ACE BRIEF FOR NEW AND EMERGING HEALTH TECHNOLOGIES

Vagus Nerve Stimulation with the VITARIA System for Heart Failure with Reduced Ejection Fraction

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Summary of Key Points

- Regardless of heart failure (HF) aetiology, autonomic dysfunction represents a hallmark of HF with reduced ejection fraction (HFrEF) pathophysiology. Chronic autonomic imbalance arising from sympathetic overdrive and parasympathetic inhibition can lead to progressive maladaptive remodelling and deleterious impact on cardiac function.
- Despite availability of pharmacological treatments for patients with HFrEF, a treatment gap exists due to inadequate reversal of autonomic imbalance, intolerance with higher dosage and patients' non-compliance with pharmacological treatments.
- The VITARIA System (LivaNova PLC) delivers autonomic regulation therapy (ART) through vagus nerve stimulation (VNS) to restore autonomic balance for better cardiac function. The device is intended for patients with moderate to severe HFrEF who remain symptomatic despite stable guideline-directed medical therapy.
- Results from the ANTHEM-HF case series showed that ART with VNS was generally safe and well-tolerated. One procedure-related serious adverse event (AE) resulting in death was reported. A high number of VNS-related AEs (n=173) was reported in the first 6 months, of which 93% occurred in the titration phase. 11 additional VNS-related AEs were reported between 6 to 42 months. All AEs were mild and transient and resolved without sequelae, with no patients requesting to discontinue the treatment.
- ART with VNS led to significant and durable improvements in left ventricle ejection fraction (LVEF), exercise capacity, HF symptoms and quality-of-life (QoL) up to 42 months compared to baseline. Improvements at 42 months post-VNS include:
    - Increased LVEF (mean difference, 5.8%)
    - Increased 6-minute walk test (6MWT) distance (mean difference, 92m)
    - Reduced Minnesota Living with Heart Failure Questionnaire score (mean difference, 28 points)
    - Reduced New York Heart Association (NYHA) functional class
- Despite durable long-term improvements, outcomes reported at 12 or 42 months were not significantly greater than at 6 months. Further, outcome improvements were sustained with a 50% reduction in stimulation frequency and concomitant 20% increase in stimulation intensity at 24 months. There was no difference between left- and right-sided VNS, except for better improvement of 6MWT with right-sided VNS at 6 months.
- The early results were limited by the lack of a control group and sparse evidence with a small sample size. Results from the ongoing ANTHEM-HFrEF pivotal randomised controlled trial (RCT) may address the shortcomings of the ANTHEM-HF case series.
- No studies on cost-effectiveness were identified. A high cost of VNS therapy is anticipated ([redacted] to [redacted]), however cost savings may be realised if ART with VNS can reduce HF-related hospitalisation and healthcare resource utilisation. This can be validated by the ongoing ANTHEM-HFrEF trial whose primary endpoint includes HF hospitalisation.
- No major implementation considerations were identified but increased demand for screening services to determine patient suitability for VNS therapy is likely.
- At present, one other VNS device for patients with HFrEF was identified but its current developmental status is unknown.

I. Background

Heart failure (HF) is a complex and multifactorial syndrome that represents the clinical endpoint of various cardiovascular disease, and is characterised by exertional dyspnoea and exercise intolerance.[1] It arises from progressive structural and functional deterioration of the myocardium, leading to impaired left ventricular (LV) performance.[1] In particular, patients with HF who have a LV ejection fraction (LVEF) of 40% or less are classified as HF with reduced ejection fraction (HFrEF).[1] Regardless of aetiology, autonomic dysfunction represents a hallmark of HFrEF pathophysiology.[2] In response to a cardiac insult that results in systolic dysfunction, the autonomic nervous system initiates a compensatory mechanism to preserve cardiac output by means of sympathetic overdrive and parasympathetic inhibition.[3] This shift in autonomic activities may be considered as a short-term compensatory response to the abnormal cardiac function.[4] However, in chronic HF, the autonomic dysfunction results in structural and functional changes within the cardiac nervous system and the cardiac tissues that they innervate, thus leading to progressive maladaptive remodelling and long-term deleterious impact on cardiac function.[5]

It is estimated that HFrEF accounts for around half of all HF cases.[6] HFrEF is associated with high morbidity and mortality despite improvement in medical therapies, with a five-year survival rate of 25% after hospitalisation for patients with HFrEF.[7] Data from the ASIAN-HF registry reported a one-year all-cause mortality rate of 13.6% and cardiovascular-related mortality rate of 59.9% for Southeast Asian patients with HFrEF.[8] Compared to patients with HF with preserved ejection fraction (HFpEF, LVEF ≥50%), Asian patients with HFrEF showed 9.6% higher one-year all-cause mortality rate than those with HFpEF despite being eight years younger.[8]

