COVER PAGE FOR PROTOCOL AND STATISITICAL ANALYSIS PLAN

Official Study Title: Treatment of Sinus Headache Using a Novel Device That Combines Acoustic Vibration with Oscillating Expiratory Pressure: Randomized Controlled Trial

NCT Number: NCT05479604

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Unique Protocol ID: 22-001904 (Mayo Clinic), CAH-003 (Sponsor)

Title Page

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Protocol Title: Treatment of sinus headache using a novel device that combines acoustic vibration with oscillating expiratory pressure: Randomized Controlled Trial

Protocol Number: CAH-003

Amendment Number: Not applicable

Brief Title: Novel device for treatment of sinus headache

Study Phase: Phase 3

SONIC

Sponsor Name: Healthy Humming LLC

Legal Registered Address: 1320 Veterans Rd. Suite D Columbia SC 29209 US

Regulatory Agency Identifier Number(s):

Registry	**ID**
ClinicalTrials.gov	NCT03906968

Approval Date:

Sponsor Signatory:

David Lewis, MD	**Date**
Owner and Operator	

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List of Abbreviations

VAS	Visual Analogue Scale
BPI-SF	Brief Pain Inventory-Short Form
NOSE	Nasal Obstruction Symptom Evaluation
AE	Adverse Events
SAE	Serious adverse events
SD	Standard Deviation
MCID	Minimal clinically important difference

1. Protocol Summary

1.1. Synopsis

A parallel group treatment, phase 3, blinded, 2-arm study to investigate facial pain improvement with twice-daily use of a novel device combing acoustic vibration with oscillating expiratory pressure compared with a sham device in male and female participants ≥ 18 years of age with sinus pain/headache lacking objective evidence of sinonasal inflammation.

Rationale:

Sinus headache is a widely prevalent chronic disabling condition associated with marked impairments in quality of life. Patients commonly use the term sinus headache to refer to the concept of facial pain/headache originating in the sinonasal or facial region. However, studies have demonstrated that most patients with a chief complaint of sinus headache present without objective evidence of sinonasal inflammation and that symptoms are often related to a primary headache disorder.[1–4] Headache disorders are an almost universal human experience. Migraine is the third most prevalent disorder and the seventh highest cause of disability worldwide. The direct and indirect socioeconomic costs of headache are estimated at 14 billion dollars per year. Embedded in the sinus headache patient population is a large group of patients with primary headache disorders. Therefore, much of the therapeutic investigation aimed at treatment of sinus headaches has mirrored the more established primary headache literature. Several studies evaluating empiric treatment of sinus headache patients have demonstrated that a majority of patients improve with triptan therapy.[5–7] Perhaps the best study, published in 2007, is a multi-center (26 centers in the United States) randomized, double-blinded, placebo-controlled investigation of sumatriptan for treatment of sinus headaches.[8] Patients with sinus headache fulfilled IHS criteria for migraine, were without active or recent evidence of sinusitis, and had no prior treatment with migraine medications. A statistically significant benefit over placebo was noted with a single 50-mg dose of sumatriptan. Sixty-nine percent and 76% of patients treated with sumatriptan had a positive headache response compared with a placebo response of 43% and 49% at 2 and 4 hours, respectively.

Just as efficacy for triptans was first demonstrated and popularized in the primary headache literature before utilization in sinus headache studies, medical devices are following a similar trend with the recent advent of transcutaneous stimulation devices.[9] Recently, two studies investigating use of acoustic vibration with oscillating expiratory pressure applied to the nasal cavity for treatment of nasal congestion were performed looking at cohorts of patients with complaint of congestion.[10,11] One study demonstrated a significant improvement in objective measures of nasal obstruction and both demonstrated improvements in subjective measures of obstruction. Of note, in both studies, investigators noted improvements in facial pain/pressure. We recently conducted an open label trial to determine if simultaneous administration of acoustic vibration and oscillating expiratory pressure (using Sinusonic device) affects the severity of facial pain among patients with complaint of sinus headache. Twenty-nine patients (mean age 49 years, 55% female) completed our preliminary study without any major adverse events. At the 4-week follow-up, facial pain visual analog scale (VAS)[5] improved from mean standard deviation(SD) of 59.6+/-15.7 to 34.6+/-21.7($p<0.001$) and approximately 70% of patients achieving a minimal clinically important difference (MCID) across all pain metrics. Eighty-six percent of subjects would use device again and recommend it to others. As the next step, we propose a randomized controlled trial. Preliminary data demonstrates that the device is low-risk, with high patient satisfaction, and patients are able to perform the intervention at home with ease.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess relative improvements in facial pain/pressure after 8-weeks of twice daily use of the SinuSonic device compare to a sham device	• Facial pain visual analogue scale (0-10) (1-week recall period) • Facial pain visual analogue scale (0-10) (immediate 5-minute post use recall) • Brief Pain Inventory-Short Form
Secondary	
• Safety data • Device use satisfaction • Nasal obstruction	• Percent achieving a minimal clinically important difference • Adverse events reported via questionnaire (pain, epistaxis, etc.) • Percentage willing to use again and recommend device to others • Nasal obstruction symptom evaluation (NOSE) Score change

Overall Design:

This is a parallel, placebo-controlled multicenter randomized trial. The study population will consist of healthy volunteers with sinus headache/pain lacking objective evidence of chronic sinusitis. This will be a single-blinded study blinded to the participants. Because this study will involve minimal intervention from the investigators (i.e. participants will fill out surveys remotely), there will be minimal influence from the investigators and analysts end. Participants will be randomized to the treatment or the sham-placebo arm and the device they received (either device or sham), will be recorded in a secure database. Following screening, investigational intervention assignment will be performed by randomization in a 1:1, investigational device: sham ratio. Data will be collected and stored in an electronic data storage system.

