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electroCore, Inc. (ECOR - NASDAQ)

The Buzz on Vagus Nerve Stimulation

Based on our multiple of earnings model and a 20% discount rate, electroCore is valued at approximately $4.00 per share. Our methodology applies a 20x multiple of earnings to 2026 EPS and discounts the result to beginning of year 2021.

Current Price (10/2/2020)	$1.89
Valuation	**$4.00**

INITIATION

electroCore is a commercial company marketing its gammaCore vagus nerve stimulation device in multiple migraine and cluster headache indications. It also has been granted Emergency Use Authorization (EUA) for respiratory-related COVID treatment.

The gammaCore device non-invasively stimulates the vagus nerve which treats headache. The device delivers an electrical pulse to activate the vagus nerve in the neck. Numerous clinical trials have been conducted supporting the efficacy and safety of gammaCore. Additional trials are underway for indications in PTSD, TBI and post-traumatic headache.

Sales are advancing in three segments: VA in the US, NHS in the UK & commercial. Low penetration at the VA, a recent expansion of the NHS program and continued efforts with commercial payors support topline advancement. COVID-related sales may have a material impact in the short term although they may fall as the pandemic dissipates.

Associations with the VA, NHS, CVS, Express Scripts & others combined with the strong safety and efficacy data for gammaCore support a long runway for topline growth in the US, European and Asian markets.

Our valuation assumes first positive earnings in 2025 and employs a multiple of 2026 earnings to generate target price.

SUMMARY DATA

52-Week High	**3.30**
52-Week Low	**0.32**
One-Year Return (%)	**-5.50**
Beta	**1.81**
Average Daily Volume (sh)	**5,563,206**
Shares Outstanding (mil)	**44.5**
Market Capitalization ($mil)	**84.2**
Short Interest Ratio (days)	**0.99**
Institutional Ownership (%)	**9.92**
Insider Ownership (%)	**26.3**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2020 Estimate	**N/A**
P/E using 2021 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**Above Average**
Type of Stock	**Small-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue
(In millions of USD)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2019	$0.4 A	$0.6 A	$0.7 A	$0.7 A	$2.4 A
2020	$0.7 A	$0.8 A	$0.8 E	$0.8 E	$3.0 E
2021					$5.2 E
2022					$9.7 E

Earnings per Share

	Q1	Q2	Q3	Q4	Year
2019	-$0.47 A	-$0.41 A	-$0.36 A	-$0.29 A	-$1.54 A
2020	-$0.27 A	-$0.13 A	-$0.12 E	-$0.12 E	-$0.60 E
2021					-$0.39 E
2022					-$0.28 E

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INITIATING COVERAGE

We are initiating coverage of electroCore, Inc. (NASDAQ: ECOR) with a valuation of $4.00 per share. This target price is based on a multiple of future earnings which reflect continued growth from sales through existing channels with the Veteran's Administration (VA) in the US, National Health Service (NHS) in the UK and domestic commercial payors. New contributions may come from other national healthcare plans, Europe and other overseas markets. The company's sole commercial product, gammaCore, is currently approved for four indications in migraine and cluster headaches and has received Emergency Use Authorization (EUA) for respiratory problems related to COVID-19.

The company's key product gammaCore Sapphire™ (nVNS) is a non-invasive vagus nerve stimulator that is FDA cleared to treat pain associated with migraine and episodic cluster headache. The device activates the vagus nerve via electrical stimulation. This approach avoids many of the side effects associated with drugs and invasive surgical procedures, allows for a portable solution and supports repeated use.

electroCore was founded in 2005 by current Chief Medical Officer Dr. Peter Staats and associated partners. The founding team sought to develop a neuromodulatory device to address asthma. During the early stages of investigation, a serendipitous side effect was identified when patients reported that their headaches were going away. Supported by previously published research[1] that had been done on vagal nerve stimulation benefitting migraineurs, the company conducted additional research to justify beginning clinical trials with a headache indication.

Since that time electroCore has obtained approval in four indications in adults including preventative treatment of migraine headache, acute treatment of pain associated with migraine headache, adjunctive use for the preventative treatment of cluster headache and acute treatment of pain associated with episodic cluster headache. The company has also received Emergency Use Authorization (EUA) for the use of gammaCore Sapphire™ for certain known or suspected COVID-19 patients.

Sales are generated from three sources including the Veteran's Administration (VA) under the Department of Defense, the National Health Service (NHS) in the United Kingdom and US commercial providers. The VA and NHS represent large markets that are only lightly penetrated. In the commercial space, CVS Caremark and Express Scripts both reimburse on behalf of beneficiaries after a co-pay. There are additional opportunities in other geographies and payor classes that provide a long-term runway for the company.

Sales are running at an annualized rate of $3 million based on 2Q:20 levels. Despite the difficulties related to the pandemic, the topline trend has been increasing both sequentially and year over year. The company is expanding distribution to its primary customer, the Veteran's Administration (VA), and the National Health Service (NHS) in the United Kingdom. Revenues are also generated from commercial payors as well. Recently, the NHS announced that electroCore would be the sole supplier for vagus nerve stimulation to patients for cluster headaches within NHS England with marketing expansion opportunities in Wales and Scotland. We see acceptance by the VA and NHS as strong validators of the technology supporting future growth with other US government and private payors and into mainland Europe and other geographies.

The headache market is large according to numerous sources which we detail in our report. Migraine affects from 12-18% of the population which is estimated to be about one billion persons around the world and anywhere from 36 to 40 million persons in the United States. Cluster headaches are less common but still comprise a sizeable group. An estimated 0.1% of the population suffers from chronic and episodic cluster headaches, which is about 330,000 to 400,000 individuals in the United States and perhaps over seven million around the world. There are over 10 million covered lives in US government programs that have access to gammaCore and about 400,000 patients visited a VA provider for headache in 2018.

[1] Sadler, R.M., *et al.* Vagal Nerve Stimulation Aborts Migraine in Patient with Intractable Epilepsy. Cephalalgia, July 1, 2002.

On June 30, 2020 electroCore held $18.9 million in cash after a raise of $7.4 million in sale of tax net operating losses, shares and notes. Subsequent to the end of the quarter, the company raised an additional $10.3 million from the sale of stock to Lincoln Park Capital Fund. For the first six months of 2020, the company has generated $1.5 million in revenues and burned $12.4 million in cash. We anticipate continued and accelerating growth over the coming quarters as penetration continues into existing channels and new markets and geographies are pursued. electroCore has a small amount of debt on its balance sheet related to the Cares Act that may be forgiven.

Key reasons to own electroCore shares:

- **Effective, non-invasive, and non-pharmaceutical method to treat migraines**
- **Portable, simple and rapid solution for preventing and treating headaches**
- **Indicated for both migraines and cluster headaches**
- **Existing and expanding relationships with VA hospitals**
- **Recharge/refill business model**
- **Supply chain simplicity: direct to customer shipping**
- **gammaCore can be prescribed through telemedicine**
- **NHS relationship in UK may provide foundation for further global expansion**
    - **Continental Europe**
    - **Asia**
- **Opportunity for COVID-related sales following EUA award**
- **Extended indications**
    - **Stroke**
    - **Trauma injury related headaches**
    - **PTSD**
    - **Mild traumatic brain injury**
    - **Inflammation**

In the following sections we review the pathophysiology behind migraine and cluster headaches, the vagus nerve and gammaCore's mechanism of action. We discuss the incidence and prevalence of migraine and cluster headaches and review other available treatments including neurostimulation and pharmaceutical options. We then detail electroCore's intellectual property, the risks the firm faces and peers and competitors. An overview of management and recent financial and operational results is also provided. Following an in-depth discussion of our model assumptions, we provide an appraisal of electroCore's valuation. Our financial model structure and assumptions are explained providing the justification for our valuation estimate for the company. We initiate electroCore Inc. at $4.00 per share.

Migraines and Cluster Headaches

Migraine

Migraines affect an estimated 39 million Americans and about 12% of the global population,[2] making it one of the most common conditions in the world. The characteristic symptoms of pain, nausea, vomiting and sensitivity to stimulus can also make it debilitating. It is a neurological disease that presents as a throbbing or pulsating pain, mostly on one side of the head and can be accompanied by nausea, vomiting, and heightened sensitivity to light and sound. Migraines can last for hours or days. In some cases, a set of warning symptoms, known as an aura, occurs before the migraine. Auras can include flashes of light or blind spots. They can also include tingling in the face, arm or leg, typically on one side, and difficulty speaking. Migraines are a complex pathology and there appear to be hereditary and sex components of the condition as well. Women are two to three times more likely than men to have migraines with the condition most common in individuals from 30 to 50 years of age.

There are many types of migraine:[3]

- Migraine without aura (most common)
- Migraine with aura
- Chronic
- Menstrual
- Hemiplegic
- Migraine with brainstem aura
- Vestibular
- Abdominal
- Cyclical vomiting syndrome

Incidence & Prevalence

According to the World Health Organization, migraine ranks as the third most common disease in the world and is the leading neurological cause of disability. With an estimated prevalence of 12-18%,[4] there are over one billion people globally[5] and about 40 million people in the US who had at least one migraine headache in the past year. Migraines can begin in childhood, adolescence or early adulthood occurring most frequently between the ages of 30 and 50. 18% of US women, about 28 million, experience migraines and women of childbearing years are especially prone. An estimated 6% and 10% of men and children experience migraines, respectively. Migraine without aura is the most common type, estimated to occur in 70-90% of cases.[6] Annual costs for the US and EU are estimated at $13 to $20 billion[7] and €18 to €27 billion,[8,9] respectively but the likely cost is higher on account of underreporting.

Risk factors include family history and age. Risk increases during adolescence and peaks around age 30. Women are three times as likely to experience migraines likely due to the presence and fluctuation in hormones. Genetic risk factors have been identified via genome-wide association studies (GWAS) and have found that multigenetic variants, rather than individual genes drive susceptibility to migraine.[10] In GWAS including samples from almost 60,000 patients and over 300,000 controls, 44 single nucleotide polymorphisms (SNPs) were associated with non-aura migraine, implicating 38 genomic loci. Unsurprisingly, the majority of loci were related to vascular function but

[2] Migraine Research Foundation. migraineresearchfoundation.org
[3] https://www.migrainetrust.org/about-migraine/types-of-migraine/
[4] Pathophysiology of Migraine: A Disorder of Sensory Processing Peter J. Goadsby, Philip R. Holland, Margarida Martins-Oliveira, Jan Hoffmann, Christoph Schankin, and Simon Akerman Physiological Reviews 2017 97:2, 553-622
[5] Pathophysiology of Migraine: A Disorder of Sensory Processing Peter J. Goadsby, Philip R. Holland, Margarida Martins-Oliveira, Jan Hoffmann, Christoph Schankin, and Simon Akerman Physiological Reviews 2017 97:2, 553-622
[6] https://www.migrainetrust.org/about-migraine/types-of-migraine/
[7] Burton, W., *et al.* The Impact of Migraine and the Effect of Migraine Treatment on Workplace Productivity in the United States and Suggestions for Future Research. Mayo Clin Proc. 2009 May; 84(5): 436–445.
[8] Olesen J, et al., and CDBE2010 study group; European Brain Council. The economic cost of brain disorders in Europe. Eur J Neurol. 2012 Jan;19(1):155-62.
[9] Stovner LJ, Andrée C; Eurolight Steering Committee. Impact of headache in Europe: a review for the Eurolight project. J Headache Pain. 2008 Jun;9(3):139-46.
[10] Andreou, A.P., Edvinsson, L. Mechanisms of migraine as a chronic evolutive condition. *J Headache Pain* **20,** 117 (2019). https://doi.org/10.1186/s10194-019-1066-0

some were related to metal ion homeostasis, a novel hypothesis which has not been fully investigated. Unfortunately, the multigenicity of the finding limits genetic predictability or targeting of a single pathway.

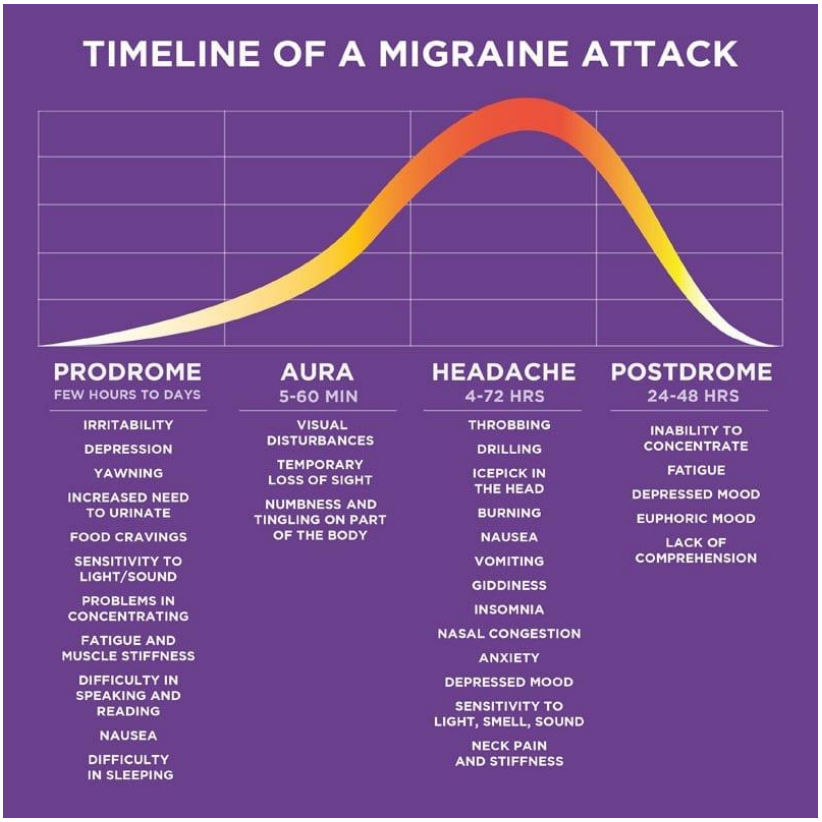
Environmental factors play a role in migraine and many triggers have been identified. Migraines disproportionately affect women during their childbearing years and hormonal changes in women have been identified as a potential trigger for migraines. Alcoholic and caffeinated beverages, stress, bright lights, loud sounds, strong smells, changes in sleep patterns, physical exertion, weather changes, medications, foods, and food additives have all been implicated as antagonists.

Symptoms

Migraines are characterized by unilateral, pulsating pain, accompanied by a variety of other symptoms, lasting from 2-72 hours. Migraines are thought to progress through four stages: prodrome (premonitory), aura, attack and post-drome; however, not all migraines progress through all of the steps, in fact, most migraines occur without aura. There may be overlap in symptoms and symptoms that occur in earlier stages may persist through all of the stages. The signs can be consistent and be strong predictors for those who suffer from migraine headaches, or as they are referred to in the field, migraineurs.

