PROTOCOL

A prospective, double-blind, sham-controlled, randomized clinical trial to assess the safety and efficacy of the mi-helper device for acute treatment of migraine in an at home setting

Short Title: Cooling to Alleviate Migraine #3 (CALM-3)

Protocol No.: COT-004

Test Article: Mi-Helper Device

Sponsor: Mi-Helper Inc.

101 West Dickman St, Suite 1050B

Baltimore, MD, 21230

Phase of Study: N/A

Principal Investigator: Jessica Ailani, MD

Study Design: A prospective, double-blind, sham-controlled, randomized study

Country of Implementation: United States

INVESTIGATOR'S SIGNATURE PAGE

Protocol Number: COT-004
Version: 3.0
Date: 27 May 2025

INVESTIGATOR'S SIGNATURE

I have read the protocol specified above and agree to participate in and comply with the procedures, as outlined herein for the conduct of this clinical trial. I also agree to comply with the applicable US Food and Drug Administration (FDA) regulations, local regulations as well as Investigational Review Board (IRB) requirements for testing on human participants. I agree to ensure that the requirements for obtaining informed consent are met.

_____ _____
Investigator's Signature Date

_____ _____
Printed Name

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AMENDMENTS AND SUMMARY OF CHANGES

Document History

DOCUMENT	VERSION	SUMMARY OF CHANGES
Protocol	1.0 20-Dec-2024	Original version.
Amendment 1	2.0 03Feb2025	Amendments include changes to the inclusion and exclusion criteria, addition of several secondary endpoints, updates to text for further clarity, and general administrative updates.
Amendment 2	3.0 27 May 2025	Amendments include, an update to exclusion criteria 14, removal of select study endpoints, addition of several exploratory endpoints ,reordering of existing study endpoints, redefinition of study populations and additional descriptive text in section "11.Statistical Analysis", and other updates to text for further description and clarity

Amendment 1

SECTION # & NAME	DESCRIPTION OF CHANGE
Title Page	Removal of the word "episodic" from the study title.
Section 2 Protocol Synopsis Section 4 Study Objectives and Endpoints	Added new secondary efficacy endpoint (Sustained Pain Relief from 2 to 24 hours post treatment)
Section 2 Protocol Synopsis Section 4 Study Objectives and Endpoints	Added definition of success criteria for secondary endpoint on participant's global impression of acute treatment effect
Section 2 Protocol Synopsis Section 4 Study Objectives and Endpoints Section 11.5.2 Secondary Endpoints	Added new exploratory endpoint (Sustained Pain Relief (SPR) from 2 to 48 hours post treatment)
Section 2 Protocol Synopsis Section 11.5.2 Secondary Endpoints	Added Most Bothersome Symptom (MBS) relief immediately post treatment and MBS freedom immediately post treatment as secondary endpoints.
Section 2 Protocol Synopsis Section 11.5.2 Secondary Endpoints	Added freedom from migraine associated symptoms (nausea, photophobia, phonophobia) immediately following treatment completion and at 2 hours post treatment completion as secondary endpoints.
Section 2 Protocol Synopsis	Inclusion criterion 1 updated to increase the upper age limit for participation

SECTION # & NAME	DESCRIPTION OF CHANGE
Section 6.1 Inclusion Criteria Section 5 Study Design	Original text: Age of 18 to 65 years, inclusive, of either sex at birth Revised text: Age of 18 to 70 years, inclusive, of either sex at birth
Section 2 Protocol Synopsis Section 6.1 Inclusion Criteria Section 5 Study Design (Overview)	Inclusion criterion 4 updated to remove the word "episodic," and removed an erroneous word. Original text: Individual has had a diagnosis of episodic migraine with or without aura over for at least 1 year. Revised text: Individual has had a diagnosis of migraine with or without aura for at least 1 year.
Section 2 Protocol Synopsis Section 6.1 Inclusion Criteria	Removed inclusion criterion 6 requiring that "Individual has been prescribed at least one acute treatment (drug or device) for their migraines
Section 2 Protocol Synopsis Section 6.2 Exclusion Criteria	Exclusion criterion 4 updated to add exclusion for sphenopalatine ganglion (SPG) blocks Original text: Participant has received Botox treatment, barbiturates, nerve blocks or trigger point injections in the head or neck within the last 4 weeks of screening. Revised text: Participant has received Botox treatment, barbiturates, SPG block, nerve blocks or trigger point injections in the head or neck within the last 4 weeks of screening.
Section 2 Protocol Synopsis Section 6.2 Exclusion Criteria	Exclusion criterion 17 updated to exclude previous study participation for 3 months prior to screening instead of 6 months. Original text: Prospective participant has participated in a migraine study or any interventional clinical study within the 6 months prior to screening. Revised text: Participation in a migraine study or any interventional clinical study within the 3 months prior to screening.
Section 2 Protocol Synopsis Section 6.2 Exclusion Criteria	Removed exclusion criterion 18 "Participant does not take acute medications to relieve their migraine attacks or symptoms."
Section 5 Study Design (Run-In Procedures)	Corrected the name of the Milliman health data platform
Section 5 Study Design (Randomization Procedures)	Updated qualifying migraine criteria to include types of rescue medications that should not be taken in the 48 hours prior to treatment Original text: Participant did not take any migraine rescue medications in the 48 hours prior to the migraine attack

SECTION # & NAME	DESCRIPTION OF CHANGE
	Revised text: Participant did not take any migraine rescue medications in the 48 hours prior to the migraine attack, such as tripans, NSAIDs, or gepants used for acute treatment.
Section 5 Study Design (Randomization Procedures) Section 9.1 Participant Completion and Withdrawal	Updated number of days that a participant has to treat a qualifying migraine attack with the study device. Original text: Participants will have up to 45 days to complete the treatment session after receiving the device. Revised text: Participants will have up to 35 days to complete the treatment session after receiving the device.
Section 7.1 Study Product Description	Updated the weight of the Mi-Helper device for accuracy Original text: The Mi-Helper device is small and lightweight, weighing 10 lbs. Revised text: The Mi-Helper device is small and lightweight, weighing 7 lbs.
Section 7.3 Study Product Handling, Storage, & Accountability	Added language describing what to do if a subject needs a supply reshipment due to a device technical issue at the end of their 35 day treatment window.
Section 11.2 Randomization	Added language to indicate that randomization will be stratified based on sex at birth.

Amendment 2

SECTION # & NAME	DESCRIPTION OF CHANGE
2. Protocol Synopsis 4. Study Objectives and Endpoints	Addition of the following exploratory endpoints: • Use of rescue medication before 2 hours post treatment completion. • Pain freedom (PF) at immediately post-treatment completion (defined as reduction in headache severity from mild/moderate/severe pain at baseline to no pain immediately after treatment completion). • Freedom from MBS immediately following treatment completion

SECTION # & NAME	DESCRIPTION OF CHANGE
2. Protocol Synopsis 4. Study Objectives and Endpoints	Removal of the Following secondary endpoint: Tolerability of the Mi-Helper device based on percent of subjects to who fail to complete the full treatment session due to discomfort Removal of the fFollowing secondary objective: To assess the tolerability of the Mi-Helper device, based on the percentage of participants who fail to complete a full treatment session
2. Protocol Synopsis 4. Study Objectives and Endpoints	Removal of the following exploratory endpoint: To assess whether blinding was maintained from a participant's perspective Removal of the following exploratory objective: Participants belief of which treatment is received(blinding assessment)
2. Protocol Synopsis 4. Study Objectives and Endpoints 11. Statistical Analysis	Reordering of remaining Secondary and Exploratory Endpoints and Objectives to align with FDA Guidance on Multiplicity of endpoints
1. List of Abbreviations	Addition of PGIC(Patient Global Impression of Change)
2. Protocol Synopsis 6. Study Population	Removal of conditions for Exclusion Criterion 14: Original Text: Participant with severe uncontrolled psychiatric conditions (such as major depressive episode, bipolar disorder, major depressive disorder, schizophrenia), dementia, or significant neurological disorders (other than migraine) that, in the Investigator's opinion, might interfere with study assessments. Revised Text: Participant with severe uncontrolled psychiatric conditions or significant neurological disorders (other than migraine) that, in the Investigator's opinion, might interfere with study assessments.

SECTION # & NAME	DESCRIPTION OF CHANGE
5. Study Design	Addition of clarifying text in overview Original Text: Blinding for this study will be applied to the PI and the study team. Revised Text: Treatment Assignment Blinding for this study will be applied to the PI and the study team.
5. Study Design	Modification of text explaining Run-In Procedures Original Text: If the subject passes the e-Diary, the Study Team will confirm their migraine diagnosis using the Milliman IRIX platform. If diagnosis history cannot be retrieved through IRIX, the participant will have the opportunity to supply evidence of their migraine diagnosis themselves. Revised Text: During the run in period ,the Study Team use the Milliman IRIX platform to confirm a diagnosis of migraine and review additional eligibility criteria.... If the subject is unable to provide evidence of diagnosis, they will be unable to continue in the study.
5. Study design	Modification of Descriptive text explaining randomization procedures to include investigator review: Original text: Once a participant meets all eligibility criteria they will be randomized, and the device shipment will occur thereafter. Participants will need to watch a video on how to set-up and use the Mi-Helper device. Once the training is completed, the participant will be able to review the study training video at any time within the Study App. Revised Text: If the participant's migraine e-diary and diagnosis confirmation are sufficient for enrollment, the virtual study team will conduct the end of run in call to review information submitted during screening and run-in period. The participant record will then be reviewed by an Investigator and, if eligible, will be randomized; the device shipment will occur thereafter. When the device kit is received, the participant will need to watch a series of videos on how to set-up and use the Mi-Helper device. Once the training is completed, they will complete a

SECTION # & NAME	DESCRIPTION OF CHANGE
	comprehension quiz. The participant will be able to review the study training video at any time within the Study App.
10. Data management 10.1 Data collection	Additional Clarifying language added Original text: All data points except flow rate will be entered into the ClinicalOne EDC. Revised Text: . All data points except flow rate will be entered into the ClinicalOne EDC by an unblinded study team member.
10.2 Data Handling	Removal of WHO drug coding Original text: AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA).) and any concomitant medications terms (if applicable) using a validated medication dictionary, WHODrug. Revised text: AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA).
11. Statistical Analysis 11.2 Randomization	Updated text to indicate that randomization will be stratified by gender instead of sex at birth Original Text: Subjects will be randomized in a 1:1 fashion, with stratification for sex at birth . Revised Text: Subjects will be randomized in a 1:1 fashion, with stratification for gender.
11.3 Populations for analyses	Removal of Safety Population and Modification to Per Protocol(PP) Population: Original Text: **Per Protocol (PP) Population** – all randomized participants who do not have a major protocol deviation related to primary endpoint(s) and complete the treatment in compliance with the protocol, with group assignment as treated, and have no use of rescue medication within 2 hours post treatment who complete the primary endpoint(s) within the protocol-specified window, have completed full administration of treatment according to device data or subject reported completion of treatment if device data is not available, whose devices demonstrate adequate randomization (i.e. flow rate matches designated treatment group per randomization

