Clinical Evaluation of Low Power Radiofrequency Energy Applied to the Posterior Nasal Nerve Area for Symptomatic Relief of Chronic Rhinitis

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A complete list of investigators will be maintained and will be available upon request.

SIGNATURES

SPONSOR

Print Name: **Scott Wolf, MD** **Title:** **Chief Medical Officer**

Signature:  **Date:** 12/17/2018

INVESTIGATOR

I, the undersigned, certify that I have reviewed this Clinical Study Plan (CSP) 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 Institutional Review Board, U.S. FDA or other regulatory agency.

Print Name: _____

Signature: _____ **Date:** _____

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1.0 PROTOCOL SYNOPSIS

Study Title:	Clinical Evaluation of Low Power Radiofrequency Energy Applied to the Posterior Nasal Nerve Area for Symptomatic Relief of Chronic Rhinitis
Study Device:	Aerin Medical InSeca ARC Stylus
Device Description:	The InSeca ARC Stylus is a disposable handheld device capable of delivering bipolar radiofrequency energy to tissue.
Indication:	The InSeca ARC Stylus is indicated for use in otorhinolaryngology (ENT) surgery for the coagulation of soft tissue in the nasal airway, to treat nasal airway obstruction by shrinking submucosal tissue.
Study Objective:	The primary objective of this study is to collect clinical data on the use of the InSeca ARC System to treat tissue in the posterior nasal nerve area to improve symptoms in adults diagnosed with chronic rhinitis.
Study Design:	Prospective, multicenter, nonrandomized, nonsignificant Risk (NSR) study.
Subject Population:	Male and female subjects who present with symptoms associated with chronic rhinitis and meet the protocol eligibility criteria.
Study Procedure:	Subjects will have BOTH nostrils treated in the portion of the nasal cavity mucosa overlying the region of the posterior nasal nerve (the posterior middle meatus and posterior inferior meatus). Follow-up visits will be scheduled and calculated from the treatment date. No repeat ("touch-up") procedures will be permitted during the 52-week follow-up period.
Study Endpoints:	Primary Efficacy Endpoint: Mean change in the rTNSS score from baseline to 12 weeks post study procedure. For study success, the mean change must show an improvement (decrease) exceeding 1 point. Primary Safety Endpoint: Safety will be assessed by characterizing the type and frequency of adverse events reported at or following the study procedure, and throughout the follow-up period.
Additional Evaluations:	Responder Rate: A responder is defined as a treated subject who experiences at least a 1 point improvement (decrease) in the rTNSS score at 12 weeks compared to baseline score. An overall responder rate of at least 55% is expected for the study. rTNSS Scores Over Time: rTNSS scores and change from baseline will be summarized at baseline and each follow-up evaluation. rTNSS Individual Nasal Symptom Scores: The scores of each survey question will be summarized at baseline and each follow-up evaluation.

	QOL Questionnaire: The responses for each of the 9 questions will be summarized at baseline and each follow-up evaluation at which the survey is administered. Subject Satisfaction Survey: The responses will be summarized for each follow-up evaluation at which the survey is administered. Nasal Status Assessment: Each component of the assessment will be summarized at baseline and each follow-up evaluation. VAS Pain Scores: VAS pain scores will be summarized at the immediate post-treatment evaluation and at the 2-, 4-, and 12-week follow-up evaluations. Medications: Medication information will be summarized and reviewed for significant trends.
Study Size:	50 subjects who meet the inclusion/exclusion criteria and enroll in the study
Number of Study Sites:	Up to 10 study sites
Anticipated Study Duration:	Enrollment completion – Q1 2019; Follow-Up completion – Q1 2020
Study Visits:	Screening/Baseline, Study Procedure, 2 weeks, 4 weeks, 12 weeks, 26 weeks, 52 weeks
Study Eligibility Criteria:	Inclusion Criteria: Eligible subject will meet all the following: 1. Age 22 to 75 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 score of ≥ 6 8. Dissatisfaction with medical management, defined as usage of intranasal steroids for a minimum of 4 weeks without adequate symptom relief, as judged by the subject

Exclusion Criteria:

Subject will not be enrolled if they meet any of the following:

1. Anatomic obstructions that in the investigator's opinion limit access to the posterior nose
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. Moderate to severe ocular allergic symptoms (such as eye tearing [epiphora], itching [pruritus], or redness [erythema])
5. History of significant dry eye
6. History of any of the following: nose bleeds in the past 3 months, rhinitis medicamentosa, head or neck irradiation
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. 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

