The RhinAer® Procedure for Treatment of CHronic RhInitis - A Prospective, MulticeNter Randomized ConTrolled TRial Comparing RhinAer to Sham Control (RHINTRAC)

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Co-Principal Investigators:

J. Pablo Stolovitzky, MD
ENT of Georgia North
1790 Presidential Cir, Suite A
Snellville, GA 30078
Phone: 404-297-4230
email: sto@entofga.com

Mas Takashima, MD
The Sinus Center at Houston Methodist Hospital
6550 Fannin Street #1701
Houston, TX 77030
Phone: 713-441-1368
email: mtakashima@houstonmethodist.org

Sponsor:

Aerin Medical, Inc.
232 E. Caribbean Drive
Sunnyvale, CA 94089

Contact: Anais Laborde
Director of Clinical Affairs
Phone: 650-518-9624
email: alaborde@aerinmedical.com

INVESTIGATOR

I, the undersigned, certify that I have reviewed this Clinical Investigational Plan and agree to abide by the terms of the study described herein and within the Investigator Agreement, Clinical Trial Agreement and according to the Declaration of Helsinki and The Belmont Report as well as any conditions imposed by the reviewing IRB, U.S. FDA or other regulatory agency.

Print Name: _____

Signature: _____ Date: _____

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Protocol Summary

Title of Study:	The **R**hinAer® Procedure for Treatment of C**H**ronic Rh**I**nitis - A Prospective, Multice**N**ter Randomized Con**T**rolled T**R**ial Comparing Rhin**A**er to Sham **C**ontrol (RHINTRAC)
Purpose:	The purpose of this study is to compare the RhinAer procedure to treat tissue in the posterior nasal nerve area to improve symptoms in adults diagnosed with chronic rhinitis with a sham procedure that duplicates the actual procedure as closely as possible absent the delivery of radiofrequency (RF) energy to the nasal tissue.
Indications for Use:	The RhinAer Stylus is indicated for use in otorhinolaryngology (ENT) surgery for the destruction of soft tissue in the nasal airway, including in posterior nasal nerve regions in patients with chronic rhinitis. The Aerin Console is an electrosurgical system intended to generate radiofrequency electrical current for the use of an Aerin Medical Stylus. The Aerin Console is indicated for use in small clinic, office, or hospital environments.
RhinAer Treatment:	The RhinAer procedure will be performed in the study clinic using the RhinAer Stylus and Aerin Console. The RhinAer Stylus is a disposable handheld device capable of delivering bipolar radiofrequency energy to tissue when connected to the Aerin Console radiofrequency generating device. Participants will have the portion of the nasal cavity mucosa overlying the region of the posterior nasal nerve (the posterior middle meatus and posterior inferior turbinate) in both nostrils treated during a single study procedure session. Each nostril will be treated at 1, 2, 3, 4 or 5 nonoverlapping positions depending on the size of the target treatment area. Treatment settings to be used are temperature 60 °C, power 4 watts, treatment time 12 seconds, and cooling time 0 seconds.
Control Treatment:	The control treatment will be performed in the study clinic using the RhinAer Stylus while audible sounds that accurately simulate the Aerin Console's active treatment are produced even though RF energy is not being generated or delivered. All other aspects of the procedure will be the same as used for the active treatment, including administration of anesthetic agent(s).
Study Design:	The study is designed as a multicenter (up to 20 sites), prospective, randomized, controlled superiority trial with a one-way crossover component available to participants randomized to the control procedure. A 2:1 site-stratified randomization will be used to allocate participants to either the RhinAer procedure or treatment with the sham (control) procedure to provide up to 120 total participants in the following groups:

	• 80 active treatment receiving the RhinAer procedure • 40 inactive treatment receiving the sham procedure All participants will be evaluated prior to treatment and following treatment at week 4 (1 month) and week 13 (3 months). The 3-month evaluation will be used for the primary endpoint analysis. The study will have an extended follow-up phase with evaluations conducted at 6 months (26 weeks), 12 months (52 weeks) and 24 months (104 weeks) to provide additional information on longer-term efficacy and duration of treatment effect. Participants receiving the sham procedure may elect to crossover and receive the active RhinAer procedure within 30 days after the 3- or 6-month evaluation provided they still meet all original eligibility criteria. New baseline information will be collected prior to the RhinAer procedure. Continued follow-up will be conducted at 1, 3, 6, 12, and 24 months after the RhinAer procedure. Participants that received the sham procedure who do not crossover or no longer meet all eligibility criteria may elect to exit from the study following the 3- or 6-month evaluation.
Study Objective:	The primary objective is to assess the performance of the RhinAer procedure compared to a sham procedure with respect to individual participant success rates when used as a treatment for chronic rhinitis. A secondary objective is evaluation of treatment effect duration through an extended follow-up to 2 years. Individual participant success (responder) is defined as at least 30% improvement (decrease) in the 24-hour reflective Total Nasal Symptom Score (rTNSS).
Primary Study Hypothesis:	The proportion of participants receiving the RhinAer procedure with a successful outcome (responders) will exceed the proportion of participants receiving the sham procedure with a successful outcome (responders) at 3 months posttreatment.
Primary Endpoint:	The primary endpoint is the responder rate at 3 months after the procedure for the randomized participants.
Secondary Endpoints:	• Mean change in rTNSS from baseline to 3 months after the procedure. • Frequency of device-related and procedure-related serious adverse events through the 3-month evaluation.
Other Effectiveness and Safety Measures:	Adverse events - Incidence (type and category) of adverse events overall and by follow-up interval. Nasal Assessment - The target posterior nasal nerve area within each nostril will be visually assessed at baseline, just prior to treatment,

immediately after treatment, at 1 month, 3 months, and 6 months after the procedure. The use of an endoscope for visual assessment is required. Representative still photographs or video of each nostril will be captured for each assessment.

Visual analog scale (VAS) for pain - perception of pain associated with the procedure on a 0 to 100 mm scale with 0 indicating no pain and 100 indicating the worst pain ever assessed posttreatment, 1 month, and 3 months.

rTNSS:

- Mean and mean change from baseline at the 3-, 6-, 12-, and 24-month follow-up evaluations.
- rTNSS Individual Nasal Symptom Scores (rhinorrhea, nasal congestion, nasal itching, and sneezing) at baseline and the 3-, 6-, 12-, and 24-month follow-up evaluations.
- Proportion of responders based on improvement in rTNSS at the 3-, 6-, 12-, and 24-month follow-up evaluations.

Other rhinitis symptoms - current symptoms of cough and postnasal drip or excess mucous in the throat, rated on a 0 to 3 scale from 'No symptoms' to 'Severe symptoms', assessed at baseline and the 3-, 6-, 12-, and 24-month follow-up evaluations.

MiniRQLQ:

- MiniRQLQ mean and change from baseline at the 3-, 6-, 12-, and 24-month follow-up evaluation.
- MiniRQLQ domain scores (activity limitations, practical problems, nose symptoms, eye symptoms, and other symptoms) at baseline and the 3-, 6-, 12-, and 24-month follow-up evaluations.

Participant satisfaction assessment - Five-question self-reported survey of satisfaction with the procedure and recommendation to others administered at the 3-, 6-, 12-, and 24-month, follow-up evaluations.

Change in amount of "as needed" medication/device use for chronic rhinitis symptoms - Self-reported assessment of an increase, no change, or decrease in medications and/or devices being used for treatment of symptoms compared to use prior to the procedure administered at the 3-, 6-, 12-, and 24-month follow-up evaluations.

Medications - Medications associated with relief or treatment of chronic rhinitis symptoms will be documented at baseline and updated as necessary at each evaluation. In addition, medications associated with treatment of adverse events will be documented.

Length of Study:	The primary endpoint will be evaluated at 3 months. In addition, evaluations at 6, 12, and 24 months after treatment will extend follow-up to 2 years for evaluation of longer-term efficacy. Participants receiving the sham procedure and meeting the original eligibility requirements may elect to crossover and receive the active RhinAer procedure within 30 days after the 3- or 6-month evaluation with continued follow-up for 24 more months for a total of up to 31 months of follow-up. Enrollment is anticipated to be completed within 12 months. Therefore, total study duration is anticipated to be approximately 43 months.
Study Centers:	up to 20
Participants:	120
Inclusion Criteria:	1. Age 18 to 85 years (inclusively). 2. Willing and able to provide informed consent. 3. Willing and able to comply with the subject-specific requirements outlined in the Study Protocol. 4. Seeking treatment for chronic rhinitis symptoms of at least 6 months duration and willing to undergo an office-based procedure. 5. Moderate to severe symptoms of rhinorrhea (rTNSS rating of 2 or 3 for rhinorrhea). 6. Mild to severe symptoms of nasal congestion (rTNSS rating of 1, 2 or 3 for congestion). 7. rTNSS $\geq$ 6.
Exclusion Criteria:	1. Anatomic obstructions that in the investigator's opinion limit access to the posterior nasal passage. 2. Altered anatomy of the posterior nose as a result of prior sinus or nasal surgery or injury. 3. Active nasal or sinus infection. 4. History of significant dry eye. 5. History of any of the following: chronic epistaxis, documented episodes of significant nose bleeds in the past 3 months, rhinitis medicamentosa, head or neck irradiation. 6. Have rhinitis symptoms only on a seasonal basis due to allergies.

7. Known or suspected allergies or contraindications to the anesthetic agents and/or antibiotic medications to be used during the study procedure session.
8. Known or suspected to be pregnant or is lactating.
9. Participating in another clinical research study.
10. Has any condition that predisposes to excessive bleeding.
11. Is taking anticoagulants (eg, warfarin, Plavix) or 325 mg aspirin that cannot be discontinued before the procedure.
12. Has previous procedure or surgery for chronic rhinitis.
13. Other medical conditions which in the opinion of the investigator would predispose the subject to poor wound healing, increased surgical risk, or poor compliance with the requirements of the study.

Schedule of Events

	Screening	Treatment		Follow-up (office)			Extended follow-up (remote)	
		Procedure	Immediate Postprocedure	1 Month (4 weeks)	3 Months[1] (13 weeks)	6 Months[1] (26 weeks)	12 Months (52 weeks)	24 Months (104 weeks)
Window (days)	**(-30)**	**(0)**	**(0)**	**(± 7)**	**(± 14)**	**(± 30)**	**(± 30)**	**(± 30)**
Activity / Assessment								
Eligibility	X							
Consent	X							
Demographics / Medical History	X							
Physician Evaluations								
Nasal assessment (physical, endoscopic)	X	X[2]	X	X	X	X		
Current medication use (study relevant)	X	X[2]	X	X	X	X	X	X
Participant Evaluations								
VAS nasal pain			X	X	X			
Rhinitis symptoms (rTNSS, cough, and postnasal drip)	X	X[2]			X	X	X	X
MiniRQLQ	X	X[2]			X	X	X	X
Participant Satisfaction Survey					X	X	X	X
Adverse Events	X	X[2]	X	X	X	X	X	X

[1]Control participants eligible to crossover and receive RhinAer procedure.

[2]Repeat only on day of treatment if screening was conducted after 72 hours day of procedure.

