Cost-Effectiveness of gammaCore (Non-Invasive Vagus Nerve Stimulation) for Acute Treatment of Episodic Cluster Headache

Mkaya Mwamburi, MD, PhD, MA (Econ); Eric J. Liebler, BA; and Andrew T. Tenaglia, BA

ABSTRACT

Cluster headache is a debilitating disease characterized by excruciatingly painful attacks that affects 0.15% to 0.4% of the US population. Episodic cluster headache manifests as circadian and circannual seasonal bouts of attacks, each lasting 15 to 180 minutes, with periods of remission. In chronic cluster headache, the attacks occur throughout the year with no periods of remission. While existing treatments are effective for some patients, many patients continue to suffer. There are only 2 FDA-approved medications for episodic cluster headache in the United States, while others, such as high-flow oxygen, are used off-label. Episodic cluster headache is associated with comorbidities and affects work, productivity, and daily functioning. The economic burden of episodic cluster headache is considerable, costing more than twice that of nonheadache patients. gammaCore adjunct to standard of care (SoC) was found to have superior efficacy in treatment of acute episodic cluster headaches compared with sham-gammaCore used with SoC in ACT1 and ACT2 trials. However, the economic impact has not been characterized for this indication. We conducted a cost-effectiveness analysis of gammaCore adjunct to SoC compared with SoC alone for the treatment of acute pain associated with episodic cluster headache attacks. The model structure was based on treatment of acute attacks with 3 outcomes: failures, nonresponders, and responders. The time horizon of the model is 1 year using a payer perspective with uncertainty incorporated. Parameter inputs were derived from primary data from the randomized controlled trials for gammaCore. The mean annual costs associated with the gammaCore-plus-SoC arm was $9510, and mean costs for the SoC-alone arm was $10,040. The mean quality-adjusted life years for gammaCore-plus-SoC arm were 0.83, and for the SoC-alone arm, they were 0.74. The gammaCore-plus-SoC arm was dominant over SoC alone. All 1-way and multiway sensitivity analyses were cost-effective using a threshold of $20,000. gammaCore dominance, representing savings, was driven by superior efficacy, improvement in quality of life (QoL), and reduction in costs associated with successful and consistent abortion of episodic attacks. These findings serve as additional economic evidence to support coverage for gammaCore. Additional real-world data are needed to characterize the long-term impact of gammaCore on comorbidities, utilization, QoL, daily functioning, productivity, and social engagement of these patients, and for other indications.

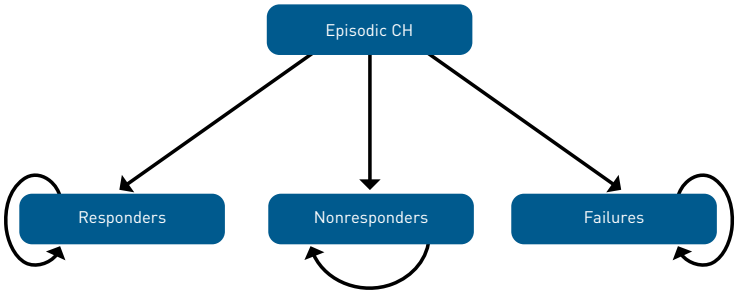
Am J Manag Care. 2017;23:S300-S306

For author information and disclosures, see end of text.

Cluster headache, a trigeminal autonomic cephalalgia, is a debilitating disease (also called "suicide headache") that is characterized by severely intense attacks that are excruciatingly painful.[1-5] Episodic cluster headache, which accounts for 80% to 90% of cluster headache patients, manifests as seasonal bouts of attacks, each lasting between 1 and 8 weeks, occurring in circadian, circannual pattern in the spring and in the fall months with periods of remission.[6,7] In contrast, chronic cluster headache refers to when the attacks occur throughout the 12 months with periods of remission of less than 1 month. Episodic cluster headache affects approximately 300,000 adults in the United States.[1] There are few treatments available, and then only with limited effectiveness for aborting acute attacks of episodic cluster headache. There are only 2 medications approved by the FDA, subcutaneous sumatriptan and sublingual ergotamine tartrate. All other forms of treatment are used off-label. The disease and treatment landscapes represent a high unmet need, with the FDA providing fast-track status for expedited review to experimental agent galcanezumab for cluster headache prevention.[8] The illness is difficult to diagnose correctly, and there are typically extensive delays between onset of symptoms and the correct diagnosis.[9] Nearly 3 out of 5 patients are diagnosed at least 3 years after onset of symptoms, while 22% of patients are diagnosed after at least 10 years.[6] Episodic cluster headache is also associated with numerous comorbidities, including depression, anxiety disorder with suicide ideation, and an increased need for medications and health utilization.[6,7,10] Episodic cluster headache also affects work, productivity, daily functioning, and travel abilities for those patients with the condition. The economic burden of episodic cluster headache is considerable. In 1 study based on claims data, episodic cluster headache patients cost more than twice that of nonheadache patients.[10]

gammaCore (non-invasive vagus nerve stimulator; electroCore, Basking Ridge, NJ) has recently been cleared by the FDA for the treatment of pain associated with episodic cluster headaches in the United States.[11] Recent randomized, sham-controlled trials (ACT1 and ACT2) demonstrated clinically significant superiority of gammaCore adjunct to standard of care (SoC) over sham-gammaCore with SoC

