

Baroreflex Activation Therapy in Patients with Heart Failure and a Reduced Ejection Fraction: Long-Term Outcomes

Michael R. Zile MD^a, JoAnn Lindenfeld MD^b, Fred A. Weaver MD^c, Faiez Zannad MD, PhD.^d, Elizabeth Galle MPH^e, Tyson Rogers MS^f, William T. Abraham MD^g

Appendices

Appendix # 1:

Trial Design, Oversight, Eligibility

Briefly, BeAT-HF was a prospective, multi-center, randomized, 2-arm, parallel group, open label with blinded endpoint evaluation trial designed to develop valid scientific evidence for the safety and effectiveness of baroreflex activation therapy (CVRx, Minneapolis, MN) in patients with HFrEF. The trial was performed at 103 centers in USA and 5 in United Kingdom. The Internal Review Board or Research Ethics Committee at each trial center approved the trial, and all patients provided written informed consent. The sponsor was CVRx. The trial was designed by the Executive Steering Committee (ESC) in collaboration with CVRx, Inc. and the United States Food and Drug Administration's (FDA) Center for Devices and Radiological Health (CDRH) through the Breakthrough Devices Program – a part of the 21st Century Cures Act for medical devices which was designed to provide a pathway that would potentially accelerate market access for promising technologies intended to treat chronically ill patients with severe unmet needs^{8,9}.

Patients underwent screening and baseline measurements as described previously⁸. Those meeting all eligibility criteria with complete baseline measurements were randomized 1:1 to receive either BAT plus optimal management (“BAT”) or optimal medical management alone (“Control”). Randomization schedules were created by an independent statistician using random permuted blocks and were stratified by site. Randomization assignments were obtained via the

electronic data capture system (eDC) after entering an intended device implant date into the eDC system. This date determined the timing of follow-up visits for those randomized to Control. The actual implant date determined the timing of follow-up visits for those randomized to BAT. Neither the patient nor the investigating team were blinded to the randomization allocation.

BAT was delivered by surgically placing a 2 mm electrode on the carotid sinus, connecting this electrode to a subcutaneously implanted pulse generator and stimulating at an average device setting of 8.4 mA amplitude, 107 ms duration, and 43 pps frequency. All components of BAT were extravascular. Optimal medical management was defined as maximally tolerated guideline-directed management in place at the time each patient was randomized ⁵.

At each scheduled trial visit, physical assessment, medications, and adverse events were assessed. At baseline, and at 6 and 12 months follow up six-minute hall walk distance was measured; At baseline, and at 6, 12 and 24 months follow up MLWHFQ and NYHA class were measured as previously described ⁸.

The ESC developed and amended the protocol and had scientific oversight on the development of the statistical analysis plan, the case report forms, the recruitment of patients, the quality and thoroughness of follow-up, and the analysis of data. The members of the ESC provided an independent interpretation of the results. An independent data and safety monitoring committee (DSMC) reviewed the safety data and the results of all interim analyses according to prespecified stopping boundaries. All data analyzed and reviewed by the DSMC were prepared by the independent statistician and kept blinded from the sponsor and the ESC. All clinical morbidity and mortality endpoints were adjudicated by an independent, blinded Clinical Events Committee (CEC). An Adverse Event Committee (AEC) adjudicated adverse events for relatedness to the device or procedure.

After data lock, data were compiled, unblinded and analyzed by the independent statistician. Statistical analyses were validated by another independent statistician and reviewed by the sponsor with oversight by the ESC. The first author, who had unrestricted access to the data, prepared the first draft of the manuscript, which was then reviewed and edited by all the authors. The authors made the decision to submit the manuscript for publication, assume full responsibility for the accuracy and completeness of the analyses, and attest to the fidelity of the trial to the protocol and the statistical analysis plan.