In the initial prodrome stage, which can occur up to 72 hours before a migraine, sufferers may experience changes in mood, activity, irritability, fatigue, food cravings, repetitive yawning, stiff neck and phonophobia. If the individual passes through the aura stage, visual disturbances, numbness, dizziness, and difficulty speaking may occur before or during the headache itself. Aura symptoms build over several minutes and can last up to an hour. The headache follows, which can last up to 72 hours if untreated. It is characterized by a throbbing and pulsating pain of the head, on one or both sides, accompanied by nausea, vomiting and sensitivity to light, sound, smell and touch. After the attack, typically a postdrome phase follows. In the postdrome phase, migraine sufferers may feel drained or confused and feel fatigue, body aches, trouble concentrating and continued sensitivity. Some may feel elated.

Exhibit I – Stages of a Migraine[11]



[11] Understanding Migraine Progression Can Help You Anticipate & Manage Your Symptoms. January 18, 2018. The American Migraine Foundation; https://americanmigrainefoundation.org/resource-library/timeline-migraine-attack/

Pathophysiology

Migraines are complex and the underlying mechanism of their causes, progression and symptoms is not fully known. There is accumulating evidence pointing to the hypothalamus as the origin of the migraine.[12] The trigeminovascular pathway appears central to the headache component of the migraine. But while much has been learned about individual aspects of the disease, the relationships between symptoms, phases and pain remain to be fully explained. In 1979, *The Lancet* published a novel hypothesis proposing the trigeminal nerve and its release of neuropeptides to play a role in migraine.[13] This paper would spawn research over the next decades further clarifying the role of the trigeminal pathway in migraine as well as the development of novel therapies, namely antibodies, targeting vasodilating neuropeptides (CGRP, sub P, PACAP) released by this pathway.

To describe the immunohistochemical and neurochemical interplay associated with the trigeminal pathway, the term "trigeminovascular" was introduced in 1983.[14] The trigeminovascular pathway encompassed the vasculature and nerves that were directly related to the head pain experienced during a migraine headache, starting with the innervated blood vessels in the meninges that had trigeminal origin. Stimulation of meningeal blood vessels was shown to be associated with headache.[15] Later, evidence suggested a role for the released CGRP and sub P, and demonstrated that ergot alkaloids could inhibit this neuropeptide release. Antisera directed against these neuropeptides blocked peripheral neurogenic inflammation. Sumatriptan and dihydroergotamine were shown to attenuate CGRP levels during spontaneous migraine attacks. Work done by Weiller *et al.* in 1995 suggested migraine was associated with imbalance between brain stem nuclei and vascular control.[16] In the 2000s, IV infusion of either CGRP or PACAP,[17] another neuropeptide, was found to trigger migraine without aura in migraineurs. The 2010s would see CGRP monoclonal antibodies enter clinical trials and later be approved for the prevention of episodic migraine.

Select mechanisms underlying the phases of migraine and accompanying studies are outlined below:

Prodrome

The prodrome (premonitory) phase marks the beginning of a migraine. It is a period of nonpainful symptoms preceding the aura or headache phase by up to 72 hours and includes changes in mood, activity, irritability, fatigue, food cravings, repetitive yawning, stiff neck and phonophobia. These symptoms may persist through subsequent stages and may arise from multiple brain areas including the hypothalamus, substantia nigra, dorsal pons and various limbic cortical areas.

Migraines are thought to start from the hypothalamus. The hypothalamus is a brain structure that is responsible for a multitude of functions including circadian rhythm, control and maintenance of homeostasis and regulation of arousal.[18] Many of the symptoms (and triggers) are associated with homeostatic functions such as arousal, sleep and feeding. Furthermore, migraine occurrence seems to have circadian rhythm; women may experience migraine in synchrony with menstrual cycles. Again, disturbances in sleep are often triggers of migraines and sleep is related to homeostatic regulation by the hypothalamus. Migraine attacks also often occur in the morning.

One important study regarding the premonitory phase was performed using positron emission tomography (PET) and observed increased blood flow in the hypothalamus during very early stages of spontaneous migraine attacks, and during the premonitory phase of nitroglycerin-induced migraines, further evidencing the causal role of the hypothalamus.[19,20]

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[12] Andreou, A.P., Edvinsson, L. Mechanisms of migraine as a chronic evolutive condition. *J Headache Pain* **20,** 117 (2019). https://doi.org/10.1186/s10194-019-1066-0

[13] MA Moskowitz, JF Reinhard, J Romero, E Melamed, DJ Pettibone
Neurotransmitters and the fifth cranial nerve: is there a relation to the headache phase of migraine?
Lancet, 2 (1979), pp. 883-885

[14] Messoud Ashina, Jakob Møller Hansen, Thien Phu Do, Agustin Melo-Carrillo, Rami Burstein, Michael A Moskowitz, Migraine and the trigeminovascular system—40 years and counting, The Lancet Neurology, Volume 18, Issue 8, 2019, Pages 795-804, ISSN 1474-4422,https://doi.org/10.1016/S1474-4422(19)30185-1.

[15] J Olesen, R Burstein, M Ashina, P Tfelt-Hansen, Origin of pain in migraine: evidence for peripheral sensitisation
Lancet Neurol, 8 (2009), pp. 679-690

[16] C Weiller, A May, V Limmroth, et al. Brain stem activation in spontaneous human migraine attacks, Nat Med, 1 (1995), pp. 658-660

[17] Pituitary adenylate-cyclase-activating polypeptide

[18] Andreou, A.P., Edvinsson, L. Mechanisms of migraine as a chronic evolutive condition. *J Headache Pain* **20,** 117 (2019). https://doi.org/10.1186/s10194-019-1066-0

[19] Denuelle M, Fabre N, Payoux P, Chollet F, Geraud G (2007) Hypothalamic activation in spontaneous migraine attacks. Headache. 47(10):1418–1426

[20] Maniyar FH, Sprenger T, Monteith T, Schankin C, Goadsby PJ (2014) Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. Brain. 137(Pt 1):232–241

Research using functional magnetic resonance imaging (fMRI) was performed to assess the deactivation pattern elicited by trigeminal nociceptive stimulation.[21] Trigeminal nociceptive sensitivity was cyclical over the course of the migraine. Compared to controls, interictal activation levels were lower and preictal levels were comparable, showing an increase in activation level leading up to the attack. The next headache attack was predictable based on the signal intensity in the spinal nuclei.

Aura

Aura occurs in up to one third of migraineurs. A transient wave of neuronal depolarization of the cortex, known as cortical spreading depression (CSD), is believed to be the mechanism underlying the aura phase.[22] CSD is thought to originate from the occipital cortex located at the rear of the brain. The aura phase is characterized by visual symptoms, namely scotoma (partial loss of vision), and these visual symptoms have provided insight into the mechanism of the aura phase. The size and location of the vision loss drifting throughout the visual field correlates with CSD. *In vivo* experiments found electroencephalogram (EEG) depressions spreading throughout the brain that were later coined CSD and attributed to the migraine aura. Human experiments using fMRI have provided additional support for the CSD-aura hypothesis. Causality between CSD/aura and headache phase is still debated. Because aura only occurs in a minority of patients, necessity of CSD/aura for headache occurrence is doubtful. Furthermore, aura can occur without headache.

Headache

Generally, the headache phase involves activation of the ascending trigeminothalamic pathway. In the past, it was thought that the vasodilation was the cause of pain, although it was later observed that spontaneous attacks were accompanied by intracranial but not extracranial arterial dilation and that the magnitude of the dilation was minimal.[23] Instead, neural hypersensitivity, especially in pain systems, results in trigeminovascular pathway activation and is thought to be responsible for the pain of migraine.[24] The migraine pain is felt in the dura mater and intracranial vasculature with sensory information flowing through the trigeminal nerve. Activation of the trigeminal nerve is known to cause neuropeptide release, further explaining pain symptoms. These neuropeptides include calcitonin gene-related peptide (CGRP) and substance P (sub P). The release of these neuropeptides leads to an inflammatory cascade with effects including arteriolar vasodilation, plasma protein extravasation and degranulation of mast cells.[25] While the pain is felt here, it does not mean it is the origin of the migraine or the attack. The trigeminal nerve synapses with the trigeminocervical complex (TCC), which then relays information to the thalamus and onto higher cortical areas. Descending networks from brainstem, midbrain and cortical nuclei modulate excitability of trigemino-thalamic pathway.

The thalamus integrates many sensory inputs and is currently being considered for its potential to influence neuronal excitability. The thalamic area is one of the main areas where triptans act. Neuroimaging and electrophysiological studies have revealed abnormal connection between the thalamus and pain-relevant cortical areas during migraine attacks and thalamo-cortical dysrhythmia which correlate with symptoms.[26] Involvement of the thalamus could explain photo- and phonosensitivity.

Parts of the brainstem have been considered as the origin of the headache phase. The dorsal pons has been called the 'migraine generator.'[27] In addition, migraines have been induced in previous non-migraineurs who had been treated with deep brain stimulation of the periaqueductal gray or PAG which is also located in the brainstem. Further work has differentiated migraine from cluster headache in that brain stem activation is distinct when comparing the two types. Brainstem activation is also ipsilateral, matching the unilaterality of migraines.

Migraine headaches are distinguished from other headaches by the presence of additional symptoms such as nausea, photo- and phonophobia, and movement sensitivity that may have persisted from preceding phases. In one influential study, regional cerebral blood flow (rCBF) was measured using PET in migraineurs during spontaneous right-sided migraine attack.[28] Increased blood flow was observed during migraine in a multitude of

[21] Stankewitz A, Aderjan D, Eippert F, May A. Trigeminal nociceptive transmission in migraineurs predicts migraine attacks. J Neurosci 31: 1937–1943, 2011.
[22] Olesen J (1998) Regional cerebral blood flow and oxygen metabolism during migraine with and without aura. Cephalalgia. 18(1):2–4
[23] FM Amin, MS Asghar, A Hougaard, et al., Magnetic resonance angiography of intracranial and extracranial arteries in patients with spontaneous migraine without aura: a cross-sectional study, Lancet Neurol, 12 (2013), pp. 454-461
[24] Burstein R, Noseda R, Borsook D. Migraine: multiple processes, complex pathophysiology. *J Neurosci*. 2015;35(17):6619-6629. doi:10.1523/JNEUROSCI.0373-15.2015
[25] Ramachandran R. Neurogenic inflammation and its role in migraine. *Semin Immunopathol*. 2018;40(3):301-314.
[26] Iadecola C (2002) From CSD to headache: a long and winding road. Nat Med 8(2):110–112
[27] Stankewitz A, Aderjan D, Eippert F, May A. Trigeminal nociceptive transmission in migraineurs predicts migraine attacks. *J Neurosci*. 2011;31(6):1937-1943. doi:10.1523/JNEUROSCI.4496-10.2011
[28] Weiller C, May A, Limmroth V, Juptner M, Kaube H, Schayck RV, Coenen HH, Diener HC. Brain stem activation in spontaneous human migraine attacks. Nature Med 1: 658 – 660, 1995.

brain regions: the cingulate and auditory association cortex, and parieto-occipital junction near visual association cortex, midbrain, dorsal rostral pons, near the PAG and raphe nuclei. The regions with increased blood flow appear to be correlates for the symptoms observed. For example, head pain and cingulate cortex, photophobia and visual association cortex and phonophobia and auditory association cortex correlate.

Postdrome

The postdrome phase follows the headache phase and lasts for hours or days and can be analogous to a migraine hangover. About 80% of migraineurs report at least one non-headache symptom during the postdrome stage.[29] The postdrome phase is the least studied of all the phases. Recently, functional imaging showed widespread reduction in brain-blood flow with the exception of the occipital cortex, which showed some persistent blood flow increase.

Genetics and Epigenetics

Reinforcing the circadian relevance of migraine, mutation in the clock-gene CK1δ, the cause of advanced sleep phase syndrome, was found to be strongly linked to migraine. Regarding epigenetics, the first genome-wide DNA-methylation study was published recently.[30] Two CpG sites were identified, SH2D5 and NPTX2, which are brain-expressed genes. The H2D5 gene encodes a protein thought to regulate synaptic plasticity indirectly, while the NPTX2 gene encodes neuronal pentraxin II protein, an excitatory synapse inhibitor. The field of epigenetics is relatively new, and extensive work has yet to be done in migraine.

Current Standard of Care

Migraine diagnosis is based on family history, medical history, physical and neurological examination, though imaging techniques may be used to rule out other potential causes of pain. Patients may begin by using over-the-counter pain relievers such as aspirin or ibuprofen as a first line of defense, although excessive use of these can cause medication-overuse headaches and gastro-intestinal complications. Lifestyle and home remedies such as relaxation techniques, maintenance of sleeping and consistent eating routines are important mechanisms to treat migraine as is ensuring adequate fluid intake and regular exercise.

Improved understanding of the mechanisms underlying migraine, namely neuropeptides, has spawned several classes of therapies. These include triptans, serotonin 5-$HT_{1B/1D}$ receptor agonists, calcitonin gene-related peptide (CGRP) receptor antagonists, 5-HT_{1F} receptor agonists, CGRP mechanism monoclonal antibodies and mGlu5 modulators.[31]

Migraine headaches are primarily treated with triptan medications, which belong to the tryptamine family of drugs. These account for approximately 80% of annual prescriptions for the acute treatment of migraines. Triptans can be administered via oral, nasal and subcutaneous routes. Their mechanism of action is to bind to serotonin receptor subgroups, inhibiting neuropeptide release, causing vasoconstriction in the brain's outer cover or meninges, countering the vasodilation and nociceptor activation. Triptans may also induce vasoconstriction in the heart which puts patients at risk. Though the triptan drug class is the current standard of care for acute treatment of migraine, according to the U.S. Pharmacist, more than 60% of patients report dissatisfaction with or contraindication to the current standard of care. The sub-25% penetration rate of available generic triptan medications may be evidence of this dissatisfaction.

Less commonly prescribed acute migraine treatments include ergotamines and analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen and anti-emetics. Like triptans, dihydroergotamine (DHE) acts as a vasoconstrictor, bearing the same cardiovascular risk profile. Opioids have also been prescribed for acute migraines, though their use has been associated with increased burden on the health care system. Opiate use, misuse and abuse are now classified as an epidemic. Certain classes of anti-epileptic medicine and beta-blocker medications have been approved by the FDA for prophylactic treatment of migraine. Hypertension medications such as propranolol, metoprolol tartrate and verapamil as well as the antidepressant amitriptyline are sometimes prescribed. Botox has been specifically approved for the prophylactic treatment of chronic, but not episodic migraine.

More recently, the FDA has approved lasmiditan, a serotonin receptor agonist, ubrogepant and rimagepant, which are calcitonin gene-related peptide (CGRP) receptor antagonists.

[29] Giffin NJ, Lipton RB, Silberstein SD, Olesen J, Goadsby PJ (2016) The migraine postdrome: an electronic diary study. Neurology. 87(3):309–313

[30] Gerring ZF, McRae AF, Montgomery GW, Nyholt DR (2018) Genome-wide DNA methylation profiling in whole blood reveals epigenetic signatures associated with migraine. BMC Genomics 19(1):69

[31] Pathophysiology of Migraine: A Disorder of Sensory Processing Peter J. Goadsby, Philip R. Holland, Margarida Martins-Oliveira, Jan Hoffmann, Christoph Schankin, and Simon Akerman Physiological Reviews 2017 97:2, 553-622

Cluster Headaches

Cluster headaches (CH) are a primary headache disorder belonging to the trigeminal autonomic cephalalgias (TACs) group, characterized by short but extremely painful headache attacks. Symptoms include excruciating pain that is typically behind or around one eye, unilateral pain and restlessness. Unilateral symptoms can include excessive tearing, eye redness, stuffy/runny nose, sweating on the forehead or face, pale skin or flushing, swelling around the eye and drooping eyelid, all on the affected side. In contrast to migraines, CH primarily affect males age 20 to 50 and affect substantially more males than females. The frequency of attacks within clusters can occur every day up to eight times in a single day and each attack can last from 15 minutes to three hours. About 85% - 90% of CH patients experience episodic CH. The clustered periods, also called bouts, can last between two and 12 weeks and typically happen twice a year. Episodic CH patients endure headaches averaging four months out of the year while chronic CH patients have no remission or remission periods lasting less than three months per year.