2.0 INTRODUCTION AND LITERATURE REVIEW

2.1 Introduction

Rhinitis is a condition of the nasal cavity in which the membrane lining the nasal cavity becomes irritated and swollen. Patients typically present with complaints of runny nose, itchy or watery eyes, sneezing, irritated throat and postnasal discharge. Rhinitis may be caused by allergens (such as pollen, pet dander, mold or dust), or by other triggers (including 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]

2.2 Nasal Anatomy

The nose is a respiratory organ that performs a prominent airflow regulatory role. Air enters the nasal cavity, where it is warmed to a temperature of approximately 31°C to 34°C, regardless of the outside temperature. The nose also humidifies the inspired air to a relative humidity of 90% to 95%[3]. These functions prevent drying of the distal airways, which allows optimal gas exchange, and helps maintain healthy body temperature. In addition to these heating and humidification roles, the nose serves to protect the airway by filtering inhaled particulates.[4]

The nasal cavity is covered with an epithelial lining made of cells which interact to serve appropriate functions in the nasal environment. Cells located in the epithelial lining include ciliated cells, goblet cells and seromucous glands. The serous cell contributes to the seromucous glands that moisten membranes, the ciliated cells produce the fine hairs that move foreign substances out of the airway and the goblet cell produces a carbohydrate called mucin which attracts water and forms a gelatin-like substance better known as mucus.[5,6]

The goblet cell is the most prominent mucus producing cell in the nasal membrane and together with the seromucous glands, works to provide the mucus fluid on the nasal 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. As a natural defense it is then cleared by movement of the cilia and disposed to the stomach.[6]

Regulation of the seromucous glands and 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.

3.0 RHINITIS DIAGNOSIS AND TREATMENT

3.1 Diagnosis

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. By having patients complete a quality of life and symptom questionnaire during the history and physical exam, the practitioner will better understand the duration, course and suspected cause of symptoms. This questionnaire typically asks patients to describe certain environmental factors that may trigger the allergy symptoms. Respiratory irritants may help differentiate if the symptoms relate to allergic or non-allergic responses.[2,7,8] One algorithm for evaluating rhinitis patients is presented in Figure 1.[1]

