electroCore™

gammaCore Sapphire™

CLINICAL STUDIES

Acute Treatment of episodic cluster headache clinical studies

Clinical data demonstrating the safety and effectiveness of gammaCore for the acute treatment of episodic cluster headache is presented from two prospective, double-blind, sham-controlled, randomized clinical trials (ACT1 and ACT2).

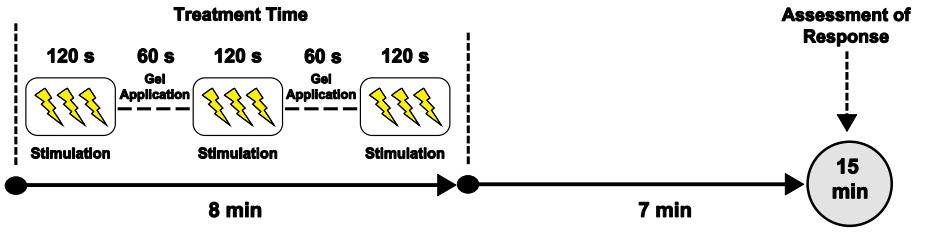
Summary

In both studies, gammaCore did not provide a significant improvement over a sham (placebo) device in the total patient population, which included patients with episodic cluster headache (eCH) and chronic cluster headache (cCH). In both studies, there was a significant improvement over sham demonstrated in patients with eCH but not cCH, which affected the results in the total study population.

Study 1: gammaCore for the Acute Treatment of Episodic Cluster Headache: The ACT1 Study

In ACT1, subjects were instructed to treat their cluster headache attack at the onset of pain with three 2-minute stimulations (Figure 1).

Figure 1. ACT1 Treatment Protocol



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Demographics

ACT1 enrolled a total of 150 patients with cluster headache. Overall, 101 of the patients had eCH and 49 had cCH. General demographics are provided in Table 1.

Table 1. ACT1 Demographics

Characteristic	By Treatment Group (N=150)		By Cohort (N=150)	
	nVNS (n=73)	Sham (n=77)	eCH Cohort (n=101)	cCH Cohort (n=49)
Age (y), mean±SD	47.1±13.5	48.6±11.7	48.4±12.5	46.8±13.0
Male, No. (%)	59 (80.8)	67 (87.0)	84 (83.2)	42 (85.7)
Race, No. (%)				
Asian	4 (5.5)	1 (1.3)	4 (4.0)	1 (2.0)
Black	5 (6.9)	7 (9.1)	9 (8.9)	3 (6.1)
White	63 (86.3)	68 (88.3)	87 (86.1)	44 (89.8)
Missing	1 (1.4)	1 (1.3)	1 (1.0)	1 (2.0)
Duration of last CH attack (min), mean±SD	86±119	64±71	76.5±104.4	68.9±75.0
CH Type, No. (%)				
eCH	50 (68.5)	51 (66.2)	101 (100.0)	0
cCH	23 (31.5)	26 (33.8)	0	49 (100.0)
Medications Used to Manage CH, No. (%)				
Triptans	42 (57.5)	54 (70.1)	68 (67.3)	28 (57.1)
Oxygen	31 (42.5)	29 (37.7)	37 (36.6)	23 (46.9)
Mild analgesics	13 (17.8)	16 (20.8)	16 (15.8)	13 (26.5)
Narcotics	4 (5.5)	4 (5.2)	5 (5.0)	3 (6.1)
Prophylactic medications	42 (57.5)	60 (77.9)	65 (64.4)	37 (75.5)
Verapamil	11 (15.1)	20 (26.0)	25 (24.8)	6 (12.2)
Lithium	3 (4.1)	3 (3.9)	4 (4.0)	2 (4.1)
Topiramate	2 (2.7)	7 (9.1)	5 (5.0)	4 (8.2)
Corticosteroids	11 (15.1)	8 (10.4)	15 (14.9)	4 (8.2)
Other	21 (28.8)	28 (36.4)	28 (27.7)	21 (42.9)
None	4 (5.5)	2 (2.6)	5 (5.0)	1 (2.0)

Abbreviations: cCH, chronic cluster headache; CH, cluster headache; eCH, episodic cluster headache; nVNS, non-invasive vagus nerve stimulation; SD, standard deviation.

Efficacy

Primary End Point

The primary efficacy end point in the ACT1 Study was the percentage of patients who reported mild or no pain 15 minutes after treatment initiation with gammaCore for the first treated CH attack in the study; rescue medication use within 60 minutes was considered a treatment failure.

The results for the primary end point in the total population were 26.7% in the nVNS group and 15.1% in the sham group, which was not significant (P=0.1). In subgroup analyses, a significantly higher response rate was demonstrated with nVNS (34.2%) than with sham treatment (10.6%) for the eCH cohort (P<0.01) but not for the cCH cohort (nVNS, 13.6%; sham, 23.1%; P=0.48). Please see Table 2 for complete details.

Key Additional End Points

Sustained treatment response rates (defined as the proportion of subjects with mild or no pain without the use of rescue medication through 60 minutes after treatment initiation for the first CH attack) for the total and eCH cohort population were significantly higher with nVNS than with sham treatment (total: nVNS, 26.7%; sham, 12.3%; P=0.04; eCH: nVNS, 34.2%; sham, 10.6%; P<0.01). For the cCH cohort, sustained response rates were similar between groups (nVNS, 13.6%; sham, 15.4%; P=1.0). Pain intensities at 15 minutes after treatment for all CH attacks were not significantly different between the nVNS and sham treatment groups (total: nVNS, 2.1; sham, 2.0; P=0.04; eCH: nVNS, 2.0; sham, 2.0; P=1.0; cCH: nVNS, 2.3; sham, 1.9; P=0.2). Please see Table 2 for complete details.

The proportion of subjects in the eCH cohort, but not in the cCH cohort or total population, who were responders (mild or no pain) at 15 minutes for ≥50% of the total number of treated attacks was significantly higher with nVNS than with sham treatment (total: nVNS, 26.7%; sham, 20.6%; P=0.41; eCH: nVNS, 34.2%; sham, 14.9%; P=0.04; cCH: nVNS, 13.6%; sham, 30.8%; P=0.19). Similarly, between-group differences favored nVNS for the change in duration of the first attack in the double-blind phase and were significant in the total population (–9.5 minutes; P=0.03) and eCH cohort (–14.4 minutes; P=0.03) but not in the cCH cohort (1.0 minute; P=0.69). Please see Table 2 for complete details.

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Table 2. ACT1 Key End Points (mITT Population Unless Otherwise Indicated)

End Point	All Subjects		eCH Cohort		cCH Cohort	
	nVNS (n=60)	Sham (n=73)	nVNS (n=38)	Sham (n=47)	nVNS (n=22)	Sham (n=26)
Primary end point (all subjects)						
Response rate (%)[a]	26.7 (16/60)	15.1 (11/73)	34.2 (13/38)	10.6 (5/47)	13.6 (3/22)	23.1 (6/26)
95% CI	16.1, 39.7	7.8, 25.4	19.6, 51.4	3.6, 23.1	2.9, 34.9	9.0, 43.7
P-value	0.1		<0.01		0.48	
Secondary end points (all subjects)						
Sustained treatment response rate (%)[a]	26.7 (16/60)	12.3 (9/73)	34.2 (13/38)	10.6 (5/47)	13.6 (3/22)	15.4 (4/26)
95% CI	16.1, 39.7	5.8, 22.1	19.6, 51.4	3.6, 23.1	2.9, 34.9	4.3, 34.9
P-value	0.04		<0.01		1.0	
Pain level,[b] mean	2.1	2.0	2.0	2.0	2.3	1.9
95% CI	1.9, 2.3	1.8, 2.2	1.8, 2.3	1.8, 2.3	1.9, 2.6	1.6, 2.3
P-value	0.04		1.0		0.2	
Other end points						
Subjects who were responders at 15 min for ≥50% of their treated attacks in the double-blind phase (%)[a]	26.7 (16/60)	20.6 (15/73)	34.2 (13/38)	14.9 (7/47)	13.6 (3/22)	30.8 (8/26)
95% CI	16.1, 39.7	12.0, 31.6	19.6, 51.4	6.2, 28.3	2.9, 34.9	14.3, 51.8
P-value	0.41		0.04		0.19	
Change in duration of attacks from baseline to the first attack in the double-blind phase (min),[c,d] mean±SD	-9.5±51.8	12.8±45.5	-14.4±59.5	16.3±51.5	1.0±28.6	5.4±29.2
n (observed cases)	n=41	n=53	n=28	n=36	n=13	n=17
95% CI	-25.8, 6.9	0.2, 25.3	-37.4, 8.7	-1.1, 33.7	-16.3, 18.3	-9.7, 20.4
P-value	0.03		0.03		0.69	

