# Endovascular Ablation of the Right Greater Splanchnic Nerve in Heart Failure with Preserved Ejection Fraction: Updated Results of the REBALANCE-HF Trial Roll-in Cohort

*Marat Fudim, MD, MHS on behalf of the REBALANCE-HF Steering Committee*
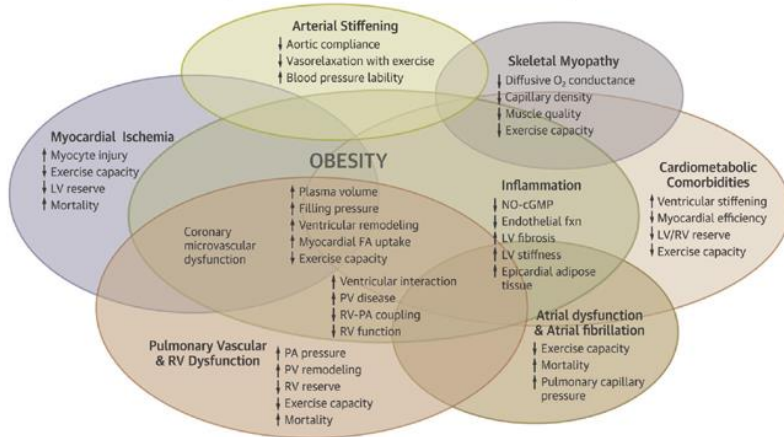
# Disclosure of Relevant Financial Relationships

-Research contracts: Doris Duke

-Consulting/Royalties/Owner/Stockholder of a healthcare company: Axon Therapies
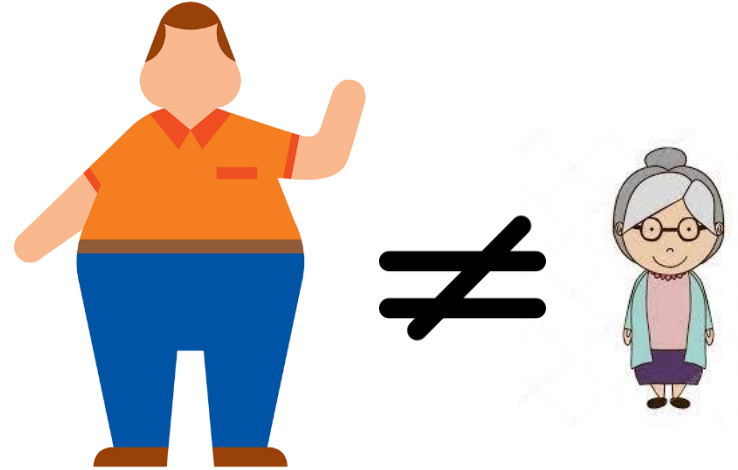
Faculty disclosure information can be found on the app
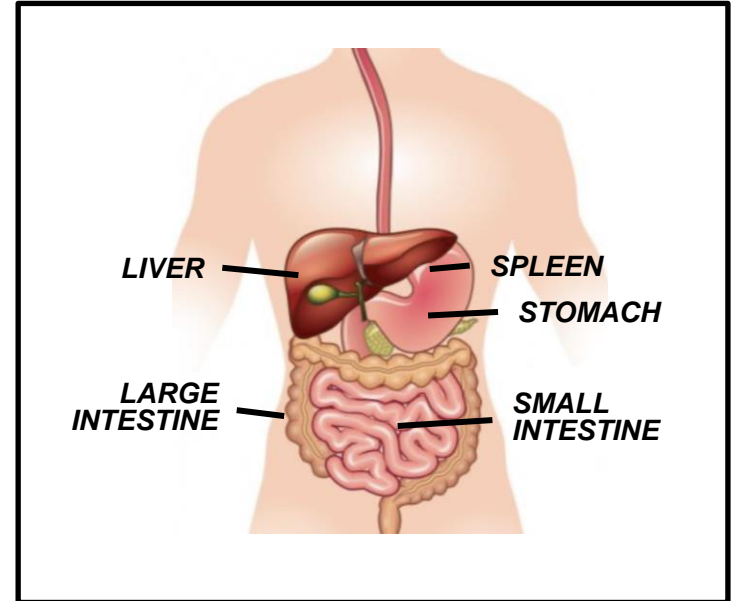
# HFpEF Phenotypes



Obokata, M. et al. J Am Coll Cardiol Img. 2020;13(1):245-57.