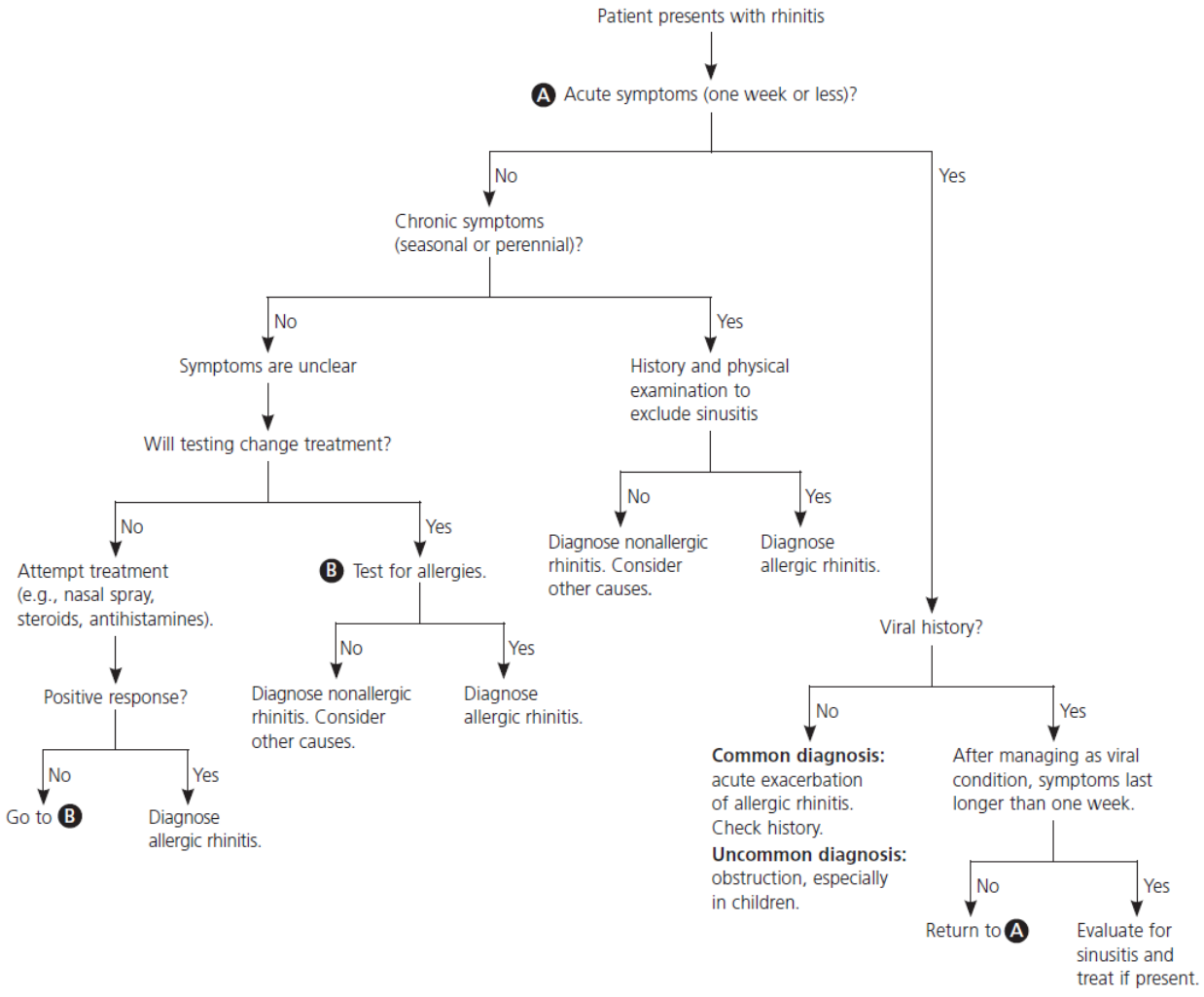


Figure 1. Algorithm for Evaluating Patients with Suspected Rhinitis
(adapted from Quillen and Feller, 2006, Figure 1)

3.1.1 Transnasal Endoscopy

Physicians observe the nasal structures by transnasal endoscopy to rule out anatomic conditions mimicking rhinitis. A small scope with a camera attached is inserted into each nostril to observe the nasal cavity. 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.

3.1.2 Allergy Testing

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]

3.2 Treatment

3.2.1 Medical Treatment

Nasal irrigation (nasal lavage) may reduce symptoms if done multiple times a day with a saline rinse. Allergic rhinitis patients usually find relief with use of over-the-counter oral or nasal antihistamines and/or corticosteroid sprays and may only require administration at specific times of the year.[2] Allergen immunotherapy may also be effective in treating allergic rhinitis.

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 usually seek further management to alleviate symptoms and may be candidates for nasal surgery.

3.2.2 Surgical Treatment – Neurectomy

Vidian neurectomy is a surgical option to relieve nasal symptoms as the vidian nerve supplies autonomic input to nasal mucosa (as well as the palate and the lacrimal gland). While this surgery has been performed for over 50 years, it is known to be highly controversial since access to the nerve proves to be technically difficult and complications with numerous surrounding important structures can occur.[9,10] Common procedural side effects include dry eyes, nasal dryness or crusting and mild pain, whereas more significant risks may include hemorrhage, vision loss and palate/lip/cheek numbness. In addition, improvement in symptoms is often unpredictable. [9]

An alternative neurectomy target is the posterior nasal nerve (PNN). The advantage of the PNN over the vidian nerve is its more limited innervation (it primarily stimulates 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 nerve neurectomy,[9] while still providing significant improvement in quality of life.[11]

A recent publication describes the use of a cryosurgical probe to ablate posterior nasal nerve tissue.[12] This article details the long-term (1 year) results of treatment in a population of 27 chronic rhinitis patients, of which 48% had allergic rhinitis. Significant improvement in total nasal symptom score was seen between baseline score and each follow-up visit. Post-procedure adverse events resolved or improved by the 30-day follow-up visit. Overall, 74% of subjects had symptom improvement by 6 months post-procedure.

4.0 CURRENT USE OF RADIOFREQUENCY ENERGY IN THE NOSE

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 daily in numerous nasal therapies. Radiofrequency turbinate reduction (RFTR), for instance, is a minimally invasive surgical option that can reduce tissue volume in a precise, targeted manner. This technique uses radiofrequency energy to create heat within the submucosal tissue of the turbinate, reducing tissue volume with minimal impact on surrounding tissues.[13] Radiofrequency turbinate reduction differs fundamentally from traditional surgical methods by using low-power radiofrequency energy to provide a relatively quick and painless procedure for tissue coagulation and/or ablation.

