Migraine affects approximately 15% of the US population, with an estimated economic burden of $78 billion annually.\(^1,2\) GammaCore (noninvasive vagus nerve stimulation [nVNS]; electroCore, Basking Ridge, NJ), was approved by the FDA in January 2018 (Figure 1) and offers a viable option for abortive therapy for many of these patients with migraine.\(^1\) Available treatments include migraine-specific medications, such as triptans; nonopiate based analgesics, such as nonsteroidal anti-inflammatory drugs (NSAIDs); opiate-based analgesics; and numerous over-the-counter medications.\(^3\) Preventive treatments such as β-blockers, antidepressants, anti-epileptics, and onabotulinumtoxinA are FDA-approved for prevention of migraine, but can have limited effectiveness, intolerable adverse effects, and restricted or conditional coverage.\(^5\) Other medications under investigation include calcitonin gene-related peptide (CGRP) antibodies, erenumab and fremanezumab.\(^6,7\)

Approximately 40% of migraine sufferers remain undiagnosed. Among those diagnosed, 25% are cared for by neurologists or headache specialists, 10% of whom are dissatisfied with the acute and preventive treatment options.\(^8,9\) Migraine is associated with symptoms of depression, anxiety disorder, and irritable bowel syndrome, among others. These symptoms increase healthcare utilization and overall costs.\(^10,11\) Patients with a combination of the moderate-to-high frequency of headache days, high propensity for comorbidities, and high healthcare utilization, constitute a subgroup of high-demand patients with migraine. A study showed migraine patients cost approximately $10,000 annually.\(^12\) Migraine, particularly in high-demand patients with migraine, also affect work, productivity, and daily functioning.\(^12,13\) The current disease and treatment landscape for migraine represents a high unmet need for these patients.\(^10\)

The recent FDA approval for gammaCore using acute treatment of migraine was based on a randomized, sham-controlled prospective study of nVNS for the acute treatment of migraine (PRESTO) study. It demonstrated superiority of gammaCore adjunct to standard of care (SOC) over sham with SOC.\(^1,5,15\) The cost-effectiveness of gammaCore compared to SOC is documented and shown to be dominant (ie, gammaCore was more effective while costing less,
[United States and Germany] and cost-effective [United Kingdom] for cluster headache). The cost-effectiveness of gammaCore for migraine treatment remains unknown and needs to be characterized. We performed a cost-effectiveness analyses of gammaCore adjunct to SOC for migraine compared to SOC alone and assessed the cost-effectiveness of treatment sequence strategies.

Methods

We developed 2 models: 1 for the treatment comparison of gammaCore plus SOC versus SOC alone, and 1 for treatment sequence strategy comparisons of starting with gammaCore for acute treatment and providing erenumab prevention for failures; and starting with and providing erenumab prevention without prior treatment with acute treatment with either gammaCore or SOC. The cost-effectiveness analyses were designed and implemented in accordance to current methodological guidelines. The main sources of primary data were the PRESTO trial, supported by additional evidence and insights from Strickland et al and Polson et al. The treatment protocol for PRESTO was 3 two-minute stimulations followed by a 3-minute break and, if pain persisted, another 3 two-minute stimulations (3-3-3 protocol). PRESTO was reviewed and approved by a relevant ethics committee and details of the trial have been previously published.

Model Structure

The model approach and structure were based on treatment of acute attacks to yield 3 potential outcomes—failures, partial responders, and persistent 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 30 minutes with no use for rescue medication) was 0%. GammaCore patients who failed were immediately identified using 1 or 2-month prescriptions with no further refills. Partial responders are patients who experienced partial efficacy, with the proportion of responses to treated attacks between 1% and 50%. These patients could be retrained to yield additional responders, additional failures, or remain as partial responders. Responders were patients who met the equivalent of PRESTO trial outcomes. The proportion of responses to attacks ≥50% (pain free) did not need other medication. Individuals in each outcome could remain in the same outcome group. In addition, failures could be offered erenumab. The model structure is shown in Figure 2. The decision tree model parameters were populated with data from the PRESTO trial providing the base case parameters. Cost data were derived from Polson et al and economic considerations driven by data from Strickland et al. Additional insights, including event rates for erenumab, were drawn from literature. The models were designed from a payer perspective with a time horizon of 1 year and built using Tree Age Pro–Healthcare (2018 R1, Williamsburg, MA). Uncertainty was incorporated by using distributions around
parameter estimates for treatment effects, costs, and utilities. In addition, 100,000 trials (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 trees are shown in Figures 3a and 3b.