# The Splanchnic Bed is the Body's Main Reservoir for Volume

## SPLANCHNIC CIRCULATION
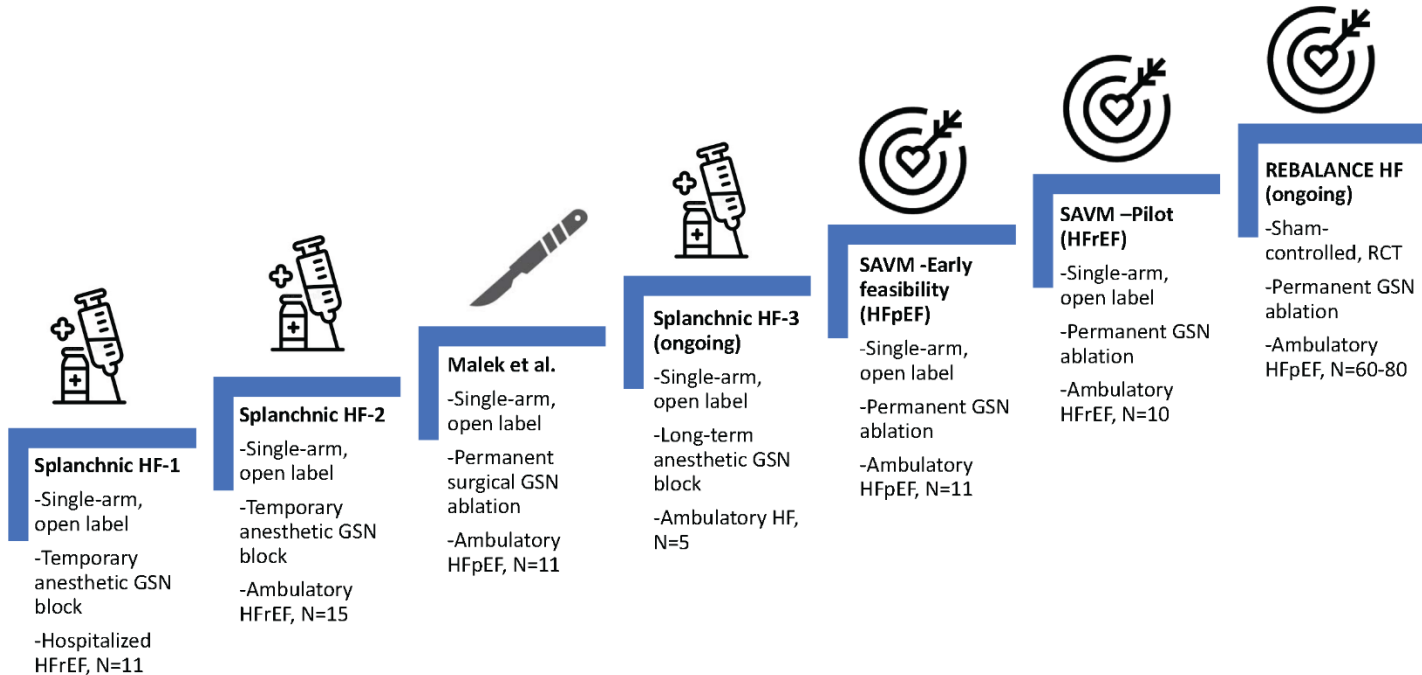
▸ The **body's main blood volume reservoir** or "buffer"

▸ **25% of all blood in the body** is in the **liver** and **spleen** alone

▸ **Activation of the sympathetic nervous system (SNS)** recruits blood from the splanchnic bed into central circulating volume