Abbreviations: cCH, chronic cluster headache; CI, confidence interval; eCH, episodic cluster headache; mITT, modified intent-to-treat; nVNS, non-invasive vagus nerve stimulation; SD, standard deviation.

[a]No rescue medication use through 60 min after treatment initiation; *P*-values are from Fisher's exact test (if ≥1 cell had an expected frequency of ≤5) or the chi-square test.

[b]Linear mixed-effect regression models were used to compare mean treatment group intensities to account for repeated measures per subject.

[c]Attacks with duration >180 min were excluded according to ***International Classification of Headache Disorders*** criteria; *P*-values are from the *t* test.

[d]Change from the last attack before randomization (based on subject recollection) to the first attack in the double-blind phase (based on objective recording).

Safety
gammaCore was found to be safe and well tolerated in this study. The majority of the adverse events were mild and transient and occurred during the time of active treatment. None of the serious adverse events were considered device related. Please see Table 3 for complete details.

Table 3. ACT1 Incidence of Adverse Events and Adverse Device Effects (All Treated Subjects)

AEs and ADEs	Double-blind Phase		Open-label Phase
	nVNS (n=73)	Sham (n=77)	nVNS (n=128)
Subjects with ≥1 AE, No. (%)	18 (24.7)	31 (40.3)	42 (32.8)
Subjects with ≥1 serious AE, No. (%)	1 (1.4)[a,b]	0	5 (3.9)[b,c]
Subjects with ≥1 ADE, No. (%)	11 (15.1)	24 (31.2)	18 (14.1)
ADEs Occurring in ≥5% of Subjects in Any Treatment Group, No. (%)			
Application site reactions			
Burning/tingling/soreness/stinging	2 (2.7)	7 (9.1)	4 (3.1)
Skin irritation/redness/erythema	0	9 (11.7)	2 (1.6)
Musculoskeletal disorders			
Lip or facial drooping/pulling/twitching	8 (11.0)	0	9 (7.0)
Nervous system disorders			
Dysgeusia/metallic taste	0	7 (9.1)	2 (1.6)

Abbreviations: ADE, adverse device effect; AE, adverse event; nVNS, non-invasive vagus nerve stimulation.
[a]Serious AE of cluster headache (2 occurrences).
[b]Serious AEs were not considered related to the study device.
[c]Serious AEs included cluster headache (1 occurrence; 1 subject); cluster headache as well as multiple left-extremity deep vein thromboses, abdominal aortic aneurysm, pneumonia, anasarca, acute respiratory failure, and urethral trauma (1 occurrence each in the same subject); mesenteric ischemia (1 occurrence; 1 subject); herniated disk (1 occurrence; 1 subject); and ureteral calculus (1 occurrence; 1 subject).

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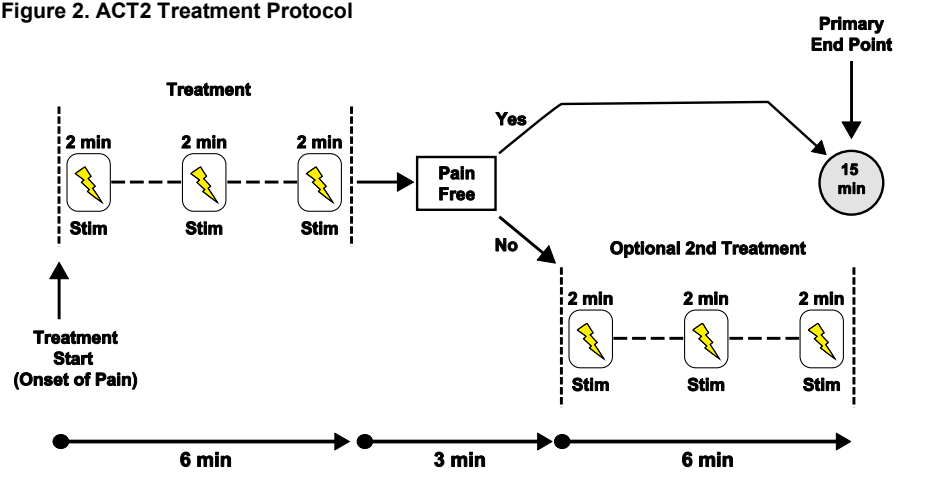
Study 2: gammaCore for the Acute Treatment of Chronic and Episodic Cluster Headache: The ACT2 Study

In ACT2, subjects were instructed to treat their cluster headache attack at the onset of pain with three 2-minute stimulations (Figure 2). If pain was still present at 9 minutes, the subjects had the option of treating with an additional three 2-minute stimulations.

Figure 2. ACT2 Treatment Protocol



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Demographics

ACT2 enrolled a total of 102 patients with cluster headache. General demographics are provided in Table 4.

Table 4. ACT2 Demographic and Baseline Characteristics (Safety Population)

Characteristic	By Treatment Group (N=102)		By Cohort (N=102)	
	nVNS (n=50)	Sham (n=52)	eCH Cohort (n=30)	cCH Cohort (n=72)
Age (y), mean±SD	43.9 (10.6)	46.9 (10.6)	42.9 (12.7)	46.5 (9.6)
Male, No. (%)	35 (70.0)	38 (73.1)	22 (73.3)	51 (70.8)
Ethnic origin, No. (%)				
White	49 (98.0)	52 (100.0)	30 (100.0)	71 (98.6)
Black	0	0	0	0
Asian	1 (2.0)	0	0	1 (1.4)
Duration of CH attacks during run-in period, mean±SD, min	69.9 (68.7)	77.4 (76.9)	69.6 (83.3)	76.1 (69.0)
CH Type, No. (%)				
eCH	15 (30.0)	15 (28.8)	30 (100.0)	0
cCH	35 (70.0)	37 (71.2)	0	72 (100.0)
Medications Used to Manage CH, No. (%)				
Triptans	37 (74.0)	34 (65.3)	19 (63.3)	52 (72.2)
Oxygen	27 (54.0)	31 (59.6)	20 (66.7)	38 (52.8)
Mild analgesics	7 (14.0)	6 (11.5)	2 (6.7)	11 (15.3)
Narcotics	3 (6.0)	0	1 (3.3)	2 (2.8)
Verapamil	18 (36.0)	23 (44.2)	11 (36.7)	30 (41.7)
Lithium	4 (8.0)	4 (7.7)	1 (3.3)	7 (9.7)
Propranolol	1 (2.0)	0	0	1 (1.4)
Tricyclic antidepressants	2 (4.0)	1 (1.9)	1 (3.3)	2 (2.8)
Serotonin receptor antagonists	2 (4.0)	2 (3.8)	1 (3.3)	3 (4.2)
Antiepileptics	10 (20.0)	6 (11.5)	3 (10.0)	13 (18.1)
Corticosteroids	1 (2.0)	2 (3.8)	1 (3.3)	2 (2.8)
Other	5 (10.0)	8 (15.4)	4 (13.3)	9 (12.5)
None	0	5 (9.6)	1 (3.3)	4 (5.6)

Abbreviations: cCH, chronic cluster headache; CH, cluster headache; eCH, episodic cluster headache; nVNS, non-invasive vagus nerve stimulation; SD, standard deviation.