Brief Summary:

The purpose of this study is to measure facial pain/pressure with a novel device using acoustic vibrations with oscillating expiratory pressure compared with a sham device in participants with sinus pain/headache lacking objective evidence of sinonasal inflammation.

Study details include:

- The study duration will be up to 12 months.
- The treatment duration will be up to 8 weeks.

- The visit frequency will be 0 visits. Participants will fill out questionnaires fielded via an electronic data capture system at 1 week, 2 weeks, 3 weeks, and 4 weeks of device use.

Number of Participants:

Approximately 120 participants will be screened to achieved 60 enrolled.

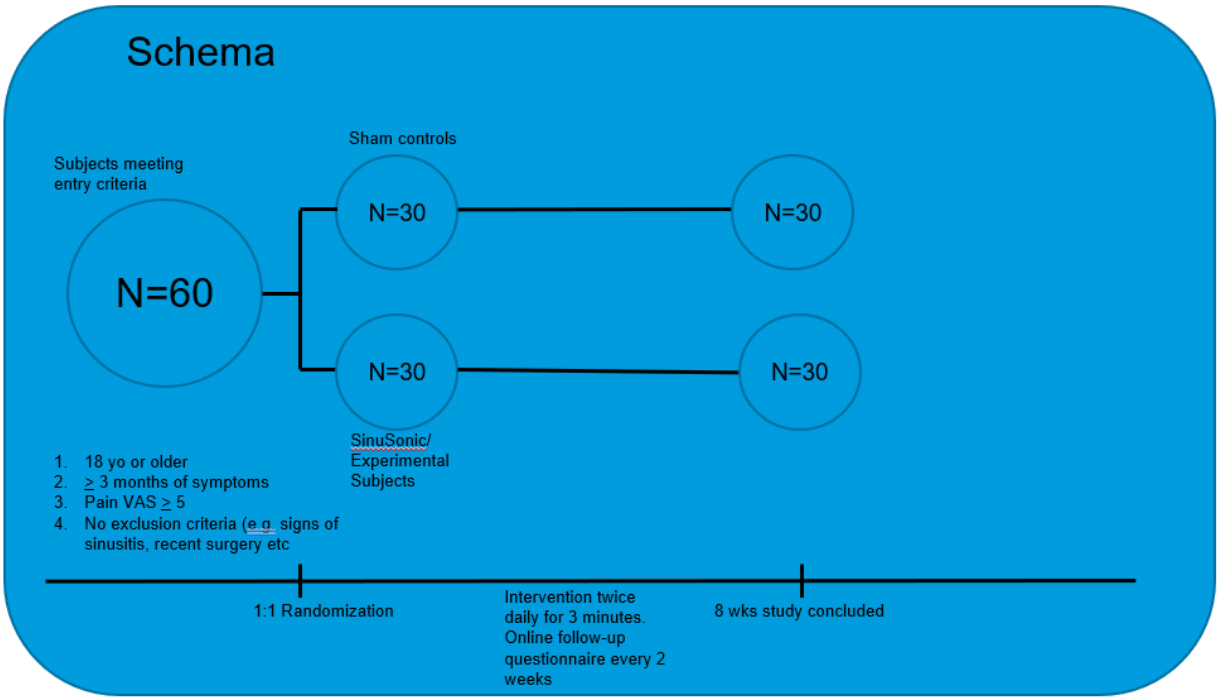
A maximum of 60 participants will be enrolled

Study Arms and Duration:

The total duration of study participation with screening, run-in (i.e., delivery of device), and device use is 11 weeks. Participants will use the investigational or sham device for 2 minutes, twice-daily for the entire 8-week study duration.

Data Monitoring/Other Committee:

1.2. Schema



1.3. Schedule of Activities (SoA)

Procedure	Screening (up to 3 weeks before Day 1)	Baseline (up to 3 weeks before Day 1)	Intervention Period (8 weeks)					E/D	Notes E/D = Early Discontinuation
			Day 1 +/- 3 Days	Week 2 +/- 3 Days	Week 4 +/- 3 Days	Week 6 +/- 3 Days	Week 8 +/- 3 Days		
Informed consent	X								
Inclusion and exclusion criteria	X								Recheck clinical status before randomization and/or first dose of investigational intervention.
Demographics	X								
Medical history (includes substance use)	X								Substances: drugs, alcohol, tobacco, and caffeine
Current medical conditions	X								
Randomization		X							
Study intervention			X	X	X	X	X		

Procedure	**Screening (up to 3 weeks before Day 1)**	**Baseline (up to 3 weeks before Day 1)**	**Intervention Period (8 weeks)**					**E/D**	**Notes** **E/D = Early Discontinuation**
			Day 1 +/- 3 Days	**Week 2** +/- 3 Days	**Week 4** +/- 3 Days	**Week 6** +/- 3 Days	**Week 8** +/- 3 Days		
AE review			←==========→						
SAE review: Including solicited administration-site events if applicable: pain or bleeding			←==========→					X	Pain Epistaxis
Device deficiencies			←==========→					X	
Concomitant medication review		X							