FIGURE 1. Model Structure Showing 3 Outcomes[a]



CH indicates cluster headache.
[a]Patients in each outcome may remain in the same outcome group. Nonresponders may change to responders or failures.

among patients treated for episodic cluster headaches; it did so by significantly reducing cluster headache attack intensity within 15 minutes of initiating treatment and eliminating the need for rescue medication.[12-14] In addition, gammaCore is practical, as it is hand-held, portable, and easy-to-use. The device is safe with no associated toxicity, drug interactions, or serious device-related adverse events (AEs). Successful treatment with gammaCore has been associated with reduced consultations and referrals in primary headaches.[15] The clinical impact of gammaCore is well documented, and for many patients in whom gammaCore works effectively, treatment with gammaCore represents a life-changing experience.[16] Other cost-effectiveness analyses of gammaCore compared with SoC have shown gammaCore to be dominant (German payer perspective) and cost-effective (United Kingdom payer perspective) as a prophylactic treatment of chronic cluster headache.[17,18] However, the economic impact and cost-effectiveness of gammaCore as an effective treatment of acute attacks of episodic cluster headache remains to be determined and characterized. We designed and performed a cost-effectiveness analysis comparing gammaCore adjunctive to SoC with SoC alone, for the acute treatment of episodic cluster headache.

Methods

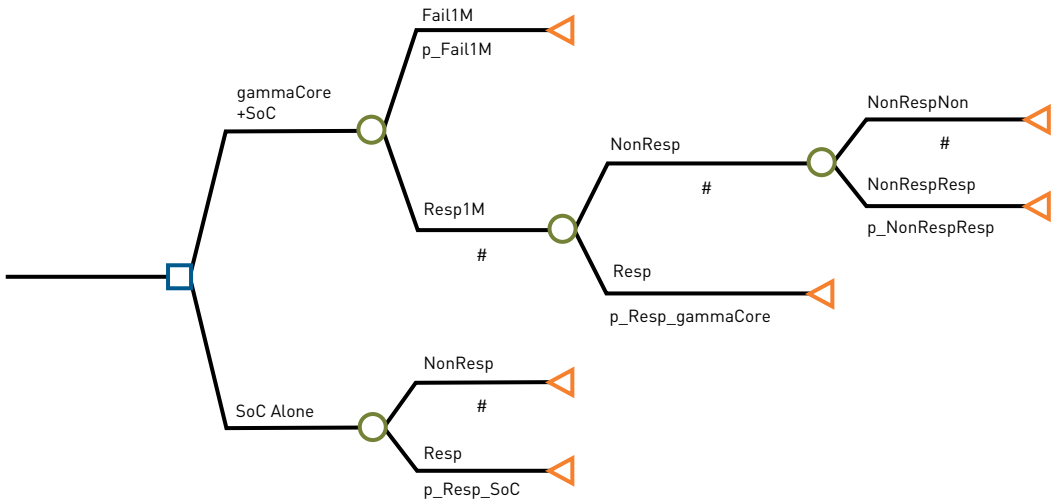
We conducted a cost-effectiveness analysis of gammaCore adjunct to SoC compared with SoC alone for the treatment of acute pain associated with episodic cluster headache attacks in accordance with current guidelines.[19] The main sources of primary data were the ACT trials, supported by additional evidence and insights from Polson et al, Choong et al, Nesbitt et al, and Rozen et al.[6,7,10,12,14,16] Both ACT1 (ClinicalTrials.gov identifier: NCT01792817) and ACT2 (ClinicalTrials.gov identifier: NCT01958125) were sham-controlled, double-blind, randomized trials comparing gammaCore adjunct with SoC to SoC alone. Both multicenter trials were reviewed and approved by relevant ethics committees. A meta-analysis of the 2 trials was conducted and also previously presented.[12] The treatment protocol for ACT1 was three 2-minute stimulations, each separated by 1 minute, delivered on the right side of the neck. Patients could use gammaCore twice daily.[14] The treatment protocol for ACT2 was three 2-minute stimulations followed by a 3-minute break, and if pain persisted, another three 2-minute stimulations would be delievered on the ipsilateral side of the cluster attack (3-3-3 protocol). Patients could use gammaCore up to 4 times in 1 day.[13] Details of both trials have been previously published.[13,14]

Model Structure

The model structure was based on treatment of acute attacks to yield 3 outcomes: failures, nonresponders, and responders. Failures were those patients who experienced lack of adherence or lack of efficacy, and the proportion of responses to treated attacks (no pain within 15 minutes with no use for rescue medications) was 0%. Nonresponders are patients who experienced partial efficacy with the proportion of responses to treated attacks between 1% and 50%. These patients also benefited from the gammaCore treatment by reduction in duration or intensity of treated attack, or both, but gammaCore did not necessarily prevent the use of rescue medications. These patients could be retrained to yield additional responders or additional failures, or to remain as partial responders. Responders were patients who met the equivalent of the trial outcomes of ACT1 and ACT2: The proportion of responses to attacks was ≥50%. Individuals in each outcome may remain in the same outcome group. The model structure is shown in **Figure 1**.

