Safety and Efficacy of BackBeat™ Cardiac Neuromodulation Therapy (CNT™) in Patients with Hypertension: Final Results of a Double-Blind Randomized Trial

Karl-Heinz Kuck, MD

On behalf of coauthors:

Z. Kalarus, B. Merkely, P. Neuzil, M. Grabowski, G. Marinskis, A. Erglis, J. Kazmierczak, P. Mitkowski, T. Sturmberger, F. Malek, A. Kolodzinska, D. Burkhoff, A. Sokal, L. Geller and the Moderato 2 Study Investigators

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Disclosure Statement of Financial Interest

I, (Karl-Heinz Kuck, MD) DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

BackBeat™ Cardiac Neuromodulation Therapy (CNT™)

- **Cardiac pacing to reduce blood pressure through two mechanisms:**
  - Reduction in LV Filling (preload) to provide an acute effect
  - Neuromodulation to maintain effect chronically (afterload)

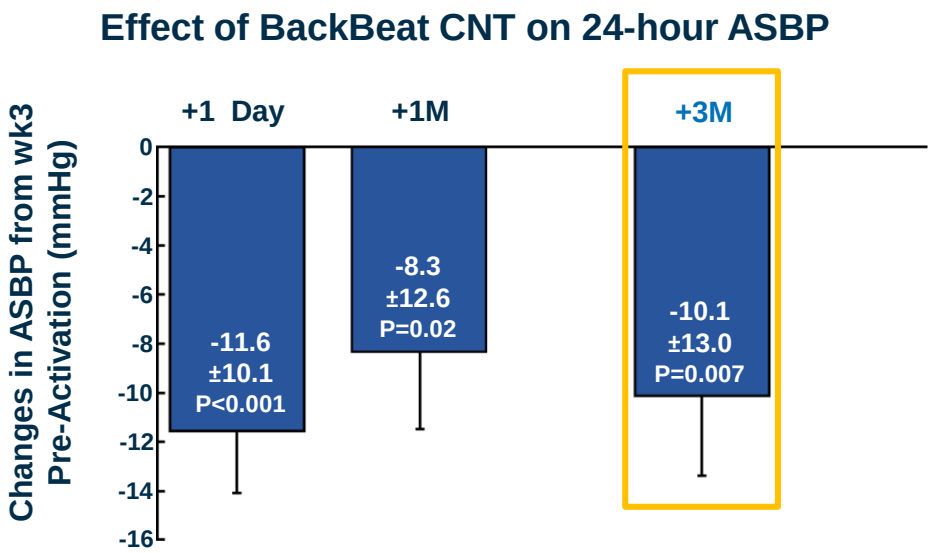
- **Delivered via implantable pulse generator (IPG) using standard lead positions**
  - IPG also provides standard pacemaker functionality

