Are Intermediate Endpoints Associated With Rates of Serious Cardiovascular Adverse Events? Results from the BEAT-HF Trial

Presenter: Michael R. Zile, MD

Charles Ezra Daniel Professor of Medicine, Medical University of South Carolina

Chief, Division of Cardiology, RHJ Department of Veterans Affairs MC

Charleston, South Carolina, USA

Co-Authors:

JoAnn Lindenfeld, MD, Vanderbilt Heart and Vascular Institute
William T. Abraham, MD, The Ohio State University
Fred A. Weaver, MD, University of Southern California
Faiez Zannad, MD, Inserm Centre d'Investigation
Tyson Rogers, MS, NAMSA Inc.
Khaled A. Awad, MD, Mercy Heart Hospital

Presenter Disclosure Information

I will discuss research examining the development of new therapies in my presentation.

I have financial relationships to disclose:

Employee of:

Department of Veterans Affairs, Medical University of SC

Consultant for:

Abbott, Boston Scientific, Corvia, CVRx, Cyclerion, EBR, Endotronics, Eli Lilly, Janssen, Medtronic, Merck, Myokardia, Novartis, ReCor, V Wave

Stockholder in: N/A

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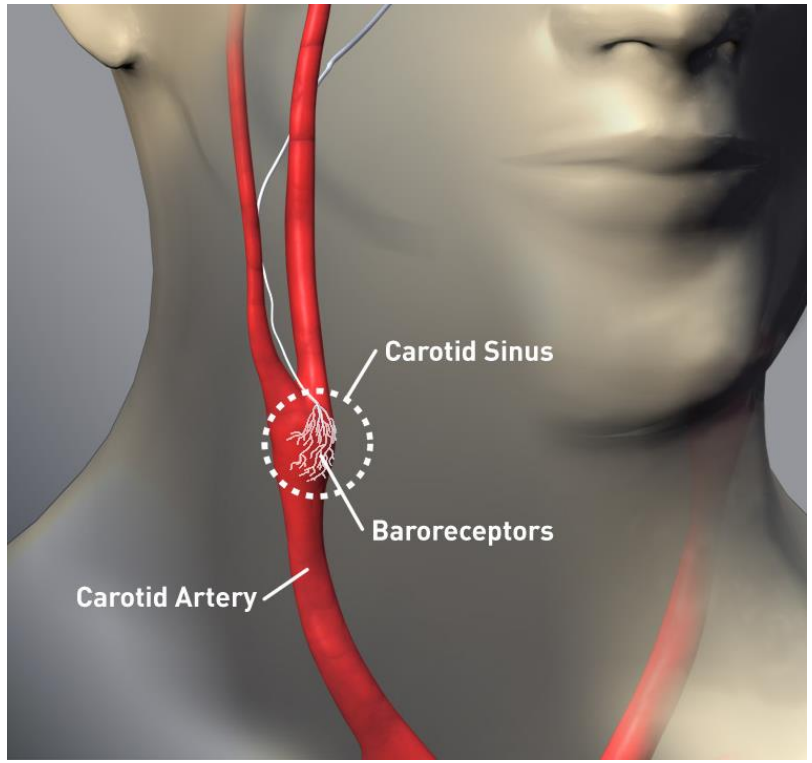
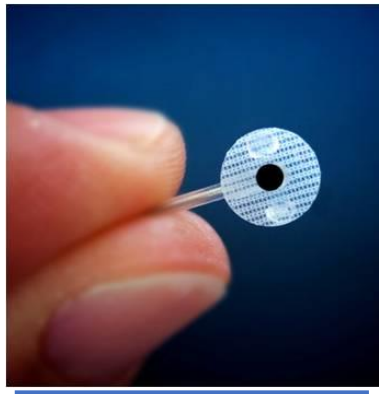
NHLBI, VA, DOD, CVRx, Medtronic, Novartis

