Supplemental Material

Appendices Figure Legends

Appendix Figure 1: BeAT-HF Trial Design

Timeline for the development of the four cohorts of patients and the sequence of design decisions made in the BeAT-HF trial. The design decisions and statistical analysis plans were developed with interaction of the Food and Drug Administration (FDA) under the auspice of the Breakthrough Devices program. Sample sizes for each cohort are specified. Timeline dates are specified.

Appendix Figure 2: BeAT-HF Study Design: Pre-Market and Post-Market Phases

Heart failure hospitalization and CV mortality rates will be examined in the Post-Market Phase of BeAT-HF. Enrollment will include a total of 480 randomized patients. The Post-Market Phase is intended to expand the indication of use to reduction of heart failure hospitalizations and cardiovascular mortality. This Post-Market Phase will be achieved when 320 mortal and morbid events have occurred. A supplemental PMA will then be submitted to the FDA.

Appendix Figure 3: Disposition of Randomized Patients in Cohort A.

Consort diagrams for cohort A detail the number of patients randomized, the number assigned to BAT (Baroreflex activation therapy) vs control groups, the number of subjects that completed 6-month (M) follow-up, and the number of patients excluded from the 6 month follow-up efficacy analyses because of the number of death, left ventricular assist (LVAD) implants and heart transplants or because the patient withdrew from the study or missed the 6 month visit.

Appendix Figure 4: Effectiveness Endpoints for the Patients in Cohort A.

Three primary effectiveness endpoints were examined in the 239 (of the 271) patients (completers approach) in Cohort A. Two of the 3 endpoints were positive. BAT resulted in a more than 13-point improvement in QOL score compared with Control; 6MHW distance increased by 48 meters in the BAT group compared with Control; however, there were no statistically significant changes in NT-proBNP.

Appendices Tables

Appendix Table 1: Sequential Changes in Device Settings

	Amplitude (mA)		Frequency (pps)		Pulse Width (μs)	
Visit	**N**	**Mean ± SD**	**N**	**Mean ± SD**	**N**	**Mean ± SD**
Implant	120	1.4 ± 0.5	120	48.5 ± 16.3	120	143.9 ± 23.7
Month 0.5	105	3.5 ± 1.0	105	48.4 ± 15.6	105	145.5 ± 25.1
Month 1	103	5.0 ± 1.5	103	47.0 ± 14.2	103	135.2 ± 33.8
Month 1.5	98	6.3 ± 1.8	98	47.0 ± 14.0	98	130.1 ± 35.8
Month 2	102	7.1 ± 2.0	102	46.7 ± 13.7	102	122.4 ± 37.4
Month 3	100	7.7 ± 2.3	100	46.0 ± 13.8	100	114.5 ± 38.6
Month 6	120	8.3 ± 2.4	120	43.6 ± 12.2	120	109.1 ± 37.5

Appendix Table 2: Demographic Differences Cohort A < 1600 vs ≥ 1600 pg/ml

	<1600 N=162	>=1600 N=109	Total N=271	
	Mean ± SD or N (%)	Mean ± SD or N (%)	Mean ± SD or N (%)	P-value
Race				N/A
Asian	1.2%	2.8%	1.8%	0.394
Black or African American	18%	20%	19%	0.638
White	72%	72%	72%	1.000
Other/Unknown	8.6%	4.6%	7.0%	0.233
Female	19%	17%	18%	0.873
Age at Screening (years)	61 ± 11	66 ± 11	63 ± 12	0.002
Age>=65	41%	54%	46%	0.035
Body Mass Index (kg/m2)	32 ± 5	28 ± 5	30 ± 6	<.001
Systolic Blood Pressure (mmHg)	121 ± 16	120 ± 21	120 ± 18	0.598
Diastolic Blood Pressure (mmHg)	73 ± 10	73 ± 14	73 ± 12	0.877
Heart Rate (bpm)	75 ± 11	76 ± 11	76 ± 11	0.507
eGFR at Screening	64.4 ± 20.3	57.9 ± 33.2	61.8 ± 26.4	0.047
Core Lab NT-proBNP (pg/mL)*	695 (469, 956)	3289 (2401, 6006)	1138 (608, 2854)	<.001
NYHA: Class III	95%	95%	95%	1.000
6 Minute Walk (m)	299 ± 72	277 ± 73	290 ± 73	0.014
Quality Of Life	54 ± 24	51 ± 25	53 ± 24	0.246
LV Ejection Fraction (%)	27 ± 6	23 ± 7	26 ± 7	<.001
QRS Interval at Screening	108.9 ± 23.6	118.7 ± 24.0	112.9 ± 24.2	0.001
Left Bundle Branch Block	1.9%	5.5%	3.3%	0.164
A Fib (screening ECG)	10%	12%	11%	0.689
A Fib (medical history)	34%	44%	38%	0.099
Paroxysmal A Fib (medical history)	22%	32%	26%	0.091
Permanent A Fib (medical history)	4.3%	4.6%	4.4%	1.000
Persistent A Fib (medical history)	6.8%	6.4%	6.6%	1.000
At Least One HF Hospitalization	50%	58%	53%	0.217
Number of HF Hospitalizations	0.7 ± 1.0	1.1 ± 1.4	0.9 ± 1.2	0.023
Number of Meds	4.2 ± 1.4	4.1 ± 1.5	4.2 ± 1.4	0.777
ACE-I/ARB	57%	55%	56%	0.710
ARNI (Sacubitril Valsartan)	30%	18%	25%	0.033
ACE/ARB/ARNI	86%	73%	81%	0.011
Beta-Blocker	94%	94%	94%	1.000