The overall trial was designed to encompass two phases:

(1) A **Pre-Market Phase** (completed April 22, 2019) demonstrated that 6 months of treatment with BAT was safe, improved the patient-centered symptomatic endpoints of QOL score (Minnesota Living With Heart Failure Questionnaire, MLWHFQ), exercise capacity (6-min hall walk distance, 6MHW), functional status (New York Heart Association Class, NYHA), and significantly decreased N-terminal pro-B-type natriuretic peptide (NT-proBNP) in patients with NYHA functional class III (or patients with NYHA functional class II who had a recent history of NYHA functional class III), EF \leq 35%, NT-proBNP <1,600 pg/ml, and who did not have a Class I indication for CRT⁸. Proof of effectiveness and safety during 6 months of treatment with BAT using these endpoints lead to an FDA approved indication for BAT on August 16, 2019 for improvement of symptoms of heart failure.

(2) A **Post-Market Phase** (completed July 19, 2022) examined the long-term effects of BAT on the primary endpoint: a composite of CV mortality and HF morbidity events; additional pre-specified endpoints included a hierarchical Win Ratio composite, all-cause mortality, durability of safety, durability of improved patient-centered symptom status endpoints (e.g. quality of life [MLWHFQ], exercise capacity [6MHW] and functional status [NYHA Class]).

Eligibility criteria for the post-market phase of the BeAT-HF trial included: NYHA functional class III symptoms or Class II (if there was a recent history of Class III), left ventricular EF \leq 35%, 6MHW 150 – 400 meters, previous HF hospitalization or NT-proBNP $>$ 400 pg/ml, NT-proBNP $<$ 1600 pg/ml and stable optimal management \geq 4 weeks, no class I indication for CRT. Patients were screened, enrolled, randomized, and all data collected by study coordinators and staff in outpatient clinical study centers. All of the BeAT-HF study sites used either WCG (WIRB [Western Institutional Review Board] Copernicus Group) or their own local institutional review board (IRB) / ethics committee (EC) for human studies to review and approve BeAT-HF before any study related procedures could be performed.

Endpoint Definitions:

A hospitalization or emergency room event for heart failure was defined as an event in which the patient was admitted for a primary diagnosis of heart failure and met the published 2014 ACC/AHA endpoint definition criteria^{10, 11}. In brief, this required documentation of at least one new or worsening symptom of heart failure and at least two physical examination findings or one physical examination finding and at least one laboratory criterion of new or worsened heart failure and initiation or intensification of treatment specifically for HF. Each of these categories were defined in the CEC charter and the statistical analysis plan (SAP, appendix 3). Recognizing the documentation required by the 2014 ACC/AHA/FDA/CDISC endpoint definition criteria constrained the definition of HF morbidity described above, and following the experience in several recent trials, an expanded definition for a heart failure event was also applied in the examination of additional prespecified endpoints described below. These events adjudicated using the expanded definition of HF morbidity did not completely meet the 2014 ACC/AHA/FDA/CDISC criteria for HF morbidity but were felt by the CEC to be consistent with

HF events and was used only in the assessment of the additional pre-specified endpoints, specifically the hierarchical composite Win Ratio analysis endpoint. Heart failure events under the expanded definition had worsening symptoms of heart failure, intensification of heart failure therapy, and CEC consensus that the hospitalization was primarily due to worsening heart failure. Changes in physical signs or laboratory tests, whenever available and documented, were considered to be supportive but not absolutely required.

It should be noted that BeAT-HF was developed and performed under the novel U.S. Food and Drug Administration (FDA) Center for Devices and Radiological Health Breakthrough Devices Program [a part of the 21st Century Cures Act (20) for medical devices] This program was developed to provide a pathway that would potentially accelerate market access for promising technologies intended to treat chronically ill patients with severe unmet needs. As such, this novel program facilitated the adaptive design used in BeAT-HF and the collaboration between CVRx (the sponsor), FDA and the executive steering committee (ESC). The sequential adaptive design changes are described in revisions to the clinical investigation plan (CIP) and the Statistical Analysis Plan (SAP):

1- The Rational and Design manuscript: Am Heart J 2018;204:139-50, described **Revision C** of the FDA approved clinical investigation plan (CIP).

