A Randomized, Controlled Trial of

Baror**e**flex **A**ctivation **T**herapy (BAT)

in Patients with

Heart **F**ailure and Reduced Ejection Fraction (HFrEF)

BeAT-HF

(ClinicalTrial.gov Identifier: NCT02627196)

The BeAT-HF Executive Steering Committee

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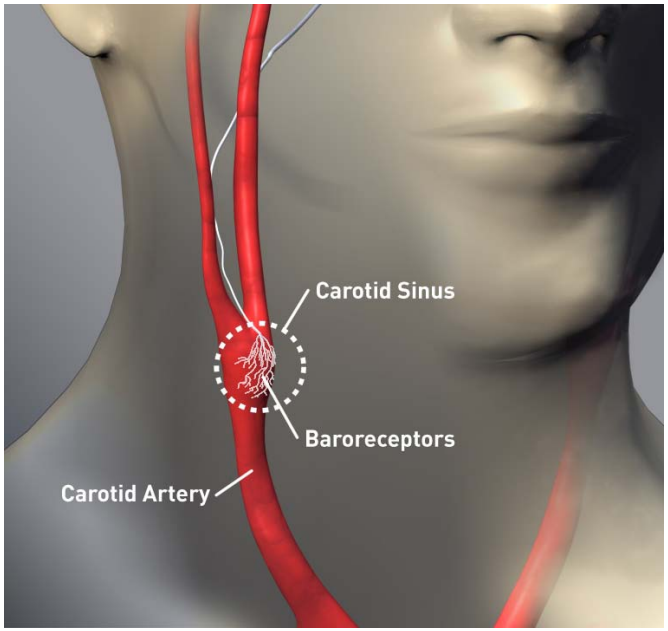
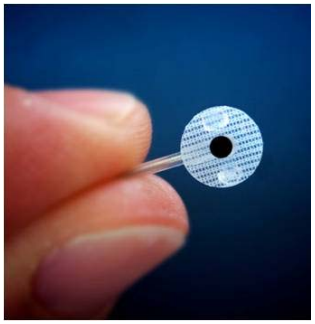
Fred A. **Weaver**, MD, Faiez **Zannad**, MD

Sponsor

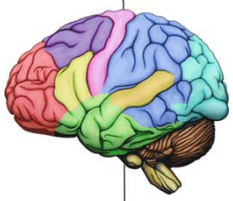
CVRx, Inc.

Mechanism of BAT in HFrEF

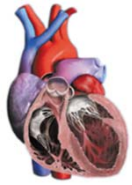




Carotid Baroreceptor Stimulation
Afferent Signaling

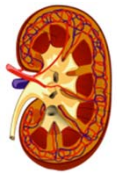


Integrated Autonomic Nervous System Response
Inhibits Sympathetic Activity
Enhances Parasympathetic Activity



↓ **Heart Rate**
↓ **Remodeling**

↑ **Vasodilation**
↓ **Elevated BP**



↑ **Diuresis**
↓ **Renin secretion**

BeAT-HF Pivotal Trial

Purpose:

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

Design:

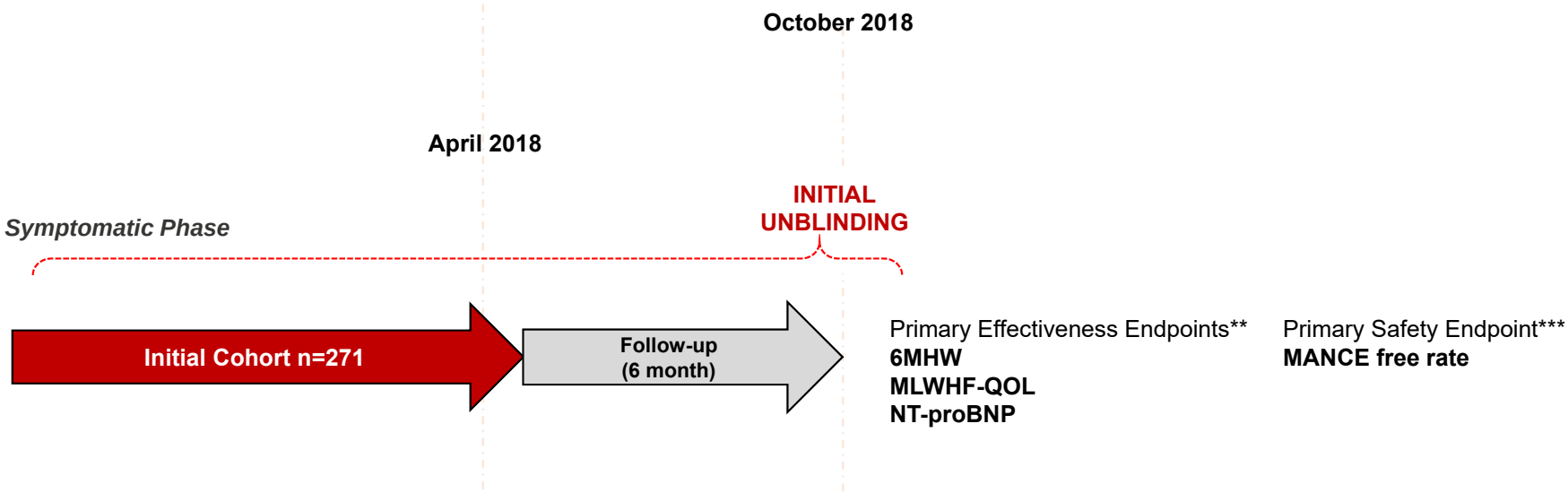
- Multicenter, prospective, randomized controlled trial
- Randomized 1:1 to receive BAT plus optimal medical management (“BAT”) or optimal medical management alone (“Control”)

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
- CRT-eligible subjects are excluded

No restriction on atrial fibrillation or flutter

BeAT-HF Trial Design*

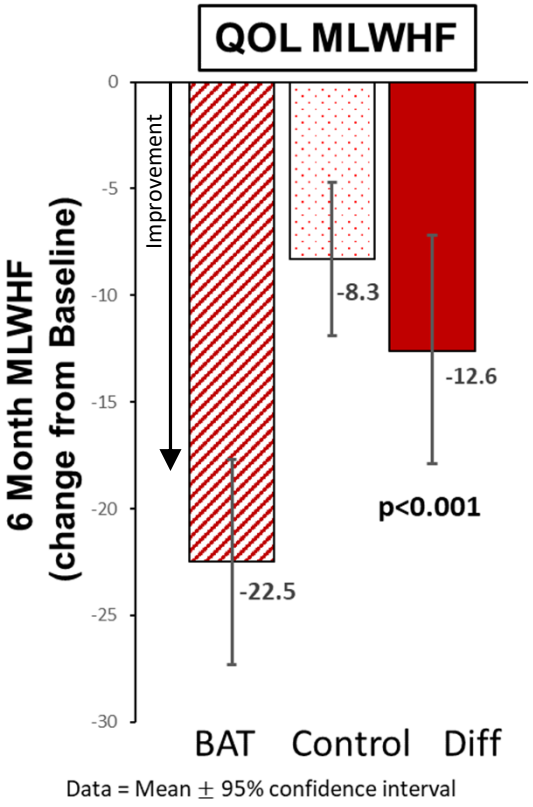


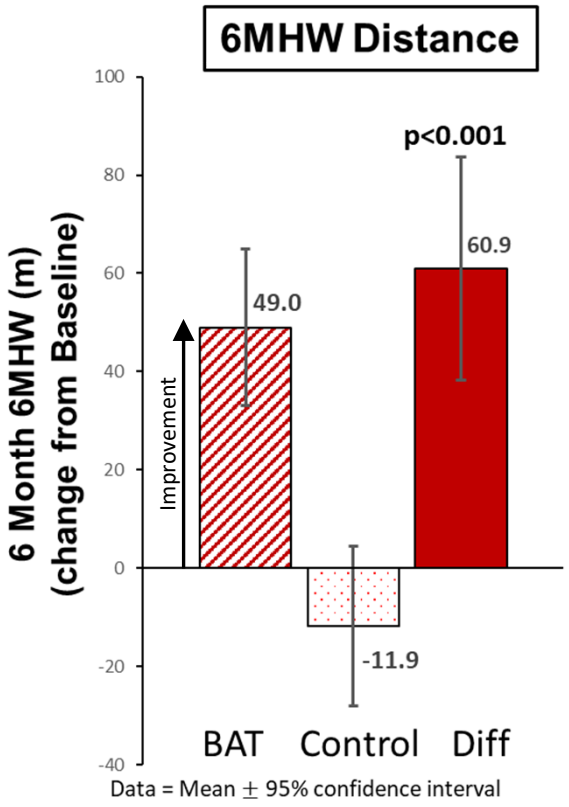
*Developed collaboratively with FDA
**Measured as changes from baseline to 6 months
***Major Adverse Neurological and Cardiovascular Event free rate, compared to a performance criteria of 85%

