New heart failure RCT: Update on BeAT-HF in the US

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BAROSTIM THERAPY SUMMIT

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BAROSTIM THERAPY™

Phase III Beat-HF Study:
Randomized, Controlled Trial of *Baroreflex Activation Therapy (BAT)* in Patients with HFrEF Ineligible for CRT

Presentation Goals

- **Clinical Evidence for Development in Heart Failure**
- **Novel Trial Design**
- **Status of BEAT-HF Study**

Clinical Evidence Development in Heart Failure and Hypertension

Stage	Heart Failure	Hypertension
Clinical Rationale	Georgakopoulos et al, J Cardiac Fail 2012 Sabbah et al, Curr Cardiol Rep 2012 Halbach et al, Expert Rev Cardiovasc Ther 2014	Ram VS, *J Clin Hypertension* 2010 Briasoulis A, Bakris G, *Eurointervention* 2013 Borisenko et al, *J Hypertension* 2013
Preclinical	Zucker et al, Hypertension 2007 Sabbah et al, Circ Heart Failure 2011 Liao et al, J Cardiovasc Pharmacol 2014	Lohmeier et al, *Hypertension* 2004, 2005, 2009, 2011, 2012
First In Man	Brandt et al, Clin Res Cardiol 2010 Madershahian et al, Europace 2014 Gronda et al, Eur J HF 2014	Schmidli et al, *Vascular* 2007 Mohaupt et al, *Hypertension* 2007
CE Mark / Phase II	Abraham et al, ACC Featured Clinical Research, March 2015 Zile et al, HRS Late Breaking Clinical Trials, May 2015 Zile et al, ESC-HF Late Breaking Clinical Trials, May 2015 Abraham et al, J Am Coll Cardiol – HF 2015 Zile et al, Eur J Heart Failure 2015 Weaver et al, Seminars in Thoracic and CV Surgery 2016 **Prospective Subgroup Analysis** **Justification for Phase III**	Illig et al, *J Vasc Surgery* 2006 Sanchez et al, *Ann Vasc Surgery* 2009 Wustmann et al, *Hypertension* 2009 de Leeuw et al, *JACC* 2010 Heusser et al, *Hypertension* 2010 Bisognano et al, *JACC* 2011 Bakris et al, *JASH* 2012 Hoppe et al, *JASH* 2012 Alnima et al, *Hypertension* 2013 Wallbach et al, *Am J Nephrol* 2014 de Leeuw et al, *Hypertension* 2014 Wallbach et al, *Hypertension* 2016
US Phase III Pivotal	BeAT-HF Randomized, Controlled Clinical Trial in progress – Morbidity / Mortality; n = 480 – FDA Expedited Access Pathway for early approval	Barostim Hypertension Pivotal Trial – Unconditional IDE approval – RCT; n = 240

Phase II Randomized Study- BAT for HFrEF: Safety Endpoints

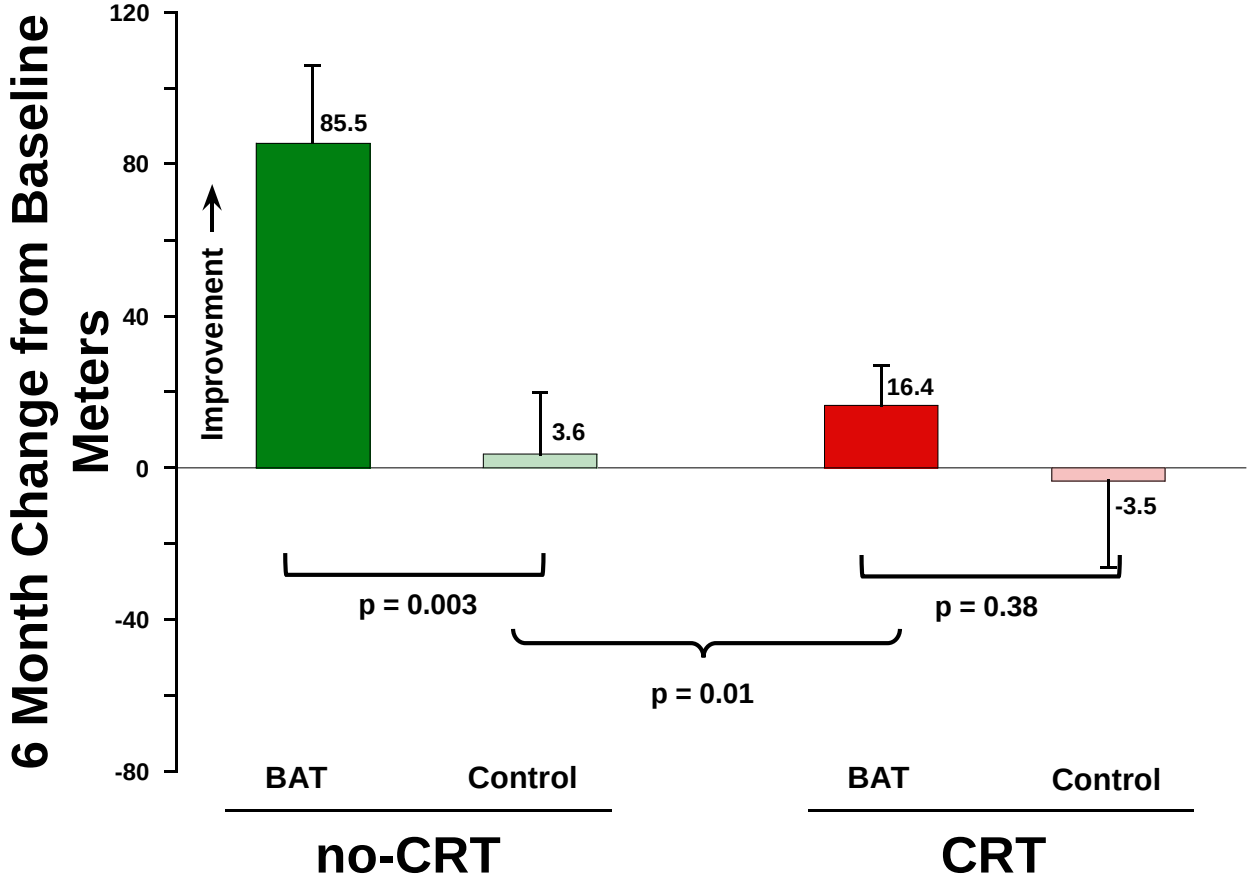
- **System- or Procedure-Related Major Adverse Neurological or Cardiovascular Events (MANCE) 6 months**
  - **97% Event-Free Rate**
  - **71 Subjects Implanted**
  - **2 Pocket hematomas (1 and 7 days from implant)**