2- The BeAT-HF Trial Pre-Market Phase (completed April 22, 2019) and published in JACC 2020;76:1–13, described **Revision D** of the FDA approved CIP. The study design was summarized in the 2020 JACC manuscript but was not the subject of a separate design manuscript.

3- The BeAT-HF Trial Post-Market Phase (completed July 19, 2022) as described in the current manuscript, described **Revision G** of the FDA approved CIP but was not the subject of a

separate design manuscript. Revision G (May 27, 2022) of the CIP is appendix #5 in a supplemental document.

In addition, the Statistical Analysis Plan (SAP) Supplement underwent several revisions all approved by the FDA. The final FDA approved SAP, **Revision E** (December 21, 2022), is appendix # 6 in a supplemental document.

It should be noted that the final versions of both the CIP and SAP were completed before the BeAT-HF Trial Post-Market Phase data were unblinded, In addition, it should be noted that the primary endpoint remained unchanged throughout these revisions.

Appendix # 4:

Non-Cardiovascular Deaths

Appendix #4 Table 1: Non-Cardiovascular Deaths

Cause of Death	BAT (N=159)	Control (N=160)
Total Non-Cardiovascular	6 (3.8%)	12 (7.5%)
Cancer	2 (1.3%)	3 (1.9%)
Infection/Sepsis	1 (0.6%)	5 (3.1%)
Other	2 (1.3%)	3 (1.9%)
Renal	1 (0.6%)	0 (0.0%)
Respiratory	0 (0.0%)	1 (0.6%)

Appendix # 5:

Committee members and investigators

Members of the data safety monitoring Board

Chair: William H. Gaasch M.D.: Professor of Medicine, University of Massachusetts, Lahey clinic, Burlington Ma. (Deceased)

Chair: Theo Meyer, M.D., PhD: Chief of Clinical Cardiology, Professor of Medicine, Director, Advance Heart Failure Program, UMass Memorial Health Care

Martin C. Burke, DO: Founder, Corvita Health & Science

Thomas Naslund, M.D.: Professor of Vascular Surgery, Vanderbilt University

Teresa Nelson, MS: Principal Statistician, Technomics Research

Members of the Clinical Events Committee

Chair: Javed Butler, MD MPH MBA; President of the Baylor Scott and White Research Institute, Dallas TX, and Distinguished Professor of Medicine, University of Mississippi, Jackson, MS

Eugene S. Chung, M.D., FACC, FHFSA: Cardiologist

David J. Whellan, M.D.: Cardiologist

Alan Miller, M.D.: Professor of Medicine, University of Florida Jacksonville

Hall M.D.: Professor and Chair, Department of Medicine, University of Mississippi Medical Center

Sheldon E. Litwin, M.D.: Alicia Spaulding-Paolozzi Professor of Cardiology, Medical University of South Carolina

Members of Adverse Event Committee

Chair: Catherine Marie Wittgen, M.D.: Catherine M. Wittgen MD FACS: Professor of Surgery, Program Director, Vascular Surgery Integrated Residency, Program Director, Vascular Surgery Fellowship, Saint Louis University

George S. Goding, JR, M.D.: Professor, Department of Otolaryngology – Head and neck Surgery, University of Minnesota, Minneapolis MN

Derrick Green, M.D., MBA: Minneapolis Veteran Affairs Hospital, Dept. of Vascular Surgery, Adjunct Asst. Professor, University of MN Department of Surgery, Minneapolis MN

James Louis Januzzi, Jr., M.D. F.A.C.C., F.E.S.C: Cardiology Division, Massachusetts General Hospital, Hutter Family Professor of Medicine, Harvard Medical School, Heart Failure Trials, Baim Institute for Clinical Research, Boston MA

Jeffrey Allen Kohen, M.D.: Minneapolis Veterans Affairs Health Care System, Minneapolis, MN