SECTION # & NAME	DESCRIPTION OF CHANGE
	schema), have no use of rescue medication within 2 hours prior to treatment, and have no use of rescue medication within 2 hours post treatment. Revised Text: **Per Protocol (PP) Population** – all participants in the mITT population who do not have a major protocol deviation related to primary endpoint and complete the treatment in compliance with the protocol, with group assignment as treated, and have no use of rescue medication within 2 hours post treatment.
11.3 Populations for Analyses	Modified populations for safety, efficacy, and sensitivity analyses Original Text: Primary efficacy analyses will be performed on the mITT and PP Populations. Secondary and exploratory analyses will be performed on the mITT population. Safety analyses will be performed on the safety population Revised Text: The ITT analysis set will serve as the main analysis set for all safety evaluations. The mITT analysis set will be the primary population used for efficacy analyses in this study. The primary and secondary efficacy assessments will also be performed on the PP and the ITT analysis sets as a sensitivity analysis

Contents

1. List of Abbreviations

TERM	DEFINITION
AE	Adverse Event
ANOVA	Analysis of Variance
app	Application
CFR	Code of Federal Regulations
CPM	Clinical Project Manager
CRPS	Complex Regional Pain Syndrome
DMS	Data Management System
EC	Ethics Committee
ED	Emergency department
EDC	Electronic Data Capture
eCRF	Electronic Case Report Forms
eIC	Electronic Informed Consent
ePRO	Electronic Patient Reported Outcomes
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council of Harmonization
IRB	Institutional Review Board
ITT	Intention-To-Treat
lbs	Pounds
LPM	Liters per minute
MBS	Most bothersome symptom
MedDRA	Medical Dictionary for Regulatory Activities
NIH	National Institutes of Health
NSAID	Non-steroidal anti-inflammatory drugs
NSR	Non-Significant Risk
OTC	Over the counter
PF	Pain Freedom
PGIC	Patient Global Impression of Change
PI	Principal Investigator
PP	Per Protocol

PR	Pain Relief
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SPF	Sustained Pain Freedom
SPR	Sustained Pain Relief
SPG	Sphenopalatine ganglion
USA	United States of America
VRS	Verbal Rating Scale
WHO	World Health Organization
woRM	without Rescue Medication

2. Protocol Synopsis

Title	A prospective, double-blind, sham-controlled, randomized clinical trial to assess the safety and efficacy of the Mi-Helper Device for acute treatment of migraine in an at home setting.
Short Title	Cooling to Alleviate Migraine #3 (CALM-3)
Clinical Study Type	Non-Significant Risk (NSR) Device Study
Product Name	Mi-Helper Device
Study Duration	~7 months
Country of Implementation	USA
Description of Sites	One decentralized site
Study Objectives	**Primary Objectives:** • To determine the safety and efficacy of one dose of Mi-Helper therapy compared to sham for the acute treatment of a single migraine attack. **Secondary Objectives:** • To assess the tolerability of the Mi-Helper device, based on the percentage of participants who fail to complete the full treatment session. • To assess sustained pain freedom between 2 and 24 hours post treatment completion without the use of rescue medication.

	• To determine the proportion of participants reporting pain relief after Mi-Helper therapy without the use of rescue medication. • To determine the effect of Mi-Helper therapy on the most bothersome symptom (MBS) other than headache post treatment completion. **Exploratory Objectives:** • To explore the use of rescue medication following a single therapeutic treatment. • To assess whether blinding was maintained from a participant's perspective. • To assess sustained pain freedom and sustained pain relief from 2 to 48 hours post treatment completion without the use of rescue medication.
Study Endpoints	**Primary Efficacy Endpoint** • Pain freedom (PF) at 2 hours post-treatment completion (defined as reduction in headache severity from mild/moderate/severe pain at baseline to no pain at 2 hours after treatment completion). Use of rescue medication prior to 2 hours post treatment completion will be considered a failure for this endpoint (i.e. patient will be assigned the status of no reduction). **Safety Endpoint** • Safety of the Mi-Helper device following study treatment, measured by the incidence of adverse events related to the study device for 48 hours post treatment completion. **Secondary Efficacy Endpoints** • Freedom from MBS at 2 hours post-treatment completion • Sustained Pain Freedom (SPF) from 2 to 24 hours after treatment completion (defined as pain freedom with no administration of rescue medication and with no recurrence of a mild/moderate/severe headache). • Pain relief (PR) at 2 hours post-treatment completion (defined as the reduction of severe or moderate pain at baseline to mild or no pain at 2 hours post treatment completion, or from mild pain at baseline to no pain at 2 hours after treatment completion). • Participants' global impression of acute treatment effect, as measured by the Patient Global Impression of Change (PGIC), which utilizes a 7-point scale, where 1=very much improved to 7=very much worse. A score of 1 or 2 will be considered a success.

	Exploratory Endpoints • Use of rescue medication before 2 hours post treatment completion. • Pain relief immediately post treatment completion (defined as the reduction of severe or moderate pain at baseline to mild or no pain, or from mild pain at baseline to no pain immediately post treatment completion). • Sustained pain freedom (SPF) from 2 to 48 hours after the initial dose (defined as pain freedom with no administration of either rescue medication and with no recurrence of a mild/moderate/severe headache). • Use of rescue medication between 2-48 hours post-treatment completion. • Relief from MBS immediately following treatment completion and at 2 hours post-treatment completion (defined as severe or moderate at baseline to mild or none, or from mild at baseline to none). MBS may be nausea, photophobia, or phonophobia as defined by each participant at baseline. • Freedom from migraine associated symptoms (nausea, photophobia, and phonophobia) immediately following treatment completion and at 2 hours post-treatment completion.
Study Population	Male and Female participants, 18 to 70 years of age, inclusive, who have had a diagnosis of migraine (with or without aura) for at least 1 year will be invited to participate in this study. Approximately 156 English-speaking participants will be recruited for this study.
Participant Duration	Participants will each receive a single treatment (active or sham [control]) and will be required to complete post-treatment assessments at scheduled timepoints.
Description of Study Intervention	The Mi-Helper Neuromodulation Device is intended for acute treatment of migraine, with or without aura, in adults. Mi-Helper has been designed for use in an at-home setting whenever the afflicted individual feels the onset of migraine-related head pain. The device delivers a controlled stream of dehumidified air into the nose. The air is mixed with a fine saline mist for added comfort and cooling efficiency. The device is lightweight and low-cost with an integrated hand-held nebulizer.
Study Implementation	Digital and social media advertisements approved by the Institutional Review Board (IRB) will be used to recruit participants. Participants who

	complete the pre-screening questionnaire and are eligible to take part in the study will be sent a link via email to download the study app and complete the registration process. Adult participants who download the study app to their personal mobile smartphone devices and provide electronic Informed Consent (eIC) will be enrolled and randomized, if eligible. eIC will include acknowledgement that the participant will be using the supplied device for one treatment only and that they agree to return the device and associated equipment shortly after its use. A total of 156 participants will be randomized equally between two groups: • Group I (active treatment): 10 Liters per minute (LPM), dehumidified air, 15 minutes total • Group II (sham [control] treatment): 2 LPM, ambient air administered intermittently via Mi-Helper, 15 minutes total After randomization, the Mi-Helper device will be shipped to the participant's address. Participants will need to confirm receipt of the device through the study app prior to continuing in the study. Participants will receive training on how to set up and use the Mi-Helper device and associated supplies, and appropriately complete all study-related procedures, including completion of the migraine eDiary. The training will also instruct the participants that the device may only be used 'once' during a qualifying migraine attack. A qualifying migraine attack must meet the following criteria based on responses to the Baseline Questionnaire: • Migraine head pain is at least mild intensity (score of 1, 2, or 3 on the 4-point VRS) • Onset of migraine head pain was no more than one hour prior to treatment • Participant did not wake up with the migraine attack • Participant is not experiencing severe sinus congestion • Participant did not have migraine related pain in the 48 hours prior to the migraine attack • Participant did not take any migraine rescue medications in the 48 hours prior to the migraine attack
Inclusion Criteria	Individuals must meet all the following criteria to be eligible to participate in the study: 1. Age of 18 to 70 years, inclusive, of either sex at birth. 2. Lives in the contiguous United States.

	3. Self-reported to be able to read and understand English sufficiently to provide electronic Informed Consent. 4. Documented Diagnosis of migraine with or without aura for at least 1 year. 5. Individual experiences 2 to 8 migraine attacks per month documented via migraine eDiary during screening. 6. Migraine onset before 50 years of age, self-reported during screening. 7. Migraine preventive medication unchanged for 4 weeks prior to study enrollment. 8. Stated willingness to comply with all study procedures and availability for the duration of the study. 9. Individuals that own a functioning smartphone device, internet connection (Wi-Fi or data plan) and are willing to download the study app.
Exclusion Criteria	Individuals that meet any one of the following criteria will be excluded from the study: 1. Participant has difficulty distinguishing his or her migraine attacks from other types of headaches such as tension, exertion, cluster, hormonal or sinus headaches. 2. Participant has 15 or more headache days per month reported via migraine eDiary and during screening. 3. Participant using any opioid medication at the time of screening. 4. Participant has received Botox treatment, barbiturates, SPG block, nerve blocks or trigger point injections in the head or neck within the last 4 weeks of screening. 5. Participant lives at an altitude of 2000 meters or more above sea level. 6. Self-reported intolerance to intranasal therapy. 7. Self-reported recurrent epistaxis or chronic rhinosinusitis. 8. Self-reported sinus or intranasal surgery within the last 4 months of screening. 9. Self-reported history of 'complicated migraine or headaches' (i.e., hemiplegic migraine, ophthalmoplegic migraine, migrainous infarction, basilar migraine, post-traumatic headaches, post-concussion syndrome). 10. Known or suspected pregnancy as self-reported by the prospective participant at the time of screening. 11. Prospective participant unable to fully understand the consent process and provide informed consent due to either language barriers or mental capacity. 12. Self-reported diagnosis of alcohol or substance abuse disorder at the time of screening.