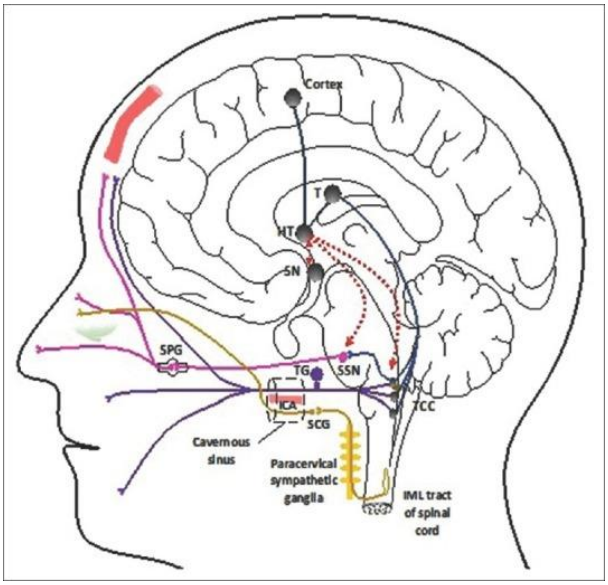
Incidence & Prevalence

The estimated prevalence of CH in the US is estimated to be about 0.1% of the total population[32] which equates to approximately 330,000 individuals. Accurate counts of those suffering from CH is limited by the diversity in symptomology, yielding estimates that place the 1-year prevalence between 3 and 150 per 100,000.[33] CH primarily affect males, age 20 to 50, at a rate 2.5x greater than females. There appears to be a genetic and hereditary component to CH, although no gene has been clearly implicated. An estimated 10% of CH are thought to be genetically driven. Race appears to play a role as well, with the gender ratios flipped, with African American women developing CH more than African American men. In clinic-based studies, Asian studies of chronic CH suggested lower prevalence in eastern Asians compared to Caucasians.

Pathophysiology

Like migraines, CH are a complex pathology, involving multiple parts of the brain and with temporal, neural, genetic and biochemical aspects that are not fully understood. It is believed that vasodilation puts pressure on the trigeminal nerve causing pain. PET scans have shown activity in the hypothalamus during CH attacks.[34] CH are characterized by the severe unilateral pain mainly in the trigeminal nerve and there are associated prominent unilateral cranial autonomic symptoms and a sense of restlessness during the attacks. The mechanism involves activation of the trigeminovascular complex and the trigeminal-autonomic reflex. The trigeminal autonomic reflex is a pathway comprising a brainstem connection between the trigeminal nerve and facial cranial nerve parasympathetic outflow and is activated with stimulation of trigeminovascular pathways. The cyclical nature of CH are also thought to involve the hypothalamus and suprachiasmatic nucleus.

Exhibit II – Trigeminovascular Pathway[35]



[32] Wei DY, Yuan Ong JJ, Goadsby PJ. Cluster headache: Epidemiology, pathophysiology, clinical features, and diagnosis. Ann Indian Acad Neurol 2018;21, Suppl S1:3-8

[33] The incidence and prevalence of cluster headache: a meta-analysis of population-based studies. *Fischera M, Marziniak M, Gralow I, Evers S, Cephalalgia. 2008 Jun; 28(6):614-8.*

[34] https://rarediseases.org/rare-diseases/cluster-headache/

[35] Wei DY, Yuan Ong JJ, Goadsby PJ. Cluster headache: Epidemiology, pathophysiology, clinical features, and diagnosis. Ann Indian Acad Neurol 2018;21, Suppl S1:3-8

Pain signals coming from the trigeminovascular system pass through the ophthalmic portion of the trigeminal nerve. Along with signals from the cranial vessels and dura mater, the inputs synapse in the trigeminocervical complex before projecting to the thalamus and cortex. This results in the sensation of pain. The trigeminovascular system can also be activated via stimulation of dural structure, which causes activation of the superior salivatory nucleus (SSN) in the pons, which is related to the parasympathetic autonomic vasodilator pathway. Activation of the parasympathetic reflex via the aforementioned SSN relays through the sphenopalatine ganglion (SPG). The combination of activating both the trigeminal and autonomic nerves is characteristic of TACs. Finally, the hypothalamus is central, interfacing with the SSN, the TCC and suprachiasmatic nucleus and is suspected to be the primary driver of CH. The suprachiasmatic nucleus, which receives input from the hypothalamus, regulates circadian rhythm through the secretion of melatonin by the pineal gland. While CH is unlike migraines in that it does not have the typical triggers such as stress, hormonal changes and foods, there is a correlation between cluster headache bouts and daylight savings time changes. Population-wide changes to circadian rhythm, appear to exacerbate CH. Further studies of cortisol, testosterone, and orexin have further supported the role of the hypothalamus in CH.

Current Standard of Care

There is currently no cure for CH. Standard of care is limited to acute and prophylactic treatments that can help to address the occurrence and recurrence of the headaches.

Acute

Of the treatments available to abort CH, oxygen is most noteworthy. Inhalation of pure oxygen via mask is safe, inexpensive and effective, with effects felt within 15 minutes of administration. Oxygen administration was able to achieve pain freedom in 78% of participants at 15 minutes.[36] The downside to oxygen therapy is the need to have an oxygen tank available at all times which can prove cumbersome and inconvenient.

Sumatriptan injection (Imitrex) and nVNS are the only FDA-approved commercially available treatments for CH. Sumatriptan belongs to the triptan family and has vasoconstrictive effects which can pose cardiovascular risk. Due to the frequent nature of acute attacks, injections are needed as attacks occur, though they are limited to fewer than 10 injections per month due to cost and toxicity, leaving a majority of attacks untreated. Furthermore, the ability to self-administer the treatment is limited by the condition and a caregiver is usually needed to provide it. While not a prescribed therapy, high-flow rate inhaled oxygen is also used to treat acute CH.

Less frequently used acute therapies include octreotide, an injectable synthetic somatostatin, local anesthetics such as lidocaine which are administered intranasally and dihydroergotamine injection, which can have vasoconstrictive effects, similar to those of triptans. Both triptans and ergot derivatives behave as 5-Hydroxytryptamine-1 ($5\text{-}HT_1$) receptor agonists.

Patients have resorted to off-label use of lithium, valproic acid and high-dose verapamil, which have unproven efficacy and risk toxicity and adverse cardiac events. In a 2016 survey, 87% of CH patients reported dissatisfaction with the treatments available at the time.

Prophylactic

Due to the clustering in CH, prophylactic measures can be administered at the onset of the first acute event in a series of events in a cluster.

Prophylactic treatments of CH include nVNS, calcium channel blockers, with verapamil being first line of defense. Corticosteroids are also used such as prednisone, which are fast-acting. Finally, lithium carbonate and nerve block are also used. Nerve block is administered by injection of an anesthetic and corticosteroid into the area surrounding the occipital nerve.[37]

Most recently, in 2019, galcanezumab, a CGRP targeted monoclonal antibody was approved for prophylactic treatment of episodic CH.

[36] Cohen AS, Burns B, Goadsby PJ. High-Flow Oxygen for Treatment of Cluster Headache: A Randomized Trial. *JAMA.* 2009;302(22):2451–2457. doi:10.1001/jama.2009.1855

[37] https://www.mayoclinic.org/diseases-conditions/cluster-headache/diagnosis-treatment/drc-20352084

gammaCore Sapphire™

Device

Exhibit III – gammaCore Sapphire™ Device[38]



gammaCore Sapphire™ is a personal use, hand-held medical device, with a display, rechargeable battery, and two electrodes. The device requires a prescription and doses are internally counted with refills dispensed via near-field card reading technology. The device is compact, about the size of a deck of cards. It is able to deliver electrical pulses via its electrodes and these pulses can selectively activate the vagus nerve. Activation of the vagus nerve has been shown clinically to be effective against migraines in both acute and prophylactic settings.

gammaCore is indicated for:

- The preventive treatment of migraine headache in adult patients.
- The acute treatment of pain associated with migraine headache in adult patients.
- Adjunctive use for the preventive treatment of cluster headache in adult patients.
- The acute treatment of pain associated with episodic cluster headache in adult patients.
- Emergency Use Authorization for acute treatment of asthma exacerbations in COVID-19

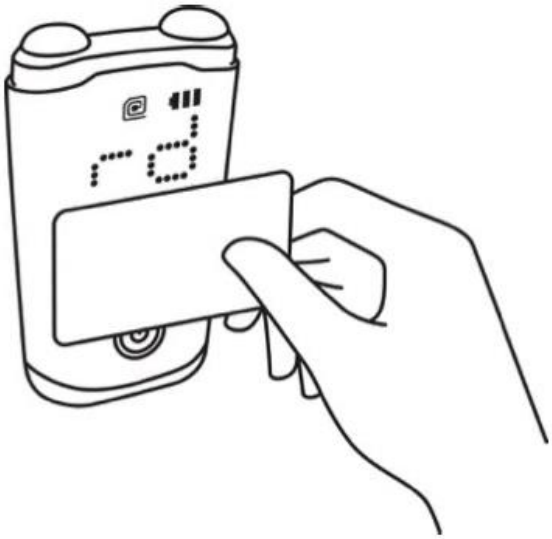
gammaCore is used by first powering on the device. The device can display the remaining available treatments that day, number of days remaining and can be adjusted for dose intensity with a numerical readout.

Exhibit IV – gammaCore Sapphire™ display example symbology[39]

Icon Description	Icon	Example Display	Description
Treatments Remaining			6 treatments remaining within a 24-hour period
Intensity Level			Intensity level is at 23
Days Remaining			30 days remaining until device will not deliver stimulations
Intensity Level at Last Use			Last delivered intensity level was 23
Battery			Battery is charging
Reload			Refill card is being read

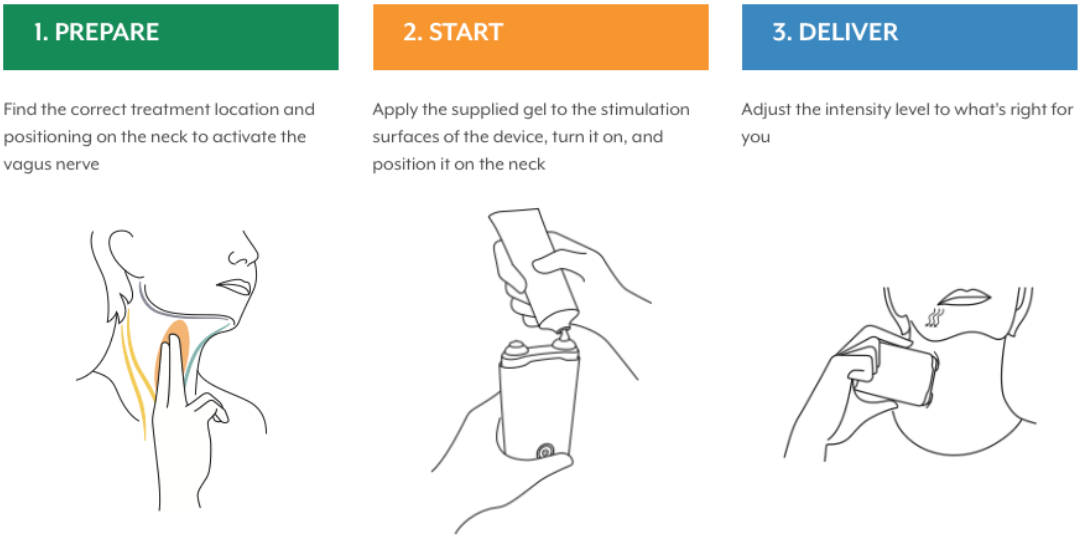
[38] https://www.electrocore.com/wp-content/themes/wp-starter/includes/images/Relief_device.jpg
[39] https://www.gammacore.com/wp-content/themes/gammacore-p2/pdf/gammacore-IFU.pdf

Exhibit V – gammaCore Sapphire™ Reload Card Placement[40]



Tutorials located on the company webpage provide examples of gammaCore use. Doses are refilled by placing the gammaCore card across the bottom of the device, beeping twice to confirm the reload. Treatment location is found by first locating the pulse along the neck. The device is manually applied, in a vertical fashion along the neck, using gel to enhance electrode contact. Once the device is held against the neck, treatment intensity can be fine tuned using the buttons on the device. At the beginning of the treatment, the intensity can be increased until muscle contractions are felt, the most common being a pull or tug at the corner of the mouth that is nearest the device. The device is then held until the device beeps twice, after about two minutes, marking the end of the treatment. The gel is then cleaned from the electrodes and neck.

Exhibit VI – Steps to use gammaCore Sapphire™[41]

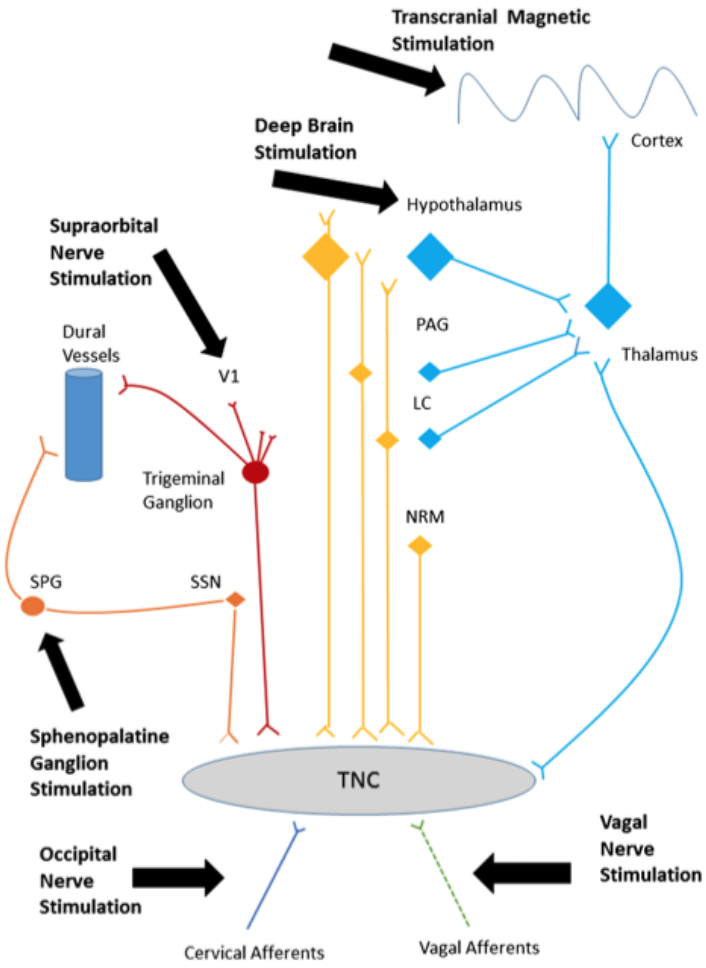


Vagus Nerve & Stimulation

The vagus nerve is responsible for regulating heart rate, gastrointestinal function, perspiration, muscle movements around the mouth and speech. The vagus nerve is also implicated in inflammation. Clinical focus has been mainly on the trigeminal nerve and the trigeminovascular pathway. There are many forms of neurostimulation aimed at activating a variety of nerves implicit in migraine and other disorders. Some techniques are invasive employing surgically implanted devices while others are externally applied.

