Panel Questions for the Advisory Committee Meeting
for the V-Wave Ventura Device – December 3, 2025

DISCUSSION QUESTIONS

Safety

1. The primary safety endpoint was the rate of device or procedure related Major Adverse Cardiovascular or Neurological Events (MACNE, including all-cause death, stroke, systemic embolism, need for open cardiac surgery, or major endovascular surgical repair) at 30 days post-randomization and was evaluated in the 250 Shunt group patients. No patient experienced a primary safety endpoint event, and the primary safety endpoint was met. Additional safety events through 2 years in Shunt and Control (sham procedure) groups are shown in Table 1. There were numerically more cerebrovascular and pulmonary embolism events, but fewer myocardial infarction events at 2-years in the Shunt group vs. the Control group. Please discuss on the clinical significance of the safety events observed in the study.

Table 1. Additional Safety Endpoints

	Shunt group (N=250)	**Control Placebo Procedure group (N=258)**	**Relative risk or difference**	**P value**
Secondary safety endpoints:				
MACNE* or BARC types 3 or 5 bleeding at 30 days[1]	2 (0.8%)	-	-	-
BARC types 3 or 5 bleeding at 30 days[1]	2 (0.8%)	1 (0.4%)	2.07 [0.19, 22.85][2]	0.54
MACNE* at 1 year[1]	0 (0.0%)	-	-	-
MACNE* at 2 years[1]	0 (0.0%)	-	-	-
Cerebrovascular events at 2 years, any[1]	11 (5.1%)	6 (2.5%)	1.92 [0.71, 5.18][2]	0.19
CNS infarction (stroke)[1,**]	7 (3.3%)	5 (2.1%)	1.46 [0.46, 4.60][2]	0.52
CNS hemorrhage (intracerebral or subarachnoid)[1,†]	0 (0.0%)	1 (0.5%)	-	0.33
Transient ischemic attack[1]	4 (1.9%)	1 (0.4%)	4.12 [0.46, 36.91][2]	0.17
Myocardial infarction at 2 years[1]	8 (3.8%)	13 (6.6%)	0.63 [0.26, 1.52][2]	0.30
Systemic embolization events at 2 years[1]	0 (0.0%)	0 (0.0%)	-	-
Pulmonary embolization events at 2 years[1]	2 (1.0%)	0 (0.0%)	-	0.16
Shunt implant embolization at 2 years[1]	0 (0.0%)	-	-	-

* MACNE was device-related or procedure-related.
** The 7 strokes in patients who were treated with the Shunt were classified by the CEC as being due to cerebrovascular disease (n=3), embolic due to atrial fibrillation (n=2) and undetermined (n=2). The 5 strokes in Control group patients who were treated with a placebo-procedure were classified by the CEC as being due to cerebrovascular disease (n=1), embolic due to atrial fibrillation (n=2), subarachnoid hemorrhage (n=1) and undetermined (n=1). Only one stroke occurred within 30 days of randomization, that being in the Control group.
† Does not include 1 additional patient in the placebo group with an ischemic stroke and hemorrhagic transformation.
1. Event rates were number of events (Kaplan-Meier time-to-first event estimates. Not done for MACNE as there were no events.
2. Hazard ratio [95% confidence interval].

Effectiveness

2. RELIEVE-HF was designed to demonstrate device effectiveness in a combined cohort of HFpEF and HFrEF patients. The primary effectiveness endpoint was a hierarchical composite of all-cause death, cardiac transplantation or LVAD implantation, HFH, Outpatient worsening HF events, and KCCQ score change. The primary analysis used the Finkelstein and Schoenfeld method and calculated a win ratio. The primary effectiveness endpoint was not met: win ratio of 0.86, 95% CI 0.62 to 1.22, p = 0.20 (Figure 1).