	13. Participant with active chronic pain syndromes, such as fibromyalgia, chronic pelvic pain, or Complex Regional Pain Syndrome (CRPS); or other pain syndrome like trigeminal neuralgia. 14. Participant with uncontrolled or severe psychiatric conditions or significant neurological disorders (other than migraine) that, in the Investigator's opinion, might interfere with study assessments. 15. Failure to adhere to or inability to complete Study App inputs and onboarding activities during the screening period. Participants who are not adherent during the screening period are not eligible for study entry. 16. Participation in a previous clinical study with the Mi-Helper device. 17. Participation in a migraine study or any other interventional clinical study within the 3 months prior to screening. 18. Participant has an uncontrolled medical issue at the time of screening. 19. Any condition for which transnasal air flow would be contraindicated, as determined by the Principal Investigator (PI).

2.1 Table 1: Schedule of Events

Study Phase	PRE-SCREENING	INFORMED CONSENT PROCEDURES	SCREENING PROCEDURES	RUN-IN PROCEDURES	RANDOMIZATION PROCEDURES	BASELINE PROCEDURES	TREATMENT PROCEDURES					END OF STUDY
							ADMINISTER TREATMENT (Day 0)	Post-treatment (0 hours) *+ 30 minutes*	Post-treatment (2 hours) *± 30 minutes*	Post-treatment (24 hours) *± 1 hour*	Post-treatment (48 hours) *± 2 hours*	
Event/Timeline		**~3 weeks**	**~1 week**	**~6 weeks**	**~1 week**	**Day 0**		**Day 0**	**Day 0**	**Day 1**	**Day 2**	
Pre-screening questionnaire	X											
Electronic Informed Consent		X										
Screening questionnaire			X									
Medical History & Demographics			X									
Concomitant medications review[1]			X					X				
Eligibility assessment			X	X[1]								
Training				X[2]	X[3]							
Migraine run-in eDiary (28 days)				X								
Participant check-in				X								
Eligibility confirmation				X								
Randomization					X							
Device shipment					X							
Head pain severity score[3,4]						X		X	X	X	X	
Most Bothersome Symptom[3,4]						X		X	X	X	X	
Nausea severity score[3,4]						X		X	X	X	X	

Photosensitivity severity score[3,4]						X		X	X	X	X		
Phonosensitivity severity score[3,4]						X		X	X	X	X		
Rescue medication use[4,5]								X	X	X	X		
Adverse Event review and evaluation						X		X					
Device tolerability and user experience questionnaire									X	X[6]			
Return of test article													X

[1]Eligibility Confirmation will include review of relevant medical records to confirm diagnosis of migraine in participants who pass the E-Diary.
[2]Training will cover how to complete the migraine eDiary.
[3]Training will cover set-up and use of the Mi-Helper Device.
[4]Based on a 4-point Verbal Rating Scale (VRS).
[5]Participants will be advised against using rescue medication until collection of the Migraine Symptom Questionnaire at 2 hours post-treatment, however, the use of rescue medication prior to 2 hours post-treatment will be captured as a treatment failure, and will be assigned a status of no reduction
[6]Select user experience questions will be repeated as a part of 24-hour post-treatment assessment.

3. Introduction and Background

3.1 Study Rationale

Migraine is a severely disabling neurologic condition and is the sixth most disabling disorder worldwide, affecting over a billion people. The majority of those with migraines experience them episodically, defined as less than 15 migraine days per month. Migraine can cause a significant reduction in quality of life as well as loss of productivity. The global economic burden of migraine is staggering at approximately $20 billion in the U.S. and $56 billion worldwide per year.

Migraine affects significantly more women than men and is the leading cause of disability in people under fifty (Steiner, 2018). First-line treatment options are medications such as triptans and NSAIDs, which are associated with adverse effects, are contraindicated in those with cardiovascular issues, and put patients at risk for medication-overuse headache. In addition, more than 50% of people with chronic migraine discontinue or change their preventive treatment at some point due to its lack of efficacy or tolerability (Ford, 2017). Neuromodulation therapies that target the autonomic nervous system are gaining traction due to their safety profile and relative effectiveness.

The prevalence of migraine in the U.S. is increasing, with 15% of the population suffering from either episodic or chronic migraine. Migraine is one of the most common reasons for emergency room visits. Despite treatment recommendations, opioids are still overprescribed for migraine patients. This is especially the case in emergency departments (EDs) where one study found that opioids are prescribed at over 50% of migraine ED visits (Minen, 2014). It is apparent that this phenomenon is contributing significantly to the growing opioid epidemic. The use of opioids in this population carries a high risk of 'medication-overuse-headache', when used more than 10 times/month, and can quickly lead to opioid dependency (Bigal, 2008). Medication overuse is also the most common reason why episodic migraine transforms into chronic migraine. There is a need for non-invasive, drug-free therapies that can be administered quickly and in the comfort of one's home.

The pathophysiology of migraine is complex, not fully understood, and not within the scope of this study. There is evidence that the headache phase of migraine is caused by activation of nociceptors in the trigeminal ganglion (Puledda, 2017). The sphenopalatine ganglion (SPG), a large ganglion located behind the superior nasal turbinate, is closely associated with the trigeminal system (Robbins, 2016). Several studies have shown that intranasal SPG nerve block with lidocaine provides relief from acute migraine headaches (Maizels, 1999; Kudrow, 1995; Binfallah, 2018). Another possible mechanism is stimulation through the nasal cerebral pathway via olfactory epithelium. The Mi-Helper transnasal cooling device has the potential, using a simple non-invasive transnasal evaporative cooling process, to activate these (or other) mechanisms, providing pain and symptom relief reduction in patients with migraine.

The Mi-Helper device is a portable, transnasal in-home therapy that uses transnasal low flow dry air to cause local cooling of the nasopharynx due to evaporation of nasal mucosal water. The device also delivers a continuous mist of saline into the nose to aid in the evaporative cooling process, prevent nasal turbinate desiccation, and minimize discomfort to the patient. The hypothesis is that optimized transnasal cooling delivered through the Mi-Helper device will reduce the intensity of migraine headaches during an acute episode. More detail can be found in the Mi-Helper Investigator Brochure.

This study evaluates the safety and efficacy of the Mi-Helper device for acute treatment of migraine in an at home setting.

3.2 Background

Mi-Helper Device

The Mi-Helper device is a non-invasive, drug-free, novel therapy that uses a patented process of dry air flow across the nasal turbinates to induce a phase change (evaporation) that extracts energy (thermodynamics) causing local cooling which modulates nerves associated with pain and other symptoms of migraine. The device delivers a controlled pressure and flow of dry room temperature air along with a nebulized saline mist for added comfort and evaporative efficiency.

The Mi-Helper device works by cooling and inhibiting structures of the pterygopalatine fossa, including the sphenopalatine ganglion (SPG) and maxillary division of the trigeminal nerve (V2). These nerve pathways have a clinically proven association with migraine pain and other symptoms (Arslan et al, 2014; Kesserwani, 2021; Urits et al, 2020).

Migraine prototype study

A single-blind, randomized trial was conducted at the Johns Hopkins Bayview Hospital headache clinic in Baltimore, MD, to study potential therapies for migraine, centered on evaporative cooling (Shah, 2021). This study evaluated the safety and efficacy of four potential therapies consisting of different air mixtures flowing in the nose and out the mouth: (1) a flow of dry oxygen, (2) a flow of dry air, (3) a flow of humidified oxygen, and (4) a flow of humidified air (control). All four gases were warmed to 37°C and delivered through a face mask (not the Mi-helper device) with the study gases flowing in the nose and freely out of the mouth. The participants were awake and otherwise healthy, excluding their migraine symptoms. The objective of the study was to assess safety and the ability to reduce symptoms from migraine.

Fifty-one (51) patients were enrolled in the study, of which 13 patients (mean age 49 years, 81% female) received humidified oxygen therapy and 9 patients (mean age 42 years, 82% female) received dry air therapy. Patients were randomized and blinded to their treatment group. There was significant pain relief at 2 hours post-treatment compared to baseline reported by patients who received dry air, dry oxygen, and humidified oxygen. Patients in the control group did not show significant pain relief from baseline to 2 hours post-treatment.

A two-way ANOVA was conducted to examine the effect of gas type and moisture content in reducing headache symptoms in migraine (pain score reduction). There was a statistically significant interaction between the effects of gas type and moisture content on the headache score reduction, $F(1,47) = 10.471$, $p = 0.002$. Simple main effects analysis showed that there were no significant differences between dry oxygen and dry air ($p = 0.906$), but there were statistically significant differences between these gases when they were humidified ($p < 0.001$).

No adverse events were reported in this study. It was concluded that high flow dry air is safe and appears to be effective in treating acute migraine pain and associated symptoms.

Migraine dose escalation study

A dose escalation and tolerability study was completed using the CoolStat device, a predecessor to the Mi-Helper that was designed for in-clinic use, at the Johns Hopkins Bayview Hospital headache clinic in Baltimore, MD. Fifteen (15) participants experiencing migraine on the day of treatment were enrolled. Three air flow rates were tested, and tolerability and efficacy were assessed for increasing air flow rates: 24 LPM, 36 LPM and 48 LPM. Five (5) participants were tested at each flow rate, starting at the lowest flow rate (24 LPM). If the majority (3/5) of the participants in the lowest flow rate group tolerated the full 10-minute treatment, the next group would receive an incrementally higher flow rate. Air flow was delivered using a double nostril, nasal mask configuration.

All the flow rates were found to be tolerable by study participants, with 13 of the 15 participants tolerating the full 10-minute treatment session. Although anecdotal (due to the small size of the study), participants also reported reductions in migraine symptoms, which appear to be related to flow, i.e., migraine symptoms reduced more with increased flow rates. 73% of the 15 participants experienced pain relief immediately after treatment compared to baseline and 53% of participants reported sustained pain relief at 2 hours post-treatment. 67% of participants reported that the benefit of the CoolStat treatment outweighed any discomfort they experienced during the treatment session and 73% said they would use the device again. 60% of participants said that CoolStat works as well or better than their current rescue medication. The adverse events that occurred were all graded as mild and anticipated (stuffy nose, burning sensation during treatment session) and resolved on their own. There were no serious adverse events or unanticipated device effects. This study demonstrated that the CoolStat is safe and tolerable for use in patients with acute migraine attacks.

Migraine in-clinic, double-blind, RCT

A multi-center, double-blind, randomized study was conducted using the CoolStat device, a predecessor of the Mi-Helper designed for in-clinic use. The objectives of this study were to assess safety, tolerability, and determine the optimal dose of dehumidified, room temperature air for the acute treatment of migraine with or without aura. The primary endpoint was pain relief at 2 hours post-treatment. Secondary endpoints included tolerability, Most Bothersome Symptom (MBS) relief and pain freedom at 2 hours post-treatment. Participants were treated

at Atrium Health in Charlotte, NC, Mayo Clinic in Scottsdale, AZ, and Michigan State University in East Lansing, MI.