List of Abbreviations

AADE – Anticipated Adverse Device Effect

ADE – Adverse Device Effect

AE – Adverse Event

ANOVA – analysis of variance

AR – allergic rhinitis

BMI – Body Mass Index

CONSORT – Consolidated Standards of Reporting Trials

CRF (eCRF) – Case Report Form (electronic Case Report Form)

CTA – Clinical Trial Agreement

EDC – Electronic data capture

ENT – Ear, Nose, Throat; medical field of otorhinolaryngology (otolaryngology)

FDA – Food and Drug Administration (US)

FWA – Federalwide Assurance for the Protection of Human Subjects

GCP – Good Clinical Practice

HIPAA – Health Insurance Portability and Accountability Act

ICH – International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

ICMJE – International Committee of Medical Journal Editors

IRB – Institutional Review Board

ISO – International Organization for Standardization

ITT – Intent-To-Treat

MCID – minimal clinically important difference

MiniRQLQ – Mini Rhinoconjunctivitis Quality of Life Questionnaire

NAR – nonallergic rhinitis

PNN – posterior nasal nerve

PRN – Pro Re Nata (as needed or as required)

RF – Radiofrequency

RFTR – Radiofrequency turbinate reduction

rTNSS – Total Nasal Symptom Score (r, reflective)

SADE – Serious Adverse Device Effect

SAE – Serious Adverse Event

SD – standard deviation

UADE (USADE) – Unanticipated (Serious) Adverse Device Effect

VAS – Visual Analog Scale

1.0 Introduction and Background

Rhinitis is a condition in which the membrane lining the nasal cavity becomes irritated and swollen. Patients typically present with complaints of congestion, runny nose, sneezing, nasal itching, irritated throat, and postnasal discharge. The 2 major classifications of rhinitis are allergic rhinitis (AR) and nonallergic rhinitis (NAR). AR may be caused by allergens such as pollen, pet dander, mold or dust. NAR may result from triggers that include chemicals, irritants, and medications.[1]

Chronic rhinitis may significantly impact a patient's quality of life by causing fatigue, headache, and sleep disturbance, resulting in cognitive impairment and diminished productivity and thereby posing both a personal and financial burden.[2]

The nasal cavity is covered with an epithelial lining made of cells which interact to serve appropriate functions in the nasal environment.[3] Cells located in the epithelial lining include ciliated cells, goblet cells and seromucous glands. The goblet cell produces a carbohydrate called mucin which attracts water and forms a gelatin-like substance better known as mucus.[3,4] The goblet cell is the most prominent mucus producing cell in the nasal membrane and, together with the seromucous glands, works to provide mucus to the nasal mucosal surface. The purpose of mucus is to protect the body from substances that can enter through the nasal cavity. Secretion is stimulated by dust or foreign substances that enter the nasal passage. Mucus is cleared by movement of the cilia and disposed to the stomach.[4] Regulation of the seromucous glands and mucosal blood supply occurs through parasympathetic and adrenergic stimulation via the vidian nerve, posterior nasal nerves and other nerves. In some situations, the mucosa may become hyperresponsive to stimuli and produce excess mucus, resulting in rhinorrhea or postnasal discharge.

Patients presenting with runny or congested nose, watery eyes, irritated throat and/or sneezing symptoms are evaluated to understand the types of triggers that may prompt the symptoms experienced. Understanding the patient's respiratory irritants may help differentiate between allergic or nonallergic responses.[2,5,6] Physicians can observe the nasal structures by transnasal endoscopy to rule out anatomic conditions mimicking rhinitis. Common anatomical obstructions that may cause rhinitis-like symptoms are nasal polyps, deviated septum, foreign bodies, nasal tumors and turbinate hypertropy.[1,2] Treatment of these anatomical causes, if present, may relieve rhinitis symptoms. The most common methods to determine allergy sensitivity are percutaneous skin testing and the allergen-specific immunoglobulin E (IgE) antibody testing. These tests can identify allergens the patient should avoid. However, if an allergic cause is eliminated through this testing, a diagnosis of nonallergic rhinitis could be made.[1,2]

Treatment to reduce symptoms may include nasal irrigation (nasal lavage) multiple times a day with a saline rinse, use of over-the-counter oral or nasal antihistamines and/or corticosteroid sprays, and allergen immunotherapy in AR patients. Patients with nonallergic rhinitis are less likely to respond to oral antihistamines, but may find their symptoms relieved with intranasal antihistamine, corticosteroid or anticholinergic sprays. Patients whose symptoms are not adequately relieved with conservative treatment often seek treatment to alleviate symptoms and may be candidates for nasal

surgery. Vidian neurectomy is a surgical option to relieve chronic rhinitis symptoms as the vidian nerve supplies autonomic input to the nasal mucosa (as well as the palate and the lacrimal gland). While this surgery has been performed for over 50 years, it is controversial since access to the nerve can be technically difficult and complications with numerous surrounding important structures can occur.[7,8] Common procedural side effects include dry eyes, nasal dryness or crusting and mild pain. More significant risks may include hemorrhage, vision loss and palate/lip/cheek numbness. In addition, improvement in symptoms is often unpredictable.[7] An alternative neurectomy target is the posterior nasal nerve (PNN). The advantage of the PNN over the vidian nerve is its more limited innervation and activity on the nasal mucosa and its physical distance from other major nerve structures. As a result, complications associated with PNN surgery are less significant and occur less frequently than those described for vidian neurectomy,[7] while still providing significant improvement in quality of life.[9] A recent development is use of a cryosurgical probe to ablate PNN tissue.[10] Significant improvement from baseline in Total Nasal Symptom Score (TNSS) using this cryosurgical probe was observed.

Radiofrequency (RF) energy has been used for decades in the fields of otorhinolaryngology, neurosurgery, cardiology, urology and general surgery. ENT surgeons currently use radiofrequency energy in numerous nasal therapies, including radiofrequency turbinate reduction (RFTR), which is a minimally invasive surgical option that can reduce tissue volume in a precise, targeted manner. There have been multiple studies analyzing the safety and outcomes of using radiofrequency energy in the RFTR procedure.[11] The technique is well tolerated and effective. Numerous studies have also demonstrated that radiofrequency tissue therapy in the nasal passage can be safe and effective in improving nasal obstruction and in preserving nasal function.[12] Aerin Medical's radiofrequency system using the Vivaer® ARC Stylus has been investigated and shown effective in treatment of nasal airway obstruction.[13]

Aerin Medical previously conducted a small feasibility study (TP220) using the Aerin Medical radiofrequency system to treat subjects with chronic rhinitis. The InSeca® Stylus was used to apply radiofrequency energy to the inferior turbinate in the PNN area. At 6-months post procedure, 73% of subjects showed improvement in their Sino-Nasal Outcomes (SNOT-22) score. There were no device-related or procedure-related serious adverse events.

The feasibility study was followed by a prospective, nonrandomized multicenter study (TP668) with 50 participants that supported regulatory clearance of the RhinAer Stylus for treating rhinitis by targeting treatment to the portion of the inferior turbinate mucosa overlying the region of the PNN. The mean reflective Total Nasal Symptom Score (rTNSS) at baseline was 8.5 (SD 1.8) and improved to 3.4 (SD 2.3) at the 12-week primary endpoint (5.1-point or 59.2% improvement). The responder rate for at least a 1-point improvement in rTNSS at 12 weeks was 94%. Responder rates based on at least 2-, 3- (~30%), and 4-point improvements in rTNSS were 92%, 88%, and 69%. Patient reported satisfaction with the procedure and quality of life improvement were high. No serious adverse events related to the device were observed and the limited number of adverse events possibly associated with the procedure or device were relatively mild,

transient, and not unexpected for this type of procedure. Together, the safety and efficacy results demonstrated the benefits of treating the PNN area of the nasal passageway with RF using the Aerin Medical procedure for relief of chronic rhinitis.

The current study is proposed to provide additional evidence for the effectiveness of the RF procedure when compared to a sham procedure through a randomized clinical trial.

2.0 Purpose

The purpose of this study is to compare the RhinAer procedure to treat tissue in the posterior nasal nerve area to improve symptoms in adults diagnosed with chronic rhinitis with a sham procedure that duplicates the actual procedure as closely as possible absent the delivery of radiofrequency energy to the nasal.

2.1 Device and Regulatory Status

The RhinAer procedure will be performed in the study clinic using the RhinAer Stylus and Aerin Console. The RhinAer Stylus is a disposable handheld device capable of delivering bipolar radiofrequency energy to tissue when connected to the Aerin Console radiofrequency generating device.

The RhinAer Stylus was cleared for use in the USA by the FDA under 510(k) K192471 and the Aerin Console was cleared under 510(k) K162810.

2.2 Indications for Use

The RhinAer Stylus is indicated for use in otorhinolaryngology (ENT) surgery for the destruction of soft tissue in the nasal airway, including in posterior nasal nerve regions in patients with chronic rhinitis.

The Aerin Console is an electrosurgical system intended to generate radiofrequency electrical current for the use of an Aerin Medical Stylus. The Aerin Console is indicated for use in small clinic, office or hospital environments.

2.3 Rationale

Patients suffering from symptoms attributed to chronic rhinitis have treatment options ranging from medications to surgical procedures that have varying degrees of effectiveness, discomfort, and potential complications. There remains a significant need for a simple, safe, nonsurgical, minimally invasive treatment that can provide sustained relief for patients suffering with symptoms of chronic rhinitis. The RhinAer procedure using RF technology has been shown to be safe, effective and durable in a single-arm trial comparing pretreatment condition with posttreatment condition. This study is being undertaken to provide additional evidence of the effectiveness of the procedure using the randomized, controlled trial, “gold standard” study design.

3.0 Study Objectives

3.1 Primary Objective

The primary objective is to assess the performance of the RhinAer procedure compared to a sham procedure with respect to individual participant success rates when used as a treatment for chronic rhinitis.

Individual participant success (responder) is defined as at least 30% improvement (decrease) in the 24-hour reflective Total Nasal Symptom Score (rTNSS).

The primary objective will be assessed through evaluation of the primary endpoint defined as comparison of the RhinAer procedure and sham procedure success rates at 3 months post procedure.

3.2 Secondary Objectives

Additional objectives include assessment and comparison of secondary endpoints and informational outcome measures between the groups receiving the RhinAer procedure and the sham control treatment.

Secondary endpoints are:

- Mean change in the rTNSS from baseline at 3 months.
- Frequency of device-related and procedure-related serious adverse events through the 3-month evaluation.

Informational outcomes include:

- Adverse events - Incidence (type and category) of adverse events overall and by follow-up interval.
- Nasal Assessment - The target posterior nasal nerve area within each nostril will be visually assessed at baseline and following the treatment procedure at all evaluations. The use of an endoscope for visual assessment is required. Representative still photographs or video of each nostril will be captured at each visit.
- Visual analog scale (VAS) for pain - perception of pain associated with the procedure on a 0 to 100 mm scale with 0 indicating no pain and 100 indicating the worst pain ever posttreatment through 3 months.
- rTNSS:
    - rTNSS mean and change from baseline at the 3-, 6-, 12-, and 24-month follow-up evaluations.
    - rTNSS Individual Nasal Symptom Scores (rhinorrhea, nasal congestion, nasal itching, and sneezing) at baseline and the 3-, 6-, 12-, and 24-month follow-up evaluations.
    - Proportion of responders based on improvement in rTNSS at the 3-, 6-, 12-, and 24-month follow-up evaluations.