[40] https://www.gammacore.com/wp-content/themes/gammacore-p2/pdf/gammacore-IFU.pdf
[41] https://www.gammacore.com/about/using-gammacore/

Exhibit VII – Stimulation Techniques vs. Neural Pathways[42]



The vagus nerve[43] is the longest cranial nerve, extending from the base of the brain to the colon and is responsible for parasympathetic control over the heart, lungs and digestive tract and projects to higher centers that are responsible for pain regulation such as the nucleus tractus solitarius and spinal trigeminal nucleus.[44] Neuroimaging studies have shown that chronic vagus nerve stimulation (VNS) inhibits activation of thalamus, limbic system, dorsal pons, locus coeruleus and nucleus tractus solitarius, all of which are implicated in headache.[45] Transcutaneous as well as direct VNS have been shown to improve symptoms of migraine and suppress spreading depression in the occipital cortex in rats.[46] Once VNS was applied, the threshold to start a spreading depression was raised more than two-fold. The frequency and propagation speed were reduced by 40% and 15%, respectively, with effects occurring within 30 minutes after stimulation and persisting for more than three hours. Furthermore, efficacy did not differ between transcutaneous and direct or ipsilateral and contralateral administration. Finally, the vagus nerve has been shown to play an important role in regulating central inflammation via an efferent, anti-inflammatory, acetylcholine-norepinephrine mediated pathway.[47]

[42] Miller S, Sinclair AJ, Davies B, et al. Pract Neurol 2016;16:362–375.
[43] Also called the pneumogastric nerve or the tenth cranial nerve (cranial nerve X).
[44] Miller S, Sinclair AJ, Davies B, et al. Pract Neurol 2016;16:362–375.
[45] Kraus T, Kiess O, Hösl K, et al. CNS BOLD fMRI effects of sham-controlled transcutaneous electrical nerve stimulation in the left outer auditory canal—a pilot study. Brain Stimul 2013;6:798–804.
[46] Chen SP, Ay I, de Morais AL, et al. Vagus nerve stimulation inhibits cortical spreading depression. *Pain*. 2016;157(4):797-805. doi:10.1097/j.pain.0000000000000437
[47] Simon B, Blake J. Mechanism of action of non-invasive cervical vagus nerve stimulation for the treatment of primary headaches. *Am J Manag Care*. 2017;23(17 Suppl):S312-S316.

Exhibit VIII – Treatment regimen for acute migraine headache[48]



Exhibit IX – Prophylactic treatment regimen for migraine headache[49]



Clinical Efficacy - Migraine

Acute

gammaCore has demonstrated clinical efficacy in the **PR**ospectiv**E S**tudy of nVNS for the Acute **T**reatment **o**f Migraine (PRESTO).[50] PRESTO was a prospective multi-center, randomized, double-blind, sham-controlled study of gammaCore for the acute treatment of migraine. Inclusion criteria for the trial was adults aged 18 to 75 years with 3-8 migraine attacks per month and fewer than 15 headache days per month. Treatment was bilateral, two minutes per side, within 20 minutes of pain onset with follow-up treatment 20 minutes after the start of treatment 1 if pain persists. If neither has improved the pain, there is an option to retreat two hours after the first treatment. Subjects were asked to abstain from rescue medication for at least two hours. The trial periods were divided into three: an observational period (4 weeks), a double-blind period (4 weeks or 5 attacks treated), and open-label period (4 weeks or 5 attacks treated). The primary endpoint of the study was achievement of a pain-free state without the use of rescue medication within 120 minutes post-treatment for the first migraine attack in the study period. Secondary endpoints included mild or no pain at 30, 60 and 120 minutes, consistency of response at 120 minutes, and ≥50% responder rates for both pain free and mild pain in those with ≥2 treated migraines. A total of 243 patients participated and were randomized into both gamamCore and sham groups. Regarding the primary endpoint, 12.7%, 21.0% and 30.4% of subjects reported being pain free versus 4.2%, 10.0% and 19.7% in the sham arm for 30, 60 and 120 minutes, respectively.

Primary endpoint was significant at the 6.7% level, while 30 and 60 minute data were significant at 1.2% and 2.3%, respectively. Including repeated-measures analysis across the three timepoints was significant at 1.2%. Overall, the trial was directionally correct and data was sufficiently favorable to support gammaCore's efficacy in acute treatment of migraine. When criteria were extended from pain-free to pain-relief, response at 120 minutes was significant at the 3% level.

[48] https://www.gammacore.com/for-migraine/migraine-dosing/
[49] https://www.gammacore.com/for-migraine/migraine-dosing/
[50] Tassorelli C, Grazzi L, de Tommaso M, et al. Noninvasive vagus nerve stimulation as acute therapy for migraine: The randomized PRESTO study. *Neurology*. 2018;91(4):e364-e373. doi:10.1212/WNL.

Secondary endpoints evaluating successful treatment in ≥50% of migraines were 47.6% in treated arm and 32.3% of subjects in sham arm representing a 15% therapeutic gain over sham. Reduction in pain intensity of the first treated migraine was directionally correct and statistically significant at 60 and 120 minutes. The results showed a sixfold greater reduction at two hours than sham. No serious adverse events (SAEs) were reported. Adverse events (AEs) were reported in five patients in the active arm compared to 16 patients in the control arm.

Exhibit X – PRESTO Adverse Events[51]

	gammaCore	Sham
AEs Occurring in ≥2% of Patients in Any Treatment Group	n = 122	n = 126
General disorders and administration-site conditions, No. (%)		
Application-site discomfort	3 (2.5)	1 (0.8)
Application-site erythema	0	3 (2.4)
Application-site pain	0	3 (2.4)
Nervous system disorders, No. (%)		
Dizziness	0	2 (1.6)

Prophylactic

As a prophylactic treatment for migraine, examined in the PREMIUM trial,[52] gammaCore showed a mean reduction in number of migraine days of 2.26 compared to sham which reduced the number of migraine by 1.53, with 85% confidence. In post-hoc analysis of the subpopulation of patients with greater than 67% adherence, nVNS produced a reduction of 2.27 days vs the sham of 1.53 days, significant at the 4.3% level. Patients with aura also experienced greater therapeutic gains than those without aura. Results also showed that 33.6% of patients were able to successfully treat 50% or more of their migraines compared to sham, significant at the 7.4% level. As shown in the EVENT study,[53] continued use may also enhance efficacy, as participants who adhered to treatment and completed eight months saw a statistically significant decrease in number of headache days as compared to those who only completed two, four and six months or treatment. Eight-month completers saw an average reduction of 7.9 headache days.

Exhibit XI – PREMIUM Adverse Events and Adverse Device Effect[54]

Most common AEs and ADEs[a]	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.
ADE: adverse device effect; AE: adverse event; nVNS: non-invasive vagus nerve stimulation; SAE: serious adverse event.

gammaCore was well tolerated in the PREMIUM trial, with all AE and ADE comparable to sham.

[51] https://www.gammacore.com/prescribing-gammacore/clinical-safety/
[52] Diener HC, Goadsby PJ, Ashina M, et al. Non-invasive vagus nerve stimulation (nVNS) for the preventive treatment of episodic migraine: The multicentre, double-blind, randomised, sham-controlled PREMIUM trial. *Cephalalgia*. 2019;39(12):1475-1487. doi:10.1177/0333102419876920
[53] Silberstein SD, Calhoun AH, Lipton RB, et al. Chronic migraine headache prevention with noninvasive vagus nerve stimulation: The EVENT study. *Neurology*. 2016;87(5):529-538. doi:10.1212/WNL.0000000000002918
[54] Diener HC, Goadsby PJ, Ashina M, et al. Non-invasive vagus nerve stimulation (nVNS) for the preventive treatment of episodic migraine: The multicentre, double-blind, randomised, sham-controlled PREMIUM trial. *Cephalalgia*. 2019;39(12):1475-1487. doi:10.1177/0333102419876920

electroCore continued to evaluate prophylactic efficacy of gammaCore in migraine with its Premium II study but it was eventually abandoned to focus on existing revenue growth. The FDA had also cleared gammaCore for prophylactic treatment of migraine in March 2020. Premium II was a randomized, double-blind, sham-controlled prospective trial for prevention of migraine. The primary endpoint for the trial was the reduction in average number of migraine days per month in the third month of the randomized period compared to baseline. Patients were required to comply and self administer no fewer than two-thirds of specified treatments per month. Approximately 60% of the 300 targeted patients were enrolled when in February 2020 patient enrollment was halted and was later terminated. Partial study results from the trial are expected to be shared by 1Q:21.

Vagus Nerve & Stimulation (Cluster Headache)

The vagus nerve is the major parasympathetic branch of the autonomic nervous system. It regulates breathing, heart rate and digestion. Through its afferent projections, the vagus nerve regulates brain physiology, chemistry, plasticity and behavior[55] and plays a role in regulating both central and peripheral inflammation. In clinical work done by Ackerman *et al.*, a murine model of cluster-like acute head pain was investigated.[56] Superior salivatory nucleus (SUS)-evoked trigeminocervical neuronal responses, intended to simulate trigeminal-autonomic pathway activation, were evaluated and VNS dosing was shown to suppress SUS response for 2.5 hours with a degree of inhibition similar to those of triptans, suggesting comparable site of action and neuropeptide inhibitory mechanism.

Clinical Efficacy – Cluster Headache

Prophylactic
gammaCore's efficacy in cluster headaches was evaluated in the **PREV**ention and **A**cute treatment of chronic cluster headache (PREVA) study. Preva was a prospective, open-label, randomised study that compared adjunctive prophylactic nVNS to standard of care alone. A total of 97 patients were randomized into both the treatment and control groups. First, a two-week baseline was established, followed by a four-week randomization phase and then a four-week extension phase. The primary endpoint of the study was the reduction in mean number of cluster headache attacks per week. Additionally, response rate, abortive medication use, safety and tolerability were assessed. Results from the randomised phase showed that the adjunctive prophylactic nNVS population had significantly greater reduction in number of attacks per week compared to the population that received only standard of care. Those in the treated population experienced a mean therapeutic gain of 3.9 fewer attacks per week and 40% of treated patients had a higher than 50% response rate vs 8.3% of patients in the control arm. The treatment arm also had a 57% decrease in frequency of acute medication use.[57]

Exhibit XII – PREVA Safety and Tolerability[58]

	SoC + gammaCore	Control
AEs reported in ≥5% of participants in any treatment group, No. (%)	n = 48	n = 49
Nervous system disorders		
Cluster headache attack	1 (2)*	5 (10)*
Dizziness	3 (6)*	3 (6)
Headache	4 (8)	1 (2)
Nasopharyngitis	1 (2)	4 (8)
Oropharyngeal pain	3 (6)*	1 (2)
Neck pain	3 (6)	0

92 of the 97 patients participating in the randomised phase continued onto the four-week extension phase. In the extension phase, all patients received nVNS and standard of care. Compared to standard of care, nVNS and standard of care led to a significantly lower mean weekly attack frequency by week two of the randomised phase, and remained significantly ($p < 0.02$) lower through week three of the extension phase. Compared to baseline, attack frequencies of the nVNS + standard of care were significantly lower ($p < 0.05$) at all time points. Response rates greater than 25%, 50% and 75% were all significant at the 1% level and 8% of patients even had a complete (100%) response rate compared to 0% of patients with standard of care alone.[59]

[55] Howland RH. Vagus nerve stimulation. *Curr Behav Neurosci Rep.* 2014;1(2):64-73. doi: 10.1007/s40473-014-0010-5.
[56] Akerman S, Holland PR, Summ O, Lasalandra MP, Goadsby PJ. A translational in vivo model of trigeminal autonomic cephalalgias: therapeutic characterization. *Brain*. 2012;135(Pt 12):3664-3675. doi: 10.1093/brain/aws249.
[57] Gaul C, Diener HC, Silver N, et al. Non-invasive vagus nerve stimulation for PREVention and Acute treatment of chronic cluster headache (PREVA): A randomised controlled study. *Cephalalgia*. 2016;36(6):534-546. doi:10.1177/0333102415607070
[58] https://www.gammacore.com/prescribing-gammacore/clinical-safety/
[59] Gaul C, *et al*. Effects of non-invasive vagus nerve stimulation on attack frequency over time and expanded response rates in patients with chronic cluster headache: a post hoc analysis of the randomised, controlled PREVA study. *J Headache Pain*. 2017;18(1):22.

ACT1 and ACT2 studies evaluated gammaCore and nVNS in acute treatment of cluster headaches. The ACT1 trial enrolled 150 subjects that were randomized into treatment and sham arms for a shorter than one-month duration double-blind phase. Those who completed the double-blind phase could enter a three-month nVNS open-label phase. Primary endpoint was response rate as defined by the proportion of subjects who achieved pain relief at 15 minutes after treatment started for the first CH attack, without the use of rescue medication through 60 minutes. The secondary endpoint evaluated the sustained response rate (15-60 minutes). The data were also evaluated in terms of episodic and chronic cluster headache cohorts. Results for ACT1 showed 26.7% of nVNS-treated subjects responding versus 15.1% of sham-treated subjects, significant at the 10% level. Response rates were higher for the episodic CH cohort versus the chronic CH cohort, with response rates of 34.2% and 13.6%, respectively. Treated response rates in the chronic CH cohort were below that of the sham arm, not only suggesting that episodic CH patients respond better, but possibly providing additional insight into CH pathophysiology. Sustained response rates were significantly higher in the nVNS treated arm of the eCH cohort (p = 0.008) and total population (p = 0.04). Adverse events were reported by 35/150 participants and 18/128 in the open-label phase.[60]

Exhibit XIII – ACT1 ADEs[61]

	Double-Blind Phase		Open-Label Phase
	gammaCore (n=73)	Sham (n=77)	gammaCore (n=128)
Application-site reactions			
Burning/tingling/soreness/stinging	2.7%	9.1%	3.1%
Skin irritation/redness/erythema	0%	11.7%	1.6%
Musculoskeletal disorders			
Lip or facial drooping/pulling/twitching	11.0%	0%	7.0%
Nervous system disorders			
Dysgeusia/metallic taste	0%	9.1%	1.6%

gammaCore was well tolerated in ACT1. The lip twitching observed in the above exhibit indicates correct placement of the gammaCore device.