Eighty-seven (87) participants were enrolled in this study and were instructed to return to the clinic when experiencing a migraine attack. Twenty-four (24) participants returned to the clinic and were randomized to flow rates of either 6 liters per minute (LPM), 18 LPM or 24 LPM. Participants were randomized in a 1:1:1 fashion. The length of treatment was 15 minutes. Air flow was delivered through a single nostril tube set configuration with a nebulizer that administered saline mist into the nasal turbinates.

Eighty-eight percent of the 6 LPM group reported pain relief at 2 hours without rescue medication (woRM). 44% of the 6 LPM group reported pain freedom at 2 hours woRM. PR at 2 hours woRM was reported by 44% and 50% in the 18 LPM and 24 LPM group, respectively. MBS relief was reported at 2 hours by 77% in the 6 LPM group. MBS relief at 2 hours was reported by 66% and 50% of the 18 LPM and 24 LPM groups, respectively. There were no adverse events in the 6 LPM group. No adverse events reported in the 18 LPM or 24 LPM groups were serious or severe. 11% of the 6 LPM group reported moderate intra-nasal discomfort during treatment. 33% percent and 83% of participants in the 18 LPM and 24 LPM groups, respectively, reported moderate or severe discomfort during treatment. There were no serious adverse events or unanticipated device adverse events. All adverse events reported in the study were anticipated and were graded as mild or moderate. No adverse events occurred in the 6 LPM group. The study was terminated due to insufficient participant accrual rate. This study demonstrated that transnasal cooling at lower flow rates is effective and tolerable for treating acute migraine attacks.

Decentralized randomized, double-blind, sham-controlled dosing study with Mi-Helper

A prospective, double-blind, sham-controlled, decentralized, randomized dosing study was conducted to evaluate the efficacy and safety of the Mi-Helper device in adult patients 18 to 65 years of age with episodic migraine with or without aura. The study, deemed Non-significant Risk (NSR) by the Sterling Institutional Review Board, aimed to determine the most effective dose of Mi-Helper compared to sham treatment. The study included a 4-week e-diary run-in period for participant eligibility confirmation and compliance with protocol before randomization.

A total of 172 participants were randomized to one of four treatment arms: three active arms with flow rates of 4, 6, and 10 LPM, and a sham arm. The primary endpoints were pain relief at 2 hours post-treatment, safety (incidence of adverse events), and tolerability (completion of the full treatment session). The safety population included 137 participants, the modified intent-to-treat (mITT) population included 128, and the per protocol (PP) population, which required full treatment compliance, included 74 participants.

The study found that the 10 LPM dose was the most effective, with 71% of participants reporting pain relief at 2 hours post-treatment without the use of rescue medication, and 47% achieving complete pain freedom, compared to only 16% achieving pain freedom in the sham

group (p=0.0407). This statistically significant difference in pain freedom between the 10 LPM and sham groups supports further study of the winning Mi-Helper dose. A blinding index confirmed successful blinding across all study arms, including the sham group.

At 24 hours post-treatment, 88% of participants in the 10 LPM group remained pain-free, with all but one subject maintaining pain freedom without rescue medication. No serious or unanticipated adverse device events were reported, and no participants discontinued treatment due to discomfort.

Overall, 82% of participants indicated they would use the Mi-Helper device again outside the study, 53% felt the device worked as well or better than their current rescue medications, and 100% rated the setup and use of the device as "very easy" or "easy."

The study demonstrated that, of those who received a study intervention, the 10 LPM dose of Mi-Helper is the most effective for acute migraine treatment and is safe, well-tolerated, and easy to use, providing strong support for further clinical trials.

This study aims to evaluate the safety and efficacy of the Mi-Helper device for acute treatment of a single migraine attack in an at home setting.

3.3 Risk/Benefit Assessment

3.3.1 Known Potential Risks

Anticipated risks associated with the Mi-Helper device are temporary nasal discomfort, dry nose or mouth, and runny nose during device use. These risks are considered minimal, transient, and likely to resolve on their own.

Participants will be trained in how to use the device. Any potential risks from incorrect use have been mitigated as per the User Failure Modes Analysis in accordance with the ISO 14971 risk management process implemented by the Sponsor.

Monitoring of study participants will provide scrutiny for unexpected outcomes and adverse effects.

3.3.2 Known Potential Benefits

Transnasal neuromodulation therapy may reduce migraine pain and associated symptoms in people with acute migraine. The set-up and use of the Mi-Helper device is relatively simple, and the treatment provided is drug-free. Using the device for 15 minutes is expected to provide targeted relief from migraine symptoms.

3.3.3 Assessment of Potential Risks and Benefits

The risks to participants in this study are considered minimal. Participants will be awake and healthy and may stop the treatment session at any time simply by moving the handheld nebulizer away from their nose. The duration of the treatment is only 15 minutes.

This is an investigational study which does not guarantee any direct benefit to the participants, but the proposed treatment may provide some relief of pain and symptoms of acute migraine. In the near term, this study may show the benefit of using a new device, the Mi-Helper, in an at-home setting, for treating migraine pain and associated symptoms using only a flow of dry, ambient air. These potential benefits are considered to outweigh the minimal risk associated with participation in this study.

Participants will be advised of the potential risks and benefits associated with this study in the IRB approved ICF.

4. Study Objectives and Endpoints

OBJECTIVES	ENDPOINTS
Primary	
To determine the safety and efficacy of one dose of Mi-Helper therapy compared to sham for the acute treatment of a single migraine attack.	Primary Efficacy Endpoint Pain freedom (PF) at 2 hours post-treatment completion (defined as reduction in headache severity from mild/moderate/severe pain at baseline to no pain at 2 hours after treatment completion). Use of rescue medication prior to 2 hours post treatment completion will be considered a failure for this endpoint (i.e. patient will be assigned the status of no reduction). Safety Endpoint Safety of the Mi-Helper device following study treatment, measured by the incidence of adverse events related to the study device for 48 hours post treatment completion

Secondary	
• To determine the effect of Mi-Helper therapy on the most bothersome symptom (MBS) other than headache post treatment completion. • To assess sustained pain freedom and sustained pain relief from 2 to 24 hours post treatment completion without the use of rescue medication • To determine the proportion of participants reporting pain relief after Mi-Helper therapy without the use of rescue medication.	• Freedom from MBS at 2 hours post treatment completion • Sustained Pain Freedom (SPF) from 2 to 24 hours after treatment completion (defined as pain freedom with no administration of rescue medication and with no recurrence of a mild/moderate/severe headache). • Pain relief (PR) at 2 hours post-treatment completion (defined as the reduction of severe or moderate pain at baseline to mild or no pain, or from mild pain at baseline to no pain at 2 hours post treatment completion). • Participants' global impression of acute treatment effect, as measured by the Patient Global Impression of Change(PGIC), on which participants use a 7 point scale, where 1=very much improved to 7=very much worse. Scores of 1 or 2 will be considered successes.
Exploratory	
• To explore the use of rescue medication following a single therapeutic treatment • To assess sustained pain freedom and sustained pain relief from 2 to 48 hours post treatment completion without the use of rescue medication	• Use of rescue medication before 2 hours post treatment completion. • Pain relief immediately post treatment completion (defined as the reduction of severe or moderate pain at baseline to mild or no pain, or from mild pain at baseline to no pain immediately post treatment completion). • Sustained pain freedom (SPF) from 2 to 48 hours after the initial dose (defined as pain freedom with no administration of either rescue medication and with no recurrence of a mild/moderate/severe headache). • Use of rescue medication 2–48 post-treatment completion. • Relief from MBS immediately following treatment completion and at 2 hours post-treatment completion (from severe or moderate to mild or none, or from mild to none). MBS may be nausea, photophobia, or phonophobia as defined by each participant at baseline. • Freedom from migraine associated symptoms (nausea, photophobia, and phonophobia) immediately following treatment completion and at 2 hours post-treatment completion.

5. Study Design

Overview

This is a prospective, double-blind, sham-controlled, randomized clinical trial. This study aims to assess the efficacy and safety of the Mi-Helper transnasal neuromodulation device for acute treatment of migraine in an at home setting.

Treatment Assignment Blinding for this study will be applied to the PI and the study team. The team members who are directly involved in the analysis of the study results, including the biostatistician, will also be blinded. Only the designated group of team members directly involved in overseeing the logistical and distribution aspects of the study products will be unblinded. As needed, the PI may be unblinded in case of an AE/SAE that may impact participant safety. If the unblinding occurs inadvertently or through PI's need due to an AE/SAE impacting participant safety, that event will be noted as a protocol deviation.

Adults aged 18 years to 70 years old ,inclusive, with a diagnosis of migraine (with or without aura) for at least one year will be recruited for this study.

Recruitment & Pre-screening

Digital and social media advertisements approved by the IRB will be used to recruit eligible participants. Participants that respond to the ad, complete the pre-screening questionnaire, and meet the study's eligibility criteria will be sent a link via email to download the Study App and complete the registration process.

Informed Consent Procedures (~3 weeks)

Adult participants that download the Study App to their personal mobile smartphone devices, complete the registration process, and provide eIC will be enrolled, if eligible. The informed consent process will include a Health Insurance Portability and Accountability Act (HIPAA) Authorization form to allow the Study Team to obtain medical records documenting the subject's diagnosis of migraine. If the subject does not agree to provide HIPAA authorization, they will be exited from the study.

Screening Procedures (~1 week)

After signing the informed consent, participants will be required to complete a screening questionnaire, medical history form, concomitant medications form, and demographic information. Participants that meet the eligibility criteria will then enter the run-in period.

Run-in Procedures (~6 weeks)

During run-in, each participant will need to complete a training on how to complete the eDiary. Training will also include a comprehension quiz to ensure participants understanding. Once participants complete the training and the comprehension quiz, they will be required to complete the migraine eDiary over a period of 28 days to assess eligibility.

During the run in period, the Study Team use the Milliman IRIX platform to confirm a diagnosis of migraine and review additional eligibility criteria. If diagnosis history cannot be retrieved through IRIX, the participant will have the opportunity to supply evidence of their migraine diagnosis themselves. If the subject is unable to provide evidence of diagnosis, they will be unable to continue in the study.

After

Randomization Procedures (~1 week)

If the participant's migraine e-diary and diagnosis confirmation are sufficient for enrollment, the virtual study team will conduct the end of run in call to review information submitted during screening and run-in period. The participant record will then be reviewed by an Investigator and, if eligible, will be randomized; the device shipment will occur thereafter.

When the device kit is received, the participant will need to watch a series of videos on how to set-up and use the Mi-Helper device. Once the training is completed, they will complete a comprehension quiz. The participant will be able to review the study training video at any time within the Study App.