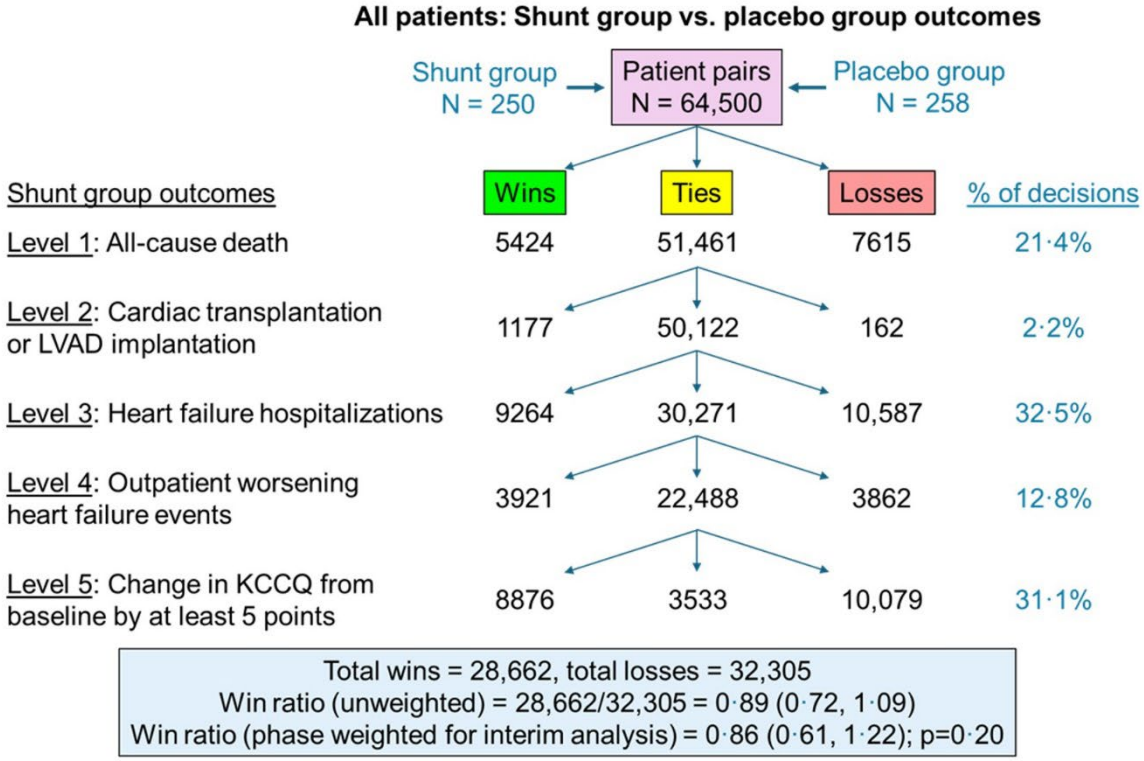

Figure 1: Win Ratio Analysis for the Primary Effectiveness Endpoint (ITT Population)

A post hoc cumulative event analysis of the primary effectiveness endpoint (excluding KCCQ) through 2 years is shown in Figure 2. Similar hazard rates were observed for the Shunt group (annualized rate 55.7%) and Control group (56.0%). The individual component rates of the primary effectiveness endpoint are shown in Table 2 and Figure 3.