- Other rhinitis symptoms: current symptoms of cough and postnasal drip or excess mucous in the throat, rated on a 0 to 3 scale from 'No symptoms' to 'Severe symptoms', assessed at baseline and the 3-, 6-, 12-, and 24-month follow-up evaluations.
- MiniRQLQ:
  - MiniRQLQ mean and change from baseline at the 3-, 6-, 12-, and 24-month follow-up evaluation.
  - MiniRQLQ domain scores (activity limitations, practical problems, nose symptoms, eye symptoms, and other symptoms) at baseline and the 3-, 6-, 12-, and 24-month follow-up evaluations.
- Participant satisfaction assessment - Five-question self-reported survey of satisfaction with the procedure and recommendation to others summarized by question at the 3-, 6-, 12-, and 24-month follow-up evaluations.
- Change in amount of PRN medication/device use for chronic rhinitis symptoms - Self-reported assessment of an increase, no change, or decrease in medications being used for treatment of symptoms compared to use prior to the procedure summarized by category at the 3-, 6-, 12-, and 24-month follow-up evaluations.
- Medications - Medications associated with relief or treatment of chronic rhinitis symptoms will be documented at baseline and updated as necessary at each evaluation. In addition, medications associated with treatment of adverse events will be documented.

3.3 Safety and Risk Profile

The safety and risk profile of the RhinAer procedure relative to the sham control procedure will be evaluated with respect to overall incidence of adverse events and treatment-related adverse events.

4.0 Study Plan

4.1 Study Design

The study is designed as a multicenter (up to 20 sites), prospective, randomized, controlled superiority trial with a one-way crossover component available to participants randomized to the control procedure A 2:1 site-stratified randomization will be used to allocate participants with chronic rhinitis to either the RhinAer procedure or treatment with the sham (control) procedure to provide up to 120 total participants:

- 80 active treatment (RhinAer procedure)
- 40 sham treatment control.

All participants will be evaluated prior to treatment and following treatment at week 4 (1 month) and week 13 (3 months). The 3-month evaluation will be used for the primary endpoint analysis.

The study will have an extended follow-up phase with evaluations conducted at 6 months (26 weeks), 12 months (52 weeks) and 24 months (104 weeks) to provide additional information on longer-term efficacy and duration of treatment effect.

The study will have an additional evaluation at 3 and 6 months at which time eligible sham control participants will be offered the opportunity to cross over and receive the RhinAer procedure. Extended follow-up will be conducted at 1, 3, 6 12 and 24 months to provide additional information on longer-term safety and duration of treatment effect.

4.2 Study Population

The target population for this study is adults who have exhibited symptoms of chronic rhinitis, such as congestion, rhinorrhea, sneezing, and itching, that may be caused by nonallergic or allergic triggers for at least 6 months. Patients with symptoms due only to seasonal allergies are to be excluded. This study requires significant symptoms demonstrated by an rTNSS ≥ 6, which includes moderate to severe symptoms of rhinorrhea and mild to severe symptoms of nasal congestion.

Patients who have anatomic obstructions that may limit access to the target treatment area or have altered posterior nasal anatomy due to prior surgery or injury are excluded from participation.

Patients must meet <u>all</u> inclusion and exclusion criteria listed below for participation in the study.

4.2.1 Inclusion Criteria

1. Age 18 to 85 years (inclusively).
2. Willing and able to provide informed consent.
3. Willing and able to comply with the participant-specific requirements outlined in the Study Protocol.
4. Seeking treatment for chronic rhinitis symptoms of at least 6 months duration and willing to undergo an office-based procedure.
5. Moderate to severe symptoms of rhinorrhea (rTNSS rating of 2 or 3 for rhinorrhea).
6. Mild to severe symptoms of nasal congestion (rTNSS rating of 1, 2 or 3 for congestion).
7. rTNSS ≥ 6.

4.2.2 Exclusion Criteria

1. Anatomic obstructions that in the investigator's opinion limit access to the posterior nasal passage.
2. Altered anatomy of the posterior nose as a result of prior sinus or nasal surgery or injury.
3. Active nasal or sinus infection.

4. History of significant dry eye.
5. History of any of the following: chronic epistaxis, documented episodes of significant nose bleeds in the past 3 months, rhinitis medicamentosa, head or neck irradiation.
6. Have rhinitis symptoms only on a seasonal basis due to allergies.
7. Known or suspected allergies or contraindications to the anesthetic agents and/or antibiotic medications to be used during the study procedure session.
8. Known or suspected to be pregnant or is lactating.
9. Participating in another clinical research study.
10. Is taking anticoagulants (eg, warfarin, Plavix) or 325 mg aspirin that cannot be discontinued before the procedure.
11. Has previous procedure or surgery for chronic rhinitis (eg, cryosurgical denervation) within 12 months.
12. Other medical conditions which in the opinion of the investigator would predispose the subject to poor wound healing, increased surgical risk, or poor compliance with the requirements of the study.

4.3 Enrollment and Randomization

Patients diagnosed with chronic rhinitis and meeting all eligibility criteria may be enrolled in the study. Randomization should occur just prior to the treatment procedure allowing sufficient time to prepare the required treatment. The randomized treatment assignment will be determined using a web-based service. Once the baseline assessments have been completed, results must be entered into the electronic data capture (EDC) system before the system will randomize the participant to a treatment group. Participants will be assigned to a treatment group (RhinAer procedure or sham control) in a 2:1 allocation, using the computer-generated randomization scheme stratified by site. To help assure balance in treatment assignment within sites a block randomization scheme will be implemented. Sites will be trained at site initiation to follow detailed randomization instructions to assure strict adherence to the randomization process.

4.4 Blinding

It will not be possible to blind the investigator administering the treatment because of obvious differences in the actual application of the RF energy versus the sham control. However, every effort should be made to keep the participant blinded as to the treatment received. Steps to help maintain blinding include:

- Following the same preparation procedures for all cases, including administration of anesthetics (topical and local).
- Application of the RhinAer Stylus in the same manner (pressure, locations, timing) for both the active and sham procedures.

- Simulation of RF energy being applied by having the Aerin Console appear to make audible sounds even though RF energy is not being generated for the sham procedure.
- Use of a blinded evaluator (nontreating physician) to conduct the follow-up visit nasal assessment when feasible; however, this is not required. Medical personnel who are unaware of the treatment received are also preferred for overseeing and coordinating the collection of the participant reported outcome measures during the follow-up evaluations. At a minimum, the treating physician should not be present when the participant reported outcomes are being collected. Site training will include the importance of maintaining the blinded nature of the study and caution against inadvertent revelation of the treatment assignment by study personnel.

4.5 Outcome Measures

4.5.1 Nasal Assessment

The target posterior nasal nerve area within each nostril will be visually assessed at baseline (pretreatment), immediately following the treatment procedure, and at the 1-month, 3-month, and 6-month evaluations. The use of an endoscope for visual assessment is required. Observations are categorized as not present, mild, moderate, or severe. Representative still photographs or video of each nostril will be captured at each visit.

Assessments include:

- Significant dry eye (yes/no)
- Bruising around orbital area
- Soreness, pain
- Numbness

Endoscope required:

- Inflammation / generalized redness
- Swelling, edema
- Bleeding at anesthetic injection site (not requiring physician intervention)
- Bleeding at treatment site (not requiring physician intervention)
- Nasal obstruction from tissue edema
- Disruption of mucosal flow / crusting.

4.5.2 Pain – Visual Analog Scale Pain Score

A horizontal 100 mm VAS[14] anchored on the left with the words “No Pain” and on the right with the words “Worst Pain Imaginable”, will be used to measure nasal pain associated with the procedure. Scores are obtained by measuring the

distance in millimeters from the left origin of the line (0) to the point indicated with a slash placed by the participant to indicate their current level of pain in and around the nose.

4.5.3 Total Nasal Symptom Score (TNSS)

The TNSS is an instrument used to collect patient self-rated severity of nasal symptoms originally comprised of 3 symptoms (nasal obstruction, itching/sneezing and secretion/runny nose)[15] that has been widely adapted to include 4 nasal symptoms: rhinorrhea, nasal congestion, nasal itching, and sneezing. The FDA cites this as a preferred measure of efficacy in trials of drug treatments for allergic rhinitis[16] and nonallergic rhinitis.[17] The TNSS requires the patient to rate 4 nasal symptoms (rhinorrhea, nasal congestion, nasal itching and sneezing) on the following 4-point scale:

- 0 = absent symptoms (no sign/symptom is evident)
- 1 = mild symptoms (sign/symptom present, but minimal awareness; easily tolerated)
- 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable)
- 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping).

The total score is the sum of the 4 nasal symptom scores with a maximum TNSS of 12 indicating the most severe symptoms.

The minimal clinically important difference (MCID) for change in mean TNSS derived from anchor-based methodologies has been shown to be 0.23 - 0.28 units and by distribution-based methodology the MCID was determined to be 0.59 units.[18] A less rigorous expert panel-based estimate of the MCID was 30% of the maximum score of 12, which is 3.6 units.[19] The evidence-based thresholds for MCID have been recommended to supersede the panel-based method.[20,21]

The 24-hour reflective TNSS (rTNSS) will be used in this study. Participants will be asked to self-evaluate their symptom severity over the preceding 24 hours.

Treatment Responder based on rTNSS improvement

Individual participant success (responder) is defined as at least 30% improvement (decrease) in the rTNSS from baseline.

4.5.4 Other Rhinitis Symptoms - Cough and Postnasal Drip

Self-reported assessment of current problems with cough and postnasal drip or excess mucous in the throat rated on the same 4-point scale used for symptoms comprising the rTNSS:

- 0 = absent symptoms (no sign/symptom is evident)

- 1 = mild symptoms (sign/symptom present, but minimal awareness; easily tolerated)
- 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable)
- 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping).

4.5.5 Mini Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ)

The RQLQ is a well-established, validated, and the most frequently used rhinoconjuctivitis disease-specific instrument.[22] The original RQLQ consisted of 28 questions across 7 domains and included ratings of 3 activities selected by the patient.[23] The validated standardized version (RQLQ(S)) uses standardized activity questions, which facilitates ease of administration.[24] The MiniRQLQ, to be used in this study, was developed and validated to further facilitate ease of use and efficiency by reducing the number of questions to 14.[25] The RQLQ(S) and the MiniRQLQ were found to be the best tests with optimal discriminant validity and responsiveness for measurement of health-related quality of life in AR patients.[26] While much of the development and validation of the RQLQ instruments have occurred in AR patients, the MiniRQLQ has also been validated for NAR patients.[27]

The instrument consists of 14 questions across 5 domains (activity limitations (n=3), practical problems (n=2), nose symptoms (n=3), eye symptoms (n=3), and other symptoms (n=3)). Responses are based on a 1-week recall and provided on a 7-point scale:

- 0 = not troubled
- 1 = hardly troubled at all
- 2 = somewhat troubled
- 3 = moderately troubled
- 4 = quite a bit troubled
- 5 = very troubled
- 6 = extremely troubled.

The total or overall MiniRQLQ score is the mean of the 14 responses and the domain scores are the mean of the questions in each domain.

The generally accepted MCID for the overall RQLQ(S) and each individual domain is 0.5[22,24,28,29] and has also been reported as $\geq$ 0.62.[30] The developers of the RQLQ instruments reported that the MCID for the MiniRQLQ was slightly higher (0.7) than for the RQLQ(S).[25] Another study using a combination of both anchor-based and distribution-based methods determined the MCID for the MiniRQLQ to be 0.42 (95% confidence interval 0.30 - 0.51).[31]

Also noteworthy for this sham-controlled study is a 1-point placebo improvement has been reported from a randomized clinical trial.[32]

4.5.6 Participant Satisfaction

Five-question self-reported survey using a 5-point scale to assess tolerability of the procedure, ease of recovery, change in drainage/rhinorrhea/runny nose symptoms, overall satisfaction with the procedure, and recommendation to others

4.5.7 Change in Amount of PRN Medication/Device Use for Chronic Rhinitis Symptoms

Self-reported assessment of an increase or decrease from baseline in as needed medications and/or devices used for treatment of nasal symptoms following the procedure.