ACT2 studied nVNS in acute treatment of cluster headaches in both episodic and chronic cohorts, randomizing 102 patients. Subjects first completed a 1-week run-in period and were afterwards randomized into treatment and sham therapy arms for a 2-week double-blind period. Primary endpoint was proportion of all treated attacks that achieved pain-free status within 15 minutes of the treatment starting without rescue treatment. The trial did not meet the primary endpoint for the total cohort, but eCH subgroup was superior to sham at the 1% level and no significant differences seen in the cCH cohort, confirming previous findings regarding efficacy and safety for acute treatment of eCH.[62] No ADEs occurred in greater than 5% in any treatment group.[63]

Intellectual Property

electroCore's US patent portfolio consists of over 100 approved patents and over 80 patent applications. The company owns all of its products' intellectual property. The approved patents offer broad protection for its neuromodulation technology across a variety of indications. These patents cover art such as the use of high-frequency signal bursts, low-pass signal filtration to ensure safe and comfortable skin transmission, remote network-enabled device communication and smartphone-based devices. In addition to migraines and cluster headaches, there are many other indications described in electroCore's patent portfolio.

[60] 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
[61] https://www.gammacore.com/prescribing-gammacore/clinical-safety/
[62] Goadsby PJ, de Coo IF, Silver N, et al. Non-invasive vagus nerve stimulation for the acute treatment of episodic and chronic cluster headache: A randomized, double-blind, sham-controlled ACT2 study. *Cephalalgia*. 2018;38(5):959-969. doi:10.1177/0333102417744362
[63] https://www.gammacore.com/prescribing-gammacore/clinical-safety/

Exhibit XIV – Indications Covered in Approved Patents[64]

Neurological		Bronchial
Alzheimer's Disease	Multiple Sclerosis	Asthma
Dementia	Postoperative cognitive dysfunction	Chronic Obstructive Pulmonary Disease
Post-concussion Syndrome	Postoperative delirium	Anaphylaxis
Chronic traumatic encephalopathy	Epilepsy	Exercise-induced bronchospasm
Parkinson's Disease	Fibromyalgia	Post-operative bronchospasm
Urinary	**Cardiac**	**Hypotension**
Overactive bladder	Atrial fibrillation	Shock
Urge/stress incontinence	Myocardial infarction	Septic shock
Painful bladder syndrome	Ventricular fibrillation	Anaphylactic shock
Urge frequency	Tachycardia	Hypovolemia
Non-obstructive urinary retention	**Gastrointestinal**	
Interstitial cystitis	Functional dyspepsia	Gastroparesis
Sinus/Nasal	**Psychological**	**Other**
Sinus headache	Anxiety	Stroke
Rhinitis	Depression	Transient ischemic attack
Sinusitis	Panic attack	Autism
Rhinosinusitis	Insomnia	Premenstrual syndromes
		Addiction/Withdrawal

electroCore's patent portfolio covers a wide variety of indications outside of migraine and cluster headache. The indications extend to conditions that have a strong neurological component and include urinary, cardiac and bronchial disorders. While all are not currently pursued, the patents create space for electroCore to expand its indications in the future.

Technologies covered by current approved patents include:

- Devices for non-invasive, capacitive electrical stimulation for VNS
- Smart VNS devices that can communicate databases via networks to support self-treatment
- Smartphone electrode for transcutaneous e-stimulation of head nerves
- Nerve modulation antennae
- Evoked potentials (feedback mechanism for VNS)
- Feedback to determine proper stimulation based on biometrics
- Low-pass filter for high frequency attenuation
- Camera on smartphone used to position handheld stimulator
- Physiological and environmental signals used to forecast acute medical event
- Magnetic, electrical, mechanical, acoustic, optical, or thermal nerve stimulation
- Pulse signal, duration and frequency
- Deep brain stimulation via sinus cavity
- Balloon-electrode (method for stimulating tissue)

The patents not only cover indications, but aspects of art related to the technology, specifically of transcutaneous neuromodulation. Foremost, the patents describe key aspects such as pulse signal, duration and frequency and low-pass filtration. Other technology seems to run parallel to electroCore's VNS pursuits including techniques to assist self-treatment and electrode placement for neuromodulation as well as smartphone-based implementations.

When compared to its competitors, electroCore's patent portfolio is sizable at over 100 patents approved. Cefaly has five, eNeura has six and Theranica has three patents approved in the US.[65] electroCore's patent portfolio not only provides broad protection but offers the company avenues to expand into as opportunities arise.

[64] US Patent and Trademark Office (USPTO). This list is not exhaustive
[65] Identified through a patent search of Assignee Name on uspto.gov

Risks

All investments contain an element of risk which reflects business uncertainty and opportunity. Some investments exhibit higher predictability, with current cash flows and established sales. These enterprises will have a lower level of perceived risk while other companies that are developing an undefined, new technology have a much higher level of perceived risk.

The medical device space includes companies at both ends of the spectrum, from mega-cap giants that have multiple products currently generating revenues, to small operations with a handful of employees conducting pre-clinical studies. Many of the risks faced by the large and small medical device firms are similar; however, there are some hazards that are particular to smaller companies that have not yet established themselves or their products. The typical risks faced by companies operating in the medical device space include risks related to the pandemic, liquidity; financing & trading, clinical trials, regulatory, personnel, intellectual property, device marketing and geopolitics.

Pandemic Risk

The pandemic has disrupted economic and other activity in the United States and around the globe. electroCore management has indicated that this disruption has impacted the company's headquarters, manufacturing and warehousing and distribution facilities. In response to the pandemic and other challenges, management terminated the Premium II trial to focus on approved indications. State-imposed and pandemic-related restrictions have forced the closure of electroCore's New Jersey corporate office and required the company to modify its daily operations. To maintain social distancing, non-essential production-related team members are now working remotely where possible, restricting business travel, cancelling certain events and limiting visitor access to facilities. Working from home has increased certain risks such as operational risk and cybersecurity risk and may also affect corporate culture including employee engagement and productivity. Furthermore, the pandemic poses risk to the health of key personnel within the company. For patients, social distancing measures may limit health care provider visits, which reduce prescriptions. These disruptions may persist into the future; however, based on the latest quarterly update, the impact has been minimal.

Liquidity, Financing & Trading

Securing funding may be difficult especially during a decline in the economic cycle. During periods of improving confidence, capital may be easy to obtain; however, during a liquidity crisis or a period of heightened risk perception, even companies with bright prospects may be in trouble if they are dependent on the financial markets to fund their work. Pre-revenue firms still developing their technologies rely primarily on equity issuance to fund their operations. The timeline for drug and device development is considerable and long periods can pass before a product is sold. Funds can be sourced through debt or grants and tax credits; however, these sources may reduce the flexibility of the company and can create difficulties if debt is unable to be repaid.

If capital is required to sustain operations and it is not readily available, a company may be forced to suspend research and development, sell equity at a substantial discount to previous valuations and dilute earlier shareholders. A lack of funding may leave potentially promising therapies without a viable route forward or force a company to accept onerous terms.

Trading volumes are lower for smaller firms, creating liquidity risk for the investor where large transactions may have a material impact on share price creating difficulties entering and exiting positions. In periods of crisis or heightened risk perception, share price may be volatile. Companies with smaller capitalizations are typically riskier and changes in sentiment may adversely affect their trading prices and volumes. Smaller firms may also have less visibility, compete for investor dollars in a shallow market and be excluded from market indices. With price volatility and periodic equity issuance, smaller companies may have difficulty meeting exchange listing requirements. Inability to comply with listing standards may result in delisting, which could severely impact trading dynamics.

Since its inception, electroCore has reported net losses and expects to continue to do so for the foreseeable future. In the six months ended June 30, 2020, the company incurred net losses of $12.7 million. As of June 30, 2020, electroCore held $18.9 million in cash and equivalents on its balance sheet, which management estimates will be sufficient to sustain the company over the next 12 months. Capital requirements for the firm will depend on progress made in gaining market acceptance and commercialization of gammaCore Sapphire™ both in the US and the UK. It will also be related to progress on programs such as expansion into the direct-to-consumer cash-pay

business channel, obtaining and negotiating payor coverage, R&D related to adding additional indications, intellectual property and personnel. Changes in the progress and needs on these fronts will affect the magnitude and timing of electroCore's capital needs.

Market Risk

electroCore began marketing gammaCore to end consumers in 2017. The commercialization strategy involves medical benefit coverage provided by private insurers as well as government agencies. Typically, collection of payments from insurance companies, patients and other payors will take longer than collecting from pharmacy benefit managers. Furthermore, the process of collecting, adhering to complex billing requirements and determining benefits coverage, combined with the high cost of claims creates receivables risk.

gammaCore Sapphire™ faces competition in the form of pharmaceutical and medical device interventions with comparable efficacy. Some of these competitors are of considerable size, with greater capital, personnel, marketing and distribution resources. The conditions for which gammaCore Sapphire™ is indicated are complex and have varying responses across patients. The combination of the complex pathology and competitors of comparable efficacy may exacerbate the already challenging task of gaining market traction.

Clinical Trials

For smaller, early-stage companies, investing in product development is a lengthy process. The timeframe for conducting pre-clinical research to eventually commercializing a medical device can take from 3 to 7 years[66] or longer given market and company-specific conditions.

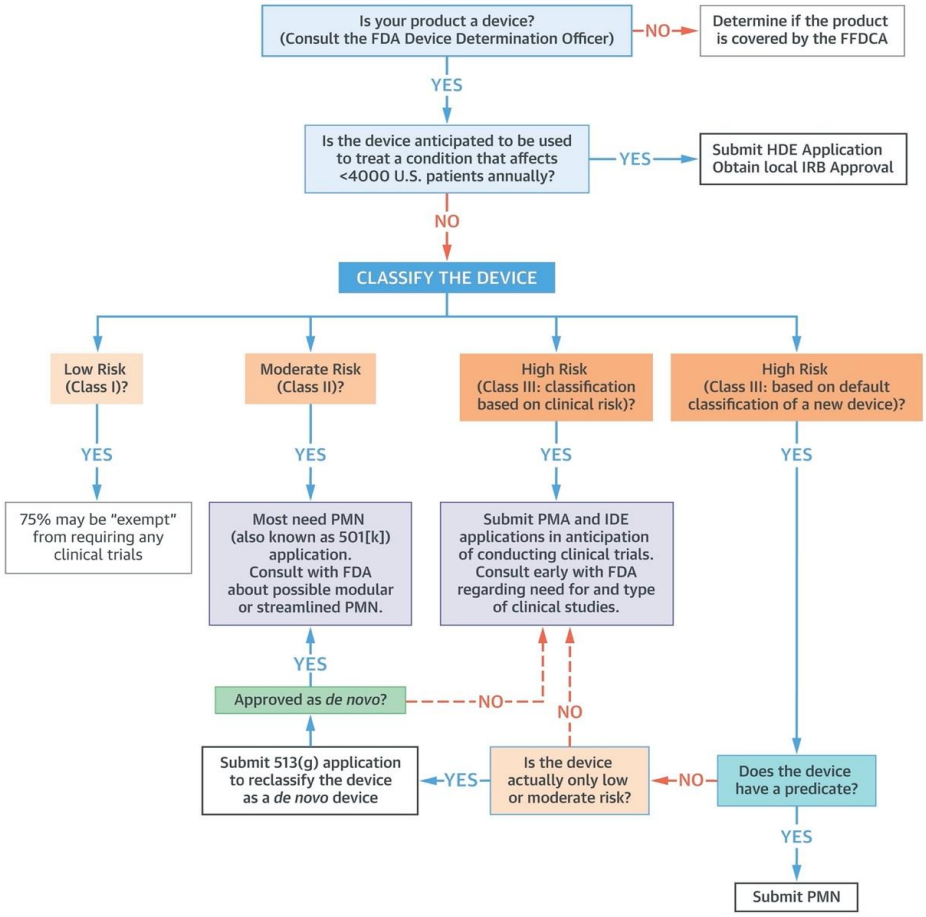
While electroCore has already received marketing authorization for multiple indications, additional success will be dependent on the data produced from expensive clinical trials. Due to the cost, magnitude and complexity typical of Phase III trials, partners are often sought to help finance and manage them. Partners may have competing demands which can adversely affect the work they are managing on behalf of the firm. CROs and subcontractors must abide by strict execution and trial parameters that if violated can jeopardize trial execution or data validity. Subcontractors supervise and execute research, ensuring protocols are followed to support data analysis. For larger target populations, clinical investigational centers need sufficient capacity and the medical device needs to be manufactured and be available for patient use. In restricted patient populations, enrolling trials can be difficult if the patient pool is small.

Regulatory

In the US, medical devices are subject to regulation by the Food and Drug Administration (FDA). Certain medical devices can leverage expedited routes to market such as those outlined in the Code of Federal Regulations Title 21, known as the 510(k) route. 510(k) relies on identification of a predicate, or a device that has already been cleared by the FDA. If a predicate is not identified and the risk is sufficient, the FDA will classify the device in a higher tier (Class III) and require clinical trials. Regulatory risk extends to the marketing phase as the safety of a device is always under scrutiny. Regulatory exposure extends beyond the United States and into other jurisdictions where medical device firms must navigate the regulatory approval and monitoring process, clinical trial requirements and marketing regulations in the jurisdiction where they seek to commercialize. electroCore is targeting both US and European markets and will need to navigate each accordingly. Substantial expense is undertaken to bring a medical device through clinical trials and address all of the regulatory agencies' concerns. Companies that have a long history of research success in device development, with opinion leaders and experts advocating for the product in the field will have an advantage. Previous success with the FDA or other regulatory agencies is another attractive attribute for a sponsor.

[66] Gail Van Norman, "Drugs, Devices, and the FDA: Part 2: An Overview of Approval Processes: FDA Approval of Medical Devices," *JACC: Basic to Translational Science* 01/04 June 2016, 277-287

Exhibit XV – FDA Medical Device Approval Pathway[67]



The rigor with which the FDA regulates a device depends on the risk it poses to the patient. The most intensive vetting is done through clinical trials, with expedited paths including the special or abbreviated 510(k), the Humanitarian and Custom Device Exemptions, Expanded Access Program (EAP) and Product Development Protocol (PDP) routes. There is also the Breakthrough Devices Program, designed to complement existing PMA, 510(k) and De Novo marketing routes while providing prioritized review of submissions. However, changes in sentiment or perceived safety of devices approved through these expedited pathways could alter the regulatory environment to demand a more thorough process and these pathways may be extended or additional requirements may be put in place. Depending on the regulatory environment, government mandates can influence marketing dynamics as well. US medical device legislation continues to evolve. In the past decade alone, there were three major revisions to medical device legislation: the Food and Drug Administration Safety and Innovation Act (FDASIA), the 21st Century Cures Act and the FDA Reauthorization Act (FDARA). While the trend in legislative revisions has been in the spirit of improving efficiency and patient access to innovation, future changes may increase the burden.

Personnel

Startups in general rely on the expertise and leadership of management to make decisions and investments on their behalf. Competition for talented and experienced management is intense and matching the optimal skill set with the right company is difficult. Change in management can be disruptive if leaders or scientists are lured away by other firms. Early stage companies are often virtual and have a small team. This can put them at a disadvantage when compared to larger firms with full-time specialized personnel. A smaller company with much of the upside tied to stock price may deter certain talent from joining the firm.

