Statistical Analysis Plan

Protocol 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.
Protocol Number:	COT-004
Version Number:	1.0
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Sponsor:	Mi-Helper Inc.
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CONTENTS

1. ABBREVIATION AND DEFINITIONS

Abbreviation	Definition
ADS	ADS
AE	Adverse Event
CRF	Case Report Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational Medical Product
M	Total number of participants with non-missing value of the variable or event
ITT	Intention to Treat
MBS	Most bothersome symptom
mITT	Modified intention to Treat
N	Number of participants in population or visit
n	Number of participants with a particular value of a variable or event
PF	Pain Freedom
PGIC	Patient Global Impression of Change
PI	Principal Investigator
PP	Per Protocol
PR	Pain Relief
PT	Preferred Term
SAE	Serious Adverse Event
SAF	Safety
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SPF	Sustained Pain Freedom
SPR	Sustained Pain Relief
Sub-I	Sub-Investigator
TLF	Table, Listing, and Figure
WHO	World Health Organization

2. INTRODUCTION

2.1. Preface

Migraine is a severely disabling neurologic condition and is the sixth most disabling disorder worldwide, affecting over a billion people. 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. Neuromodulation therapies that target the autonomic nervous system are gaining traction due to their safety profile and relative effectiveness. Moreover, there is a need for non-invasive, drug-free therapies that can be administered quickly and in the comfort of one's home.

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.

2.2. Scope

This document describes the analysis plan for the statistical analysis of the study COT-004. This Statistical Analysis Plan (SAP) will provide details to further elaborate statistical methods outlined in the study protocol and describe the analysis conventions to guide the statistical programming work.

These analyses will assess the efficacy and safety of the Mi-Helper device for acute treatment of a single migraine attack in an at home setting and will be included in the clinical study report.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports." 1,2

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

- 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.

3.1.2. Secondary Objectives

- 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 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.

3.1.3. 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 from 2 to 48 hours post treatment completion without the use of rescue medication
- To assess effect of Mi-Helper therapy on migraine associated symptoms (nausea, photophobia, and phonophobia).

3.2. Endpoints

3.2.1. 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).

3.2.2. Secondary Efficacy Endpoints

- 1. Freedom from Most Bothersome Symptom (MBS) at 2 hours post treatment completion
- 2. 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).
- 3. 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 post treatment completion).
- 4. 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.

3.2.3. 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

3.2.4. 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).
- 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 between 2- and 48-hours post treatment).
- Use of rescue medication 2–48 post-treatment completion.
- Freedom from MBS immediately following 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.

4. STUDY METHODS

4.1. General Study Design and Plan

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. Blinding for this study will be applied to the Principal Investigator (PI), Sub-Investigator (Sub-I), 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.

4.1.1. 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.

4.1.2. 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 participant's diagnosis of migraine. If the participant does not agree to provide HIPAA authorization, they will be exited from the study.

4.1.3. 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.

4.1.4. Run-in Procedures (~6 weeks)

During run-in, each participant will need to complete 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. If the participant 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

After diagnosis history review is complete, the Study Team will conduct a check-in with participant to review information submitted during screening and run-in period. Once participants meet all eligibility criteria and eligibility is confirmed by the PI or Sub-I, they will be randomized to a study treatment arm.

4.1.5. Randomization Procedures (~1 week)

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.

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 tripans, 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.

4.1.6. 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 symptoms (MBS) which will be recorded within the Study App prior to treatment initiation.

4.1.7. 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.

4.1.8. 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.

4.2. General Study Population

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

4.2.1. 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

4.2.2. 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 is 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 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.
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.

4.3. Randomization and Blinding

For this study, a total of 156 participants will be randomized equally into two groups. 1:1 randomization will be performed with a block size of 6, and stratified by gender to ensure balance with regards to gender.

- 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

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. For variables that that have an absolute SMD larger than 0.2, adjustments may be made to minimize any possible imbalance on those variables using multivariable analysis.

Participants will be randomized in a 1:1 fashion, with stratification for gender. The randomization schema for this study will be implemented within the ObvioGo platform.