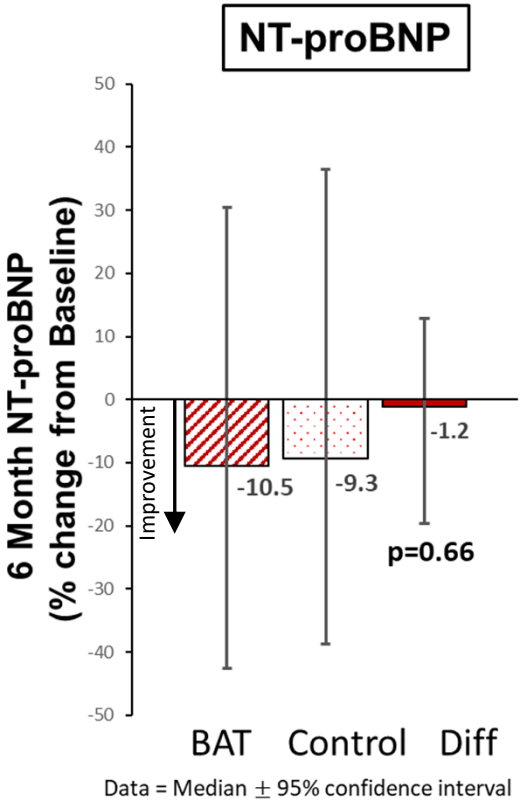
BEAT-HF Initial Cohort: 3 of 4 Primary Endpoints Positive

MANCE

- MANCE-free rate : **94%** (118/125)
- Exceeded performance criteria of 85% with p-value < 0.001

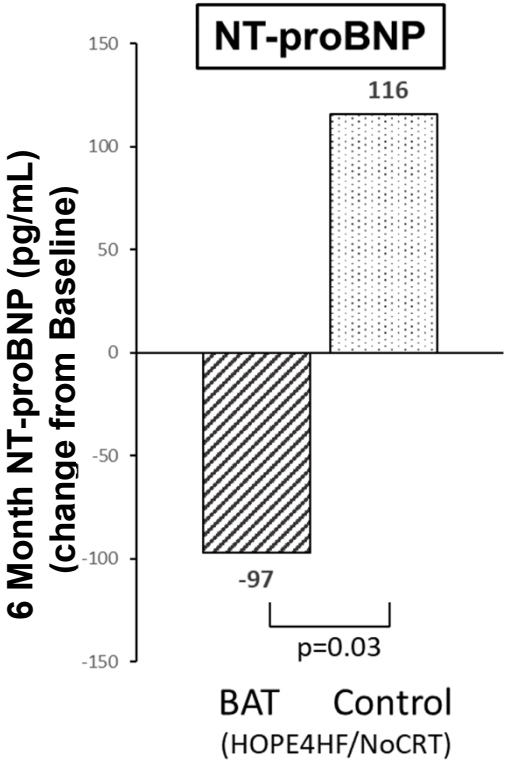






BeAT-HF: Defining an Intended Use Population

- HOPE4HF (Phase 2 prespecified subgroup) showed strong NT-proBNP reduction with BAT
- FDA recommended that we conduct analyses to understand differences between HOPE4HF and BeAT-HF (Phase 3)



Eligibility Criteria	HOPE4HF / NoCRT (phase 2)	BeAT-HF (phase 3)
NYHA / LVEF	Class III / < 35%	Class III / < 35%
6MHW	≥ 150m AND ≤ 400	≥ 150m AND ≤ 400
CRT	Exclude CRT	Exclude CRT
NT-proBNP	N/A	Prior HFH OR **NT-pro BNP ≥ 1600 pg/mL**