Presentation Goals

- Device Design, Mechanism of Action
- Clinical Evidence Development in Heart Failure
- BeAT-HF Trial Data
- Rate of Serious Cardiovascular Adverse Events
- Patients who should be considered for BAT

Device Design





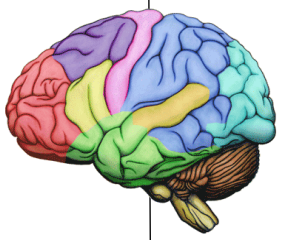
2 mm electrode
7mm silicone backer
Unipolar design

4-5 year longevity
RF telemetry
Programming flexibility

8.7 mA amplitude
125 ms duration
40 pps frequency

Mechanism of BAT in HFrEF

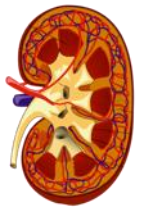
Carotid Baroreceptor Stimulation
Afferent Signaling



Integrated Autonomic Nervous System Response
Inhibits Sympathetic Activity
Enhances Parasympathetic Activity

↓ **Heart Rate**
↓ **Remodeling**

↑ **Vasodilation**
↓ **Elevated BP**

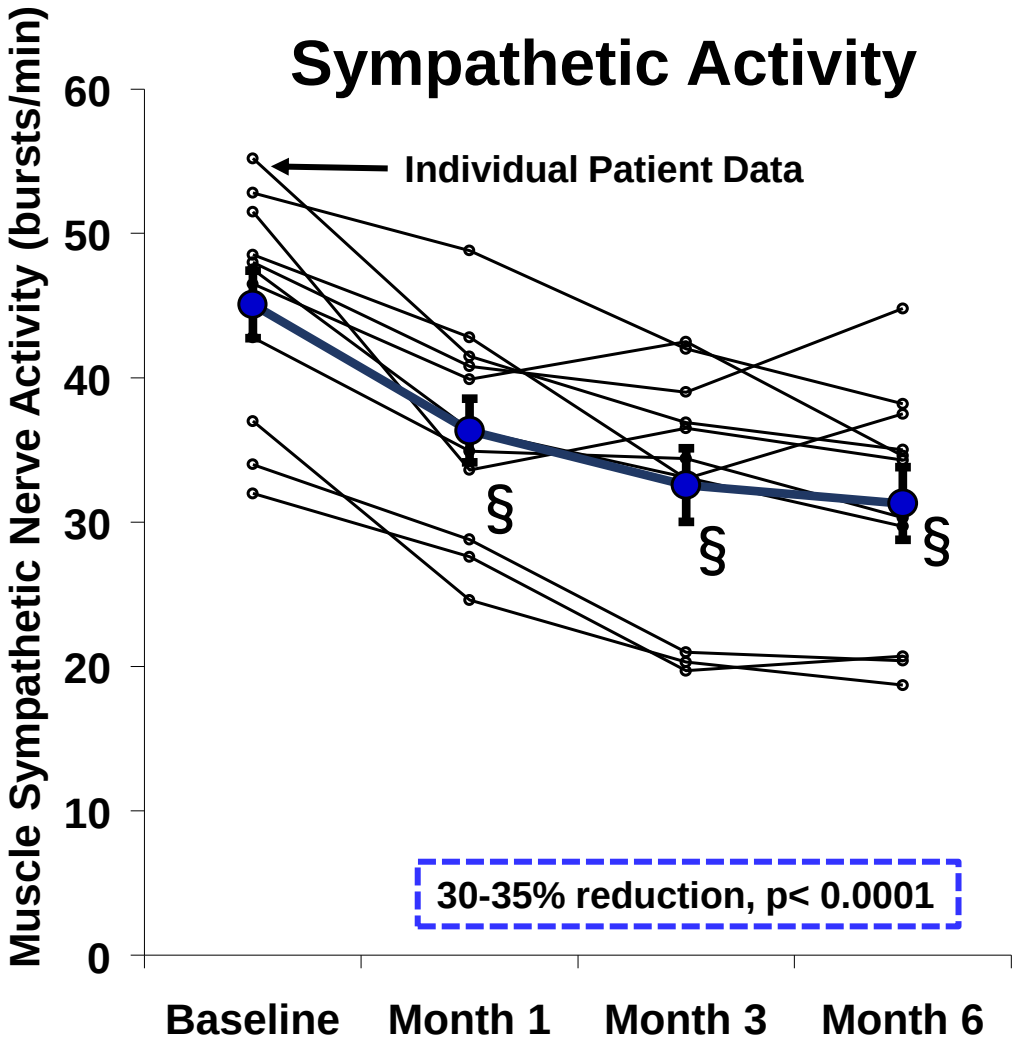


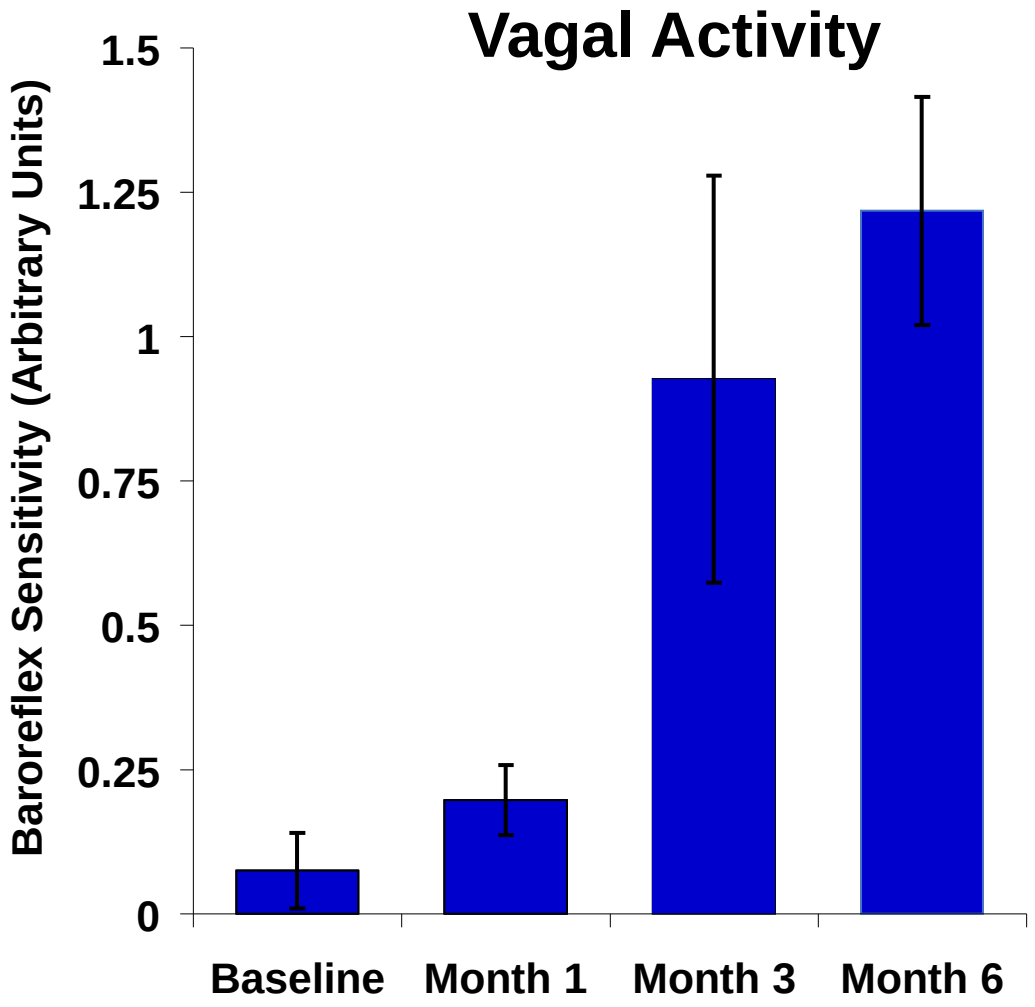
↑ **Diuresis**
↓ **Renin secretion**

Clinical Evidence Development in Heart Failure

	Phase I: BAT in HF 1st Enrollment 12/2011	Phase II: HOPE4HF 1st Enrollment 5/2012	Phase III: BeAT-HF 1st Enrollment 4/2016
Objective	• Assess safety • Demonstrate mechanism of action with GDMT	• Assess safety and Effectiveness	• Demonstrate safety and effectiveness, including morbidity & mortality • Assess health economics
