Non-invasive Vagus Nerve Stimulator (gammaCore®) Was Not Associated With Meaningful Cardiovascular Adverse Effects

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Introduction

- The vagus nerve regulates the autonomic activity of the respiratory, gastrointestinal, endocrine, and cardiovascular (CV) systems[1-3]
- Vagus nerve stimulation (VNS) has demonstrated efficacy in the treatment of epilepsy[4] and depression[5] and is also under investigation for the treatment of pain associated with migraine[6] and cluster headache[7] and bronchoconstriction in patients with asthma[8]
- Despite the efficacy of VNS in various disease states, its use has resulted in adverse cardiac effects; ie, bradycardia and ventricular asystole were observed in patients who received VNS via an implanted device for the treatment of epilepsy[9-12]
- A non-invasive VNS (nVNS) device that stimulates the afferent fibers of the cervical vagus nerve has been developed for the treatment of asthma symptoms
- This report describes the CV safety of the nVNS device when used to treat acute bronchospasm in patients with asthma

Methods

Study Design and Objective

- BC-US-06 was an open-label, phase 2, multicenter, prospective, single-arm interventional pilot study conducted between January 27, 2012, and May 14, 2012
- The primary objective of BC-US-06 was to obtain preliminary data regarding the safety and clinical benefits of nVNS for the relief of acute bronchoconstriction in subjects with asthma

Patient Population

- Men or women aged 18 to 65 years with a history of mild to moderate asthma exacerbations (as per the Global Initiative for Asthma guidelines[13]) for at least 1 year prior to enrollment
- Use of an inhaled short-acting β-agonist (eg, albuterol) to reverse asthma symptoms
- Reversibility of forced expiratory volume in the first second of expiration of ≥12% within 15 to 30 minutes after 4 inhalations of albuterol

Intervention

- The nVNS device (**Figure 1**) produces a low-voltage electric signal that comprises a series of 5-kHz sine waves occurring over 1 millisecond; the series recurs at a frequency of 25 Hz (ie, every 40 milliseconds)
- The device delivers a maximum voltage of 24 V and a maximum output current of 60 mA
  - The stimulation amplitude is adjusted by the user
- A small amount of conductive gel enables delivery of stimulations via a pair of stainless steel contact surfaces
- Subjects self-administered a single 90-second nVNS stimulation to the right side of the neck for the treatment of asthma symptoms

Figure 1. nVNS Device

Assessment of Cardiac Function

- Patients had 12-lead electrocardiograms (ECGs) obtained at 3 study visits
  - Baseline
  - Treatment
    - Before nVNS stimulation (ie, pre-nVNS)
    - During stimulation
    - Immediately after and at 5, 15, 30, 60, and 90 minutes after nVNS stimulation (ie, post-nVNS)
  - Follow-up at 7 days after treatment
- The following ECG parameters were measured
  - Heart rate, PR interval, corrected QT (QTc) interval, and QRS duration
- The ECG findings and the impact of nVNS on cardiac rhythms were reviewed by an independent cardiologist, documented, and summarized

Evaluation of Adverse Events

- Adverse events (AEs) were categorized according to their intensity
  - *Mild* AEs were noticeable to the patient but did not interfere with routine activity or require medical treatment
  - *Moderate* AEs interfered with routine activity and usually required treatment but responded to symptomatic therapy or rest
  - *Severe* AEs substantially limited the patient's ability to perform routine activities despite symptomatic therapy
- *Serious* AEs were defined as those resulting in death, a life-threatening event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity, or substantial disruption of the ability to conduct normal life functions or a congenital anomaly/birth defect
- The relationship of AEs to treatment with the nVNS device was also evaluated

Statistical Analyses

- Descriptive statistics (ie, mean values +/- standard error of the mean [SEM]) were used to assess ECG parameters
- No other formal statistical analyses were performed

Demographics and Baseline Characteristics

- Thirty subjects were enrolled at 4 investigational sites in the United States
- Demographic and baseline characteristics of all enrolled subjects are shown in **Table 1**

Table 1. Demographics and Baseline Characteristics

BC-US-06 Study Population (N=30)	
Mean Age, y (SD; range)	35.1 (12.4; 20–60)
Sex, n (%)	
Male	7 (23.3)
Female	23 (76.7)
Ethnicity, n (%)	
Caucasian	17 (56.7)
African American	8 (26.7)
Hispanic	4 (13.3)
Other	1 (3.3)
Body Mass Index, n (%)	
>30 kg/m²	10 (33.3)
≤30 kg/m²	20 (66.7)
Mean Heart Rate, bpm (SD; range)	75.3 (9.2; 56–88)
Mean Number of Years With Asthma, (SD; range)	27.3 (11.4; 2–52)
History of Smoking, n (%)	
Yes	3 (10)
No	27 (90)