A total of 156 participants will be randomized equally to one of two groups:

- Group I (active treatment): 10 LPM, dehumidified air, 15 minutes total
- Group II (sham [control] treatment): 2 LPM, ambient air administered intermittently via Mi-Helper, 15 minutes total

Upon receipt of the Mi-Helper device, the participant will be instructed to store the shipment at room temperature and to not open the desiccant cartridge and tube set prior to use. The training will also instruct the participants that the device may only be used 'once', during a qualifying migraine attack. A qualifying migraine attack must meet the following criteria based on responses to the Baseline Questionnaire:

- Migraine head pain is at least mild intensity (score of 1=mild, 2=moderate, or 3=severe on the 4-point VRS).
- Onset of migraine head pain was no more than one hour prior to treatment.
- Participant did not wake up with the migraine attack.
- Participant is not experiencing severe sinus congestion.
- Participant did not have migraine related pain in the 48 hours prior to the migraine attack.
- Participant did not take any migraine rescue medications in the 48 hours prior to the migraine attack, such as triptans, NSAIDs, or gepants used for acute treatment.

The participant may reach out to the study team via the Study App, email, or phone to address any questions they have about any study-related procedures.

Participants will have up to 35 days to complete the treatment session after receiving the device.

Baseline Procedures (pre-treatment)

Baseline assessments will be initiated at the onset of a migraine attack. Baseline assessments will include questions about the participant's head pain, nausea, photosensitivity, phonosensitivity, and the most bothersome symptom (MBS) which will be recorded within the Study App prior to treatment initiation.

Treatment Procedures (48 hours)

Participants will be instructed to use the Mi-Helper device once their migraine head pain has reached at least mild intensity. This will be determined by their response to the question about their head pain within the Study App. Participants will be instructed to use the Mi-Helper within 1 hour from the time of migraine head pain onset.

Once the migraine headache score is recorded as being mild to severe (score of 1 to 3 recorded on the 4-point VRS scale) and the participant has confirmed that they have not used any acute migraine medications in the last 48 hours, the Study App will instruct the participant to initiate treatment with the Mi-Helper device and dose treatment (active or sham) for a total of 15 minutes based on their group allocation. Participants will be advised against using any rescue medication until collection of the Migraine Symptom Questionnaire at 2 hours post-treatment with the Mi-Helper device. However, if participants do need to administer rescue treatment after administering treatment with Mi-Helper, they will need to report this using the 'Rescue Medication Form' within the Study App. Use of rescue medication within 2 hours of treatment will be considered a treatment failure. In the instance that abortive treatments have been used 48-hours prior to the start of treatment or the time of onset of migraine head pain exceeds 1 hour, the participant will need to wait until their next migraine episode of at least mild intensity, to use the device.

Participants will be instructed that they may stop treatment if they are unable to tolerate it by moving the nebulizer away from their nose, and report this within the Study App.

Participants will be required to respond to questions about their head pain, nausea, photosensitivity, phonosensitivity, and the most bothersome symptom (MBS) within the Study App immediately post-treatment and then at 2 hours, 24 hours and 48 hours post-treatment.

At 2 hours post-treatment, participants will also be required to respond to questions about the device tolerability and user experience questionnaire. Select user experience questions will be repeated in the 24-hour assessment.

Participants can report any changes in their health through the Study App while participating in this study.

If migraine symptoms have not resolved, participants will be able to use rescue medication between the 2-to-48-hour period after using the device. Participants will be instructed to report rescue medication use in the 'Rescue Medication Form' within the Study App. This form will be

available for participant use during the entire post-treatment period through the Study App and will not be timepoint bound.

End of Study Procedures

All participants will receive a single treatment with the Mi-Helper device. After completing the 24-hour assessment, they will be prompted to return the device body utilizing the packaging and prepaid shipping labels provided within the original device shipment.

Participation in the study will be complete once the participant completes the 48-hour questionnaire and returns their device.

6. Study Population

Participants need to meet the following eligibility criteria to be considered for enrollment in this study.

6.1 Inclusion Criteria

To be eligible for participation in this study, a participant must meet all the following criteria:

1. Age of 18 to 70 years, inclusive, of either sex at birth.
2. Lives in the contiguous United States.
3. Self-reported to be able to read and understand English sufficiently to provide informed consent.
4. Individual has had a diagnosis of migraine with or without aura for at least 1 year.
5. Experiences 2 to 8 migraine attacks per month documented via migraine eDiary during screening.
6. Migraine onset before 50 years of age, self-reported during screening.
7. Migraine preventive medication unchanged for 4 weeks prior to study enrollment.
8. Stated willingness to comply with all study procedures and availability for the duration of the study.
9. Individual owns a functioning smartphone device, internet connection (Wi-Fi or data plan) and are willing to download the Study App

6.2 Exclusion Criteria

A participant who meets any of the following criteria will be excluded from participation in the study:

1. Participant has difficulty distinguishing his or her migraine attacks from other types of headaches such as tension, exertion, cluster, hormonal or sinus headaches.
2. Participant has 15 or more headache days per month reported via migraine eDiary and during screening.
3. Participant using any opioid medication at the time of screening.
4. Participant has received Botox treatment, barbiturates, SPG block, nerve blocks or trigger point injections in the head or neck within the last 4 weeks of screening.

5. Participant lives at an altitude of 2000 meters or more above sea level.
6. Self-reported intolerance to intranasal therapy.
7. Self-reported recurrent epistaxis or chronic rhinosinusitis.
8. Self-reported sinus or intranasal surgery within the last 4 months of screening.
9. Self-reported history of 'complicated migraine or headaches' (i.e., hemiplegic migraine, ophthalmoplegic migraine, migrainous infarction, basilar migraine, post-traumatic headaches, post-concussion syndrome).
10. Known or suspected pregnancy as self-reported by the prospective participant at the time of screening.
11. Prospective participant unable to fully understand the consent process and provide informed consent due to either language barriers or mental capacity.
12. Self-reported diagnosis of alcohol or substance abuse disorder at the time of screening.
13. Participant with active chronic pain syndromes, such as fibromyalgia, chronic pelvic pain, or complex regional pain syndrome (CRPS); or other pain syndrome like trigeminal neuralgia.
14. Participant with severe uncontrolled psychiatric conditions or significant neurological disorders (other than migraine) that, in the Investigator's opinion, might interfere with study assessments.
15. Failure to adhere to or inability to complete Study App inputs and onboarding activities during the screening period. Participants who are not adherent during the screening period are not eligible for study entry.
16. Participation in a previous clinical study with the Mi-Helper device.
17. Participated in a migraine study or any interventional clinical study within the 3 months prior to screening.
18. Participant has an uncontrolled medical issue at the time of screening.
19. Any condition for which transnasal air flow would be contraindicated, as determined by the PI.

6.3 Screen Failures

Participants who do not meet study inclusion criteria or meet study exclusion criteria prior to randomization will be screen failed.

6.4 Recruitment and Retention

Adult participants will be targeted for recruitment using digital and social media advertisements within the contiguous US. A sufficient number of adults will be screened to be enrolled after consent is provided and subsequently randomized to obtain approximately 156 eligible participants, as described in Section 5. An anticipated attrition rate of 25% is expected to result in the completion of 116 participants. Participants will have completed the study upon completion of all post-treatment study procedures and return of the study device.

7. Study Intervention

7.1 Study Product Description

7.1.1 Test and Sham Device Description

Test Device Description

Mi-Helper has been designed for use in an at-home setting, whenever patients feel the onset of a migraine attack. The device delivers a controlled stream of dry air into the nose. The air is mixed with a fine saline mist for added comfort and efficiency. It is a lightweight, low-cost device with an integrated nebulizer, disposable tube set and desiccant cartridge. It is software controlled.

The Mi-Helper neuromodulation device is intended for acute treatment of migraine, with or without aura, in adult patients.

The Mi-Helper device is small and lightweight, weighing 7 lbs. It is designed to sit on a tabletop next to an afflicted individual. This device produces a low flow of dry, filtered air to induce neuromodulation via local evaporative cooling in the nasal turbinates. This air flow is delivered through a handheld nebulizer and air hose connected to the device. The nebulizer delivers ultrasonic misting to keep the turbinates moist and facilitate continued evaporative cooling. The nebulizer sits at the entrance of the nose and does not cannulate into the nostrils. The handpiece can be connected to the side of the device via a magnet when not in use.

The primary functional component inside the device is a blower which generates the flow of air. Inlet air is pulled into the device from the local ambient room air; the internal blower is then used to pump the air across a desiccant material to extract any moisture from the incoming air stream. The desiccant material is in a disposable cartridge that is placed into the Mi-Helper at the time of treatment.

Once treatment is initiated, the flow of air enters the individual's nostril and exits the other nostril, inducing an evaporative cooling energy exchange in the turbinates and upper airway. The blower inside the device provides the motive force to move the air supply over the desiccant material and across the individual's turbinates. The Mi-Helper will deliver treatment for 15 minutes and will turn off once the treatment is complete.

The Mi-Helper neuromodulation device is designed for investigational use and does not allow users to modify air flow rate or saline. The desiccant cartridge is also electrically erasable programmable read-only memory (EEPROM) configured and will only operate for a single use. Participant randomization assignments will be programmed within the EEPROM configuration.

An Operator's Manual and Quick Start Guide for use during the study have been developed and will be available for participant training and will be available to participants upon delivery of device.

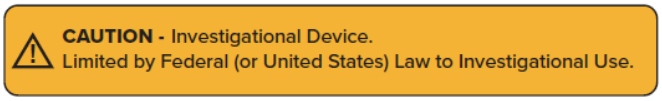
Sham Device Description

The sham treatment will be administered through the Mi-Helper device using cartridges that contain inactive material of comparable size and weight as the active desiccant material, which will not dehumidify air entering the blower. Additionally, participants will receive less than 2 LPM of air flow, with the device blower cycling on and off periodically (approximate period of active flow will be 70% of the time) during the 15-minute treatment session.

