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Clinical Data

Nerivio was evaluated in six clinical studies. The first study was a prospective, double-blind, randomized, crossover, sham-controlled pilot study. The second study was a multi-center, prospective, randomized, double-blind, sham-controlled pivotal study.

The other two studies were prospective, open label studies that evaluated the safety and efficacy of the Nerivio device in patients with chronic migraines (>15 headache days/month)

The fifth study was a prospective, open label studies that evaluated the safety and efficacy of the Nerivio device in adolescene patients (aged 12-17)The six study was a prospective, double-blind, randomized, crossover, sham-controlled study that evaluated the safety and efficacy of the Nerivio device as a migraine preventive therapy.

Pilot Study

The results of the pilot study were published in Neurology, March 2017:
https://n.neurology.org/content/88/13/1250.short

The pilot study was a single-center, prospective, double-blind, randomized, crossover, sham-controlled pilot study aimed to assess the safety and efficacy of non-invasive remote electrical neuromodulation (REN) with the Nerivio device for the acute treatment of migraine. In this study, 86 people with migraine with or without aura (in accordance with ICHD classification criteria) who had 2–8 attacks per month without preventive medications for at least 2 months were recruited. The participants were requested to treat migraine episodes at home using the device, which randomly provided four different stimuli programs differentiating in pulse width and one sham stimulus. Pain levels were self-reported via a smartphone application at onset and 10, 20, and 120 minutes after stimulation onset. The primary endpoint was the proportion of participants reporting pain decrease of at least 50% at 2 hours post-treatment in at least 50% of completed treatments. The analysis of the primary endpoint was performed on 71 participants who successfully treated at least one migraine attack and have not used rescue medications concurrently with REN treatments. This analysis revealed a 64% rate of at least 50% pain reduction at 2 hours post-treatment, in at least 50% of completed active treatments. This rate was significantly higher than the 26% rate found for the sham treatment (p=0.005). In this study, no device-related adverse events and no side effects were reported.

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Pivotal Study

The results of the pivotal study were published in Headache, May 2019:
https://headachejournal.onlinelibrary.wiley.com/doi/full/10.1111/head.13551

This study was a prospective, randomized, double-blind, sham controlled multi-center pivotal study aiming to demonstrate the efficacy and safety of Nerivio. The study was performed in 7 sites in the USA and 5 sites in Israel. The study initiation was in December 2017. The first randomization procedure was performed at the end of January 2018. The end of the double-blind phase was in October 2018.

Eligible patients were 18–75 years old females and males who met the International Classification of Headache Disorders (ICHD) third edition criteria for migraine with or without aura, with at least two and no more than eight migraine headaches per month, with no more than 12 headache days per month, and with stable (or no) migraine preventive medications in the last two months prior to recruitment.

The study included two phases. In the first ("roll-in") phase, participants were asked to keep a headache diary for one month in which all migraine episodes were documented. This phase was conducted to verify the number of migraine episodes experienced in one month (and thus, the eligibility of the patient), and to confirm the participant's ability to use the application and comply with the migraine episode reporting requirements. The second phase was a double-blind treatment phase, in which eligible participants were randomly allocated in a 1:1 ratio to either active stimulation (treatment group) or sham stimulation (sham group), in a double-blind manner. All participants underwent training on how to use the device for the treatment of migraine and how to provide feedback using the application.

Participants were asked to treat each migraine episode within 60 minutes of symptom onset. The participants used the application (installed on their personal phones) to record pain scores (scale: none, mild, moderate, or severe) at baseline, 2 hours post-treatment and 48 hours post-treatment, and to record the presence/absence of associated migraine symptoms (nausea, photophobia, phonophobia). The first reported treatment was considered a "run-in test" treatment, aimed to verify that the participants use the device properly, and was only included in the safety analysis. The efficacy endpoints were evaluated on the first reported treatment following the "run-in test" treatment (hereby termed "Test treatment").

Efficacy outcome

The primary efficacy endpoint was the proportion of participants who achieved pain relief at 2 hours post-treatment in the "Test" treatment. The co-secondary efficacy endpoints were the proportions of participants who achieved most bothersome symptom (MBS) relief, pain relief and MBS relief, pain-free and MBS free at 2 hours post-treatment. Exploratory endpoints included the proportion of participants showing 48-hour sustained pain-free response with device single use, 48-hour sustained headache reduction with device single use, 48-hour sustained pain-free response with device reuse, 48-hour sustained headache reduction with device reuse, 48-hour sustained MBS relief with device single use, and 48-hour sustained MBS relief with device reuse.

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Disposition of patients

296 participants were recruited to the study, 252 participants were randomized at the end of the roll-in phase. 126 of these eligible participants were randomly assigned to receive active Nerivio device (active group) and 126 were randomly assigned to receive sham Nerivio device (sham group). Among the 252 randomized participants, 7 participants withdrew from the study (4 in the active group and 3 in the sham group). 3 participants (1 from the sham group and 2 from the active group) withdrew from the study due to intolerance to the sensation of the stimulation (two participants withdrew during the randomization visit after the training, so the devices were never used at home) and 4 participants (2 in the active group and 2 in the sham group) were lost to follow up. 237 participants completed at least one treatment (the run-in treatment) and 202 participants completed the test treatment within one hour from symptom onset and reported a pain level at 2 hours (figure 1).

A modified intent to treat (mITT) group was defined as all randomized subjects who treated at least one attack (excluding the "run-in test" attack) within 1 hour from the attack onset.