A treatment gap for HFrEF exists due to the inadequate reversal of autonomic imbalance by current drug therapies, the inability to up-titrate potential drugs due to intolerance and patients' non-compliance with pharmacological treatments.[4]

II. Technology

Autonomic regulation therapy (ART) is an emerging therapy to treat HF using bioelectric approaches to alleviate the maladaptive processes and to stabilise imbalances within selected elements of the cardiac neuronal hierarchy, with the aim to maintain myocardial viability and function.[5] To this end, vagus nerve stimulation (VNS) has been shown to counterbalance the sympathetic hyperactivity by upregulating the parasympathetic activity, inhibit sympathetic overdrive through afferent signals and inhibit the release of inflammatory cytokines, preventing arrhythmogenesis and sudden cardiac death.[3]

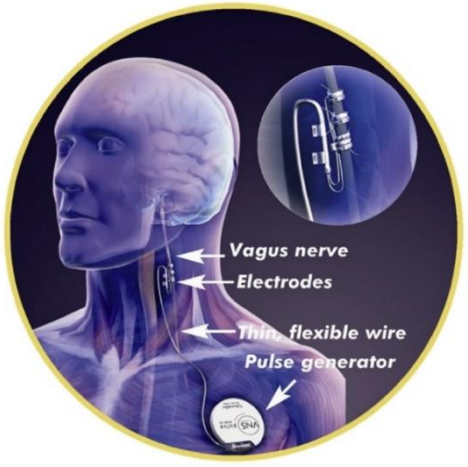

Figure 1. Illustration of the VNS device. Adapted from Dicarlo et al. (2013).[9]

The VITARIA System (LivaNova PLC) is designed to deliver ART through VNS. The device is intended for patients with moderate to severe HFrEF who remain symptomatic despite stable guideline-directed medical therapy (GDMT). It consists of an implantable pulse generator (IPG) and lead, and an external programming system used to change stimulation settings. The IPG can be implanted under the skin in the chest and the electrode leads can be tunnel to the vagus nerve (Figure 1). By stimulating the vagus nerve to modulate the sympathetic and parasympathetic activities, the VITARIA System aims to restore autonomic balance to achieve better cardiac function.

Neuromodulation with VNS is an established approach to treat patients with refractory epilepsy and migraine and was recently FDA-approved to treat moderate to severe upper extremity motor deficits associated with chronic ischemic stroke. In cardiology, VNS represents a novel and emerging approach to manage HF, particularly the underlying autonomic imbalance. It serves to address the current treatment gap for patients with chronic HFrEF who are refractory to pharmacotherapies. The VITARIA System may represent a first-in-its-class VNS therapy for HF if approved and commercialised.

III. Regulatory and Subsidy Status

The VITARIA System was granted the CE mark in 2015 to deliver ART for patients who have moderate to severe HF (New York Heart Association (NYHA) Class II/III) with LV dysfunction (ejection fraction <40%), and who remain symptomatic despite stable, optimal HF drug therapy. The VITARIA System has not been commercialised.

It was granted the Breakthrough Device Designation by the US Food and Drug Administration (FDA) and is currently pending trial results for FDA approval.

IV. Stage of Development in Singapore

The VITARIA System is based on the VNS technology, which has been approved for use in Singapore for the management of patients with refractory epilepsy and chronic migraine.

☐	Yet to emerge	☐	Established
☐	Investigational / Experimental (subject of clinical trials or deviate from standard practice and not routinely used)	☒	Established *but* modification in indication or technique
☐	Nearly established	☐	Established *but* should consider for reassessment (due to perceived no/low value)

V. Treatment Pathway

Based on current guidelines for HF management in Singapore, pharmacological treatment is used as a first-line therapy followed by interventional procedures for patients with HFrEF.[10] In particular, the first-line pharmacological treatments include angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and beta-blockers which serves to inhibit

the neurohormonal axis.[10] Patients who remain symptomatic can be prescribed with mineralcorticoid receptor antagonist, angiotensin receptor neprilysin inhibitor, ivabradine or vasodilators.[10] Cardiac implantable electronic devices, such as implantable cardioverter-defibrillators therapy (ICD) and cardiac resynchronisation therapy (CRT), or their combination, may be considered for a selected group of patients with HFrEF such as those with systolic dysfunction or arrhythmia.[10] In addition, surgical option may be offered to patients with HFrEF with aggravating factors that are amenable to surgery. Last line options include heart transplantation, or mechanical circulatory support devices that can either serve as a bridge to transplant or a destination therapy for patients with advanced HF who are not candidates for heart transplantation.[10]

At present, neurostimulation using VNS remains as a novel treatment option for patients with HFrEF. If introduced into the local treatment pathway, it may serve as an adjunct therapy in addition to GDMT for patients with HFrEF to modulate the autonomic imbalance.