Efficacy

The primary efficacy end point in the ACT2 Study was the percentage of total attacks that were pain-free 15 minutes after the initiation of treatment with the device with no use of rescue medication through the treatment period (30 minutes).

The results for the primary end point in the total population were 13.5% in the nVNS group and 11.5% in the sham group and were not statistically significant *P*=0.71). In the eCH cohort, a significantly higher percentage of attacks were pain free with nVNS than with sham treatment (nVNS, 47.5%; sham 6.2%; P<0.01) but not for the cCH cohort where the sham group performed better but the difference was not statistically significant (nVNS, 4.8%; sham, 12.9%; *P*=0.13). Please see Table 5 for complete details.

Key Additional End Points

The proportion of each patient's attacks that responded (ie, had mild or no pain) 30 minutes after the initiation of gammaCore treatment was significantly better than the sham results in the total population but did not achieve significance in the eCH or cCH cohorts (total: nVNS, 43%; sham, 28%; *P*=0.05; eCH: nVNS, 58%; sham, 25.5%; *P*=0.07; cCH: nVNS 37%; sham 28.5%; *P*=0.34). In patients with eCH there was a significant reduction in the reported average pain intensity 15 minutes after treatment on a 5-point scale (nVNS, –1.7; sham, –0.6; *P*=0.01) that did not achieve significance in the total population or the cCH cohort (total: nVNS, –1.3; sham, –0.9; P=0.06; cCH: nVNS, –1.2; sham, –1.0; *P*=0.52). The percentage of patients who reported mild or no pain 30 minutes after treatment initiation for ≥50% of their attacks was significantly higher for both the total and eCH groups, but not the cCH group (total: nVNS, 39.6%; sham, 13.6%; *P*=0.01; eCH: nVNS, 64.3%; sham, 15.4%; *P*=0.01; cCH: nVNS, 29.4%; sham, 12.9%; *P*=0.11). The percentage of subjects who reported mild or no pain at 15 minutes for their first treated attack was not significantly different for any of the observed groups. Please see Table 5 for complete details.

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Table 5. ACT2 Key End Points (mITT Population Unless Otherwise Indicated)

End Point	All Subjects		eCH Cohort		cCH Cohort	
	nVNS (n=48)	Sham (n=44)	nVNS (n=14)	Sham (n=13)	nVNS (n=34)	Sham (n=31)
Primary end point (all subjects)						
Attacks that were pain free at 15 min, % (n/N)[a]	13.5 (67/495)	11.5 (46/400)	47.5 (48/101)	6.2 (5/81)	4.8 (19/394)	12.9 (41/319)
Odds ratio (95% CI)	1.22 (0.42, 3.51)		9.19 (1.77, 47.80)		0.41 (0.13, 1.30)	
P-value[b]	0.71		<0.01		0.13	
Secondary end points (all subjects)						
Percentage of attacks per subject that responded at 30 min, mean±SD[a]	42.7±37	27.6±33	57.5±40	25.5±37	36.6±34	28.5±31
nVNS vs sham difference, mean±SE	15.1± 7.0		32.0± 15.0		8.1± 8.0	
P-value[c]	0.05		0.07		0.34	
Change in pain level at 15 min,[a] mean±SE	-1.3±0.2	-0.9±0.1	-1.7±0.4	-0.6±0.2	-1.2±0.2	-1.0±0.2
No. (observed cases)	36	31	11	8	25	23
P-value[d]	0.06		0.01		0.52	
Other end points (all subjects)						
Subjects who achieved responder status at 30 min for ≥50% of treated attacks, No. (%)[a]	19 (39.6)	6 (13.6)	9 (64.3)	2 (15.4)	10 (29.4)	4 (12.9)
P-value[e]	0.01		0.01		0.11	
Subjects who achieved responder status at 15 min for their first treated attack, No. (%)[a]	18 (37.5)	13 (29.5)	7 (50.0)	2 (15.4)	11 (32.4)	11 (55.0)
P-value[f]	0.03		0.03		0.69	

Abbreviations: cCH, chronic cluster headache; CI, confidence interval; eCH, episodic cluster headache; mITT, modified intent-to-treat; nVNS, non-invasive vagus nerve stimulation; SD, standard deviation; SE, standard error.
[a]No rescue medication use at any point after treatment initiation for the attack.
[b]*P*-values are from generalized estimating equations model, which was adjusted for site for the total cohort and cCH subgroups but not adjusted for site in the eCH subgroup; odds ratio >1 favors nVNS.
[c]*P*-values are from the Wilcoxon rank-sum test stratified by study site.
[d]*P*-values were derived from 2-sided t tests.
[e]*P*-values were determined from the chi-square or Fisher's exact test, as appropriate.
[f]*P*-values were derived from the Cochran-Mantel-Haenszel test stratified by site.

Safety

gammaCore was found to be safe and well tolerated in this study. The majority of the adverse events were mild and transient and occurred during the time of active treatment. None of the serious adverse events were considered device related. Please see Table 6 for complete details.

Table 6. ACT2 Incidence of Adverse Events and Adverse Device Effects (All Treated Subjects)

AEs and ADEs	Double-blind Phase		Open-label Phase
	nVNS (n=50)	Sham (n=52)	nVNS (n=83)
Subjects with ≥1 AE, No. (%)	23 (46.0)	22 (42.3)	28 (33.7)
Subjects with ≥1 serious AE, No. (%)	1 (2.0)[a]	1 (1.9)[b]	0
Subjects with ≥1 ADE, No. (%)	13 (26.0)	13 (25.0)	14 (16.9)
ADEs occurring in ≥5% of subjects in any Treatment Group, No. (%)			
No ADEs occurred in ≥5% of subjects in any treatment group			

Abbreviations: ADE, adverse drug effect; AE, adverse event; nVNS, non-invasive vagus nerve stimulation; SAE, serious adverse event.

[a]One subject in the gammaCore group reported severe lower abdominal and lower back pain. These events were not considered related to treatment and resolved without intervention.

[b]One subject in the sham group reported severe depression and anxiety. These events were not considered by the investigator to be related to the sham device. The subject discontinued from the study, and the SAEs resolved.

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Summary Analysis of ACT1 and ACT2 Studies

To further define the therapeutic benefit of gammaCore for the acute treatment of pain associated with episodic cluster headache, the results of both studies were examined to assess the overall response to each study's primary end point. Please see Table 7 for complete details.

Table 7. ACT1 Primary End Point: Mild or Pain Free at 15 Minutes, No Rescue Medication, First Attack in Randomized Period

	nVNS n/N (%)	95% CI	Sham n/N (%)	95% CI	*P*-value (Chi-square or Fisher's Exact Test)
ACT1 Population					
Total	16/60 (26.7)	16.1, 39.7	11/73 (15.1)	7.8, 25.4	0.10
Episodic CH	13/38 (34.2)	19.6, 51.4	5/47 (10.6)	3.6, 23.1	<0.01
Chronic CH	3/22 (13.6)	2.9, 34.9	6/26 (23.1)	9.0, 43.7	0.48
ACT2 Population					
Total	18/48 (37.5)	23.4, 51.6	13/44 (29.5)	15.7, 43.4	0.35
Episodic CH	7/14 (50.0)	21.1, 78.9	2/13 (15.4)	0, 37.2	0.06
Chronic CH	11/34 (32.4)	16.0, 48.7	11/31 (35.5)	17.9, 53.0	0.79

Abbreviations: CH, cluster headache; CI, confidence interval; nVNS, non-invasive vagus nerve stimulation.