Model Design and Parameter Estimates

**Primary Model Considerations**

The probability of failing treatment within 1-month is \( \text{prob}_\text{Fail1M} \). The probability of responders who benefit adequately (≥50% pain-free response) from gammaCore and will reduce the need for other medications is \( \text{prob}_\text{Resp gammaCore} \) while the probability of being a responder in the SOC arm is \( \text{prob}_\text{Resp SOC} \). The probability of partial-responders that may benefit and continue to use gammaCore is \( \text{prob}_\text{NonRespResp} \) and to still fail after retraining is \( \text{prob}_\text{NonRespNon} \). The impact of consistent success of gammaCore treatment reduces the costs of care for migraine patient is \( \text{reduction\_Factor} \). The number of monthly gammaCore prescriptions per patient for a 12-month period is \( \text{months\_Prescription} \), the cost per prescription to payers is \( \text{cost\_gammaCore} \), (rounded up from average wholesale price (AWP) at minus 15%). The overall annual cost of care for the target migraine patient population based on current SOC is \( \text{cost\_SOC\_Care} \). Utility estimates were derived from Strickland et al based on EQ-5D index measurements for failures, partial responders, and responders. Model assumptions were based on insights from the literature.6,23-25

**Secondary Treatment Sequence Model Considerations**

The annual cost of erenumab plus administration is \( \text{cost\_Erenumab\_Annual} \), the probability of response while on erenumab is \( \text{prob\_Resp\_Erenumab} \), and the utility for patients on erenumab group is \( \text{utility\_Erenumab} \). Parameter definitions and base case and corresponding sensitivity analyses estimates are shown in Table 1.6,15,20,23

**Model Outputs**

The model outputs were ICERs for cost per QALY. These were derived from the difference in overall costs between gammaCore plus SOC (\( C_{\text{gammaCore}} \)) and SOC alone (\( C_{\text{soc}} \)), and then divided by the difference in effectiveness, and QALY between gammaCore plus SOC (\( E_{\text{gammaCore}} \)) and SOC alone (\( E_{\text{soc}} \)). The approach was similar for the secondary model. We compared gammaCore-based sequences to corresponding SOC-based and non-prerequisite sequences, as well as corresponding erenumab-based sequences. A series of 1-way deterministic sensitivity analyses were performed for high and low values shown in Table 1. Additional probabilistic sensitivity analyses were performed.

**Results**

**ICER**

**gammaCore plus SOC arm versus SOC alone**

The annual mean costs for gammaCore plus SOC arm (\( C_{\text{gammaCore}} \)) was $9,543, and for SOC alone (\( C_{\text{soc}} \)) was $10,010. The mean QALYs for gammaCore plus SOC arm (\( E_{\text{gammaCore}} \)) was 0.67 and for SOC alone arm (\( E_{\text{soc}} \)) was 0.63. Thus, gammaCore plus SOC arm was dominant (ie, was more effective but cost less) over SOC alone. See Table 2.

**Sequencing Strategy Options**

The annual mean costs and QALYs for gammaCore followed by erenumab were $10,678 and 0.70, respectively, while the annual mean costs and QALYs for SOC followed by erenumab were $11,583.
and 0.67, respectively. The mean costs and QALYs for initiating erenumab with no prior gammaCore or SOC treatment were $13,766 and 0.65, respectively. GammaCore followed by erenumab for failing patients was dominant over all other strategies, as shown in Table 3.

### Sensitivity Analyses

All results of the 1-way sensitivity analyses were cost-effective, with a conservative willingness-to-pay threshold of US $20,000. The results of the series of 1-way sensitivity analyses are shown in the Tornado Diagram in Figure 4a. The most influential factors in the one-way sensitivity analyses were the cost reduction factor, the number of months of prescription per year, and the cost of SOC care for high-demand migraine patients. More than 95% of simulations were cost-effective at a threshold of $40,000. The cost-effectiveness scatter plot and acceptability curve are shown in Figure 4b and Figure 4c.