There have been multiple studies analyzing the safety and outcomes of using radiofrequency energy in the RFTR procedure. In 2009, Hytonen, et al.[14] completed a systematic literature review of the RFTR technique and concluded that the technique is well tolerated and effective.

Numerous studies have demonstrated that radiofrequency tissue therapy in the nasal passage can be safe and effective in improving nasal obstruction and in preserving nasal function[15]. Kezirian et al.[16] reported 1 minor complication of crusting in 89 adult patients treated with radiofrequency ablation of the turbinates. The same authors also reported no moderate or major complications after RFTR based on a review of published literature results.

5.0 STUDY RATIONALE

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. At 6-months postprocedure, 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 current study is intended to further evaluate the use of the InSeca Stylus for treating rhinitis by targeting treatment to the portion of the inferior turbinate mucosa overlying the region of the posterior nasal nerve.

6.0 SUMMARY DEVICE DESCRIPTION

The Aerin Medical InSeca ARC System (Figure 2) includes two FDA-cleared products: the InSeca ARC Stylus (Figure 3), which is a disposable handheld device capable of delivering bipolar radiofrequency energy to tissue, and the Aerin Medical Console (Figure 4), a temperature-controlled generator that delivers low doses of radiofrequency energy to the Stylus. The Stylus is attached to the Aerin Medical Console via a flexible cable. The Stylus has received FDA clearance for "the coagulation of soft tissue in the nasal airway, to treat nasal airway obstruction by shrinking submucosal tissue."

The InSeca ARC Stylus consists of a handle, shaft and treatment tip. The tip (Figure 5) comprises two rows of electrodes placed on either side of a non-conductive mold. A probe located in the center of the tip between the two electrode rows contains a thermocouple that constantly measures the temperature of the tissue, providing feedback to the generator and allowing the generator to automatically adjust energy delivery as necessary. The stylus tip is temporarily inserted into the nose to deliver low-power RF energy to the treatment area. It generates heat within the submucosal tissue and creates a coagulation lesion. The stylus may be used to treat multiple locations in one or both nostrils of a single patient. If the straight InSeca ARC Stylus cannot access the target treatment area, the Stylus may be bent using the Oratec Probe Bender (Figure 6). The Stylus should only be manipulated in the bender one time and should not be bent more than 20 degrees.