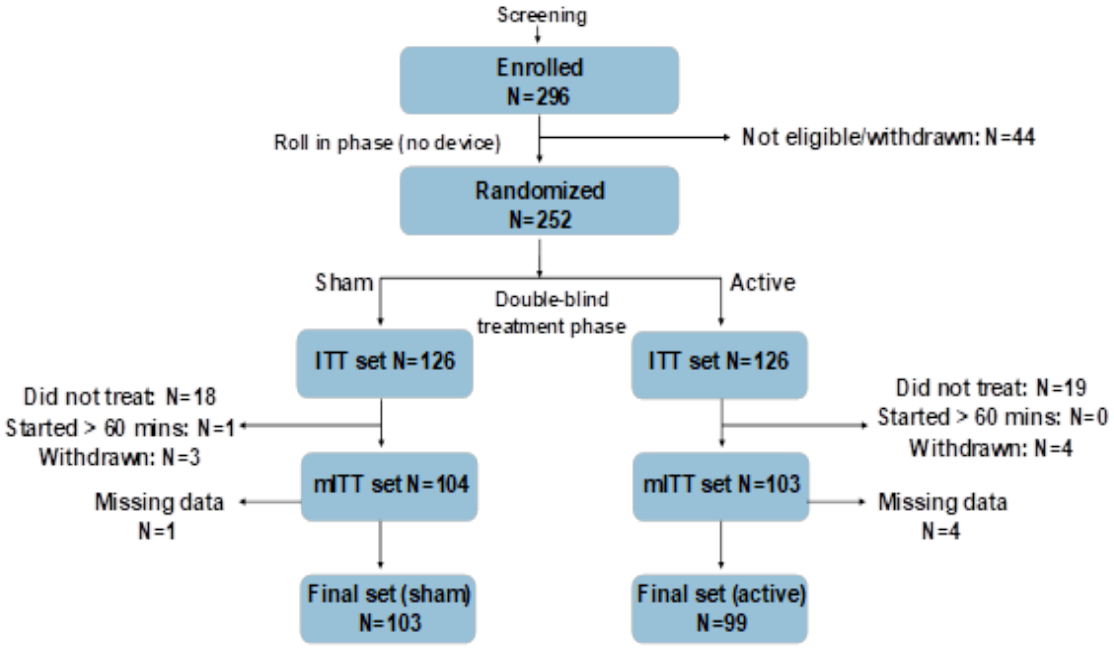

Figure 1 - Participant disposition

The majority of patients were female (81%), and the mean age was 42.7±12.1 years. The demographic characteristics were generally similar among groups (**table 1**).

		All	Active group	Sham group	P value
TOTAL		252	126	126	
Gender	**Male**	19.3% (48/249)	19.4% (24/124)	19.2% (24/125)	0.9753
	Female	80.7% (201/249)	80.6% (100/124)	80.8% (101/125)	
Race	**Caucasian****	87.7% (221/252)	86.5% (109/126)	88.9% (112/126)	0.6595
	Asian	0.8% (2/252)	1.6% (2/126)	0%	
	African-American	7.1% (18/252)	8.1% (10/124)	6.3% (8/126)	

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	Native Hawaiian	0.8% (2/252)	0.8% (1/126)	0.8% (1/126)	
	African/ Eastern Arabs	1.2% (3/252)	1.6% (2/126)	0.8% (1/126)	
	Other	2.4% (6/252)	1.6% (2/126)	3.2% (4/126)	
Age	**Mean (SD)**	42.7 (12.06)	43.8 (12.25)	41.6 (11.81)	0.1462
Height	**Mean (SD)**	166.4 (9.00)	166.4 (9.46)	166.4 (8.56)	0.9730
Weight	**Mean (SD)**	75.4 (18.79)	75.1 (20.47)	75.6 (17.03)	0.8182

Table 1 - TCH-003 study demographic

Efficacy

Primary Endpoint

In the mITT analysis set, the proportion of participants achieving a pain-relief response 2 hours after treatment was 66.7% (66/99) in the treatment group compared to 38.8% (40/103) in the sham group (therapeutic gain 27.9%; p<0.0001). The active treatment was also superior to the sham for the reduction of pain for each one of the possible baseline pain levels (severe, moderate, and mild).

Secondary Endpoints

In the mITT dataset, the active stimulation treatment was significantly more effective than the sham treatment for the proportion of participants achieving 2 hours of MBS relief (46.3% vs. 22.2%; p=0.0.0008) and for the proportion of participants who achieved both headache relief and MBS relief at 2 hours post-treatment (40.0% vs. 15.2%; p=0.0004. For pain-free 2 hours post-treatment, the active device was superior to the sham device, with statistical significance (37.4% vs. 18.4%; p=0.0036). There was no significant difference between active and sham treatment for MBS-free 2 hours post-treatment (40.7% vs. 36.4%; p=0.0.55).

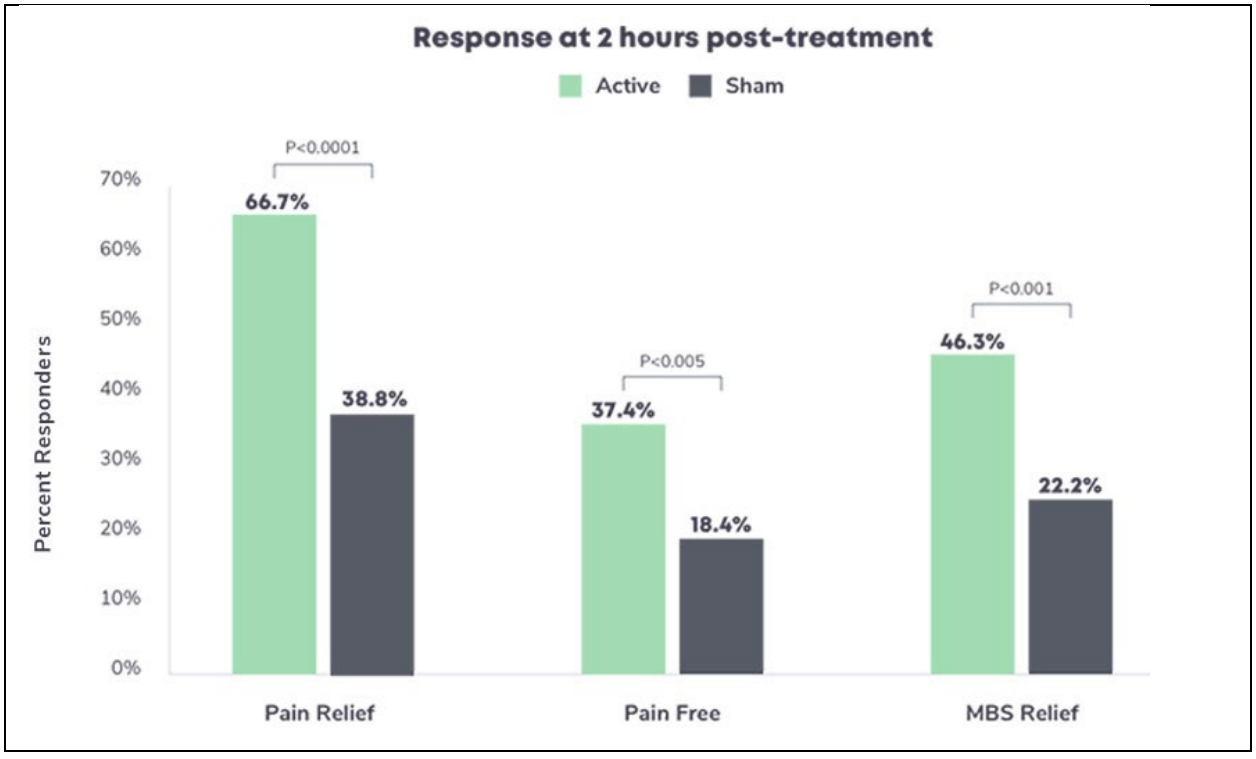

Figure 2 – Main endpoints results

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Furthermore, the active treatment was significantly more effective than the sham treatment for all measures of sustained efficacy, including 48-hour sustained pain-free response with device single use (p=0.007), 48-hour sustained headache reduction with device single use (p=0.0015), 48-hour sustained pain-free response with device reuse (p=0.0148), and 48-hour sustained headache reduction with device reuse (p=0.0010). In addition, the consistency of pain reduction over multiple treatments was also significantly higher in the treatment group (62.6%) compared to the sham group (45.6%, p=0.0154)