### Discussion

This cost-effectiveness analysis found gammaCore to be dominant over SOC for acute treatment of migraine. On average, if gammaCore is used as an adjunct to SOC, compared to the current SOC alone, it will result in cost-savings from a payer perspective in the United States, because of reduced utilization and overall patient costs. In addition, we examined the role of gammaCore in treatment sequence strategies and considered scenarios in which patients started with acute treatment using gammaCore or SOC options then providing erenumab prevention for those who do not respond to the acute treatment as an alternative to initiating care with erenumab prevention right from the start. We also found that strategies involving gammaCore helped cost savings, compared to corresponding strategies with SOC or nothing prior to erenumab prevention. For chronically ill patients, optimized treatment sequencing is key for patients and payers. Many migraine patients who need care

**TABLE 1.** Parameter Estimates for Probabilities, Costs, and Utilities and Other Parameters6,15,20,23

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Estimate</th>
<th>Low</th>
<th>High</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main model</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cost_gammaCore</td>
<td>Monthly cost of gammaCore (AWP-15%)</td>
<td>$500</td>
<td>450</td>
<td>600</td>
<td>electroCore Projections</td>
</tr>
<tr>
<td>cost_SOC_Care</td>
<td>Cost of care for target migraine patients</td>
<td>$9990±5000</td>
<td>7500</td>
<td>17,000</td>
<td>Polson et al (adjusted)</td>
</tr>
<tr>
<td>prob_Fail1M</td>
<td>Probability of immediate failure on gammaCore</td>
<td>0.20</td>
<td></td>
<td></td>
<td>PRESTO</td>
</tr>
<tr>
<td>prob_Fail_SOC</td>
<td>Response of failure on SOC</td>
<td>0.30</td>
<td></td>
<td></td>
<td>PRESTO</td>
</tr>
<tr>
<td>prob_Resp_gammaCore</td>
<td>Probability of response on gammaCore</td>
<td>0.32±0.048</td>
<td></td>
<td></td>
<td>PRESTO</td>
</tr>
<tr>
<td>prob_Resp_SOC</td>
<td>Probability of response on SOC</td>
<td>0.18±0.038</td>
<td></td>
<td></td>
<td>PRESTO</td>
</tr>
<tr>
<td>prob_NonRespResp</td>
<td>Probability of staying on gammaCore after partial response</td>
<td>0.5</td>
<td></td>
<td></td>
<td>PRESTO</td>
</tr>
<tr>
<td>prob_NonRespNon</td>
<td>Probability of stopping gammaCore after partial response</td>
<td>0.5</td>
<td></td>
<td></td>
<td>PRESTO</td>
</tr>
<tr>
<td>utility_Failure</td>
<td>QOL for gammaCore group</td>
<td>0.58±0.05</td>
<td></td>
<td></td>
<td>Strickland et al</td>
</tr>
<tr>
<td>utility_Partial</td>
<td>QOL for partial responders</td>
<td>0.64±0.05</td>
<td></td>
<td></td>
<td>Strickland et al</td>
</tr>
<tr>
<td>utility_Resp_SOC</td>
<td>QOL for SOC responders</td>
<td>0.70±0.05</td>
<td></td>
<td></td>
<td>Strickland et al</td>
</tr>
<tr>
<td>utility_Resp_gammaCore</td>
<td>QOL for gammaCore responders group</td>
<td>0.74±0.12</td>
<td></td>
<td></td>
<td>Strickland et al</td>
</tr>
<tr>
<td>reduction_Factor</td>
<td>Cost reduction factor due to gammaCore</td>
<td>0.6</td>
<td>0.5</td>
<td>0.7</td>
<td>PRESTO; Strickland et al</td>
</tr>
<tr>
<td>months_Prescription</td>
<td>Months of prescription/year</td>
<td>6</td>
<td>4</td>
<td>8</td>
<td>electroCore projections</td>
</tr>
<tr>
<td><strong>Secondary Model</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cost_Erenumab_Annual</td>
<td>Annual cost of erenumab plus administration</td>
<td>$5000</td>
<td>$4000</td>
<td>$7000</td>
<td>Assumptions/projections</td>
</tr>
<tr>
<td>prob_Resp_Erenumab</td>
<td>Probability of response on erenumab</td>
<td>0.49</td>
<td></td>
<td></td>
<td>Goadsby et al</td>
</tr>
<tr>
<td>utility_Erenumab</td>
<td>QOL for erenumab group</td>
<td>0.70±0.05</td>
<td></td>
<td></td>
<td>Assumptions</td>
</tr>
</tbody>
</table>

AWP indicates average wholesale price; SOC, standard of care; QOL, quality of life
* Response based on number of responders with responses ≥50% pain-free responses for attacks

**TABLE 2.** Incremental Cost-effectiveness Ratio for Primary Model for gammaCore Plus SOC arm vs SOC Alone

<table>
<thead>
<tr>
<th></th>
<th>gammaCore Plus SOC</th>
<th>SOC Alone</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs ($)</td>
<td>9453</td>
<td>10,101</td>
<td>-557</td>
</tr>
<tr>
<td>Effectiveness (QALYs)</td>
<td>0.67</td>
<td>0.63</td>
<td>0.04</td>
</tr>
<tr>
<td>ICER ($/QALY)</td>
<td>-</td>
<td>-</td>
<td>Cost-saving</td>
</tr>
</tbody>
</table>