LIVER

SPLEEN

STOMACH

LARGE INTESTINE

SMALL INTESTINE

*Fudim et al. JACC 2022*
*Birch et al. J Vasc Res 2008*

CRF
THT

# Splanchnic Nerve Modulation: Scaling Up



**Splanchnic HF-1**

-Single-arm, open label

-Temporary anesthetic GSN block

-Hospitalized HFrEF, N=11

**Splanchnic HF-2**

-Single-arm, open label

-Temporary anesthetic GSN block

-Ambulatory HFrEF, N=15

**Malek et al.**

-Single-arm, open label

-Permanent surgical GSN ablation

-Ambulatory HFpEF, N=11

**Splanchnic HF-3 (ongoing)**

-Single-arm, open label

-Long-term anesthetic GSN block

-Ambulatory HF, N=5

**SAVM -Early feasibility (HFpEF)**

-Single-arm, open label

-Permanent GSN ablation

-Ambulatory HFpEF, N=11

**SAVM –Pilot (HFrEF)**

-Single-arm, open label

-Permanent GSN ablation

-Ambulatory HFrEF, N=10

**REBALANCE HF (ongoing)**

-Sham-controlled, RCT

-Permanent GSN ablation

-Ambulatory HFpEF, N=60-80

# REBALANCE-HF: Study Design

**<u>Largest Feasibility Study in HFpEF</u>**

- ➤ **Goal #1: Establish Safety**
- ➤ **Goal #2: Enroll a Broad Spectrum of HFpEF**
- ➤ **Goal #3: Identify Responder and Non-Responders in Order to Help Design the Pivotal Trial**

- ✓ **Open Label Run-in → Presented here**

- ✓ **Then RCT – Sham-controlled**

- ✓ **Hemodynamic Endpoint: Baseline to 1 Month Wedge Pressure (legs up and exercise)**

# REBALANCE-HF: Inclusion Criteria

| | | |
|---|---|---|
| **Chronic Heart Failure defined as:** | Symptoms of HF requiring current treatment with diuretics for > 30 days, AND | |
| | NYHA class II through ambulatory NYHA class IV symptoms, AND | |
| | At least one of the following: | • > 1 HF hospital admission (with HF as the primary, or secondary diagnosis) |
| | | • Treatment with diuresis for HF in a healthcare facility within past 12 months |
| | | • NT-pro BNP value > 150 pg/ml in normal sinus rhythm, > 450 pg/ml in atrial fibrillation within the past 6 months |
| | | • BNP value > 50 pg/ml in normal sinus rhythm, > 150 pg/ml in atrial fibrillation within the past 6 months |

▸ **LVEF ≥ 50% (site-determined) in the past 3 months**

▸ **Ongoing stable GDMT HF management and management of potential comorbidities**

# Splanchnic Ablation for Volume Management (SAVM)
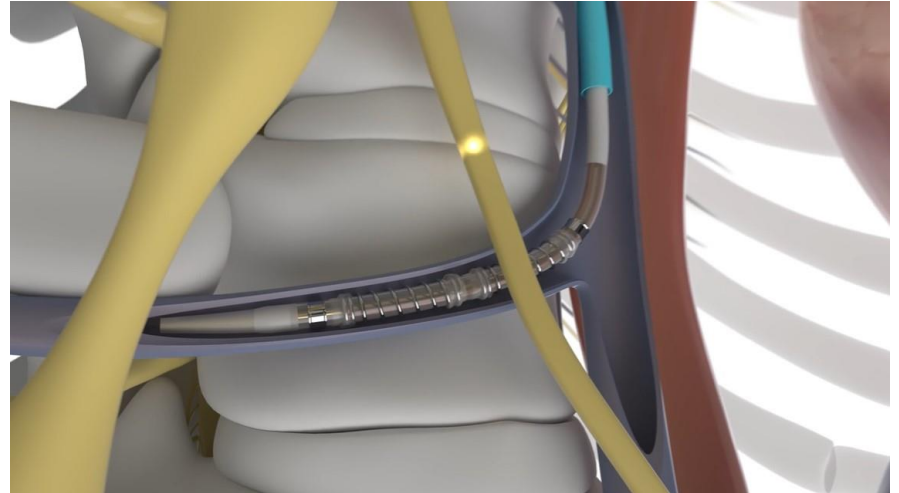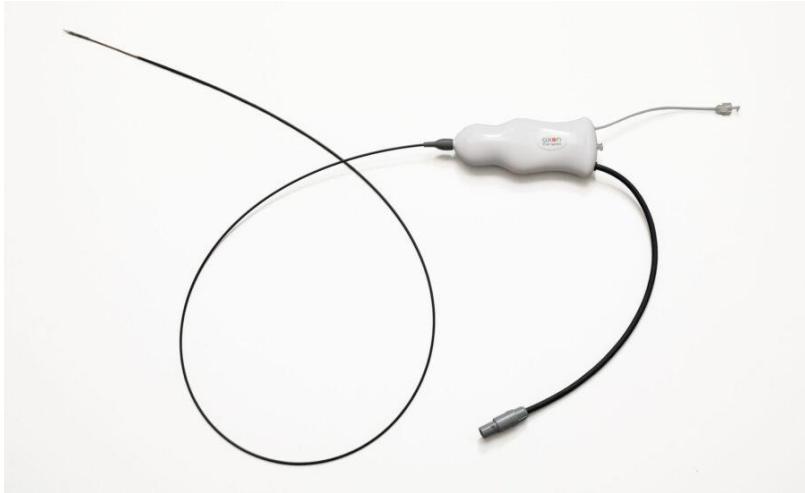
# Baseline Demographics and Clinical Characteristics