5. SAMPLE SIZE CALCULATION

The sample size for this study was calculated to test the null hypothesis with a two-tailed 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 participants in the active treatment arm will have pain freedom at 2 hours post treatment versus 16% in the sham arm, then 116 evaluable participants are required (58 per group). Allowing for a 25% dropout rate, a total of 156 (78 active versus 78 sham) participants should be enrolled in the study.

6. GENERAL ANALYSIS CONSIDERATIONS

6.1. Analysis Populations

For the purposes of analysis, the following analysis sets are defined:

6.1.1. Intent-to-Treat (ITT) Population

- All participants who were randomly assigned to a treatment.

6.1.2. Modified Intention to Treat (mITT) Population

- All participants who used the study intervention and completed a baseline and 2-hour post-dose pain assessment.

6.1.3. Per Protocol (PP) Population

- All participants in the mITT population that do not have a major protocol deviation related to primary endpoint(s), and completed the primary endpoint(s) and completed the treatment in compliance with the protocol, with group assignment as treated.

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.

6.2. Missing Data

Missing values will not be imputed.

7. SUMMARY OF STUDY DATA

7.1. Data Display

Tables will have columns corresponding to or be stratified by the treatment groups where appropriate:

- Group I (Active Treatment)
- Group II (Sham Treatment))

In general, all data will be listed by treatment group, participant and visit/time point where appropriate. The total number of participants under the stated population (N) will be displayed in the header of summary tables.

Data will be summarized using descriptive statistics for continuous variables. Unless otherwise specified, descriptive statistics will include number of participants, mean, standard deviation, minimum, median, maximum and interquartile range. The statistic "Missing" will also be presented as the number of missing entries/participants, if any at that visit/timepoint, and presented as a summary statistic only when non-zero. The minimum and maximum statistics will be presented to the same number of decimal places as the original data. The mean and median will be presented to one more decimal place than the original data, whereas the standard deviation will be presented to two more decimal places than the original data.

In summary tables of categorical variables, counts and percentages will be used. The count [n] indicates the actual number of participants with a particular value of a variable or event, which should always be less than or equal to the total number of participants with non-missing value of the variable or event [M]. Percentage will be obtained by: % = (n/M)*100. Unless otherwise stated, all percentages will be expressed to one decimal place. Both lower and upper limits will carry the same number of decimal places as the original value for 95% confidence intervals.

P-values will be displayed with 4 decimals, e.g., p=0.0001 and p-values below 0.0001 will be displayed as p<0.0001.

In by-visit summary tables only scheduled visits/timepoints will be summarized. In listings, all visits and timepoints with any data collected will be included.

The change from baseline values will be derived for each participant as the post-baseline evaluation minus the baseline evaluation.

All dates will be displayed in ISO 8601 date format (YYYY-MM-DD).

Table 1. Efficacy Endpoint Variables

Variable	Role	Data Source	Analysis Plan
2hr Pain Freedom	Primary Efficacy Endpoint	Baseline Migraine Symptom Questionnaire 2-hour Post Treatment Migraine Symptom Questionnaire	n% Achieved if Head Pain changes from Severe, Moderate, or Mild at baseline to None at 2hrs post-treatment.
2hr MBS Freedom	Secondary Efficacy Endpoint	Baseline Migraine Symptom Questionnaire 2-hour Post Treatment Migraine Symptom Questionnaire	n% Achieved if MBS changes from Severe, Moderate, or Mild at baseline to None at 2hrs post-treatment.
2-24hr Sustained Pain Freedom	Secondary Efficacy Endpoint	Episodic Rescue Medication Questionnaire Baseline Migraine Symptom Questionnaire 2-hour Post Treatment Migraine Symptom Questionnaire 24-hour Post Treatment Migraine Symptom Questionnaire	n% Achieved if Pain Freedom is sustained from 2 hours post-treatment until 24 hours with no administration of rescue medication and with no recurrence of a mild/moderate/severe headache.
2hr Pain Relief	Secondary Efficacy Endpoint	Baseline Migraine Symptom Questionnaire 2-hour Post Treatment Migraine Symptom Questionnaire	n% Achieved if Head Pain changes from Severe or Moderate at baseline to Mild or None at 2 hours post-treatment, OR if Head Pain changes from Mild at baseline to None at 2 hours post-treatment.
Global Impression of Acute Treatment Effect	Secondary Efficacy Endpoint	24-Hour Post Treatment User Experience Questionnaire	Patient Global Impression of Change measure
Rescue Medication use 0-2hrs Post Treatment	Exploratory Endpoint	Episodic Rescue Medication Questionnaire	