In each of the studies, nVNS showed a significant (ACT1) and/or clinically meaningful (ACT2) improvement in the eCH cohort that was not observed in the cCH cohort for the primary end point of the ACT1 study. The results of the cCH group negatively affected the results for the total study population, which were not significant.

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Table 8. ACT2 Primary End Point: Number (%) of All Attacks in Randomized Period Pain Free at 15 Minutes, No Rescue Medication

	nVNS		Sham		*P*-value
	n/N[a] (%)	GEE Model Adjusted % (95% CI)[b]	n/N[a] (%)	GEE Model Adjusted % (95% CI)[b]	GEE Model[b]
ACT1 Population					
Total	28/259 (10.8)	11.5 (7.0, 18.4)	26/319 (8.2)	8.4 (4.9, 14.0)	0.38
Episodic CH	24/158 (15.2)	15.4 (9.5, 24.1)	13/206 (6.3)	6.1 (3.0, 12.0)	0.03
Chronic CH	4/101 (4.0)	5.3 (1.1, 22.5)	13/113 (11.5)	14.6 (6.1, 31.0)	0.25
ACT2 Population					
Total	67/495 (13.5)	15.0 (9.0, 23.8)	46/400 (11.5)	8.7 (4.2, 16.9)	0.20
Episodic CH	48/101 (47.5)	35.2 (19.1, 55.5)	5/81 (6.2)	7.4 (1.6, 28.4)	0.04
Chronic CH	19/394 (4.8)	7.4 (3.3, 15.9)	1/319 (12.9)	9.2 (4.3, 18.6)	0.69

Abbreviations: CH, cluster headache; CI, confidence interval; GEE, generalized estimating equation; nVNS, non-invasive vagus nerve stimulation.
[a]Number of successful responses/number of attacks.
[b]Generalized linear mixed effects regression models (SAS proc glimmix) were utilized to estimate the proportion of successful responses allowing for both subject-specific and population-averaged inference in non-normally distributed data. *P*-values for comparison between nVNS and sham are from resulting F-tests.

In both studies nVNS showed a significant and clinically meaningful improvement over the sham device in the eCH cohort but not in the cCH cohort for the primary end point of ACT2. The results of the cCH group negatively affected the results for the total study population, which were not significant.

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Acute Treatment of Migraine Headache Clinical Study

Clinical data demonstrating the safety and effectiveness of gammaCore for the acute treatment of migraine headache is presented from one prospective, double-blind, sham-controlled, randomized clinical trial (The PRESTO Study).

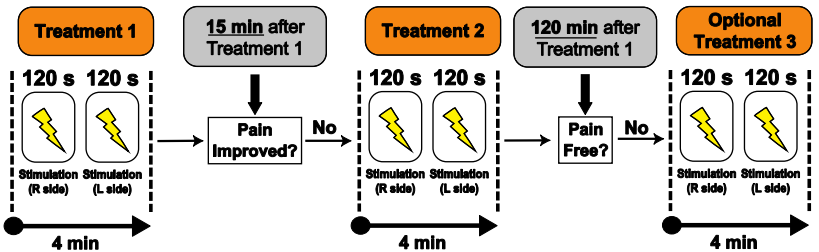
Summary

This randomized, sham-controlled trial demonstrated the safety and efficacy of gammaCore for the acute treatment of episodic migraine with or without aura. gammaCore was safe and well tolerated in this study.

gammaCore for the Acute Treatment of Migraine Headache: The PRESTO Study

In PRESTO, subjects were instructed to treat their migraine headache within 20 minutes of the onset of pain. Each self-administered treatment consisted of bilateral 2-minute stimulations to the right and left sides of the neck. If the pain had not decreased 15 minutes after initial treatment, subjects were instructed to repeat the bilateral stimulations, and if not pain-free 2 hours after initial treatment, a third set of bilateral stimulations was allowed. (Figure 3)

Figure 3. PRESTO Treatment Protocol



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Demographics

PRESTO enrolled a total of 243 patients with migraine. General demographics are provided in Table 9.

Table 9. PRESTO Demographics and Subject/Attack Characteristics (ITT Population)

Characteristic	By Treatment Group (N=243)	
	nVNS (n=120)	Sham (n=123)
At Baseline		
Age (y), mean±SD	38.8 ± 11.0	39.6 ± 11.8
Age of migraine onset (y), mean±SD	29.4 ± 11.2	28.5 ± 11.5
Female, No. (%)	95 (79.2)	91 (74.0)
Race, No. (%)		
Asian	0	0
Black	0	0
White	120 (100)	123 (100)
Other	0	0
Migraine Type, No. (%)		
Migraine with aura	8 (6.7)	9 (7.3)
Migraine without aura	112 (93.3)	114 (92.7)
Attacks in the last 4 weeks (No.), mean±SD	5.4 ± 1.7	5.3 ± 1.7
Headache days in the last 4 weeks (No.), mean±SD	6.3 ± 2.3	6.2 ± 2.1
Attacks per month in the last 6 months (No.), mean±SD	5.4 ± 1.5	5.4 ± 1.5
Acute migraine medication use per month (d), mean±SD	5.6 ± 1.7	5.3 ± 1.7
Preventive medication use, No. (%)	42 (35.0)	35 (28.5)
At Attack Onset[a]		
Migraine attack severity (first treated attack), No. (%)[b]		
Mild	40 (33.6)	46 (38.7)
Moderate	51 (42.9)	55 (46.2)
Severe	28 (23.5)	18 (15.1)
Migraine attack severity (all treated attacks), No. (%)[b]		
Mild	113 (31.5)	105 (31.9)
Moderate	156 (43.5)	166 (50.5)
Severe	90 (25.1)	58 (17.6)

Abbreviations: ITT, intent-to-treat; nVNS, non-invasive vagus nerve stimulation; SD, standard deviation.
[a] Subjects with no reported severity at attack onset are excluded from this analysis.
[b] First treated attack: nVNS, n=119; sham, n=119; all treated attacks: nVNS, n=359; sham, n=329.

Efficacy

Primary End Point

The proportion of participants who became pain-free for the first treated migraine attack approached but did not reach statistical significance at 120 minutes (nVNS, 30.4%; sham, 19.7%; *P*=0.067; primary end point; logistic regression analysis); however, a consistent trend was observed, with significance achieved at both 30 minutes (nVNS, 12.7%; sham, 4.2%; *P*=0.012) and 60 minutes (nVNS, 21.0%; sham, 10.0%; *P*=0.023). A repeated-measures test examined the inconsistency between the 120-minute finding and the 30- and 60-minute findings and found that nVNS was superior to the sham through 120 minutes (odds ratio: 2.3; 95% CI: 1.2, 4.4; *P*=0.012). Please see Table 10 for complete details.

Key Additional End Points

Results for the secondary endpoints further demonstrated the significant clinical benefits of gammaCore. The mean percentage change in pain score from baseline to 120 minutes for all attacks in the double-blind period was -34.8% in the nVNS group and -5.4% in the sham group (*P*=0.004). Responder rates for mild or no pain at 120 minutes were significantly higher with nVNS (40.8%) than with sham (27.6%) for the first treated migraine attack *P*=(0.030). The percentage of patients who achieved mild or no pain at 120 minutes for at least 50% of their treated attacks during the double-blind period was significantly higher with nVNS (47.6%) than with sham (32.3%) *P*=(0.026). Statistical significance favoring gammaCore was also achieved for ≥50% pain-free responder rates for all treated attacks (nVNS, 32.4%; sham, 18.2%; *P*=0.020) Please see Table 10 for complete details.