The model was designed to compare patients treated with gammaCore adjunct to SoC versus SoC alone using a decision tree. The decision-tree model parameters were populated with data from pooled analysis of the 2 ACT trials with data from the meta-analysis providing the base case parameters.[12] For clinical outcomes, findings from ACT1 and ACT2 provided lower and upper limits respectively for estimates for sensitivity analyses.[13,14] Cost data were derived from Polson et al and epidemiological considerations were driven by data from Rozen et al.[7,10] Additional insights were drawn from the literature.[3-6,15,16] The model is designed from a payer perspective with a time horizon of 1 year. The model was designed and built using TreeAge Pro Healthcare, v2017.R1 (TreeAge Software; Williamstown, Massachusetts). Uncertainty was incorporated by using distributions around parameter estimates for treatment effects, costs, and utilities. In addition, 100,000 trials or iterations (Monte Carlo simulations) were performed to yield a mean estimate of costs, effectiveness, and incremental cost-effectiveness ratio (ICER). A range of sensitivity analyses were also performed to evaluate the robustness of the model and test the impact of modifying parameter estimates on the models output. The decision tree is shown in **Figure 2**.

FIGURE 2. Model Decision Tree



Fail1M indicates immediate failure; NonResp, nonresponder; NonRespNon, no response after retraining nonresponders; NonRespResp, response after retraining nonresponders; p_NonRespResp, probability of response after retraining nonresponders; p_Resp_GammaCore, probability of response on gammaCore; p_Resp_SoC, probability of response on SoC; p_Fail1M, probability of immediate failure; Resp1M, response observed; SoC, standard of care. p_= prob_ denoting probability.

Model Design and Parameter Estimates

Patients who fail to respond to gammaCore do so within the duration covered by the first device. Therefore, failures would not need prescriptions for additional devices, would not have changes in utilities from baseline, and the costs associated with their care would remain the same as for patients in SoC; ie, there is no benefit conferred to them for receiving the 1 month's worth of gammaCore treatment for which they did not respond. The base case probability of failing treatment within 1 month is 0.2 (*prob_Fail1M*). Those who do not fail within 1 month may be responders or nonresponders in the gammaCore arm. Responders are those who benefit adequately from gammaCore and will not need rescue medications for the attacks to which they respond. The effective probabilities of being a responder in the gammaCore arm and the SoC-alone arm are 0.42 (*prob_Resp_gammaCore*) and 0.15 (*prob_Resp_SoC*), respectively. Nonresponders partially benefit from using gammaCore, may return to the provider, and may be retrained to achieve better performance from gammaCore. A proportion of nonresponders who may respond favorably enough for them to continue to use gammaCore, even if using for partial benefit, is 0.50 (*prob_NonRespResp*). This assumption is based on insights from the literature and patient experiences.[3,4,7,10,12-16,18,20-22] Others, even after retraining, may not benefit further and will stop using gammaCore by the second device. The probability among nonresponders is also 0.50 (*prob_NonRespNon*). The impact of consistent success of gammaCore treatment is a reduction in costs of care for episodic cluster headache patients by 50% (*reduction_Factor*). For a 12-month period, the base case average number of gammaCore prescriptions per patient is 6 (*months_Prescription*). While the more realistic average number of prescriptions annually may be closer to 4, a more conservative analysis using 6 was used.

The cost per prescription to payers (*cost_gammaCore*) will be $590 (rounded up from average wholesale price [AWP] minus 15%). For nonresponders in the gammaCore arm who undergo retraining, the associated cost that may be charged by doctors is $100 (*cost_Training*). The overall annual cost of care for episodic cluster headache patients based on current SoC (Polson et al) was $24,820 for 3 years = $8270/year in 2013 US$.[10] Based on appreciating costs at 5% inflation annually, the per-year medical cost in 2017 US$ would be $10,040 ± $490 (*cost_SoC_Care*). Utility estimates were derived from the ACT2 trial data based on EQ-5D health index measurements. We used utilities averaged by treatment group for the gammaCore-plus-SOC arm of 0.82 ± 0.046 (*utility_gammaCore*) and for the SoC-alone arm of 0.72 ± 0.046 (*utility_SoC*) as the base case. Utilities averaged by response—responders, 0.90 ± 0.048 (*utility_Resp*); nonresponders, 0.71 ± 0.038 (*utility_NonResp*); failures, 0.71 ± 0.038 (*utility_NonResp*)—were used for sensitivity analyses. Parameter definitions and estimates are shown in **Table 1**. The model output was ICER for cost per quality-adjusted life year (QALY), derived as the ratio between marginal costs (the difference in costs associated with gammaCore plus SoC minus costs associated with SoC alone) and marginal effectiveness (the difference in effectiveness ie, QALYs associated with gammaCore plus SoC minus QALYs associated with SoC alone) $[(C_{gammaCore} - C_{SoC}) / (E_{gammaCore} - E_{SoC})]$.