Procedure	**Screening (up to 3 weeks before Day 1)**	**Baseline (up to 3 weeks before Day 1)**	**Intervention Period (8 weeks)**					**E/D**	**Notes** **E/D = Early Discontinuation**
			Day 1 +/- 3 Days	**Week 2** +/- 3 Days	**Week 4** +/- 3 Days	**Week 6** +/- 3 Days	**Week 8** +/- 3 Days		
Efficacy questionnaire assessment: • VAS facial pain (1 week recall)	X		X	X	X	X	X		
Efficacy questionnaire assessment: • BPI-SF		X	X	X	X	X	X		
NOSE		X					X		
Device use satisfaction questionnaire							X		

2. Introduction

Sinusonic is an FDA registered novel medical device employing simultaneous acoustic vibrations and positive expiratory pressure to the nasal cavity that has been studied for management of nasal congestion and, more recently, sinus headache.

Sinus headache is a widely prevalent chronic disabling condition associated with marked impairments in quality of life. Patients commonly use the term sinus headache to refer to the concept of facial pain/headache originating in the sinonasal or facial region. However, studies have demonstrated that most patients with a chief complaint of sinus headache present without objective evidence of sinonasal inflammation and that symptoms are often related to a primary headache disorder.[4] Headache disorders are an almost universal human experience. Migraine is the third most prevalent disorder and the seventh highest cause of disability worldwide. The direct and indirect socioeconomic costs of headache are estimated at 14 billion dollars per year. Embedded in the sinus headache patient population is a large group of patients with primary headache disorders. Therefore, much of the therapeutic investigation aimed at treatment of sinus headaches has mirrored the more established primary headache literature. Several studies evaluating empiric treatment of sinus headache patients have demonstrated that a majority of patients improve with triptan therapy.[5–7] Perhaps the best study, published in 2007, is a multi-center (26 centers in the United States) randomized, double-blinded, placebo-controlled investigation of sumatriptan for treatment of sinus headaches.[8] Patients with sinus headache fulfilled IHS criteria for migraine, were without active or recent evidence of sinusitis, and had no prior treatment with migraine medications. A statistically significant benefit over placebo was noted with a single 50-mg dose of sumatriptan. Sixty-nine percent and 76% of patients treated with sumatriptan had a positive headache response compared with a placebo response of 43% and 49% at 2 and 4 hours, respectively.

Just as efficacy for triptans was first demonstrated and popularized in the primary headache literature before utilization in sinus headache studies, medical devices are following a similar trend with the recent advent of transcutaneous stimulation devices.[9] Recently, two studies investigating use of acoustic vibration with oscillating expiratory pressure applied to the nasal cavity for treatment of nasal congestion were performed looking at cohorts of patients with complaint of congestion.[10,11] One study demonstrated a significant improvement in objective measures of nasal obstruction and both demonstrated improvements in subjective measures of obstruction. Of note, in both studies, investigators noted improvements in facial pain/pressure.

We recently conducted an open label trial to determine if simultaneous administration of acoustic vibration and oscillating expiratory pressure (using Sinusonic device) affects the severity of facial pain among patients with complaint of sinus headache. Twenty-nine patients (mean age 49 years, 55% female) completed our preliminary study without any major adverse events. At 4-weeks follow-up, facial pain visual analog scale (VAS) improved from mean standard deviation(SD) of 59.6+/-15.7 to 34.6+/-21.7($p<0.001$) and approximately 70% of patients achieving a minimal clinically important difference (MCID) across all metrics. Eighty-six percent of subjects would use device again and recommend it to others. As the next step, we propose a randomized controlled trial. Preliminary data demonstrates that the device is low-risk, with high patient satisfaction, and patients are able to perform the intervention at home with ease.

In regards to device use, the device comes with a clear plastic tab a the base of the device. This tab must be removed prior to device use. For a full session, there is a trigger that must be held down after which

subjects should breathe in and out through their nose with a normal amount of force and speed. A gentle humming will be felt and heard and during exhalations, a fluttering sound will be appreciated. After a full session of use (2 minutes), the device will go into a rest mode for 6 minutes.

2.1. Study Rationale

An open label, single-arm trial to determine if simultaneous administration of acoustic vibration and oscillating expiratory pressure (using Sinusonic device) affects the severity of facial pain among patients with complaint of sinus headache was recently conducted. Twenty-nine patients (mean age 49 years, 55% female) completed this preliminary study without any major adverse events. At 4-weeks follow-up, facial pain visual analog scale (VAS) improved from mean standard deviation(SD) of 59.6+/-15.7 to 34.6+/-21.7($p<0.001$) and approximately 70% of patients achieving a minimal clinically important difference (MCID) across all metrics. Eighty-six percent of subjects would use device again and recommend it to others. As the next step, we propose a randomized controlled trial. Preliminary data demonstrates that the device is low-risk, with high patient satisfaction, and patients are able to perform the intervention at home with ease. The next step to determine device efficacy for the indication of sinus headache is to perform a randomized, controlled, clinical trial.

