**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 (s)** | |
| --- | --- | --- | --- | --- | --- | --- |
| **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 |
| 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/m2) | 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 |
| 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/m2) | 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 |
| 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/m2) | 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 |
| 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/m2) | 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 |
| 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 |