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Table 10. PRESTO Key Efficacy End Points (Double-blind Period; ITT Population; N=243)

	30 Min.		60 Min.		120 Min.	
	gammaCore	Sham	gammaCore	Sham	gammaCore	Sham
Primary endpoint (pain-free) – logistic regression[a]						
%	12.7	4.2	21.0	10.0	30.4	19.7
95% CI	7.2, 21.6	1.7, 9.6	14.1, 30.1	5.6, 17.4	22.2, 39.9	13.0, 28.6
P-value	0.012		0.023		0.067	
30, 60, and 120 minutes – repeated-measures[a,b]						
Odds Ratio	–		–		2.3	
95% CI	–		–		1.2, 4.4	
P-value	–		–		0.012	
Secondary endpoint (mild/no pain)[c]						
%	26.7	18.7	35.8	24.4	40.8	27.6
95% CI	19.0, 35.5	12.2, 26.7	27.3, 45.1	17.1, 33.0	32.0, 50.2	20.0, 36.4
P-value	0.138		0.052		0.030	
Mean percentage change in pain intensity[b,d]						
%	−18.1	−5.2	−25.4	−7.7	−34.8	−5.4
95% CI	−28.0, −8.3	−14.8, 4.3	−36.7, −14.1	−19.5, 4.0	−45.9, −23.7	−21.7, 11.0
P-value	0.064		0.033		0.004	
≥50% pain-free responder rate[b,c,e]						
%	–	–	–	–	32.4	18.2
95% CI	–	–	–	–	23.6, 42.2	11.2, 27.2
P-value	–		–		0.020	
≥50% responder rate (mild/no pain)[c,e]						
%	–	–	–	–	47.6	32.3
95% CI	–	–	–		37.8, 57.6	23.3, 42.5
P-value	–		–		0.026	

Abbreviations: CI, confidence interval; ITT, intent-to-treat.
[a]No rescue medication use through 120 min after treatment completion for the first treated migraine attack; the repeated-measures analysis used generalized linear mixed-effects regression models, both with adjustment for the participants' baseline pain score, use of preventive therapies, and presence of aura.
[b]Post-hoc analysis.
[c]No rescue medication use through 120 min after treatment completion for the first treated migraine attack. Patients with mild pain at both baseline and 30/60/120 minutes were not considered responders; *P*-values were derived from the Chi-square test or Fisher's exact test, as appropriate.
[d]*P*-values were derived from two-sample t tests.
[e]For patients who had ≥2 treated migraine attacks.

Safety

gammaCore was found to be safe and well tolerated in the PRESTO study. The majority of the adverse events were mild and transient and occurred during the time of active treatment. None of the serious adverse events were considered device related. Please see Table 11 for complete details.

Table 11. PRESTO Incidence of Adverse Events and Adverse Device Effects (Safety Population)

AEs and ADEs		**gammaCore** n = 122	**Sham** n = 126
Patients with ≥1 AE	No. (%)	22 (18.0)	3 (18.3)
Patients with ≥1 serious AE		0	0
Patients with ≥1 ADE		7 (5.7)	10 (7.9)
Patients with ≥1 AE leading to discontinuation		0	2 (1.59)
AEs Occurring in ≥2% of Patients in Any Treatment Group		n = 122	n = 126
General disorders and administration site conditions			
Application site discomfort	No. (%)	3 (2.5)	1 (0.8)
Application site erythema		0	3 (2.4)
Application site pain		0	3 (2.4)
Infections and infestations			
Influenza	No. (%)	0	3 (2.4)
Nasopharyngitis		2 (1.6)	3 (2.4)
Nervous system disorders			
Dizziness	No. (%)	0	3 (2.4)

Abbreviations: ADE, adverse device effect; AE, adverse event.
Data are No. (%) of subjects.

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Adjunctive Use for the Preventive Treatment of Cluster Headache Clinical Study

Clinical data demonstrating the safety and effectiveness of gammaCore for the preventive treatment of cluster headache are presented from one prospective, open-label, controlled, randomized clinical trial comparing adjunctive nVNS with individual standard of care (The PREVA Study).

Summary

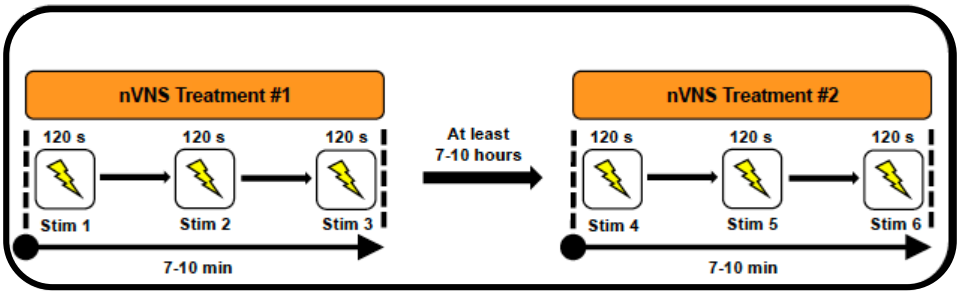
This randomized, controlled trial demonstrated the safety and efficacy of gammaCore for the preventive treatment of cluster headache. gammaCore was safe and well tolerated in this study.

gammaCore for the Preventive Treatment of Cluster Headache: The PREVA Study

Based on the clinical trial conducted with gammaCore for the preventive treatment of cluster headache, and unless otherwise directed by an HCP, each self-administered treatment should consist of three 2-minute stimulations, on either side of the neck, as follows: first daily treatment - within 1 hour of waking; second daily treatment – at least 7-10 hours following the first daily treatment (Figure 4).

Stimulations may be applied to either side of the neck.

Figure 4. PREVA Treatment Protocol



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Demographics

PREVA enrolled a total of 114 patients with cluster headache. General demographics are provided in Table 12.

Table 12. Demographics and Baseline Characteristics (ITT Population)

Characteristic	gammaCore + SoC (n=48)	SoC Alone (n=49)
Age, y, mean (SD)	45.4 (11.0)	42.3 (11.0)
Sex, n (%)		
Male	34 (71)	33 (67)
Time since onset of chronic CH disorder, y, mean (SD)[a]	4.7 (3.9)	5.0 (3.7)
CH attack duration, min, mean (SD)		
With acute pharmacologic medications/oxygen[b]	27.4 (19.8)	29.3 (29.9)
Without acute pharmacologic medications/oxygen[c]	95.2 (57.7)	103.3 (66.8)
Number of CH attacks in the 4 weeks before enrollment, mean (SD)[c]	67.3 (43.6)	73.9 (115.8)
Use of prophylactic medications for CH, n (%)		
Verapamil/verapamil hydrochloride	25 (52)	26 (53)
Lithium/lithium carbonate	6 (13)	9 (18)
Topiramate	7 (15)	7 (14)
Corticosteroids	2 (4)	2 (4)
Use of pharmacologic medications/oxygen for the acute treatment of CH, n (%)		
Pharmacologic medications	43 (90)	44 (90)
Oxygen	32 (67)	34 (69)

Abbreviations: CH, cluster headache; SD, standard deviation; SoC, standard of care; IIT, intent-to-treat
[a]Data were missing for 2 subjects in the control group.
[b]Data were missing for 1 subject in the control group.
[c]Data were missing for 1 subject in the gammaCore + SoC group.

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Efficacy

Primary End Point

In the ITT population (Standard of Care (SoC) plus nVNS, n=45; control, n=48), subjects receiving SoC plus nVNS during the randomized phase had a greater reduction from baseline (−5.9; SE, 1.2) in the number of CH attacks per week than those receiving control (−2.1; SE, 1.2), for a mean therapeutic gain of 3.9 fewer CH attacks per week (95% CI: 0.5, 7.2; *P*=0.02). In the site-adjusted model, the mean therapeutic gain was 4.2 fewer headache attacks per week (95% CI: 0.8, 7.5; *P*=0.02). Please see Table 13 for complete details.