Study Subjects	• n = 11	• n = 146	• n = 408
Outcomes	• BAROSTIM Therapy is safe • Mechanism of action demonstrated through muscle sympathetic nerve activity & HR Variability	• BAROSTIM Therapy is safe and effective in heart failure • CE Mark Approval	• BAROSTIM Therapy is a safe, effective and an economically attractive solution for heart failure patients • FDA Approval

Effect of BAT in HFrEF on Sympatho-Vagal Balance





All Rx GDMT (> 90% ACE-I/ARB, β-blker, MRA)
Replicated using High, Low HR Variability Studies

Gronda et al Eur J HF 16: 977-983, 2014

A Phase III Randomized, Controlled Trial of Baroreflex Activation Therapy (BAT) in Patients with Heart Failure and Reduced Ejection Fraction (HFrEF)

BeAT-HF

(ClinicalTrial.gov Identifier: NCT02627196)

The BeAT-HF Executive Steering Committee

Michael R. **Zile**, MD, William T. **Abraham**, MD, JoAnn **Lindenfeld**, MD, Fred A. **Weaver**, MD, Faiez **Zannad**, MD

Sponsor

CVRx, Inc.

Zile MR, et.al Am Heart J. 2018 Jul 22; 204:139-150.

BeAT-HF Phase III Study

Purpose:

- Demonstrate safety and effectiveness of BAT in HFrEF patients using the FDA Breakthrough Devices Program

Design:

- Multicenter, prospective, randomized controlled trial
- Randomized 1:1 to receive BAT plus optimal medical management (“BAT”) or optimal medical management alone (“Control”)

Zile MR, et.al Am Heart J. 2018 Jul 22; 204:139-150.

BeAT-HF Key Eligibility Criteria

- NYHA Functional Class III
- Left ventricular ejection fraction ≤ 35%
- Six-minute hall walk distance (6MHW) 150 – 400 m
- Elevated NT-proBNP or previous Heart Failure Hospitalization
- Stable optimal medical therapy ≥ 4 weeks
- Subjects not indicated for CRT
- No restriction on AF, QRS width or concomitant devices

Zile MR, et.al Am Heart J. 2018 Jul 22; 204:139-150.

BeAT-HF Baseline Demographics

Variable	BAT (n=130)	Control (n=134)
Age (years)	62 ± 11	63 ± 10
Gender: Female	19%	22%
Race: Caucasian	75%	72%
NYHA: Class III	93%	95%
MLWHF QOL Score	53 ± 24	52 ± 24
6 Minute Hall Walk Distance (m)*	316 ± 68	294 ± 73
HR (bpm)	75 ± 10	75 ± 11
SBP (mmHg)	120 ± 17	121 ± 16
DBP (mmHg)	73 ± 10	73 ± 10
LVEF (%)	27 ± 7	28 ± 6
NT-pro BNP (pg/mL, Median [IQR])	731 [475, 1021]	765 [479, 1052]
eGFR (mL/min)	64 ± 17	62 ± 20
QRS Interval	109 ± 18	110 ± 26
History of Atrial Fibrillation	29%	43%
History of Coronary Artery Disease	62%	69%
Previous HF hospitalization	42%	51%