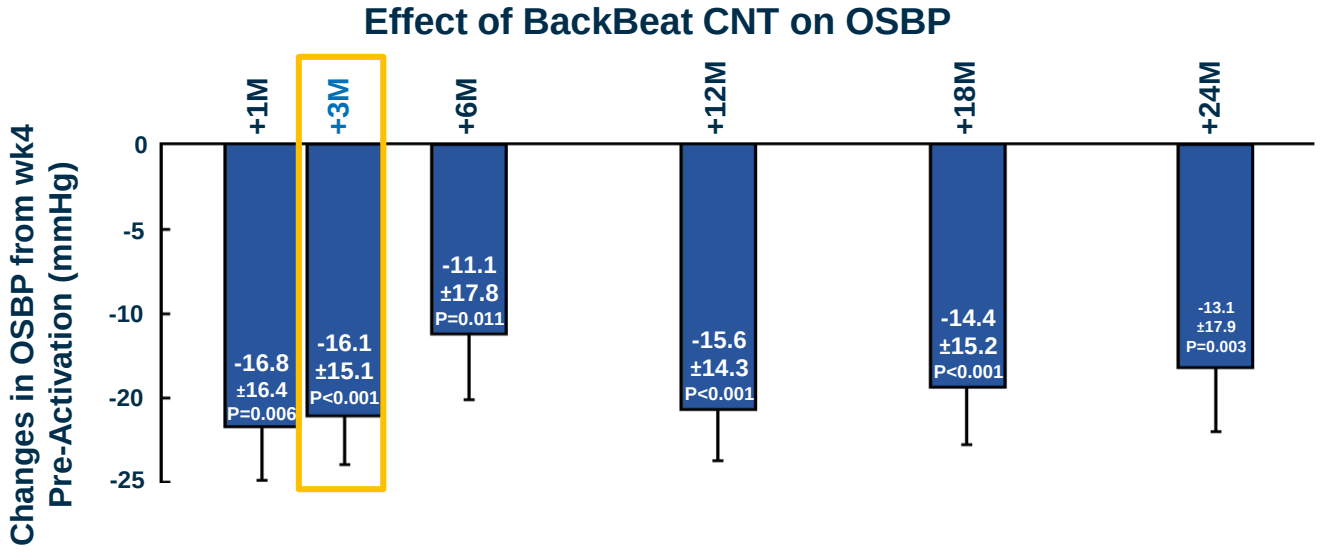
BackBeat CNT Initial Target Population

- **Hypertension patients indicated for pacemaker**
  - >1M pacemaker implants globally per year
  - >70% of pacemaker patients have hypertension
    - ~ 60% uncontrolled despite treatment
  - Older, co-morbid population at increased risk of major events
  - High rate of Isolated Systolic Hypertension (ISH)

MODERATO I Study

- Prospective, single-arm study of 27 patients with **hypertension** (office BP >150 mmHg) despite two or more anti-hypertensive medications **and an indication for a pacemaker**





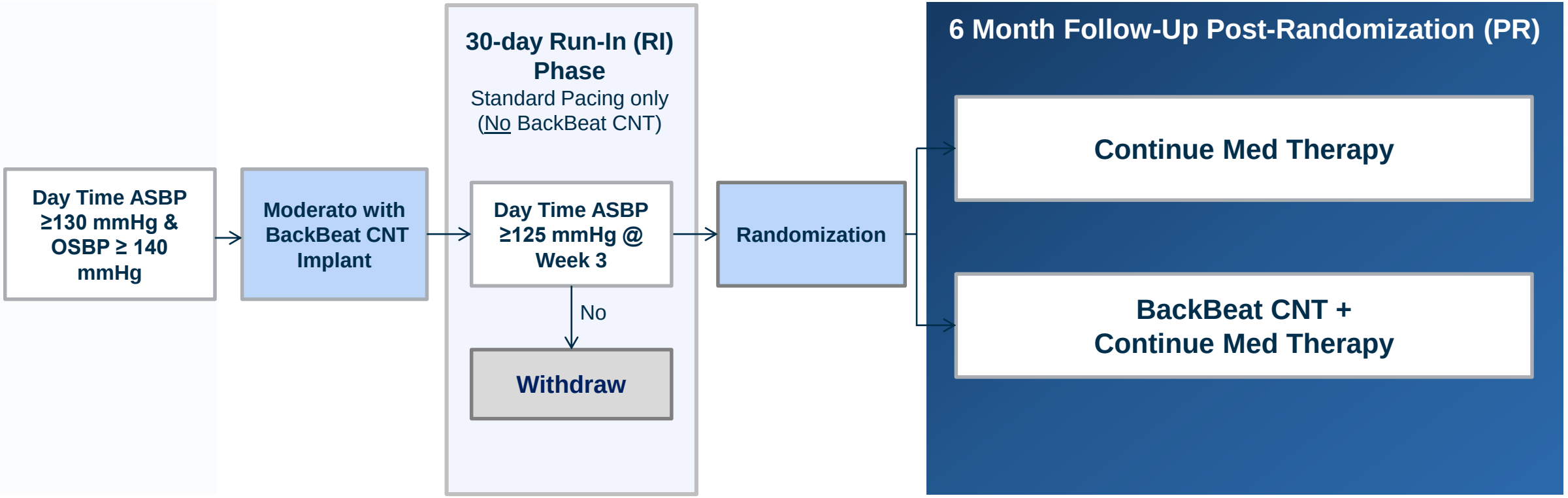
Petr Neuzil, et. al. Pacemaker-Mediated Programmable Hypertension Control Therapy. J Am Heart Assoc. 2017; Dec 23;6(12): e006974. DOI: 10.1161/JAHA.117.006974