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

- **BAT is compatible with co-existing cardiac rhythm management devices**

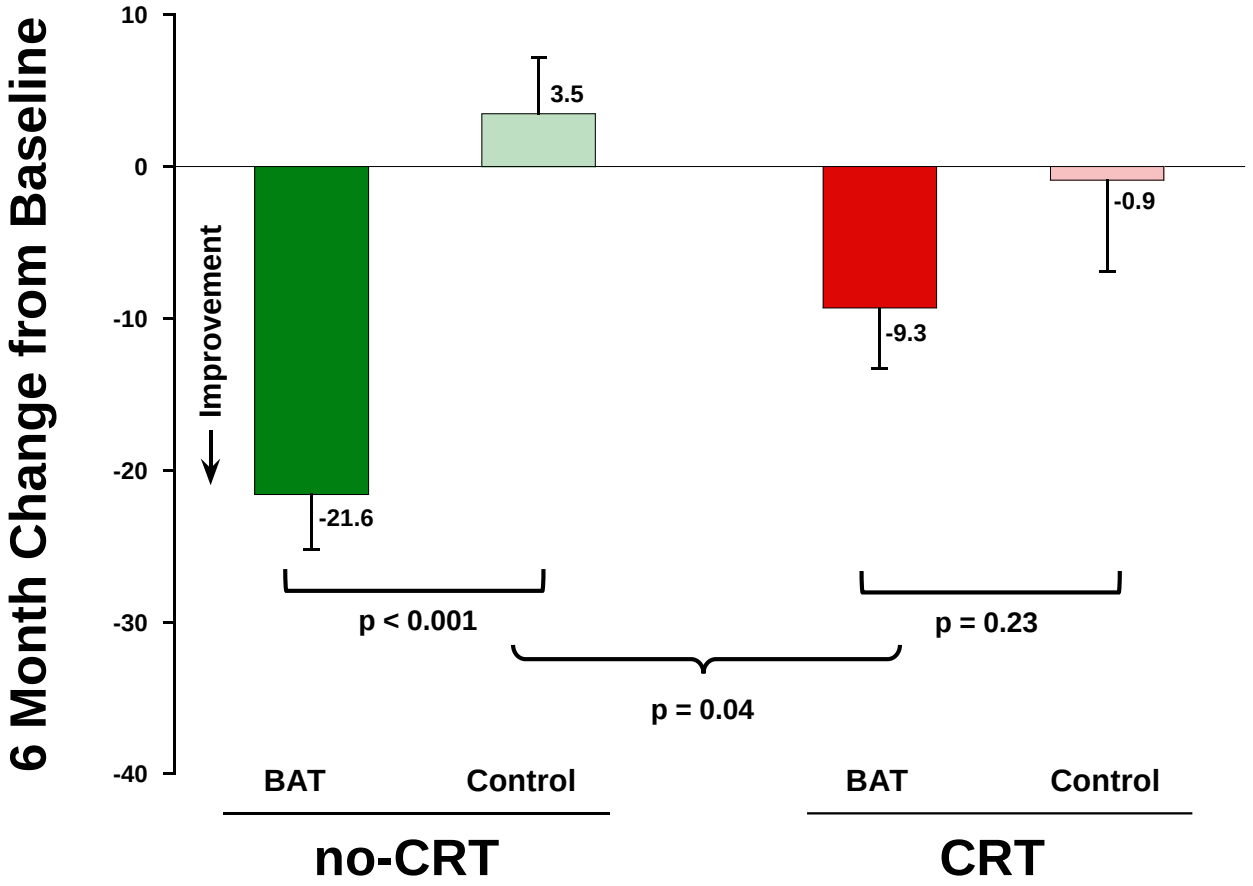
JACC-HF 3:487-96, 2015

CRT vs no-CRT: 6 Minute Hall Walk (MHW) Distance



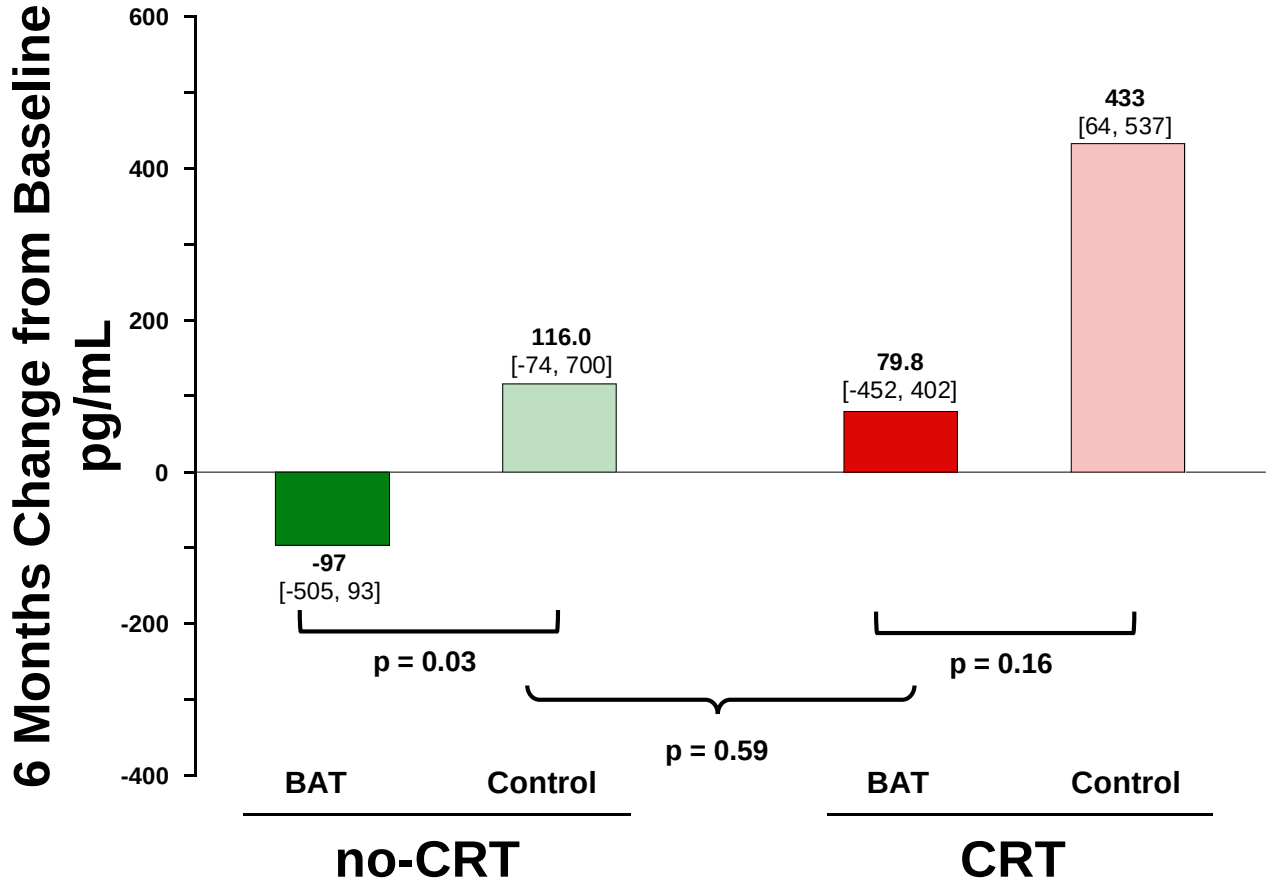
Euro J Heart Failure 17:1066-77, 2015

CRT vs no-CRT: Minnesota Living with Heart Failure (MLWHF) Score



Euro J Heart Failure 17:1066-77, 2015

CRT vs no-CRT: NT-proBNP



Euro J Heart Failure 17:1066-77, 2015

Twelve month (Durable) change from baseline no-CRT

Parameter	BAT + GDMT (N/Value)		GDMT (N/Value)		Repeated Measures Model	P-value
SBP (mmHg)	38	+4.2 ± 3.1	31	-4.0 ± 2.5	+6.5 ± 2.9	0.03
NTproBNP (pg/mL)	24	-102 (-1141, 134)	25	+152 (-314, 866)	-160	0.01
6MHW (meters)	33	+86.6 ± 20.8	28	+20.7 ± 24.4	+77 ± 24.7	0.003
QOL (points)	37	-13.6 ± 3.6	31	+1.2 ± 3.3	-17 ± 4.6	<0.001

Weaver et al, Seminars in Thoracic and Cardiovascular Surgery, 2016

Summary – Phase II Randomized Study- BAT for HFrEF

- Baroreflex Activation Therapy is safe in HFrEF patients.
- BAT significantly improves:
  - quality of life score
  - exercise capacity
  - NT-proBNP
  - possibly the burden of HF hospitalizations.
- Results were most pronounced in No-CRT patients.
- Results are durable (12 months F/U).

Phase III -- Beat-HF Study: Randomized, Controlled Trial of Baroreflex Activation Therapy (BAT) in Patients with HFrEF Ineligible for CRT