Safety

Safety analyses were performed on all 252 participants from the ITT population. 773 treatments were performed during the study (including the run-in treatment). The percentage of participants with at least 1 adverse event (regardless of its suspected cause) was 13.5% (34/252) and was comparable across treatment groups (15.1% (19/126) in the active group and 11.9% (15/126) in the sham group, $p_{Fisher's}$=0.58). The incidence of device-related adverse events was low (3.6%), and similar between treatment groups (active group: 6/126 [4.8%]; sham group: 3/126 [2.4%]; pFisher's=0.49). Notably, there were no unanticipated adverse device effects.

23 device-related adverse events were reported during 773 treatments (2.7%), 14 in the active group and 9 in the sham group. All device-related adverse events reported were mild in severity, did not require treatment and were resolved. No serious adverse events related to the device were reported. No statistically significant differences were found between treatment groups in either the type or rate of adverse events during the double-blind treatment phase.

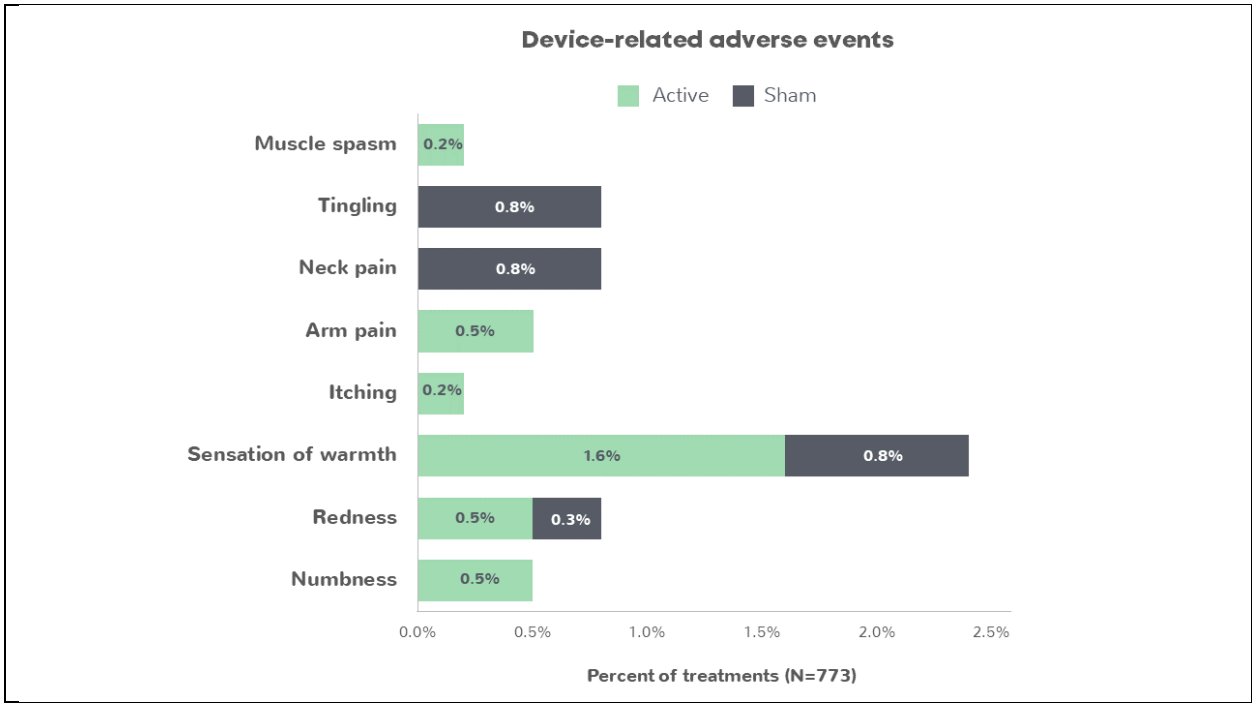

Figure 3 – Device related adverse events

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Conclusions

The findings of this study were robust and clinically meaningful. The study confirms that Nerivio is well tolerated and is associated with treatment efficacy and treatment satisfaction. From a risk-benefit perspective, treatment with Nerivio achieved significant pain relief without serious side effects. Therefore, Nerivio offers an alternative for current pharmacological and non-pharmacological treatments that combines efficient treatment with minimal side effects.

Pilot study with chronic migraine patients

The results of the pilot study were published in Pain and Therapy, July 2020.
https://link.springer.com/article/10.1007/s40122-020-00185-1

This study was a prospective, open-label, single arm, multicenter study conducted at 2 sites. 42 patients were recruited in this study. Eligible participants were adults (18–75 years old) who met the International Classification of Headache Disorders (ICHD-3) criteria for chronic migraine (at least 15 headache days a month, with at least eight days a month on which their headaches and associated symptoms meet diagnostic criteria for migraine).
Participants treated their migraine attacks at home for 4 weeks (treatment phase), within one hour from migraine symptom onset. Participants were instructed to avoid taking rescue medications prior or within two hours post-treatment. Pain scores, absence/presence of associated migraine symptoms, and functional disability were recorded at baseline, 2- and 24-hours post-treatment using the electronic diary application installed on the participants' smartphones.

The primary efficacy endpoint was the proportion of participants who achieved pain relief at 2 hours post-treatment in the test treatment, defined as improvement from severe or moderate pain to mild or none, or improvement from mild pain to none.

38 participants completed at least one treatment in response to a migraine. A total of 296 qualifying migraine headaches were treated with Nerivio. Pain relief and pain-free at 2 hours were achieved by 50.0% (19/38; $CI_{95\%}$ 33.4-66.6%) and 26.3% (10/38; $CI_{95\%}$ 13.4-43.1%) participants, respectively. Pain relief was sustained for 24 hours in 83.3% (10/12; $CI_{95\%}$ 51.6-97.9%) of the participants (7 participants did not report pain level at 24 hours and were thus excluded from the analysis). Nausea, photophobia, and phonophobia disappeared at 2 hours in 58.8% (10/17; $CI_{95\%}$ 32.9-81.6%)), 37.5% (9/24; $CI_{95\%}$ 18.8-59.4%), and 50.0% (8/16; $CI_{95\%}$ 24.7-75.3%) participants, respectively. Furthermore, 46.7% (14/30; $CI_{95\%}$ 28.3-65.7%) participants experienced improvement in functional ability at 2 hours and 72.7% (16/22; $CI_{95\%}$ 49.8-89.3%) participants experienced improvement in functional ability at 24 hours (8 participants with missing data at 24 hours were excluded from the analysis). Consistency analyses across all attacks (excluding the training treatment) demonstrated that 73.7% (28/38) of the participants experienced pain relief in at least 50% of their treated attacks.