	<1600 N=162	>=1600 N=109	Total N=271	
	Mean ± SD or N (%)	Mean ± SD or N (%)	Mean ± SD or N (%)	P-value
Digitalis	19%	17%	18%	N/A
Diuretic	86%	93%	89%	0.118
Ivabradine	1.9%	2.8%	2.2%	0.687
MRA	47%	34%	42%	0.044
ICD	79%	78%	79%	0.880
*Result reported as median (IQR), analysis used an ITT approach				

Appendix Table 3: Sensitivity of the NT-proBNP Cutoffs in Cohort A

NT-proBNP Cutoff Value		Initial Cohort			
		N=	**QOL**	**% Reduction NT-proBNP***	**6MHW**
<1000	BAT	57	-19.4	-8	47.6
	Control	61	-9.1	11	-3.4
	Difference		**-10.4**	**-19**	**58.6**
			0.007	*0.09*	*<0.001*
<1400	BAT	70	-21.3	-9.6	49
	Control	76	-10.2	1.5	-7.3
	Difference		**-11**	**-11.1**	**61**
			<0.001	*0.08*	*<0.001*
<1500	BAT	70	-21.3	-9.6	49
	Control	80	-10	1.5	-9.8
	Difference		**-11**	**-11.1**	**63**
			<0.001	*0.1*	*<0.001*
<1600	BAT	70	-21.3	-9.6	49
	Control	83	-9	5.5	-11.9
	Difference		**-12.1**	**-15.1**	**65.4**
			<0.001	*0.07*	*<0.001*
<1700	BAT	70	-21.3	-9.6	49
	Control	86	-9.4	7.5	-11.3
	Difference		**-11.7**	**-17.1**	**64.7**
			<0.001	*0.06*	*<0.001*
<1800	BAT	71	-21.9	-9.1	48.4
	Control	87	-8.8	5.5	-12.4
	Difference		**-12.6**	**-14.6**	**65.2**
			<0.001	*0.09*	*<0.001*
<2000	BAT	76	-21.6	-9.6	41.4
	Control	92	-8.5	3.5	-11.5
	Difference		**-12.4**	**-13.1**	**56.5**
			<0.001	*0.1*	*<0.001*

* Medians, difference between medians, non-parametric Wilcoxon Rank Sum test two-sided p-value

Appendix Table 4: Effects of BAT on Effectiveness Endpoints in Cohort D in Patients with Six Month Visits

NT-proBNP	Control		BAT		
Visit	**N**	**Median(IQR)**	**N**	**Median(IQR)**	**p-value**
Baseline*	125	784.0 (479.0, 1058.0)	120	687.5 (474.5, 996.5)	
6-Month^	123	771.0 (437.0, 1118.0)	120	570.5 (275.5, 965.5)	
Change from Baseline to 6 months[&]	123	-19.0 (-213.0, 260.0)	120	-127.5 (-279.0, 85.5)	0.02
% that ↓ ≥ 25% at 6 months c/w baseline (responder)	123	30.1%	120	40.8%	0.08
Abbreviations: *= 0 patients with value missing at baseline, ^ = 2 patients with value missing at 6 months, & = corrected for baseline values, analysis used a modified ITT completers approach.					
6MHW	**Control**		**BAT**		
Visit	**N**	**Mean (SEM)**	**N**	**Mean (SEM)**	**p-value**
Baseline*	125	295.2 (6.4)	120	317.4 (6.2)	
6-Month^	120	289.0 (9.8)	118	367.1 (7.8)	
Change from Baseline to 6 months[&]	120	-6.2 (1.8)	118	-20.7 (2.3)	<0.001
% that ↑ ≥ 25 m at 6 months c/w baseline (responder)	120	32.5%	118	67.8%	<0.001
Abbreviations: * = 0 patients with value missing at baseline, ^ = 7 patients with value missing at 6 months, & = corrected for baseline values. analysis used a modified ITT completers approach.					
MLWHF QOL	**Control**		**BAT**		
Visit	**N**	**Mean (SEM)**	**N**	**Mean (SEM)**	**p-value**
Baseline*	125	51.5 (2.2)	120	52.4 (2.2)	
6-Month^	125	45.2 (2.3)	120	31.7 (2.2)	
Change from Baseline to 6 months[&]	125	-7.9 (8.1)	120	48.6 (6.1)	<0.001
% that ↓ ≥ 12 points at 6 months c/w baseline (responder)	125	35.2%	120	60.0%	<0.001
Abbreviations: * = 0 patients with value missing at baseline, ^ = 0 patients with value missing at 6 months, & = corrected for baseline values, analysis used a modified ITT completers approach.					