ICER indicates incremental cost-effectiveness ratio; QALY, quality adjusted life years; SOC, standard of care.
from a neurologist or headache specialist are dissatisfied with the current SOC medications, representing a high-unmet need that may be overcome by gammaCore for some of these patients. The current SOC medications for acute treatment of migraine headache may not be consistently effective, and can have significant drug-related adverse effects and coverage may be restricted. The cost-effectiveness, particularly among high-demand migraineurs who cost payers the most, is driven by the unique combination of gammaCore’s superiority in efficacy, favorable safety profile, improvement in quality of life (QOL), and effect of reducing overall healthcare needs and costs for patients when gammaCore consistently effective.

These findings align with previous cost-effectiveness analyses findings of gammaCore for acute treatment and prevention in episodic and chronic cluster headache, which is another primary headache disorder for which gammaCore is an FDA approved treatment. GammaCore also has 5 Conformité Européenne (CE) marks for primary headache disorders, bronchoconstriction, epilepsy, gastric motility disorders, depression, and anxiety. These are commonly described symptoms in adults with medically unexplained symptoms (MUS).

When gammaCore is used for acute treatment of migraine, it works by enhancing vagal tone and often results in alleviating others associated with multiple comorbidities in addition to migraine pain. Patients with migraine cost almost 3 times more than nonheadache patients, due to MUS resulting in more diagnostic testing, emergency department visits, home infusion, specialty treatment, hospital admissions, and physician office visits. Successful treatment with gammaCore reduces migraine pain intensity, comorbid manifestations, and utilization significantly. In addition, gammaCore is a nonpharmaceutical treatment that is relatively safe, free from drug interactions, and adverse events have been mild and transient. GammaCore is also portable, easy to use, and convenient. The decrease in medication needs also includes a reduction in opioid prescriptions and lessening the risk for opioid addiction and abuse.

### TABLE 3. Cost-effectiveness Analyses for Secondary Model for Treatment Sequence Strategy

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Costs</th>
<th>QALYs</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>gammaCore Followed by Erenumab</td>
<td>10,678</td>
<td>0.70</td>
<td>0.65</td>
</tr>
<tr>
<td>SOC Followed by Erenumab</td>
<td>11,583</td>
<td>0.67</td>
<td>Dominant</td>
</tr>
<tr>
<td>ICER (CgC-CEren) / (EgC-EEren)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erenumab Alone</td>
<td>13,766</td>
<td>0.65</td>
<td>Dominant</td>
</tr>
</tbody>
</table>

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

### FIGURE 4A. Tornado Diagram for 1-way Deterministic Sensitivity Analyses for Primary Model

- Cost reduction factor on successful gammaCore (0.5 to 0.8)
- Average months of prescription per year (4.0 to 8.0)
- Annual cost of migraine patient (8,000.0 to 12,000.0)
- Prescription cost of gammaCore (450.0 to 600.0)
- Refund for gammaCore for failures (0.0 to 1.0)

### FIGURE 4B. Cost-effectiveness Scatter Plot for Primary Model With WTP Threshold Line for $50,000 and 95% Confidence Ellipse

WTP indicates willingness to pay.
As the primary model of this research compares treatment options for gammaCore versus SOC, the secondary model is a more complex comparison of strategies for the overall approach of a patient rather than the individual selection of treatment options. Current payer coverage for onabotulinumtoxinA, for example, is conditional and restricted to patients with 15 or more headache days per month who have failed 2 or 3 treatment options, depending on specific plans.36,37 Such policy strategies are typically reserved for costly, higher tier, usually injectable or invasive treatment options, among which onabotulinumtoxinA is included. Similarly, CGRP receptor inhibitors, such as erenumab and fremanezumab, would likely fall into this category. As monoclonal antibodies, they are projected to cost approximately $6900 annually ($5000 with an expected 27% discount).