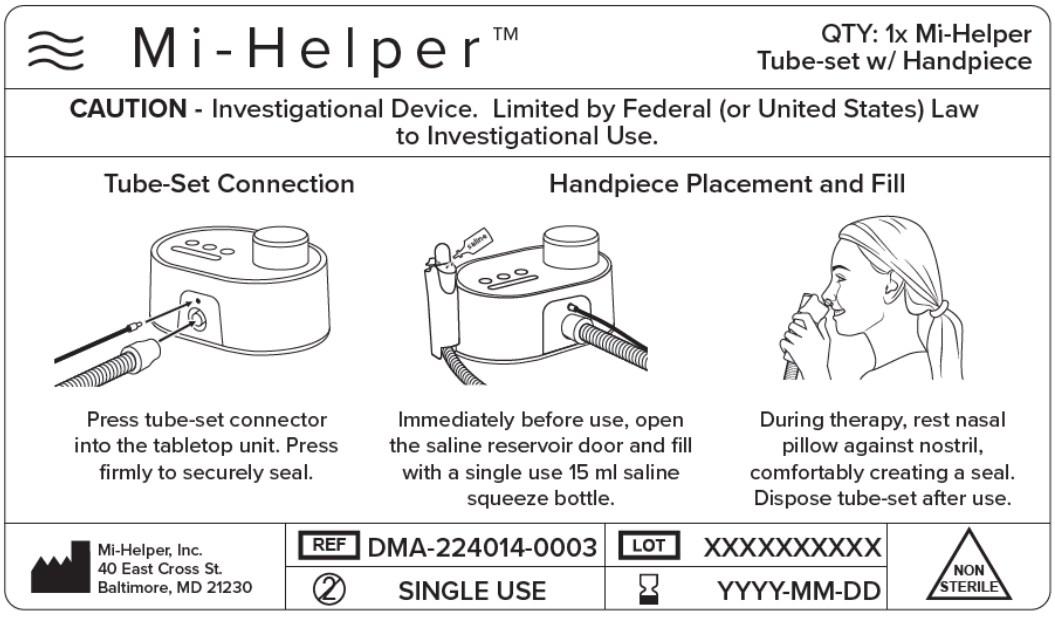
7.1.2 Formulation, Appearance, Packaging, & Labeling

The Mi-Helper device with accompanying AC adapter, one desiccant cartridge, one disposable tube set, and two sterile saline packets will be shipped to participants directly from the contract manufacturer. Study materials will arrive in one box containing the device and disposable materials. It will contain the Mi-Helper device and an internal box that will contain the desiccant cartridge, tube set and saline. The Mi-Helper device will be in the inner packaging box that will include the return shipping label (See Appendix 1 for Device Packaging). The investigational label will be prominently located on the back of the device.

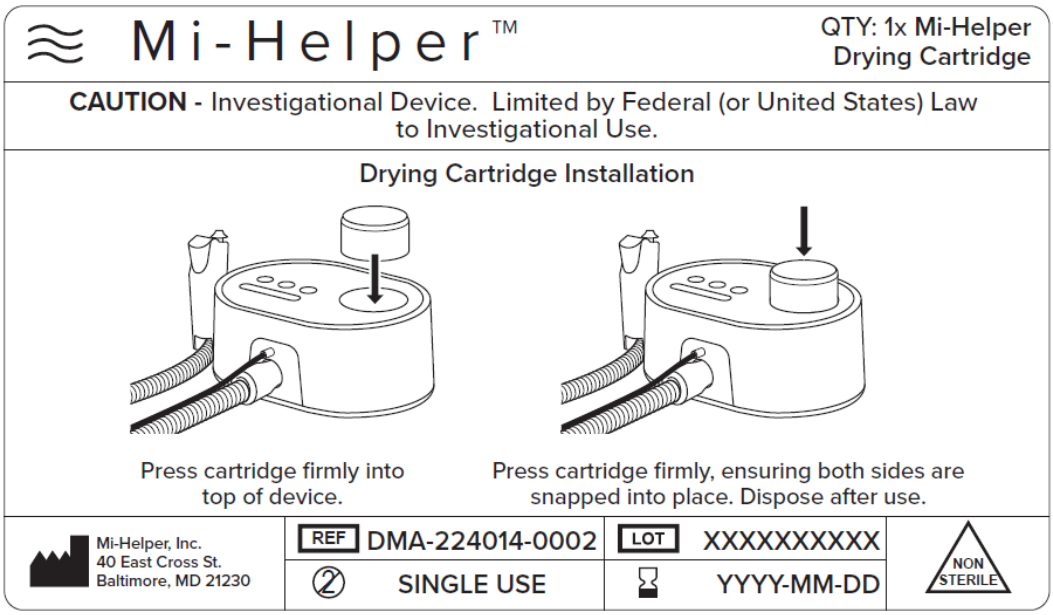
Investigation device label:



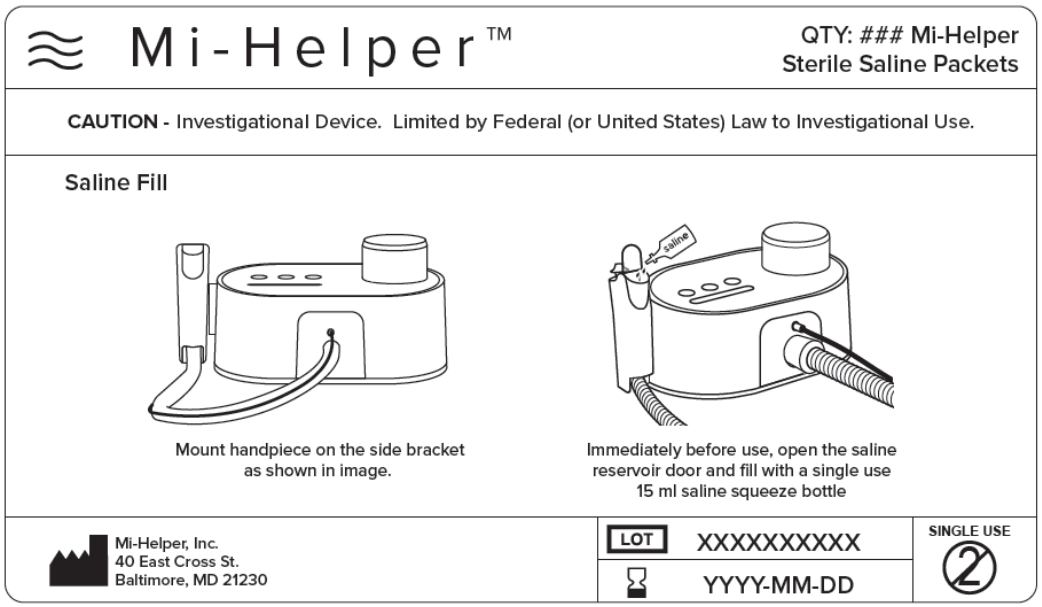
The tube set will be shipped in sealed plastic packaging with a label that will be affixed to the front of the packaging.



The desiccant cartridge will be shipped in a sealed package.

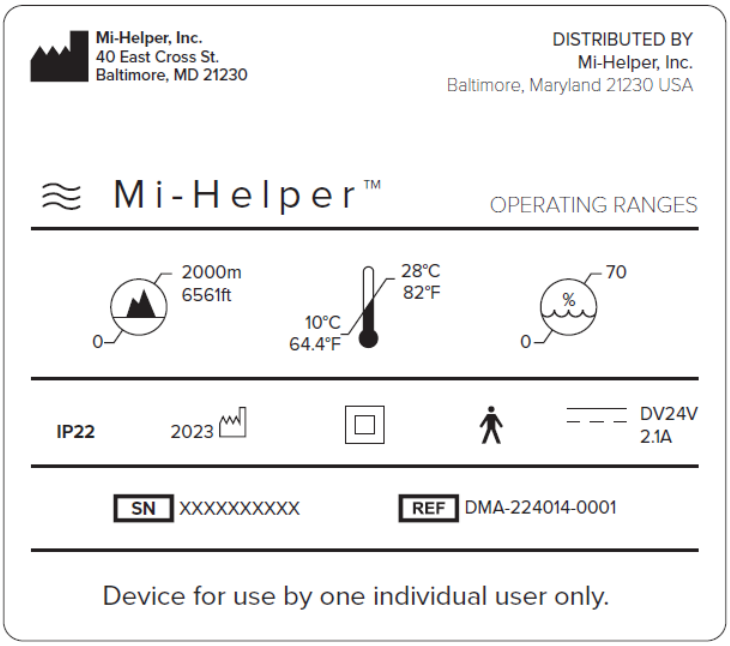


The sterile saline packets will be shipped in zip-sealed plastic packaging. This label will be affixed to the front of the packaging.

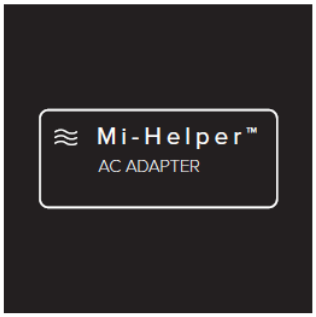


Saline use only label: 

The label below indicates temperature, altitude, and humidity ranges that are required for device functionality. It will be located on the bottom of the durable device base.



AC adapter label has been shown below.



Do not open packaging label has been shown below.

7.2 Study Product Administration

Each participant will administer the Mi-Helper device therapy once and will be required to report on their migraine-related symptoms at specific timepoints post-treatment. All assessments will be recorded within the Study App.

Instructions on how to use the Mi-Helper device are described in the Quick Start Guide and trial user manual.

7.3 Study Product Handling, Storage, & Accountability

Shipping, Handling and Accountability: After enrollment and randomization, the Mi-Helper device will be shipped to the participant's home address. Device shipping will be organized by the participant through the Study App. Study devices will be shipped to the subject directly. The participant will be required to confirm receipt through the Study App prior to initiating any study-related activities and will be required to record the serial number of the material received. Once the device is received and the participant confirms receipt, they can use the device when they experience a headache that reaches at least mild intensity pain (based on the 4-point VRS scale) as recorded in their eDiary. After the single treatment with the device and completion of all post-treatment assessments, the participant will need to return the device via courier service, which can be organized through the Study App. A log of devices shipped out to participants and received back from the participants will be maintained. See the Investigational Product Management Plan for more details.

If a participant experiences a technical difficulty with the Mi-Helper device that cannot be resolved with real-time troubleshooting, they may be shipped a replacement tubeset and desiccant cartridge to treat their next attack, If this occurs during the last week of their 35 day treatment period, a protocol exception may be granted to extend their treatment period at the discretion of the sponsor and/or investigator.

Storage: The Mi-Helper device, disposable desiccant cartridge, sterile saline bottles and tube set will be stored at room temperature. External packaging for the disposable components will have an additional label stating "do not open before use" to reduce the risk of premature damage or use of study materials. All components should stay in original packaging until the time of treatment.

Refer to the Mi-Helper Quick Start Guide and trial user manual for further details.

7.4 Concomitant Diets, Treatments, and Medications

Participants are prohibited from using their acute migraine medications within 48 hours prior to using the Mi-Helper device. Acute medication may include over-the-counter medications like non-steroidal anti-inflammatory drugs (i.e., aspirin or ibuprofen) and acetaminophen; prescription medications like triptans (i.e., sumatriptan, zolmitriptan, etc.), gepants

(ubrogepant, Rimegepant,etc.), antiemetics (metoclopramide, prochlorperazine, or promethazine); or another medical neuromodulation device like Cefaly®.