Appendix Table 5: Baseline Demographic Characteristics and Treatment Cohort A

	Control N=132	BAT N=107	Total N=239	
	Mean ± SD or N (%)	Mean ± SD or N (%)	Mean ± SD or N (%)	P-value
Race				N/A
Asian	2.3%	1.9%	2.1%	1.000
Black or African American	19%	19%	19%	1.000
White	68%	75%	71%	0.315
Other/Unknown	11%	4.7%	7.9%	0.100
Female	19%	19%	19%	1.000
Age at Screening (years)	63 ± 11	62 ± 12	63 ± 11	0.354
Age>=65	46%	42%	44%	0.601
Body Mass Index (kg/m^2)	31 ± 6	30 ± 5	30 ± 6	0.063
Systolic Blood Pressure (mmHg)	120 ± 19	121 ± 17	120 ± 18	0.770
Diastolic Blood Pressure (mmHg)	72 ± 12	74 ± 11	73 ± 12	0.352
Heart Rate (bpm)	76 ± 11	76 ± 11	76 ± 11	0.769
eGFR at Screening	63.2 ± 32.4	63.3 ± 19.3	63.2 ± 27.2	0.965
Core Lab NT-proBNP (pg/mL)*	1105 (575, 2469)	940 (579, 2412)	1018 (579, 2424)	0.512
NYHA: Class III	95%	96%	95%	0.759
6 Minute Walk (m)	288 ± 69	304 ± 74	295 ± 71	0.085
Quality Of Life	50 ± 24	55 ± 24	52 ± 24	0.117
LV Ejection Fraction (%)	26 ± 7	26 ± 7	26 ± 7	0.631
QRS Interval at Screening	112.2 ± 26.0	110.2 ± 20.0	111.3 ± 23.5	0.523
Left Bundle Branch Block	4.5%	2.8%	3.8%	0.735
A Fib (screening ECG)	10%	9.3%	10%	1.000
A Fib (medical history)	40%	33%	37%	0.281
Paroxysmal A Fib	28%	25%	27%	0.662
Permanent A Fib	2.3%	3.7%	2.9%	0.703
Persistent A Fib	9.1%	2.8%	6.3%	0.060
At Least One HF Hospitalization	54%	49%	51%	0.438
Number of HF Hospitalizations	0.8 ± 0.9	0.8 ± 1.1	0.8 ± 1.0	0.752
Number of Meds	4.2 ± 1.4	3.9 ± 1.4	4.1 ± 1.4	0.105
ACE-I/ARB	61%	53%	57%	0.293
ARNI (Sacubitril/Valsartan)	25%	28%	26%	0.659

	Control N=132	BAT N=107	Total N=239	
	Mean ± SD or N (%)	Mean ± SD or N (%)	Mean ± SD or N (%)	P-value
ACE/ARB/ARNI	85%	80%	83%	0.392
Beta-Blocker	95%	94%	95%	0.771
Digitalis	17%	18%	17%	N/A
Diuretic	89%	85%	87%	0.332
Ivabradine	4.5%	0.0%	2.5%	0.034
MRA	45%	39%	42%	0.431
ICD	78%	79%	78%	1.000
*Results reported as median (IQR), analysis used a modified ITT completers approach.				