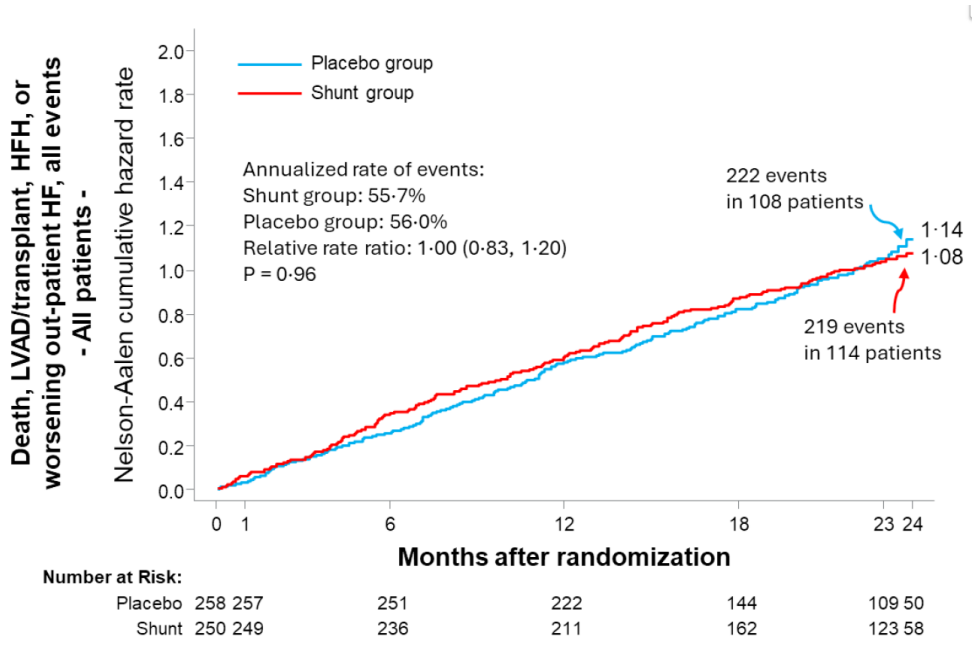

Figure 2. Post-hoc Nelson-Aalen cumulative event analysis of the composite of death, LVAD/transplant, heart failure hospitalization and worsening outpatient heart failure events

Table 2: Rates of Individual Components of the Primary Effectiveness Endpoint (Except KCCQ)

	Shunt group	Control group	Relative risk
All-cause death	35 (15.6%)	27 (13.7%)	1.31 [0.79, 2.16]
Cardiac transplantation or LVAD	1 (0.6%)	6 (3.4%)	0.17 [0.02, 1.38]
HFHs (no. of events/total no. of patient-yrs, (annualized rate)	128/392.7 (32.6%)	125/396.1 (31.6%)	1.09 [0.79, 1.50]
Worsening outpatient HF events (no. of events/total no. of patient-yrs (annualized rate)*	55/392.7 (14.0%)	64/396.1 (16.2%)	0.88 [0.61, 1.26]

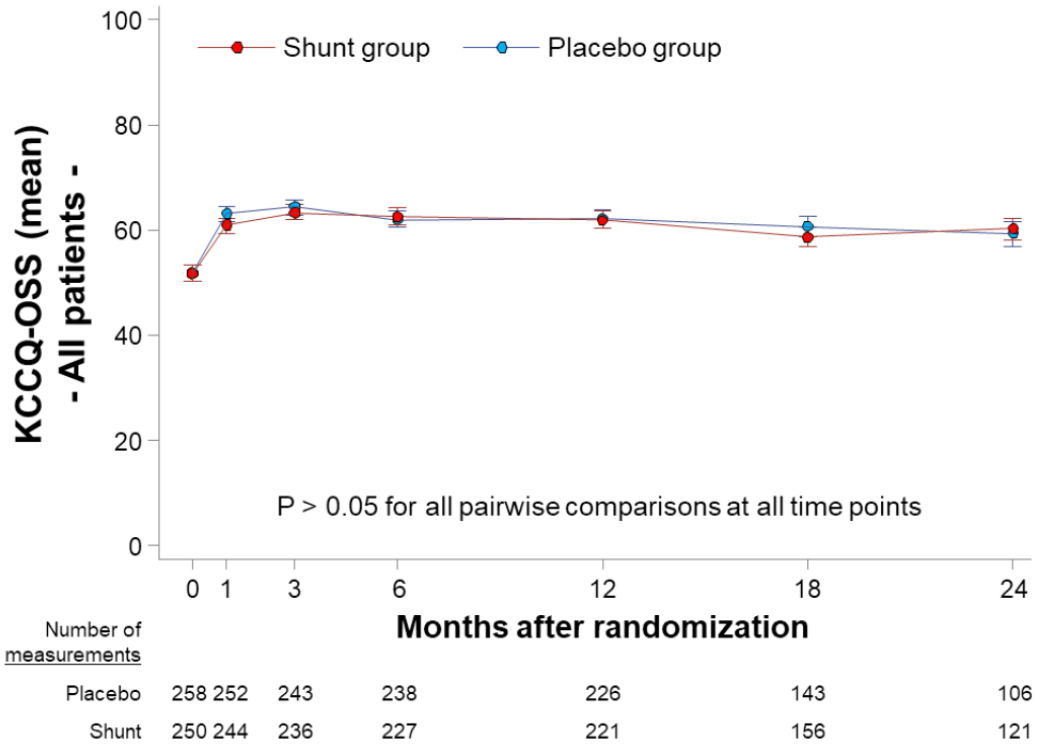

Figure 3: KCCQ outcomes over 2 years (ITT population)

Please discuss the clinical significance of the primary effectiveness endpoint results.

3. RELIEVE-HF was designed to show that the shunt would be safe and effective in HF patients independent of HF phenotype. Per the statistical analysis plan, the shunt benefit was expected to be more pronounced in the HFpEF (LVEF >40%) subgroup vs. the HFrEF (LVEF ≤40%) subgroup.