Uncertainty was incorporated using distributions around the mean estimates for treatment effects, utilities, and cost of care. In addition, the model was performed by running 100,000 second-order

TABLE 1. Parameter Estimates for Probabilities, Costs and Utilities, and Other Parameters

Parameter	Description	Estimate ± SE	Low	High	Source
cost_gammaCore	Monthly cost of gammaCore (AWP minus 15%)	$590	$500	$650	electroCore projections
cost_Training	Cost of retraining after initial failure	$100	$0	$200	Discussion with doctors
cost_SoC_Care	Cost of care for episodic cluster headache	$10,056 ± $490	$8000	$12,000	Polson et al (adjusted)
prob_Fail1M	Probability of immediate failure	0.20	0	0.3	ACT1, ACT2
prob_NonRespResp	Response after retraining nonresponders	0.40	0.3	0.5	ACT1, ACT2
prob_Resp_gammaCore	Probability of response on gammaCore[a]	0.42 ± 0.048	0.24	0.64	ACT1, ACT2
prob_Resp_SoC	Probability of response on SoC	0.15 ± 0.038	0.07	0.15	ACT1, ACT2
utility_gammaCore	QoL among responders	0.82 ± 0.046	--	--	ACT2
utility_SoC	QoL for nonresponders	0.72 ± 0.046	--	--	ACT2
reduction_Factor	Cost reduction factor due to gammaCore	50%	50%	70%	ACT1, ACT2, Strickland et al
months_Prescription	Months of prescription/year	6	4	8	electroCore projections

[a]Response based on number of responders with responses in ≥50% of attacks.
AWP indicates average wholesale price, QoL, quality of life; SoC, standard of care.

TABLE 2. Incremental Cost-Effectiveness Ratio

	gammaCore plus SoC	SoC alone	Difference
Costs ($)	9510	10,040	–530
Effectiveness (QALYs)	0.83	0.74	0.09
ICER ($/QALY)	--	--	–5890

ICER indicates incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care.

parameter sample analyses (Monte Carlo simulations) and reporting the mean of all the iterations. A range of deterministic and probabilistic sensitivity analyses were also performed to test the robustness of the model.

Sensitivity Analyses

A series of 1-way sensitivity analyses was performed in accordance with high and low values as shown in Table 1. Additional 1-way sensitivity analyses were performed without the 1-month failure feature in the decision tree and without the patient retraining feature for the nonresponders. Three 2-way combinations and a 3-way of the 3 most influential factors were performed for the multiway sensitivity analysis.

Results

Incremental Cost-Effectiveness Ratio (ICER)

The mean annual costs associated with patients in the gammaCore-plus-SoC arm ($C_{gammaCore}$) were $9660, and the mean annual costs associated with patients in the SoC-alone arm (C_{SoC}) were $10,020. The mean QALYs for the gammaCore-plus-SoC arm ($E_{gammaCore}$) were 0.83 and for the SoC-alone arm (E_{SoC}) they were 0.74. The gammaCore-plus-SoC arm was dominant over SoC alone (**Table 2**).