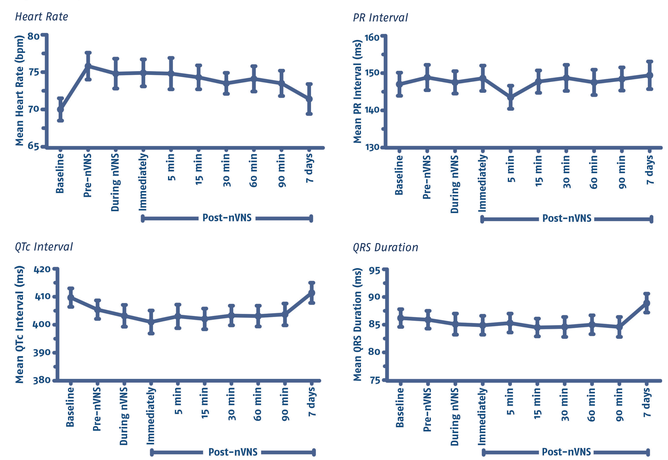
Abbreviations: SD, standard deviation; bpm, beats per minute.

Results

ECG Findings

- A total of 284 ECGs were performed for 29 of 30 patients
  - One subject was excluded because only 1 ECG reading was taken during the treatment visit
- No clinically significant ECG changes were noted, either in isolated readings or in comparison to baseline, in the 29 patients with evaluable ECGs
- Treatment with nVNS had no meaningful effect on heart rate, PR interval, QTc interval, or QRS duration (**Figure 2**)
- Stimulation produced an ECG artifact in 24% (7 of 29) of patients, which resulted in incorrect indications of pacemaker presence

Figure 2. Impact of nVNS on ECG Parameters



Abbreviations: nVNS, non-invasive vagus nerve stimulation; ECG, electrocardiogram; bpm, beats per minute. Error bars represent SEM.

Impact of nVNS on Cardiac Rhythm

Premature Atrial and Ventricular Contractions (PACs and PVCs)

- Isolated PACs and PVCs occurred in 13.8% (4 of 29) of subjects throughout the study (**Table 2**); the occurrences were consistent with those reported in the general population[14,15]
  - No PACs or PVCs were observed at baseline or pre-nVNS
  - PACs occurred in 4 subjects: 1 subject each during nVNS, immediately post-nVNS, at 30 minutes post-nVNS, and at 7 days post-nVNS treatment
  - PVCs occurred in 1 subject at 60 minutes post-nVNS treatment
- The reported PACs and PVCs did not indicate an increase in supraventricular ectopy post-nVNS treatment

Arrhythmias

- No atrial or ventricular arrhythmias were reported
- Benign sinus arrhythmia (SA) occurred 43 times in 44.8% (13 of 29) of subjects throughout the study (**Table 2**)
  - SA occurred at multiple time points in 10 subjects; 1 subject experienced benign SA at each time point throughout the study
  - Four subjects had SA at baseline and/or pre-nVNS; 3 of these subjects had SA at both baseline and pre-nVNS; 1 subject had SA at baseline only
  - Three subjects experienced SA during nVNS treatment
  - SA occurred 33 times post-nVNS treatment in 11 subjects; 5 of these subjects experienced SA immediately post-nVNS treatment
- Treatment with nVNS may have contributed to SA; however, benign SA is common in young patients and is not considered clinically meaningful; moreover, the frequency of SA did not exceed that observed in the general population

Table 2. Number of Subjects With Changes in Cardiac Rhythm by Evaluation Time Point

BC-US-06 Study Population (N=29)										
Change in Cardiac Rhythm, n	**Baseline**	**Pre-nVNS**	**During nVNS**	**Immediately Post-nVNS**	**5 min Post-nVNS**	**15 min Post-nVNS**	**30 min Post-nVNS**	**60 min Post-nVNS**	**90 min Post-nVNS**	**7 Days Post-nVNS**
PAC[a]	0	0	1	1	0	0	1	0	0	1
PVC[a]	0	0	0	0	0	0	0	1	0	0
SA[b,c]	4	3	3	5	4	6	7	5	5	1

Abbreviations: nVNS, non-invasive vagus nerve stimulation; PAC, premature atrial contraction; PVC, premature ventricular contraction; SA, sinus arrhythmia.
[a] Total number of patients evaluated for PACs and PVCs at each time point ranged from 26 to 29.
[b] Some patients experienced SA at multiple time points.
[c] Includes 1 patient who experienced a benign SA at every evaluation time point during the study.

Incidence of Adverse Events

- A total of 16 AEs were reported in 10 subjects (**Table 3**)
  - Most AEs (14 of 16; 87.5%) were mild in intensity and 13 (81.2%) resolved without further intervention
  - No unanticipated AEs were reported
  - No serious AEs occurred during the study
  - A total of 10 AEs that were *related* or *possibly related* to treatment with the nVNS device were noted in 5 subjects

Table 3. Incidence of Adverse Events

BC-US-06 Study Population (N=30)	
Subjects With ≥1 AE, n (%)	10 (33.3)
Subjects With AEs by Intensity, n (%)[a]	
Mild	9 (30)
Moderate	1 (3.3)
Severe	1 (3.3)[b]
Subjects With ≥1 AE Related/Possibly Related to Treatment, n (%)	5 (16.7)[c]

Abbreviation: AE, adverse event.
[a] Some subjects experienced >1 AE.
[b] Muscle tightness/spasms on the right side of the body, extending from the ear to the wrist.
[c] Includes pain in the neck region at the site of stimulation, hoarseness, chest congestion, tightness/muscle spasms on the right side of the body, jitteriness in the upper body, excess mucus in the oropharynx, erythema on the anterior biceps (bilateral), musculoskeletal tension/tightness in the upper body, tingling on the right side of the neck where the stimulation was applied, and torticollis.

