
</tr>
<tr>
<td></td>
<td>Liao et al, J Cardiovasc Pharmacol 2014</td>
</tr>
<tr>
<td><strong>First In Man</strong></td>
<td>Brandt et al, Clin Res Cardiol 2010</td>
</tr>
<tr>
<td></td>
<td>Madershahian et al, Europace 2014</td>
</tr>
<tr>
<td></td>
<td>Gronda et al, Eur J HF 2014</td>
</tr>
<tr>
<td><strong>CE Mark / Phase II</strong></td>
<td>Abraham et al, ACC Featured Clinical Research, March 2015</td>
</tr>
<tr>
<td></td>
<td>Zile et al, HRS Late Breaking Clinical Trials, May 2015</td>
</tr>
<tr>
<td></td>
<td>Müller-Ehmsen et al, ESC-HF Late Breaking Clinical Trials, May 2015</td>
</tr>
<tr>
<td></td>
<td>Abraham et al, J Am Coll Cardiol – HF 2015</td>
</tr>
<tr>
<td></td>
<td>Zile et al, Eur J Heart Failure 2015</td>
</tr>
<tr>
<td><strong>US Phase III Pivotal</strong></td>
<td>Beat-HF Pivotal Clinical Trial in progress</td>
</tr>
<tr>
<td></td>
<td>- Randomized, controlled clinical trial; n = 480</td>
</tr>
<tr>
<td></td>
<td>- Composite of CV death and HF hospitalization</td>
</tr>
<tr>
<td></td>
<td>- FDA Expedited Access Pathway for early approval</td>
</tr>
</tbody>
</table>
BAT for HFrEF: Primary Safety Endpoint

System- or Procedure-Related Major Adverse Neurological or Cardiovascular Events (MANCE) at 6 months

97% Event-Free Rate
71 Subjects Implanted

2 Pocket hematomas (1 and 7 days from implant)
BAT for HFrEF: Other Safety Observations

- BAT does not cause hypotension in patients with advanced heart failure
  - No reports of symptomatic hypotension
  - SBP significantly increased in BAT group; DBP unchanged

- BAT is compatible with co-existing cardiac rhythm management devices
CE – Approval in Heart Failure

- NYHA functional Class III, and
- Left ventricular ejection fraction ≤35%
- Despite treatment with guideline-directed therapy

Irrespective of:
- ECG morphology
- Treatment with cardiac rhythm management devices
- Presence of atrial fibrillation
Pre-specified Subgroup Analyses: AF, ICD, Gender, CRT

### Differences in the response to therapy with BAT in AFib compared with No-Afib patients

<table>
<thead>
<tr>
<th>Measure</th>
<th>Estimate</th>
<th>P-value</th>
<th>Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA Class</td>
<td>0.045</td>
<td>0.81</td>
<td>Neither</td>
</tr>
<tr>
<td>QoL Score</td>
<td>-5.43</td>
<td>0.42</td>
<td>Neither</td>
</tr>
<tr>
<td>6MHW (meters)</td>
<td>12.61</td>
<td>0.71</td>
<td>Neither</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>1955</td>
<td>0.15</td>
<td>Neither</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.81</td>
<td>0.80</td>
<td>Neither</td>
</tr>
<tr>
<td># HF Hospitalization Days</td>
<td>0.42</td>
<td>0.39</td>
<td>Neither</td>
</tr>
</tbody>
</table>

### Differences in the response to therapy with BAT in ICD compared with No-ICD patients

<table>
<thead>
<tr>
<th>Measure</th>
<th>Estimate</th>
<th>P-value</th>
<th>Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA Class</td>
<td>-0.18</td>
<td>0.43</td>
<td>Neither</td>
</tr>
<tr>
<td>QoL Score</td>
<td>12.65</td>
<td>0.15</td>
<td>Neither</td>
</tr>
<tr>
<td>6MHW (meters)</td>
<td>8.51</td>
<td>0.83</td>
<td>Neither</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>1258</td>
<td>0.55</td>
<td>Neither</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.39</td>
<td>0.91</td>
<td>Neither</td>
</tr>
<tr>
<td># HF Hospitalization Days</td>
<td>12.12</td>
<td>0.08</td>
<td>Neither</td>
</tr>
</tbody>
</table>