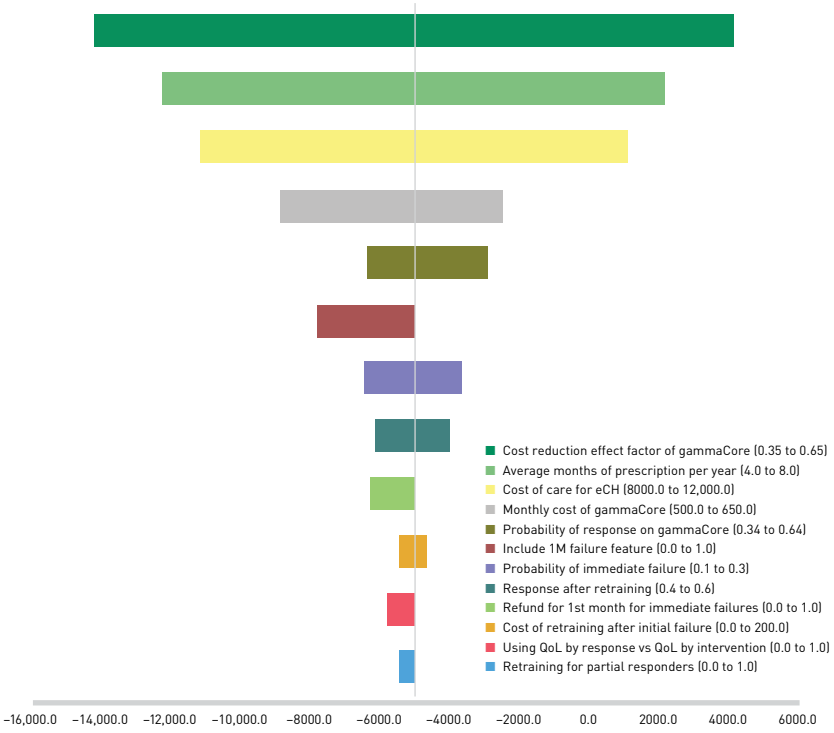
Sensitivity Analyses

All results of the 1-way sensitivity analyses were cost-effective with a conservative willingness-to-pay threshold of US $25,000. The results of the series of 1-way sensitivity analyses are shown in the tornado diagram in **Figure 3**. The most influential factors in the 1-way sensitivity analyses were the 1) cost reduction factor; 2) number of months of prescription per year; and 3) cost of SoC care for episodic cluster headache patients. More than 95% of simulations were cost-effective at a cost-effectiveness threshold of $20,000. The cost-effectiveness scatter plot and the acceptability curve are shown in **Figures 4a** and **4b**, respectively.

Discussion

The pre-gammaCore disease and treatment landscapes for episodic cluster headache represented a high unmet need. With only 2 FDA-approved medications for abortive treatment for episodic cluster headache attacks, all other treatments, including high-flow oxygen, opiates, and prophylactic medication, are used off-label. What's more, not all treatments are consistently effective, available, or covered by health insurance.[9,23,24] Ergotamine tartrate is rarely used and, as is the case with triptans, it has significant AEs, can interact adversely with other medications, has limited daily usage, and payers impose monthly limits on its coverage. In addition, ergotamine tartrate has contraindications for episodic patients with cardiovascular risk factors. High-flow oxygen requires large, nonportable tanks, so its use is mainly confined to the home environment. gammaCore is efficacious, practical, convenient to use, consistently effective, and portable; it presents a significant opportunity to mitigate unmet needs of these patients.[13-16,25] This cost-effectiveness analysis found gammaCore to be dominant over SoC.

FIGURE 3. Tornado Diagram for 1-Way Deterministic Sensitivity Analyses



1M indicates one -month; eCH, episodic cluster headache; QoL, quality of life.

gammaCore use, on average, would result in cost savings from a payer perspective in the United States. These findings are consistent with the cost-effectiveness analyses of gammaCore for prevention in chronic cluster headache.[17,18] The cost-effectiveness was driven by gammaCore's superior efficacy, improvement in quality of life (QoL), and propensity to reduce costs for patients when it is consistently effective in aborting attacks (ie, ≥50% or more of the attacks). The model time horizon was limited to 1 year, because data were only available to support projecting the effect of treatment up to 12 months.[25] The base case average number of prescriptions per year used in the analysis was 6, assuming 3 per seasonal bout. Typical seasonal bouts last approximately 1 to 8 weeks.[7] Regarding the number of prescriptions annually, the more conservative analysis using 6 was used, even though 4 or 5 may be more realistic.

The base case efficacy inputs were also conservative. The FDA-cleared treatment protocol is based on the ACT2 treatment protocol, which was 3-3-3 protocol on the ipsilateral side of the cluster attack, with patients allowed to use gammaCore up to 4 times in 1 day.[11,13] In contrast, the treatment protocol for ACT1 was less intensive, with three 2-minute stimulations each separated by a 1-minute break on the right side of the neck, with patients only allowed to use gammaCore for a maximum of 2 times in 1 day.[14] It is therefore reasonable to consider the ACT2 trial results more representative of gammaCore performance in the real world. However, the more conservative meta-analysis estimates were used as the base case inputs from the pooled analysis, consistent with accepted practice of using all available evidence and using ACT2 results as a sensitivity analysis.[12] The sensitivity analyses results using either the more realistic estimates of 4 prescriptions annually or using results from ACT 2 efficacy data resulted in more cost dominant findings.

Cluster patients attribute some adverse health outcomes and comorbidities to the severity of attacks when they do not respond to treatment. The prospect of the intensity of future attacks causes fear, anxiety, depression, suicidal ideation, and social isolation.