Study Sites, Principle Investigator, Study Coordinator

Chan Heart Rhythm Institute - Dr. Rodrigo Chan - Olivia Rivera

St. Louis Heart & Vascular - Dr. Gil Vardi - Paige Brown

University Medical Center of Southern Nevada - Dr. Chowdhury Ahsan - Jennifer Robinson

Mercy Hospital St. Louis - Dr. Khaled Awad - Elizabeth King

Phoenix Cardiovascular Research Group - Dr. Marwan Bahu - Helen Foughi

Cone Health - Dr. James Allred - Kimberly Lutterloh

Via Christi Research - Dr. Wassim Shaheen - Angie Vincent

Arizona Arrhythmia Research Center - Dr. Vijay Swarup - Latanya Watson

Sharp Chula Vista Medical Center - Dr. GilAnthony Ungab - Cary Murphy

Herndon Surgery Center - Dr. Thampi John - Carmen Martinez

Tyler Cardiovascular Consultants - Dr. Raul Torres - Kevin Thornton

Texas Health Physicians Group - Dr. Martin Berk - Tram Nguyen

University of Southern California - Dr. Michael Fong - Silvia Perez

AdventHealth Orlando - Dr. Nirav Raval - Maggie Warrington

Medical University of South Carolina - Dr. Adrian Van Bakel - Renne Baxley

North Colorado Medical Center - Dr. Lin Wang Dong - Debra Kroll

Washington Regional Medical Center - Dr. Joel Carver - Callie McQueen

Ochsner Clinic Foundation - Dr. Freddy Abi-Samra - Magen Parker

Intermountain Heart Institute - Dr. Rami Alharethi - Iris Musso

Heart & Rhythm Solutions, PLLC - Dr. Himel Shah - Heather Court

Southern California Permanente Medical Group - Dr. Nigel Gupta - Dalia Salazar and Dyanna Chung

Detroit Medical Center Cardiovascular Institute - Dr. Randy Lieberman - Heidi Carl

Washington University - Dr. Gregory Ewald - Janice Amsler

Mercy Hospital Springfield - Dr. Shang-Chiun Lee - Sherri Swafford

Virginia Mason Medical Center - - Leslie Stevens

Central Cardiology Medical Center - Dr. Peter Nalos - Ritika Sharma

HealthCare Partners Clinical Research - Dr. Dhiraj Narula - Linda Cortes

John Muir Health Clinical Research Center - Dr. Paul McWhirter - Craig Griffiths

University of California San Francisco - Dr. Liviu Klein - Natalia Dikinov

Wake Forest Baptist Health - Dr. Prashant Bhave - Lisa Wilkerson and Sandra Soots

St. Elizabeths Medical Center - 2597 - Rina Vaquerano

NorthShore University Health System - Dr. Robert Gordon - Saritha Theegala

University of Utah - Dr. Stavros Drakos - Shannon Wooley

Clearwater Cardiovascular Consultants - Dr. Marilyn King - Laura Jenkins

Oklahoma Cardiovascular Research Group - Dr. Pamela Craven - Julia Myers

University of South Florida - Dr. Fadi Matar - Mia Eifrid

St. Alphonsus Medical Center - Dr. Margot Vloka - Joy Furlipa

Chula Vista Cardiac Center - Dr. Brett Berman - Jessica Montero

Providence-Providence Park Hospital - Dr. Nathan Foster - Jean Kelly

University of Kentucky - Dr. Aaron Hesselton - Jennifer Isaacs

Avanza Medical Research Center - Dr. Rohit Amin - Garwin Ho

Adventist Heart Institute - Dr. Kathleen Tong - Karen Martin

WellStar Medical Group - Dr. Brian Howard - Donna Lahay

Drexel University - Dr. Shelley Hankins - Shawn Cone

University of Mississippi Medical Center - Dr. Charles Moore - Memrie Price

Medical Center of the Rockies Research - Dr. C. Patrick Green - Sara Turner

Glendale Adventist Medical Center - Dr. John McKenzie - Javier Valeriano

Los Alamitos Cardiovascular - - Roy Kim

Oregon Health & Science University - Dr. Albert Camacho - John Halvorson

ACRC - Cardiology - Dr. Debra Weinstein - Kristina Feyler

Ohio State University - Dr. Rami Kahwash - Alexa Coressel

St. Francis Hospital - Long Island - Dr. Rita Jermyn - Ruth Sorg

University of California, San Francisco - Fresno - Dr. Richard Kiel - Rebekah Garcia