BeAT-HF™

Presentation Goals

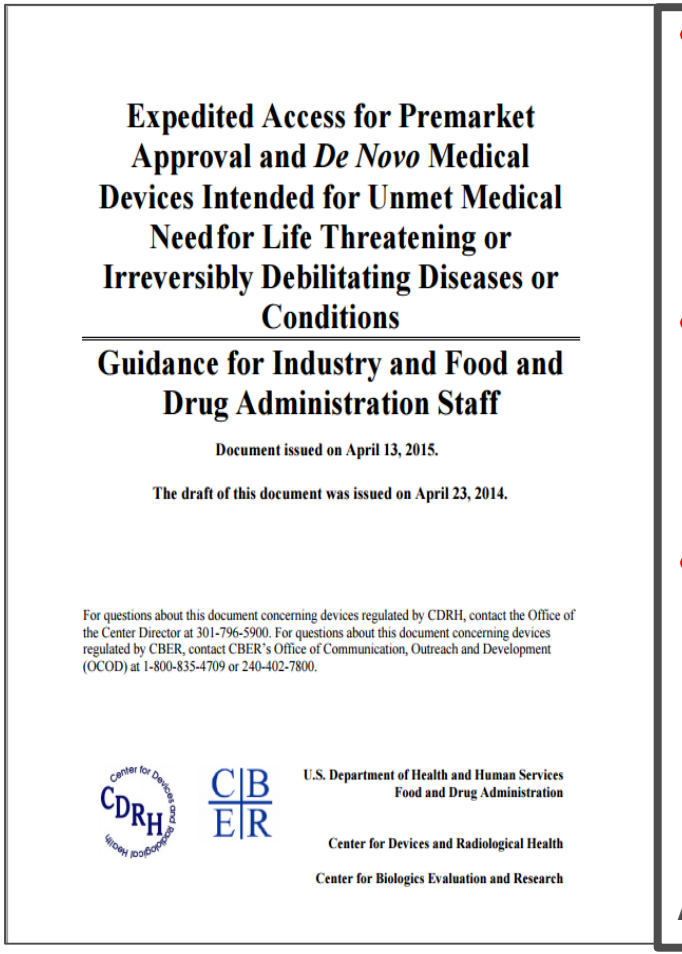
- Clinical Evidence for Development in Heart Failure
- Novel Trial Design
  - Expedited Access Pathway for Premarket Approval (EAP)
    - Phase I and II
    - Statistical Analysis (Frequentist and Bayesian)
  - Enrollment Criteria (Revision D)
- Status of BEAT-HF Study

Baroreflex Activation Therapy for Heart Failure (BeAT HF)

Develop valid scientific evidence for safety and effectiveness of Baroreflex Activation Therapy™ in heart failure with a reduced EF:

- **NYHA functional Class II-III**
- **Left ventricular ejection fraction ≤ 35%**
- **GDMT**
- **Excludes eligible for, or treatment with, CRT**

FDA Expedited Access Pathway (EAP)



Expedited Access for Premarket Approval and *De Novo* Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions

Guidance for Industry and Food and Drug Administration Staff

Document issued on April 13, 2015.

The draft of this document was issued on April 23, 2014.

For questions about this document concerning devices regulated by CDRH, contact the Office of the Center Director at 301-796-5900. For questions about this document concerning devices regulated by CBER, contact CBER's Office of Communication, Outreach and Development (OCOD) at 1-800-835-4709 or 240-402-7800.