Participants should continue to take any prescribed migraine preventive medications as instructed by their physician.

Participants may use rescue medication(s) after administering treatment with Mi-Helper, however, rescue medication used within 2 hours of treatment will be considered a treatment failure. Participants will be advised against using their rescue medication until collection of the Migraine Symptom Questionnaire at 2 hours post-treatment. An ad hoc rescue medication form will be available on the Study App's dashboard after administration of study treatment (control or active) for participants to fill out if they decide to use rescue medication(s) prior to collection of the Migraine Symptom Questionnaire at 2-hours post-treatment. They will be asked about their migraine symptoms when they fill out the ad hoc rescue medication form.

No dietary restrictions are required for this protocol.

8. Safety and Adverse Events Management

8.1 Adverse Events

8.1.1 Definition of Adverse Events

An Adverse Event (AE) means any untoward medical occurrence associated with the use of an intervention in humans, whether considered intervention-related or not (21 CFR 312.32 (a)).

8.1.2 Definition of Serious Adverse Events (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (21 CFR 312.32 (a)).

8.1.3 Adverse Event Reporting

For the purposes of this study the period of observation for AEs begins after baseline procedures and continues through to the participants completion of the study. Any health-related changes prior to the randomization will be recorded as medical history.

All AEs occurring during the study will be individually assessed by the PI, reported and recorded, regardless of seriousness or relationship to the study device. Participants will be able

to report possible AEs for consideration by filling out the ad hoc Change in Health form within the Study App. There will be delegated unblinded Study Team members for the purposes of coordinating shipment logistics in relation to randomization. The participants may also report any changes to their health by chat function in the Study App and may choose to contact the Study Team via phone or email. Once a change in health is reported by the participant, the PI or designee will reach out to the participant in near real-time (within 1 business day) to make health assessments and advise on further steps, including referral to their local doctor for further assessment and treatment, if applicable. The participants will be directed by the Study App or Study Team to go to the nearest emergency room if it's a medical emergency.

The following information will be documented in each case:

- Participant ID
- AE Term
- Start Date of event
- End Date of event or Ongoing
- Severity or Intensity
- Seriousness
- Action taken with study device
- Action taken to treat event
- Outcome
- Relationship to study device
- Expectedness
- Participants health status assessed by PI

8.1.4 Anticipated Adverse Events

The following adverse events have been documented in previous studies with the Mi-Helper Device and/or its prototype:

- Nasal discomfort (nasal pain, congestion, nasal irritation, runny nose, rhinorrhea, post-nasal drip)
- Ear discomfort (ear pressure, ear pain, tinnitus)
- Sore Throat
- Sinusitis

8.1.5 Adverse Event Severity and Causality Assessments

The severity of AEs will be defined by the following criteria.

Mild - Symptoms hardly perceived, only slight impairment of general well-being

Moderate - Clearly noticeable symptoms, but tolerable without immediate relief

Severe - Overwhelming discomfort

The investigator will assess the possibility of a link between the study device use and an AE based on the following criteria:

Unrelated

- There is an evident other explanation for the AE
- The AE is in accordance with the effect or adverse effect of the concomitant medication being taken by participant
- The AE occurred prior to the administration of the study product

Unlikely relation

- Reasonable temporal relationship with the intake of the study product, although there is another plausible explanation for the occurrence of the AE

Possible relation

- Reasonable temporal relationship with the intake of the study product, although there are a number of other factors that could have caused the AE

Probable relation

- Reasonable temporal relationship with the intake of the study product although other plausible reasons point to a causal relationship with the study product

Certain relation

- Reasonable temporal relationship with the intake of the study product, and
- There is no other explanation for the AE, and
- Subsidence or disappearance of the AE on withdrawal of the study product (discontinuation), and
- Recurrence of the symptoms on reintroduction

8.1.6 Unanticipated Problems

Definition

Unanticipated problems (UAP) involving risks to participants or others includes, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Notification to Regulatory Authorities and IRBs

The investigator will report UAPs to the IRB per required timelines (typically within 10 business days), and the Sponsor will notify the Food and Drug Administration (FDA) as applicable.

8.1.7 Serious Adverse Event Reporting and Follow-Up

For any **SAE** the PI must notify the Sponsor's Medical Monitor, within 24 hours of becoming aware of the event and send the completed Serious Adverse Event/Unanticipated Adverse Device Effect (SAE/UADE) Report to the Sponsor's Medical Monitor within 48 hours. In addition, all IRB reporting requirements will be followed.

Any SAE or UADE must be reported to the Sponsor's Medical Monitor via telephone, fax, or email within 24 hours of becoming aware of the event.

In the event of an SAE, the investigator will document the following in addition to information outlined in section 8.1.3:

- Seriousness criteria: life threatening, hospitalization, persistent/significant disability, congenital anomaly/birth defect, death [if marked, then date of death]
- Event Description: where a narrative would capture the details of the event
- Relevant Medical History: any medical history pertinent to the event

Within 48 hours after the initial report, the Investigator must provide further information to the Sponsor's Medical Monitor on the SAE or UADE in the form of a written narrative. This should include a copy of the completed SAE/UADE Report Form and any other related diagnostic information that will assist in the understanding of the event. Significant new information on ongoing SAEs should be provided promptly to the Sponsor's Medical Monitor. All identifiable reference to the subject except for the subject screening number will be redacted from any report sent to the Sponsor's Medical Monitor.

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to the FDA and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as FDA request.

8.1.8 Pregnancy Reporting

Participants who self-report pregnancy will be excluded from the study at screening. If the participant reports being pregnant after enrollment, they will be withdrawn from the study and a pregnancy form within the study application portal will be filled out by the PI or designee and the Sponsor will be alerted of the pregnancy.

9. Participant Completion and Withdrawal

9.1 Participant Completion and Withdrawal

Participants will have completed the study once the device is used, all post-treatment procedures are completed at stipulated timepoints, and the study device is returned.

The participant may withdraw from the study at any time by notifying the Study Team. Participants may be withdrawn from the study by the investigator if study procedures have not been followed or if the investigator determines the participant is not able to safely continue with the study due to an AE or other health-related issue.

Participants will have up to 35 days to complete the treatment session after receiving the device, after which they will have to return the device and will be withdrawn from the study.

10. Data Management

10.1 Data Collection

Study data will be collected in the ObvioHealth app. ObvioHealth will maintain accurate documentation (source data) that supports the information entered in the eCRF.

Management of clinical data will be performed in accordance with ObvioHealth's applicable standards and data cleaning procedures with oversight by the Sponsor to ensure integrity of the data, for example, to remove errors and inconsistencies in the data.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into ClinicalOne, a 21 CFR Part 11-compliant data capture system provided by the study Sponsor. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be automatically transferred from the ObvioGo Platform into ClinicalOne via a continuous API integration.

In addition to clinical data, device performance data is extracted and reviewed once the Mi-Helper device body is returned post treatment. These logs include treatment start and stop time, confirmation of the flow rate, back pressure, humidity, and any voluntary or involuntary treatment interruptions. This data will be accessible by the unblinded sponsor team

representative. All data points except flow rate will be entered into the ClinicalOne EDC by an unblinded study team member.

To protect the privacy of participants, no personal information (including the participant's name or initials) is to be recorded in the eCRF or as part of the query text. Identifiable data are isolated to a special team at ObvioHealth and these data will not be transferred/available to the Sponsor.

The Sponsor will obtain and retain all eCRFs and associated study data as applicable at the completion of the study.

10.2 Data Handling

Documentation of all data management activities should allow step-by-step retrospective assessment of data quality and study performance.

Any changes or corrections to data will be performed in the Oracle Clinical One Electronic Data Capture Platform and will include rationale for changes. The EDC system has an audit trail, which will provide a complete record of the changes and corrections endorsed by the Investigator.

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA).

10.3 Computerized Edit Checks

The database will incorporate the needed programmed edit checks to ensure consistent and complete data entry. The data management team will perform edit checks as the data are being entered into the system, and queries will be entered on a Data Issues Log for the decentralized site staff to address. The data manager will raise queries as needed on safety data to code the terms (AEs and Drugs or concomitant medication) appropriately.

10.4 Audit Trail

The clinical Data Management System (DMS) complies with Good Clinical Practice (GCP) predicated rule requirements, laws and regulations (Personal data protection) for clinical trials and allows an audit of actions performed by users.

All original entries and changes made in the database will be captured by an audit trail which will include the date and time of the entry or change, and the individual making the entry or change who will be identified via their unique user ID.

11. Statistical Analysis

11.1 Determination of Sample Size

The sample size for this study was calculated to test the null hypothesis with Fisher's exact test.

The sample size is calculated to test the null hypothesis with 80% power at a 5% level of significance using PASS 2024 software, version 24.0.2.

If we assume that 41% of the subjects in the active treatment arm will have pain freedom at 2 hours post treatment versus 16% in the sham arm, then 116 evaluable subjects are required (58 per group). Allowing for a 25% dropout rate, a total of 156 (78 active versus 78 sham) subjects should be enrolled in the study.

11.2 Randomization

For this study, a total of 156 participants will be randomized equally into two groups:

- Group I (active treatment): 10 LPM, dehumidified air, 15 minutes
- Group II (sham [control] treatment): 2 LPM, ambient air administered intermittently via Mi-Helper, 15 minutes total

Following randomization, balance between the two arms will be evaluated and confirmed using standardized mean differences (SMD), where absolute SMD values less than 0.2 will be considered as indicating good balance on a given variable or confounder. Subjects will be randomized in a 1:1 fashion, with stratification for gender.

11.3 Populations for Analyses

- **Intent-to-Treat (ITT) Population** – all participants who were randomly assigned to a treatment.
- **Modified Intention to Treat (mITT) Population** – all participants who used the study intervention and completed a baseline and 2-hour post-dose pain assessment.
- **Per Protocol (PP) Population** – all participants in the mITT population who do not have a major protocol deviation related to primary endpoint and complete the treatment in compliance with the protocol, with group assignment as treated, and have no use of rescue medication within 2 hours post treatment.

The ITT analysis set will serve as the main analysis set for all safety evaluations.

The mITT analysis set will be the primary population used for efficacy analyses in this study.

The primary and secondary efficacy assessments will also be performed on the PP and the ITT analysis sets as a sensitivity analysis.

11.4 General Considerations

All statistical analyses will be performed using Stata software (version 19, StataCorp LLC, College Station, Texas).

The Pearson chi-squared test will be used to compare randomized arms with regards to primary and secondary endpoints. Logistic regression modeling will estimate odds ratios and

95% confidence intervals for pain relief/ freedom endpoints to compare the two groups. The absolute difference in rates of freedom from pain will be estimated with 95% confidence intervals. Binomial exact 95% confidence intervals will be constructed for the incidence of primary and secondary endpoints within each group.