VI. Summary of Evidence

An assessment was performed based on the Population, Intervention, Comparison and Outcome (PICO) criteria presented in Table 1. All evidence identified were based on the ANTHEM-HF case series and was summarised in Table A1 (Appendix A). Amongst the three reports included in this brief, Premchand et al. (2014)[11] reported on the 6-month follow-up while extended follow-ups of 12 and 42 months were reported by Premchand et al. (2016)[12] and Sharma et al. (2021)[13] respectively. The study design was summarised in Table A2 (Appendix A).

Table 1: Summary of PICO criteria.

Population	Heart failure patients with reduced ejection fraction (<40%), and who remain symptomatic despite stable, optimal heart failure drug therapy
Intervention	Autonomic regulation therapy with vagus nerve stimulation (VITARIA System) in addition to guideline-directed medical therapy
Comparison	Guideline-directed medical therapy, if available
Outcomes	Safety, clinical and cost effectiveness

Safety

Out of a total of 38 serious adverse events (SAEs) reported up to 42 months, only one SAE was adjudicated to be procedure related (Table 2). One death from post-operative embolic stroke was reported in a patient with severe obstructive carotid disease, which may be due to plaque disruption during manipulation of the carotid artery during dissection of the vagus nerve.[11] Other non-related SAE includes sudden death, HF hospitalisation and ventricular tachycardia (Table B1 in Appendix B). Overall, the procedure-related mortality rate arising from VNS therapy was 1.7% (1 out of 60 patients).

A high number of VNS-related adverse events (AEs) was reported in the first 6 months, with a total of 173 AEs reported. Common AEs include dysphonia, cough and oropharyngeal pain which were all mild and resolved without sequelae. Of note, 93% of these AEs occurred between the implantation and end-titration phase where stimulation parameters were adjusted and up-titrated to levels that elicited VNS-related side effects to establish the

tolerance zone boundary.[11] An additional 11 VNS-related AEs were reported between 6 to 42 months.[12,13] No patients requested to discontinue the treatment throughout all follow-up visits.[11-13] In general, stimulation-related AEs were transient as it could be ameliorated with adjustment of stimulation parameters.[11] Patients were also randomised 1:1 to either a left- or right-sided VNS implantation to determine bilateral differences in outcomes and AEs between left- and right-sided VNS were largely similar (Table B2 in Appendix B).[11-13] In addition, no device malfunction was reported.[11-13]

Table 2: Summary of safety outcomes.

Safety outcomes	Premchand et al. (2014)[11]	Premchand et al. (2016)[12]	Sharma et al. (2021)[13]
	0 to 6 months	6 to 12 months	12 to 42 months
Total patients, N	60	49	33
Number of patients with SAE, n (%)	16 (26.7)	–	–
Total events			
Any SAE, n	21	7	10
Procedure-related death	1	0	0
Unrelated SAE	20	7	10
Any related AE, n	173	5	6
Dysphonia	19	3	3
Cough	13	–	–
Oropharyngeal pain	8	–	2
Shoulder pain	–	1	–
Implant site pain	–	1	1
Device malfunction, n	0	0	0

Abbreviations: AE, adverse event; SAE, serious adverse event.

Effectiveness

In the ANTHEM-HF case series, successful VNS implantation and titration were performed in 59 out of 60 patients.[11] The VNS therapy led to durable and statistically significant improvements in LVEF and functional outcomes up to 42 months compared to baseline (Table 3). At 42 months post-VNS, the improvement in LVEF (mean difference of 5.8%, p=0.005) was clinically meaningful based on the minimal clinically important difference (MCID) of ≥5%.[13,14] In terms of functional outcomes, clinically meaningful improvement in 6-minute walk test (6MWT) distance (mean difference of 92m, p<0.0001; MCID≥30m) and the HF-related quality-of-life (QoL) score (mean difference in Minnesota Living with Heart Failure Questionnaire of 28 points, p<0.0001; MCID of 8.2 points) were reported at 42 months.[13,15,16] In addition, 77% of patients reported improvement in the New York Heart Association (NYHA) functional class at 6 months compared to baseline, with sustained significant improvements up to 42 months.[11-13] Overall, these results point to improved cardiac function, exercise capacity, HF symptoms and patient's QoL. However, the impact of VNS on cardiac parameters including LV end-systolic volume (LVESV) and diameter (LVESD), 24-hour heart rate and plasma biomarkers remains ambiguous (Table B3 in Appendix B).[11-13]