MODERATO II Study

- **Prospective, multi-center, randomized, double-blind study of BackBeat CNT vs. Medical Therapy (Control)**
  - 9 sites in EU
  - Pilot study to inform the design and power of the pivotal study

- **Objective**: to assess the efficacy and safety of BackBeat CNT in reducing blood pressure in patients with hypertension despite medical therapy who are also indicated for a pacemaker

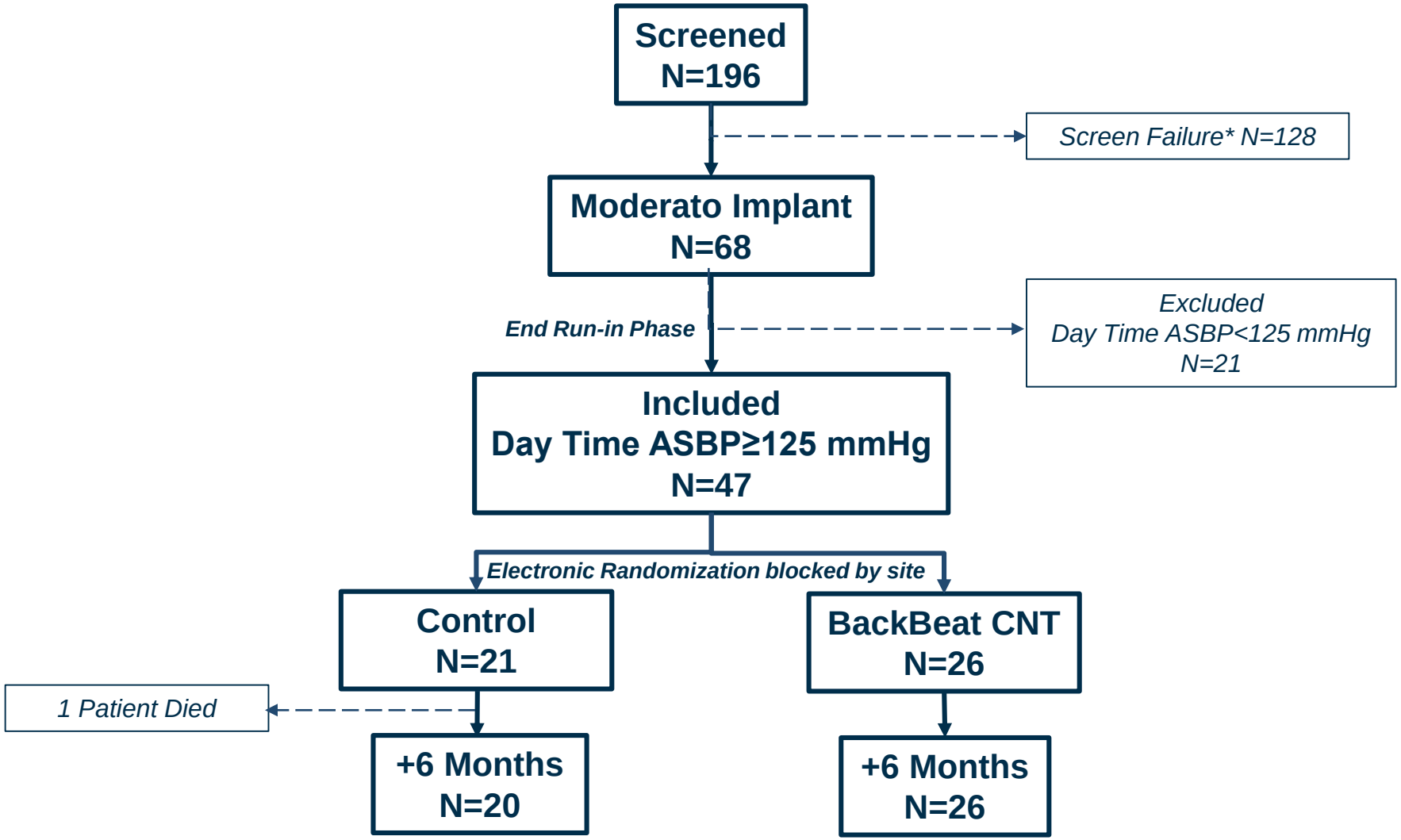
MODERATO II: Study Design



MODERATO II: Main Patient Selection Criteria

Inclusion	Exclusion
1. ≥ 18 years of age **2. Requires the implant or replacement of a dual chamber pacemaker** **3. Stable hypertension treatment with at least 1 anti hypertensive drug for >1 month** **4. Average day time ambulatory systolic blood pressure (ASBP) of ≥130 mmHg and office systolic blood pressure (OSBP) ≥140 mmHg**	**1. Permanent atrial fibrillation or significant paroxysmal atrial fibrillation** **2. LV ejection fraction <50%** **3. Symptoms of heart failure NYHA Class II or greater** 4. Stroke or TIA within 12 months 5. Hypertrophic or restrictive cardiomyopathy or interventricular septal