2.2. Background

The SinuSonic device utilizes acoustic vibration with oscillating expiratory pressure and was first studied for the indication of nasal obstruction. A previous study of acoustic vibrations with oscitating expiratory pressure found significant improvements in objective and subjective metrics of nasal congestion/obstruction suggesting that physiologic changes may occur within the nasal cavity in response to device use. There have been two studies from separate institutions investigating use of acoustic vibrations on nasal congestion and interestingly patients noted improvement in secondary symptoms of facial pain and pressure. Although these study were focused on patients with nasal congestion, subjects improvements in facial pressure was an interesting finding. The question thus arose whether a device employing simultaneous acoustic vibrations and positive expiratory pressure to the nasal cavity could improve symptoms in patients with chief complaint of sinus headache. We recently conducted an open label trial to determine if simultaneous administration of acoustic vibration and oscillating expiratory pressure (using Sinusonic device) affects the severity of facial pain among patients with complaint of sinus headache. Twenty-nine patients (mean age 49 years, 55% female) completed our preliminary study without any major adverse events. At the 4-week follow-up, facial pain visual analog scale (VAS) improved from mean standard deviation(SD) of 59.6+/-15.7 to 34.6+/-21.7($p<0.001$) and approximately 70% of patients achieving a minimal clinically important difference (MCID) across all facial pain metrics. Eighty-six percent of subjects would use device again and recommend it to others. As the next step, we propose a randomized controlled trial. Preliminary data demonstrates that the device is low-risk, with high patient satisfaction, and patients are able to perform the intervention at home with ease.

2.3. Benefit/Risk Assessment

Based on available clinical studies, application of acoustic vibration with positive end expiratory pressure to the nasal cavity is a relatively low-risk intervention. In two separate studies investigating its use for nasal congestion, no adverse events were reported in 90 subjects. In a more recent study looking specifically at patients with sinus headache, one patient noted mild epistaxis that resolved following use.

Similarly, four patients noted some mild-moderate discomfort during device use. No permanent or major adverse events were noted.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of SinuSonic device may be found in the package insert and summary of product characteristics.

2.3.1. Risk Assessment

Theoretical risks of device use include transient discomfort, nasal irritation, and epistaxis. In order to minimize risks, patients with any nasal crusting or ulceration on exam, or history of severe epistaxis will be excluded from the study.

2.3.2. Benefit Assessment

Benefits include the potential for this therapy to be efficacious in treating sinus headache and offer a low-risk solution with minimal side effects.

2.3.3. Overall Benefit Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with the SinuSonic device are justified by the anticipated benefits that may be afforded to participants with Sinus headache.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
• To determine superiority of SinuSonic intervention versus control in treatment of facial pain for patients with complaint of sinus headache that lack objective evidence of sinonasal inflammation	• Change in facial pain visual analogue scale at 8 weeks • Change in Brief Pain Inventory Short Form at 8 weeks
Secondary	
• To determine safety of device use	• Number and percent of subjects reporting pain with device use • Number and percent of subjects reporting epistaxis • Change in Nasal Obstruction Symptom Evalution (NOSE) Score at 8 weeks
Tertiary	
• To determine device use satisfaction	• Number and percent of subjects that would use the device again • Number and percent of subjects that would recommend the device to others

Primary estimand

The primary clinical question of interest is:

What is the improvement in facial pain measured by facial pain VAS, and BIP-SF in patients with sinus headache treated with SinuSonic device versus a sham device regardless of discontinuation of investigational intervention for any reason and regardless of initiation of rescue medication or change in background medication.

The estimand is described by the following attributes:

- Population: Patients with complaint of sinus headache lacking objective evidence of sinonasal inflammation of nasal endoscopy or imaging
- Endpoint:

  change from baseline to 8 weeks in facial pain VAS, and BPI-SF
- Treatment condition:

the investigational interventions regardless of discontinuation for any reason, with or without rescue medication or change in background medication (treatment policy strategy).

- Remaining intercurrent events:

  The intercurrent events “intervention discontinuation for any reason” and “initiation of rescue medication or change in background medication (dose and product)” are addressed by the treatment condition of interest attribute. There are no remaining intercurrent events anticipated at this time.

- Population-level summary:

  difference in mean changes between treatment conditions

Rationale for estimand: Facial pain is the primary complaint impacting quality-of-life in patients with sinus headache. Thus, we propose using 3 validated pain metrics to assess response to therapy. , .

Secondary estimand(s)

The clinical question of interest is for the secondary objective :

What is the difference in the proportion of sinus headache patients experiencing adverse events of pain and epistaxis between investigational SinuSonic treatment arm compared to sham control arm.

The estimand is described by the following attributes:

- Population:

  Patients with Sinus Headache

- Endpoint:

  Number and percent of subjects reporting pain with device use. Number and percent of subjects reporting epistaxis.

  Nasal obstruction symptom evaluation (NOSE) Score change

- Treatment condition:

  the investigational interventions regardless of discontinuation for any reason, with or without rescue medication or change in background medication (treatment policy strategy)

- Remaining intercurrent events:
- The intercurrent events “intervention discontinuation for any reason” and “initiation of rescue medication or change in background medication (dose and product)” are addressed by the treatment condition of interest attribute. There are no remaining intercurrent events anticipated at this time
- Population-level summary:

  Difference in proportion of patients experiencing adverse event

Rationale for estimand: Safety is a secondary endpoint and will be assessed by specifically tracking incidence of pain with device use and epistaxis. These adverse events are based on prior study results.