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Endpoint	Result
Pain relief at 2 hours post-treatment[a] (in the test treatment)	50.0% (19/38)
Pain-free at 2 hours post-treatment[b] (in the test treatment)	26.3% (10/38)
Disappearance of associated symptoms at 2 hours post-treatment	
Disappearance of nausea and/or vomiting	58.8% (10/17)
Disappearance of photophobia	37.5% (9/24)
Disappearance of phonophobia	50.0% (8/16)
Sustained pain relief at 24 hours post-treatment (in the test treatment)	83.3% (10/12)
Within-subject consistency of pain relie	71.1% (27/38)
Within-subject consistency of pain free	26.3% (10/38)
Improvement in functional ability at 2 hours	46.7% (14/30)
Improvement in functional ability at 24 hours	78.9% (15/19)

Table 1 – Efficacy outcome

One device-related adverse event was reported (1.8% of patients [1/42] or 0.003% of treatments [1/296]). This adverse event included bilateral tingling in the temples, disturbed and double vision. The event resolved within 48 hours following drug therapy. There were no device-related serious adverse events and none of the participants withdrew from the study due to device-related adverse events.

The findings of the study demonstrated that Nerivio is effective for the acute treatment of migraine in people with chronic migraine. Acute treatment of migraine headaches resulted in clinically meaningful benefits. Pain relief and pain freedom rates were generally similar to those found in people with non-chronic migraine as reported in the Nerivio pivotal clinical study TCH003. Overall, the data reveal consistent response rates from treatment to treatment, with no evidence of reduction in therapeutic benefits over time. Specifically, over 73% of the patients achieved pain relief at 2 hours in more than half of their attacks. The findings of this study also show that the device is safe and well-tolerated. No safety issues were associated with the more frequent use of the device in patients with chronic migraine.

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Main study with chronic migraine patients

The results of the main study will be published in Pain Reports, November 2021.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8519197/

This was a prospective, open-label, single arm, multicenter study conducted at 9 sites in the USA. Eligible participants were adults (18–75 years old) who met the International Classification of Headache Disorders (ICHD-3) criteria for chronic migraine (at least 15 headache days a month, with at least eight days a month on which their headaches and associated symptoms meet diagnostic criteria for migraine).
Following a 4 weeks “Run-in” phase, eligible participants were asked to treat their migraine attacks at home for 4 weeks with their optimal stimulation intensity, as soon as possible after migraine headache began and always within one hour of attack onset. Participants were instructed to avoid taking rescue medications prior or within the first two hours post-treatment. Pain scores, absence/presence of migraine associated symptoms, and functional disability were recorded at baseline, 2- and 24-hours post-treatment using the electronic diary application.

The primary efficacy endpoint was the proportion of participants who achieved pain relief at 2 hours post-treatment in the test treatment, defined as improvement from severe or moderate pain to mild or none, or, improvement from mild pain to none.

97 participants completed at least one treatment of a qualifying migraine headache (the training treatment) and 91 participants completed the test treatment with evaluable data at baseline and at 2 hours, forming the final analysis set (5 participants did not have qualifying migraine headaches and 3 participants had missing data in the test treatment at baseline or at 2 hours).

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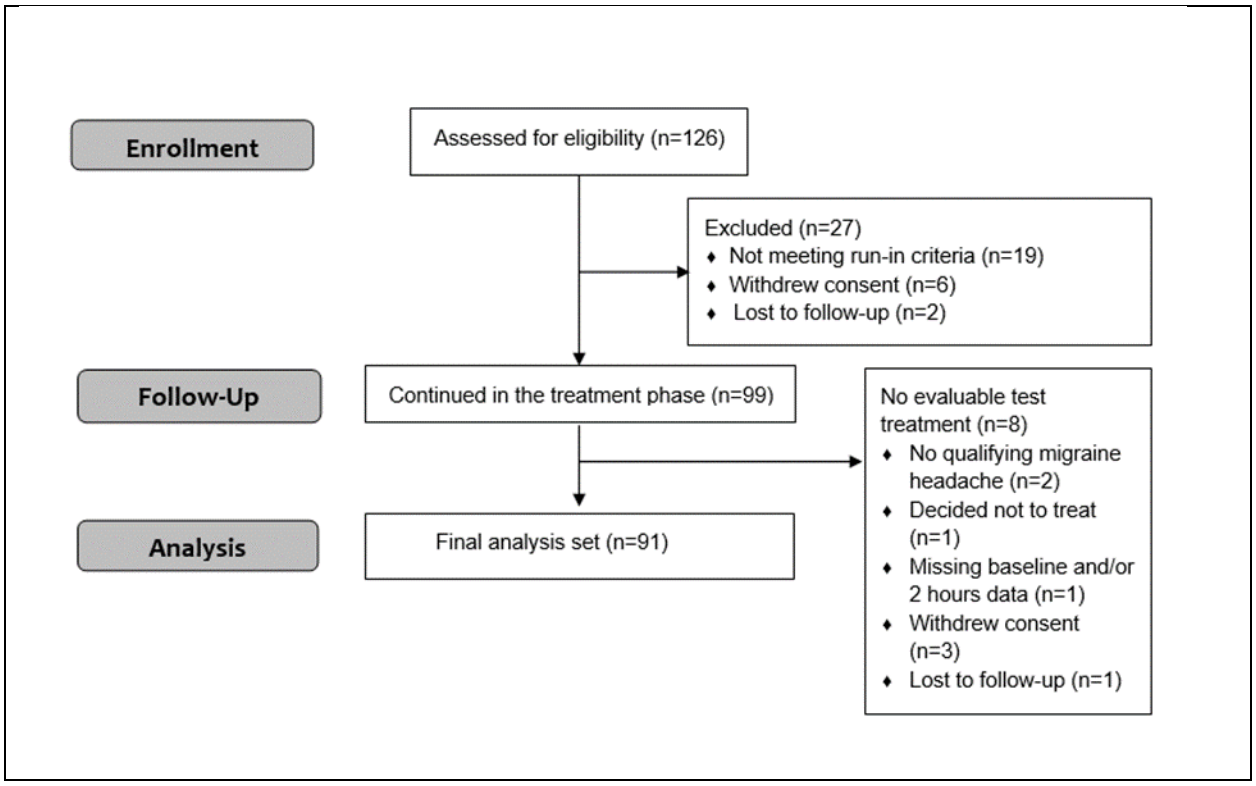

Figure 1 - Participant disposition

Results

"Run-in" phase

A total of 997 qualifying migraine attacks were reported during the run-in phase by the 126 enrolled patients, with an average of 7.9 attacks per participant. Of these, pain level at baseline was reported on 993 reported attacks.