thickness ≥15 mm 6. Estimated Glomerular Filtration Rate (GFR) <30 ml/min/1.73m^2 7. Prior neurological events (stroke or TIA) within the past year 8. Known carotid artery disease 9. Dialysis 10. Known secondary cause of HTN 11. Average ambulatory or office systolic BP >195 mmHg 12. Cannot or is unwilling to provide informed consent

MODERATO II: Study Flow



*50 (39%) AMBP < 130 mmHg; 34 (27%) OBP < 140 mmHg; 15 (12%) withdrew consent; 5 (4%) EF < 50%, Other reasons (18%)

Patient Demographics:

No Significant Differences Between Groups

	Control (n=21)	BackBeat CNT (n=26)	p-value (Control vs BackBeat CNT)
Age	**74.9 ± 8.5**	**73.2± 9.0**	**0.518**
Gender	15 M / 6 F	15 M / 11F	0.375
Weight (kg)	88.5±16.0	86.1±17.5	0.63
LV EF (%)	58.4±4.9	59.8±6.3	0.414
Medical History			
Diabetes	9 (42.9%)	12 (46.2%)	0.999
Prior Atrial Fibrillation	6 (28.6%)	5 (19.2%)	0.505
Coronary Artery Disease	9 (42.9%)	10 (38.5%)	0.775
Stroke	0 (0%)	1 (3.8%)	0.999
Medications	**3.3±1.4**	**3.3±1.6**	**0.886**

Patient Demographics:

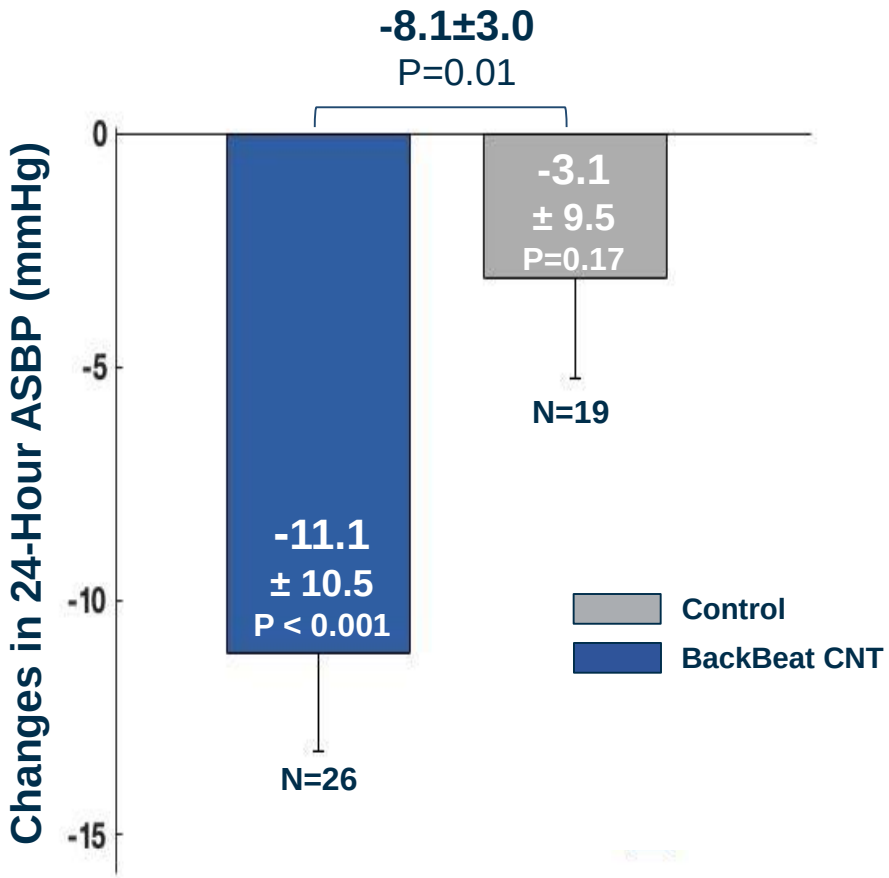
Blood Pressure Prior to Randomization Comparable Between Groups