Desert Regional Medical Center - Dr. Hetal Bhakta - Claudia Fortiche

Liverpool Heart and Chest Hospital - Dr. Jay Wright - Sophie Twiss

Stern Cardiovascular Foundation - Dr. Frank McGrew - Kimberly Meshun Briscoe

The Christ Hospital - Dr. Thomas OBrien - David White

Baptist Health Lexington - Dr. Gery Tomassoni - Julie Ayers

Holy Cross Hospital - Dr. Joshua Larned - Christine Lepurage

Huntington Hospital - Dr. Vyshali Rao - Samia Solh

Texas Cardiac Arrhythmia Research Foundation - Dr. Andrea Natale - Deb Cardinal

Allegheny-Singer Research Institute - Dr. Srinivas Murali - Sheila Bernardini

Dignity Health - Dr. Arash Aryana - Svetlana Brazhnikova

Advanced Cardiovascular Specialists - Dr. Geoffrey Yoon - Janet Lamm

Methodist Richardson Medical Center - Dr. John George - Brittney Parker and Melissa Galicia

Cardiovascular Consultants, Ltd. - Dr. Kishlay Anand - Caroline Saglam

Memorial Health Services - Dr. Kenneth Deck - Jessy McCollum

Prairie Education and Research Cooperative - Dr. Nasar Nallamotheu - Christine Shugart and
Melissa McHugh

WakeMed - Dr. Marc Silver - Rhonda Norton

CHI Franciscan Health Research Center - Dr. David Zhang - Boyoung Moore

Memorial Cardiovascular Institute - Dr. Daniel Benhayon Lanes - Doris Alaby

Nebraska Heart Institute - Dr. Steven Krueger - Deb Baehr

Cardiovascular Institute of the South - Dr. Richard Abben - Vicky Parfait

Hackensack University Medical Center - Dr. Massimo Napolitano - Jana Tancredi

McLeod Cardiology Associates - Dr. Rajesh Malik - Robin McCaskill

Presbyterian Heart Group - Dr. Leonardo Macias - Susan Salazar

Advocate Medical Group - Dr. Maria Costanzo - Josilyn Klimek

Royal Papworth Hospital NHS Foundation Trust - Mr. Steven Tsui - Sarah Dennis

Sharp Center for Research - Grossmont - Dr. Bryant Nguyen - Cary Murphy

Tulane University Heart & Vascular Institute - Dr. Colleen Johnson - Suzanne Bowers

Ascension St. Marys Research Institute - Dr. Peter Fattal - Valerie Conachan (Bitzer)

Private Practice Leadership - Dr. Amir Kashani - Jessica Schneider

Royal Brompton & Harefield NHS Foundation Trust - Dr. Rebecca Lane - Alkida Bucaj and

Paula Rogers

University of Kansas Medical Center Research Institute, Inc. - Dr. Bhanu Gupta - Kartik Munshi

University of Rochester - Dr. John Bisognano - Mary Bourret

Belfast Health & Social Care Trust - Dr. Eng Wooi Chew - Michelle McEvoy

Bonometti, Inc. - Dr. Claudio Bonometti - Jaime Marks

Columbia St. Marys Hospital - Dr. Sanjay Deshpande - Cynthia Lessila

Deborah Heart and Lung Center - Dr. Mark Moshiyakhov - Elizabeth Scott

Hoag Memorial Hospital - Dr. Rajesh Banker - Wendy Price

Mercer University - Dr. Jalal Ghali - Michelle Damron0.32

UC Irvine Health - Dr. Dawn Lombardo - Wei Zhou (Yi Syuu)