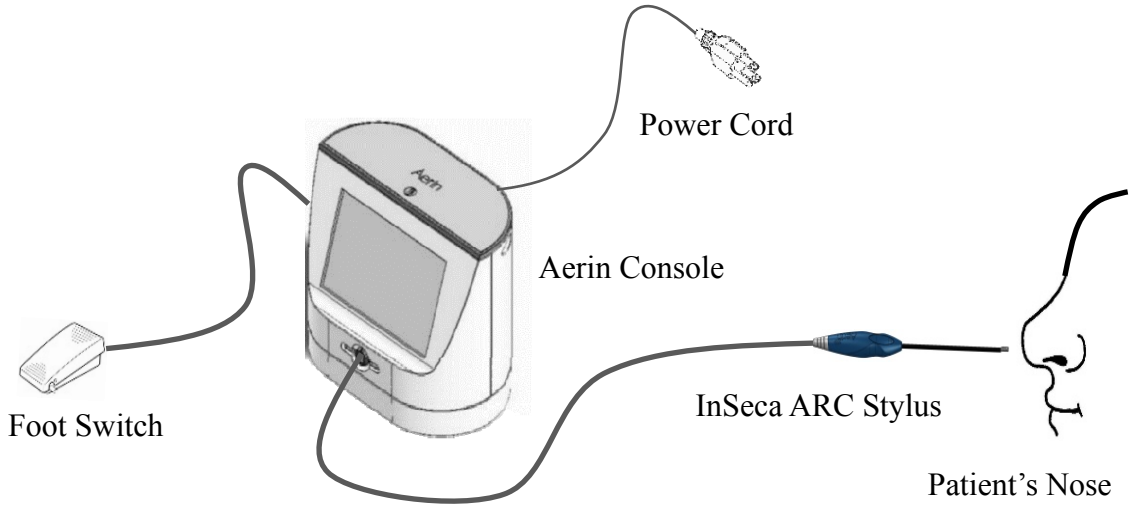


Figure 2. InSeca ARC Stylus with Aerin Console

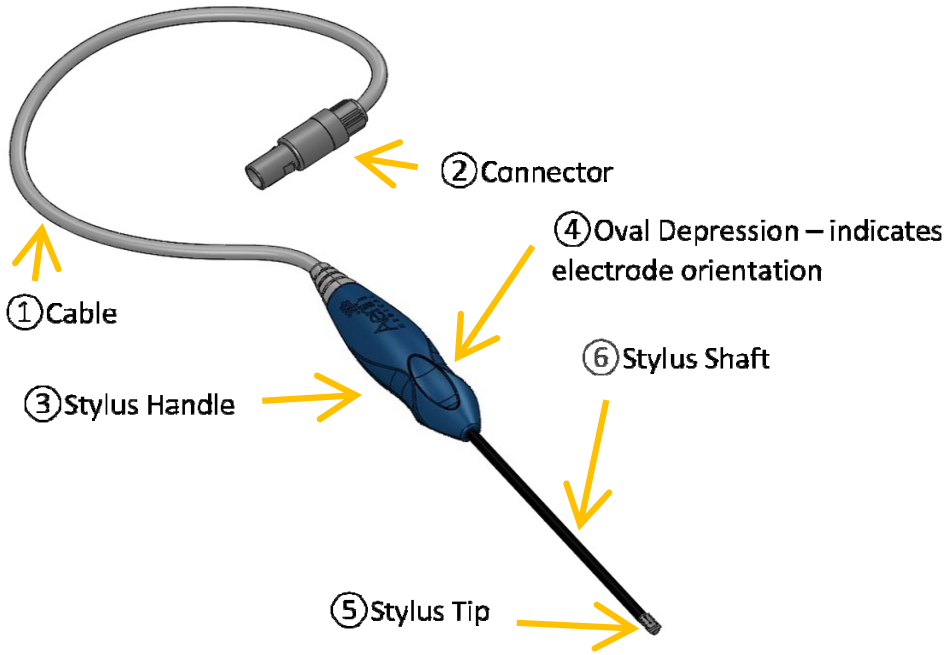


Figure 3. InSeca ARC Stylus (not to scale)

Figure 4. Aerin Medical Console

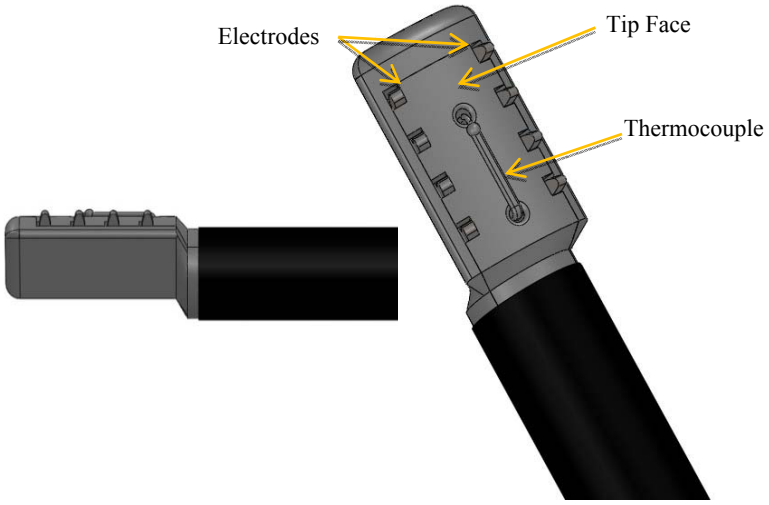


Figure 5. InSeca ARC Stylus Treatment Tip (not to scale)

Figure 6. Oratec Probe Bender With InSeca ARC Stylus

7.0 STUDY DESIGN AND ENROLLMENT

7.1 Study Design and Objectives

This study is a prospective, multicenter, nonrandomized, nonsignificant risk (NSR) study of the Aerin Medical InSeca ARC Stylus. The primary objective of this study is to evaluate treatment outcomes when the InSeca ARC System is used to treat the posterior nasal nerve area of the nasal passageway to improve symptoms in adults diagnosed with chronic rhinitis.

The design encompasses a 2-phase enrollment. Up to 10 subjects will be enrolled in the first phase. Further enrollment will be suspended until all initial subjects have completed their 4-week evaluation. Information from these patients will be used to assure the safety of the procedure as well as the adequacy of treatment settings and treatment locations.

7.2 Subject Population

The population being targeted for this therapy consists of patients who have exhibited symptoms of chronic rhinitis for at least six months. To evaluate the severity of a patient's rhinitis symptoms both before and after the procedure, this study will use the 4-item Total Nasal Symptom Scale (TNSS). The maximum TNSS score is 12 and indicates the most severe symptoms. Aerin Medical has chosen a baseline 12-hour reflective TNSS (a 12-hour rTNSS) score of at least 6 for inclusion in the study, with the additional requirements that the subject have at least moderate (score of 2) rhinorrhea symptoms and at least mild (score of 1) 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.