Treatment phase

A total of 493 evaluable treatments (excluding the training treatment) of qualifying migraine headaches were conducted by the 91 participants included in the analyses, with an average of 5.4±2.8 evaluable treatments per patient per 4 weeks. Medication at 2 hours was used in 54 of the 493 treatments (89.0% compliance rate). Use of medication was considered a treatment failure.

The primary, secondary, and exploratory endpoints of a single attack were conducted on the test treatment of the final analysis set of 91 participants. Pain relief and pain-free at 2 hours were achieved by 59.3% (54/91; CI95% 48.5-69.5%) and 20.9% (19/91; CI95% 13.0-30.6%) of the participants, respectively. Pain relief was sustained for 24 hours in 71.1% (32/45; CI95% 51.6-97.9%) of the participants (9 participants did not report pain level at 24 hours and were thus excluded from the analysis). Nausea, photophobia, and phonophobia disappeared at 2 hours in 48.8% (20/41; CI95% 32.8-64.8%), 40.5% (30/74; CI95% 29.2-52.5%), and 44.6% (29/65; CI95% 32.2-57.4%) participants, respectively. Furthermore, 59.4% (19/32; CI95% 40.6-76.3%) of the participants experienced improvement in functional ability at 2 hours (participants with missing data at baseline or at 2 hours were excluded from the analysis) and 50.0% (7/14; CI95% 23.0-

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76.9%) of the participants experienced improvement in functional ability at 24 hours (participants with missing data at baseline or at 24 hours were excluded from the analysis).
Consistency analyses across all attacks (excluding the training treatment) demonstrated that 57.1%
(52/91) of the participants experienced pain relief in at least 50% of their treated attacks.

Endpoint	Result
Pain relief at 2 hours post-treatment[a] (in the test treatment)	59.3% (54/91)
Pain-free at 2 hours post-treatment[b] (in the test treatment)	20.9% (19/91)
Disappearance of associated symptoms at 2 hours post-treatment (in the test treatment)	
Disappearance of nausea and/or vomiting	48.8% (20/41)
Disappearance of photophobia	40.5% (30/74)
Disappearance of phonophobia	44.6% (29/65)
Sustained pain relief at 24 hours post-treatment (in the test treatment)	73.3% (33/45)
Improvement in functional ability at 2 hours[c] (in the test treatment)	59.4% (19/32)
Improvement in functional ability at 24 hours[c] (in the test treatment)	50.0% (7/14)
Within-subject consistency of pain relief[d]	57.1% (52/91)

Table 1 – Efficacy outcome

One device-related adverse event was reported (1.0% [1/99]) in which pain in the arm was felt following the use of the device on that arm. The device-related adverse event was mild, resolved within 24 hours without medication.

Conclusions

The findings of the study show that Nerivio is effective for the acute treatment of migraine in people with chronic migraine. Acute treatment of migraine headaches resulted in clinically meaningful benefits. Pain relief and pain freedom rates were generally similar to those found in people with non-chronic migraine, indicating that Nerivio provides an alternative acute migraine treatment independent of the frequency and severity of migraine headaches.
The results of the study show that Nerivio is safe to use and is well-tolerated. The incidences of device-related adverse events were low with no device-related serious adverse events. The rate of all device-related adverse events was below 2%, which compares favorably to the reported rates for current pharmacological treatments.

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Study with adolescence migraine patients

The results of the pivotal study were published in Headache, December 2020. https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/head.14042

A clinical study of the Nerivio device in adolescents with migraine (ages 12-17 years old) was performed to assess the safety and clinical efficacy of Nerivio in adolescents with migraine.
The study was a prospective, open-label, single arm, multicenter study conducted at 12 sites in the USA. Eligible participants were adolescents (12–17 years old, inclusive) who met the International Classification of Headache Disorders (ICHD-3) criteria for migraine. all the inclusion criteria and none of the exclusion criteria.

Following a 4 week “run-in” phase, eligible participants were asked to treat 4 qualifying migraine attacks at home with their optimal stimulation intensity, as soon as possible after migraine headache began and always within one hour of attack onset. Participants were instructed to avoid taking rescue medications prior or within the first two hours post-treatment. Pain scores, absence/presence of migraine associated symptoms, and functional disability were recorded at baseline, 2- and 24-hours post-treatment using the electronic diary application. Improvement in migraine-related disability following the treatment phase was assessed using the Pediatric Migraine Disability Assessment (PedMIDAS) questionnaire.

Efficacy and safety outcome

The primary safety endpoint was assessed by the incidence of adverse events in general and by seriousness, severity and association to the device. Treatment tolerability was assessed by the percent of subjects who fail to complete the study because of adverse events.

The secondary endpoints were related to device efficacy and included the proportion of participants who achieved pain relief at 2 hours post-treatment, defined as improvement from severe or moderate pain to mild or none, or improvement from mild pain to none; proportion of participants who achieved pain-free (improvement from mild, moderate, or severe pain to none) at 2 hours, and disappearance of associated symptoms (nausea/vomiting, photophobia, and phonophobia) at 2 hours post-treatment.

Exploratory endpoints included sustained pain relief at 24 hours, sustained pain-free at 24 hours, and improvement in functional ability at 2 hours and at 24 hours. Within-subject consistency of pain relief and pain-free responses, defined as the proportion of participants achieving pain relief/pain-free at 2 hours post-treatment in at least 50% of their treated headaches, were also assessed.