| Characteristics | REBALANCE-HF Roll-in Cohort (N=26) |
|---|---|
| Age, yrs | 71.1 (65.9, 78.6) |
| Female | 73% |
| Race Black/White/Other | Black: 12%, White: 85%, Other: 4% |
| Comorbidities | |
|    History of atrial fibrillation/atrial flutter | 54% |
|    Diabetes | 31% |
|    Coronary artery disease | 38% |
| HF or HTN Medication | |
|    Loop diuretic | 81% |
|    ACE or ARB | 38% |
|    Beta-blocker | 69% |
|    Mineralocorticoid receptor antagonist | 69% |
|    Sacubitril/valsartan | 8% |
|    SGLT2 inhibitors | 38% |
| Biometrics | |
|    Body mass index, kg/m2 | 36.3 (26.9, 41.5) |
|    NYHA Class II/III/IV | II: 7.7%, III%: 88.5%, IV: 3.8% |
|    Systolic blood pressure, mmHg | 123.5 (114.0, 136.0) |
|    Estimated glomerular filtration rate, mL/min/1.73 m2 | 48.0 (43.0, 67.0) |
|    NT-proBNP, pg/mL | 265.5 (162.0, 745.0) |
| Echocardiography | |
|    LVEF (core lab measured), % | 59.0 (55.0, 63.0) |
|    E/e' (septal) (unitless) | 13.1 (9.5, 21.8) |

# Safety Profile

| Variable[†] | REBALANCE-HF Roll-in Cohort (N=26) |
|---|---|
| **Primary Safety Outcomes at 1-month – no. of events (% of patients)** | |
| Device or procedure related SAE | 1 (3.8%) |
| Worsening heart failure | 1 (3.8%) |
| **Secondary Safety Outcomes up to 12-months – no. of events (% of patients)** | |
| Serious device related or vascular event | 4 (15.4%)* |
| AKI requiring RRT | 0 (%) |
| Worsening GFR >50% | 1 (3.8%) |
| All adverse events | 31 (53.8%) |
| Incidence of all-cause mortality (including CV and HF related) | 0 (%) |

†CEC adjudicated adverse events. *3 were adjudicated relating to absence of GSN.