BeAT-HF: Defining an Intended Use Population

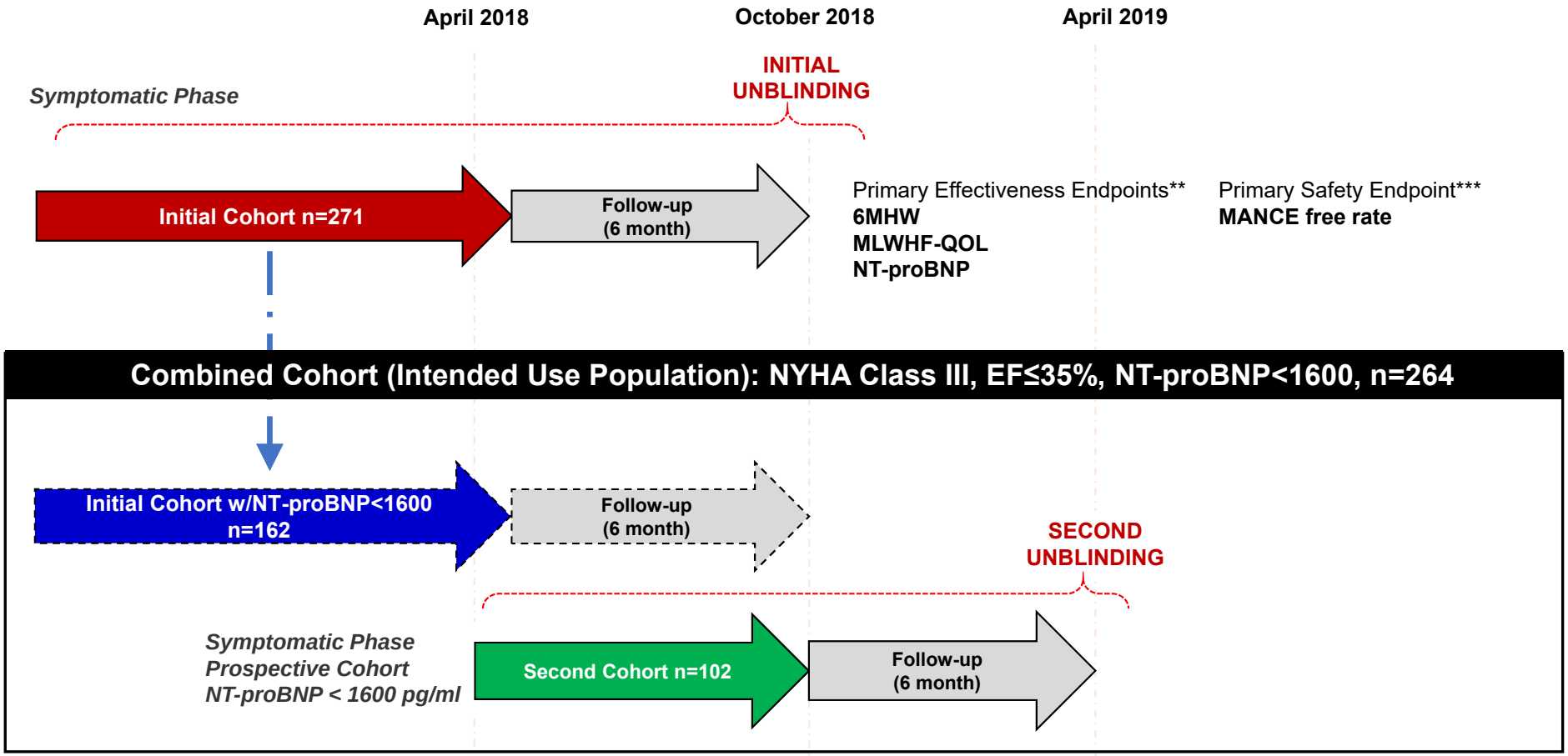
NT-proBNP<1600 pg/ml

- Recent studies* suggested greater response to HF therapies in lower NT-proBNP
- BeAT-HF patients with NT-proBNP ≥ 1600 have more advanced heart failure:
  - Older
  - Lower LVEF
  - Shorter walk distance
  - Higher diuretic use
  - Higher number of previous HF hospitalizations