4. Study Design

4.1. Overall Design

- This is a parallel, two-arm, sham placebo controlled multicenter (Mayo AZ, Mayo FL and Mayo RST), clinical trial investigating use of the novel SinuSonic Device for sinus headache.
- The control group will be a sham device of similar appearance to the investigational device
- Participants will be healthy volunteers with complaint of sinus headache lacking objective evidence of sinonasal inflammation on exam or endoscopy
- Primary outcome measures of facial pain measured using facial pain VAS and BPI-SF will be assessed at baseline, Day 1, 2 week, 4 week, 6 week, and 8 weeks.
- Participants will be randomized in a 1:1 fashion; SinuSonic arm: Sham device, respectively.
- Total Duration of study participation will be 11 weeks; 2-3 weeks for screening and randomization and 8 weeks for the intervention component.

4.2. Scientific Rationale for Study Design

Sinus headaches are a widely prevalent condition and accounts for a significant portion of Otolaryngologic clinic visit. Patients lacking objective evidence of sinonasal inflammation are thought to have a primary headache disorder. The direct and indirect socioeconomic costs of headache are estimated at 14 billion dollars per year. Established barriers to headache therapy include failure to consult the appropriate subspecialty professional, failure to arrive at a specific diagnosis, and lack of appropriate acute and preventative therapy.(Dodick) There are frequently long wait times for patients to see neurologists. Many otolaryngologists are unfamiliar with prescribing neuroactive medications. From a patient's perspective, there is stigma associated with a diagnosis of headache disorders making it difficult sometimes for patients to accept this reality. SinuSonic utilizes acoustic vibration with positive end expiratory pressure and has been shown to improve subjective and objective measures of nasal obstruction. Interestingly, multiple studies using similar technology found improvements in patients complaining of facial pain. This led to a single-arm study investigating the devices use for treatment of sinus pain and results demonstrated a significant benefit across three pain metrics. The next logical step is to perform a randomized, sham-controlled trial. The parallel design comparing the investigational device to a sham device is best practice. The primary endpoint of interest includes facial pain measured by facial pain VAS, and BPI-SF,– two validated pain metrics. The primary end point of facial pain patient reported questionnaires directly impacts and assesses how patients feel and function. In order to be inclusive, all male and female patients 18 years and older are eligible to participate.

4.3. Justification for Dose

For this device, the term *dose* refers to the number of 3-minute treatment sessions.

Justification for device use is based on manufacturer's recommendation and efficacy with use in prior studies. The device will be turned on and silicone nasal mask placed over the nose and participants will breathe similar to their baseline nasal breathing against the device for 2 doses (two 3-minute treatment session). The device will be used twice daily, any the protocol will not allow any deviations in treatment.

4.4. End-of-Study Definition

The end of the study is defined as the date of the last questionnaire submission of the last participant in the.

A participant is considered to have completed the study if the participant has completed all periods of the study including submitting the final questionnaire, which is after 4 weeks of device use.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Participant must be ≥18 years of age inclusive, at the time of signing the informed consent.
2. Participants who are overtly healthy as determined by medical evaluation including medical history and physical examination.
3. Capable of giving signed informed consent
4. Facial pain or pressure for ≥ 3 months of symptom duration
5. Pain/pressure VAS score of ≥ 5
6. Lund MacKay Score of ≤ 3 with no single sinus score of 2

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Upper respiratory illness within the last 2 weeks
2. History of severe epistaxis
3. Allergic sensitivity to silicone or any other component of device
4. Sinonasal surgery in the last 3 months
5. Topical decongestant use in the last week
6. Nasal polyposis, purulence/edema, or other signs of sinusitis on exam
7. Sinusitis on imaging
8. Nasal crusting or ulceration on exam
9. Inability to read or understand English

5.3. Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently assigned to study intervention/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6. Study Intervention(s) and Concomitant Therapy

Study interventions are all pre-specified, investigational devices~~)~~ intended to be administered to the study participants during the study conduct.

6.1. Study Intervention(s) Administered

Table 1. Study Intervention(s) Administered

Intervention Label	Active	Sham
Intervention Name	SinuSonic device	Sham SinuSonic device
Intervention Description	The SinuSonic consists of a fully-disposable medical grade silicone nosepiece mounted to a resin body. The device is equipped with a flutter valve located at the top of the device which creates gentle, self-guided oscillating expiratory resistance. It provides administration of acoustic vibration at 128Hz and oscillating positive expiratory pressure.	Sham device with similar appearance that lacks positive end expiratory pressure and emits noise at non-therapeutic frequency.
Type	Active Device	Sham device
Dose Formulation	Other	Other
Unit Dose Strength(s)	2 minutes of device use	2 minutes of device use
Dosage Level(s)	Sinusonic device for 2 minutes, twice daily for 8 weeks	sham device for 2 minutes, twice daily for 8 weeks
Route of Administration	Other	Other
Use	experimental	sham comparator
IMP and NIMP/AxMP.	NIMP	NIMP
Sourcing	Acquired from the Healthy Humming LLC, Columbia, SC by the study PI	Acquired from the Healthy Humming LLC, Columbia, SC by the study PI
Packaging and Labeling	Device for study intervention will be provided in cardboard box. The active and sham device will be labelled identically and will include instructions on use and storage.	Sham device will be provided in a cardboard box. The active and sham device will be labelled identically and will include instructions on use and storage.