U.S. Department of Health and Human Services
Food and Drug Administration

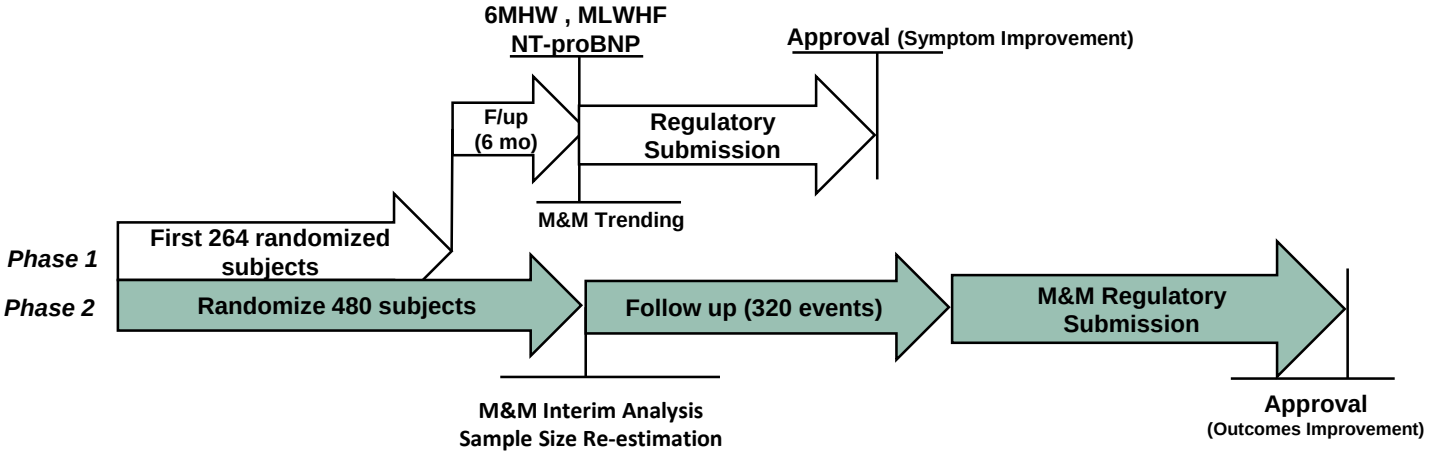
Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

- Established for therapies intended to treat a life-threatening or irreversibly debilitating disease and that demonstrate the potential to address unmet medical needs…
- "FDA may, as a basis for approval, rely on assessments of a device's effect on an intermediate or surrogate endpoint…"
- "Improvement according to an intermediate endpoint is generally of value to patients even if this does not lead to reduced morbidity or mortality, and could be considered as a basis for marketing approval by FDA."

April 23, 2014

Endpoint Strategy: EAP Approved Approach



	Sample Size	Analysis Timing	Clinical Evidence
Phase 1	N = 264 randomized subjects	Subjects (N=264) complete six months of follow-up (*enrollment continues*)	• Safety evaluation • NT-proBNP • Six minute hall walk • Minnesota living with heart failure (QOL) • Accumulated morbidity and mortality trend
Phase 2	N = 480 randomized subjects (N=264 subjects from Phase 1 + additional N=216 new subjects)	Sufficient morbidity and mortality data collected on all subjects (320 events collected)	• Full morbidity and mortality • Totality of evidence

Indication for Use Statements

Phase 1

Reduction of the symptoms of heart failure

patients who remain symptomatic (NYHA Functional Class III), LVEF ≤ 35%, despite GDMT, neither eligible for nor treated with CRT.

Phase 2

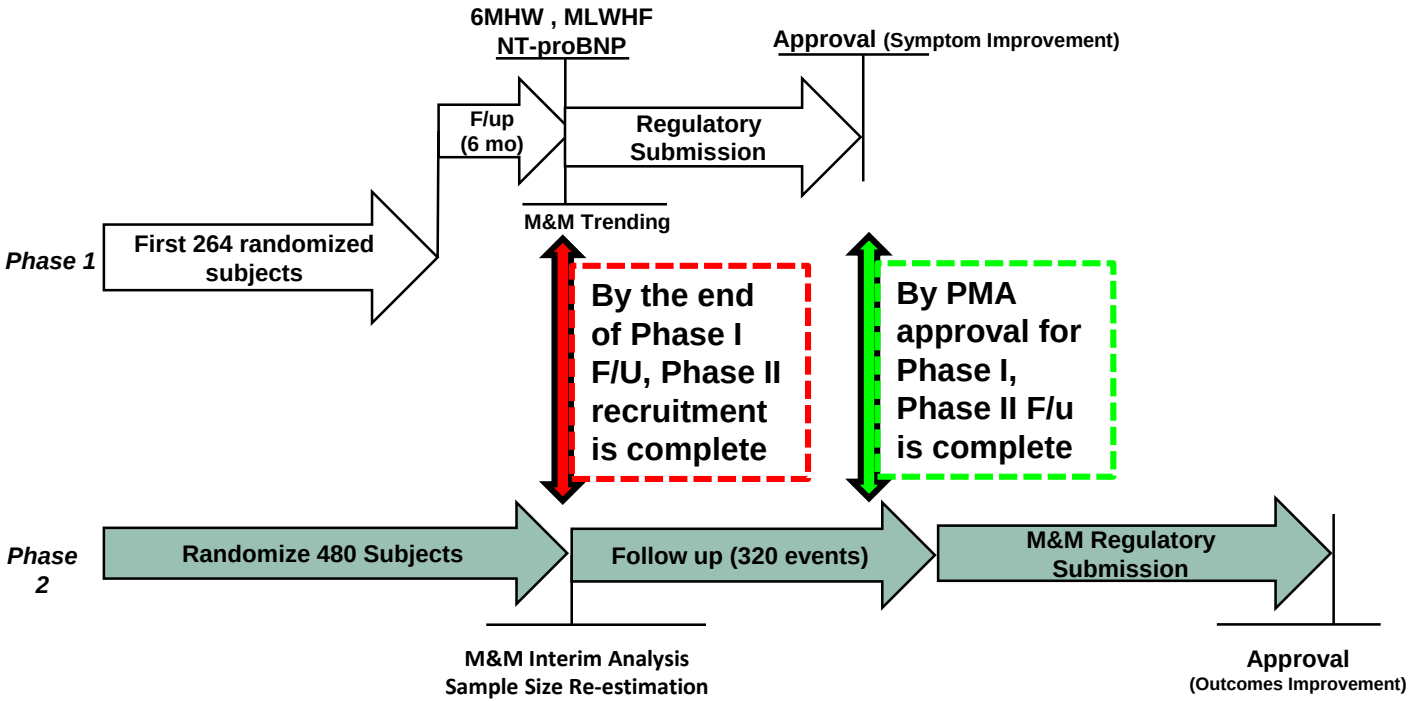
Indicated for treatment of patients with heart failure.
Heart failure is defined as:

NYHA functional Class III, LVEF ≤ 35% despite GDMT, including subjects neither eligible for nor treated with CRT.