4.5.8 Medication and Other Therapies for Symptoms of Chronic Rhinitis

The current use of medication, devices or other therapies for symptoms of chronic rhinitis, medication name, frequency, and dose will be recorded at each evaluation visit. Medications may be categorized for reporting purposes.

4.5.9 Adverse Events

Adverse events will be documented according to Section 7.2.

4.6 Success/Failure Criteria

Determinations of the successfulness of the treatment will be made on 2 levels, the individual participant level and in terms of the overall treatment group success relative to the sham control group. Each level has its own criteria for success.

4.6.1 Participant Success

The primary outcome success measure for individual participant success (responder) is defined as at least 30% improvement (decrease) in the rTNSS from baseline at the 3-month primary endpoint.

4.6.2 Participant Failure

A participant will be considered a nonresponder at the 3-month evaluation if the success criterion has not been attained.

4.6.3 Study Success

The study will be considered a success if the proportion of participants achieving a successful outcome (responder) that received treatment with the RhinAer procedure is statistically significantly greater than the proportion achieving individual success when treated with the sham control procedure when evaluated at 3 months after the procedure.

4.7 Duration of the Study

The primary outcome will be evaluated at 3 months. In addition, evaluations at 6, 12, and 24 months after treatment will extend follow-up to 2 years for evaluation of longer-term efficacy. Participants receiving the sham procedure and meeting original eligibility requirements may elect to crossover and receive the active RhinAer procedure within 30 days after the 3- or 6-month evaluation with continued follow-up for 24 more months for a total of up to 31 months of follow-up. Enrollment is anticipated to be completed within 12 months. Therefore, total study duration is anticipated to be approximately 43 months.

4.8 Site Staffing and Responsibilities of Study Personnel

The principal investigator is responsible for ensuring that he/she has sufficient and qualified staff to conduct the clinical study and that all study-related tasks have been appropriately delegated and documented. Roles may include:

- Treating physician – The treating physician will perform the procedure and discharge assessments. The treating physician must be a medical doctor with experience in ENT procedures and trained in administering the RhinAer procedure.
- Blinded physician evaluator (not required) – A physician experienced in ENT procedures, trained for participation in this study, and unaware of the treatment received may be used to conduct the follow-up nasal assessment. The blinded evaluator may also be responsible for the initial assessment and treatment of adverse events; however, in some cases it may be necessary to refer the event to the treating physician. If a blinded evaluator is not available, the treating physician or principal investigator will conduct the follow-up assessments.
- Oversight of participant reported outcomes and other data collection – Medical or office staff with relevant knowledge and experience as determined by the principal investigator to interact with study participants to ensure collection of study data and participant reported outcomes. Ideally, these individuals would be unaware of the treatment received by the participants.

Due to differences between the actual and sham control procedures, staff may also become aware of the treatment being administered. Staff with knowledge of the treatment assignment should not communicate any information to the participant or blinded evaluator (if used) in order to minimize any potential bias.

4.9 Device Description

The RhinAer procedure incorporates use of the RhinAer Stylus (Model FG815), which is a cleared (FDA - K192471) disposable handheld device capable of delivering bipolar radiofrequency energy to tissue, and the Aerin Console (Model FG226), a cleared (FDA - K162810) RF generator with temperature control capable of delivering very low doses of energy.

The RhinAer Stylus (Figure 1) consists of a handle, shaft and treatment tip. An array of bipolar electrodes is positioned on a nonconductive tip (Figure 2) that is attached to the handle via a nonconductive shaft. A temperature sensor is located on the Stylus tip to monitor tissue temperature during RF energy delivery. The Stylus is powered by an external temperature-controlled radiofrequency generator via a flexible cable (Figure 3). The Stylus incorporates features to allow compatibility with and authentication by only the Aerin Console. The connector for the RhinAer Stylus has a pin configuration that prevents its use with other RF generators, making it only compatible with the Aerin Console. Authentication of the Stylus is achieved via a crypto chip that is built into the Stylus handle assembly. The chip is read and written to by the Aerin Console. Information stored on the chip includes the Stylus model information, default treatment parameters (Power 4W, Temperature 60 °C, Duration 12s, Cooling Time 0s), custom treatment setting ranges (Power 3-5W, Temperature 50-70°C, Duration 10-18s, Cooling 9-12s), usage timestamp data, and a count of the remaining treatment cycles (based upon pre-set maximum).

The RhinAer Stylus is temporarily inserted into the nose to access the treated area. The Stylus requires the application of conductive media to the treatment tip prior to use. The conductive media helps to ensure good contact with tissue at all points of the treatment tip to facilitate energy transmission. Application of the RF energy is controlled by a foot switch connected to the Console. The RhinAer Stylus treats symptoms of chronic rhinitis by modifying the tissues of the nasal airway through the use of low doses of radiofrequency energy to destroy tissue in the posterior nasal nerve regions. The low-power radiofrequency energy generates heat within the submucosal tissue, destroying local tissue, mucous cells, and glands, and creating a coagulation lesion. This destruction of tissue in posterior nasal nerve regions improves symptoms of chronic rhinitis.

The procedure requires local anesthesia only. The Stylus is manufactured and supplied sterile and for single use only by Aerin Medical and may be used to treat both nostrils of the patient.

Figure 1. RhinAer Stylus

Figure 2. RhinAer Stylus tip

Figure 3. Aerin Console with RhinAer Stylus

4.10 Risk/Benefit Analysis

4.10.1 Risks

Potential risks associated with the use of the RhinAer Stylus do not differ from commonly used devices and treatments for chronic rhinitis, but due to the nonsurgical nature of the therapy, small treatment area, low energy delivery, and lack of need for general anesthesia, the overall risk to the participant may be less than presented by other surgical treatments.

Potential risks associated with the use of the RhinAer Stylus and the associated local anesthetics are listed below. Participants will be monitored closely as part of this study to allow for early detection of potential problems and prompt treatment if required.

Adverse events or side effects that may occur as a result of the treatment include:

- External deformity
- Blanching (generalized whiteness)
- Bruising including around the orbital area (black eyes)
- Infection
- Bleeding (other than during the treatment at treatment sites and greater than anticipated by the investigator)

- Mucosal changes
- Scar formation leading to nasal obstruction
- Sensory changes at treatment site
- Dry eye
- Vasovagal response secondary to the procedure

Anticipated observations that are expected in and around the treatment area and are considered minor include:

- Inflammation / generalized redness
- Temporary swelling, edema
- Temporary numbness/tingling
- Temporary soreness/pain
- Mild bleeding at anesthetic injection and/or treatment site (not requiring physician-level intervention, such as cautery)
- Temporary nasal obstruction from tissue edema
- Disruption of mucosal flow/intranasal crusting
- Scab formation.

These observations will be assessed in the nasal assessment and recorded at study visits if they occur. Should any of the following require mitigation by the treating physician or be greater in severity or degree of incidence than anticipated, they will be considered an adverse event and will be recorded on the study Adverse Event CRF.

Symptomatic improvements may not be achieved in all participants receiving the RhinAer procedure and may not be durable beyond the 3-month evaluation in all participants with relief at 3 months.

An additional risk to participants receiving the sham procedure is a potential for higher likelihood of the treatment not relieving their chronic rhinitis symptoms compared to those receiving the RhinAer procedure.

4.10.2 Mitigation of Risks

The study was developed based on previous preclinical and clinical experience and includes a number of steps to minimize any additional risks to participants in the study:

- Careful consideration has been given to the inclusion/exclusion criteria in order to select appropriate candidates for treatment.
- Patients will be fully informed of the study requirements prior to enrollment.

- Only physicians with experience in nasal surgical and minimally invasive procedures, and with specific training using the RhinAer Stylus for performing the RhinAer procedure will be permitted to participate in the study.
- The study will be reviewed and approved by an Institutional Review Board(s) and conducted according to applicable regulations with ongoing review by the IRB.
- Study procedures, follow-up, and study monitoring are designed to detect and respond to any adverse events in a timely manner.
- Preclinical mechanical and bench evaluations have been conducted to demonstrate that the design characteristics of the study device are appropriate for reliable clinical use of the device.
- The RhinAer Stylus and Console have been cleared for use by the FDA based in part on prior clinical studies demonstrating safety and efficacy of their use.
- Participants receiving the sham control procedure will be offered the RhinAer procedure if they have not responded to the sham procedure by the 3- or 6-month evaluation.

4.10.3 Benefits

The potential benefit associated with the RhinAer procedure is to offer a minimally invasive treatment method that has been shown in a previous study to help alleviate symptoms of chronic rhinitis and which has been cleared for use by the FDA. The RhinAer procedure treats symptoms of chronic rhinitis by modifying the tissues of the nasal airway through the use of low doses of radiofrequency energy to destroy tissue in the posterior nasal nerve regions. The low-power radiofrequency energy generates heat within the submucosal tissue, destroying local tissue, mucous cells, and glands, and creating a coagulation lesion. This destruction of tissue in posterior nasal nerve regions improves symptoms of chronic rhinitis. These benefits may last beyond the length of the study.

The procedure will be provided at no cost to participants. Participants randomized to the sham control procedure will be offered the opportunity to receive the RhinAer procedure within 30 days after the 3- or 6-month evaluation if the control procedure has not alleviated their symptoms.

4.10.4 Potential Risks to Participant Confidentiality

In all clinical studies, confidentiality of protected health information may be breached due to study-related activities beyond those of routine clinical care. This risk will be minimized by not entering personally identifying information into the EDC system through the study's electronic case report forms (eCRF). Risks to participant confidentiality are further minimized by allowing only

authorized individuals to access the EDC system and the database that stores the electronically entered data. The 21CRF Part 11 compliant and validated system maintains audit trails on all entries, changes or corrections to eCRFs. If a person with authority to complete but not sign eCRFs makes changes to an already signed eCRF, the investigator will be required to re-sign the eCRF, thereby protecting the integrity of the data collection process and the data.

4.10.5 Study Justification in Relation to Risk

The study sponsor believes that any additional risks presented by participating in this study are very low and that adequate testing, safeguards, and risk monitoring have been incorporated into the study to further minimize and mitigate the risks relative to the potential benefits, including relief from symptoms of chronic rhinitis, that may be realized by participation in this study.

5.0 Study Schedule and Procedures

This section provides summaries of the study schedule of events and flow of participants through the study, as well as more detailed information on study procedures and processes.