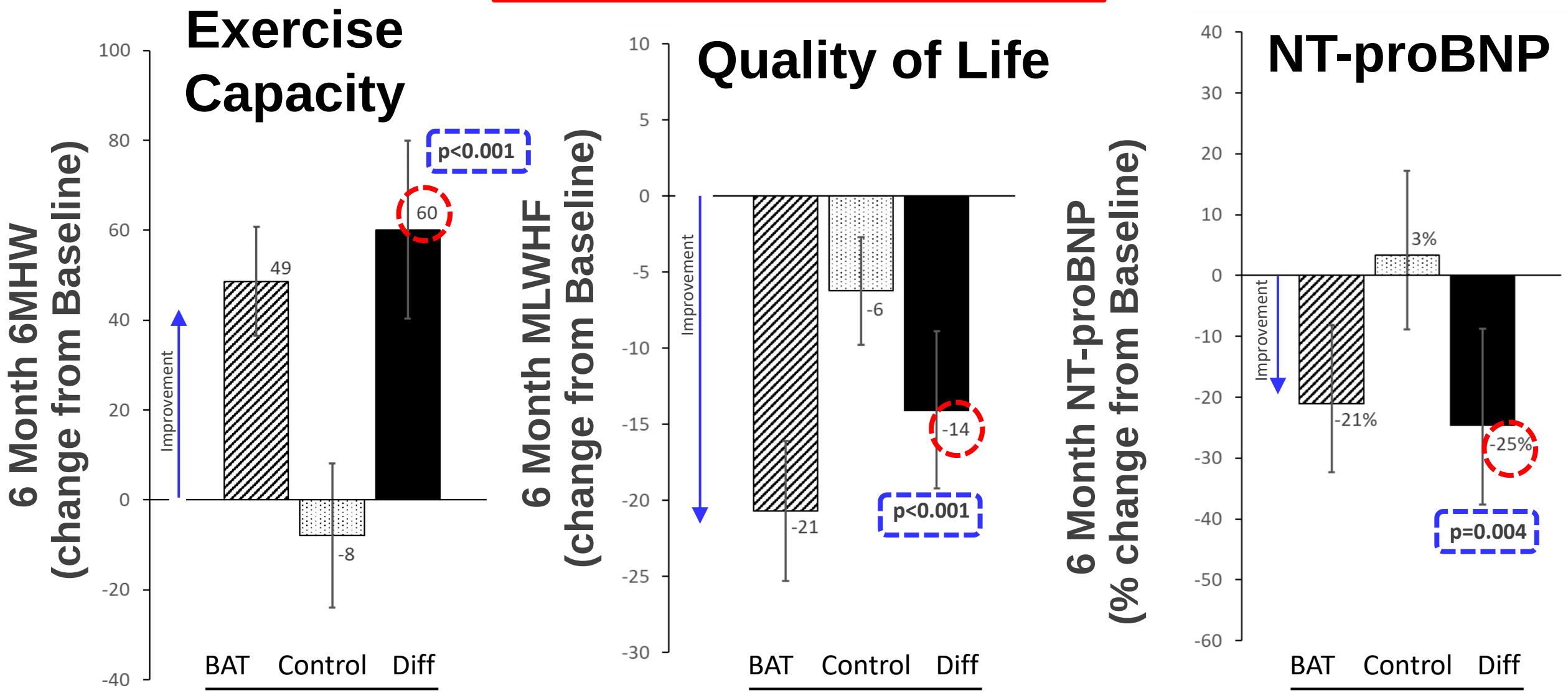
No significant difference between BAT and Control: none below 0.01, 6MHW p=0.015, AF p=0.03, all others > 0.05

BeAT-HF Baseline Therapies

Variable	BAT (n=130)	Control (n=134)
Number of Meds	3.9 ± 1.2	4.1 ± 1.4
ACE-I/ARB/ARNI	89%	84%
Beta-Blocker	95%	95%
MRA	49%	42%
Diuretic	85%	87%
Ivabradine	2%	5%
ICD	78%	79%