# Exercise RHC at pre- and post-procedure
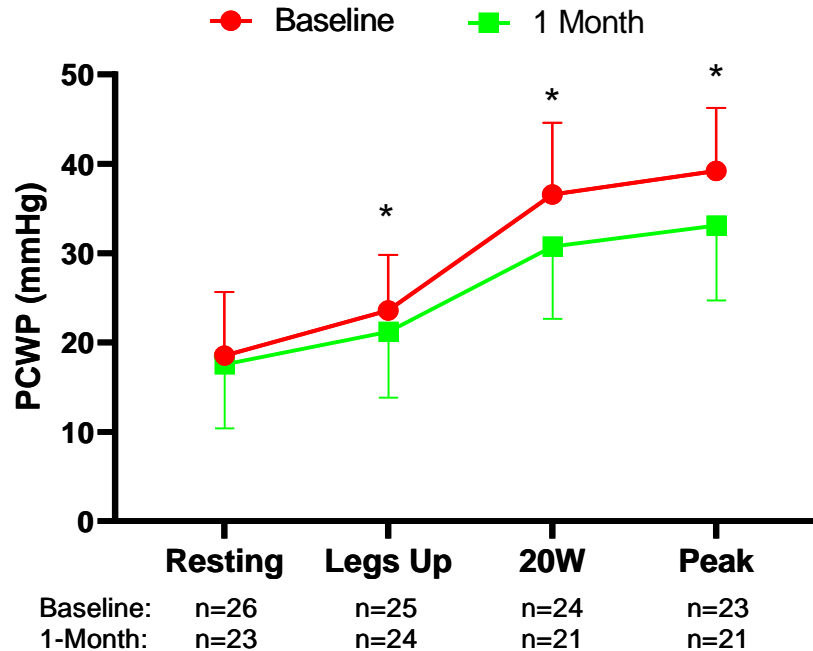


*P<0.05 – derived from a mixed effects repeated measures model with an unstructured correlation structure

# Hemodynamics – PCWP

|  | Baseline | 1-Month | 1M - BL | p-value* |
|---|---|---|---|---|
| **Resting** |  |  |  |  |
| Mean ± SD (N) | 18.5 ± 7.13 (26) | 17.6 ± 7.17 (23) | **-0.9** | 0.24 |
| Median (Min, Max) | 17.0 (4.0, 34.0) | 20.0 (5.0, 31.0) | **-3** |  |
| **Legs-Up** |  |  |  |  |
| Mean ± SD (N) | 23.6 ± 6.20 (25) | 21.2 ± 7.37 (24) | **-2.4** | 0.03 |
| Median (Min, Max) | 24.0 (11.0, 34.0) | 22.5 (3.0, 32.0) | **-1.5** |  |
| **20W** |  |  |  |  |
| Mean ± SD (N) | 36.6 ± 8.02 (24) | 30.8 ± 8.12 (21) | **-5.8** | 0.003 |
| Median (Min, Max) | 35.0 (22.0, 50.0) | 30.0 (15.0, 47.0) | **-5** |  |
| **Peak** |  |  |  |  |
| Mean ± SD (N) | 39.2 ± 7.05 (23) | 33.10 ± 8.40 (21) | **-6.1** | 0.016 |
| Median (Min, Max) | 37.0 (26.0, 50.0) | 35.0 (15.0, 47.0) | **-2** |  |

*P-value is derived from a mixed effects repeated measures model with an unstructured correlation structure.

# Exercise Capacity

| | Baseline | 1-Month | 1M - BL | p-value* |
|---|---|---|---|---|
| Exercise Duration – Min | | | | |
| Mean ± SD (N) | 6.9 ± 3.4 (26) | 7.9 ± 5.3 (25) | **+1** | 0.28 |
| Median (Min, Max) | 6 (3, 15) | 7 (2, 28) | **+1** | |
| Peak Exercise Stage – W | | | | |
| Mean ± SD (N) | 43.8 ± 21.9 (26) | 48.0 ± 25.2 (25) | **+4.2** | 0.26 |
| Median (Min, Max) | 40 (20, 100) | 40 (20, 100) | **0** | |
| Work Index PCWP – mmHg/W/kg | | | | |
| Mean ± SD (N) | 135.4 ± 63.8 (24) | 112.2 ± 54.1 (21) | **-23.2** | 0.04 |
| Median (Min, Max) | 130.5 (42.6, 282.7) | 114.6 (41.5, 236.6) | **-15.9** | |