	Control (n=21)	BackBeat CNT (n=26)	p-value Control vs BackBeat CNT
Isolated Systolic HTN	**71.4%**	**88.5%**	**0.263**
Screening			
24-Hr Ambulatory SBP	**142.8±11.8**	**139.3±10.3**	**0.287**
24-Hr Ambulatory DBP	75.2±9.8	73.8±5.0	0.533
AMB Heart Rate (24H)	64.7±12.5	64.1±8.02	0.857
Screening Office BP			
Office SBP	165.2±15.4	161.4±14.1	0.381
Office DBP	**82.4±13.0**	**82.6±8.49**	**0.955**
Office Heart Rate	63.7±16.6	64.4±8.3	0.860
Week 3 Run-In Phase			
24-Hr Ambulatory SBP	**136.3±12.5**	**136.3±9.2**	**0.995**
AMB DBP (24H)	72.6±6.7	74.0±6.9	0.478
AMB Heart Rate (24H)	68.4±8.5	69.6±9.5	0.670
Week 4 Run-In Phase			
Office SBP	154.4±15.5	153.1±15.8	0.781
Office DBP	**81.6±12.4**	**83.0±10.8**	**0.693**
Office Heart Rate	66.5±10.9	67.1±12.0	0.848

Primary Efficacy Endpoint (ITT)

24-Hour ASBP at 6 Months Post-Randomization vs. Week 3 Run-In

Primary Efficacy Endpoint met: **8.1 +/-3.0, (p=0.01)** Difference in BP Reduction at 6 Months



24-Hour ASBP (mmHg)		
	Week 3 Run-In	6 months Post-Randomization
BackBeat CNT	136.3	125.2
Control	136.3	132.0

Primary Safety Endpoint (ITT)