Appendix Table 6: Baseline Demographic Characteristics and Treatment Cohort B

	Control N=83	BAT N=70	Total N=153	
	Mean ± SD or N (%)	Mean ± SD or N (%)	Mean ± SD or N (%)	P-value
Race				N/A
Asian	1.2%	1.4%	1.3%	1.000
Black or African American	16%	20%	18%	0.528
White	71%	73%	72%	0.858
Other/Unknown	12%	5.7%	9.2%	0.261
Female	17%	20%	18%	0.677
Age at Screening (years)	63 ± 10	61 ± 12	62 ± 11	0.301
Age>=65	45%	39%	42%	0.512
Body Mass Index (kg/m^2)	32 ± 5	31 ± 5	32 ± 5	0.308
Systolic Blood Pressure (mmHg)	120 ± 16	121 ± 16	121 ± 16	0.516
Diastolic Blood Pressure (mmHg)	71 ± 11	75 ± 10	73 ± 10	0.039
Heart Rate (bpm)	75 ± 11	75 ± 10	75 ± 11	0.658
eGFR at Screening	64.3 ± 21.9	65.5 ± 19.0	64.8 ± 20.6	0.712
Core Lab NT-proBNP (pg/mL)*	716 (370, 1025)	700 (483, 923)	716 (431, 975)	0.635
NYHA: Class III	95%	96%	95%	1.000
6 Minute Walk (m)	286 ± 70	314 ± 73	299 ± 73	0.016
Quality Of Life	53 ± 23	54 ± 24	54 ± 23	0.934
LV Ejection Fraction (%)	28 ± 5	27 ± 7	27 ± 6	0.385
QRS Interval at Screening	110.9 ± 27.7	106.2 ± 18.5	108.8 ± 24.0	0.223
Left Bundle Branch Block	1.2%	2.9%	2.0%	0.593
A Fib (screening ECG)	10%	10%	10%	1.000
A Fib (medical history)	40%	26%	33%	0.085
Paroxysmal A Fib	27%	19%	23%	0.334
Permanent A Fib	2.4%	4.3%	3.3%	0.661
Persistent A Fib	10%	2.9%	6.5%	0.111
At Least One HF Hospitalization	53%	44%	49%	0.331
Number of HF Hospitalizations	0.7 ± 0.9	0.7 ± 1.1	0.7 ± 1.0	0.897
Number of Meds	4.2 ± 1.4	4.0 ± 1.3	4.1 ± 1.4	0.385
ACE-I/ARB	59%	56%	58%	0.744

	Control N=83	BAT N=70	Total N=153	
	Mean ± SD or N (%)	Mean ± SD or N (%)	Mean ± SD or N (%)	P-value
ARNI (Sacubitril/Valsartan)	28%	34%	31%	0.386
ACE/ARB/ARNI	86%	89%	87%	0.637
Beta-Blocker	95%	93%	94%	0.733
Digitalis	19%	17%	18%	N/A
Diuretic	86%	86%	86%	1.000
Ivabradine	3.6%	0.0%	2.0%	0.251
MRA	43%	50%	46%	0.422
ICD	80%	79%	79%	1.000
*Results reported as median (IQR), analysis used a modified ITT completers approach..				

Appendix Table 7: Baseline Demographic Characteristics and Treatment Cohort C

	Control N=42	BAT N=50	Total N=92	
	Mean ± SD or N (%)	Mean ± SD or N (%)	Mean ± SD or N (%)	P-value
Race				N/A
Asian	2.4%	4.0%	3.3%	1.000
Black or African American	14%	14%	14%	1.000
White	71%	82%	77%	0.319
Other/Unknown	12%	0.0%	5.4%	0.017
Female	29%	18%	23%	0.319
Age at Screening (years)	64 ± 10	64 ± 10	64 ± 10	0.943
Age>=65	48%	46%	47%	1.000
Body Mass Index (kg/m^2)	29 ± 5	30 ± 5	30 ± 5	0.333
Systolic Blood Pressure (mmHg)	125 ± 16	117 ± 16	121 ± 17	0.016
Diastolic Blood Pressure (mmHg)	75 ± 9	72 ± 10	73 ± 10	0.091
Heart Rate (bpm)	75 ± 10	74 ± 10	75 ± 10	0.571
eGFR at Screening	58.2 ± 13.8	60.9 ± 13.4	59.6 ± 13.6	0.350
Core Lab NT-proBNP (pg/mL)*	883 (613, 1062)	688 (457, 1137)	807 (492, 1078)	0.421
NYHA: Class III	93%	92%	92%	1.000
6 Minute Walk (m)	313 ± 74	322 ± 60	318 ± 67	0.529
Quality Of Life	48 ± 26	51 ± 25	49 ± 25	0.580
LV Ejection Fraction (%)	27 ± 5	27 ± 6	27 ± 6	0.740
QRS Interval at Screening	109.5 ± 23.4	110.1 ± 14.3	109.8 ± 18.9	0.876
Left Bundle Branch Block	0.0%	0.0%	0.0%	0.593
A Fib (screening ECG)	10%	2.0%	5.4%	0.174
A Fib (medical history)	50%	30%	39%	0.057
Paroxysmal A Fib	33%	22%	27%	0.248
Permanent A Fib	2.4%	0.0%	1.1%	0.457
Persistent A Fib	14%	6.0%	10%	0.292
At Least One HF Hospitalization	43%	36%	39%	0.527
Number of HF Hospitalizations	0.5 ± 0.6	0.5 ± 0.9	0.5 ± 0.7	0.858
Number of Meds	3.9 ± 1.1	3.7 ± 1.0	3.8 ± 1.1	0.598

	Control N=42	BAT N=50	Total N=92	
	Mean ± SD or N (%)	Mean ± SD or N (%)	Mean ± SD or N (%)	P-value
ACE-I/ARB	62%	56%	59%	0.672
ARNI (Sacubitril/Valsartan)	21%	34%	28%	0.246
ACE/ARB/ARNI	83%	90%	87%	0.370
Beta-Blocker	95%	98%	97%	0.590
Digitalis	10%	10%	10%	N/A
Diuretic	90%	80%	85%	0.245
Ivabradine	7.1%	4.0%	5.4%	0.657
MRA	36%	48%	42%	0.291
ICD	79%	72%	75%	0.629
*Results reported as median (IQR) , analysis used a modified ITT completers approach..				