Disposition of patients

60 patients were enrolled, of which 1 participant was lost to follow-up during the run-in phase, and 14 completed the run-in but were not eligible to continue according to protocol specifications. Among the 45 participants who entered the treatment phase, all participants completed at least one treatment (the training treatment) and 39 participants completed the test treatment, forming

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the final analysis set (two participants had missing data at 2 hours post-treatment, three participants did not have migraine headaches and one participant was a lost to follow-up).
A total of 159 qualifying migraine headaches were treated with Nerivio for which pain data was recorded at baseline and at 2 hours post-treatment (average of 3.5 treatments per participant). Pain levels at baseline were 15.7% mild (25/159), 48.4% moderate (77/159) and 35.8% severe (57/159). Participant disposition is presented in figure 1

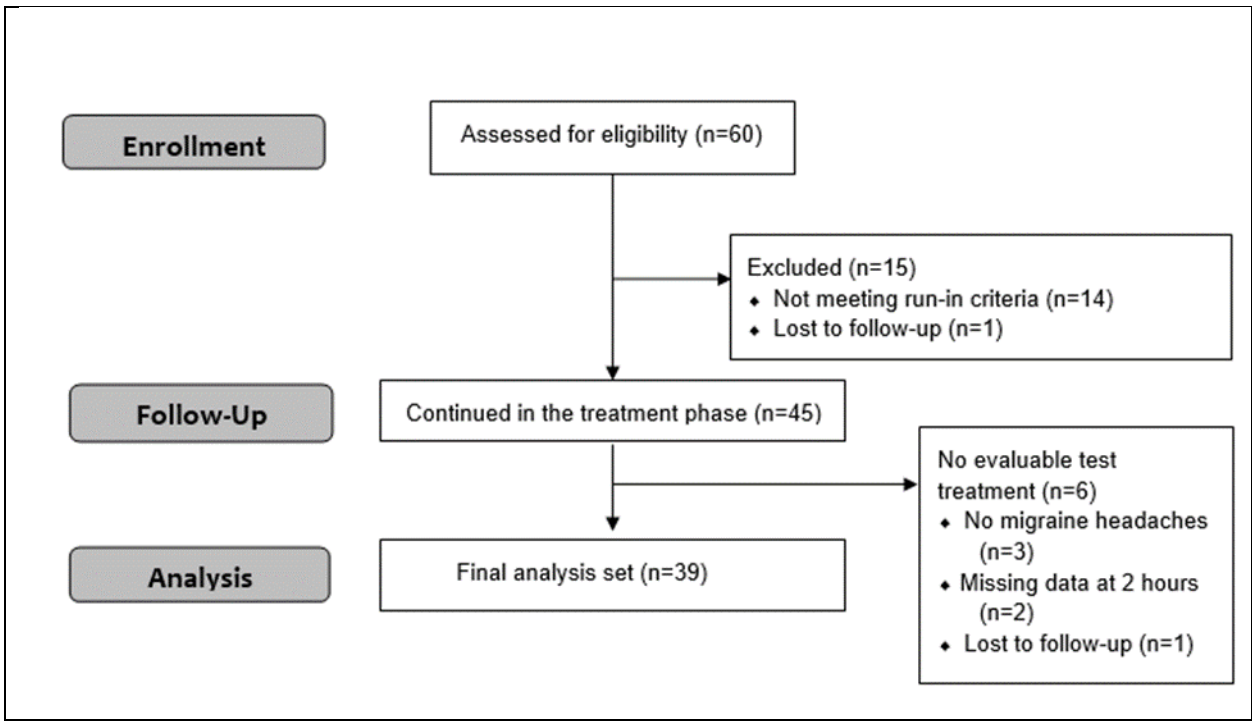

Figure 1 - Participant disposition

Results

The participants demographic information is shown in table 1.

Characteristic	
Age, y (SD)	15.4 (1.8)
Female, % (n/N)	60.0% (36/60)
Race, % (n/N)	
Caucasian (including Hispanic)	86.6% (52/60)
African/ Eastern Arab	1.66% (1/60)
African American	10.0% (6/60)
American Indian or Alaskan Native	1.66% (1/60)

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Average number of headache days per month	9.6 (4.6)
Average number of migraine headache days per month	7.9 (3.9)
Triptan users, % (n/N)	30.0% (18/60)
Migraine with aura, % (n/N)	31.7% (19/60)
MBS % (n/N)*	
Nausea	35.0% (21/60)
Photophobia	43.3% (26/60)
Phonophobia	16.7% (10/60)
None	5.0% (3/60)

Table 1 - TCH-004 study demographic

Results:

"Run in" phase:

A total of 267 qualifying migraine attacks were reported during the run-in phase by 54 of the 60 enrolled patients (6 patients did not report any migraines during the run-in phase), with an average of 4.9 migraine attacks per participant.

Treatment phase

Safety analysis

Safety analyses were performed on all 45 participants who used the device at least once. 10 participants (22.2%) reported at least one adverse event. There was one device-related adverse event (2.2%) in which a temporary pain in the arm was felt. This adverse event was mild and resolved after the treatment without requiring medication or any other intervention. The other adverse events which were deemed unrelated to the device included common cold (1 participant), chest congestion (2 participants), influenza (2 patients), leg pain (1 patient), streptococcus pharyngitis (1 participant), and upper respiratory infection (1 patient). One (1) patient suffered from a migraine attack that was not treated by the device where the migraine presented as severe, and the patient was treated in the ER.

There were no device-related serious adverse events and none of the participants withdrew from the study due to device-related adverse events.

Efficacy analysis

The efficacy endpoints were conducted on the test treatment of the final analysis set of 39 participants. Pain relief and pain-free at 2 hours were achieved by 71.8% (28/39) and 35.9% (14/39) participants, respectively. For the primary efficacy endpoint, missing data was imputed using a worst-case scenario, in which all treatments with missing pain level data were considered failures. According to this sensitivity analysis, pain relief was achieved by 68.3% (28/41) of the participants.

Pain relief was sustained for 24 hours in 90.9% (20/22) of the participants, and pain freedom was sustained for 24 hours in 90.9% (10/11) of the participants (only subjects achieving relief/freedom at 2 hours were included in the analyses; 6 participants did not report pain level at 24 hours and were thus excluded from the analysis). Nausea, photophobia, and phonophobia disappeared at 2 hours in 54.5% (12/22), 41.9% (13/31), and 40.0% (10/25) participants, respectively. Furthermore, 69.7% (23/33) participants experienced improvement in functional ability at 2 hours

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(only participants with functional disability at baseline were included in the analysis) and 69.0% (20/29) participants experienced improvement in functional ability at 24 hours (only participants with functional disability at baseline were included in the analysis; 4 participants with missing data at 24 hours were excluded from the analysis). In order to assess long-term response to the treatment, a consistency analysis was conducted across all treated attacks (excluding the training treatment). This analysis demonstrated that 66.7% (26/39) of the participants experienced pain relief in at least 50% of their treated attacks, and 33.3% (13/39) of the participants experienced pain-free in at least 50% of their treated attacks.

Headache disability as determined by the impact of recurrent headaches on a patient's quality of life was assessed using the Pediatric Migraine Disability Assessment (PedMIDAS) questionnaire. 42 participants who completed the questionnaire both at baseline and at the end of treatment phase were included in the analysis. The change between the PedMIDASs at enrollment (37.1±30.4) and the end of the treatment phase (18.5±26.8) was 18.6 ± 23.4. These results indicate that treating migraine headaches with Nerivio significantly decreases migraine disability. Interestingly, the average decrease observed in the current study is similar to the reduction shown for migraine preventive treatments in the pediatric population. These findings suggest that Nerivio is effective for improving patients' quality of life.