   RELIEVE-HF enrollment was stratified by HF phenotype, and there was a pre specified analysis comparing the primary effectiveness endpoints results between the HFrEF and HFpEF subgroups. The HF phenotype subgroup analysis results were discordant suggesting Shunt benefit in the HFrEF cohort (win ratio 1.40, 95% CI 0.80 to 2.46) and harm in the HFpEF subgroup (win ratio 0.61, 95% CI 0.39 to 0.98). The interaction test analysis showed a nominally significant p-value of 0.0146.

   Although RELIEVE-HF enrollment was stratified by LVEF and there was an expectation the that the treatment effect may differ in degree between the subgroups, the study was designed to evaluate the effect in the total population, not in each LVEF subgroup separately. There was no pre-specified plan to control Type I error in a subgroup analysis.

   The Sponsor performed multiple post hoc analyses on the HFREF and HFpEF subgroups to gain insights into the discordant results.

HFrEF (LVEF ≤40%) subgroup (n = 206 randomized subjects) post hoc analyses

- 5-level (all-cause death, cardiac transplant/LVAD, HFH, outpatient WHF, and KCCQ change) win ratio analysis: No statistically significant difference between Shunt and Control groups
- 4-level (excluding KCCQ change) win ratio analysis: No statistically significant difference between Shunt and Control groups
- HF events (along with HF event in combination components of the primary effectiveness composite endpoint, excluding KCCQ) utilizing multiple analytic models favored the Shunt group
- All-cause death and transplant/LVAD rates favored the Shunt group
- Cardiovascular death rates similar between Shunt and Control groups
- Similar KCCQ scores in Shunt and Control groups

HFpEF (LVEF >40%) subgroup (n = 302 randomized subjects) post hoc analyses

- 5-level (all-cause death, cardiac transplant/LVAD, HFH, outpatient WHF, and KCCQ change) win ratio analysis: Favored the Control group
- Death and HF event rates favored the Control group

Pathophysiologic insights

- The Sponsor conducted post-hoc, exploratory analyses of between group differences in transthoracic echocardiographic (TTE) changes at baseline and 12 months
- N=508 randomized patients; 12.2% missing 12-month follow-up TTEs
- Among the 16 TTE parameters assessed, follow-up TTEs showed :
    - Reverse left ventricular remodeling in HFrEF subgroup Shunt subjects.
    - A smaller increase in estimated pulmonary artery systolic pressure in the HFrEF Shunt group vs. the Control group
    - Increased right ventricular, right atrial and inferior vena cava size and pulmonary artery systolic pressure in HFpEF Shunt subjects vs. Controls.

a. Please discuss the strengths and limitations of the evidence (and your level of uncertainty) that the Shunt is beneficial in HFrEF patients.
b. Please discuss the strengths and limitations of the evidence (and your level of uncertainty) that this Shunt is harmful in HFpEF patients.

Benefit/Risk

4. Given the totality of the evidence presented regarding the safety and effectiveness of the device, please comment on the benefit-risk profile of the device.

Labeling

5. The sponsor has proposed the following indications for use statement:

> *The Ventura Shunt is indicated for NYHA Class III heart failure patients who remain symptomatic despite guideline-directed medical therapy, have a LVEF of ≤ 40%, and*

who are judged by a Heart Team to be appropriate for Shunt therapy, to reduce the risk of hospitalization for heart failure.

a. Please discuss whether the available clinical data support the proposed indications for use.
b. The Shunt proposed indications for use is limited to patients with LVEF ≤40%. Do you agree with the use of LVEF for patient selection? Please discuss any clinical implications including variability and measurement error in LVEF assessments, the potential for LVEF to change over time with therapy or disease progression, and the challenges this may present for clinical decision making for individual patients.

Postmarket Study

6. The sponsor has proposed the following approach to postmarket clinical data collection:
    - Continued follow-up of implanted subjects from the RELIEVE-HF study for 5 years;
    - A single-arm new enrollment post-approval study (PAS) with a performance goal; and
    - A post-approval registry for all commercial US patients not included in the post-approval study.

    Please discuss the strengths and limitations of the proposed approach to postmarket data collection. Please also comment on whether any additional study objectives, design features, or surveillance are recommended.