Table 2. Study Arm(s)

Arm Title	Arm 1	Arm 2
Arm Type	Active device	Sham comparator
Arm Description	Sinusonic device for 2 minutes, twice daily for 8 weeks	sham device for 2 minutes, twice daily for 8 weeks
Associated Intervention Labels	Not applicable	No applicable

6.1.1. Medical Devices

1. The Healthy Humming LLC manufactured medical devices (SinuSonic and sham device) will be provided for use in this study.
2. Instructions for medical device use are provided **in document "Healthy Humming Instructional Booklet'**
3. All device deficiencies (including malfunction, use error and inadequate labelling) shall be documented and reported by the investigator throughout the clinical investigation

6.2. Preparation, Handling, Storage, and Accountability

4. Only participants enrolled in the study may receive study intervention, and participants themselves may administer study intervention.
5. The investigator is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

6.3. Assignment to Study Intervention

On Day 0 (baseline), participants will be assigned a unique number (Subject ID) in ascending numerical order at each study site. The randomization will be implemented in the EDC system, according to the randomization schedule generated prior to the study by the statistics department at Mayo Clinic. Each participant will be dispensed blinded study intervention .

6.4. Blinding, Masking

Participants will be randomly assigned in a 1:1 ratio to receive study intervention. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. To maintain this blind, an otherwise uninvolved third party will be responsible for the reconstitution and dispensation of all study intervention and will endeavor to ensure that there are no differences in time taken to dispense following randomization.

Sponsor safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or sponsor policy.

6.5. Study Intervention Compliance

Participant will self-administer the medical intervention and compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning during the study visits, where participants will be asked to report the number of days in past two weeks that they used the study intervention and documented in the source documents and relevant form. The adherence to the prescribed dosage regimen should be recorded.

Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

6.6. Dose Modification

Any dose modification, including the duration and frequency of administration of sinusonic/sham device will not be permitted.

6.7. Continued Access to Study Intervention after the End of the Study

There will be no provision to provide continued access to study intervention after the end of the study. However, the active study intervention (sinusonic device) is available for purchase commercially.

6.8. Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

There are no restrictions on the concomitant medications given that the Sinusonic device is not expected to have an interaction with the study medication. However, to prevent confounding effects of a newly initiated treatment, participants will be required to be stable on their medication for at least 7 days before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Acetaminophen, at doses of ≤ 2 grams/day, is permitted for use any time during the study. Initiation of other concomitant medications during the study period may be considered on a case-by-case basis by the investigator.

6.8.1. Rescue Medicine

The study site will not supply any rescue medication.

The use of rescue medications is allowable at any time during the study. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

6.9. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant should, if at all possible, remain in the study to be evaluated for 1 week. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

6.10. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).
- A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from the study intervention and the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

6.11. Lost to Follow up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

7. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management [(eg, blood count, ENT examination)] and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.
- Safety/laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

7.1. Efficacy and/or Immunogenicity Assessments

Study outcomes will be assessed using the facial pain visual analogue scale (VAS)[5], and Brief Pain Inventory-Short Form (BPI-SF)[13,14]. The facial pain VAS score is a scale from 0-100 millimeters (mm) and asks patients to rate the severity of their facial pain over a previous one week recall period with higher scores indicating greater pain intensity. Additionally, a current VAS pain score and an immediate 5-minute post-use current VAS pain score will be assessed. A prior study looking at orofacial pain reported a minimal clinically important difference (MCID) of 1.2 for VAS pain. The BPI-SF assesses pain at its "worst", "least", "mean", and "now" (current pain). In clinical trials, the items "worst" and "mean" have been each used singly to represent the pain severity. Worst and mean pain will be assessed over a previous one week recall period. BPI-SF also measures how much pain interferes (BPI interference) with seven daily activities including general activity, walking, work, mood, enjoyment of life, relations with others, and sleep. BPI pain interference is typically scored as the mean of the seven interference items. All items are rated on a 0-10 scale with 0 representing no pain/no interference and 10 representing pain as bad as you can imagine/interferes completely. A distribution-based approach using one-half the SD will be used to determine MCID values for BPI-SF, as there is a paucity of research assessing the MCIDs for these pain measures for facial pain/headache. Planned timepoints for all efficacy assessments are provided in the SoA.

7.2. Safety Assessments

The use of SinuSonic device is not associated with significant safety concerns in prior studies. However, to assess safety information, study team will conduct a detailed medical review of systems at each visit (including baseline) to establish the presence of any ongoing medical issues at the time of study entry and track changes in these issues during the course of study participation. The medical review of system will

also allow for detection of any new onset medical issue (that may post safety concern) with the use of SinuSonic device. Planned timepoints for all safety assessments are provided in the SoA.

7.2.1. Physical Examinations

- Patients will be evaluated in ENT clinic with nasal endoscopy and/or CT imaging prior to study enrollment as part of standard of care evaluation. If patient has complaint of sinus headache and is without objective evidence of sinonasal inflammation (Lund MacKay score ≤ 3 without a single sinus score of 2), they will be offered referral to the study.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.2.2. Pregnancy Testing

The use of SinuSonic device is not expected to impact fetus. Therefore, pregnancy testing will not be conducted during the course of study. However, if a participant reports becoming pregnant, it will be recorded in the study and outcome of the pregnancy will be monitored with participant's permission.