[67] Gail Van Norman, "Drugs, Devices, and the FDA: Part 2: An Overview of Approval Processes: FDA Approval of Medical Devices," *JACC: Basic to Translational Science* 01/04 June 2016, 277-287

electroCore currently relies on its management and sales teams to secure gammaCore's position in the market. The firm has experienced turnover in the past, and any future change in management may cause disruption to operations. CEO, Daniel Goldberger, and CFO, Brian Posner are key to the strategy and execution of the firm while Dr. Peter Staats, Founder and Chief Medical Officer is the cornerstone of the company's research and development efforts.

Intellectual Property

electroCore's patent portfolio offers broad protection. These patents cover art related to the use of high-frequency signal bursts for treatment of certain medical conditions and low-pass signal filtration to ensure safe and comfortable skin transmission and non-invasive treatment of headache conditions, valid until 2031 and 2029 respectively. Other patents related to remote network-enabled communication for neuromodulation therapy across a range of medical conditions will provide protection until 2033. While the patents cover key aspects of electroCore's technology, detection and pursuit of infringement is a costly ordeal that challenges the time and capital resources of smaller companies. Terms of protection rely on legal definition of technology that is ever evolving. Furthermore, patent acquisition, monitoring and defense in ROW will depend on the specific geography. While electroCore primarily has its sights set on the US and Europe, intellectual property protection outside of these regions may be weaker. There is no guarantee that any current or future patent applications will be granted.

Geopolitical

Recent trade tensions between the US and China threaten the world economy, and have been exacerbated by the recent pandemic. There has historically been a cross-pollination of capital and technology development between China and the United States which may slow as a result of the trade and political dispute between the countries. This conflict may reduce the availability of capital, partnerships and future development deals between companies in the two nations. The UK withdrew from the European Union on January 31, 2020. Previously, a drug approved under the centralized procedure in the European Union would be approved in all member states. However, with the withdrawal of the UK additional efforts and expense may be required to obtain marketing approval in this top five European market.

Peers and Competitors

electroCore's peers and competitors can be defined by both neurostimulation technology and the migraine and cluster headaches for which gammaCore is indicated. In terms of migraine, two transcutaneous neurostimulatory technologies, one peripheral nerve pain inhibition and one transcranial magnetic stimulation technology occupy the market along with gammaCore. We review and compare device-based and pharmaceutical competitors with respect to efficacy.

Exhibit XVI – gammaCore vs. Competitors, Efficacy, Migraine

Company & Device	Pain-free at 120 min.	≥50% Resp. Rate	Mean Δ in mig. days	Mean Δ in hdache days
electroCore gammaCore	30.4% (22.2%,39.9%)	31.9% (23.4%,41.8%)	-2.26 (-2.81,-1.72)	-2.73 (-3.37,-2.09)
Cefaly Dual	N/A[68]	38.1%[69]	-2.06[70]	N/A
eNeura sTMS mini	39.0%[71]	46% (37%,56%)	N/A	-2.75
Theranica Nerivio	37.4%[72]	N/A[73]	N/A	NA

Exhibit XVII – gammaCore vs. Competitors, Use, Migraine

Company	Device	Use – Acute	Use – Prophylactic	Method
electroCore	gammaCore Sapphire™	2x 2min, 0, 20min, and 120min	2X 2min, 3X daily	Gel applied to electrodes, held against neck
Cefaly	Dual	60min	20min daily	Reusable self-adhesive electrode on forehead
Eneura	sTMS mini	3X pulses, 3X per attack	4X pulses, 2X daily	Held behind head
Theranica	Nerivio	45min	N/A[74]	Reusable self-adhesive electrode on upper arm

Cefaly

Cefaly offers a transcutaneous neurostimulatory device called the Dual that targets the trigeminal nerve supraorbitally via the ophthalmic branch. The device is indicated for use in patients at least 18 years of age for both acute (with or without aura) and prophylactic treatment of migraine headaches. The Dual is not indicated for cluster headaches. The Dual is worn on the forehead and attaches via a reusable self-adhesive electrode. For acute migraines, the device is worn for 60 minutes. For prophylactic treatment, daily, 20-minute sessions are instructed. Before applying the Dual, the skin of the forehead is first cleaned, then the reusable self-adhesive electrode is removed from its plastic sleeve, the electrode is applied to the forehead with the bottom curve between the eyebrows, the device itself is then magnetically guided and adhered to the electrode on the forehead. The treatment program is selected, either acute or prophylactic; pressing the button once engages a 60-minute program at the onset of migraine, two presses begin the "prevent" session which lasts 20 minutes. Once the session has ended, the device is removed, and the electrode is peeled from the forehead and placed back in its sleeve for future use.

Clinical efficacy for Cefaly's Dual was evaluated in two trials, ACute treatment of Migraine with External trigeminal nerve stimulation (ACME) and PREvention of MIgraine using the STS Cefaly study (PREMICE) for acute and prophylactic treatment of migraine, respectively. ACME was designed as a prospective, double-blind, randomized, sham-controlled trial. Participants were randomized 1:1 into treatment and sham arms with treatment duration of one hour. Primary endpoint was mean change in pain intensity at one hour compared to baseline. Pain intensity was scored using visual analog scale (0-10 with 10 being the most painful). Altogether, 106 patients were enrolled with 52 and 54 patients in treatment and sham groups, respectively. The treated group had -3.46 mean change in pain at 1 hour versus -1.7 in the sham group, significant at the 0.01% level ($p < 0.0001$). In the patient subgroup without aura, pain scale reduction at one hour was -3.3 versus -1.7 in treatment and sham groups, respectively,

[68] Cefaly Dual for acute migraine study used a pain scoring system that is not directly comparable with other devices' clinical readouts.
[69] 95% Confidence Interval Not accessible via abstract.
[70] 95% Confidence Interval Not accessible via abstract.
[71] 95% Confidence Interval Not accessible via abstract.
[72] 95% Confidence Interval Not accessible via abstract.
[73] The Nerivio is not indicated for prophylactic treatment of migraine.
[74] The Nerivio is not indicated for prophylactic treatment of migraine.

significant at 0.06%.[75] Migraine with aura subgroup did not achieve statistical significance. No SAEs were reported; five AEs occurred in the treatment group.[76] The PREMICE study[77] was double-blinded, randomized and sham-controlled. Patients enrolled had at least two migraines a month and were randomized into two groups, treatment and sham. Treatment was daily stimulation for three months. Primary outcome was change in migraine days per month and 50% responder rate. Compared to the sham arm, the treatment arm achieved a 6.94 mean reduction in migraine days versus 4.88, significant at 2.3%. The 50% responder rate was also significantly greater in treated vs sham at 38.1% and 12.1%, respectively. Monthly migraine attacks, monthly headache days and monthly acute antimigraine drug intake were all significantly reduced compared to the sham group. No adverse events were reported in either group.

eNeura

eNeura is indicated for both acute and prophylactic treatment of migraine headache in users age 12 and older, and is not indicated for cluster headache. The single-pulse transcranial magnetic stimulation (sTMS) mini, as its name implies, functions via single-pulse magnetic stimulation which is believed to inductively neuromodulate. The device is activated to prime via the power button then ready to use within one minute of activating. It must be used within 45 seconds of priming. The device is then held to the back of the head, cradling the base of the skull, the treatment delivery buttons are triggered and after pressing, the treatment is administered.

In the eNeura SpringTMS Post-Market Observational U.S. Study of Migraine (ESPOUSE) study, sTMS efficacy in prophylactic treatment of migraine was evaluated. The study was a prospective, open label, observational study. Enrolled patients began by documenting a 1-month baseline headache diary, followed by three months of treatment. Treatment was four pulses, twice daily for prophylactic treatment, and, in the case of an acute attack, three pulses per dose, and up to three doses per attack. The primary endpoint was mean reduction in headache days compared to baseline, compared to a statistically derived placebo estimate. Secondary endpoints included 50% responder rate, acute headache medication consumption, HIT-6,[78] and mean reduction in total headache days from baseline of any intensity. Results from the study showed that patients experienced a -2.75 mean change in headache days from baseline compared to the performance goal of -0.63 days. The 50% responder rate was 46% compared to the performance goal of 20%. HIT-6 reduced by 3.1, and total headache days of any intensity reduced by 3.16 days. These endpoints were met significantly, compared to the respective performance goals, at the 0.01% level. Additionally, acute medication use was observed to be reduced by a mean of 2.93 days. There were no SAEs and the most common adverse events were lightheadedness, tingling and tinnitus.[79] Acute treatment of migraines was evaluated in another study.[80] The acute study was randomized, double-blind, parallel-group, two-phase, and sham-controlled. Adults aged 18-68 were enrolled into phase one, meeting international criteria for migraine with aura, with visual aura preceding at least 30% of migraines, followed by moderate or severe headache in more than 90% of attacks. 66 patients discontinued the trial during phase one, leaving 201 patients in phase two who were randomized into treatment and sham arms. Participants were instructed to treat up to three attacks over three months while experiencing aura. Primary endpoint was pain-free response at two hours after the first attack. Co-primary outcomes were noninferiority at two hours for nausea, photo- and phonophobia. Results of the study showed that pain-free response rates at two hours were significantly higher in treated vs. sham arms at 39% and 22%, respectively, a therapeutic gain of 17%, significant at the 1.8% level. Sustained response favored the treatment arm and non-inferiority was shown for nausea, photo- and phonophobia. No SAEs were reported.

Theranica

Theranica's Nerivio works via neuromodulation, although it does so by activating nerves of the arm, rather than those of the brain and head. Nerivio is classified as a remote electrical neuromodulation (REN) wearable and is indicated for acute treatment of migraine, with or without aura, in patients 18 years and older without chronic migraine. Nerivio is not indicated for prophylactic treatment of migraine nor is it indicated for cluster headache.

[75] Chou DE, Shnayderman Yugrakh M, Winegarner D, Rowe V, Kuruvilla D, Schoenen J. Acute migraine therapy with external trigeminal neurostimulation (ACME): A randomized controlled trial. *Cephalalgia*. 2019;39(1):3-14. doi:10.1177/0333102418811573

[76] Chou, D. E., Shnayderman Yugrakh, M., Winegarner, D., Rowe, V., Kuruvilla, D., & Schoenen, J. (2019). Acute migraine therapy with external trigeminal neurostimulation (ACME): A randomized controlled trial. Cephalalgia, 39(1), 3–14. https://doi.org/10.1177/0333102418811573

[77] Schoenen J, Vandersmissen B, Jeangette S, et al. Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. *Neurology*. 2013;80(8):697-704. doi:10.1212/WNL.0b013e3182825055

[78] HIT-6 is a headache impact test, scoring the functional disruption of headaches. http://dizziness-and-balance.com/testing/resources/HIT6.pdf

[79] Starling, A. J., Tepper, S. J., Marmura, M. J., Shamim, E. A., Robbins, M. S., Hindiyeh, N., … Dodick, D. W. (2018). A multicenter, prospective, single arm, open label, observational study of sTMS for migraine prevention (ESPOUSE Study). Cephalalgia, 38(6), 1038–1048. https://doi.org/10.1177/0333102418762525

[80] Lipton, Richard B, et al. "Single-Pulse Transcranial Magnetic Stimulation for Acute Treatment of Migraine with Aura: a Randomised, Double-Blind, Parallel-Group, Sham-Controlled Trial." The Lancet Neurology, vol. 9, no. 4, 2010, pp. 373–380., doi:10.1016/s1474-4422(10)70054-5.

Nerivio operates on conditioned pain modulation where conditioning stimulation can inhibit pain in remote body regions, an endogenous analgesic mechanism. The device needs to be used within 60 minutes of the attack, with improved results when used earlier. Nerivio must be used with the accompanying smartphone application. The device and the application are connected and the device can then be operated from the phone. The protective film of the adhesive electrode is removed, and the device is placed on the upper arm, midway between elbow and shoulder. The arm band is used to secure the device to the arm and ensure electrode contact. The 45 minute treatment is then initiated from the smartphone app where intensity can be tuned. Once the treatment has completed, the device is removed from the arm, and the protective film placed over the electrodes.

The study was randomized, double-blind and sham-controlled. Patients enrolled met the International Classification of Headache Disorders criteria for migraine with 2-8 migraines per month. The patients were randomized 1:1 into treatment and sham arms. The REN wearable, controlled via smartphone, was applied for 30-45 minutes on the upper arm within an hour of attack onset. Stimulation was set at a perceptible but not pain-inducing intensity, migraine pain levels were recorded at baseline, 2 and 48 hours post treatment. The primary endpoint was proportion of participants achieving pain relief at two hours post-treatment. Relief of most bothersome symptoms (MBS) and pain-free at two hours were secondary endpoints. Results showed that treatment arm achieved a therapeutic gain of 27.9%, significant at the 0.01% level. More of those in the treatment arm were pain-free and had MBS relief at two hours, significant at 0.3% and 0.08%, respectively. It was reported that pain relief and pain-free therapeutic effects compared to sham were sustained at 48 hours post treatment. Finally, adverse event incidence was low and similar between treatment groups.[81]

Device Competitor Comparison

The competing devices vary in their indication, use and efficacy. All are non-invasive alternatives to medication and are more targeted compared to medications that are systemic. The devices vary greatly in their use and administration. While the gammaCore device is held in place manually, it is only applied for a two minute session. The Cefaly Dual requires 60 minutes of use in an acute attack. If a patient suffers a migraine attack in a public setting, the Cefaly Dual's treatment duration and prominent visibility can be a hindrance to its use. The Theranica Nerivio is more visually discrete, able to be hidden under a garment sleeve, in contrast to Cefaly Dual on the forehead and the gammaCore device on the neck. Both the eNeura sTMS mini and electroCore gammaCore Sapphire™ can be administered in the privacy of a restroom or vehicle in case of an attack and the treatments are short, lasting no more than 3-5 minutes for either device. The eNeura sTMS mini, despite the reduction in size and weight from its predecessor, still remains quite large. Its size prohibits the carry of the device in smaller bags and packs, whereas the gammaCore is much smaller and can be placed in a pocket. All four devices were indicated for the acute treatment of migraine, all devices except for the Nerivio were indicated for prophylactic treatment of migraine and only gammaCore was indicated for acute and prophylactic treatment of cluster headaches.

Efficacy in acute and prophylactic treatment of migraine was comparable between the devices. 30.4%, 39.0% and 37.4% of patients enrolled in the studies reported being pain-free at 120 minutes for the gammaCore, sTMS mini and Nerivio, respectively. The Cefaly Dual was clinically evaluated in terms of acute treatment using a pain scale and was not directly comparable to the clinical results of the other devices. While the clinical results of the four devices differ, many of the results overlap gammaCore's results' confidence intervals.[82] The reported means from competing devices' studies' endpoints all fall within the gammaCore studies' confidence intervals, in all of the clinical objectives that were shared in common and comparable between the trials with the exception of 50% responder rate. 31.9% of patients in gammaCore's PREMIUM trial had a 50% or greater reduction in headache days with a 95% confidence interval between 23.4% and 41.8%. The ESPOUSE study, evaluating the sTMS mini, had a 50% responder rate of 46% (46% of patients achieving 50% or greater reduction in headache days), with a 95% confidence interval between 37% and 56%. The sTMS mini's responder rate of 46% exceeded the upper bound of gammaCore's 95% confidence interval, 41.8%. Both studies recorded the percentage of patients experiencing 50% or more reduction in headache days, although they differed slightly in population inclusion, further obscuring the comparison. The PREMIUM (gammaCore) trial defined responders as patients who recorded a reduction of at least 50% from baseline to the last 4 weeks of the double-blind period, and migraine and headache day reductions in the open-label period while the ESPOUSE (sTMS mini) included those in the "completed cases" population who met eligibility requirements and completed the 3-month diary. This review demonstrates that the devices are largely comparable in efficacy.