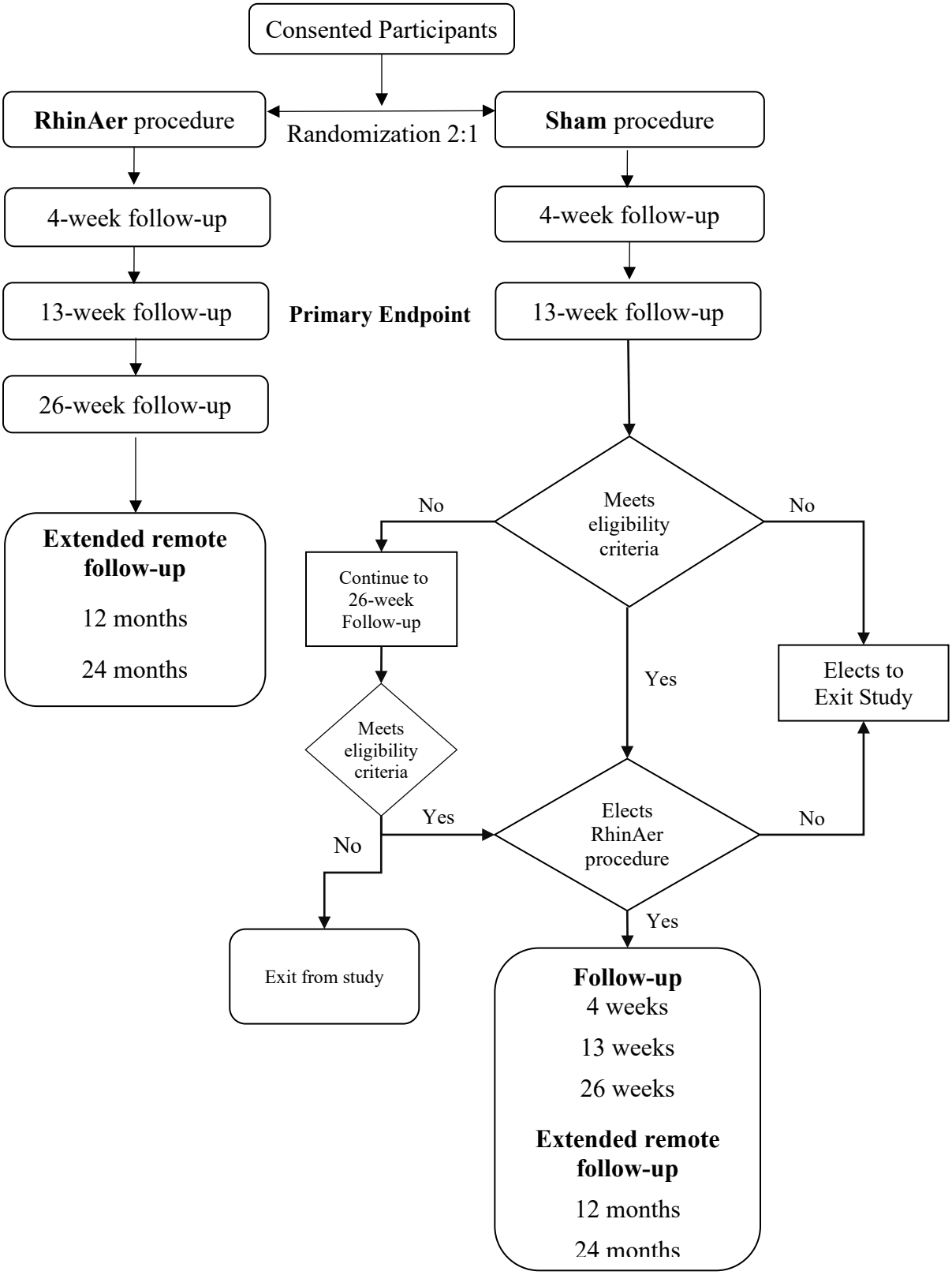
5.1 Schedule of Events

	Screening	Treatment		Follow-up (office)			Extended follow-up (remote)	
		Procedure	Immediate Postprocedure	1 Month (4 weeks)	3 Months[1] (13 weeks)	6 Months[1] (26 weeks)	12 Months (52 weeks)	24 Months (104 weeks)
Window (days)	**(-30)**	**(0)**	**(0)**	**(± 7)**	**(± 14)**	**(± 30)**	**(± 30)**	**(± 30)**
Activity / Assessment								
Eligibility	X							
Consent	X							
Demographics / Medical History	X							
Physician Evaluations								
Nasal assessment (physical, endoscopic)	X	X[2]	X	X	X	X		
Current medication use (study relevant)	X	X[2]	X	X	X	X	X	X
Participant Evaluations								
VAS nasal pain			X	X	X			
Rhinitis symptoms (rTNSS, cough, and postnasal drip)	X	X[2]			X	X	X	X
MiniRQLQ	X	X[2]			X	X	X	X
Participant Satisfaction Survey					X	X	X	X
Adverse Events	X	X[2]	X	X	X	X	X	X

[1]Control participants eligible to crossover and receive RhinAer procedure.

[2]Repeat only on day of treatment if screening was conducted after 72 hours day of procedure.

5.2 Participant Flowchart



5.3 Enrollment and Baseline Assessment

Screening

The investigator or designated research staff will perform an evaluation of the study candidate for study eligibility, which may include a history and physical examination of the nasal area, review of overall medical history, understanding of general health and discussion of any conservative measures used chronic rhinitis. In addition, patients will complete standard questionnaires to document current symptoms associated with chronic rhinitis (rTNSS, MiniRQLQ).

Patients must be diagnosed with chronic rhinitis prior to entry into the study. The use of diagnostic procedures and screening tests to determine a diagnosis and assess whether patients are appropriate candidates for inclusion in the study is an appropriate pre-entry activity. While the availability of the study may be discussed with a prospective participant without first obtaining consent, informed consent must be obtained prior to initiation of any clinical procedures dictated by the protocol that are performed solely for the purpose of determining eligibility to participate in the study. Once the pretreatment assessments are completed the study procedure should be scheduled within 30 days.

Informed consent

Informed consent must be obtained in accordance with FDA regulation 21 CFR Part 50. The clinical investigator or designated staff member is responsible for ensuring that informed consent is obtained for each participant prior to participation in the study. The patient must be fully counseled with an explanation of the study background, randomized nature of the study, study procedure, follow-up schedule, and informed of their options, risks and benefits, and have every opportunity to ask questions about participation in the study. This process includes a thorough explanation of the informed consent document that the patient will be asked to sign acknowledging that they understand and desire to participate in the study. The explanation and discussion should be conducted in such a way as to:

- avoid coercion or influence of patient to participate in the study,
- ensure the patient understands that their legal rights are not waived at any time,
- use language at a level the patient can understand, and
- ensure the patient understands that after providing signature on the Informed Consent, the patient may still withdraw at any time before, during or after study treatment.

Evaluation of inclusion and exclusion criteria

The Screening Visit / Study Eligibility CRF will be used to document the participant's eligibility status.

Pretreatment (baseline) data and assessments

The following data will be obtained prior to treatment and recorded on the Baseline Visit Demographics and Treatment History CRF:

- Demographics
  - Sex
  - Height (inches)
  - Weight (pounds)
  - Date of birth
  - Race / Ethnicity
- Nasal symptoms, history of treatments, nasal visual exam
  - History (duration) of rhinitis
  - Rhinitis triggers (allergic or nonallergic)
  - Medications used to treat rhinitis
  - Previous ENT treatments
  - Turbinate enlargement, nasal polyps, and other significant findings

The nasal assessment data (each nostril) including photos or video (physical and endoscopic) will be recorded and entered into EDC. If treatment is not provided the same day as screening, then this assessment will be repeated on the day of the procedure immediately prior to treatment.

Current use of medication, devices, or other therapies for symptoms of chronic rhinitis, including medication name, frequency, and dose will be detailed on the Medication Log.

Rhinitis symptom severity, including the rTNSS, cough and postnasal drip, will be completed by the participant on the rTNSS CRF. If treatment is not provided the same day as screening, then this assessment will be repeated on the day of the procedure immediately prior to treatment.

The MiniRQLQ will be completed by the participant on the MiniRQLQ CRF.

5.4 Treatment Visit and Procedure

Randomization should occur just prior to performing the procedure but allowing enough time for preparation of the selected treatment. If the participant meets eligibility criteria and signs the IRB approved informed consent, the participant is considered enrolled once the RhinAer Stylus enters the nasal passageway.

The treatment procedure is summarized below. Consult the RhinAer Stylus and Aerin Console IFUs for full detail of the treatment procedure and step-by-step instructions for preparation and use of the RhinAer Stylus and Aerin Console.

Preparation

The procedure will be performed in the study clinic. The participant will be in a reclined or supine position on the procedure table in the physician's office. A visual physical and endoscopic nasal assessment conducted just prior to the procedure will be documented on the appropriate CRF. The study physician will map out the treatment area by evaluating the middle meatus and surrounding structures of the nasal cavity to understand access of the study device to the mucosal area for treatment. Participants will have both posterior nasal nerve areas treated in a single study procedure session. Each nostril will be treated at up to 5 nonoverlapping positions within the posterior portion of the middle meatus and posterior portion of the inferior turbinate (Figure 4).

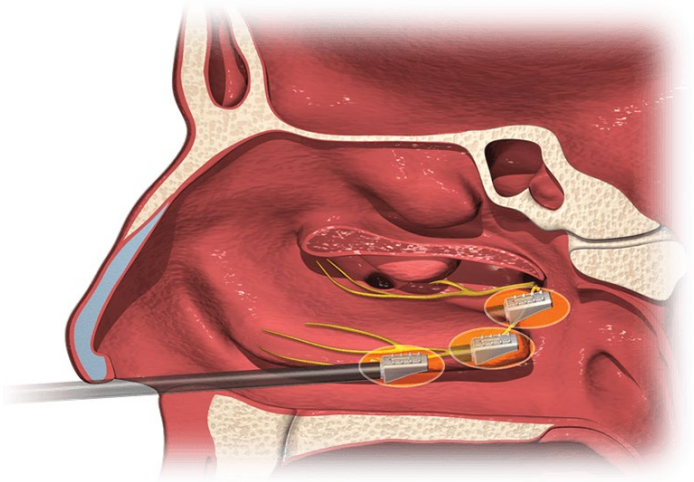


Figure 4. RhinAer Stylus in the nose.

The physician will anesthetize the treatment area by using a topical swab/gauze or spray of lidocaine to numb the mucosal tissue, wait approximately 20 minutes, and then inject anesthesia to the treatment area after initial numbness has occurred. The sham control participants will receive the same anesthesia as the actively treated participants.

Treatment administration

An endoscope will be inserted into the nasal cavity so the physician can visualize the mucosal area of treatment. The RhinAer Stylus will then be inserted to access the treatment area. The Stylus will be connected to the Aerin Console generator and the RF energy level will be set on the generator.

The default settings for the RhinAer Stylus will be used for the study:

Temperature	60 °C
Power	4 Watts
Treatment Time	12 secs
Cooling Time	0 secs

The physician will apply the treatment tip of the RhinAer Stylus to the target tissue prior to energy delivery. The energy is turned on by maintaining downward pressure on the foot pedal. With the energy on, the physician continues to apply the Stylus tip to the mucosal surface consistent with the IFU. A tone will be heard when energy is being delivered until the treatment is complete. After the treatment time is reached, the Aerin Console will cease to delivery energy and reset for subsequent treatments.

When conducting a sham control procedure, the physician will activate an audible tone mimicking the activation of the Aerin Console; however, no energy will be transmitted to the Stylus. The physician should apply the Stylus to the mucosal surface with similar pressure and in similar locations as would be done if energy was actually being applied.

No repeat ("touch-up") procedures will be permitted during the study follow-up period.

Procedure data collection

Data relating to the procedure and the products used will be recorded on the Procedure CRF. The following information will be recorded:

- Date of procedure
- Preprocedure nasal assessment (each nostril) including photos or video (physical and endoscopic)
- Preprocedure and procedure medications
- RhinAer Stylus and Aerin Console information
- Aerin Console settings
- Procedure start and end times
- Number of sites treated
- Occurrence of device malfunction, protocol deviation, or adverse events.

5.5 Postprocedure Assessments and Care

An endoscopic nasal assessment will be conducted prior to discharging the participant and reported on the Procedure CRF.