		2-hour Post Treatment Migraine Symptom Questionnaire	
0hr Pain Freedom	Exploratory Endpoint	Baseline Migraine Symptom Questionnaire Immediate Post Treatment Migraine Symptom Questionnaire	n% Achieved if Head Pain changes from Severe, Moderate, or Mild at baseline to None immediately post-treatment.
0hr Pain Relief	Exploratory Endpoint	Baseline Migraine Symptom Questionnaire Immediate Post Treatment Migraine Symptom Questionnaire	n% Achieved if Head Pain changes from Severe or Moderate at baseline to Mild or None immediately post-treatment, OR if Head Pain changes from Mild at baseline to None immediately post-treatment.
2-48hr Sustained Pain Freedom	Exploratory Endpoint	Episodic Rescue Medication Questionnaire Baseline Migraine Symptom Questionnaire 2-hour Post Treatment Migraine Symptom Questionnaire 48-hour Post Treatment Migraine Symptom Questionnaire	n%, Chi-Square Achieved if Pain Freedom is sustained from 2 hours post-treatment until 48 hours post-treatment, with no administration of either rescue medication and with no recurrence of a mild/moderate/severe headache.
0hr MBS Relief	Exploratory Endpoint	Baseline Migraine Symptom Questionnaire Immediate Post Treatment Migraine Symptom Questionnaire	n% Achieved if MBS changes from Severe or Moderate at baseline to Mild or None at 2 hours post-treatment, OR if MBS changes from Mild

			at baseline to None at 2 hours post-treatment.
2hr MBS Relief	Exploratory Endpoint	Baseline Migraine Symptom Questionnaire 2-hour Post Treatment Migraine Symptom Questionnaire	n% Achieved if MBS changes from Severe or Moderate at baseline to Mild or None immediately post-treatment, OR if MBS changes from Mild at baseline to None immediately post-treatment.
0hr MBS Freedom	Exploratory Endpoint	Baseline Migraine Symptom Questionnaire Immediate Post Treatment Migraine Symptom Questionnaire	n% Achieved if MBS changes from Severe, Moderate, or Mild at baseline to None immediately post-treatment.
0hr Nausea Freedom	Exploratory Endpoint	Baseline Migraine Symptom Questionnaire Immediate Post Treatment Migraine Symptom Questionnaire	n% Achieved if Nausea changes from Severe, Moderate, or Mild at baseline to None immediately post-treatment.
2hr Nausea Freedom	Exploratory Endpoint	Baseline Migraine Symptom Questionnaire 2-hour Post Treatment Migraine Symptom Questionnaire	n% Achieved if Nausea changes from Severe, Moderate, or Mild at baseline to None at 2hrs post-treatment.
0hr Photophobia Freedom	Exploratory Endpoint	Baseline Migraine Symptom Questionnaire	n% Achieved if Photophobia changes from Severe, Moderate, or Mild at baseline to None

		Immediate Post Treatment Migraine Symptom Questionnaire	immediately post-treatment.
2hr Photophobia Freedom	Exploratory Endpoint	Baseline Migraine Symptom Questionnaire 2-hour Post Treatment Migraine Symptom Questionnaire	n% Achieved if Photophobia changes from Severe, Moderate, or Mild at baseline to None at 2hrs post-treatment.
0hr Phonophobia Freedom	Exploratory Endpoint	Baseline Migraine Symptom Questionnaire Immediate Post Treatment Migraine Symptom Questionnaire	n% Achieved if Phonophobia changes from Severe, Moderate, or Mild at baseline to None immediately post-treatment.
2hr Phonophobia Freedom	Exploratory Endpoint	Baseline Migraine Symptom Questionnaire 2-hour Post Treatment Migraine Symptom Questionnaire	n% Achieved if Phonophobia changes from Severe, Moderate, or Mild at baseline to None at 2hrs post-treatment.