[81] Yarnitsky, D., Dodick, D.W., Grosberg, B.M., Burstein, R., Ironi, A., Harris, D., Lin, T. and Silberstein, S.D. (2019), Remote Electrical Neuromodulation (REN) Relieves Acute Migraine: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial. Headache: The Journal of Head and Face Pain, 59: 1240-1252. doi:10.1111/head.13551

[82] If the means of two samples are within each other's 95% confidence intervals, we assume that there is a material chance that they could be the same, *i.e.* statistically indistinguishable from one another.

User satisfaction with the devices is also important. A migraine attack can strike at any time and can do so without the warning of an aura. Portability and convenience are important characteristics that encourage proper use and are correlated with product efficacy. gammaCore and Nerivio are portable and quick with gammaCore having a treatment duration of four minutes per application (12 minutes maximum per attack) compared to Nerivio's 45-minute dose. The size of the device and treatment duration of the Dual largely relegate it to home use; however, there are more discrete options that can be used in wider settings and for acute and prophylactic treatment, such as the gammaCore and sTMS mini, negating the need for two devices. The Nerivio is not indicated for prophylactic use. The higher portability of the gammaCore, absence of treatment visibility, efficiency of dosing and flexibility in both acute and prophylactic treatment give gammaCore users the best chance for treatment adherence across real-life scenarios. Physician choice as to which therapy to administer depends on a variety of factors relating to headache intensity and disability, nausea, tempo of pain escalation, early intervention, headache recurrence, combination treatment, medication overuse and avoiding the use of opioids and barbiturates.[83]

Pharmaceutical Competition

Acute Migraine

Acute treatment can be compared based on the percentage of patients that achieve pain freedom at the two hour mark using the therapy. In a systematic review by Oldman, Smith, McQuay and Moore, the triptan with highest apparent pain-free at two hour efficacy was 6 mg of sumatriptan, which had a number needed to treat (NNT) of 2.1, comparable to the derived NNT of gammaCore of 3.3.[84] Side effects of sumatriptan include flushing, tingling, numbness, prickling, heat, tiredness, weakness, drowsiness, or dizziness and can cause side effects mimicking the symptoms of heart attack such as chest, jaw, left arm pain, shortness of breath and unusual sweating.[85]

Prophylactic Migraine

Prophylactic pharmaceutical options currently used include alpha antagonists, anti-convulsants, beta-blockers, botulinum-A, calcium channel blockers, serotonin agonists, serotonin reuptake inhibitors and tricyclic anti-depressants.[86] Work done in a meta-review analysis by Jackson *et al.* provided confirmatory evidence for the effectiveness of amitriptyline, atenolol, flunarizine, fluoxetine, metoprolol, pizotifen, propranolol, timolol, topiramate and valproate in reducing episodic migraine headaches. Amitriptyline appeared to produce the greatest benefit at a pooled standardized mean difference of a 1.2 headaches per month reduction compared to gammaCore's 2.7 mean reduction in headache days per month. Baseline for the migraine sufferers averaged about six migraines per month and most of the drugs reduced the number of headaches by 1-2 per month. Likewise, the analysis showed that about 1 in 7 would be a 50% responder, or about ~14.3% compared to gammaCore's 31.9%. Side effects are another consideration and the listed potential side effects of Amitriptyline, for example, included drowsiness, dizziness, dry mouth, blurred vision, constipation, weight gain, or trouble urinating.

There is also a new class of migraine drugs centered on calcitonin gene-related peptide (CGRP). CGRP is a neuropeptide, long thought to play an integral role in migraines. CGRP has been shown *in vitro* to be released from trigeminal neurons under conditions mimicking neurogenic inflammation and that pharmacotherapies can reduce CGRP release and inhibit CGRP transcription. These studies also show that tumor necrosis factor-α (TNF-α), an endogenous inflammatory mediator, can stimulate CGRP transcription.[87] This premise suggests that a feed-forward CGRP-proinflammatory mediator relationship with time scale on the order of 4-72 hours matches closely to observed migraine progression and could very well be an underlying mechanism of migraine. This hypothesis spawned the drug class of triptans that have an agonist effect on serotonin 5-HT_{1B} and 5-HT_{1D} receptors in blood vessels (causing their constriction) and nerve endings in the brain. In February 2020, Biohaven's Nurtec ODT (rimegepant) received FDA approval. The ODT formulation stands for orally disintegrating tablet, assisting in rapid treatment of acute migraine. Nurtec ODT is the only CGRP receptor antagonist available in orally dissolving compound. In Phase III, rimegepant was able to achieve pain freedom at two hours in 21% of participants compared to gammaCore which achieved pain freedom in 31.9% of participants. Adverse events were rare and included nausea and urinary tract infection.

[83] Ong JJY, De Felice M. Migraine Treatment: Current Acute Medications and Their Potential Mechanisms of Action [published correction appears in Neurotherapeutics. 2018 Jan 8;:]. *Neurotherapeutics*. 2018;15(2):274-290. doi:10.1007/s13311-017-0592-1

[84] Oldman, Anna D.; Smith, Lesley A.; McQuay, Henry J.; Moore, Andrew R.∗ Pharmacological treatments for acute migraine: quantitative systematic review, Pain: June 2002 - Volume 97 - Issue 3 - p 247-257
doi: 10.1016/S0304-3959(02)00024-6

[85] https://www.webmd.com/drugs/2/drug-7741/sumatriptan-oral/details

[86] Jackson JL, Cogbill E, Santana-Davila R, et al. A Comparative Effectiveness Meta-Analysis of Drugs for the Prophylaxis of Migraine Headache. *PLoS One*. 2015;10(7):e0130733. Published 2015 Jul 14. doi:10.1371/journal.pone.0130733

[87] Durham PL. Calcitonin gene-related peptide (CGRP) and migraine. *Headache*. 2006;46 Suppl 1(Suppl 1):S3-S8. doi:10.1111/j.1526-4610.2006.00483.x

Acute Cluster Headache

Oxygen inhalation can provide dramatic relief and is safe and inexpensive. However, oxygen tanks and concentrators are heavy and bulky, and even the smallest, most portable versions may not fit in a purse or bag. Furthermore, oxygen is not considered a prophylactic treatment of cluster headache.[88] Oxygen administration was able to achieve pain freedom in 78% of participants at 15 minutes[89] compared to gammaCore with 26.7% of patients achieving pain relief within the same time frame.

Like migraines, acute cluster headaches can be treated with triptans. Triptans may be administered via injection or nasal spray, with the injection being more effective. As explained previously, triptans can have side effects. Additionally, injections are quite invasive and if the patient is alone, administering an injection while suffering from a cluster headache may be difficult. Sumatriptan is not recommended if the patient has hypertension or heart disease, nor has sumatriptan been shown to be effective prophylactically.

Another treatment is octreotide (sandostatin), injectable synthetic somatostatin that is overall less effective and slower acting than triptans. Local anesthetics like lidocaine may be effective administered via nasal spray. Likewise, injectable dihydroergotamine (D.H.E. 45) may be an effective pain reliever as well; the intranasal form has not been proven to be effective.

Prophylactic Cluster Headache

Calcium Channel Blockers, corticosteroids, lithium carbonate, and combination anesthetic and corticosteroid injection around the occipital nerve are used for prophylactic treatment of cluster headaches. Calcium channel blockers such as verapamil are first choice. Work done by Petersen, Barloese and Snoer reported attack burden reduction on average of one attack per day in episodic CH patients and half of chronic CH patients experienced benefit from prophylactic verapamil. This is not directly comparable to the 3.9 day mean reduction in attacks seen in gammaCore's prophylactic evaluation in a chronic cluster headache population because gammaCore's study focused only on chronic CH population, and the evaluation was done in terms of mean attack reduction, versus Petersen *et al.*'s report of experiencing benefit. Side effects of verapamil include dizziness, slow heartbeat, constipation, upset stomach, nausea, headache or tiredness.[90]

[88] https://www.mayoclinic.org/diseases-conditions/cluster-headache/diagnosis-treatment/drc-20352084
[89] Cohen AS, Burns B, Goadsby PJ. High-Flow Oxygen for Treatment of Cluster Headache: A Randomized Trial. *JAMA.* 2009;302(22):2451–2457. doi:10.1001/jama.2009.1855
[90] https://www.webmd.com/drugs/2/drug-7086-225/verapamil-oral/verapamil-extended-release-capsule-oral/details

Management Profiles

Daniel S. Goldberger, Chief Executive Officer and Director

Mr. Goldberger joined electroCore in October of 2019 wielding over 35 years of experience in medical devices and instruments, having served as the CEO and Director of multiple firms and has acted as advisor to financial firms. Before taking the helm at electroCore, Mr. Goldberger served as CEO, Director and President of Repro Med Systems Medical Products (KORU Medical Systems), Synergy Disc Replacement; Inc., Xtant Medical, Sound Surgical Technologies (Solta Medical), Xcorporeal, Glucon, OSI Systems, and Optiscan Biomedical. Mr. Goldberger holds his bachelor's in mechanical engineering from Massachusetts Institute of Technology and his master's in the same from Stanford University. Mr. Goldberger has also attended the Stanford Directors College.

Brian M. Posner, Chief Financial Officer

Mr. Posner joined the electroCore team in May 2019, bringing over 30 years of management experience in both private and public companies, in biomedical sciences and other industries, of up to USD 1 billion in value. Before joining electroCore, Mr. Posner has served as CFO for Cellectar Biosciences; Inc., Alliqua BioMedical; Inc., Ocean Power Technologies, Power Medical Interventions, Pharmacopeia and Phytomedics. Mr. Posner earned his B.S. in accounting from Queens College and his MBA from Pace University.

Peter S. Staats, MD, MBA, Chief Medical Officer

Dr. Staats is a co-founder and past board member of electroCore and serves as its Chief Medical Officer. Dr. Staats oversees the ongoing clinical development of gammaCore and the pursuit of potential new indications. In addition to his role at electroCore, he is the President Elect of the World Institute of Pain and serves as CMO for National Spine and Pain Centers. He is also the founder of the Division of Pain Medicine at Johns Hopkins University and served as Director for a decade. Dr. Staats is internationally recognized for his work in neuromodulation strategies and minimally invasive procedures for chronic pain and is a past President of the North American Neuromodulation Society, American Society of Interventional Pain Physicians, New Jersey Society of Interventional Pain Physicians and the Southern Pain Society. He received his medical degree from the University of Michigan Medical School in Ann Arbor and completed his residency and fellowship training at Johns Hopkins University School of Medicine.

Operational and Financial Results

Corporate Milestones

electroCore has multiple approved indications and is currently pursuing additional indications in migraine for adolescents and reactive airway disease among other targets which are at varying stages of advancement. Below we list recent milestones and anticipated future events.

- Commercial Launch of gammaCore for
  - Acute treatment of episodic cluster headaches – 3Q:18
  - Acute treatment of migraine – 3Q:18
  - Prophylactic treatment of cluster headache – 1Q:19
  - Prophylactic treatment of migraine – 1Q:20
  - Emergency Use for respiratory distress in COVID-19 – 3Q:20
- Launch additional COVID-19 trials – 4Q:20
- Clinical publications for PTSD, PTH & TBI – 4Q:20/1Q:21
- Premium II data readout – 4Q:20/1Q:21
- Savior 1 & 2 data readout – 1Q:21/2Q:21
- EU stroke data – 1Q:21/2Q:21
- Distribution partner announcements outside US – 3Q:21/4Q:21

Operational Results

electroCore began 2020 by announcing a rebate agreement with Ascent Health Services for gammaCore. Ascent Health Services acted on behalf of Express Scripts, one of the nation's leading pharmacy benefit managers (PBMs), to select gammaCore as a preferred brand on all of its Standard National Formularies, targeting specific benefit designs that do not differentiate between drugs and devices at a monthly co-pay of roughly $25-$45.

On March 23, 2020, electroCore announced FY 2019 results. The company reported highlights:

- Net sales of $2.4 million for 2019,
- 829 paid months shipped to VA and DoD facilities during 4Q:19, and
- 961 paid months of therapy shipped to the UK during 4Q:19

During the investor update, management noted that the pandemic had affected physician access to headache patients and suspended revenue guidance. Three days later, electroCore announced changes to its Board of Directors with John Gandolfo, Tom Patton and Peter Cuneo joining the Board, adding medical technology experience in operations, finance and turnarounds. The company also announced that Nick Colucci, Jim Tullis and Carrie S. Cox would step down from the board and Michael G. Atieh would assume the role of Chairman. electroCore closed out an eventful March by announcing a common stock purchase agreement for up to $25 million with Lincoln Park Capital (LPC) and label expansion for gammaCore into migraine prevention. The stock purchase agreement acts as a line of credit, where, at electroCore's discretion, the company can sell up to $25 million in stock to LPC over a 36-month period.

On April 2, 2020, electroCore announced that it had submitted an Emergency Use Authorization (EUA) application to the FDA for use of gammaCore Sapphire™ CV to alleviate respiratory symptoms associated with COVID-19. On April 8th, the company announced the extension of the NHS Innovation and Technology Payment (ITP) program. The ITP program reimbursing gammaCore use was extended to September 30, 2020. On April 27th, electroCore announced that an investigator-initiated, randomized, controlled clinical trial of nVNS therapy had commenced enrolling COVID-19 patients in Spain for its SAVIOR trial. The trial is designed to assess the ability of nVNS to decrease the number of hospitalized COVID-19 patients requiring ventilator use. gammaCore would be used prophylactically, three times a day, as well as acutely to improve patient breathing, decreasing the reliance on mechanical ventilation. A second investigator-initiated, randomized, controlled trial protocol SAVIOR-2 was approved by the Institutional Review Board and would commence shortly.

On the 14th of May, electroCore announced 1Q:20 financial results and also receipt of 510(k) clearance to expand gammaCore into migraine prevention. On May 29, 2020, electroCore announced and presented at Little Grapevine's G1 Microcap Virtual Conference. On July 9th, electroCore announced that it would participate in three additional investor conferences, held virtually: MaximGroup/M-Vest COVID-19 Virtual Conference Series on July 16th, Zooming with LD Micro on July 21st and Canaccord Genuity 40th Annual Growth Conference on August 11th.

electroCore announced on July 13th that the FDA had issued EUA authorization for the use of gammaCore Sapphire™ CV non-invasive vagus nerve stimulation (nVNS) at home or in a healthcare setting for acute treatment of patients known or suspected to have COVID-19 who are experiencing exacerbated asthma-related dyspnea and reduced airflow where approved drug therapies are not tolerated or provide insufficient symptom relief. Commercialization of the product was made available through the agreement with UpScript, LLC publicized in an announcement on September 24th. UpScript will be the exclusive online telehealth provider for gammaCore Sapphire™ CV where patients can use the provider's telehealth platform to obtain a prescription and have the device shipped directly to their home.