Participants will be asked to indicate the pain level experienced during the study procedure from anesthesia delivery to procedure completion using the VAS pain score instrument (vertical line marked on the 100 mm line) on the Pain VAS CRF.

At the discretion of the physician, the following care may be provided:

- Apply compression to the treatment area internally for 5 minutes.
- Apply petroleum jelly to the treatment area as needed.
- Use of nasal saline spray or ointment as needed.
- The participant should be instructed not to blow their nose for 24 hours.

Participants should have their first follow-up visit (4 weeks) scheduled within the visit window prior to release.

Participants should not generally receive other concomitant nasal treatment therapies or interventions after the procedure or during the study follow-up period to avoid confounding the evaluation of the effect of the treatment, unless the additional care is in response to an adverse event or is considered in the best interest of the participant. Therapies, interventions, and pain medication will be monitored at follow-up evaluations.

5.6 Follow-up Evaluations and Study Exit

Follow-up visit dates will be calculated from the study procedure date. Follow-up visits should be scheduled within the specified visit windows described in Section 5.1 and Table 1 (Section 8.3.2). In-office follow-up evaluations are scheduled for 4 weeks (1 month), 13 weeks (3 months), and 26 weeks (6 months) after the treatment procedure. Evaluations at 12 and 24 months will be conducted remotely by telephone assessment by site personnel. The timing of all follow-up evaluations is based on the date of the procedure and should not be altered based on the actual time of preceding follow-up visits. Participants who make nonstudy visits should be evaluated for possible adverse events and an Adverse Event CRF should be submitted if appropriate.

All participants who receive the RhinAer procedure, as well as sham procedure participants who choose to have the RhinAer procedure within 30 days after their 3, or 6-month evaluation, should be followed through the final evaluation visit at 2 years postprocedure regardless of their success/failure classification. Participants who receive the sham procedure and are evaluated at 13 weeks or 26-weeks and continue to meet all of the original inclusion and exclusion criteria, including rTNSS $\geq$6, will be offered the opportunity to have the RhinAer procedure performed. Participants who choose to have the procedure will maintain their original study ID and will follow the same pretreatment, treatment, and follow-up processes as any newly enrolled participant.

Sham control procedure participants who choose not to have the RhinAer procedure or who fail to meet inclusion and exclusion criteria may elect to exit from the study following the 3- or 6-month evaluation. Refer to the Participant Flowchart, Section 5.2 for depiction of study process.

Every effort should be made to avoid having participants withdraw from the study(Section 9.5). If a participant does choose to withdraw from the study, it is very important to record information regarding the reason(s) and the last known status of the participant.

The following assessments will be conducted as indicated for each follow-up time point and recorded on the corresponding CRFs:

In-office evaluations: 4-week (1-month), 13-week (3-month), and 26-week (6-month) follow-up

- Nasal assessment (each nostril) including photos or video
- Current use of medication, devices or other therapies for symptoms of chronic rhinitis, including medication name, frequency, and dose
- Participant reported change in use of as needed medications and devices for chronic rhinitis symptoms (completed by participant) (no 1-month)
- rTNSS (completed by participant) (no 1-month)
- Cough and postnasal drip symptoms (completed by participant) (no 1-month)
- MiniRQLQ (completed by participant) (no 1-month)
- VAS pain score (completed by participant)
- Adverse events

Remote (telephone) evaluations: 12-month (52-week) and 24-month (104-week) follow-up

- rTNSS (verbal administration by site personnel)
- Cough and postnasal drip symptoms (verbal administration by site personnel)
- MiniRQLQ (verbal administration by site personnel)
- Participant reported change in use of as needed medications and devices for chronic rhinitis symptoms (verbal administration by site personnel)
- Patient satisfaction survey (verbal administration by site personnel)
- Current use of medication or other therapies for symptoms of chronic rhinitis, including medication name, frequency, and dose (study staff follow-up required if participant indicates changes)
- Adverse events (study staff follow-up required if participant indicates changes).

Participants meeting the study requirements as planned will be exited upon completion of their 24-month (104-week) follow-up visit. If a participant reaches the 24-month (104 week) follow-up visit and is experiencing a new or ongoing adverse event, the study sponsor should be contacted to discuss the need and/or methods for continued surveillance of the event.

5.7 Product Handling and Accountability

A system that allows tracking of orders, shipping and returns will be used to control RhinAer Stylus and Aerin Console inventory. The devices will be packaged and labeled to clearly indicate that they are for clinical study use only and must only be used for participants enrolled in this study. All devices not used must be returned to the sponsor or disposed of in accordance with the sponsor's instructions. The

investigator is responsible for adequate record keeping regarding the receipt, use, and final disposition of study inventory.

6.0 Statistical Considerations

6.1 Study Design

This is a prospective, multicenter, randomized, sham-controlled study to compare the RhinAer procedure for treatment of chronic rhinitis with a sham procedure that duplicates the actual procedure as closely as possible absent the delivery of radiofrequency (RF) energy to the nasal tissue. Participants will be randomized using a 2:1 allocation to receive either the RhinAer procedure or a sham procedure (control). This study is designed to demonstrate the superiority of the active RhinAer treatment compared to the sham control.

6.2 Study Hypotheses

The null hypothesis (H_0) for this superiority study is that there is no difference between the success (responder) rate for the sham control and the success (responder) rate for the RhinAer procedure:

$H_0: \pi_C - \pi_T = 0$ vs. $H_1: \pi_C - \pi_T \neq 0$

where:

π_C=proportion of responders in the sham procedure control group

π_T=proportion of responders in the RhinAer procedure treatment group.

Rejection of the two-sided null hypothesis in favor of the alternative (H_1) hypothesis means that there is evidence for a statistically significant difference in responder rates between the 2 groups.

6.3 Sample Size Estimate

The study will enroll up to 120 participants. The power analysis was performed such that there is adequate power to reject the null hypothesis of no difference between treatments. Sample size estimation was based on the test for differences between 2 proportions[33] using an exact test and on the following assumptions:

- Significance level $\alpha = 0.05$ (two-sided)
- Power = 80%
- $\pi_C = 0.50$ (allowance for a 50% control responders)
- $\pi_T = 0.80$ (assumed 80% responders in the treated group)
- Treatment allocation is 2:1
- 10% dropout and nonevaluable.

The 80% responder rate assumed for the active RhinAer procedure group is an estimate based on the prior clinical study of this procedure in which 43 of 50

participants (86%) were responders at 12 weeks. The one-sided lower 95% confidence bound on the responder rate of 86% is 76%, which supports the estimate of 80% responders assumed for the purpose of sample size calculation.

Studies of randomized placebo-controlled efficacy trials of drugs used to treat allergic rhinitis have found high response to placebo including up to a 57% share of the therapeutic effect for AR[34] and up to a 25% reduction in TNSS for perennial allergic rhinitis[35] with a strong placebo effect observed where the evaluating parameters tend to be physical or subjective rather than objective indicators of drug efficacy.[36] The 50% responder rate assumed for the sham control procedure is based on the literature for placebo and sham controls in therapeutic and device studies suggesting from 30% to 60% responder rates, with device studies tending to be at the higher end of the range[37].

The minimum number of participants to achieve 80% power with a 2:1 active treatment to sham control allocation is 66 in the active treatment group and 33 in the sham group. The sample size, allowing for 10% loss (nonevaluable) in each group and adjusting for a balanced distribution across 20 sites is 120 participants (80 active treatment (RhinAer procedure), 40 sham procedure control).

It is anticipated that participants will be enrolled at sites on a competitive basis; however, a reasonable balance of participants among sites may be maintained by potentially capping enrollment at individual sites based on the final number of participating sites.

6.4 Timing of Analysis

The primary evaluation phase of the study lasts until all participants have reached the primary endpoint at 13 weeks (3 months) postprocedure. The primary and secondary endpoints will be analyzed using the data from the primary evaluation phase for an interim study report when these data become available. Informational outcomes will be analyzed and included in interim reports after all participants have reached each of the successive follow-up time points. A final study report will be provided after all participants have reached the final follow-up evaluation of the extended follow-up phase of the study, including sham procedure control participants who subsequently received the RhinAer procedure.

6.5 Analysis Populations

The primary endpoint analysis will be based on the intent-to-treat (ITT) principle. Participants will be analyzed in the originally randomized treatment group regardless of actual treatment received. The effects of protocol deviations will only be examined when the validity of the study conclusion is in question. All secondary and other analyses and reports will include an ITT population analysis. Following data reporting conventions, statistics on the per protocol population will also be reported. The per protocol population is defined as all participants who received treatments, with 13-week (3-month) follow-up data and no major protocol deviations.

6.6 Missing Data

All missing data in each treatment group will be imputed for the primary endpoint by assuming the missing outcomes are nonresponders. In addition, a post hoc sensitivity analyses may be performed, including a worst-case analysis (all missing primary outcomes in the RhinAer procedure group are considered nonresponders and all missing outcomes in the sham procedure control group are responders) and/or a change-point analysis, to assess the effect of missing data on the primary analysis. The results of the sensitivity analysis will not be used to adjust the conclusions drawn from the primary analysis.

Secondary outcome measures and additional observational measurements will be analyzed by using available data only.

6.7 Pooling

All study data will be pooled across study sites to facilitate hypothesis testing in accordance with the sample size estimation and power analysis (Section 6.3). Comparability between study sites may be shown using summary statistics calculated by site.

6.8 Participant Disposition

A detailed description of participant disposition will be provided by treatment group using a CONSORT diagram and summaries of participants falling in various subgroups of interest, such as, enrolled but not treated with any study treatment, not treated as randomized, discontinued, excluded from ITT, protocol deviations, deaths, and withdrawals. All study population exclusions and reasons will be summarized. All randomized participants entered in the study will be accounted for in the summary. Follow-up by visit will be presented, showing theoretical, expected, and actual follow-up visits.

6.9 Demographics and Characteristics

Demography, baseline characteristics and the comparability of active treatment group and sham control group participants will be summarized using frequencies and percentages for categorical factors and mean, median, standard deviation, minimum and maximum for continuous factors. Demographic characteristics will be reported to describe the profile of samples. Comparability between treatment groups will not be statistically assessed in this prospective randomized clinical trial.

Baseline covariates with possible impact on outcomes at 3 months are:

- Age
- Race
- Sex
- BMI
- Allergic status (allergic rhinitis - nonallergic rhinitis).

Results may be evaluated by allergic status if sufficient numbers are obtained in both categories.

6.10 Primary Endpoint Analysis

Primary efficacy will be evaluated using the proportions of successful outcomes (responders) on the primary outcome measure (improvement in rTNSS) at 13 weeks.

The proportions of responders at 13 weeks in each group will be compared using Fisher's Exact test.

Confidence intervals (95%) will be provided for all proportions and comparisons.

6.11 Secondary Endpoints Analysis

Secondary endpoints will be tested only after the primary objective of the study is met. Confidence intervals (95%) will be included for all secondary outcome measures.

- Mean change in the rTNSS from baseline to 13 weeks
  The mean changes from baseline at 13 weeks in each group will be compared with a 2-sided t-test with a null hypothesis of no difference between groups.
- Device-related and procedure-related serious adverse events through 13 weeks
  The proportions of serious device-related adverse events through 13 weeks in each group will be compared using Fisher's Exact test.