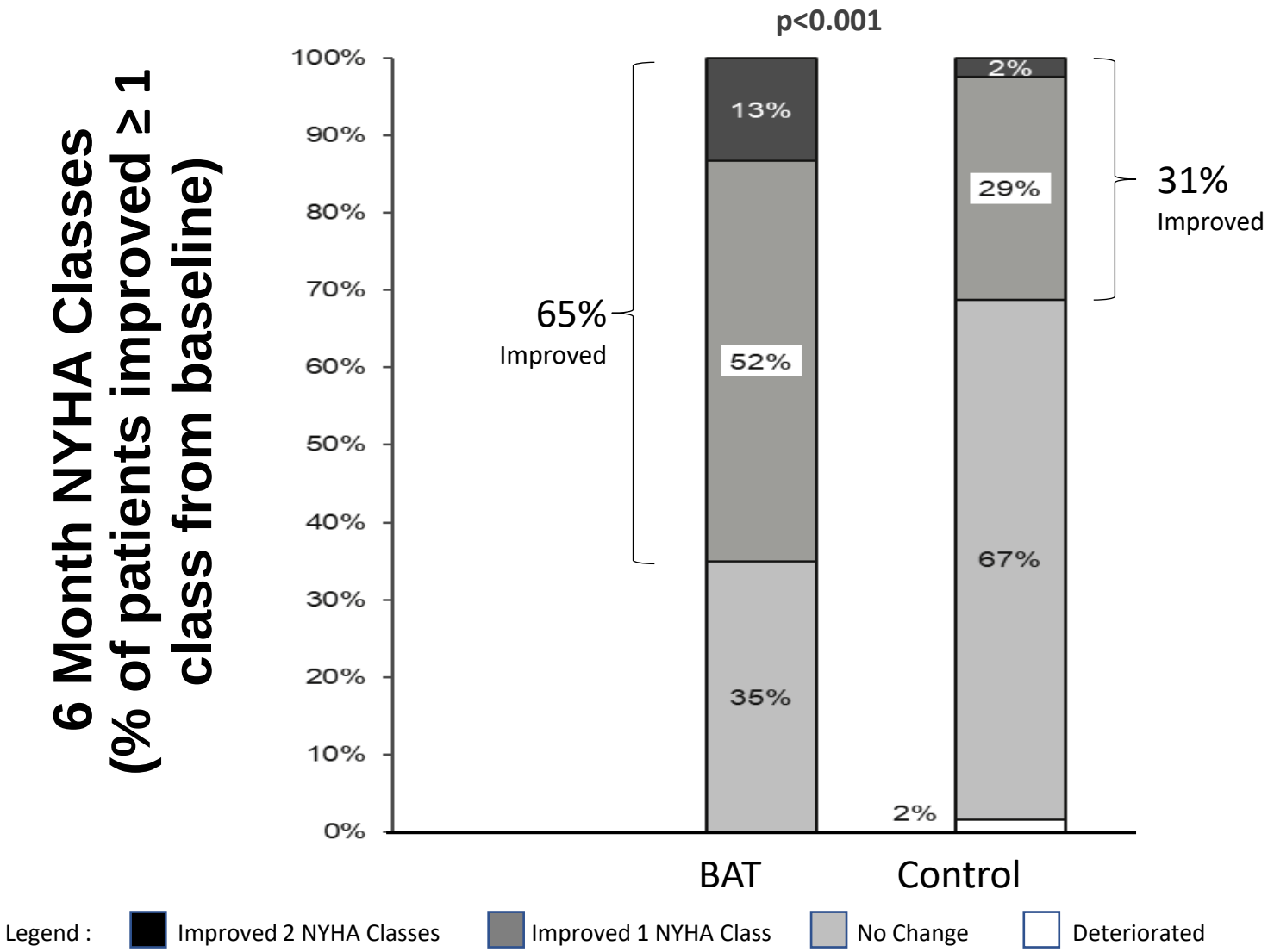
No significant difference between BAT and Control