As July concluded, electroCore announced the publication of the paper "Non-invasive vagus nerve stimulation for primary headache: a clinical update," in *Cephalalgia*, as well as provided an update on the availability of gammaCore Sapphire™ CV for acute asthma exacerbation in known or suspected COVID-19 patients beginning July 31st. In a release on August 27, 2020, electroCore announced the publication of a paper entitled, "Non-invasive vagal nerve stimulation decreases brain activity during trauma scripts," by Wittbrodt *et al.* in the journal *Brain Stimulation*. The double-blind, sham-controlled pilot study showed nVNS ability to decrease fear associated with emotional stress, hinting at a potential indication for the medium- to long-term horizon of the company. An additional study was launched and sponsored by the Department of Veteran's Affairs to study non-invasive vagal nerve stimulation in mild traumatic brain injury (mTBI) and post-traumatic stress disorder (PTSD). The work builds on other research[91] that has been published by Dr. Douglas Bremner, the principal investigator for the trial. The study is supported by a VA Merit Award.

electroCore was also fortunate to have received an extension of the NHS' Innovation and Technology Payment (ITP) program to fund continued use of gammaCore in England, made public in an early October announcement. The proposed contract will extend the ITP program until March 2024 and electroCore will continue to receive reimbursement for patients with cluster headache who respond to the therapy. The value of the additional three years could be up to approximately £3.6 million or approximately $4.6 million. The additional contract length will increase availability of the device for those who suffer from cluster headache and is a vote of confidence from the NHS that gammaCore is providing a benefit to patients. This extension is separate from the anticipated entry into Wales and Scotland.

Financial Results

For the second quarter of 2020, electroCore reported net sales of $753,000, compared with $622,700 in 2Q:19 representing 21% revenue growth. The increase was due primarily to increased sales to the Veteran's Administration and the United Kingdom, offset partially by reduced US commercial channel sales. Measured against the same period in the previous year, SG&A expense declined to $5.3 million from $9.4 million, R&D expense decreased to $1.0 million versus $2.5 million and operating expenses were $6.4 million versus $12.8 million due to a reduction in both personnel and non-personnel costs for sales and marketing activities and termination of Premium II clinical trial. Severance expenses of $99,600 were recorded in 2Q:20 compared to restructuring costs of $849,800 in 2Q:19 as per the restructuring plan in 2019. These resulted in a net loss including income tax benefits for 2Q:20 of approximately $4.7 million as compared to a loss of $12.1 million in 2Q:19. electroCore held $18.9 million in cash, equivalents and liquid securities at the end of the second quarter, and burned ~$12.4 million in cash during the first half of 2020. Following the end of the June 30 reporting period, electroCore raised $10.3 million from sales of common stock to Lincoln Park. Quarterly cash burn for the remainder of 2020 is expected to be below $4.5 million.

[91] Bremner JD. PTSD and mild traumatic brain injury. In: J. D. Bremner, ed. Posttraumatic Stress Disorder: From Neurobiology to Treatment Hoboken, N.J.: Wiley-Blackwell; 2016: 321-344.

Valuation

Migraine and cluster headaches affect near 40 million persons in the United States and over a billion worldwide. The economic impact of the condition is in the billions of dollars in the US and EU largely due to loss of productivity and this does not take into account the headaches' human toll on quality of life. There are a variety of treatments available, including pharmaceuticals and competing nerve stimulation devices. However, many of the pharmaceuticals are not consistently effective, are costly and have negative side effects. Other devices employing nerve stimulation are available but lack the strong research support that has distinguished gammaCore.

Annualized revenues are $2.8 million on a trailing 4Q basis and we expect 2020 revenues of over $3.0 million. Growth in subsequent years is anticipated to be high off of a small base which we discuss in further detail below. electroCore was able to generate strong revenue growth despite the negative impact of the pandemic and we believe that 2021 growth will resume the fast pace of pre-pandemic periods. Gross margin was 64% in the most recent quarter. As sales increase, we anticipate gross margins moving into the mid-70% range by 2023. Research and development costs had been high in previous quarters reaching almost $10 million in 2019 as clinical trials were underway. Now that gammaCore has been approved in four indications, the company is shifting its efforts away from R&D and towards sales and marketing. R&D expense for 2020 will be less than half of 2019 levels and is estimated to be about $1 million per year by 2022 and beyond. It is likely that electroCore will pursue other indications in the future and we will add the relevant development expense and anticipated revenues at that time.

SG&A exceeded $35 million in 2019. Since then electroCore has dramatically cut its expenses and we forecast just over $20 million in expense in 2020 and under $20 million in 2021, followed by normal inflationary increases after 2021. The company has a sufficiently sized sales team to achieve substantial growth over the next few years and we anticipate only incremental additions to the team over the next few years. Sales outside the United States will be handled by partners and distributors and gammaCore will be sold at a transfer price, which will not require additional sales assets.

Our model forecasts no cash taxes until 2029 as the company works through an anticipated $130 million in net operating losses which will begin to be drawn down in 2025. After the NOLs are exhausted, we apply a 25% combined tax rate to earnings representing both federal and state levies. Shares outstanding are increased to reflect anticipated capital raises until the company becomes profitable.

There are a number of drivers for our sales estimates including expansion of gammaCore sales in the United Kingdom as penetration into existing markets increases and coverage expands to Scotland and Wales. Success with the NHS could provide a bridge to commercialize the device in mainland Europe. Asia is another attractive market electroCore is working with partners to develop. The Veteran's Administration is the largest component of company sales making up 55% of total revenues in 2Q:20. 67 VA/DoD facilities have prescribed gammaCore and only half of the targeted facilities have been penetrated. The Veteran's Administration has over 10 million lives covered and over 400,000 patients that met with VA providers for headache in 2018. The VA is also working to expand the types of headache that can be treated with gammaCore into post-traumatic headache, post-traumatic stress disorder and traumatic brain injury.

gammaCore prescriptions to provide relief from the symptoms of the coronavirus via the EUA are a short term opportunity for electroCore. While the company has not reported any sales for this indication, we believe they may have begun given the substantial immediate need and the agreement with UpScript. The EUA will expire when the declaration of emergency ends and the product must pursue clinical trials to obtain full approval for this indication. We anticipate that there will be a material amount of COVID-related sales over the next several quarters which will not only help drive topline but also increase market familiarity with the device. However, we do not expect this to persist over the long term.

Being non-invasive, effective, portable and with limited side effects, we forecast continued penetration into both current and new channels and geographies. We provide a summary of our revenue, expense and earnings assumptions until 2026 below.

Exhibit XVIII – Income Statement Forecast 2019 – 2026[92]

electroCore, Inc.	2019 A	2020 E	2021 E	2022 E	2023 E	2024 E	2025 E	2026 E
Total Revenues ($US '000)	**$2,390**	**$3,032**	**$5,200**	**$9,650**	**$16,800**	**$28,280**	**$48,076**	**$72,114**
YOY Growth	141%	27%	72%	86%	74%	68%	70%	50%
Cost of Goods Sold	$1,157	$1,243	$2,080	$2,895	$4,368	$7,353	$12,500	$18,750
Product Gross Margin	52%	59%	60%	70%	74%	74%	74%	74%
Research & Development	$9,902	$4,074	$1,800	$1,000	$1,000	$1,000	$1,000	$1,000
Selling, General & Administrative	$35,422	$21,834	$19,000	$20,000	$21,250	$22,800	$23,000	$23,500
Restructuring & Other	$1,997	$465	$0	$0	$0	$0	$0	
Income from operations	($46,089)	($24,584)	($17,680)	($14,245)	($9,818)	($2,873)	$11,576	$28,864
Operating Margin	*-1928%*	*-811%*	*-340%*	*-148%*	*-58%*	*-10%*	*24%*	*40%*
Other Expense	($958)	($65)	$0	$0	$0	$0		
Pre-Tax Income	($45,130)	($24,519)	($17,680)	($14,245)	($9,818)	($2,873)	$11,576	$28,864
Net Income	**($45,148)**	**($23,348)**	**($17,680)**	**($14,245)**	**($9,818)**	**($2,873)**	**$11,576**	**$28,864**
Net Margin	*-1889%*	*-770%*	*-340%*	*-148%*	*-58%*	*-10%*	*24%*	*40%*
Reported EPS	**($1.54)**	**($0.60)**	**($0.39)**	**($0.28)**	**($0.19)**	**($0.05)**	**$0.21**	**$0.52**
YOY Growth		*-61%*	*-35%*	*-27%*	*-35%*	*-71%*	*# DIV/0!*	*# DIV/0!*
Basic Shares Outstanding	29,380	38,908	45,000	50,000	53,000	54,000	55,000	55,500

Source: Company Filing // Zacks Investment Research, Inc. Estimates

Our valuation employs a 20x multiple of future earnings per share as our primary valuation metric. The value is then discounted to present using a 20% rate. When we apply our 20x multiple to 2026 estimated earnings of $0.52, we generate a 2026 target price of $10.40. Discounting this to present using a 20% discount rate generates a value of approximately $4.00. The valuation approach is sensitive to assumptions regarding revenue growth, net margins, earnings multiples and discount rates. A one percentage point increase in net margin would result in a $0.013 change in 2026 reported EPS and a 2.5% change in valuation. Delaying the $0.52 in EPS by one year would reduce our valuation by 17% while a one year advance of electroCore's recognition of earnings would increase the target price by 20%. Below is a sensitivity table that shows present value of 2026 price to earnings (P/E) based valuation. Our target price implies a 2026 Price/Sales multiple of ~8x.

Exhibit XIX – Valuation Sensitivity Table[93]

P/E Multiple: 2026 EPS	Discount Rate				
	15.0%	17.5%	20.0%	22.5%	25.0%
15.0	$3.88	$3.48	$3.14	$2.83	$2.56
17.5	$4.52	$4.06	$3.66	$3.30	$2.98
20.0	$5.17	$4.64	$4.18	$3.77	$3.41
22.5	$5.82	$5.22	$4.70	$4.24	$3.83
25.0	$6.46	$5.81	$5.23	$4.71	$4.26

Based on the assumptions identified in our financial model, we generate a valuation of $4.00 per share.

[92] Source: Company filings, author's estimates
[93] Source: Author's own work.

Conclusion

electroCore is off to a strong start after receiving approval in four headache indications. The company has made inroads into the VA, NHS and commercial payors and is at the early stages of its potential in these groups. There are also other geographies and groups that can take advantage of the safe, portable and effective gammaCore device for preventing and treating headaches. Relationships with the VA and NHS provide validation and reputational benefits that can help expand into other government health care agencies, private health care providers and other geographies such as mainland Europe and Asia. In addition to current approved indications, gammaCore was granted EUA for treating COVID related asthma and is also participating in a number of investigator-led studies for other types of traumatic headache, mild traumatic brain injury, PTSD, stroke and inflammatory diseases.

gammaCore is attractive compared to other approaches as it has almost no side effects and is able to provide relief with only a few minutes of treatment. Cost is low compared with expensive triptans that are frequently limited in the number of treatments that can be administered per month. The device is also portable and can be used at work, home or while travelling.

Despite the impact of the pandemic, electroCore has increased sales both sequentially and year over year. We anticipate continued and accelerating topline growth next year off of a small base as the company penetrates existing markets and expands into new ones. As sales rise, we expect improving gross margins and stable operating costs as commercialization assets are already in place. Future sales outside the US will be conducted by partners which will purchase the device from electroCore and use their own commercialization assets to market.

Around 40 million individuals suffer from migraine and cluster headache in the United States and one billion globally. Many of the current treatments are only partially effective and leave the patient with numbness, nausea and other side effects. The most common pharmaceutical treatments cannot be used by patients with many common risk factors such as heart disease, high blood pressure and high cholesterol. This provides a substantial opportunity where even low levels of penetration can provide substantial revenues in future periods.

Key reasons to own electroCore shares:

- **Effective, non-invasive, and non-pharmaceutical method to treat migraines**
- **Portable, simple and rapid solution for preventing and treating headaches**
- **Indicated for both migraines and cluster headaches**
- **Existing and expanding relationships with VA hospitals**
- **Recharge/refill business model**
- **Supply chain simplicity: direct to customer shipping**
- **gammaCore can be prescribed through telemedicine**
- **NHS relationship in UK may provide foundation for further global expansion**
    - **Continental Europe**
    - **Asia**
- **Opportunity for COVID-related sales following EUA award**
- **Extended indications**
    - **Stroke**
    - **Trauma injury related headaches**
    - **PTSD**
    - **Mild traumatic brain injury**
    - **Inflammation**

Based on our review and analysis of the migraine and cluster headache market and the benefits of the gammaCore device, we anticipate continued and accelerating revenue growth as the company advances its strategic plan. Our valuation work takes into account continued success with the VA, NHS and existing commercial payors and anticipates future success in new geographies. For our valuation, we apply a multiple of future earnings to generate our target price of $4.00 per share.

PROJECTED FINANCIALS

electroCore, Inc. - Income Statement

electroCore, Inc.	2019 A	Q1 A	Q2 A	Q3 E	Q4 E	2020 E	2021 E	2022 E
Total Revenues ($US '000)	**$2,390**	**$734**	**$753**	**$765**	**$780**	**$3,032**	**$5,200**	**$9,650**
YOY Growth	141%	79%	21%	12%	16%	27%	72%	86%
Cost of Goods Sold	$1,157	$298	$273	$344	$328	$1,243	$2,080	$2,895
Product Gross Margin	52%	59.4%	63.7%	55%	58%	*59%*	*60%*	*70%*
Research & Development	$9,902	$1,523	$1,031	$800	$720	$4,074	$1,800	$1,000
Selling, General & Administrative	$35,422	$6,561	$5,273	$5,000	$5,000	$21,834	$19,000	$20,000
Restructuring & Other	$1,997	$365	$100	$0	$0	$465	$0	$0
Income from operations	($46,089)	($8,013)	($5,923)	($5,379)	($5,268)	($24,584)	($17,680)	($14,245)
Operating Margin	*-1928%*	*-1092%*	*-787%*	*-703%*	*-675%*	*-811%*	*-340%*	*-148%*
Other Expense	($958)	($54)	($11)	$0	$0	($65)	$0	$0
Pre-Tax Income	($45,130)	($7,959)	($5,912)	($5,379)	($5,268)	($24,519)	($17,680)	($14,245)
Net Income	**($45,148)**	**($7,959)**	**($4,742)**	**($5,379)**	**($5,268)**	**($23,348)**	**($17,680)**	**($14,245)**
Net Margin	*-1889%*	*-1085%*	*-6.29722626*	*-703%*	*-675%*	*-770%*	*-340%*	*-148%*
Reported EPS	**($1.54)**	**($0.27)**	**($0.13)**	**($0.12)**	**($0.12)**	**($0.60)**	**($0.39)**	**($0.28)**
YOY Growth		*-43.5%*	*-68.6%*	*-66.8%*	*-59.1%*	*-61%*	*-35%*	*-27%*
Basic Shares Outstanding	29,380	29,774	36,659	44,500	44,700	38,908	45,000	50,000

Source: Company Filing // Zacks Investment Research, Inc. Estimates

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HISTORICAL STOCK PRICE

electroCore – Share Price Chart[94]



[94] Source: Zacks Research System

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