Eligible subjects must meet the inclusion and exclusion criteria described in Sections 7.3 and 7.4. Any questions regarding a potential subject's eligibility for enrollment must be discussed with the Sponsor prior to scheduling the subject for the procedure.

7.3 Inclusion Criteria

To be eligible to participate in this study, a patient must meet all the following criteria:

1. Age 22 to 75 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 score of ≥ 6
8. Dissatisfaction with medical management, defined as usage of intranasal steroids for a minimum of 4 weeks without adequate symptom relief, as judged by the subject

7.4 Exclusion Criteria

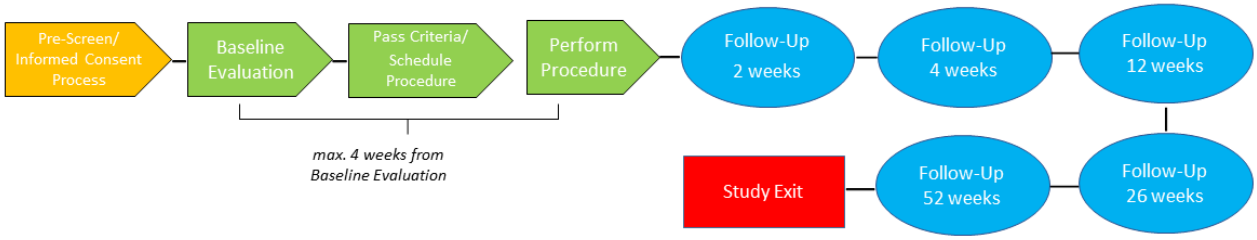
A patient who meets any of the following criteria is not eligible to participate in the study:

1. Anatomic obstructions that in the investigator's opinion limit access to the posterior nose
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. Moderate to severe ocular allergic symptoms (such as eye tearing [epiphora], itching [pruritus], or redness [erythema])
5. History of significant dry eye
6. History of any of the following: nose bleeds in the past 3 months, rhinitis medicamentosa, head or neck irradiation
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. 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

8.0 STUDY PHASES

The study will be conducted in four phases as subjects are consented, evaluated for eligibility, treated and followed until study exit:

Phase 1 - Pre-Screen / Informed Consent Process
Phase 2 - Screening / Baseline Evaluation
Phase 3 - Enrollment / Study Procedure
Phase 4 - Follow-up / Study Exit



The different study phases are described in Sections 8.1 through 8.4. Section 8.5 provides a table of required study visits, the visit windows, and the assessments to be done at each visit, as well as a description of each assessment type.

8.1 Phase 1: Pre-Screen and Informed Consent Process

Patients presenting with symptoms associated with rhinitis will be approached with the study and asked if they are willing to volunteer participation. Patients will initially be asked about duration of symptoms and conservative measures used for their condition. Any known concomitant nasal conditions and past nasal surgeries or injuries will be discussed to understand if they are potential candidates for the study.

Informed Consent

Informed consent will be obtained as outlined in 21 CFR Part 50 and the Good Clinical Practice E6(R2): Integrated Addendum to ICH E6(R1) (March 2018).

A research study member at the approved study site will speak with the study candidate about the purpose of the study. Explanation of the study background, study procedure (including risks and benefits), and follow up visit schedule will be reviewed in detail with the patient. Patients will be given the time they need to read through the study information and informed consent document and ask as many questions as necessary to make them comfortable with the study and the requirements. For those potential candidates who agree to participate in the study by signing the IRB-approved Informed Consent Form (ICF), a baseline evaluation will be conducted.

8.2 Phase 2: Screening and Baseline Evaluation

During the screening/baseline visit in the study clinic, the Investigator or designated research staff will perform a formal evaluation of the study candidate for study eligibility, which will 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 for rhinitis.

The following data will be collected:

- Patient demographics
- Medical history including prior tests and treatments for rhinitis
- Current medications and conditions for which they are prescribed
- Physical exam and vital signs
- Reflective TNSS questionnaire (symptom severity over the preceding 12 hours as reported by the subject)
- Investigator visual assessment (using an endoscope) of the target treatment area (posterior nasal nerve area) and any anatomy that might hamper necessary device access

Subjects who agree to participate and meet the enrollment criteria must be scheduled to undergo the study procedure **within 4 weeks** of the baseline visit.