Statistical Analysis Approaches

Frequentist	• **Analyses of Phase 1 Endpoints (Symptom-Limited Approval)** • **Final analysis Phase 2 Morbidity and Mortality Endpoint (M&M Approval)**
Bayesian	• **Predictive probability calculations** ***probability of a significant final M&M analysis conditional on M&M events up to end of Phase I, Phase I endpoints (longitudinal model), and baseline events before trial entry*** **- Part of Symptom-Limited Approval** **- Also used in sample size decisions**

Endpoint Strategy: EAP Approved Approach



Enrollment Criteria

- **Heart Failure**
  NYHA Class II or III;
  For Class II, NYHA Class III within 3 months prior to enrollment.

- **LVEF** ≤ 35%

- **6MHW** ≥ 150 m AND ≤ 400 m

- **Natriuretic Peptide**
  BNP≥100 or NT-proBNP≥400,
  BNP/NT-proBNP measured as outpatient when subject is clinically stable.
  If taking sacubitril/valsartan (i.e. Entresto), NT-proBNP must be used

OR

- **HF hospitalization** in past 12 months.
  HF hospitalization includes an overnight hospital or hospital-based observation unit or an emergency room.

Screening and Baseline Procedures

Procedure	Screen	Baseline	Comment
Subject Informed Consent	X		
Demographics/Medical History	X		
Physical Assessment	X	X	Pregnancy test when appropriate
Subject Medications	X	X	
Adverse Events	X	X	
LVEF	X*		Local
Six Minute Hall Walk	X*	X	
BNP or NT-proBNP	X*		Local
Core lab NT-proBNP		X	Shipped corelab
Serum eGFR	X		Local
Carotid Duplex Ultrasound†	X		Local, historical value accepted
AHA/ACC Stage	X		
NYHA Classification	X*	X	
Voice / Eating Tool		X	
Electrocardiography (ECG)	X		Local
MLHF and EQ-5D Questionnaires		X	Patient completed
CRM Arrhythmia Log		O	Previous 12 months

Follow-Up Procedures

Procedure	Months from Implant									
	.50	1	1.5	2	3	6	9	12	15-24*	After 24***
Physical Assessment	X	X	X	X	X	X	X	X	X	X
Subject Medications	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X
Six Minute Hall Walk						X		X		
Core lab NT-proBNP						X		X		
NYHA Classification						X		X	X**	
MLWHF Questionnaire						X		X	X**	
EQ-5D Questionnaire						X		X	X**	
CRM Arrhythmia Log						O		O	O**	O
Device Programming	X	X	X	X	X	X	X	X		

Phase III Beat-HF Study: Randomized, Controlled Trial of *Baroreflex Activation Therapy (BAT)* in Patients with HFrEF Ineligible for CRT

Presentation Goals

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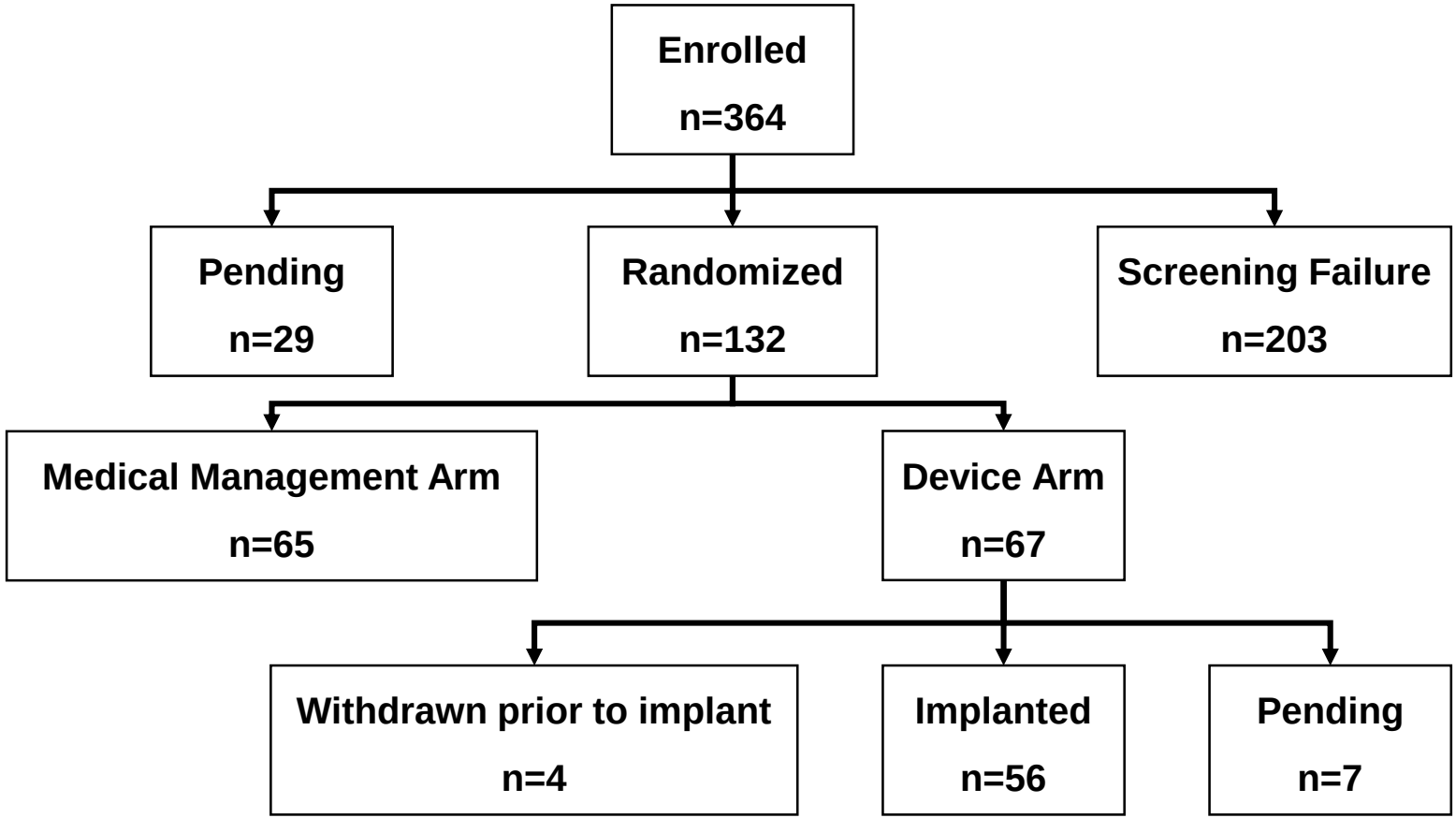
- Novel Trial Design
- Status of BEAT-HF Study