Despite durable long-term improvements, outcomes reported at 12- or 42-month were not significantly greater than the 6-month results (p=NS for all outcomes at 6 *vs.* 12 months; Table

B4 in Appendix B).[12,13] The reason for this is not clear, but it was postulated that VNS may be insufficient in fully addressing the underlying cardiac impairment.[12] Of note, improvement in outcomes were sustained with 50% reduction in stimulation frequency (10 Hz to 5 Hz) and a concomitant 20% increase in stimulation intensity (2.0 ± 0.6 mA to 2.4 ± 0.6 mA) at 24 months (Table B5 in Appendix B).[13] The reduction in stimulation frequency may reduce stimulation-related side effects while the increase in stimulation intensity may increase autonomic engagement and therapeutic efficacy.[13]

In terms of bilateral difference in outcomes, only 6MWT showed better improvement with right-sided VNS at 6 months (mean improvement of left *vs.* right, 34 *vs.* 77m; Table B6 in Appendix B).[11] No significant bilateral difference in outcomes were reported at extended follow-ups.[12,13]

In addition, the ability of VNS therapy to ameliorate autonomic dysfunction was evident from the significant increase in heart rate variability (mean difference range, 11 to 17 ms) up to 42 months compared to baseline (Table B3 in Appendix B).[11-13] This was further supported by post-hoc analyses of the ANTHEM-HF study where improvements in heart rate recovery, heart rate dynamics, T-wave alternans and baroreceptor sensitivity were reported.[17-20]

Table 3: Summary of clinical outcomes from the ANTHEM-HF case series.

Clinical outcomes	Time point	Premchand et al. (2014)[11]	Premchand et al. (2016)[12]	Sharma et al. (2021)[13]
		Follow up: 6 mo; N=59	Follow up: 12 mo; N=49	Follow up: 42 mo; N=33
LVEF, mean ± S.D. (%)	Baseline	–	33.2 ± 7.4	35.0 ± 6.9
	Follow-up	–	39.5 ± 10.4	40.8 ± 12.5
	Mean difference	4.5 (95% CI, 2.4 to 6.6)	6.3 (p<0.0005)	5.8 (p=0.005)
LVESV, mean ± S.D. (mL)	Baseline	–	102.0 ± 37.6	92.8 ± 31.3
	Follow-up	–	91.6 ± 43.5	92.7 ± 51.2
	Mean difference	-4.1 (95% CI, -9.0 to 0.8)	-10.4 (p=0.001)	-0.1 (NS)
LVESD, mean ± S.D. (mm)	Baseline	–	50 ± 8	48.0 ± 7.9
	Follow-up	–	48 ± 8	46 ± 12
	Mean difference	-1.7 (95% CI, -2.8 to -0.7)	-2.0 (p=0.003)	-2.0 (NS)
NYHA class (I/II/III/IV)	Baseline	NR*	0/26/20/0	0/19/14/0
	Follow-up		32/14/0/0	20/12/1/0
	P-value		p<0.0005	p<0.0001
6MWT, mean ± S.D. (m)	Baseline	–	288 ± 64	297 ± 62
	Follow-up	–	352 ± 62	389 ± 70
	Mean difference	56 (95% CI, 37 to 75)	64 (p<0.0005)	92 (p<0.0001)
QoL score (MLHFQ), mean ± S.D.	Baseline	–	39 ± 12	38 ± 12
	Follow-up	–	18 ± 9	10 ± 12
	Mean difference	-18 (95% CI, -21 to -16)	-21 (p<0.0005)	-28 (p<0.0001)

Note: Data by Premchand et al. (2014)[11] were reported as marginal means (95% confidence interval).

* No numerical outcomes were reported for NYHA functional class. 77% of patients were reported to improve from baseline to the 6-month follow-up with no worsening of NYHA functional class in all patients.