It has been described as "living in terror" and as a relentless search for treatment alternatives, "having tried everything else." Often, patients visit many doctors, each of whom performs multiple diagnostic tests.[3-5] In addition to eliminating the need for rescue medications when gammaCore successfully aborts attacks and when it is consistently effective, gammaCore will alleviate the fears, anxiety, depression, and suicidal ideation associated with thoughts of future attacks described by patients.[3,4] Patients who responded to gammaCore reduced medication use, had fewer consultations and referrals, and improved QoL.[15,16,25] The 50% reduction in patient costs used in the model is consistent with observational data of cluster patients followed for 1 year who reduced oxygen use by 55% and triptan use by 48%.[16]

Episodic cluster headache attacks each typically last between 15 minutes and 3 hours; the typical average duration is 45-90 minutes. During an active bout, patients experience 1-4 attacks per day on average, but this can reach 8 attacks per day at peak frequency. Often patients contemplate suicide during attacks, and cluster headache is also associated with depression, anxiety, and sleep disorders. Cluster headache affects work, productivity, daily functioning, and travel abilities for those afflicted. More than 10% of cluster headache patients attribute their inability to work to the illness. The economic burden of episodic cluster headache is more than twice that of nonheadache patients.[10] The study by Polson et al also found that episodic cluster patients spend almost twice as much on diagnostic testing, 1.5 times as much on visits to the emergency department, 3 times as much on home infusion/specialty treatment, 1.5 times on hospital outpatient treatment, and more than twice as much

on physician office visits (all *P* values <.001).[10] Successful and consistently effective treatment with gammaCore may reduce these AEs and comorbidity manifestations and significantly impact utilization needs.[15,16,25]

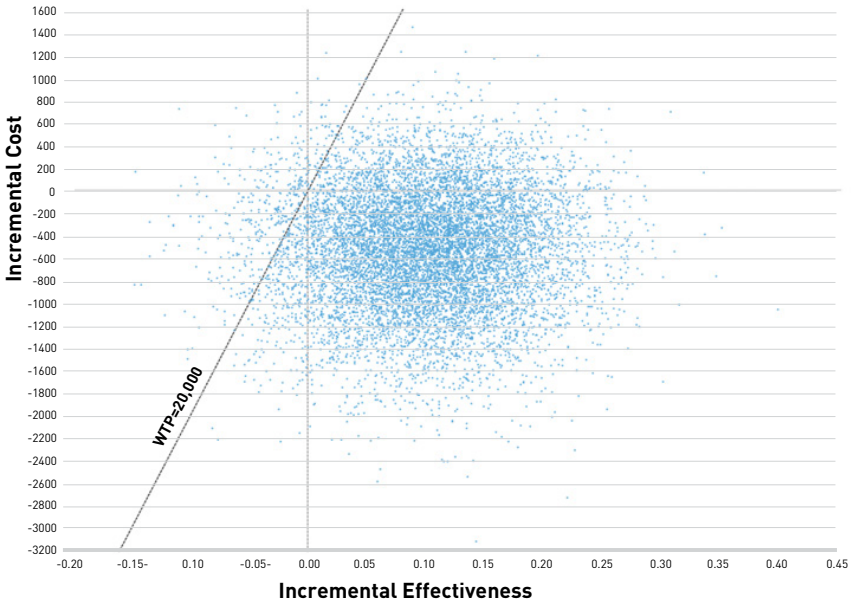
gammaCore is a hand-held, portable, practical, and easy-to-use device that can be used numerous times a day, every day. gammaCore is also the only treatment that can be used consistently any time of the day. It is safe with no toxicity, drug interactions, or serious device-related AEs. For many patients in whom gammaCore works well, consistently aborting attacks within 15 minutes and eliminating the need for rescue medication, gammaCore represents a life-changing experience: It improves QoL, daily functioning, and social engagements.

This cost-effectiveness analysis provides further economic evidence to support the modification of current treatment guidelines and coverage policies for episodic cluster headache in response to the recent FDA clearance for gammaCore. In addition, should ongoing clinical trials for new anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies be positive in phase 3 trials for both episodic and chronic cluster headache, resulting in their FDA approval, they may be expected to be quite expensive; gammaCore may lessen the need for these anti-CGRP monoclonal antibodies in episodic patients. LY2951742 and TEV-48125 are being studied for both episodic cluster headache (NCT02397473 and NCT02945046, respectively) and chronic cluster headache (NCT02438826 and NCT02964338, respectively).