Key Additional End Points

≥50% Response rates

Among subjects in the *ITT population,* a significantly higher ≥50% response rate during the randomised phase was observed in the SoC plus nVNS group (40% [18/45]) than in the control group (8.3% [4/48]) (*P*<0.001). Please see Table 13 for complete details.

Abortive medication use

The number of times abortive medications were measured in the mITT population (patients who had measurable observations for this endpoint) during the last 2 weeks of each study phase. During the randomised phase, a 57% decrease in the frequency of abortive medication use was noted in the SoC plus nVNS group (Δ=−15.0 [95% CI: −22.8, −7.2]; *P*<0.001). In contrast, subjects assigned to the control group did not experience a substantial reduction in abortive medication use (Δ=−2.0 [95% CI: –9.4, 5.4]; *P*=0.59). Changes in abortive medication use among subjects assigned to SoC plus nVNS were a >60% reduction in the use of subcutaneous sumatriptan (Δ=−4.4 [95% CI: −7.6, −1.2]; *P*=0.007) as well as a significant decrease in inhaled oxygen (Δ=−10.8 [95% CI: −19.4, −2.2]; *P*=0.02). Please see Table 13 for complete details.

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Table 13. PREVA Key Efficacy End Points (Double-blind Period; ITT Population; N=93)

	gammaCore + SoC	SoC Alone
Primary endpoint (ITT population[a])	**n=45**	**n=48**
Change in number of CH attacks per week (mean ± SE)	−5.9 ± 1.2	−2.1 ± 1.2
Mean therapeutic gain (fewer CH attacks per week)		
Unadjusted	3.9	
95% CI	0.5, 7.2	
P-value (gammaCore + SoC vs SoC alone)	0.02	
Adjusted (by site)	4.2	
95% CI	0.8, 7.5	
P-value (gammaCore + SoC vs SoC alone)	0.02	
≥50% response rate (ITT population[a])	**n=45**	**n=48**
Patients with a ≥50% reduction in weekly attacks (%)	40.0	8.3
Therapeutic gain (%)	31.7	
P-value (gammaCore + SoC vs Soc alone)	<0.001	
Abortive medication use (mITT population[b])	**n=32**	**n=42**
Change in medication use[c]	−15.0	−2.0
95% CI	−22.8, −7.2	−9.4, 5.4
P-value (baseline vs randomized phase)	<0.001	0.59
Change in SC sumatriptan use[c]	−4.4	0.7
95% CI	−7.6, −1.2	−
P-value (baseline vs randomized phase)	0.007	−
Change in inhaled oxygen use[c]	−10.8	−1.8
95% CI	−19.4, −2.2	−
3-value (baseline vs randomized phase)	0.02	−

Abbreviations: CH, cluster headache; CI, confidence interval; ITT, intent-to-treat; mITT, modified intent-to-treat; SC, subcutaneous; SE, standard error; SoC, standard of care.

[a] Patients who had ≥1 efficacy recording in the headache diary after randomization.

[b] Patients who had measurable observations for this endpoint.

[c] From the last 2 weeks of the baseline phase to the last 2 weeks of the randomized phase.

Safety

gammaCore was found to be safe and well tolerated in the PREVA study. The majority of the adverse events were mild and transient and occurred during the time of active treatment. None of the serious adverse events were considered device related. Please see Table 14 for complete details.

Table 14. PREVA Incidence of Adverse Events and Adverse Device Effects (Safety Population)

Incidence of AEs	gammaCore + SoC (n=48)	SoC Alone (n=49)
Participants with ≥1 AE, n (%)	25 (52)	24 (49)
Participants with ≥1 AE leading to discontinuation, n (%)	3 (6)[a]	4 (8)[b]
Participants reporting any serious AE[c], n (%)	2 (4)	2 (4)
Participants with ≥1 device-related AE, n (%)	13 (27)[d]	7 (14)[e]
AEs reported in ≥5% of participants in any treatment group, n (%)		
Nervous system disorders		
CH attack	1 (2)[f]	5 (10)[f]
Dizziness	3 (6)[f]	3 (6)
Headache	4 (8)	1 (2)
Infections and infestations		
Nasopharyngitis	1 (2)	4 (8)
Respiratory, thoracic, and mediastinal disorders		
Oropharyngeal pain	3 (6)[f]	1 (2)
Musculoskeletal and connective tissue disorders		
Neck pain	3 (6)	0

Abbreviations: AE, adverse event; CH, cluster headache; SoC, standard of care.

[a] Included feeling hot, malaise, hematoma after scheduled surgery, and depressed mood.

[b] Included chest pain, fatigue, depressed mood, and CH.

[c] Cholecystitis and hematoma after scheduled surgery were reported in 2 participants in the gammaCore + SoC group; genital herpes simplex virus infection and exacerbation of CH were reported in 2 participants in the control group.

[d] Includes depressed mood, malaise, oropharyngeal pain, CH, paresthesia, muscle twitching, muscle spasms, feeling hot, hot flush, acne, pain, throat tightness, dizziness, hyperhidrosis, toothache, decreased appetite, and skin irritation.

[e] Included erythema, facial edema, CH, chest pain, fatigue, depressed mood, pruritus, musculoskeletal stiffness, and parosmia, all of which occurred during the extension phase.

[f] Included ≥1 AE determined by causality assessment to be related to treatment.

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Preventive Treatment of Migraine Headache Clinical Study

Clinical data demonstrating the safety and effectiveness of gammaCore for the preventive treatment of migraine headache are presented from one prospective double-blind, sham-controlled, randomized clinical trial comparing nVNS with a sham arm (the PREMIUM Study).

Summary

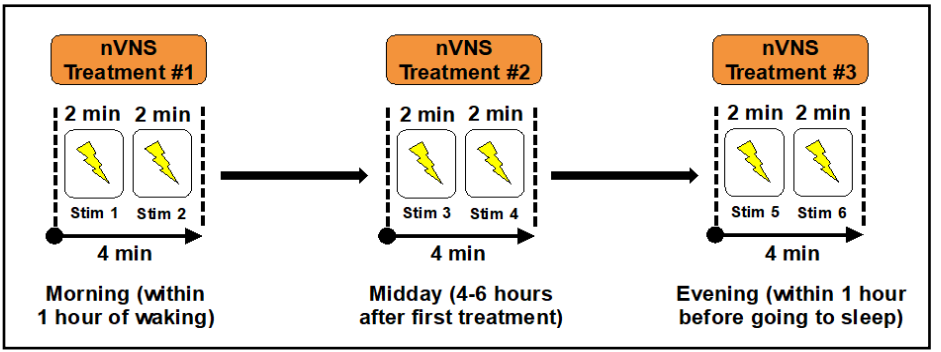
This randomized controlled trial demonstrated the safety and efficacy of gammaCore for the preventive treatment of migraine headache. gammaCore was safe and well tolerated in this study.

gammaCore for the Preventive Treatment of Migraine Headache: The PREMIUM Study

Based on the clinical trial conducted with gammaCore for the preventive treatment of migraine headache, and unless otherwise directed by an HCP, each self-administered treatment should consist of three 2-minute stimulations, on either side of the neck, as follows: first daily treatment within 1 hour of waking, second daily treatment 4-6 hours following the first daily treatment, and a third daily treatment within 1 hour of going to sleep (Figure 5).

Stimulations may be applied to either side of the neck.

Figure 5. Treatment Protocol for Preventive Treatment of Migraine Headache



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Demographics

PREMIUM enrolled a total of 332 patients with migraine headache. General demographics are provided in Table 15.