Endpoint	**Result**
Pain relief at 2 hours post-treatment[a] (in the test treatment)	71.8% (28/39)
Pain-free at 2 hours post-treatment[b] (in the test treatment)	35.9% (14/39)
Disappearance of associated symptoms at 2 hours post-treatment	
Disappearance of nausea	54.5% (12/22)
Disappearance of photophobia	41.9% (13/31)
Disappearance of phonophobia	40.0% (10/25)
Sustained pain relief at 24 hours post-treatment (in the test treatment)	90.9% (20/22)
Sustained pain free at 24 hours post-treatment (in the test treatment)	90.9% (10/11)
Improvement in functional ability at 2 hours[c]	69.7% (23/33)
Improvement in functional ability at 24 hours[c]	69.0% (20/29)

Table 2 – Efficacy outcome

The perceived usability of Nerivio was assessed using the system usability scale (SUS). 42 participants who completed the questionnaire at the end of treatment phase were included in the analysis. The mean SUS score was 85.1±12.7. These results indicate high levels of acceptability, ease of use, learnability and confidence when using Nerivio.
The results of the study show that Nerivio is safe and effective for the acute treatment of migraine in adolescents.

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Conclusions:
Performance data demonstrate that the Nerivio is safe and effective for acute treatment of migraine in adolescents as it is in adult patients, resulted in clinically meaningful benefits (pain relief and pain freedom)

The results of the study show that Nerivio is safe and effective for the acute treatment of migraine in adolescents. There was one device-related adverse event in which a temporary feeling of pain in the arm was felt. This adverse event was mild and resolved after the treatment without requiring medication or any other intervention. This rate of device-related adverse events compares favorably to the reported rates for current pharmacological treatments.

Study of migraine prevention by Nerivio

The results of the pivotal study were published in Headache. 2023 Jan 27. doi: 10.1111/head.14469,

This was a Randomized, Controlled Trial (RCT) of the Nerivio device in migraine patients to assess the Nerivio safety and clinical efficacy in prevention of migraine. Specifically, it assessed the capability of the Nerivio device to reduce the number of migraine days, number of headache days and number of moderate/severe headache days in patients with migraine. The study was in compliance with 21 CFR parts 50, 56, and 812.
The study was a prospective, randomized, sham-controlled, multicenter study conducted at 15 sites. Eligible participants were adults (18–75 years old) who met the International Classification of Headache Disorders (ICHD-3) criteria for migraine, with 6 to 24 headaches per month (with at least 4 days a month on which their headaches and associated symptoms meet diagnostic criteria for migraine).
Participants had a 4-weeks period of “Baseline” phase. During that phase, participants were asked to complete a daily migraine diary using the electronic diary application installed on the participants’ smartphones, while continue with their standard practice for migraine. Following the baseline period, and if were qualified to continue according to the study requirements, participants went into an 8-weeks period of “Treatment” phase. During that phase, participants were asked to treat with the Nerivio device every other day with their optimal stimulation intensity and complete a daily migraine diary using the electronic diary application installed on the participants’ smartphones, while continue with their standard practice for migraine. Participants were asked NOT to use the Nerivio for acute treatment during the Treatment phase, in order to reduce bias between the active and the sham groups. At the end of the treatment phase, participant went into a 4-weeks period of “follow-up” phase.

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Efficacy outcome

The primary efficacy endpoint was the mean change in number of migraine days per month comparing the 4-week baseline phase (weeks 1-4) with the last 28 days of the treatment phase (weeks 9-12). The main secondary endpoints were the mean changes in numbers of moderate/severe headache days, and headache days per month comparing the 4-week baseline phase (weeks 1-4) with the last 28 days of the treatment phase (weeks 9-12).

Disposition of patients

248 participants were eligible for randomization at the end of the baseline phase (weeks 1-4) and were randomly assigned to receive either active Nerivio device (Active group, n=128) or sham Nerivio device (Sham (Placebo) group, n=120).

Among the randomized participants, 8 participants withdrew or were lost to follow-up during the treatment phase (n=5 and n=3 in the Active and Sham groups, respectively). During weeks 9-12, 23 participants did not complete at least 22 daily reports (n=12 and n=11 in the Active and Sham groups, respectively), 19 participants did not perform at least 12 treatments (n=7 and n=12 in the Active and Sham groups, respectively) and 19 participants did not complete both (n=9 and n=10 in the Active and Sham groups, respectively). Thus, the mITT dataset has 179 participants (n=95 and n=84 in the Active and Sham groups, respectively) that reported at least 22 daily reports and performed at least 12 treatment with the study device during weeks 9-12 of the study. 248 participants were eligible to be randomized into the treatment groups (Active 128. Sham 120), and made the ITT dataset.