6.12 Other Outcome Measures Analyses

Additional outcome measures will be collected for information and hypothesis generating purposes. The primary analysis methods will be descriptive and exploratory and presented by evaluation to more completely understand the time course of treatment effect. Measures will be summarized using frequencies and percentages for categorical measures and mean, median, standard deviation, minimum and maximum for continuous factors. Confidence intervals for differences between treatment groups will be included where appropriate. Statistical comparisons will either not be performed or used for information purposes. Proportions may be compared using exact tests or chi-square tests. Continuous outcomes may be compared using t-tests, ANOVA or nonparametric equivalents. Repeated measures ANOVA may be used for longitudinal analysis across evaluations.

Other outcome measures include:

- Nasal Assessment - The visual physical and endoscopic assessment factors will be summarized to include frequency and percentage of responses in each category for each component of the nasal assessment by treatment group at baseline, just prior to treatment, immediately after treatment, at 4 weeks, and at 3 months after the procedure.

- Visual analog scale (VAS) for pain - Summary will include mean VAS pain scores assessed posttreatment, 4 weeks, and at 3 months for both treatment groups.
- rTNSS - The rTNSS and its individual components will be subject to multiple summary methods and analyses including the:
    - Mean and mean change from baseline at the 3-, 6-, 12-, and 24-month follow-up evaluations for each group and differences between groups.
    - Mean, mean change from baseline, and response distribution of the 4 components of the rTNSS (rhinorrhea, nasal congestion, nasal itching, and sneezing) at baseline and the 3-, 6-, 12-, and 24-month follow-up evaluations for each group and differences between groups.
    - Proportion of responders based on 30% improvement in rTNSS at the 3-, 6-, 12-, and 24-month follow-up evaluations for each group and differences between groups.
- Other rhinitis symptoms (cough and postnasal drip) - Mean, mean change from baseline, and distribution of the 4 response categories (0-3 points) at baseline and the 3-, 6-, 12-, and 24-month follow-up evaluations for each group and differences between groups.
- MiniRQLQ: The MiniRQLQ and its individual components will be subject to multiple summary methods and analyses including the:
    - MiniRQLQ mean and mean change from baseline at the 3-, 6-, 12-, and 24-month follow-up evaluations for each group and differences between groups.
    - MiniRQLQ domain scores (nose symptoms, eye symptoms, non-eye/nose symptoms, sleep problems, practical problems, activity limitations, and emotional function) at baseline and the 3-, 6-, 12-, and 24-month follow-up evaluations for each group and differences between groups..
- Participant satisfaction assessment - mean response for each of the 5 survey questions will be summarized by group at the 3-, 6-, 12-, and 24-month follow-up evaluations.
- Change in amount of PRN medication use for chronic rhinitis symptoms - Proportions of participants reporting increase, decrease, or no change in medications being used for treatment of symptoms compared to use prior to the procedure will be summarized by group for the 3-, 6-, 12-, and 24-month follow-up evaluations.
- Medications - A listing of medications associated with relief or treatment of chronic rhinitis symptoms or associated with treatment of adverse events

will be provided by group. Medication use by categories may also be presented as percentages of participants in each group.

6.13 Safety Analysis

All adverse events will be analyzed for all participants. Adverse events will be coded using a custom Aerin Medical dictionary so that adverse events may be categorized for analysis at an appropriate level of detail. Listings will be provided to detail individual events. The number of participants, number of AEs, and the proportion of participants reporting each AE will be summarized. Seriousness and severity of AEs and their relationship to the device and procedure will be summarized. A time course of adverse events will be presented. Any unexpected adverse device experiences or adverse events that occur at an unexpectedly high incidence rate will receive detailed analyses. Narratives will be presented for all deaths, serious adverse events, unexpected adverse device experiences, and participants withdrawn due to an adverse event.

6.14 Extension Phase Analysis

The extension phase analyses will be similar to those detailed above with a particular emphasis on the summarization of all adverse events occurring throughout the entire study and the maintenance of the treatment effect over time. Missing data analyses and imputation will not be performed on data collected during the extension phase.

6.15 Standard Methods of Report

Summary descriptive statistics including means, medians, standard deviations and histograms for continuous measures, and frequencies and percentages for categorical outcomes will be presented for all variables of interest. Outcome measures (primary, secondary, and informational) will be presented by treatment group and time.

7.0 Adverse Events and Product Complaints

7.1 Adverse Events

Adverse events (AEs) may occur during the treatment phase or during the follow-up phase. Adverse events occurring after the baseline assessment but before the treatment procedure will be documented in the participant's medical record but will not count as related to the study device or procedure.

7.1.1 Definitions

Following are definitions associated with adverse events:

Adverse Event (AE) - any untoward medical occurrence, unintended disease or injury, or untoward clinical sign or symptom (including an abnormal laboratory finding), in subjects whether or not related to the investigational drug or medical device product. This includes events related to investigational drug or medical device product, comparator and/or events related to the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices.

Serious Adverse Event (SAE) - any untoward medical occurrence that: (a) led to death, (b) resulted in a life-threatening illness or injury, (c) resulted in permanent impairment of a body structure or body function, (d) required inpatient hospitalization or prolongation of existing hospitalization, (e) resulted in medical or surgical intervention to prevent permanent impairment to a body structure or body function or (f) led to fetal distress, fetal death or a congenital abnormality or birth defect.

Adverse Device Effect (ADE) - Adverse event related to the use of an investigational medical device. This includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, or operation, or any malfunction of the investigational medical device and also includes any event resulting from use error or from intentional misuse of the investigational medical device.

Serious Adverse Device Effect (SADE) - An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

Anticipated Adverse Device Effect (AADE) - A device-related event described in the investigational protocol or informed consent for the clinical trial of an investigational device.

Unanticipated (Serious) Adverse Device Effect (UADE or USADE) - A serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Relationship to device and procedure
The potential relationship of the event to the device or procedure:

- Not related

  An adverse event for which sufficient information exists to indicate that there is no causal connection between the event and the device or procedure. The adverse event is due to and readily explained by the participant's underlying disease state or is due to concomitant medication or therapy not related to the use of the device or the procedure. In addition, the adverse event may not follow a reasonable temporal sequence following the treatment procedure.

- Possibly related

  There is a reasonable possibility that the adverse event may have been primarily caused by the device or procedure. The adverse event has a

reasonable temporal relationship to the use of the device or the procedure and follows a known or expected response pattern to the device or procedure, but alternative etiology is equally or more likely compared to the potential relationship to the use of the device or the procedure.

- Probably related

  There is a reasonable probability that the adverse event may have been primarily caused by the device or procedure. The adverse event has a reasonable temporal relationship to the use of the device or the procedure and follows a known or expected response pattern to the device or procedure.

- Definitely related

  The adverse event has a strong causal relationship to the device or procedure. The adverse event follows a strong temporal relationship to the use of the device or the procedure, follows a known response pattern to the device or procedure, and cannot be reasonably explained by known characteristics of the participant's clinical state or other therapies.

Every effort should be made to determine the cause of each adverse event, because a judgment must be made as to the relationship to the device or procedure. If an investigator cannot assign a causality category the event will be considered possibly related for reporting and analysis.

NOTE: The occurrence of a diagnostic or elective surgical procedure for a pre-existing condition, unless the condition becomes more severe or increases in frequency, would not be considered procedure-related or device-related.

Intensity of adverse events:

- Mild

  The adverse event is noticeable to the participant but does not interfere with routine activity.

- Moderate

  The adverse event interferes with routine activity but responds to symptomatic therapy or rest.

- Severe

  The adverse event significantly limits the participant's ability to perform routine activities despite symptomatic therapy. The adverse event requires medical or surgical treatment or results in hospitalization.

7.1.2 Documentation and Reporting of Adverse Events

All adverse events must be reported on the Adverse Event Form. All adverse events will be followed until they are adequately resolved or reach a chronic,

stable state. If a participant reaches the 24-month follow-up visit and is experiencing a new or ongoing adverse event, the study sponsor should be contacted to discuss the need and/or methods for continued surveillance of the event. Adverse events will be evaluated by the investigator and differentiated by:

- Seriousness
- Intensity (mild, moderate, severe)
- Causality (in relation to the device or procedure)
- Unexpectedness.

Signs and symptoms considered normal postprocedure recovery (eg, postprocedure pain, transient sensory symptoms, fever, postanesthesia symptoms) do not have to be reported as adverse events. If these events require treatment outside that which is considered normal, they should be reported as adverse events.

All adverse events classified as an Unanticipated Adverse Device Effect, Serious Adverse Device Effect, or Serious Adverse Event need to be reported to the Sponsor within 24 hours of learning of the event.

Sponsor Contact: Anais Laborde
Telephone: (650) 518-9624
email: alaborde@aerinmedical.com

Investigators must also report promptly all unanticipated problems to their IRB involving risks to participants or others and report adverse events according to the local reporting requirements. Reporting instructions and contact information will be provided in the site's Regulatory Binder for this study.

7.2 Product Complaints

7.2.1 Definitions

Product Complaint - Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of an Aerin product (medical device) after it is released for distribution [per 21 CFR 820.3(b)].

Complaint – written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, usability, safety or performance of a medical device that has been released from the organization's control or related to a service that affects the performance of such medical device. [per ISO 13485:2016]

Reportable Complaint – Any product complaint that represents an event, which must be reported to a regulatory agency including:

- US Food and Drug Administration (per 21 CFR Part 803)

- A Competent Authority within the European Community or a Notified Body (MDD)
- The Canadian HPFB
- Any regulatory agency, within the country of distribution.

7.2.2 Documentation and Reporting of Complaints

All product complaints, deficiencies, and malfunctions associated with devices will be documented on the appropriate case report form and/or communicated to Aerin within 24 hours of first becoming aware of the event.

8.0 Study Administration

This study will be conducted in accordance with elements of E6 Good Clinical Practice Consolidated Guidance, ICH, April 1996, Abbreviated Requirements of 21 CFR 812 for nonsignificant risk device studies, the Declaration of Helsinki, the Belmont Report and any conditions imposed by the reviewing IRB or US FDA or other regulatory agency.

The study sponsor has the overall responsibility for the conduct of the study according to all applicable regulatory requirements. The study sponsor will have certain direct responsibilities and will delegate other responsibilities to the investigator and study site. The study sponsor and investigator will ensure that the study is conducted according to all applicable regulations. All personnel participating in the conduct of this study will be qualified by education and experience to perform their tasks.

The study sponsor, treating physician, or any person acting for or on behalf of a sponsor or treating physician shall act in accordance the applicable standards, guidelines and regulations.

8.1 Investigator Training

Site initiation training will occur prior to the first procedure at a site. Investigators will be trained on the treatment procedure and use the RhinAer Stylus and Aerin Console. All study staff will be trained, as necessary, to ensure compliance with the protocol and regulatory requirements, as well as to ensure accurate data collection. Site training will include a detailed review of this protocol, use of the EDC system, eCRF completion instructions, adverse event reporting, product handling and inventory, randomization instructions, monitoring logistics, and regulatory requirements.

8.2 Study Monitoring

Study monitoring will be carried out in compliance with FDA regulations and GCP guidelines. The first monitoring visit should occur shortly after the first participants have been enrolled and at least one treatment has occurred at the site. Subsequent monitoring visits will occur as the frequency of enrollment dictates but no less than annually. A final close-out monitoring visit will occur when the study has been completed or terminated.

The monitoring for this study will be carried out by monitors qualified by experience and training who are Aerin Medical employees or individuals contracted by Aerin to conduct monitoring activities.