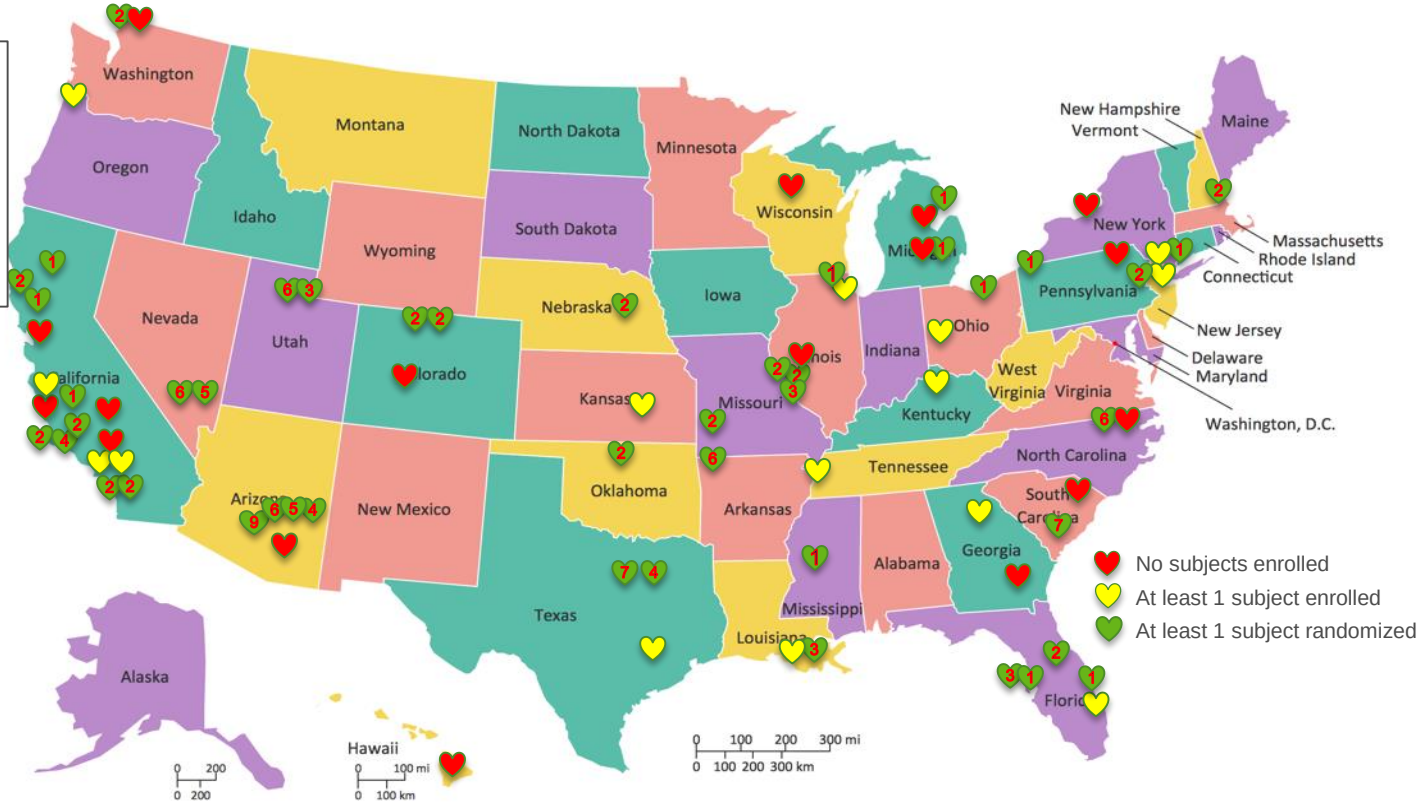
Patient Status Flow Chart



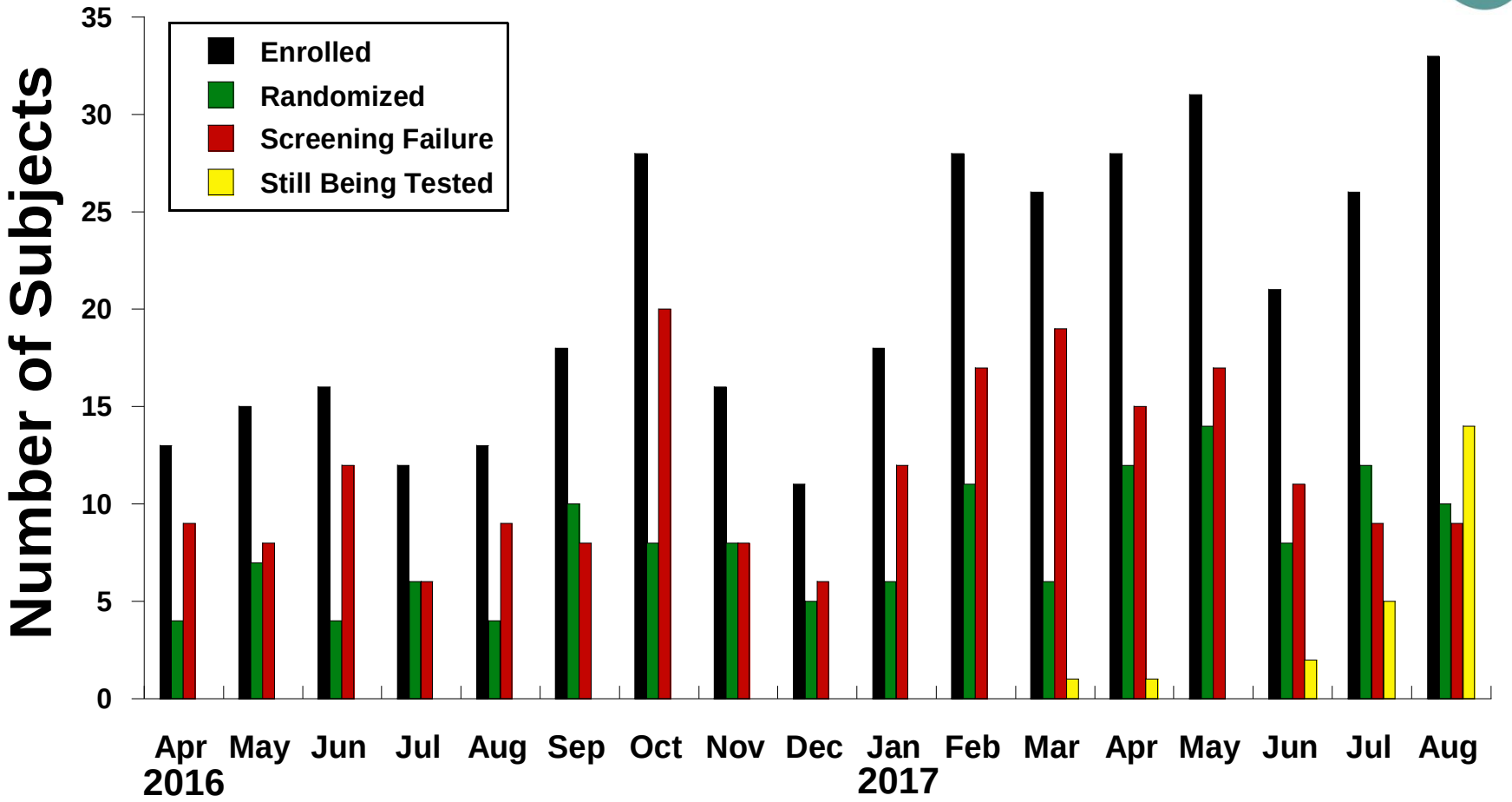
US Sites Status