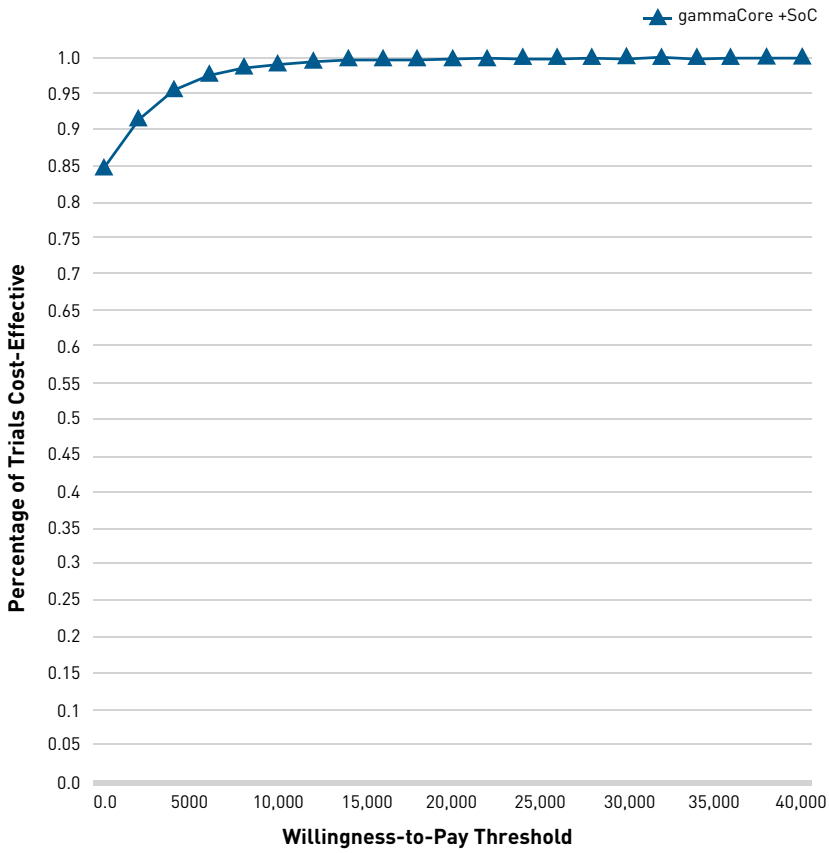
Strengths of this analysis are that the model is designed and conducted to current accepted recommendations and standards.[19] The parameter estimates were derived from primary, patient-level data from randomized, double-blind, sham-controlled trials. The model is a simple and transparent design, and its execution accounts for treatment failures in addition to responders and nonresponders. The design maps realistic episodic cluster headache patient care and an extensive set of sensitivity analyses, including a wide range of 1-way and multiway deterministic and probabilistic approaches.

FIGURE 4. Cost-Effectiveness

A. Cost-effectiveness scatter plot



B. Cost-effectiveness acceptability curve showing percentage of Monte Carlo trials that yielded cost-effective outputs at varying levels of willingness-to-pay thresholds



SoC indicates standard of care.

Limitations

Limitations are that the cost and impact on cost estimates used are not itemized by specific medications and dosages as that level of detail were not available. However, the estimates used are based on assumptions supported by evidence.[7,10,15,16] The model may also underestimate cost savings as the use of gammaCore may also enable patients to have fewer suboccipital steroid injections and sphenopalatine ganglion blocks, and fewer preventive medications, which were not accounted for explicitly in this model due to lack of data.

Conclusions

gammaCore, which is clinically superior to SoC and was recently cleared by the FDA, adds significant economic value to the acute treatment of episodic attacks of cluster headaches. These findings serve as additional robust economic evidence to support the need to modify current treatment guidelines and coverage policies. With the recent launch of gammaCore in the United States, additional real-world data are needed to characterize the long-term impact of gammaCore on comorbidities, utilization, QoL, daily functioning, productivity, and social engagement of cluster headache patients. ■

Author affiliations: electroCore, LLC, Basking Ridge, NJ (ATT, DD, EJL); profecyINTEL, LLC, New York, NY (MM).

Funding source: This supplement was sponsored by electroCore LLC.

Author disclosures: Dr Mwamburi has disclosed that he has provided research services to produce the manuscript and owns shares in ElectroCore LLC; Mr Liebler has disclosed that he is an employee and owner of equity in electroCore, LLC; Mr Tenaglia has disclosed that he is an employee of and stock owner in electroCore, LLC.

Authorship information: Acquisition of data (EJL, MM); analysis and interpretation of data (EJL, MM); concept and design (ATT, EJL, MM); critical revision of the manuscript for important intellectual content (ATT, EJL, MM); drafting of the manuscript (ATT, MM); obtaining funding (ATT); statistical analysis (MM).