8.3 Documentation of Study Findings

8.3.1 Data Management

A secure EDC and management system will be used for entry, storage, review, and management of study data. The system will use the Medrio EDC platform (Medrio, Inc. San Francisco, CA) and be compliant with applicable GCP and regulatory requirements. Sites will be trained in the use of the system for entering study data and uploading supporting documents. Data monitoring will be performed to verify data accuracy and ensure queries are resolved.

8.3.2 Case Report Forms

All study data will be entered by study personnel through eCRFs into the electronic database for each participant enrolled in the study. A unique ID number will be assigned to each participant.

The following CRFs and log will be used in this study and submitted at the intervals outlined in Table 1:

- Screening Visit / Study Eligibility (01)
- Baseline Visit Demographics and Treatment History (02)
- Follow-up (03)
- rTNSS / Cough and Postnasal Drip (04)
- Procedure (05)
- Pain VAS - Patient form (06A)
- Pain VAS - Site (06B)
- Study Exit (07)
- Device Malfunction (08)
- Protocol Deviation (09)
- Adverse Event Report (10A) (reference AE Code List (10B))
- MiniRQLQ (11)
- Serious Adverse Event / Unanticipated Adverse Device Effect (12)
- Patient Satisfaction Survey (13)
- Concomitant Medication Log (14)

Table 1. Schedule of case report forms and related materials.

Visit	Visit window (days)	CRF	Other
Screening / Baseline	n/a	01, 02, 04, 11, 14	Informed Consent Nasal assessment images†
Treatment Procedure	within 30 days of Baseline‡	05, 06A, 06B	Nasal assessment images†
4-Week (In-office)	±3	03, 04, 06A, 06B, 11	Nasal assessment images†
13-Week (In-office)	±14	03, 04, 06A, 06B, 11	Nasal assessment images†
6-Month (In-office)	±30	03, 04, 11, 13	Nasal assessment images†
12-Month (Remote)	±30	03, 04, 11, 13	
24-Month (Remote)	±30	03, 04, 07, 11, 13	
As Needed	n/a	07, 08, 09, 10A, 12, 14	

†Transfer to USB flash drive and provide to Sponsor.
‡If the procedure does not occur on the day of screening the nasal assessment, rTNSS, and MiniRQLQ should be repeated, and medication use updated before starting the procedure.

8.3.3 Investigator Responsibilities, Records, and Reports

Responsibilities

The investigator is responsible for ensuring that the study is conducted according to the protocol and all IRB requirements. In addition, the investigator is responsible for obtaining participant's written authorization for disclosure and use of health information as required under the Health Insurance Portability and Accountability Act (HIPAA; 45 CFR Parts 160 and 164).

Records

The investigator will maintain complete, accurate and current study records. Investigator records including:

1. Relevant communication that documents any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, or adverse event reporting, including that with the IRB, the sponsor, the study monitors, other investigators, and regulatory agencies.
2. Accountability records of receipt, use and disposition of all study products, including the type and quantity of the product, the dates of their receipt and the lot numbers.
3. Participant records, including the participant's informed consent form, case history, procedure dictation, adverse events, progress notes, follow-up evaluations, case report forms and all supporting documents, such as diagnostic studies.
4. Study Protocol, amendments, and documentation (dates and reasons) of any deviations from the protocol.

5. IRB records, including original and ongoing study approvals, all correspondence, and the approved informed consent form.
6. IRB membership list, FWA#, statement of compliance and written procedures pertaining to AE and protocol deviation reporting (if available).
7. Study agreement, curricula vitae of investigator(s), financial disclosure, signature authorization log (delegation of responsibility), protocol signature page, and patient screening/enrollment log.
8. Reports (including safety reports, progress reports and a final report from the investigator).
9. Any other records, as required by the IRB and the sponsor.

Reports

Investigators are required to prepare and submit the following reports in a complete, accurate and timely fashion:

1. Adverse Experiences: In the event of an adverse experience that is serious or unexpected, or which requires action by sponsor to prevent an unreasonable risk of substantial harm to public health, notice shall be given immediately (but in no event later than 24 hours after learning of such experience) by telephone, facsimile, or email to the Sponsor and the IRB. Any notices made by telephone shall be confirmed in writing within 2 days of the initial notification. The site shall provide all associated documentation (eg, lab reports, death summary, operative reports, etc.) for each adverse experience.
2. Unexpected adverse device effects and serious adverse events should be reported to the sponsor within 24 hours of event discovery. If the adverse event is alarming, the investigator shall report the event immediately.
3. Investigators shall promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to participants and others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent hazards to the participants.
4. Withdrawal of IRB approval to the sponsor within 5 working days. The report will include a complete description of the reason that approval was withdrawn.
5. Progress reports must be submitted to the IRB at regular intervals dictated by the IRB but no less than annually.
6. A final report must be submitted to the IRB within 3 months after 1) termination or completion of the study; or 2) the investigator's work on the study ceases.

7. Any deviation from the protocol to protect the life or physical well-being of a participant in an emergency is to be reported to the sponsor and IRB no later than 5 working days after the emergency occurs. Deviations to the informed consent process (eg, use of study product without informed consent) must be reported to the Sponsor and the IRB immediately but no later than 5 working days after the use occurs. Deviations from the randomization scheme must be reported to the sponsor as soon as possible after they are recognized.
8. Other: upon request, the investigator will supply accurate, complete and current information about any aspect of the study to the sponsor.

8.3.4 Retention of Study Records

The sponsor must ensure that all study participant records are stored for at least 2 years after the later of the following 2 dates: the date on which the study is terminated or completed (all subjects through final follow-up), or the date that the records are no longer required by the study site record retention policy. To avoid error, the site should contact the sponsor prior to the destruction of study records to ensure that they no longer need to be retained. In addition, the sponsor should be contacted if the study site is acquired or shuts down so that arrangements can be made for the handling or transfer of study records.

8.3.5 Data Quality Assurance

The sponsor, or the sponsor's representative, may conduct audits at the study sites. Audits may include, but are not limited to, device supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. The investigator agrees to participate with audits conducted at a reasonable time, in a reasonable manner.

8.3.6 Confidentiality

All information provided to investigators, IRBs, and generated in this study must be considered highly confidential and must not be disclosed to any persons not directly involved with the study without prior written permission from the sponsor. However, authorized regulatory officials and sponsor personnel (or their representatives) will be allowed full access to inspect and copy the records. All study products must be used solely in accordance with this protocol. Privacy and confidentiality of information about each participant shall be preserved in the reports and in any publication. Each participant in this study will be assigned a unique identifier. All data will be tracked, evaluated, and stored using only this unique identifier.

The study site will maintain a confidential list (paper or electronic) identifying all participants. This list will contain the assigned participant's unique identifier and name. The treating physician bears responsibility for keeping this list confidential. This list will not be provided to the study sponsor and is only to be used at the study site.

Monitors and auditors will have access to the study patient list and other personally identifying information of participants to ensure that data reported corresponds to the person who signed the informed consent form and the information contained in original source documents. Such personal identifying information may include, but is not limited to the participant's name, address, date of birth, gender, race and medical record number.

8.3.7 Publication Policies

The Clinical Trial Agreement (CTA) mutually signed by the investigator(s) and Aerin Medical, defines and describes the nature of the study agreement. The data and results from this study are the sole property of Aerin Medical. Aerin Medical shall have the right to access and use all data and results generated during the clinical investigations. Publication authorship will be established according to ICMJE guidelines and Aerin Medical policy. Clinical study design will be publicly disclosed on ClinicalTrials.gov, and summary results posted per FDAAA 801 Requirements. Additionally, an investigator may only publish data generated by this trial in accordance with the terms of the Clinical Trial Research Agreement.

It is Aerin Medical's intent to encourage and facilitate the publications of scientifically important results, while simultaneously ensuring minimization of duplicative data publication and the priority publications of multicenter results ahead of single-center investigations.

Aerin Medical intends to provide research sites with a standardized study report containing aggregated site study data.

8.4 Early Termination

The study can be discontinued at the discretion of the sponsor for reasons including, but not limited to, the following:

- Obtaining new scientific knowledge that shows that the study is no longer valid or necessary,
- Insufficient recruitment of patients,
- Persistent noncompliance with the protocol.

If the study is discontinued or suspended prematurely, the sponsor shall promptly inform all participating study sites and treating physicians of the termination or suspension and the reason(s) for the termination or suspension. The IRB shall also be informed promptly and provided with the reason(s) for the termination or suspension by the sponsor. Regulatory authorities and the personal physicians of the participants may also need to be informed if deemed necessary.

9.0 Ethics

9.1 Institutional Review Board

This study may not be initiated at a site until applicable Institutional Review Board, or similarly named research review committee, approval is obtained. The Study Protocol, all Study Protocol amendments, written study participant information, informed consent form, and any other appropriate study-related information must be reviewed and approved by the IRB.

To assure proper review and study oversight, the IRB must comply with the responsibilities, functions, and records requirements defined in the federal regulations (21 CFR Part 56).

The investigator at each site is responsible for submitting the appropriate study documentation to the IRB for review and approval in accordance with federal regulations. The investigator is responsible for providing accurate, complete, and current information to the IRB throughout the course of the study.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements governing clinical studies of marketed products. Compliance with these requirements also constitutes conformity with the ethical principles that have their origin in the Declaration of Helsinki.

The sponsor will promptly review all information relevant to the safety of the product that is received and comply with all regulatory device safety reporting requirements.

9.3 Participant Privacy

The privacy of participants in this study will be protected by all reasonable means. The investigator is responsible for study records at the study site and must only disclose information as provided for in the site's Authorization to Use and Disclose Health Information. Each participant must give permission for use and disclosure of their information by signing the Authorization to Use and Disclose Health Information. This form may be a separate document from the informed consent form, or it may be contained within or as an addendum to the informed consent form. Although the sponsor is not a covered entity under HIPAA, access to study records, particularly participant information, will be strictly limited by the sponsor to the investigator, the sponsor's clinical research personnel, authorized representatives of the sponsor and the Food and Drug Administration under applicable federal regulations. No public reporting or publications of the results of this study will contain identifiable references to individual participants in the study.

9.4 Participant Reimbursement

Participants will be reimbursed for their time for completing questionnaires as allowed by study site policies. Participants will not be reimbursed for questionnaires not completed.

9.5 Participant Withdrawal

Participants may withdraw from the study at any time for any reason without impact to their future medical care at the study site. Any participant withdrawing from the study for any reason will continue to receive medically necessary follow-up care as determined by the investigator. Every attempt should be made to follow a participant withdrawing either because they failed to obtain a desired effect or suffered an adverse event.

When a participant chooses to withdraw, the investigator and study coordinator will make all possible efforts to collect and report the final visit observations. All reasons for withdrawals and documentation will be recorded in source documentation and the appropriate case report form. In addition, within the informed consent process, participants will be asked to provide consent for the study staff to contact them by mail or phone to follow up on safety-related issues as appropriate.

9.6 Protocol Modifications

This protocol shall not be amended without the approval of the sponsor. The sponsor may amend the protocol to clarify study procedures or to implement changes to the protocol that do not affect the validity of the data; the risk to benefit ratio; the scientific soundness of the protocol; or the rights, safety, or welfare of the participants. All modifications must be reviewed and approved by the IRB at each study site, or a central IRB before implementation.

9.7 Protocol Adherence and Deviations

The investigator(s) agree to conduct the study in accordance with this protocol. An investigator must not make any changes in the study without first receiving approval in writing from the IRB, except when necessary to eliminate apparent immediate hazards to a participant. Investigators will also adhere to procedures for reporting study deviations to their IRB in accordance with their specific IRB reporting policies and procedures.

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