*P-value is derived from a mixed effects repeated measures model with an unstructured correlation structure.
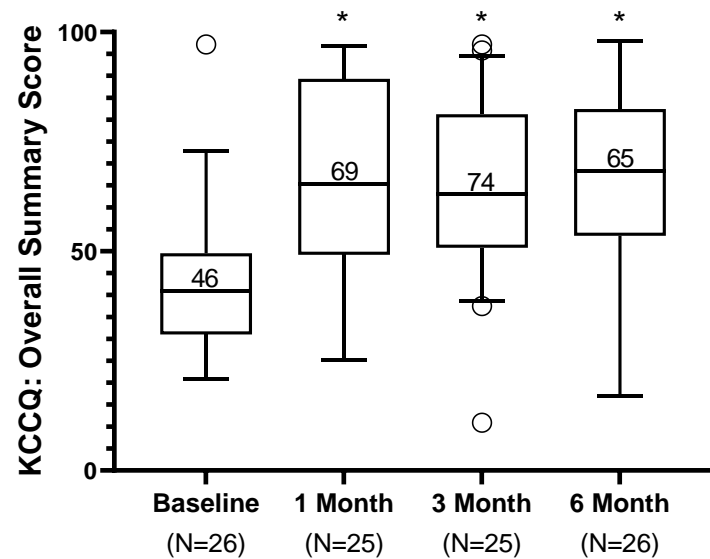
# Health Status

## NYHA Functional Class
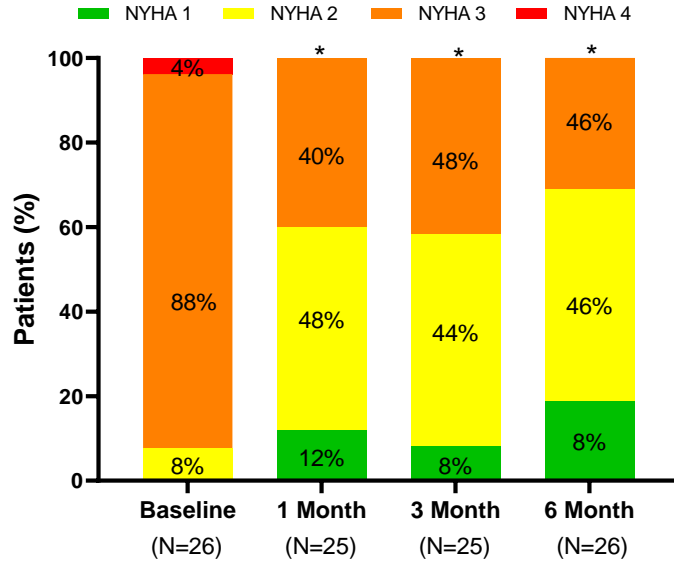


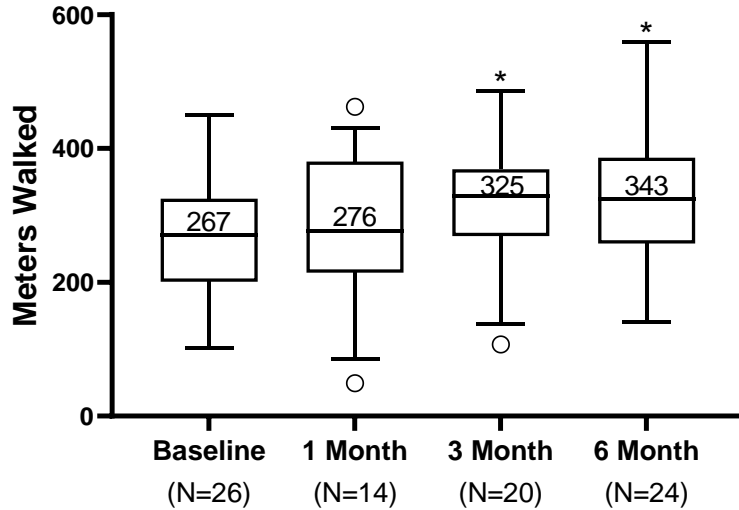More patients in NYHA 1&2 class at follow-up visits (*p<0.001)