Therefore, NT-proBNP < 1600 defines the Intended Use Population

*CORONA, I-PRESERVE, TOPCAT

BeAT-HF Final Trial Design*



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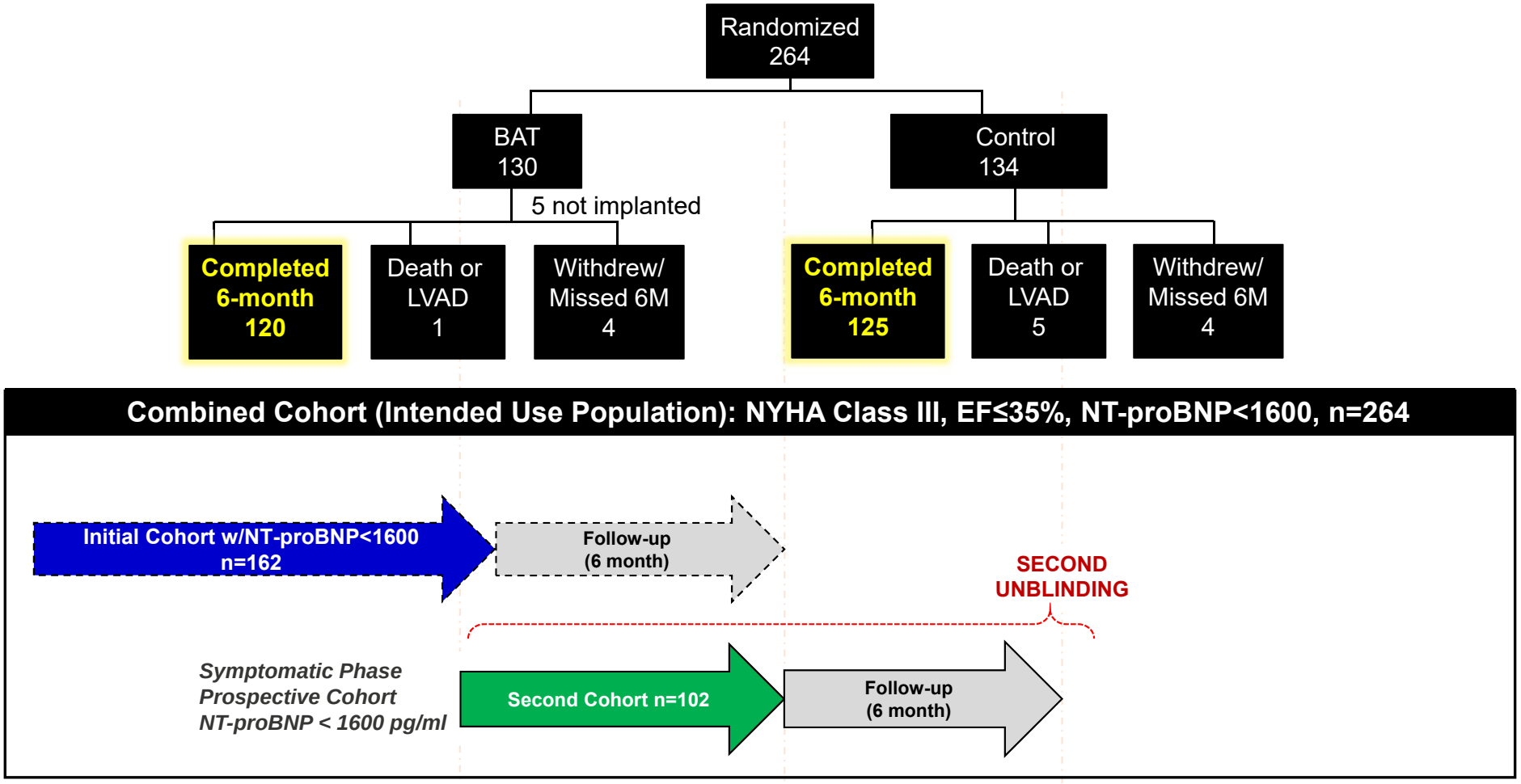
BeAT-HF Final Trial Design*



*Developed collaboratively with FDA

BeAT-HF Baseline Demographics for Combined Cohort

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%	42%
History of Coronary Artery Disease	62%	69%
Previous HF hospitalization	42%	51%

