

# Autonomic Regulation Therapy for the Improvement of Left Ventricular Function and Heart Failure Symptoms: The ANTHEM-HF Study

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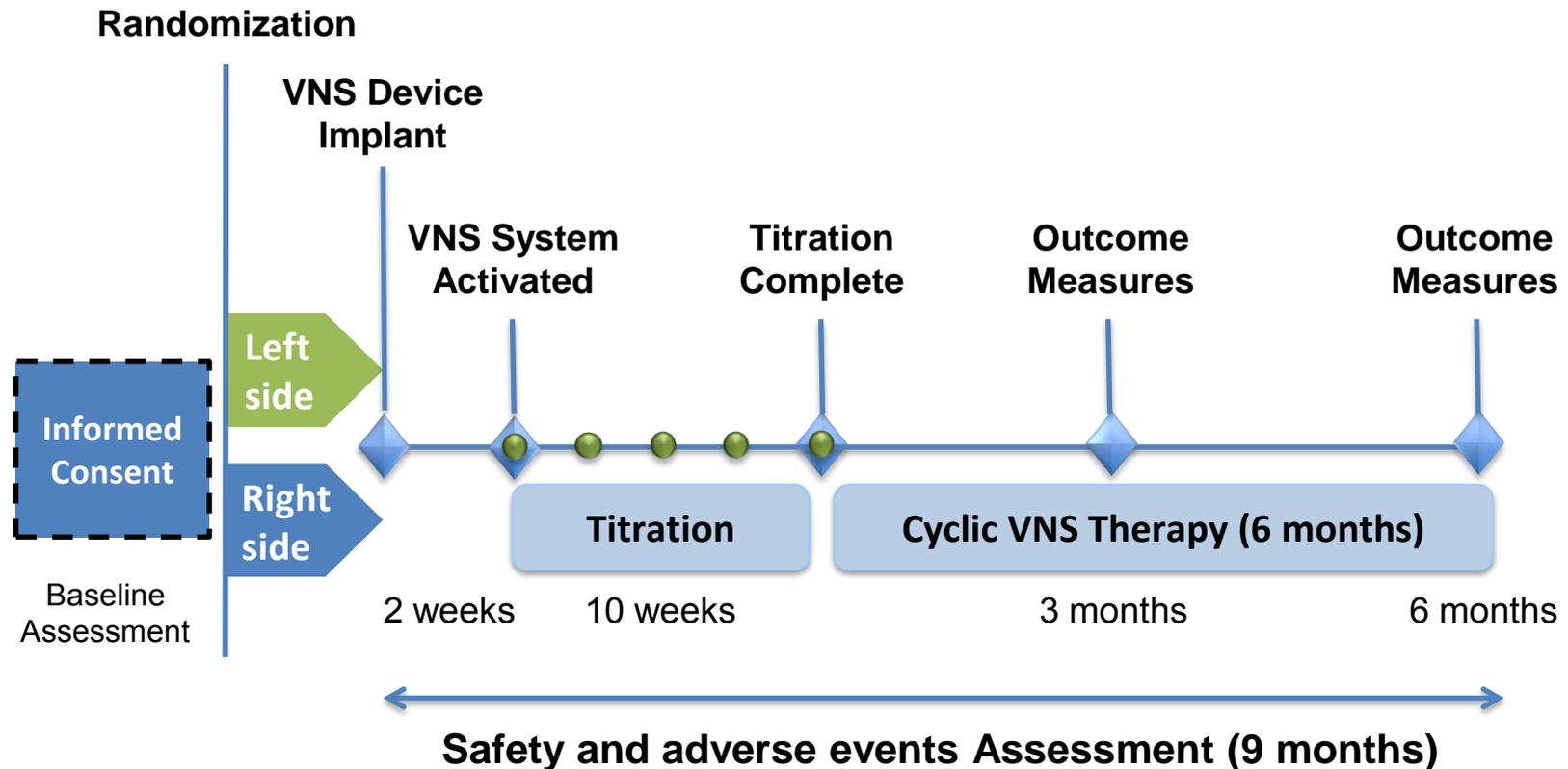
# Background & Objective

- Autonomic imbalance in HF is characterized by increased sympathetic activity and withdrawal of parasympathetic activity
- Autonomic imbalance is associated with progression of HF and worse outcomes
- Pre-clinical & clinical studies suggest electrical stimulation of the vagus nerve may restore autonomic balance
- Left-sided VNS, which could be combined with devices, has not been evaluated in HF patients, and the effects of left and right VNS have not been directly compared

**Objective:** Evaluate a new autonomic regulation therapy (ART) with left or right VNS, for the treatment of chronic symptomatic heart failure with reduced ejection fraction