Appendix Table 8: Baseline Demographic Characteristics and Treatment for All Randomized Subjects

	Control N=209	BAT N=199	Total N=408	
	Mean ± SD or N (%)	Mean ± SD or N (%)	Mean ± SD or N (%)	P-value
Race				N/A
Asian	2.4%	2.5%	2.5%	1.000
Black or African American	16%	19%	18%	0.516
White	71%	73%	72%	0.742
Other/Unknown	10%	5.5%	7.8%	0.100
Female	22%	19%	20%	0.461
Age at Screening (years)	63 ± 10	63 ± 12	63 ± 11	0.639
Age>=65	47%	44%	46%	0.620
Body Mass Index (kg/m^2)	30 ± 5	30 ± 5	30 ± 5	0.197
Systolic Blood Pressure (mmHg)	121 ± 18	118 ± 17	119 ± 18	0.112
Diastolic Blood Pressure (mmHg)	73 ± 11	72 ± 11	73 ± 11	0.375
Heart Rate (bpm)	75 ± 11	76 ± 11	75 ± 11	0.696
eGFR at Screening	60.7 ± 27.3	61.9 ± 18.0	61.3 ± 23.2	0.603
Core Lab NT-proBNP (pg/mL)*	1064 (631, 2394)	1048 (560, 2434)	1058 (594, 2424)	0.598
NYHA: Class III	94%	93%	94%	0.687
6 Minute Walk (m)	292 ± 71	298 ± 74	295 ± 72	0.358
Quality Of Life	51 ± 25	55 ± 25	53 ± 25	0.127
LV Ejection Fraction (%)	26 ± 7	25 ± 7	26 ± 7	0.196
QRS Interval at Screening	113.4 ± 26.3	112.8 ± 19.9	113.1 ± 23.3	0.785
Left Bundle Branch Block	3.8%	2.0%	2.9%	0.382
A Fib (screening ECG)	11%	11%	11%	1.000
A Fib (medical history)	44%	34%	39%	0.034
Paroxysmal A Fib	29%	23%	26%	0.178
Permanent A Fib	3.3%	4.5%	3.9%	0.615
Persistent A Fib	11%	5.0%	8.1%	0.030
At Least One HF Hospitalization	51%	46%	49%	0.277
Number of HF Hospitalizations	0.7 ± 0.9	0.8 ± 1.2	0.7 ± 1.1	0.535
Number of Meds	4.2 ± 1.4	4.0 ± 1.3	4.1 ± 1.4	0.259
ACE-I/ARB	60%	56%	58%	0.424

	Control N=209	BAT N=199	Total N=408	
	Mean ± SD or N (%)	Mean ± SD or N (%)	Mean ± SD or N (%)	P-value
ARNI (Sacubitril/Valsartan)	24%	29%	26%	0.311
ACE/ARB/ARNI	83%	84%	84%	0.894
Beta-Blocker	95%	95%	95%	1.000
Digitalis	15%	19%	17%	N/A
Diuretic	90%	87%	89%	0.277
Ivabradine	4.3%	2.0%	3.2%	0.261
MRA	43%	41%	42%	0.764
ICD	78%	78%	78%	1.000
*Results reported as median (IQR), analysis used an ITT approach..				

Appendix Table 9: System or Procedure Related MANCE Events in BAT Subjects in Cohort D

	BAT Implanted Subjects (N=125)		
Event	**Number of Events**	**Number of Subjects**	**Event Rate**
CV Death	0	0	0.0%
Stroke	1	1	0.8%
Cardiac Arrest	0	0	0.0%
Acute MI	0	0	0.0%
Acute Decompensated HF	1	1	0.8%
Hypertensive Crisis	0	0	0.0%
Severe Complication of HF Treatment	0	0	0.0%
Systemic and Pulmonary Thromboembolism	0	0	0.0%
Infection Requiring Explant	2	2	1.6%
Cranial Nerve Damage	0	0	0.0%
Non-Elective Major Restorative Procedures	0	0	0.0%
Total	**4**	**4**	**3.2%**

Appendix Table 10: Serious Related Adverse Events within 30 Days of Implant in Cohort D

	BAT Implanted Subjects (N=125)		
Event	**Number of Events**	**Number of Subjects**	**Event Rate**
Heart Failure, Acute Decompensated Heart Failure	1	1	0.8%
Other, specify, Dizziness	1	1	0.8%
Respiratory, Other Respiratory, Acute hypercarbic respiratory failure	1	1	0.8%
Respiratory, Pneumonia	1	1	0.8%
Stroke (CVA), Ischemic	1	1	0.8%
Surgical or Anesthetic Complications, Infection at Implant Site (No Explant)	1	1	0.8%
Surgical or Anesthetic Complications, Infection at Implant Site Requiring Explanation	2	2	1.6%
Surgical or Anesthetic Complications, Other Surgical Complication, prolonged intubation	1	1	0.8%
Total	**9**	**7**	**5.9%**