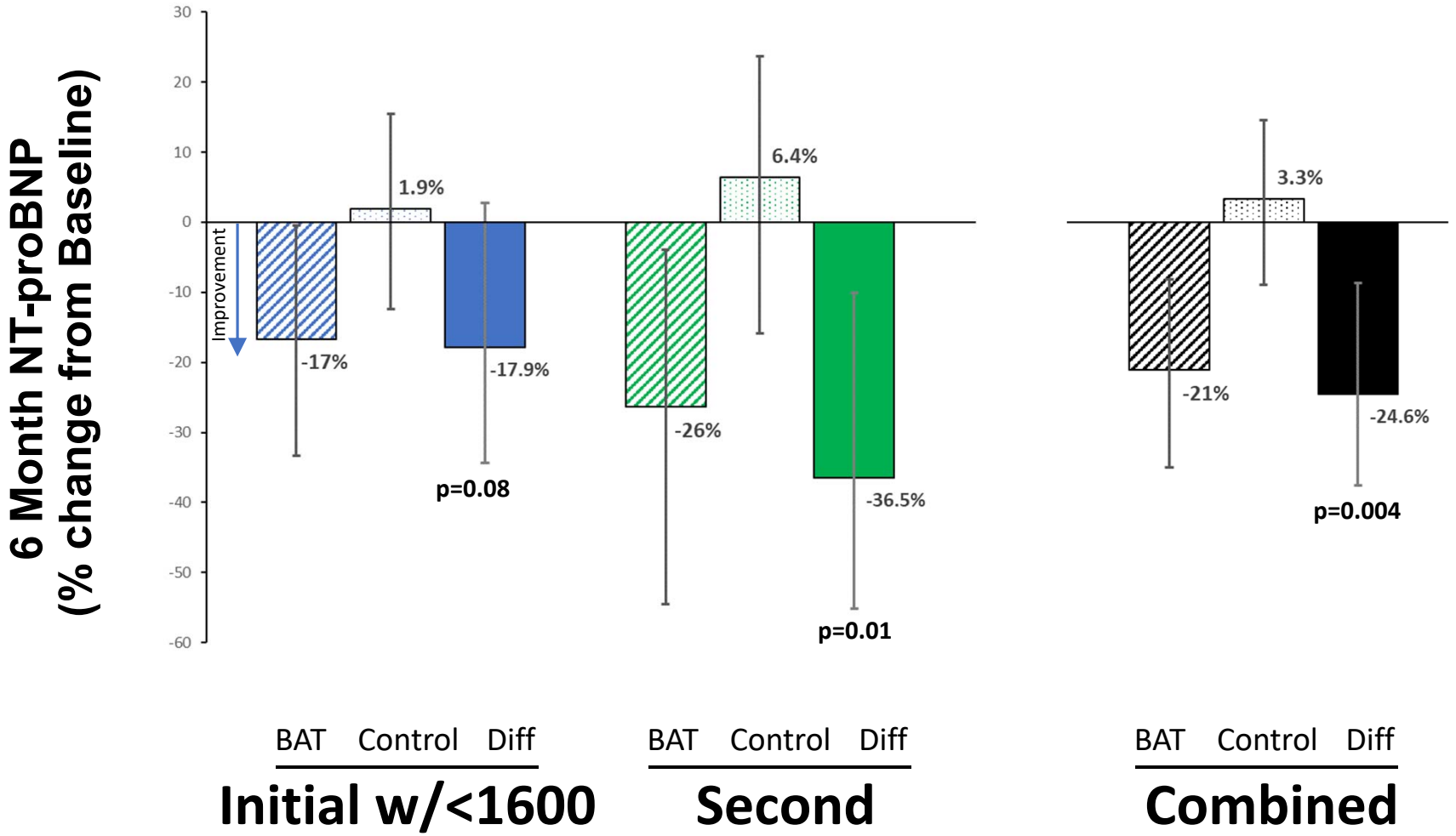
No significant difference between BAT and Control: none below 0.01, 6MHW p=0.015, AF p=0.03, all others > 0.05