7.2.3. Suicidal Ideation and Behavior Risk Monitoring

There will not be a separate suicidal ideation and behavior (SIB) risk monitoring as the study device (SinuSonic) is not known to be active in the CNS, will not be studied for activity in CNS, and is not being developed for any psychiatric or neurologic indication. The Sinusonic device is not known to affect mood, cognition, or behavior via their direct or indirect effects on the CNS and the study device is not similar to any other intervention that have had SIB reported. However, information about SIB will be collected as part of the assessment of psychiatric system in the medical review of system.

7.3. Adverse Events (AEs) Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of device-related safety events, adverse device effects (ADEs), and serious adverse device effects (SADEs) can be found in Appendix 1. Device deficiencies are covered in Section 8.4.9.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 1.

7.3.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the start of study intervention until exit from the study at the timepoints specified in the SoA (Section 1.3).

All AEs will be collected from the start of study intervention until the exit from study at the timepoints specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 1. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

7.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

7.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 1.

7.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IDFU and will notify the IRB/IEC, if appropriate according to local requirements.

7.3.5. Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

The following disease-related events (DREs) are common in participants with Sinus Headache and can be serious/life threatening:

- None

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of an SAE. These events will be recorded within the appropriate timeframe.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an AE/SAE (instead of a DRE):

The event is, in the investigator’s opinion, of greater intensity, frequency, or duration than expected for the individual participant.

The investigator considers that there is a reasonable possibility that the event was related to study intervention.

7.3.6. Medical Device Deficiencies

Medical devices are being provided for use in this study as the study intervention. To fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Appendix 1.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will follow the processes outlined in Appendix 1 of the protocol.

7.3.6.1. Time Period for Detecting Medical Device Deficiencies

- Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such a deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device deficiencies is provided in Appendix 1.

7.3.6.2. Follow-up of Medical Device Deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

7.3.6.3. Prompt Reporting of Device Deficiencies to the Sponsor

- Device deficiencies will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device deficiency.
- The medical device deficiency report form will be sent to the sponsor by email.
- The sponsor will be the contact for the receipt of device deficiency reports.

7.3.6.4. Regulatory Reporting Requirements for Device Deficiencies

- The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

8. Statistical Considerations

The analysis and reporting will be done on all data from all participants at the time the study ends.

8.1. Statistical Hypotheses

The primary objective is to demonstrate that Sinusonic device is superior to Sham control in achieving improvements in facial pain measured by facial pain VAS, and BPI-SF at 8 weeks. Thus, the null hypothesis to be tested in relation to the primary estimand is as follows:

- Null hypothesis: Sinusonic is not different from sham control with respect to the achievement of improvement in facial pain VAS, and BPI-SF at 8 weeks.

The null and alternative hypotheses corresponding to the secondary estimands are as follows:

Secondary objective [1]:

- Null hypothesis: SinuSonic device is not different from Sham control with respect to the achievement of adverse event rate at 8 weeks.

Secondary objective [2]:

- Null hypothesis: Sinusonic device is not different from Sham control with respect to device satisfaction rate at 8 weeks

8.1.1. Multiplicity Adjustment

A closed testing procedure that controls the family wise error rate in the strong sense at the overall [5]% level will be applied. The statistical comparisons for the primary efficacy endpoint and the key secondary endpoints will be carried out in the hierarchical order as indicated in Section 9.1. This means that the statistical hypotheses are tested in the prespecified order at the same significance level of $\alpha = [0.05]$ as long as all preceding hypotheses are rejected. Once a hypothesis is not rejected, subsequent hypotheses cannot be formally tested and therefore cannot be rejected.

8.2. Analysis Sets

Example 1:

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

Participant Analysis Set	Description
Full analysis set (FAS)	• All randomized participants.
Safety analysis set (SAS)	• All participants who are exposed to investigational intervention.

The full analysis set will be used to analyze endpoints related to the efficacy objectives and the safety analysis set will be used to analyze the endpoints and assessments related to safety.

For the efficacy analyses, participants will be included in the analyses according to the planned investigational intervention; whereas for safety analyses, participants will be included in the analyses according to the investigational intervention they received.

8.3. Statistical Analyses

8.3.1. General Considerations

Statistical analysis will be conducted using SPSS version 25 (Armonk, NY: IBM Corp). Descriptive statistics such as means, range, standard deviations, frequencies, and percentages will be generated in order to present the baseline characteristics of both treatment arms. All continuous variables will be tested for normal distribution as determined by the Shapiro-Wilk test. To evaluate differences in outcome metrics between treatment arms (SinuSonic group vs sham control), paired t-tests will be used for normally distributed variables. Wilcoxon signed rank tests were used for non-normally distributed or ordinal variables. For all tests, a value of $p \leq 0.05$ will be considered statistically significant. The mean change between baseline and follow-up variables of interest will be calculated and measured against previously reported MCID thresholds when available or by using one-half of the baseline SD if not previously reported. Any missing data points will be excluded from analysis and handled similarly across all data points.