Appendix Table 11: Serious Related Adverse Events within Six Months of Implant in Cohort D

	BAT Implanted Subjects (N=125)		
Event	**Number of Events**	**Number of Subjects**	**Event Rate**
Heart Failure, Acute Decompensated Heart Failure	1	1	0.8%
Other, specify, Dizziness	1	1	0.8%
Respiratory, Other Respiratory, Acute hypercarbic respiratory failure	1	1	0.8%
Respiratory, Pneumonia	1	1	0.8%
Stroke (CVA), Ischemic	1	1	0.8%
Surgical or Anesthetic Complications, Infection at Implant Site (No Explant)	1	1	0.8%
Surgical or Anesthetic Complications, Infection at Implant Site Requiring Explanation	2	2	1.6%
Surgical or Anesthetic Complications, Other Surgical Complication, prolonged intubation	1	1	0.8%
Total	**9**	**7**	**5.9%**

Appendix Table 12: Subjects Adding New Class of Heart Failure Drugs by Six Months in Cohort D

	Control (N=125)	BAT (N=120)	Difference (95% CI)	P-value *
Any Medication Class	36 (28.8%)	21 (17.5%)	11.3% (0.8, 21.8)	0.049
ACE / ARB	5 (4.0%)	4 (3.3%)	0.7% (-4.0, 5.4)	1.000
ARNI (Sacubitril/Valsartan)	20 (16.0%)	5 (4.2%)	11.8% (4.5, 19.2)	0.003
Beta Blocker	4 (3.2%)	3 (2.5%)	0.7% (-3.5, 4.9)	1.000
Digitalis	3 (2.4%)	0 (0.0%)	2.4% (-0.3, 5.1)	0.247
Diuretic	3 (2.4%)	5 (4.2%)	-1.8% (-6.2, 2.7)	0.493
Ivabradine	1 (0.8%)	3 (2.5%)	-1.7% (-4.9, 1.5)	0.362
MRA	4 (3.2%)	3 (2.5%)	0.7% (-3.5, 4.9)	1.000
Other HF Meds	9 (7.2%)	2 (1.7%)	5.5% (0.5, 10.6)	0.060

* p-value from 2 sided Fisher's exact test

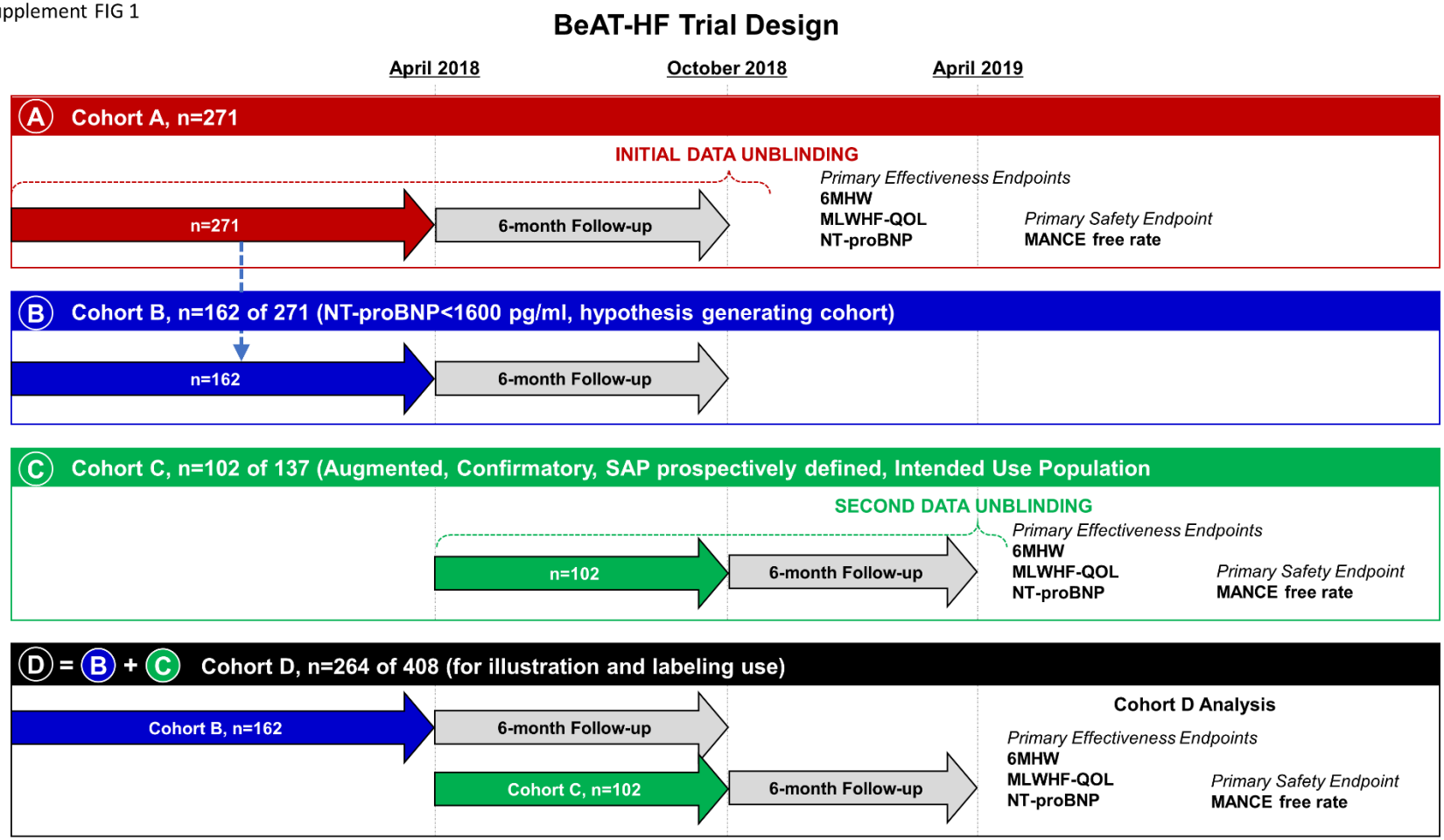
Appendix Table 13: Cardiovascular Serious Events