MACE through 6 Months Post-Randomization

Primary Safety Endpoint Met: **No Difference** in MACE at 6 Months

6 Month MACE*		
	BackBeat CNT	Control
n	26	21
MACE	0 (0.0%)	2 (9.5%)

Control MACE Patients

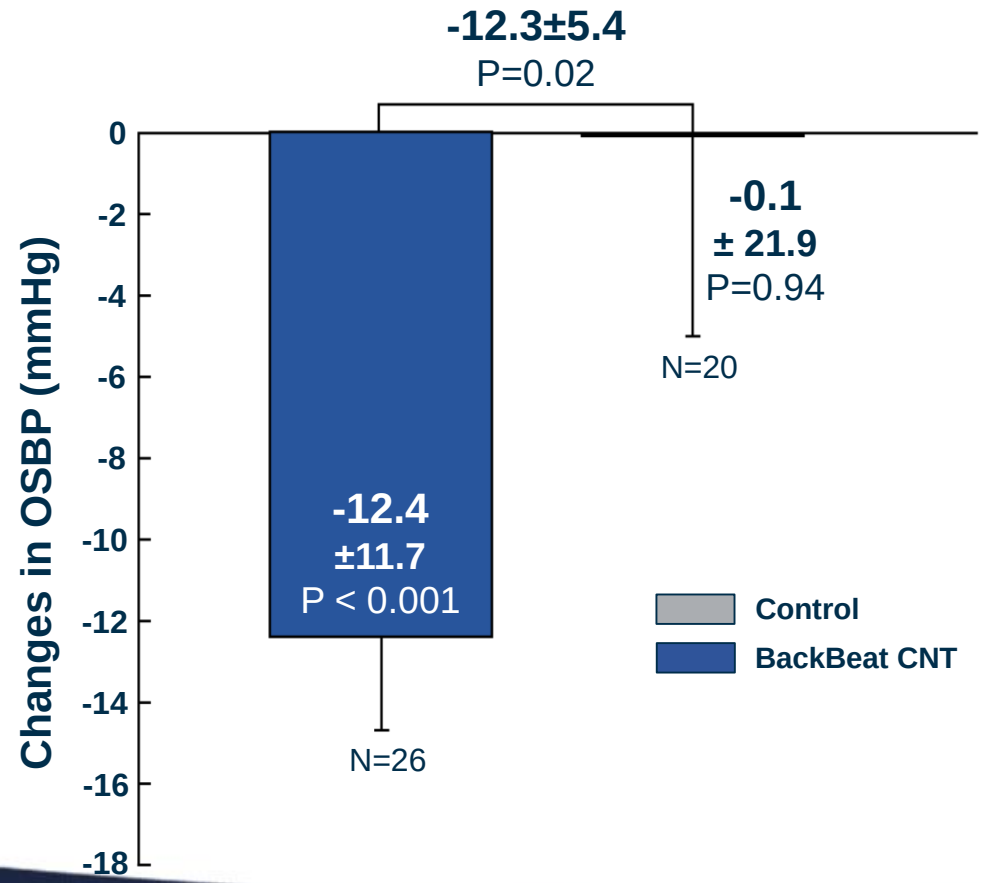
- Pt 1: Death as a result of disseminated adenocarcinoma.
  Angina pectoris leading to right coronary angioplasty and stenting
- Pt 2: Worsening atrial fibrillation requiring cardioversion

MACE: major cardiac adverse events [including death, heart failure, clinically significant arrhythmias (i.e., persistent or increased atrial fibrillation, serious ventricular arrhythmias), myocardial infarction, stroke and renal failure] in treatment versus control groups calculated per patient

Office Systolic Blood Pressure (OSBP)

6 Months Post-Randomization vs. Week 4 Run-In

Significant Difference Between BackBeat CNT and Control in OSBP Reduction:
-12.3 +/-5.4 (p=0.02)