Sept 22nd

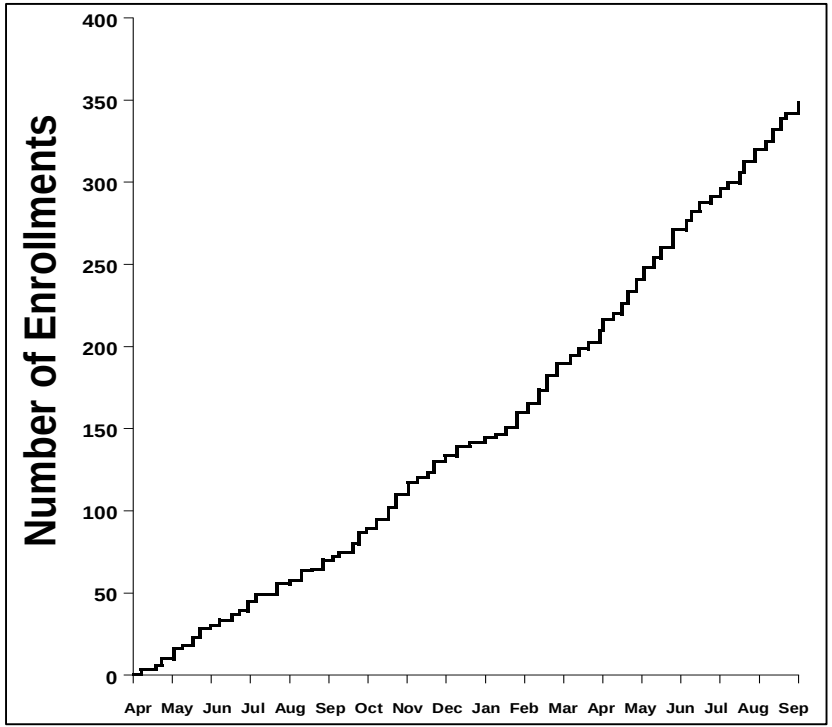
- 77 sites active
- 364 enrollments (60 sites)
- 132 randomizations (45 sites)