Abbreviations: 6MWT, 6-minute walk test; CI, confidence interval; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; LVESV, left ventricular end systolic volume; MLHFQ, Minnesota Living with Heart Failure Questionnaire; m, meter; mL, millilitre; mm, millimetre; mo, months; NR, not reported; NS, not significant; NYHA, New York Heart Association; S.D., standard deviation; QoL, quality-of-life.

Cost effectiveness

No studies that reported on cost-effectiveness for ART using VNS was identified. However, a cost-impact analysis was identified for autonomic modulation using baroflex activation therapy (BAT) in patients with HFrEF. Similar to VNS, BAT represents a form of ART that addresses the autonomic dysfunction by reducing sympathetic and increasing parasympathetic activities. From the perspective of the United States healthcare system, the expected per patient cost of BAT with GDMT was US$29,526 higher at baseline compared to GDMT alone due to BAT device and implantation cost.[21] After 3 years, the per patient cost was US$9,521 lower for BAT with GDMT compared to GDMT alone due to lower rates of HF hospitalisations, cardiovascular-related hospitalisations and resource intensive procedures.[21]

Similarly, if the VITARIA System can reduce HF-related hospital admission rates and interventional procedures, it may possibly lead to cost savings for the local healthcare system in the long run.

Ongoing clinical trial

One ongoing trial was identified from the ScanMedicine database (NIHR Innovation Observatory) (Table 4). The ANTHEM-HFrEF is a pivotal randomised controlled trial (RCT) to evaluate the VITARIA System with GDMT compared to GDMT alone in patients with HFrEF. The primary endpoint of the ANTHEM-HFrEF RCT includes a composite of cardiovascular mortality and HF hospitalisation.

In addition, HF function and symptoms are assessed in an embedded study within the ANTHEM-HFrEF RCT to support a premarket approval (PMA) submission to the FDA, which will be made after the first 300 randomised patients have completed their 9-month follow-up visit and at least 400 patients have been randomised. In April 2021, LivaNova PLC announced that it has achieved its clinical milestone where randomisation of the 300th patient was conducted.

Table 4: Summary of ongoing clinical trials for the VITARIA System.

Study name; Trial ID	Estimated enrolment	Study design, aim and follow-up period	Estimated study completion date
ANTHEM-HFrEF; NCT03425422	800	Multi-center, open label 2:1 RCT to evaluate Autonomic Regulation Therapy with the VITARIA system in patients with HFrEF with VITARIA system implantation on the right cervical vagus nerve in addition to stable guideline-directed medical therapy (therapy arm), or to continue receiving stable guideline-directed medical therapy alone (control arm). Data for safety and efficacy assessments will be collected for both study arms at 4 weeks post-randomization, every 3 months for the first 12 months, and every 4 months thereafter.	December 2024

Summary

ART with VNS was generally safe and well-tolerated, with one procedure-related SAE that resulted in death from embolic stroke. The number of VNS-related AEs were high in the first 6 months possibly due to the up-titration of stimulation parameters while 11 VNS-related AEs were reported between 6 to 42 months. All AEs were mild and transient and resolved without sequelae, with no patients requesting to discontinue the treatment.

In terms of effectiveness, ART with VNS led to significant and durable improvements in LVEF, exercise capacity, HF symptoms and patient's QoL up to 42 months compared to baseline. Notably, outcomes reported at 12 or 42 months were not significantly greater than at 6 months. There was no major bilateral difference in outcomes reported, except for better 6MWT improvement with right-sided VNS at 6 months. In addition, outcome improvements were sustained with a 50% reduction in stimulation frequency and 20% increase in stimulation intensity at 24 months. Nevertheless, the benefits of VNS on LVESV, LVESD, heart rate and plasma biomarkers remain uncertain. In addition, cost savings may be realised if ART with VNS can lead to reduced HF-related hospitalisation and healthcare resource utilisation, which have to be validated with upcoming results from the ANTHEM-HFrEF RCT.

However, caution is warranted when interpreting the early results of ART with VNS for patients with HFrEF. The current evidence base is sparse with a small sample size. Moreover, the ANTHEM-HF case series lacks a control group and the results observed may not be attributed to VNS. Results from the ongoing ANTHEM-HFrEF pivotal RCT may address the shortcomings of the ANTHEM-HF case series.

VII. Estimated Costs

The cost of the VITARIA System is not available. As a reference, VNS therapy is locally used for patients with refractory epilepsy and chronic migraine, with a cost between [redacted] to [redacted] (Cost data from [redacted]).

VIII. Implementation Considerations

In terms of surgical procedure, it is critical to ensure proper attachment of the leads to the appropriate vagus nerve fibres for long-term success and outcomes to be realised. As VNS implantation has not been performed in the cardiac setting, training may be required.