BeAT-HF Top-Line Results



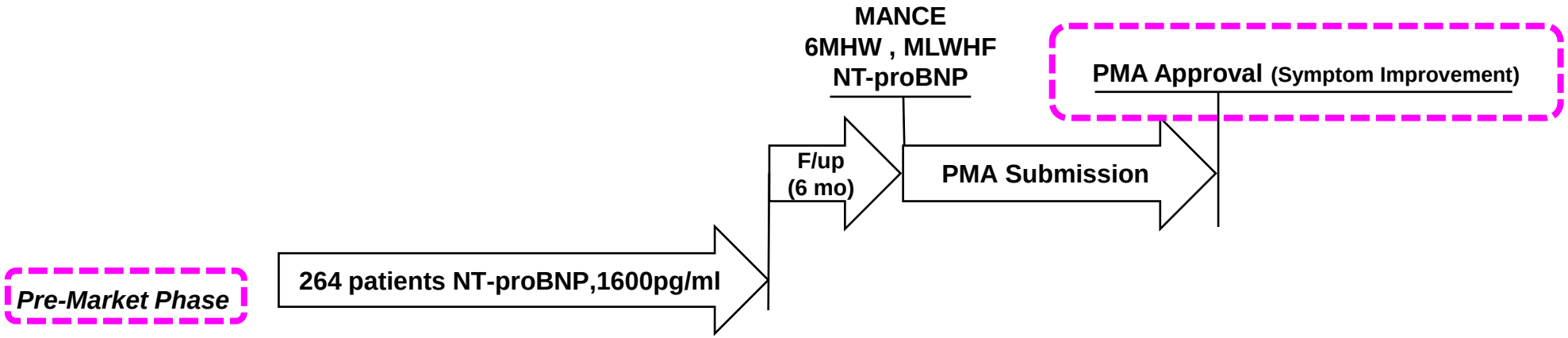
BeAT-HF Top-Line Results

Functional Status



Endpoint Strategy: Breakthrough Devices Program Approved Approach

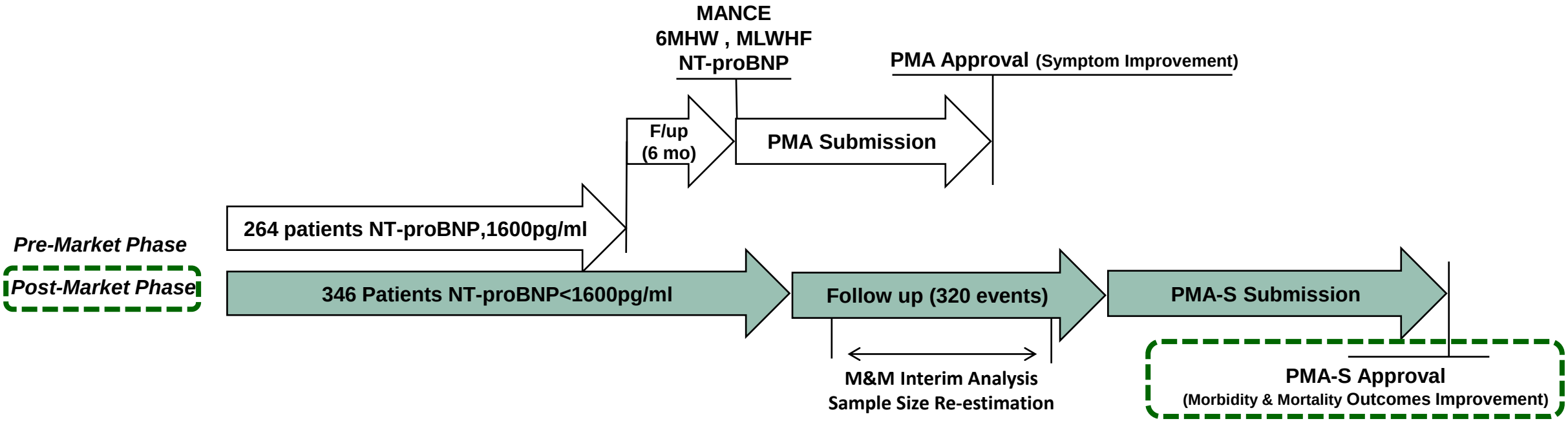
-- Completed



	Sample Size	Analysis Timing	Clinical Evidence
Pre-Market Phase	N = 264 randomized subjects	N = 264 complete 6 months follow-up	• Safety evaluation (MANCE) • NT-proBNP • Six minute hall walk • Minnesota living with heart failure (QOL)

Endpoint Strategy: Breakthrough Devices Program Approved Approach

-- Ongoing



	Sample Size	Analysis Timing	Clinical Evidence
Pre-Market Phase	N = 264 randomized subjects	N = 264 complete 6 months follow-up	• Safety evaluation (MANCE) • NT-proBNP • Six minute hall walk • Minnesota living with heart failure (QOL)
Post-Market Phase	N = 336 randomized subjects (N=264 subjects from Pre-Market Phase + additional N=72 new subjects)	Sufficient morbidity and mortality data collected on all subjects (320 events collected)	• Full morbidity and mortality • Heart Failure Hospitalization • CV Death • Totality of evidence

Serious Cardiovascular Adverse Events: Definition

- **Heart Failure Events (HF Hospitalization or CV Death) were excluded. BeAT-HF Post-Market Phase is ongoing and these events remain blinded.**

- **Serious Adverse Event:** An adverse event that led to death, or led to serious deterioration in the health of the subject in the following categories:
  - **Cardiac Arrhythmias / Cardiac Arrest**
  - **Hypotension / Syncope**
  - **Myocardial Infarction / Angina**

- A cardiovascular event is any event related to the heart or vascular system.
- All serious cardiovascular adverse events were adjudicated by an independent committee.