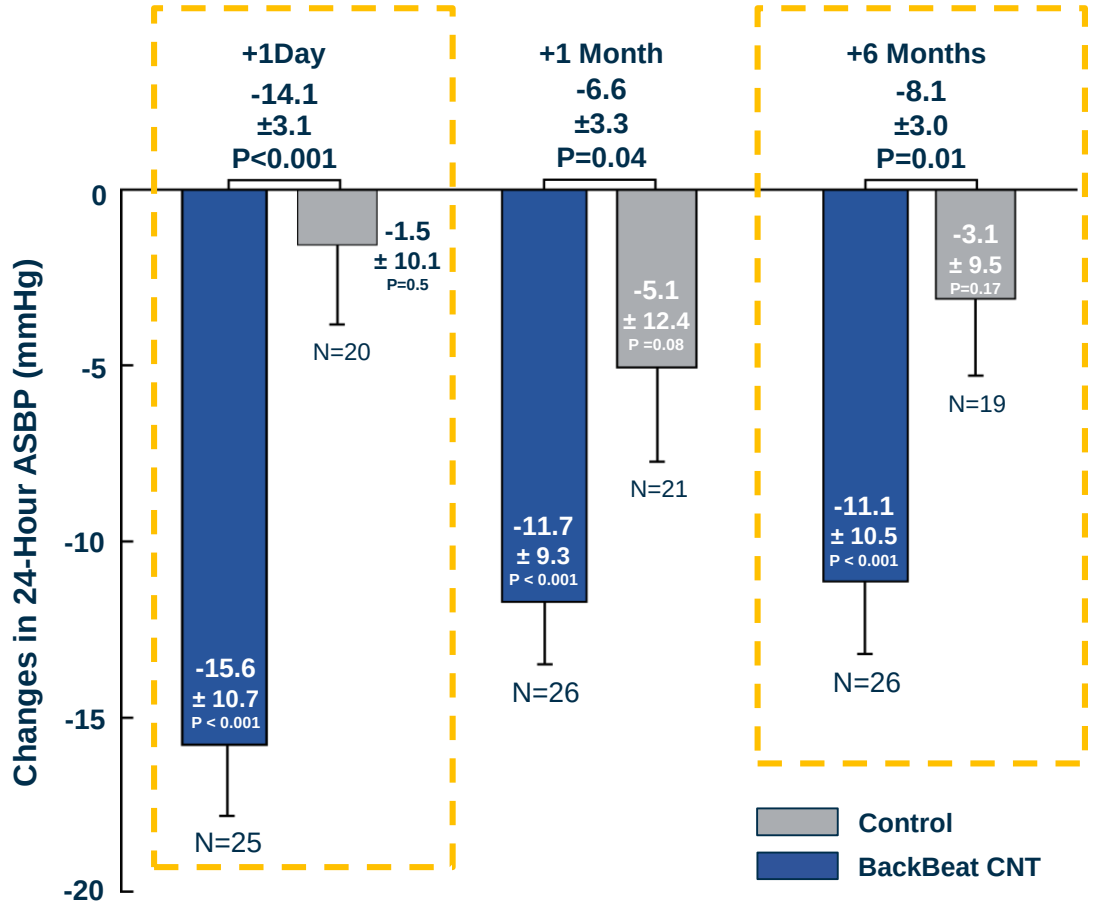
OSBP (mmHg)		
	Week 4 Run-In	6 months Post-Randomization
BackBeat CNT	153.1	140.8
Control	154.4	154.0

24-Hour ASBP

Post-Randomization vs. Week 3 Run-In

ASBP Reduction Observed at Day 1 Post-Randomization and

Maintained Through 6 Months



BackBeat CNT Responder Analysis

6 Months Post-Randomization vs. Week 3 Run-In

High Overall Response Rate to BackBeat CNT with 54% Experiencing >10 mmHg Reduction in ASBP Despite Lower Starting ASBP and High % ISH

	BackBeat CNT (n=26)	Control (n=19)
% with Increase in ASBP	15%	47%
% with Reduction in ASBP	**85%**	**53%**
% with >5 mmHg Reduction in ASBP	65%	42%
% with >10 mmHg Reduction in ASBP	**54%**	**21%**

Changes in Medications Throughout the Duration of the Study

Improvement in ASBP in the BackBeat CNT Group
Not Driven by Increase in Medications

	BackBeat CNT n=26		Control n=21	
Number of pts w/ changes in prescribed medications	**3 (11.5%)**		**7 (33.0%)**	
	Increase	**Decrease**	**Increase**	**Decrease**
	2 (7.7%)	**1 (3.8%)**	**5 (23.8%)**	**1 (4.8%)**

Increase = increase in dose or additional drug(s) added
Decrease = decrease in dose or drug(s) removed

Changes in Diastolic Blood Pressure, Heart Rate and Echo at 6 Months

No significant differences in Diastolic Blood Pressure, Heart Rate or Echo Parameters (EF, EDV, ESV) between BackBeat CNT and control groups

MODERATO II Conclusions

- **In patients with arterial hypertension and an indication for a pacemaker, Backbeat CNT demonstrated:**
  - Significant reduction in mean ASBP and OSBP
  - No difference in MACE
  - No differences in diastolic blood pressure (DBP), heart rate (HR) or echo parameters
  - High responder rate despite 88.5% of patients with isolated systolic hypertension (65% reduced > 5 mmHg; 54% reduced > 10 mmHg)

- ***Next steps:*** pivotal, double-blind study to test safety and efficacy