The use of VNS for patients with HFrEF may also increase demand for healthcare resources. As not all patients with HFrEF may have autonomic imbalance, assessment of autonomic activity to determine patients most suited for VNS therapy may be required.[4] Patient assessment can include screening of 24-hour heart rate and 24-hour standard deviation of normal to normal R-R interval.[22] Other complex assessment of autonomic modulation can include power spectral analysis of heart rate and blood pressure variability or sympathetic microneurography.[22] The increase in demand for these screening services, along with the additional associated costs, should be considered when introducing the VITARIA system into the local healthcare system.

Furthermore, the local cost of VNS therapy for current approved indications is relatively high. Considering the potential high cost of the VITARIA System and the high prevalence of patients with HF, the introduction of the VITARIA System into the local healthcare system may potentially lead to a high upfront healthcare cost. However, downstream cost savings may be realised if the VITARIA System can reduce HF-related hospitalisation and resource use.

IX. Concurrent Developments

At present, there are no other known VNS devices that are in ongoing active development for patients with HFrEF. The CardioFit System was granted the CE mark in 2009 but it discontinued its FDA IDE trial due to futility of primary efficacy endpoints. Its current developmental status is not known (Table 5).

Table 5: Ongoing development of VNS therapy for patients with HFrEF.

Technology (Manufacturer)	Brief Description	Regulatory status
CardioFit system (BioControl Medical Ltd)	The CardioFit system is designed for cardiac use and consists of a stimulator, a sensor lead and a stimulation lead and implanted under the skin of the chest. Once activated, the stimulator's electrical pulses are transferred via the stimulation lead to the vagus nerve.	• CE marked in 2009 • FDA IDE study (INOVATE-HF) terminated due to futility of primary efficacy endpoint

X. Additional Information

The ANTHEM-HF case series is sponsored by LivaNova PLC. Most of the authors of the studies included in the evidence summary either served as scientific advisors or are employed by LivaNova PLC.

The VITARIA System is currently monitored by the Patient-Centered Outcomes Research Institute (PCORI). It was initially reported in the Horizon Scanning Status Report in March 2020 (Volume 2, Issue 1) and has been consistently monitored in the subsequent five reports.[23] In addition, the VITARIA System was classified as an investigational therapy in a recent review article published by the American College of Cardiology.[24]

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Appendix

Appendix A: Studies identified and study design.

Table A1: List of studies identified and included.

Type of studies	Description	Number of studies identified	Number of studies included
Key studies	Reported on outcomes prespecified in the ANTHEM-HF case series	3	3
Post-hoc studies	Reported on post-hoc outcomes based on the ANTHEM-HF case series	6	0

Note:
1. Inclusion criteria
   a. Studies that fulfil the PICO criteria listed in Table 1.
2. Exclusion criteria
   a. Studies that reported on outcomes not pre-specified in the ANTHEM-HF case series.

Table A2: Study design of the ANTHEM-HF case series.

Trial Design	Multi-centre, open label study to test the safety and feasibility of VNS in patients with chronic HF
Study size and follow up period	Premchand et al. (2014)[11]: n=60; 6 months Premchand et al. (2016)[12]: n=49; 6 and 12 months Sharma et al. (2021)[13]: n=33; 12, 24, 30 and 42 months
Population	NYHA Class II/III, LVEF ≤40%, remain symptomatic despite optimal medical therapy
Intervention	VNS stimulation, randomised to either left or right-sided VNS
Comparator	NIL
Outcomes	Primary: Procedure and device-related AEs, changes in LVEF and LVESV Secondary: LVESD, NYHA functional class, 6MWT, MLHFQ, mean HR and HR variability and plasma biomarkers

Abbreviations: 6MWT, 6-minute walk test; AE, adverse event; HF, heart failure; HR, heart rate; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; LVESV, left ventricular end systolic volume; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NYHA, New York Heart Association; VNS, vagus nerve stimulation.

Appendix B: List of supplementary tables.

Table B1: Serious adverse events reported in the ANTHEM-HF case series.