7.2. Participant Disposition

Participant disposition will be summarized by study group and overall using Screened, Enrolled, ITT (Randomized/Safety Population), mITT, and PP populations. The number and percentage of participants for each study product will be presented for ITT, mITT, and PP populations. The denominator for percentages will be the number of participants randomized per group.

Discontinued participants will be summarized by product group and overall based on discontinued reasons.

A listing for disposition will include the participants who are randomized and will cover the following information: population assigned (ITT, mITT, and PP), study completion status and reason for discontinuation/screen failure.

7.3. Demographics and Baseline Characteristics

Age and other continuous demographic and baseline variables will be summarized using descriptive statistics such as mean, range, median and standard deviation. Age group, gender, race, ethnicity, and

other categorical demographic and baseline variables will be summarized using frequency counts and percentages for the ITT, mITT, and PP populations.

7.4. Protocol Deviations

A summary table and a listing for individual participants will be presented to describe the significant protocol deviations for this study based on the safety population.

7.5. Prior and Concomitant Medications

Concomitant medications taken during the study will be listed for the ITT population by participant. The listing will include reason for the medication as well as the start and stop date/time.

7.6. Concurrent Illnesses and Medical Conditions

Medical Histories will be listed for the Safety Population by System Organ Class (SOC) and Preferred Term (PT).

7.7. Descriptive Statistics

Descriptive statistics of the quantitative variables will be summarized using number of participants with non-missing observations (n). The qualitative variables will be summarized using counts and percentages of participants in each category. Summaries will be presented by the treatment group and time point (where relevant) for the ITT, mITT and Per Protocol Populations.

Study Product exposure and concomitant medications will be summarized using counts and percentages of participants by treatment group for the safety population.

8. EFFICACY ANALYSIS

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.

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

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

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

8.1. Primary Efficacy Analysis

- 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. Pain freedom will compare the active arm to the sham arm 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.

8.2. Secondary Efficacy 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.
- 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.
- Global Impression of Treatment Effect will also be summarized by descriptive statistics per treatment group and compared between the groups with a t-test.

8.3. Exploratory Efficacy Analyses

- 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.

9. SAFETY ANALYSIS

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

Safety of the Mi-Helper device measured by incidence of adverse events with groups compared using Fisher's exact test for proportions.

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.

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

9.1. Adverse Events

9.2. Deaths, Serious Adverse Events and other Significant Adverse Events

9.3. Pregnancies

10. OTHER ANALYSIS

11.1 Blinding assessment

An additional assessment using the Bang Blinding Index will be performed to determine whether the study blinding has been maintained. The Bang 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.

11. REPORTING

11.1. Statistical Analysis Output

A Statistical Analysis Outputs will be developed and provided by SPRIM PRO. The report will include all required results in tables, listings, and figures agreed upon in the TLF Shells document. The Statistical Analysis Outputs will be output as either one file compiling all tables, listings, and figures, or a zip folder that houses the output items in separate files.

11.2. Clinical Study Report

A Clinical Study Report will be developed and provided by SPRIM PRO blinded statisticians after database lock, delivery of the statistical analysis, and the TLF deliverable is approved by the client. The report will address study background, methodology, and all required results including tables, listings, and figures agreed upon in the SAP.

12. QUALITY ASSURANCE

Analysis related to the primary, secondary, and exploratory objectives will be validated by two biostatisticians or statistical programmers.

All discrepancies identified during the output review will be corrected or documented until there are no findings, or they can be explained. At the end of the study, all data sets used for analysis and final output will be archived.

COT-004 Statistical Analysis Plan v1.0

Final Audit Report 2025-06-24

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