BeAT-HF Baseline Therapies for Combined Cohort

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

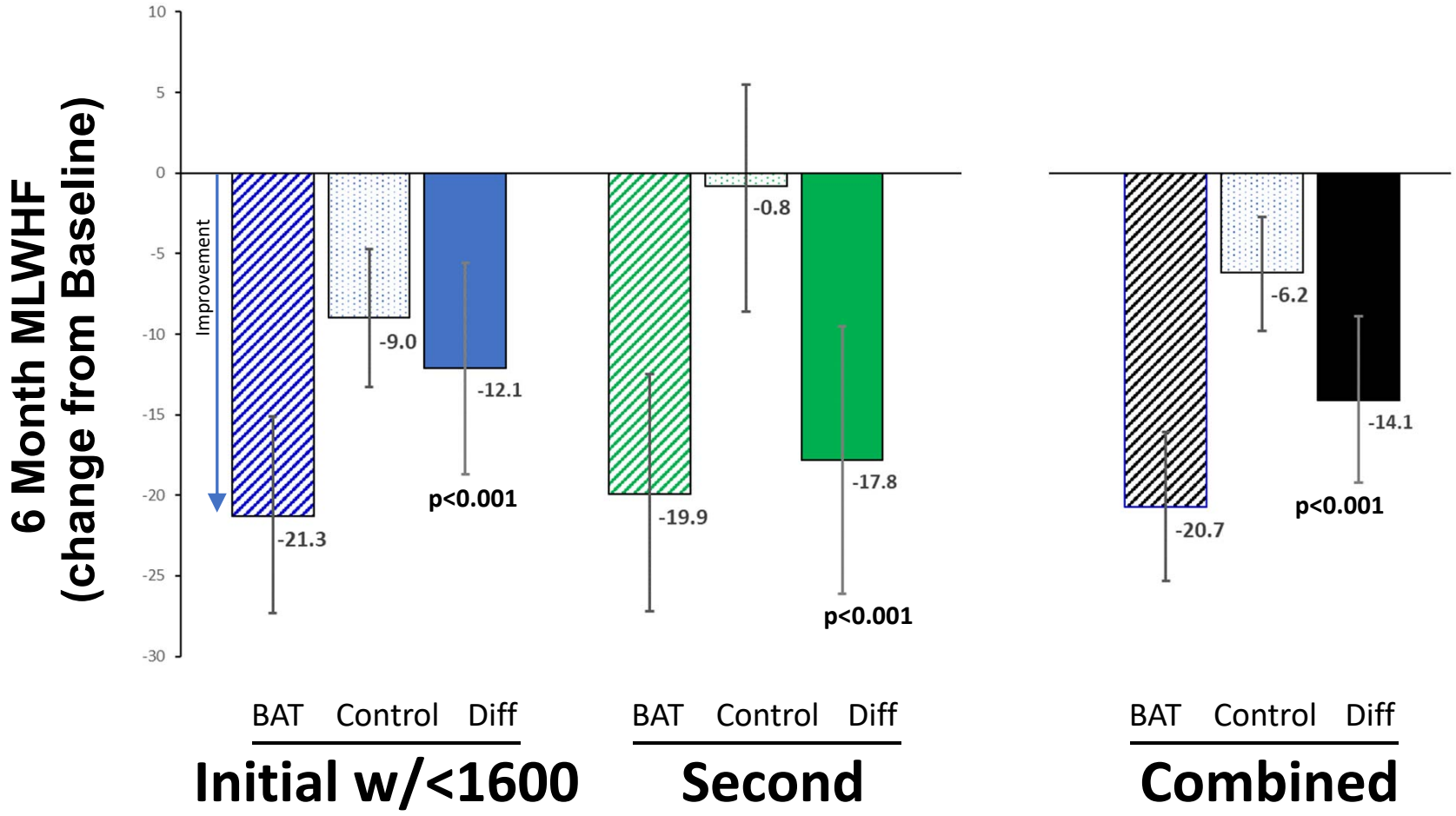
No significant difference between BAT and Control