Safety outcomes	Premchand et al. (2014)[11]	Premchand et al. (2016)[12]	Sharma et al. (2021)[13]
	0 to 6 months	6 to 12 months	12 to 42 months
Related SAE			
Death (embolic stroke)	1	0	0
Unrelated SAE			
Death (sudden death)	1	2	2
Death (heart failure)	1	1	0
Death (cardiac arrhythmia)	0	0	1
Death (CVA with ischemic stroke)	0	0	1
Death (acute shortness of breath)	0	0	1
Congestive heart failure	0	0	1
HF hospitalisation	6	1	0
Unstable angina	2	0	0
Ventricular tachycardia	2	1	0
Bone fracture	1	0	0
Cataract	1	1	0

Dengue fever	1	0	0
Hernia	1	0	0
Pneumonia	1	0	0
Stroke	1	1	0
Urine retention	1	0	0
Weight loss	1	0	0

Abbreviations: CVA, cerebrovascular accident; SAE, serious adverse event.

Table B2: Bilateral difference in safety outcomes in the ANTHEM-HF case series.

Safety outcomes	Premchand et al. (2014)[11]		Premchand et al. (2016)[12]		Sharma et al. (2021)[13]	
	Left	Right	Left	Right	Left	Right
Related SAEs	1	0	0	0	0	0
Unrelated SAEs	9	11	4	3	3	7
Related AEs	82	91	1	4	2	4

Abbreviations: AE, adverse event; SAE, serious adverse event.

Table B3: Summary of supplementary outcomes reported in the ANTHEM-HF case series.

Clinical outcomes	Time point	Premchand et al. (2014)[11]	Premchand et al. (2016)[12]	Sharma et al. (2021)[13]
		Follow up: 6 mo; N=59	Follow up: 12 mo; N=49	Follow up: 42 mo; N=33
HR variability, mean ± S.D. (SDNN; ms)	Baseline Follow-up Mean difference	– – 17 (95% CI, 6.5 to 28)	95 ± 29 109 ± 40 14 (p<0.01)	96 ± 27 107 ± 28 11 (p<0.025)
24-h HR, mean ± S.D. (bpm)	Baseline Follow-up Mean difference	– – -3.9 (95% CI, -6.3 to -1.5)	78 ± 12 70 ± 10 -8 (p<0.0005)	74 ± 10 78 ± 11 4 (NS)
NT-proBNP, mean ± S.D. (pg/mL)	Baseline Follow-up Mean difference	– – 140 (95% CI, -828 to 1108)	6640 (IQR 267; 1748) 887 (IQR 359; 1691) -5753 (p=NS)	NR
CRP, mean ± S.D. (pg/dL)	Baseline Follow-up Mean difference	– – -2.9 (95% CI, -5.1 to -0.7)‡	1.5 (IQR 0.8; 4.0) 1.2 (IQR 0.6; 3.1) -0.3 (p=NS)	NR

‡ Values reported as mg/dL.

Abbreviations: bpm, beats per minute; CRP, C-reactive protein; dL, decilitre; HR, heart rate; IQR, interquartile range; mL, millilitre; mo, months; ms, millisecond; NR, not reported; NS, not significant; NT-proBNP, N-terminal pro-B-type natriuretic peptide; pg, picogram; S.D., standard deviation; SDNN, standard deviation of normal to normal intervals.

Table B4: Extended 12 months outcomes of the ANTHEM-HF case series reported by Premchand et al. (2016)[12].

Outcomes	Baseline	6 mo	12 mo	p-value		
				0 vs 6 mo	0 vs 12 mo	6 vs 12 mo
LVEF (%)	33.2 ± 7.4	38.5 ± 10.2	39.5 ± 10.4	0.0001	<0.0005	NS
LVESV (mL)	102.0 ± 37.6	96.9 ± 44.3	91.6 ± 43.5	NS	0.001	NS
LVESD (mm)	50 ± 8	48 ± 8	48 ± 8	<0.0025	0.003	NS
NYHA class (I/II/III/IV)	0/26/20/0	26/21/2/0	32/14/0/0	<0.0001	<0.0005	NS
6MWT (m)	288 ± 64	348 ± 77	352 ± 62	<0.0001	<0.0005	NS

MLHFQ	39 ± 12	20 ± 9	18 ± 9	<0.0001	<0.0005	NS
24-hour HR (bpm)	78 ± 12	72 ± 10	70 ± 10	<0.005	<0.0005	NS
SDNN (ms)	95 ± 29	106 ± 43	109 ± 40	<0.01	<0.01	NS

Note: Results reported as mean ± S.D.

Abbreviations: 6MWT, 6-minute walk test; bpm, beats per minute; HR, heart rate; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; LVESV, left ventricular end systolic volume; m, metre; MLHFQ, Minnesota Living with Heart Failure Questionnaire; mL; millilitre; mm, millimetre; mo, months; ms, millisecond; NS, not significant; NYHA, New York Heart Association; SDNN, standard deviation of normal to normal intervals.