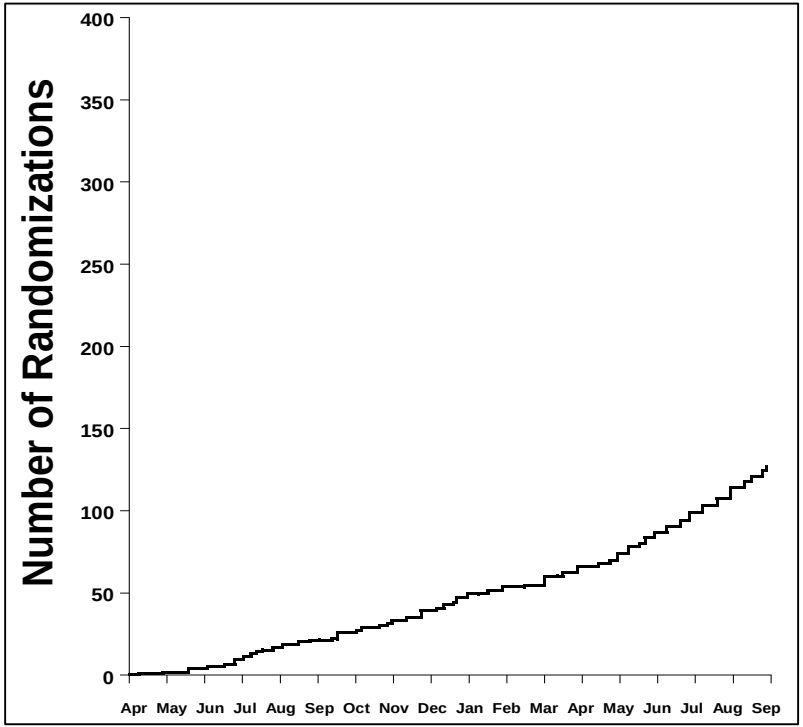


Patient Recruitment Status



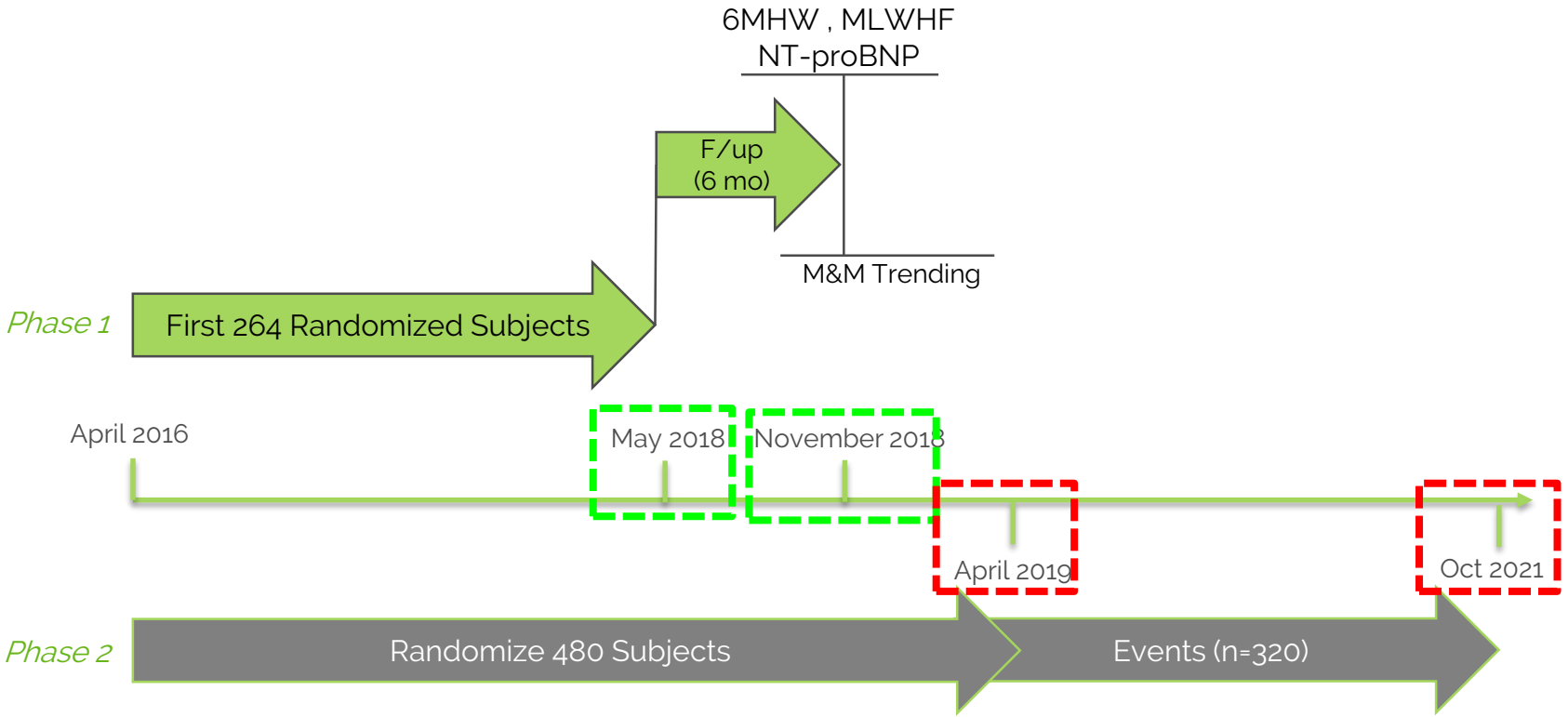
Enrollment / Randomization Data





	Number of Subjects	Total Years of Follow-Up	Number of Events	Events per Year
Primary Endpoint Event Rate	117	58.5	24	0.41

BeAT-HF Study Timeline



Baseline Demographics

Variable	N	Mean ± SD or N (%)	Range
Race			
Asian	132	5 (3.8%)	N/A
Black or African American	132	29 (22.0%)	N/A
White	132	85 (64.4%)	N/A
Other	132	9 (6.8%)	N/A
Unknown or Not Reported	132	4 (3.0%)	N/A
Female	132	22 (16.7%)	N/A
Age (years)	132	63 ± 12	32 - 93
Age>=65	132	59 (44.7%)	N/A
BMI (kg/m2)	132	29 ± 5	16 - 40
SBP (mmHg)	132	119 ± 16	75 - 179
DBP (mmHg)	132	74 ± 11	50 - 115
HR (bpm)	132	76 ± 12	54 - 109
LVEF (%)	132	26 ± 6	10 - 35

Baseline Characteristics

Variable	N	Mean ± SD or N (%)	Range
BNP (pg/mL) – median (IQR)	67	381 (182, 782)	102 - 4601
NT-proBNP (pg/mL) – median (IQR)	57	1465 (638, 3744)	221 - 20618
BNP>=400 or NT-proBNP>=1600 – median IQR)	124	57 (46.0%)	N/A
100<=BNP<400 or 400<=NT-proBNP<1600 AND HF Hosp	124	42 (33.9%)	N/A
NYHA: Class III	132	123 (93.2%)	N/A
6 Minute Walk (m)	132	289 ± 73	140 - 431
eGFR	132	61.8 ± 31.2	27 - 347
QRS Interval	132	111.3 ± 24.1	13 - 188
LBBB	132	4 (3.0%)	N/A
A Fib (screening ECG)	132	13 (9.8%)	N/A
A Fib (medical history)	132	48 (36.4%)	N/A
Paroxysmal A Fib (medical history)	132	36 (27.3%)	N/A
Permanent A Fib (medical history)	132	6 (4.5%)	N/A
Persistent A Fib (medical history)	132	6 (4.5%)	N/A
At Least One HF Hospitalization	132	85 (64.4%)	N/A
Number of HF Hospitalizations	132	1.1 ± 1.2	0 - 6

Baseline Medications

Variable	N	Mean ± SD or N (%)	Range
Number of Meds	132	4.4 ± 1.5	1 - 8
ACE-I/ARB Use	132	81 (61.4%)	N/A
Beta-Blocker Use	132	124 (93.9%)	N/A
Diuretic Use	132	122 (92.4%)	N/A
Ivabradine Use	132	4 (3.0%)	N/A
MRA Use	132	66 (50.0%)	N/A
Entresto Use	132	28 (21.2%)	N/A
Other HF Meds Use	132	54 (40.9%)	N/A
ICD	132	109 (82.6%)	N/A
PM	132	18 (13.6%)	N/A
Other cardiac device (e.g., CardioMEMS)	132	5 (3.8%)	N/A
ACE-I/ARB Percent of Max Daily Dose	75	25.7 ± 25.9	3 - 150
Beta-Blocker Percent of Max Daily Dose	121	32.5 ± 34.7	3 - 250
Diuretic Percent of Max Daily Dose	114	21.5 ± 25.4	1 - 150
MRA Percent of Max Daily Dose	60	57.9 ± 29.6	25 - 100

Take Home Conclusions

Baroreflex Activation Therapy (BAT) Provides:

- Novel approach to management of HFrEF
- Integrated Autonomic Nervous System Response
  - Inhibits Sympathetic Activity
  - Enhances Parasympathetic Activity
- Innovative and stepwise development program
  - Preclinical through Phase III
- EU/US Phase II robust evidence of safety and efficacy
- Europe: CE Mark indication
- US: Phase III ongoing Beat-HF Study under Expedited Access Pathway

The Medical University of South Carolina

Thank you.

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