BAT Significantly Reduces NT-proBNP



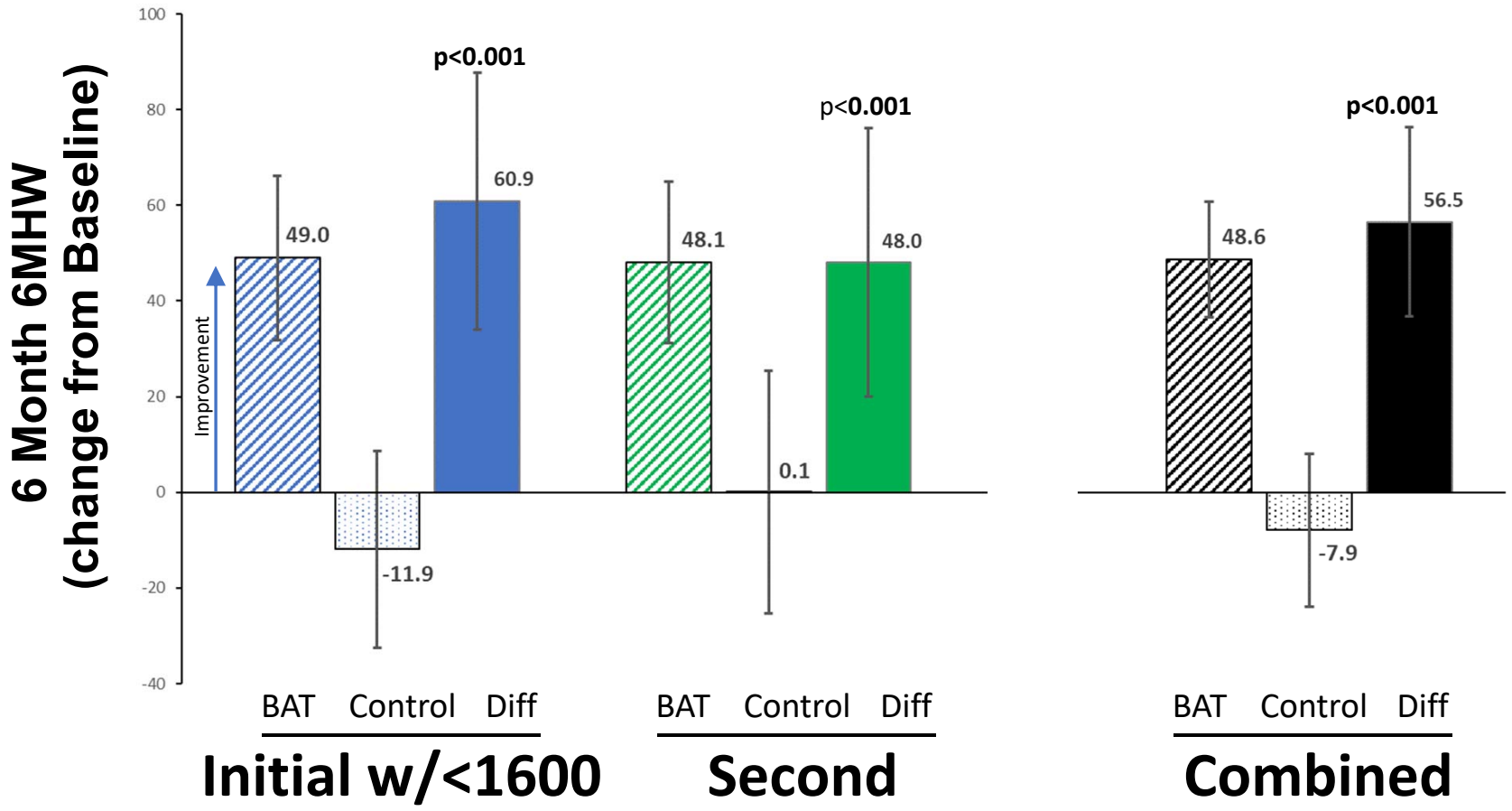
Data = Mean ± 95% confidence interval, all differences analyzed using Log10 transformed NT-proBNP by ANCOVA adjusted for baseline values

BAT Significantly Improves Quality of Life



Data = Mean ± 95% confidence interval, all differences analyzed by ANCOVA adjusted for baseline values

BAT Significantly Improves Functional Capacity



Data = Mean ± 95% confidence interval, all differences analyzed by ANCOVA adjusted for baseline values

BeAT-HF Conclusions

- Baroreflex Activation Therapy is safe in HFrEF patients.
- BAT significantly improves patient-centered symptomatic endpoints
  - quality of life score
  - exercise capacity.
- These results are supported by objective evidence of significant reduction of NT-proBNP.
- These significant differences in treatment effect were observed despite an increase in the number of medications in the control arm.
- To our knowledge, this is the first successful pivotal trial of a device-based neuromodulation therapy in HFrEF patients.

This slide was added to the slide deck after the Presentation

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For a list of all potential benefits and risks go to:
www.beathf.com/risksbenefits/