	BAT (N=125)		**Control (N=134)**			
Serious Adverse Event	**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**

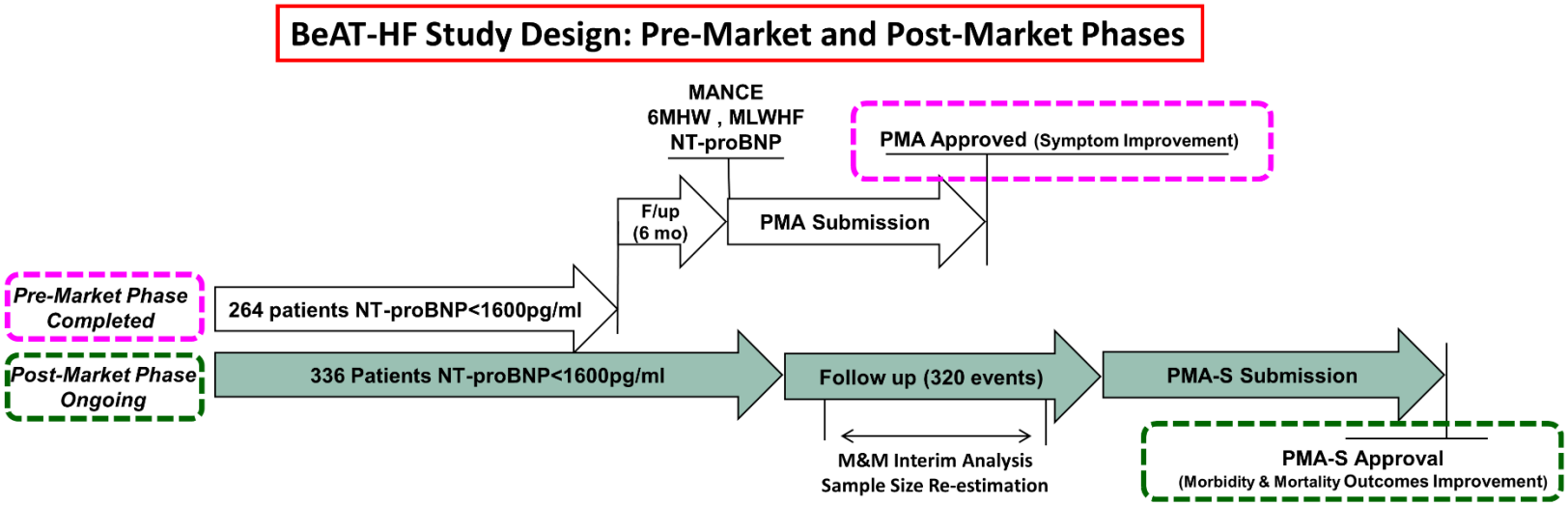
Appendix Table 14: Effects of BAT on Arterial Blood Pressure and Heart Rate in Cohort D