Table 15. Demographics and Baseline Characteristics for the PREMIUM Study

Characteristic[a]	nVNS (n=165)	Sham (n=167)
Age, y	43.5 ± 11.1	41.4 ± 12.3
Age at migraine onset, y	19.6 ± 9.6	19.4 ± 9.8
Female, n (%)	142 (86.1)	138 (82.6)
Caucasian, n (%)	160 (97.0)	154 (92.2)
Migraine type, n (%)		
Migraine with aura[b]	36 (21.8)	42 (25.2)
Migraine without aura[b]	129 (78.2)	125 (74.9)
Migraine days in the last 4 weeks, n	7.9 ± 2.2	8.1 ± 2.0
Headache days in the last 4 weeks, n	8.9 ± 2.6	9.1 ± 2.6
Acute migraine medication use per month, d	6.8 ± 2.7	7.0 ± 2.8

[a] Data are mean ± SD unless otherwise indicated and are from the ITT population.

[b] Presence/absence of aura was based on diagnosis provided in subject medical history at enrollment.

Abbreviations: ITT, intent-to-treat; nVNS, non-invasive vagus nerve stimulation; SD, standard deviation.

Efficacy

Primary Endpoint

The primary efficacy endpoint of the study was the mean reduction in the number of migraine days from the 4-week run-in period to the last 4 weeks of the double-blind period. In the mITT population, this reduction was significantly greater for the nVNS group (–2.27) than for the sham group (–1.53), resulting in a mean therapeutic gain of 0.74 (95% CI, –1.45 to –0.02; *P*=0.043). This clinical benefit was not significant in the ITT population. Please see Table 16 for complete details.

Key Additional Endpoints

≥50% Response rates

Among subjects in the mITT population, a higher ≥50% response rate during the double-blind phase was observed in the nVNS group (33.6%) than in the sham group (23.4%) (*P*=0.074). Please see Table 16 for complete details.

Reduction in headache days and acute medication days

Consistent and significant benefits of nVNS over sham therapy for reduction in headache days (nVNS, –2.85 vs. sham, –1.99; *P*=0.045) and reduction in acute medication days (nVNS, –1.94 vs. sham, –1.14; *P*=0.039) were also seen in the mITT population but not in the ITT population. Please see Table 16 for complete details.

Table 16. PREMIUM Efficacy Outcomes for the ITT and mITT Populations

	ITT		mITT[a]	
Outcome	**nVNS (n=165)**	**Sham (n=167)**	**nVNS (n=138)**	**Sham (n=140)**
Reduction in migraine days[b]				
Mean (95% CI)	–2.26 (–2.81, –1.72)	–1.80 (–2.32, –1.27)	–2.27 (–2.89, –1.65)	–1.53 (–2.13, –0.93)
Difference (95% CI)	–0.47 (–1.10, 0.16)		–0.74 (–1.45, –0.02)	
P value	0.15		0.043	
Migraine ≥50% responder rate[c]				
% (95% CI)	31.9 (23.4, 41.8)	25.0 (17.8, 34.0)	33.6 (23.7, 45.1)	23.4 (15.7, 33.5)
Odds ratio (95% CI)	1.4 (0.85, 2.32)		1.65 (0.95, 2.87)	
P value	0.19		0.074	
Reduction in headache days[b]				
Mean (95% CI)	–2.73 (–3.37, –2.09)	–2.11 (–2.74, –1.49)	–2.85 (–3.58, –2.12)	–1.99 (–2.70, –1.29)
Difference (95% CI)	–0.62 (–1.36, 0.13)		–0.86 (–1.70, –0.02)	
P value	0.10		0.045	
Reduction in acute medication days[b]				
Mean (95% CI)	–1.90 (–2.47, –1.32)	–1.35 (–1.91, –0.79)	–1.94 (–2.60, –1.28)	–1.14 (–1.77, –0.50)
Difference (95% CI)	–0.55 (–1.22, 0.12)		–0.80 (–1.56, –0.04)	
P value	0.11		0.039	

[a] Post hoc analysis. [b] Results are from linear regression adjusted for treatment group, center, presence/absence of aura, and number of migraine days in the run-in period.[c] Results are from logistic regression adjusted for treatment group, center, presence/absence of aura, and number of migraine days in the run-in period.
Abbreviations: CI, confidence interval; ITT, intent-to-treat; mITT, modified intent-to-treat; nVNS, non-invasive vagus nerve stimulation.

Safety

gammaCore was found to be safe and well tolerated in the PREMIUM study. The majority of the adverse events were mild and transient and occurred during the time of active treatment. None of the serious adverse events were considered device related. Please see Table 17 for complete details.

Table 17. PREMIUM Incidence of Adverse Events and Adverse Device Effects (Safety Population)

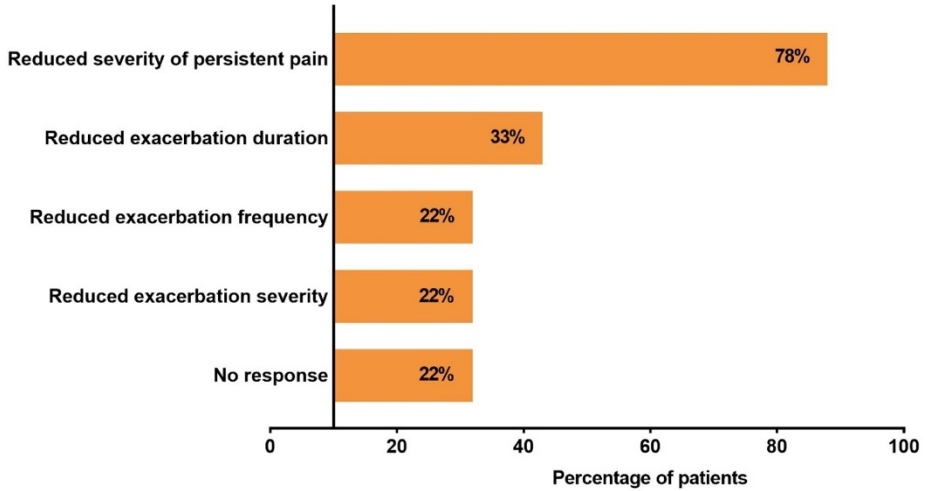
AEs and ADEs[a]	Double-blind Period		Open-label Period (n=269)
	nVNS (n=169)	Sham (n=172)	
Subjects with ≥1 AE	74 (43.8)	91 (52.9)	118 (43.9)
Subjects with ≥1 SAE	2 (1.2)	1 (0.6)	2 (0.7)
Subjects with ≥1 ADE	31 (18.3)	57 (33.1)	29 (10.8)
Subjects with ≥1 AE leading to discontinuation	2 (1.2)	9 (5.2)	10 (3.7)
Most common AEs and ADEs[a]	**All Study Periods**		
	nVNS (n=169)		**Sham (n=172)**
AEs			
Nasopharyngitis	29 (17.2)		17 (9.9)
Influenza	16 (9.5)		12 (7.0)
Application site pain	6 (3.6)		10 (5.8)
Oropharyngeal pain	9 (5.3)		7 (4.1)
Dizziness	8 (4.7)		4 (2.3)
ADEs			
Application site rash	1 (0.6)		12 (7.0)
Application site pain	5 (3.0)		10 (5.8)
Application site erythema	3 (1.8)		8 (4.7)
Application site discomfort	7 (4.1)		5 (2.9)
Dizziness	5 (3.0)		3 (1.7)

[a] Data are n (%) of patients with the event and are from the safety population.
Abbreviations: ADE, adverse device effect; AE, adverse event; nVNS, non-invasive vagus nerve stimulation; SAE, serious adverse event.