REFERENCES

1. Fischera M, Marziniak M, Gralow I, Evers S. The incidence and prevalence of cluster headache: a meta-analysis of population-based studies. *Cephalalgia.* 2008;28(6):614-618. doi: 10.1111/j.1468-2982.2008.01592.x.
2. Gaul C, Diener HC, Müller OM. Cluster headache: clinical features and therapeutic options. *Dtsch Arztebl Int.* 2011;108(33):543-549. doi: 10.3238/arztebl.2011.0543.
3. Beck J. Cluster headaches: the worst possible pain? *The Atlantic* website. www.theatlantic.com/health/archive/2013/11/cluster-headaches-the-worst-possible-pain/281524/. Published November 19, 2013. Accessed September 6, 2017.
4. Fletcher J. Why cluster headaches are called "suicide headaches." *J Neurol Stroke.* 2015;3(3):00092. doi: 10.15406/jnsk.2015.03.00092.
5. Palacios-Ceña D, Talavera B, López-Ruiz P, et al. Living with cluster headache: a qualitative study of patients' perspectives. *Headache.* 2016;56(7):1171-1182. doi: 10.1111/head.12886.
6. Choong CK, Ford JH, Nyhuis AW, et al. Clinical characteristics and treatment patterns among patients diagnosed with cluster headache in U.S. healthcare claims data [published online June 5, 2017]. *Headache.* doi: 10.1111/head.13127.
7. Rozen TD, Fishman RS. Cluster headache in the United States of America: demographics, clinical characteristics, triggers, suicidality, and personal burden. *Headache.* 2012;52(1):99-113. doi: 10.1111/j.1526-4610.2011.02028.x.
8. Schuster NM, Rapoport AM. New strategies for the treatment and prevention of primary headache disorders. *Nat Rev Neurol*. 2016;12(11):635-650. doi: 10.1038/nrneurol.2016.143.
9. Halker R, Vargas B, Dodick DW. Cluster headache: diagnosis and treatment. *Semin Neurol.* 2010;30(2):175-185. doi: 10.1055/s-0030-1249226.
10. Polson M, Lord TC, Evangelatos T. Real world analysis of health plan medical and pharmacy claims data to assess differences in healthcare utilization and total cost in patients suffering from cluster headaches compared with patients without headache-related conditions. Paper presented at: Academy of Managed Care Pharmacy Nexus 2016; October 3-6, 2016; National Harbor, MD.
11. gammaCore [package insert]. Basking Ridge, NJ: electroCore, LLC; 2017.
12. Coo I, Marin JCA, Silberstein SD, et al. Non-invasive vagus nerve stimulation (nVNS): acute treatment of episodic and chronic cluster headache: pooled analysis of ACT1 and ACT2 studies. Paper presented at: American Academy of Neurology 2017 Annual Meeting; April 22-28, 2017; Boston, MA.
13. Goadsby PJ dCI, Silver N. Non-invasive vagus nerve stimulation for the acute treatment of episodic and chronic cluster headache: findings from randomized, double-blind, sham-conrolled ACT2 trial. Paper presented at: American Association of Neurology 2017 Annual Meeting; April 22-28, 2017; Boston, MA.
14. Silberstein SD, Mechtler LL, Kudrow DB, et al. Non-invasive vagus nerve stimulation for the ACute Treatment of cluster headache: findings from the randomized, double-blind, sham-controlled ACT1 study. *Headache.* 2016;56(8):1317-1332. doi: 10.1111/head.12896.
15. Strickland I, Davis S, Ward J, Amato F, Errico JP. Non-invasive vagus nerve stimulation as a treatment for headache patients with multi-morbidity: real world experience in English primary care. Paper presented at: ISPOR 21st Annual International Meeting; May 21-25, 2016; Washington, DC.
16. Nesbitt AD, Marin JC, 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. doi: 10.1212/WNL.0000000000001394.
17. Jenks M, Davis S, Amato F, Errico J, Strickland I. A preliminary cost-utility analysis of non-invasive vagus nerve stimulation therapy in patients suffering with headache and functional disorder multi-morbidity. *Value in Health*. 2016;19(7): A698. doi: 10.1016/j.jval.2016.09.2017
18. Morris J, Straube A, Diener HC, et al. Cost-effectiveness analysis of non-invasive vagus nerve stimulation for the treatment of chronic cluster headache. *J Headache Pain.* 2016;17:43. doi: 10.1186/s10194-016-0633-x.
19. Husereau D, Drummond M, Petrou S, et al; ISPOR Health Economic Evaluation Publication Guidelines-CHEERS Good Reporting Practices Task Force. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. *Value Health*. 2013;16(2):231-250. doi: 10.1016/j.jval.2013.02.002.
20. Becker WJ. Cluster headache: conventional pharmacological management. *Headache.* 2013;53(7):1191-1196. doi: 10.1111/head.12145.
21. Holle-Lee D, Gaul C. Noninvasive vagus nerve stimulation in the management of cluster headache: clinical evidence and practical experience. *Ther Adv Neurol Disord.* 2016;9(3):230-234. doi: 10.1177/1756285616636024.
22. Gaul C, Finken J, Biermann J, et al. Treatment costs and indirect costs of cluster headache: a health economics analysis. *Cephalalgia*. 2011;31(16):1664-1672. doi: 10.1177/0333102411425866.
23. Lademann V, Jansen JP, Evers S, Frese A. Evaluation of guideline-adherent treatment in cluster headache. *Cephalalgia.* 2016;36(8):760-764. doi: 10.1177/0333102415612774.
24. Robbins MS, Starling AJ, Pringsheim TM, Becker WJ, Schwedt TJ. Treatment of cluster headache: the American Headache Society evidence-based guidelines. *Headache.* 2016;56(7):1093-1106. doi: 10.1111/head.12866.
25. Marin J, Consiglio E, McClure C, Liebler E. Non-invasive vagus nerve stimulation (nVNS) for treatment of cluster headache: early UK clinical experience. Paper presented at: European Headache and Migraine Trust International Congress; September 15-18, 2016; Glasgow, United Kingdom. Abstract 161.