	Baseline		Implant		2-Week		Month 1		Month 3		Month 6		P-value (BL to M6)	
Value	**Control**	**BAT**	**Control**	**BAT**	**Control**	**BAT**	**Control**	**BAT**	**Control**	**BAT**	**Control**	**BAT**	**Control**	**BAT**
N	125	120	0	111	108	101	103	99	101	101	125	120		
SBP (mmHg)	122 ± 16	120 ± 16	N/A	120 ± 21	122 ± 17	121 ± 21	119 ± 15	121 ± 19	122 ± 16	122 ± 20	121 ± 18	120 ± 17	0.814	0.778
DBP (mmHg)	73 ± 10	74 ± 10	N/A	70 ± 15	74 ± 11	75 ± 12	72 ± 9	75 ± 11	71 ± 11	74 ± 13	74 ± 11	73 ± 11	0.767	0.580
Heart Rate (bpm)	75 ± 11	75 ± 10	N/A	71 ± 11	75 ± 11	76 ± 10	74 ± 12	77 ± 12	75 ± 12	76 ± 12	75 ± 14	75 ± 11	0.448	0.535
Pulse Pressure (mmHg)	49 ± 13	46 ± 13	N/A	50 ± 16	48 ± 12	47 ± 15	47 ± 11	46 ± 13	51 ± 13	48 ± 13	48 ± 14	47 ± 14	0.568	0.435

Supplement FIG 1

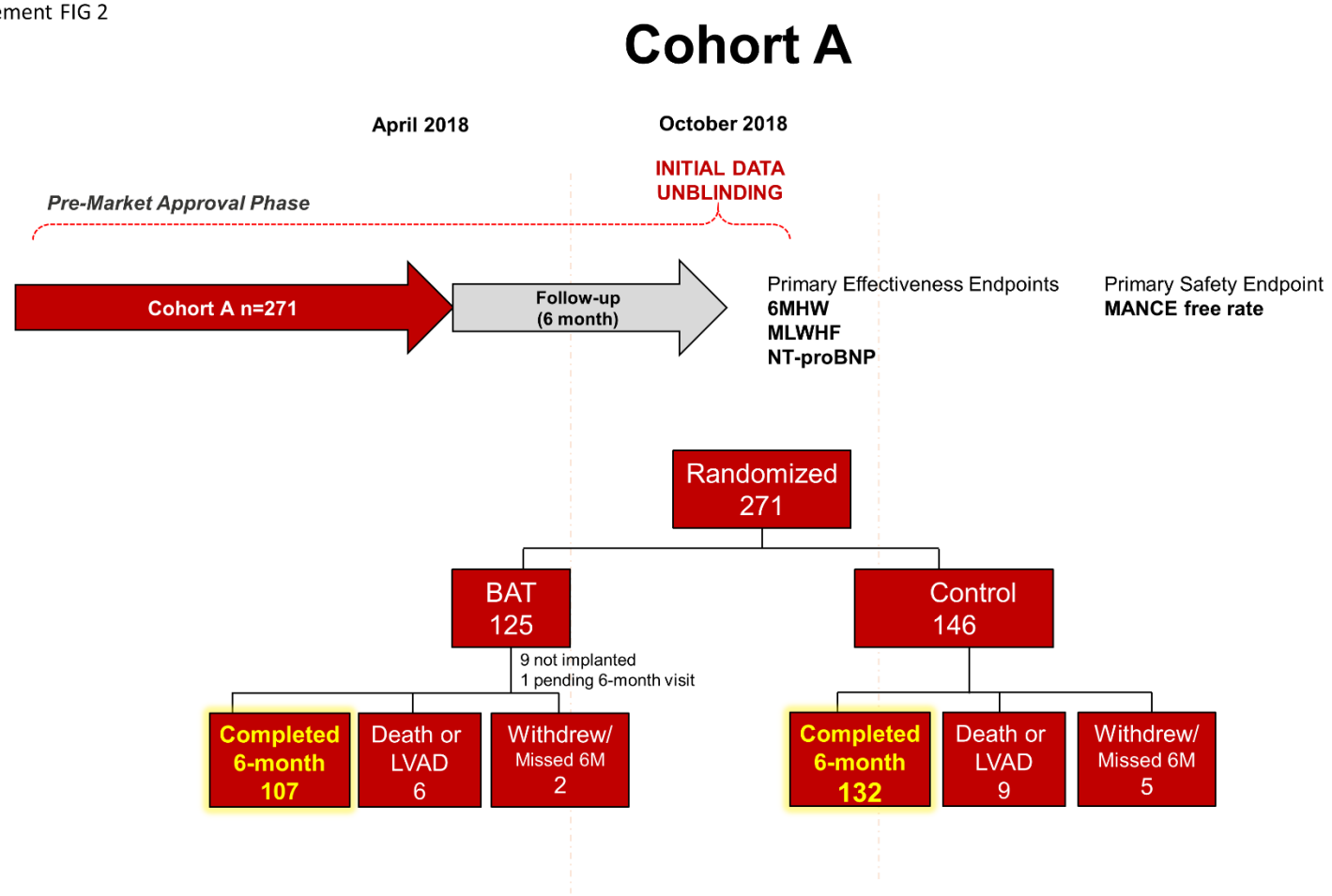


Supplement FIG 4



	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 Completion projected 2022	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

Supplement FIG 2



Supplement FIG 3