Serious Cardiovascular Adverse Events

	BAT N=125		Control N=134			
CV SAE	**Number of Events (# subjects)**	**Event Rate per patient year of follow-up**	**Number of Events (# subjects)**	**Event Rate per patient year of follow-up**	**Relative Reduction in Event Rate (95% CI)**	**p-value**
Cardiac Arrhythmias/Cardiac Arrest	8 (6)	0.054	18 (12)	0.109	0.50 (-0.14, 0.78)	0.100
Hypotension/Syncope	2 (2)	0.014	6 (4)	0.036	0.63 (-0.85, 0.92)	0.226
MI/Angina	5 (4)	0.034	10 (10)	0.060	0.44 (-0.63, 0.81)	0.288
Total	**15 (11)**	**0.101**	**34 (22)**	**0.206**	**0.51 (0.10, 0.73)**	**0.023**

Conclusions

- BAT significantly improved patient-centered symptomatic endpoints
  - quality of life score
  - exercise capacity, and
  - functional status.
- These results were supported by objective evidence of significant reduction of NT-proBNP.
- Within the first six months, BAT patients had significantly fewer serious cardiovascular adverse events than the Control patients.
- The ongoing BEAT-HF trial post-market phase remains blinded to Heart Failure events (HF Hospitalizations and CV Death).

FDA Approval 8/16/2019 : Instruction For Use

The BAROSTIM NEO® System is indicated for the improvement of symptoms of heart failure – quality of life, six-minute hall walk and functional status, for patients who remain symptomatic despite treatment with guideline-directed medical therapy, are NYHA Class III or Class II (who had a recent history of Class III), have a left ventricular ejection fraction ≤ 35%, a NT-proBNP < 1600 pg/ml and excluding patients indicated for Cardiac Resynchronization Therapy (CRT) according to AHA/ACC/ESC guidelines.