8.3 Phase 3: Enrollment and Study Procedure

Study subjects will be considered enrolled once they arrive at the study clinic to undergo the procedure. At this time a study subject identification number will be assigned along with the study subject binder. The procedure will be performed in the study clinic. Subjects will have all treatments in a single study procedure session. The area to be treated is the portion of the nasal cavity mucosa overlying the region of the posterior nasal nerve (the posterior middle meatus and posterior inferior meatus). **Both nostrils** will be treated at 1, 2 or 3 non-overlapping positions (depending on the size of the subject's target treatment area).

Treatment settings to be used are:

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

No repeat ("touch-up") procedures will be permitted during the 52-week follow-up period.

NOTE: Device Malfunction or Failure
If any component of the InSeca System is associated with a malfunction or failure during a study procedure, the sponsor should be contacted immediately for instructions.

Sponsor Contact:	Andrew Frazier, VP of Engineering
Telephone:	(650) 776-3061
Email:	afrazier@aerinmedical.com

Immediate Post-Procedure Care (prior to leaving the clinic)
Subjects will be asked to mark a vertical line on a 10-cm visual analog scale (VAS) to represent the pain level experienced during the study procedure session. The score will include the overall pain experience from anesthesia delivery to procedure completion.

Recommended post-procedure care includes:

- The physician may apply Aquaphor® or similar ointment to the treatment area post therapy.
- The patient should be instructed to:
  - Avoid manipulation of the treatment site for 24 hours unless necessary for hemostasis.
  - Use over-the-counter saline nasal sprays as appropriate.
  - Avoid forceful nose blowing. If patient needs to blow nose, they should do so gently.

Study subjects should be reminded of their next follow-up visit prior to leaving the clinic.

8.4 Phase 4: Follow-Up and Study Exit

The follow-up period begins after the study procedure session. Subjects will undergo follow-up visits at **2 weeks, 4 weeks, 12 weeks, 26 weeks and 52 weeks,** calculated from the study procedure date. Visits should be scheduled within the visit windows specified in Table 1. Requirements for each follow-up visit are described in Section 8.5 and shown in Table 1.

Subjects meeting the study requirements as planned will be exited from the study at the 52-week follow up visit. If a subject reaches the 52-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.

8.5 Types of Assessments

The following assessments will be obtained from the study subjects at the specified study follow-up visits:

Total Nasal Symptom Score (TNSS) – The TNSS is an instrument used to collect patient self-rated severity of four 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[17] and nonallergic rhinitis[18]. The TNSS requires the subject to rate four 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 symptom (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/symptoms that is hard to tolerate; causes interference with activities of daily living and/or sleeping)

For the purposes of this study, the subject will be asked to evaluate symptom severity over the preceding 12 hours.

Visual Assessment of Treatment Area – The target posterior nasal nerve area within each nostril will be visually assessed at baseline and following the treatment procedure at the time points described in Table 1. The use of an endoscope for visual assessment is required. For consistency in reporting across sites, a study CRF will outline specific observations to be assessed.

Video should be captured and archived during the endoscopic evaluation. These videos will allow for future evaluation or comparison, if necessary. If video capture is unavailable, representative still photographs may be collected instead.

Visual Analog Scale (VAS) for Pain Intensity[19] – The Pain VAS will be used to rate pain associated with the treatment (i.e., in the treatment area) immediately following the procedure and at each follow-up visit through 12 weeks. Subjects will be asked to mark their pain level on a 10-cm line anchored by verbal descriptors: 0 = no pain and 10 = worst pain imaginable. The study staff will measure with a metric ruler from the 0, the beginning of the line, to the vertical mark made by the subject. The result, expressed in millimeters, will represent the subject's VAS Pain Score.

Study-Specific Quality of Life (QOL) Questionnaire – The QOL questionnaire will be used to gain understanding of the impact of chronic rhinitis on the subject's daily activities, feelings, symptoms and medication use. The QOL will be completed by the subject both prior to the treatment procedure, and at the 12-week, 26-week and 52-week follow-up visits.

Subject Satisfaction Survey – The Satisfaction Survey will be used to assess patient acceptance of the treatment procedure and results. Subjects will be asked to complete the Satisfaction Survey at the 12-week and 52-week follow-up visits.

Adverse Event Evaluation – Subjects will be asked about possible side effects or adverse experiences related to the study procedure. All events will be documented on the Adverse Event Log and Adverse Event Case Report Form. Anticipated observations related to the study procedure will be tabulated but will not be categorized as adverse events unless they require mitigation by the treating physician or are greater in severity, duration or degree of incidence than anticipated. Refer to Table 2 for a listing of anticipated observations as well as anticipated frequency, severity and duration.