Deviations from the planned analysis will be described, with proper justification, in the clinical study report.

11.5 Significance Level and Handling of Type I Error

Type I Error: The overall significance level for this study is 5% using two-tailed tests

Hierarchy Approach for Secondary Endpoint Analysis: A hierarchical testing approach will be employed using a fixed-sequence procedure to control type I error due to multiple endpoint testing. The primary endpoint will first be tested and only if $p<0.05$, will the secondary endpoints be tested. Testing will proceed sequentially, and each endpoint must achieve statistical significance at the 0.05 level to proceed to the next endpoint. If any endpoint in the sequence fails to achieve significance, all subsequent endpoints will not be formally tested and will be considered exploratory.

11.6 Efficacy Analysis

The Chi-square test will be used to compare randomized arms with regards to primary and secondary endpoints. Logistic regression modeling will estimate odds ratios and 95% confidence intervals for pain relief/ freedom endpoints to compare the two groups. The absolute difference in rates of freedom from pain will be estimated with 95% confidence interval. Binomial exact 95% confidence intervals will be constructed for the incidence of primary and secondary endpoints within each group

11.6.1 Primary Endpoint(s)

Pain freedom at 2 hours is defined as the reduction in head pain to "none", i.e., from severe, moderate, or mild head pain to none. Pain will be rated on a scale from 0 to 3, where 0 is no pain and 3 is severe pain. The proportion of subjects with pain freedom in the active arm will be compared to the sham using a chi-squared test.

Use of rescue medication prior to 2 hours post treatment completion will be considered a failure for this endpoint (i.e., patient will be assigned the status of no reduction).

A sensitivity analysis of the primary endpoint will be performed to assess the impact of missing data on the study outcome. This will be done on the ITT analysis set, where missing 2-hour pain assessment is considered not to be pain free.

Subgroup analyses will be conducted to evaluate whether treatment effects on the primary endpoint differ by gender, age group, use of preventive medications, and baseline headache

severity. These analyses will help assess the generalizability of the treatment effect across diverse patient populations.

11.6.2 Secondary Endpoint(s)

The secondary efficacy variables will be summarized by a count and percentage and compared with a chi-squared test. Analysis of secondary endpoints will follow the hierarchical testing approach outlined above to control type I error due to multiple endpoints.

Patient Global Impression of Change will also be summarized by descriptive statistics per treatment group and compared between the groups with a t-test.

11.7 Safety Analysis

The primary safety outcome is the incidence of adverse events related to the study device for 48 hours post treatment completion.

AEs will be categorized as related, probable, possible, unlikely, or unrelated prior to database lock. The number of AEs/SAEs and number of participants with AEs/SAEs will be listed and tabulated.

Adverse event rates will be compared between the study groups with a Fisher's exact test.

Treatment tolerability will be compared between the study groups. The number and percentage of subjects who fail to complete the study treatment due to discomfort and the number and percentage of subjects who fail to complete the study because of Adverse Events will be presented as well.

11.8 Exploratory Analysis

The exploratory variables will be summarized by a count and percentage and compared with a chi-squared test

Frequency of use of rescue medications will be summarized by descriptive statistics per treatment group and compared between the groups with a t-test.

11.9 Blinding Assessment

An additional assessment using the Blinding Index will be performed to determine whether the study blinding has been maintained. The Blinding index is on a scale of 0 to 1 where 0 indicates complete lack of blinding and 1 indicates perfect blind. 95% confidence intervals will also be presented.

12. Quality Control and Assurance

12.1 Acceptability of Case Report Forms (Source Documents)

A case report form is a printed, optical, or electronic document designed to record the protocol required information to be reported to the sponsor on each trial participant. This study will utilize electronic Case Report Forms (eCRFs) within the ClinicalOne Electronic Data Capture (EDC) platform.

All study data, including electronic patient reported outcomes, will be collected in the ObvioHealth Study App, ObvioGo. Such data will be transferred from the ObvioHealth study platform to the oracle ClinicalOne EDC to be stored in eCRFs. ObvioHealth will provide data management services for this protocol, with SPRIM PRO providing site-based services.

The study team will maintain accurate documentation (source data) that supports the information entered in eCRF. To protect the privacy of participants, no personal information (including the participant's name or initials) is to be recorded in the eCRF or as part of the query text. Personally Identifiable data will not be transferred/available to the Sponsor.

The study monitor will perform ongoing review the of the eCRFs in accordance with the monitoring plan, to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

All source data should be reviewed by the study staff and the study monitor to ensure accurate transcription of data and that any potential AEs or concomitant medications reported on these documents are discussed with the participant and transcribed accurately to the eCRF and/or DMS. ePROs that are classed as source data will be retained by the investigator and true/certified copies may be sent to the Sponsor or a designated vendor as required. Any AEs or concomitant medications collected as ePRO will be reviewed and transcribed to the eCRF by a member of the study team.

The Sponsor will obtain and retain all eCRFs and associated study data at the completion of the study.

12.2 Modification of Protocol

The Investigator will not make any changes to this protocol without prior written consent from Sponsor and subsequent approval by the IRB. Any permanent change to the protocol, whether it is an overall change or a change for a specific study center(s), must be handled as a protocol amendment. The written amendment must be submitted to the chairperson of the IRB identified with this responsibility. Except for 'administrative amendments', Investigators must await IRB approval of protocol amendments before implementing the change(s). Administrative amendments are defined to have no effect on the safety of the research participants scope of the investigation, or quality of the trial. However, a protocol change

intended to eliminate an apparent immediate hazard to participants should be implemented immediately, and the IRB notified within five days.

When, in the judgment of the reviewing IRB, the investigators and/or Sponsor, the amendment to the protocol substantially alters the study design and/or increases the potential risk to the participant, the currently approved written informed consent form will require similar modification. In such cases, repeat informed consent will be obtained from participants enrolled in the study before expecting continued participation.

12.3 Reporting Protocol Deviations

A protocol deviation is any non-compliance with the clinical study protocol or International Conference on Harmonization Good Clinical Practice (ICH GCP). The non-compliance may be either on the part of the participant, the investigators, or the study staff. It is the responsibility of the Investigator to identify and report deviations per IRB requirements.

Protocol non-compliance will be logged, and a corrective action plan will be implemented. The main categories of non-compliance that will be targeted are:

- Informed consent process not adequately performed
- Deviation from Inclusion and/or Exclusion criteria
- Non-compliance with study related assessments
- Any other good clinical practice (GCP) non-compliance

Protocol non-compliance will be tracked and logged in the Protocol Deviation Log in the Oracle ClinicalOne EDC.

12.4 Monitoring

The study will be monitored on an ongoing basis beginning with enrollment of the first participant until the study exit of the last enrolled participant.

The monitor will perform ongoing review of the eCRFs in accordance with the monitoring plan for completeness, clarity and consistency with the information in participants file (source data checking). Monitoring will begin with an initiation visit prior to study commencement to clarify all aspects of the protocol and documentation. The purpose of later visits during the implementation period will be to evaluate study progress and adherence to protocol. The monitor will check that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements; and that the safety and rights of participants are being protected. At the end of the trial the monitor will make a study closing visit to ensure that all documentation is complete. In all cases, it is the responsibility of the CPM / monitor to maintain participant confidentiality.

The following measures are in place to ensure consistent and regular participant contact:

- Study Team members will review study compliance daily during business hours
- Study Team members will maintain electronic or telephone communication with the participant as needed
- Under some circumstances, the Investigator or designee may call the participant to determine the compliance with study protocol and/or to provide additional compliance tracking

An unblinded Study Team member will be available should participants require support with troubleshooting the Mi-Helper device and to maintain the blind.

13. Ethics and Regulatory Requirements

13.1 Institutional Review Board/Independent Ethics Committee

The study protocol will be submitted by the Investigator for examination by the IRB. Commencement of the clinical study is not permitted without written approval of the IRB.

The study will initiate after approval from the IRB which follows the guidance of USA regulatory bodies and general GCP regulations and standards set by the ICH.

This study will be conducted according to the principles and rules laid down in the Declaration of Helsinki and its subsequent amendments.

13.2 Investigator Responsibilities

The Investigator or designee is responsible for the following:

- Obtaining the written and dated approval of the applicable IRB and other regulatory agency, if any, prior to the conduct of the study.
- Selecting participants in accordance with the inclusion and exclusion criteria after the eIC is signed.
- Confirming an existing diagnosis of migraine that satisfies the protocol eligibility criteria.
- Maintaining confidentiality and safety of participants in accordance with the Declaration of Helsinki.
- Adhering to the study protocol and the spirit of GCP.
- Following procedure if modification becomes necessary. The PI or designee will provide a rationale in a protocol amendment, which is signed by the Investigator and Sponsor for submission to the IRB. After the protocol amendment approval, participants still active in the study must re-sign the eIC to remain in the study.
- Providing accurate, complete and timely data reported to the Sponsor.
- Providing participants with any newly available information that may be relevant to them during the study.

- Identifying AEs and notifying the Sponsor, IRB and health authorities, as applicable
- Cooperating in the case of an audit and/or regulatory inspections, providing direct access to data and/or documents.

13.3 Informed Consent Process

A signed electronic Informed Consent (eIC) is required prior to participation in the study. This will be done prior to conducting any study-related activities and will be done in accordance with all applicable regulatory requirements.

The dia before the participant decides they want to participate. The IRB/Ethics Committee (EC) will approve the eIC language. Any amendments to these documents must be approved by the IRB/EC prior to distribution or use.

The participant must be informed of the study risks and benefits and provide an electronic signature consenting to participate prior to the initiation of any study-related activities.

The decision of the participant to participate in the study is entirely voluntary. It will be clearly stated to the participant within the eIC language that the consent to participate can be withdrawn at any time without penalty or loss of benefits to which the participant is otherwise entitled.

14. Study Closure

Premature Termination of Study

Should it prove necessary to discontinue the study permanently prior to completion, the Sponsor will notify SPRIM PRO and the IRB of the rationale. Participants will be informed by SPRIM's Study Team. All relevant study documents and data will then be returned to the Sponsor, and the study devices will be returned to the shipping fulfilment center.

Termination of Study

After the completion or termination of the study, all relevant study documents and data will then be sent to the Sponsor. Any remaining study devices in the field will be returned to the shipping fulfillment center. The Investigator will inform the IRB of the end of the study and a certificate of study closure will be issued.

15. Publication & Data Sharing Policy

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-

reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 5 years after the completion of the primary endpoint by contacting the study Sponsor.

The final publication for this study will be a Clinical Study Report authored by SPRIM PRO and the Principal Investigator, Dr. Jessica Ailani.

16. References

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17. Appendices

17.1 Appendix 1: Device Packaging