8.3.1.1. Main Analytical Approach

Statistical analysis will be conducted using SPSS version 25 (Armonk, NY: IBM Corp). Descriptive statistics such as means, range, standard deviations, frequencies, and percentages will be generated in order to present the baseline characteristics of both treatment arms. All continuous variables will be tested for normal distribution as determined by the Shapiro-Wilk test. To evaluate differences in outcome metrics between treatment arms (SinuSonic group vs sham control), paired t-tests will be used for normally distributed variables. Wilcoxon signed rank tests were used for non-normally distributed or ordinal variables. For all tests, a value of $p \leq 0.05$ will be considered statistically significant. The mean change between baseline and follow-up variables of interest will be calculated and measured against previously reported MCID thresholds when available or by using one-half of the baseline SD if not previously reported. Any missing data points will be excluded from analysis and handled similarly across all data points.

8.3.2. Other Analyses

Subgroup analyses of the primary endpoint and confirmatory secondary endpoints will be made to assess consistency of the investigational intervention effect across the following subgroups:

- Age group: < 65 vs ≥ 65 years
- Sex: female vs male
- Race: white vs black vs. other

If the number of participants is too small (less than [10%]) within a subgroup, then the subgroup categories may be redefined prior to unblinding the study. The analyses will be conducted using a test for heterogeneity and results will be presented on forest plots presenting the estimated study arm difference and 95% confidence intervals. Further details on the statistical analysis will be provided in the SAP.

8.4. Sample Size Determination

Approximately 60 participants will be enrolled. The sample size calculation is based on the primary efficacy estimand and its endpoint.
It is assumed that the proportion of participants achieving response for facial pain VAS is [30]% in the placebo intervention arm and [70]% in the arm receiving [intervention SinuSonic]. Using the normal approximation method for a 2-sided statistical test as described in Section 9.3.2, a study with an overall sample size of N = 60] participants will have over 90% power to detect a treatment difference between the two investigational interventions at a type-1 error level of 5%.

9. Supporting Documentation and Operational Considerations

9.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
    - Applicable ICH Good Clinical Practice (GCP) guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator's brochure, IDFU, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations

Investigators and sub investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

9.1.2. Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

9.1.3. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

9.1.4. Dissemination of Clinical Study Data

The trial will be listed on clinicaltrial.gov and there is plan for publication following analysis of data to a peer-reviewed journal

9.1.5. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in online questionnaire.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 10 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

9.1.6. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in source data acknowledgement
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the CRF 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.

9.1.7. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

9.1.8. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

9.1.9. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of Unsolicited and Solicited AE

- An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during an interview with the participants and by review of available medical records at the next visit.
- Solicited AEs are predefined local and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease, or more severe than expected for the participant's condition)
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>not</u> Meeting the AE Definition

- Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

9.1.10. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. Is life threatening

The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions not resulting in hospitalization, or development of intervention dependency or intervention abuse.

9.1.11. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild:
  A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate:
  A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe:
  A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- New or updated information will be recorded in the originally submitted documents.

9.1.12. Reporting of SAEs

SAE Reporting to via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to medical monitor/SAE coordinator will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the medical monitor/SAE coordinator by telephone.

SAE Reporting to medical monitor/SAE coordinator **via Paper Data Collection Tool**

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.

9.2. Appendix 1: Medical Device AEs, ADEs, SAEs, SADEs, USADEs and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).
- Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 6.1.1 for the list of sponsor medical devices.

9.2.1. Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition

- A medical device AE is any untoward medical occurrence in a clinical study participant, users, or other persons, temporally associated with the use of study intervention, whether or not considered related to the investigational medical device. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices.
- An adverse device effect (ADE) is defined as an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

9.2.2. Definition of Medical Device SAE, SADE and USADE

A Medical Device SAE is an any serious adverse event that:

a. Led to death

b. Led to serious deterioration in the health of the participant, that either resulted in:

- A life-threatening illness or injury. The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe.
- A permanent impairment of a body structure or a body function.
- Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- Chronic disease (MDR 2017/745).

c. Led to fetal distress, fetal death, or a congenital abnormality or birth defect

SADE definition

- An SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE.
- Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

Unanticipated SADE (USADE) definition

- An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is defined as a serious adverse device effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report (see Section 2.3).

9.2.3. Definition of Device Deficiency

- A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequacy of the information supplied by the manufacturer.

9.2.4. Recording and Follow-Up of Medical Device AE and/or SAE and Device Deficiencies

Medical Device AE, SAE, and Device Deficiency Recording

- When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one of the following categories:

- Mild:
  A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate:
  A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

- Severe:
  A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency. The investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship, cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IDFU or product information as part of the assessment.
- The investigator must review and provide an assessment of causality for each AE/SAE/device deficiency and document this in the medical notes.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to medical monitor/SAE coordinator. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to medical monitor/SAE coordinator.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of Medical Device AE/SAE and device deficiency

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by medical monitor/SAE coordinator to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed form.
- The investigator will submit any updated SAE data to medical monitor/SAE coordinator within 24 hours of receipt of the information.

9.2.5. Reporting of Medical Device SAEs

Medical Device SAE Reporting to medical monitor/SAE coordinator **via an Electronic Data Collection Tool**

- The primary mechanism for reporting an SAE to medical monitor/SAE coordinator will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next table) to report the event within 24 hours.

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next table) or to the medical monitor/SAE coordinator by telephone.

Medical Device SAE Reporting to medical monitor/SAE coordinator **via Paper Data Collection Tool**

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the medical monitor/SAE coordinator.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE paper data collection tool within the designated reporting time frames.

9.2.6. Reporting of SADEs

SADE Reporting to medical monitor/SAE coordinator

NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- The sponsor will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.

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