Conclusions

- **Despite previous reports of cardiac effects in patients receiving implanted VNS for the treatment of epilepsy, these effects appear to be a relatively rare occurrence[12] and may be associated with**
  - **Electrode placement[12]**
  - **Variations in vagus nerve anatomy[12]**
  - **Disease state (eg, status epilepticus)[9]**
  - **Modification of vagus nerve susceptibility to chronic stimulation by antiepileptic drugs[9]**
- **nVNS treatment had no clinically meaningful effect on CV function in subjects with asthma**
- **Occurrences of PAC and PVC were transient and benign and did not reflect an increase in ventricular ectopy post-nVNS treatment**
- **Although nVNS treatment may have contributed to the development of SA, all observed SAs were transient and benign and were not unexpected for the study population**
- **Most AEs were mild, and no serious AEs occurred in any patient**
- **The CV safety findings for nVNS reported in this study may support the safe use of nVNS in neurological disease states (eg, epilepsy, depression, migraine and cluster headache)**
- **A number of large-scale studies of nVNS have been completed, and additional studies are under way to further validate the safety of this therapy in the treatment of multiple neurological conditions**
- **No cardiac AEs have been reported to date in completed or ongoing clinical studies of nVNS in the European Union or the United States**

References

1. Krahl SE. Vagus nerve stimulation for epilepsy: a review of the peripheral mechanisms. *Surg Neurol Int*. 2012;3(suppl 1):S47–S52.
2. De Couck M, Nijs J, Gidron Y. You may need a nerve to treat pain: the neurobiological rationale for vagal nerve activation in pain management. *Clin J Pain*. 2014;30(12):1099–1105.
3. Pirola FT, Potter EK. Vagal action on atrioventricular conduction and its inhibition by sympathetic stimulation and neuropeptide Y in anaesthetised dogs. *J Auton Nerv Syst*. 1990;31(1):1–12.
4. Orosz I, McCormick D, Zamponi N, et al. Vagus nerve stimulation for drug-resistant epilepsy: a European long-term study up to 24 months in 347 children. *Epilepsia*. 2014;55(10):1576–1584.
5. Aaronson ST, Carpenter LL, Conway CR, et al. Vagus nerve stimulation therapy randomized to different amounts of electrical charge for treatment-resistant depression: acute and chronic effects. *Brain Stim*. 2013;6(4):631–640.
6. Goadsby PJ, Grosberg BM, Mauskop A, Cady R, Simmons KA. Effect of noninvasive vagus nerve stimulation on acute migraine: an open-label pilot study. *Cephalalgia*. 2014;34(12):986–993.
7. Nesbitt AD, Marin JCA, Tompkins E, Ruttledge MH, Goadsby PJ. Initial use of a novel noninvasive vagus nerve stimulator for cluster headache treatment. *Neurology*. 2015;84(12):1249–1253.
8. Miner JR, Lewis LM, Mosnaim GS, Varon J, Theodoro D, Hoffmann TJ. Feasibility of percutaneous vagus nerve stimulation for the treatment of acute asthma exacerbations. *Acad Emerg Med*. 2012;19(4):421–429.
9. Iriarte J, Urrestarazu E, Alegre M, et al. Late-onset periodic asystolia during vagus nerve stimulation. *Epilepsia*. 2009;50(4):928–932.
10. Ardesch JJ, Buschman HP, van der Burgh PH, Wagener-Schimmel LJ, van der Aa HE, Hageman G. Cardiac responses of vagus nerve stimulation: intraoperative bradycardia and subsequent chronic stimulation. *Clin Neurol Neurosurg*. 2007;109(10):849–852.
11. Ali II, Pirzada NA, Kanjwal Y, et al. Complete heart block with ventricular asystole during left vagus nerve stimulation for epilepsy. *Epilepsy Behav*. 2004;5(5):768–771.
12. Frei MG, Osorio I. Left vagus nerve stimulation with the neurocybernetic prosthesis has complex effects on heart rate and on its variability in humans. *Epilepsia*. 2001;42(8):1007–1016.
13. Global Initiative for Asthma. *Global Strategy for Asthma Management and Prevention*. http://www.ginasthma.org/local/uploads/files/GINA_Report_2014_Aug12.pdf. Revised 2014. Accessed March 8, 2015.
14. Conen D, Adam M, Roche F, et al. Premature atrial contractions in the general population: frequency and risk factors. *Circulation*. 2012;126(19):2302–2308.
15. Simpson RJ Jr, Cascio WE, Schreiner PJ, Crow RS, Rautaharju PM, Heiss G. Prevalence of premature ventricular contractions in a population of African American and white men and women: the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J*. 2002;143(3):535–540.

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