Table B5: Long-term outcomes of the ANTHEM-HF case series reported by Sharma et al. (2021)[13].

Outcomes	Baseline	12 months	24 months*	30 months	42 months	p-value of 0 *vs* 42 months
LVEF (%)	35.0 ± 6.9	42.6 ± 10.4	41.7 ± 10.0	44.8 ± 12.0	40.8 ± 12.5	0.005
LVESV (mL)	92.8 ± 31.3	77.6 ± 35.7	81.6 ± 35.6	82.4 ± 47.2	92.7 ± 51.2	NS
LVESD (mm)	48.0 ± 7.9	45 ± 7.0	47 ± 7.5	47 ± 10	46 ± 12	NS
NYHA class (I/II/III/IV)	0/19/14/0	23/10/0/0	21/11/1/0	20/12/1/0	20/12/1/0	<0.0001
6MWT (m)	297 ± 62	354 ± 58	359 ± 47	367 ± 40	389 ± 70	<0.0001
MLHFQ score	38 ± 12	17 ± 9	21 ± 11	17 ± 9	10 ± 12	<0.0001
SDNN (ms)	96 ± 27	107 ± 32	112 ± 44	110 ± 30	107 ± 28	<0.025
24-h HR (bpm)	74 ± 10	75 ± 9	77 ± 10	76 ± 9	78 ± 11	NS

Note: Results reported as mean ± S.D.

* Reduction in stimulation frequency by 50% (10 Hz to 5 Hz) and increase in stimulation intensity by 20% (2.0 ± 0.6 mA to 2.4 ± 0.6 mA).

Abbreviations: 6MWT, 6-minute walk test; bpm, beats per minute; HR, heart rate; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; LVESV, left ventricular end systolic volume; m, metre; MLHFQ, Minnesota Living with Heart Failure Questionnaire; mL; millilitre; mm, millimetre; ms, millisecond; NYHA, New York Heart Association; SDNN, standard deviation of normal to normal intervals.

Table B6: Bilateral difference in efficacy outcomes in the ANTHEM-HF case series at 6 months.[11]

Efficacy outcomes	Left sided VNS	Right sided VNS	Left-Right difference
LVEF (%)	4.6 (1.5 to 7.7)	4.4 (1.3 to 7.5)	0.2 (-4.4 to 4.7)
LVESV (mL)	-2.2 (-9.5 to 5.1)	-5.9 (-13.1 to 1.2)	3.7 (-7.0 to 14.4)
LVESD (mm)	-1.1 (-2.6 to 0.5)	-2.4 (-3.9 to -0.9)	1.3 (-0.9 to 3.6)
6MWT (m)	34 (5.4 to 62)	77 (49 to 105)	-43 (-85 to -1.3)
MLHFQ	-17 (-20 to -13)	-20 (-24 to -17)	3.6 (-1.8 to 8.8)
24-hour HR (bpm)	-3.4 (-7.0 to 0.2)	-4.3 (-7.9 to -0.8)	0.9 (-4.4 to 6.2)
SDNN (ms)	20 (4.6 to 36)	14 (-1.8 to 30)	6.3 (-17 to 30)
NT-proBNP (pg/mL)	1,109 (-325 to 2,542)	-828 (-2,262 to 606)	1,936 (-179 to 4,052)
CRP (mg/dL)	-3.3 (-6.6 to -0.1)	-2.5 (-5.7 to 0.7)	-0.8 (-5.6 to 3.9)
eGFR (mL min^{-1} m^{-2})	-1.7 (-14 to 11)	-8.6 (-22 to 4.4)	6.8 (-12 to 26)

Notes:

1. Values were presented as marginal means (95% confidence interval)
2. Left-right difference was adjusted baseline values of change variable, history of ischemic etiology, heart rate and heart failure medications, including angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, loop diuretic, spironolactone, and digoxin (all were on a beta-blocker).

Abbreviations: 6MWT, 6-minute walk test; bpm, beats per minute; CRP, C-reactive protein; dL, decilitre; eGFR, estimated glomerular filtration rate; HR, heart rate; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; LVESV, left ventricular end systolic volume; m, metre; mg, milligram; MLHFQ, Minnesota Living with Heart Failure Questionnaire; mL; millilitre; mm, millimetre; ms, millisecond; NT-proBNP, N-terminal pro-B-type natriuretic peptide; pg, picogram; SDNN, standard deviation of normal to normal intervals.