Treatment of Hemicrania Continua Clinical Audits

An audit of clinical records by Tso et. al. included 9 patients with hemicrania continua, 7 of whom received nVNS as monotherapy and 2 of whom received nVNS as adjunctive therapy. The duration of nVNS therapy ranged from 3 months to 2.7 years. Seventy-eight percent of patients had a reduction in the severity of their persistent pain with nVNS therapy (Figure 6); the magnitude of this reduction ranged from 15% to 80%. Reductions in the frequency, duration, and/or severity of exacerbations were also reported by some patients. Two patients had no response to nVNS therapy.

Figure 6. Reductions of Persistent Pain



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Treatment of Paroxysmal Hemicrania Clinical Audits

Clinical audit by Kamourieh et al

An audit of clinical records by Kamourieh et. al. included 8 patients with paroxysmal hemicrania who had previously experienced an inadequate response to a mean of 3 preventive treatments (range, 1-5 treatments) and were followed up for a median of 7 months (range, 3-19 months). At both month 3 and the last follow-up for each individual patient, median attack severity and duration had decreased significantly from baseline (Figure 7A and 7B). Mean headache frequency also significantly decreased from baseline by 68% at month 3 (p=0.012) and by 75% at the final follow-up (p=0.003). At the final follow-up, 6 patients (75%) had a favorable response, which was defined as a >50% decrease from baseline in monthly headache frequency. The mean estimated patient global improvement was 64% at month 3 and 72% at the final follow-up.

Attack severity (7A) and duration (7B) in patients with paroxysmal hemicrania treated with nVNS (n=8)

Figure 7A. Severity

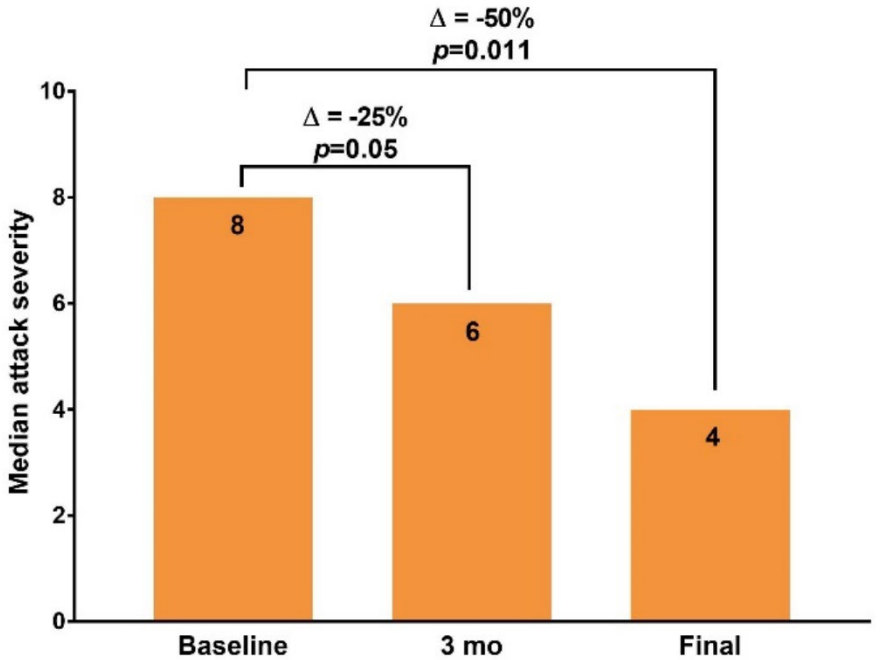
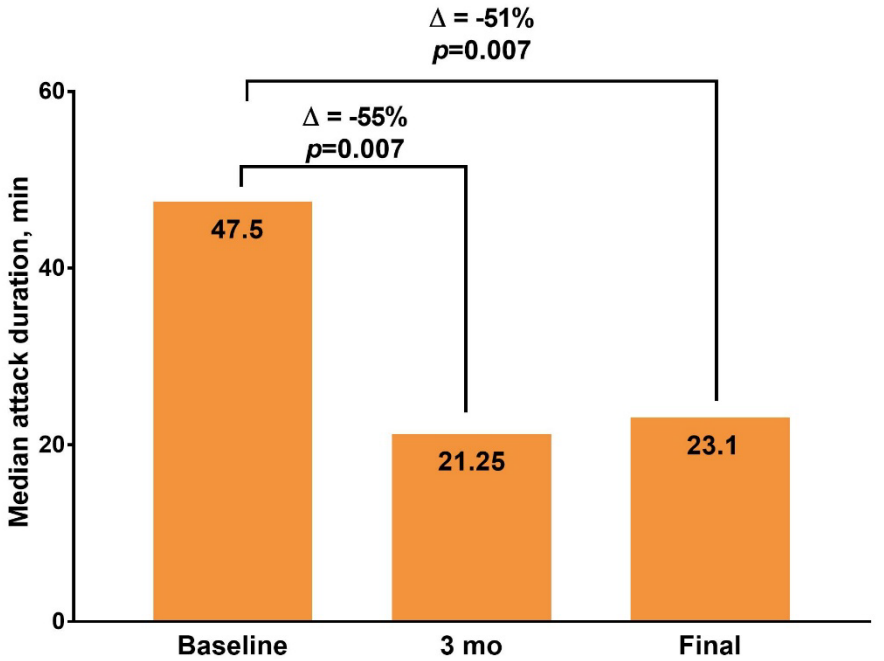


Figure 7B. Duration

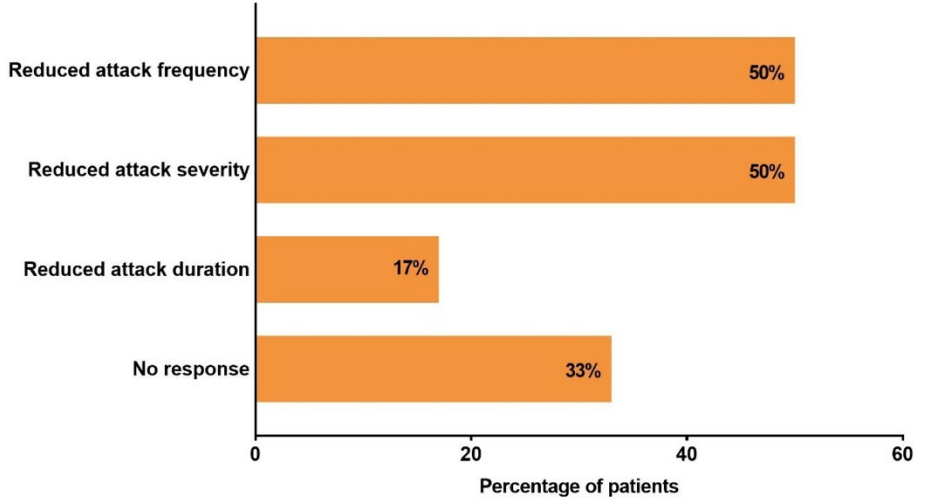


Attack severity was rated on a scale from 0 (no pain) to 10 (very severe pain).
nVNS indicates non-invasive vagus nerve stimulation.

Clinical audit by Tso et al

The clinical audit by Tso et al included 6 patients with paroxysmal hemicrania who were treated with nVNS (3 as monotherapy, 3 as adjunctive therapy) for 3 months to 5 years. Three patients (50%) had reductions in attack frequency (Figure 8), including 1 who reported complete cessation of attacks. Three patients (50%) had decreases in attack severity, one of whom also reported a reduction in attack duration from 20 to 40 minutes at baseline to 10 minutes with nVNS therapy.

Figure 8. Results from a clinical audit of records from patients with paroxysmal hemicrania (n=6)



Safety

Clinical audits and case series/case reports have included 19 patients with hemicrania continua and 14 patients with paroxysmal hemicrania who were treated with nVNS between 8 weeks and 5 years. No serious or unexpected adverse events were reported.

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