### Differences in the response to therapy with BAT in Male compared with Female patients

<table>
<thead>
<tr>
<th>Measure</th>
<th>Estimate</th>
<th>P-value</th>
<th>Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA Class</td>
<td>-0.23</td>
<td>0.29</td>
<td>Neither</td>
</tr>
<tr>
<td>QoL Score</td>
<td>11.27</td>
<td>0.17</td>
<td>Neither</td>
</tr>
<tr>
<td>6MHW (meters)</td>
<td>9.49</td>
<td>0.81</td>
<td>Neither</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>1207</td>
<td>0.59</td>
<td>Neither</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.30</td>
<td>0.93</td>
<td>Neither</td>
</tr>
<tr>
<td># HF Hospitalization Days</td>
<td>-0.26</td>
<td>0.67</td>
<td>Neither</td>
</tr>
</tbody>
</table>

*Müller-Ehmsen, ESC-HF Late Breaking Clinical Trials 2015*
Baroreflex Activation Therapy for the Treatment of Heart Failure with a Reduced Ejection Fraction:

Safety and Efficacy in Patients Without Cardiac Resynchronization Therapy

Michael Zile, MD, William Abraham, MD, Fred Weaver, MD, Christian Butter, MD, Anique Ducharme, MD, Marcel Halbach, MD, Didier Klug, MD, Eric Lovett, PhD, Jochen Müller-Ehmsen, MD, Jill Schafer, MS, Michele Senni, MD, Vijay Swarup, MD, Rolf Wachter, MD, William Little, MD
QOL (MLWHF)

6 Month Change from Baseline

-21.6

3.5

p < 0.001

6 Min Hall Walk

6 Month Change from Baseline

85.5

3.6

p = 0.003
NT-proBNP

6 Months Change from Baseline (pg/mL)

- BAT: $-0.97$ [[-505, 93]]
- Control: 116.0 [-74, 700]

$p = 0.03$

LV Ejection Fraction

6 Month Change from Baseline (%)

- BAT: $4.3$
- Control: $-0.1$

$p < 0.03$
U.S. Phase III Pivotal Clinical Trial

Steering Committee

- Michael Zile, MD, Medical University of SC, Chair
- William Abraham, MD, Ohio State University
- Joann Lindenfeld, MD, Vanderbilt University
- Faiez Zannad, MD, University of Nancy (France)
- Fred Weaver, MD, University of Southern California
Primary Safety Endpoint
System- and Procedure-related complications through 6 months of follow-up

Outcome Efficacy Endpoint
Composite of cardiovascular mortality and worsening heart failure leading to:
  – Hospitalization
  – Permanent cardiac assist device
  – Heart transplant

Adaptive trial design with interim analysis for sample size re-estimation
Expeditied Access Pathway Features

Enrollment (n=480) → Follow up (320 events) → PMA-S Submission

M&M Interim Analysis
Sample Size Re-estimation

PMA-S Approval
Expedited Access Pathway Features

**Stage 1**
- First 264 patients

**Stage 2**
- Enrollment (n=480)
- Follow up (320 events)
- M&M Interim Analysis
  - Sample Size Re-estimation

- M&M Trending
- 6MHW, MLWHF, NT-proBNP

**PMA Submission**
- PMA Approval
- PMA-S Submission
- PMA-S Approval
BeAT-HF Progress

- Sites (90)
- Enrollment (1,000)
- Randomization (480)
Thank you.

The Barostim neo System is CE Marked for the treatment of heart failure and for the treatment of resistant hypertension.