# Study Design

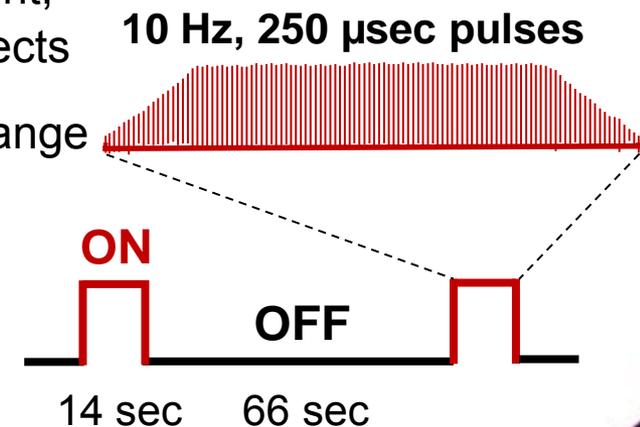
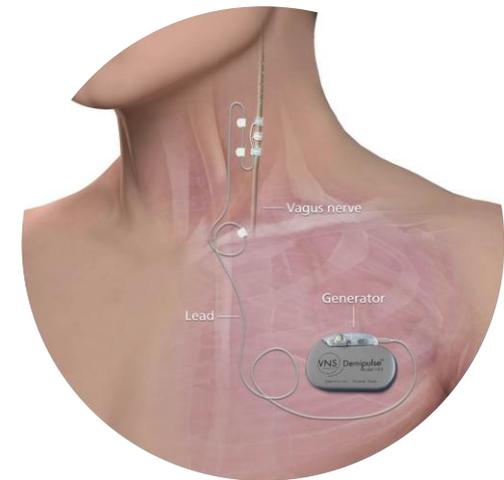


Patients (n=60) with heart failure with reduced ejection fraction (LVEF  $\leq$ 40%, NYHA Class II / III) on optimal medical therapy (100%  $\beta$ -blocker, 85% ACEI/ARB)



# Autonomic Regulation Therapy

- VNS Therapy System (Cyberonics, Houston, USA)
  - 100,000+ left-sided implants in epilepsy patients
  - Implanted on L or R vagus nerve by surgeon
  - Without RV sensing lead
- Chronic intermittent stimulation delivered to vagus
  - 10 Hz (natural frequency), 250  $\mu$ sec pulse width
  - VNS intensity titrated over 10 wks to max tolerable current; below the of threshold sensation, HR change or side effects
  - ECG monitored continuously to confirm no acute HR change
  - Side-effect threshold gradually increased over time
  - Average stimulation current:  $2.0 \pm 0.6$  mA



# Primary Safety Outcomes

	Left	Right	Pooled
<b>SAEs</b>	10	11	21
Related	1	0	1*
Unrelated	9	11	20†
<b>Most Common Related Non-Serious AEs</b>			
Voice alternation, hoarseness	11	8	19
Cough	6	7	13
Oropharyngeal pain	4	4	8
<b>Implant-Related Infections</b>			
System Malfunctions	0	0	0
Therapy Inhibition via Magnet	0	0	0

\* Post-surgical embolic stroke

† Including 1 unrelated HF death and 1 unrelated sudden death



# Primary and Secondary Efficacy Endpoints

	Baseline	6 Months	Change	p-value
<b>LVEF (%)</b>	32.4 ± 7.2	37.2 ± 10.4	<b>4.5</b>	0.0001
<b>LVESV (mL)</b>	108 ± 40	101 ± 46	<b>-4.1</b>	0.12
<b>LVEDD (mm)</b>	52 ± 8	49 ± 8	<b>-1.7</b>	<0.0025
<b>NYHA Class (I/II/III/IV)</b>	0 / 33 / 24 / 0	30 / 24 / 3 / 0		<0.0001
<b>6MWD (m)</b>	287 ± 66	346 ± 78	<b>56</b>	<0.0001
<b>MLHFQ score</b>	40 ± 1	21 ± 10	<b>-18</b>	<0.0001
<b>HRV (SDNN, ms)</b>	93 ± 43	111 ± 50	<b>17</b>	<0.01
<b>HR (bpm)</b>	78 ± 10	73 ± 11	<b>-3.9</b>	<0.005
<b>NT-proBNP, IQR (pg/mL)</b>	864 [322-1788]	888 [376-1729]	<b>24</b>	NS
<b>CRP, IQR (pg/dL)</b>	1.7 [0.9-6.0]	1.3 [0.6-2.9]	<b>-0.4</b>	<0.025



# Conclusions

- The ANTHEM-HF approach to ART (chronic, low-amplitude, natural frequency), on either the left or right side, was feasible and well-tolerated
- Safety assessment did not raise concerns
- Both left and right-sided ART were associated with improvements in cardiac function (LVEF, LVESD, HRV) and heart failure symptoms (NYHA class, 6-minute walk distance, quality of life)
- Further investigation of ART in a controlled clinical study is warranted