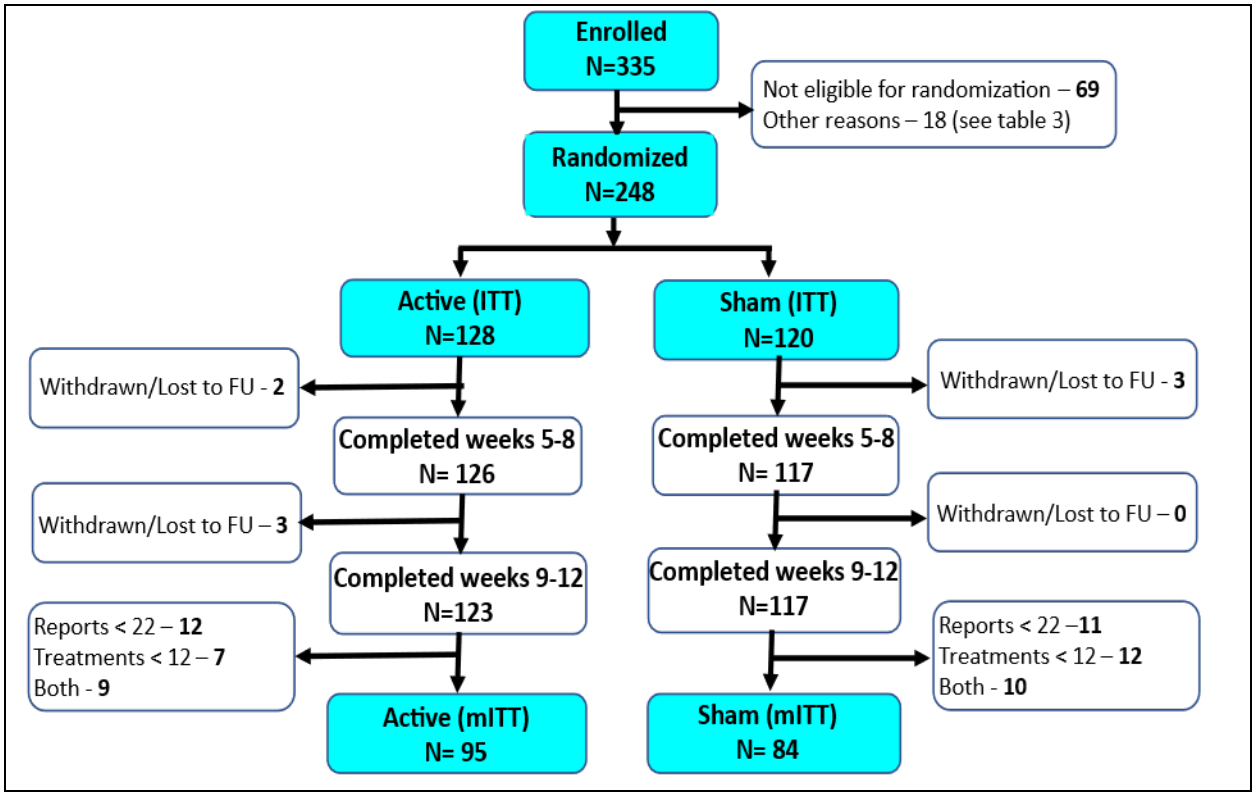

Figure 1 - Participant disposition

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Results:

In order to demonstrate the balance between the two groups, an analysis of the demographic and migraine history data was performed for both active and sham groups for both mITT and ITT datasets. No statistically significant differences were found between the active and the sham groups.

The findings of the study show that treatment with Nerivio every other day is significantly more effective than sham.

There was a reduction of 3.97±0.41 Vs. 1.28±0.43 of migraine days in the active and sham groups, respectively (mean±SEM, p<0.001), with a therapeutic gain of -2.69 ($CI_{95\%}$ -3.87, -1.51) migraine days. The results indicate significant clinical benefit of the device. Importantly, the therapeutic gain is statistically significant in each one of the chronic and episodic sub-groups with gains of -3.04 ($CI_{95\%}$ -4.88, -1.21) and -2.26 ($CI_{95\%}$ -3.74, -0.78) migraine days in the chronic and episodic participants, respectively, indicating that Nerivio is effective for migraine preventive treatment of both chronic and episodic migraine.

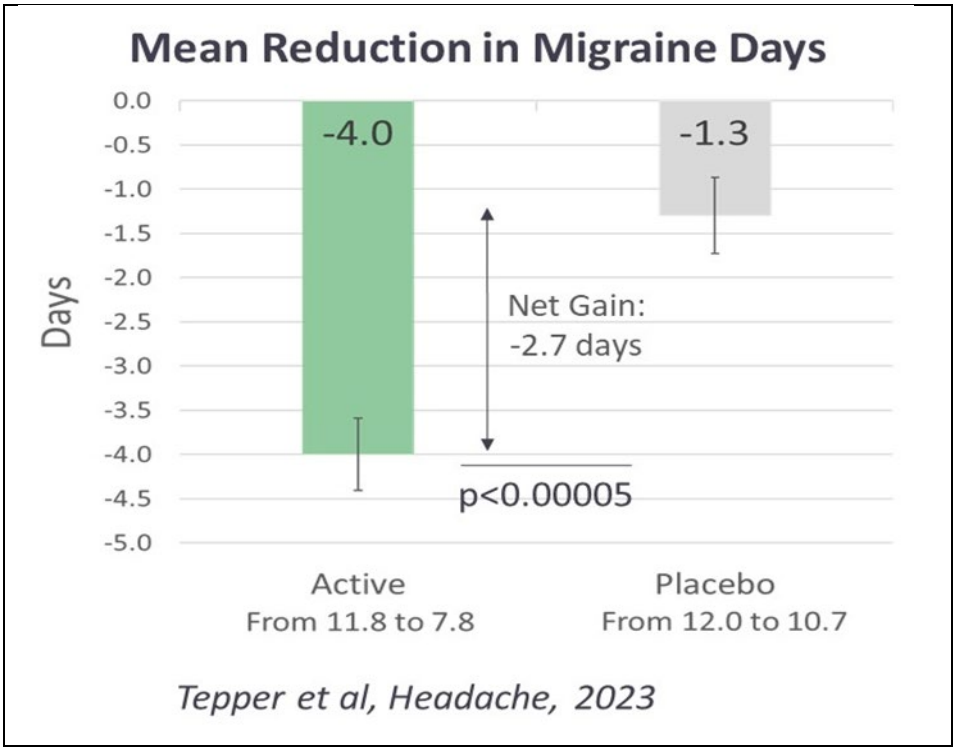

Figure 2 – results of primary endpoint

Nerivio was statistically significant more effective than sham in the mean change in number of moderate/severe headache days per month in the last month of double-blind treatment phase: mean change of -3.82±0.40 days Vs. -2.23±0.39 in the Active and Sham groups, respectively (mean±SEM, p=0.005), with a therapeutic gain of -1.59 ($CI_{95\%}$ -2.70, -0.48) moderate/severe headache days.

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Nerivio was statistically significant more effective than sham in the mean change in number of total headache days per month in the last month of double-blind treatment phase: mean change of -4.46±0.42 Vs. -1.77±0.50 in the Active and Sham groups, respectively (mean±SEM. p<0.0001], with a therapeutic gain of -2.69 ($CI_{95\%}$ -3.87, -1.51) headache days.
Nerivio was more effective than sham in the percentage of participants with at least a 50% reduction in the mean number of headache days per month in the last month of double-blind treatment phase. In the Active group, 26.3% of the participants (25 out of 95) demonstrated reduction of at least 50% in their number of headache days, compared to 11.9% of the participants in the Sham group (10 out of 84), resulted in 2.21 folds in favor of the Active group (p=0.015).
Nerivio was statistically-significantly more effective than sham in the mean change in number of acute headache/migraine medication days per month from weeks 1-4 to weeks 9-12, with a reduction of 3.5±0.42 in Active group Vs. 1.4±0.47 in the Sham group (mean±SEM, p=0.001), with a therapeutic gain of -2.08±0.63 ($CI_{95\%}$ [-3.33, -0.83]) acute headache/migraine medications days.

There were two serious adverse events (SAEs) during the study (suicidal attempt and a case of Appendicitis), which were deemed to be non-related to the study device or study procedures. There was only one device-related adverse event, in the sham group (0.83%, [1/120]).

Conclusions

The study demonstrates the effectiveness and safety of the Nerivio as a therapy for prevention of migraine. The results are clinically meaningful and demonstrates that peripheral neurostimulation aiming can invoke conditioned pain modulation that induces a reduction in the number of monthly migraine days. No statistically significant differences were found between the Active and Sham groups in either the type or rate of adverse events during the treatment phase.

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