It was important to determine the cost effectiveness of strategies that require gammaCore (or SOC) before providing prevention with a CGRP receptor inhibitor. We used erenumab as the CGRP receptor inhibitor in our study because of the availability of the data. Because successful acute treatment with gammaCore may reduce the reliance of both acute and preventive medications, it makes sense to evaluate a sequence strategy that requires failure of acute treatment prior to initiating an efficacious preventive medication for cost-effectiveness. Our treatment sequencing strategy analysis should not be mistaken as comparisons between acute treatments and preventive medications. We included the preceding SOC strategy to emulate scenarios where a provider is dealing with a newly diagnosed moderate-high frequency episodic or chronic migraine patient or a similar new referral to a neurologist or headache specialist. Because the existing coverage policies for onabotulinumtoxinA, for which the annual cost estimate of onabotulinumtoxinA (4 cycles per year) is more costly than erenumab, are already conditional for failure of previously failed treatments. We did not include it in our sequence strategy analysis in the secondary model.36,37

The secondary model finding in this study affirms that initiating erenumab only after patients fail SOC or gammaCore are more cost effective than starting patients on erenumab straightaway, with the gammaCore-based sequence being the most cost-efficient. Also, as preventive agents, with their effectiveness measured as reducing frequency of headache days, typically a reduction of 50% or more is considered responsive. Although this is a major benefit to the patient, it also means that many patients remain with symptoms and, thus, QoL is not completely improved. Patients may need to continue to use acute treatment options, including gammaCore for the residual attacks. Another key point is that, while these preventive agents are efficacious, and response can be acknowledged relatively rapidly, for example within 3 months, it still takes 9 to 18 months to determine whether the preventive medication has failed. The costs incurred on the medications for the 9 to 18 months are significantly more compared with costs incurred on gammaCore, where treatment failure is determined within 1 or 2 months, thus saving payers. Finally, gammaCore Sapphire has incorporated RFID-based dose loading and wireless Bluetooth technologies for seamless communication with other devices including laptops, smartphones, and other mobile devices as well as server- and cloud-based services. This unique attribute allows for passive monitoring of dose usage and the occurrences of clinical events and outcomes for strategic future real-world data assessments. GammaCore therefore provides a data monitoring platform for pay-for-performance strategies and coverage policies. Pay-for-performance strategies could take advantage of optimized patient selection, follow-up, and long-term care at no or minimal additional cost, which is not as effortlessly possible when using pharmaceutical options. This presents further incentive for stakeholders, including payers, to make gammaCore even more cost-effective and economically attractive. The importance of successful and consistent treatment of migraine has recently been reinforced with the long-term findings that migraine sufferers are associated with increased risk of cardiovascular diseases in addition to what is already known regarding numerous other comorbidities.

Strengths of this analysis include the model designed and conducted to current accepted recommendations and standards.38 The parameter estimates were mostly derived from primary patient-level data from randomized, double-blind, sham-controlled trials. The models are simple and transparent designs and their execution account for treatment failures in addition to responders and partial-responders. Acute treatment response was based on pain-free outcomes.38 The design maps realistic high-demand migraine patient care and tests extensive sensitivity analyses, such as deterministic and probabilistic approaches. The cost estimates used were based on itemized data on specific medications and dosages as available. Estimates that are based on assumptions are supported by evidence.39,40 A potential weakness is that there is no comparative cost data for less expensive options that are also less effective oral preventative treatments.
Conclusions

Given that gammaCore is clinically superior to SOC and is cleared by the FDA, it significantly adds economic value for the acute treatment of migraine. Because gammaCore is dominant, its use represents savings to payers and patients as a treatment option and a component of treatment sequence strategies involving back-up preventive agents. These findings serve as additional robust economic evidence to support the need to update current migraine treatment guidelines and patient coverage policies. Additional real-world data are needed to characterize the long-term impact of gammaCore on comorbidities, utilization, QOL, economic outcomes, daily functioning, productivity, and social engagement of these patients. ■

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Author Disclosure: Mr Liebler reports to having employment with electroCore, Inc. Dr Mwamburi reports to serving on an advisory board, receiving a receipt for payment, preparing a manuscript, owning stock, and having employment with profecyINTEL, LLC. Dr Mwamburi also reports to owning stock with Pharmacy Nexus 2017. Dr Staats reports to having board membership with World Institute of Pain (WIP) and serving on an advisory board for Medtronic, Abbott Laboratories, Nalu, and SPA Therapeutic. He also reports to having employment with National Spine and Pain Centers and electroCore, Inc. and to attending a meeting or conference at Angar Securities Redefine Preference, WIP, AMS Technologies AGS. Dr Staats has stock ownership with electroCore, Inc. and d reports a conflict with electroCore, Inc., as it is a manufacturer of gammaCore, a therapy used in headaches. Mr Tenaglia reports to having stock and employment with electroCore, Inc. as it sells gammaCore.

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

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REFERENCES