## KCCQ Overall Score



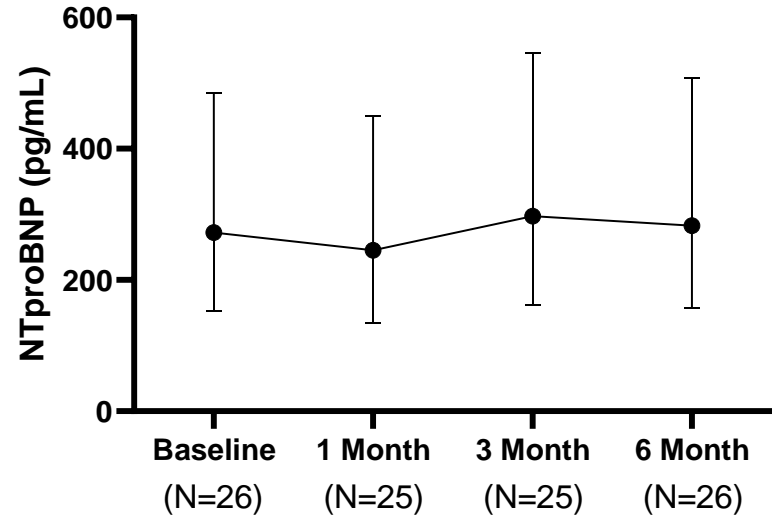Sustained improvements in KCCQ Overall Summary Score through 6-months (*p<0.05)

# Functional Status and NTproBNP

## 6-Minute Walk Test

## NTproBNP

Improvement in 6MWT at 3- and 6-month follow-up (*p<0.05)

No changes in geometric mean NTproBNP relative to baseline

# Echocardiographic Assessment

|  | Baseline | 6-Month | P-value |
|---|---|---|---|
| Ejection Fraction |  |  |  |
| Mean ± SD (N) | 59.1 ± 5.6 (26) | 59.4 ± 4.8 (24) | 0.85 |
| Median (Min, Max) | 60.5 (44, 68) | 60 (50, 69) |  |
| E/e' ratio (mean) |  |  |  |
| Mean ± SD (N) | 14.0 ± 7.1 (24) | 13.4 ± 6.2 (24) | 0.19 |
| Median (Min, Max) | 11.6 (5.5, 36.7) | 12.0 (5.7, 32.9) |  |
| Left atrial end-diastolic volume index |  |  |  |
| Mean ± SD (N) | 22.0 ± 12.3 (26) | 20.6 ± 11.4 (23) | 0.09 |
| Median (Min, Max) | 18.4 (6.6, 48.7) | 17 (8.2, 45.6) |  |
| Left ventricular end-diastolic volume index |  |  |  |
| Mean ± SD (N) | 40.4 ± 8.9 (26) | 37.2 ± 7.3 (23) | 0.04 |
| Median (Min, Max) | 39.8 (23.7, 56.3) | 36.5 (25.7, 57.3) |  |

*P-value is derived from a mixed effects repeated measures model with an unstructured correlation structure.

# Responder Framework

- Responder score analysis by giving one point for each six key variables above median score of the entire population

| Variable | Threshold |
|----------|-----------|
| NYHA Class | 1+ functional class |
| KCC-Q Overall Score | +20 points |
| 6-MWT Distance | +45 meters |
| Weight loss | -0.7 kg |
| NT-pro BNP | -11% baseline |
| PCWP – Peak | -2.5 mmHg |

**Non-Responder**  **Responder**

0  1  2  3  4  5  6

**Responder Score**
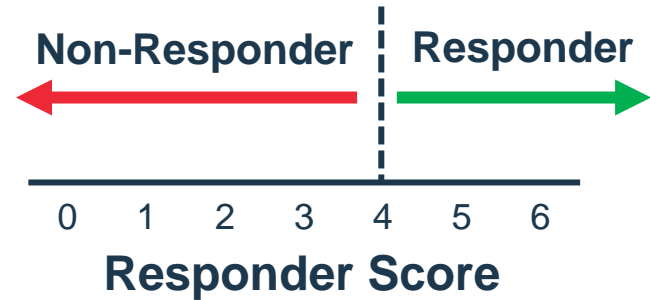
# REBALANCE-HF Team

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# Conclusions

- Preliminary open-label results from the REBALANCE-HF roll-in cohort support the safety and efficacy of SAVM in HFpEF

- GSN ablation reduced the PCWP with exercise and showed signal for improvement in functional capacity, symptoms, and health status of patients with HFpEF

- Results are limited by the single-arm, open-label design, which makes the results subject to treatment and observation bias

- The findings presented here require confirmation in the ongoing randomized, sham-controlled portion of the REBALANCE-HF trial