Medications – Updates to current medications and any new or changed medications will be requested at each follow-up visit. The medication log will be updated to reflect any changes. In addition, any medications required as a result of intervention related to the study procedure will be documented and correlated with the Adverse Event Case Report Form.

Table 1 outlines the assessments to be performed at each required visit and specifies the required visit windows.

Table 1. Schedule of Assessments

Assessments	**Screening / Baseline**	**Study Procedure** (within 4 weeks of Baseline visit)	**Immediately Post-Treatment**	**2-Week Follow-Up** (+/- 3 days)	**4-Week Follow-Up** (+/- 1 week)	**12-Week Follow-Up** (+/- 2 weeks)	**26-Week Follow-Up** (+/- 3 weeks)	**52-Week Follow-Up** (+/- 4 weeks)
Demographics and Medical History	X							
Physical Exam and Vital Signs	X							
Medication Review	X	X		X	X	X	X	X
Study Procedure		X						
Endoscopic Assessment of treatment area (with video or photo capture)	X	X*	X*	X	X	X	X	X
rTNSS Score	X			X	X	X	X	X
Subjective Pain VAS			X	X	X	X		
QOL Questionnaire	X					X	X	X
Subject Satisfaction Survey						X		X
Adverse Event review			X	X	X	X	X	X
Pregnancy test (if female)		X						

*Endoscopic assessment to be done both immediately prior to and after procedure

9.0 SUBJECT REIMBURSEMENT

Subjects may be reimbursed for their time and travel and any expenses associated with each study visit, as allowed by study site policies. Subjects will not be reimbursed for those scheduled study visits that they do not attend.

10.0 STUDY WITHDRAWAL

Subjects may be terminated or withdrawn from the study for the following reasons:

- Voluntary withdrawal – meaning that the subject voluntarily chooses not to further participate in the study
- *Lost to follow-up – meaning that the subject is more than one month late (beyond the late visit window) to a study visit and 3 documented attempts to contact the subject are unsuccessful. A subject who misses a study visit but attends a subsequent visit will no longer be considered lost to follow-up.
- *In the physician's opinion, it is not in the best interest of the subject to continue study participation.
- Subject death.

**Where possible, subjects will be followed for safety to study completion. Safety follow-up will include a review of adverse events (AEs). A safety follow-up assessment may be performed either via a phone or email contact or a physician visit.*

Any study subject who does not attend a scheduled follow-up visit should be contacted by site personnel to determine the reason for the missed appointment(s). The reason for the missed visit should be determined and documented in the subject's study records. All subjects enrolled (including those withdrawn or lost to follow-up) shall be accounted for with appropriate documentation.

11.0 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 subject's medical record but will not count as related to the study device or procedure.

Each adverse event will be recorded in the corresponding subject's CRF. Each adverse event will be judged by the Investigator as to its relationship and level of relatedness to the study device and/or study procedure. In addition, the Investigator will identify the date of onset, severity and duration of the AE. All adverse events will be monitored until they are adequately resolved or explained. If a subject reaches the 52-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.

The Investigator must submit to the Sponsor a report of any Serious Adverse Event (SAE), Serious Adverse Device Effect (SADE) or Unanticipated Adverse Device Effect (UADE) within 24 hours of knowledge of the event.

Sponsor Contact: Scott Wolf, MD
Telephone: (650) 597-0111
Facsimile: (650) 597-0111
Email: swolf@aerinmedical.com

In addition, the Investigator will report adverse events to the reviewing IRB / EC *(as applicable)* according to the local reporting requirements.

12.0 RISK – BENEFIT ASSESSMENT

12.1 Potential Risks

Potential risks associated with the use of the InSeca ARC System do not differ from those of the commonly used devices and procedures to treat chronic rhinitis discussed previously, but due to the non-surgical nature of the therapy, small treatment area, low-power delivery and lack of need for general anesthesia, the overall risk to the patient may be less than from other procedures such as vidian neurectomy, septoplasty and/or functional rhinoplasty.

Potential risks associated with the use of the InSeca System and/or the associated local anesthetics are outlined below. Subjects will be monitored closely as part of this study to allow for detection of symptoms, should they be present. This, in turn, should allow for early treatment or intervention, if necessary.

The following are adverse events or side effects that may occur as a result of the treatment:

- Infection
- Bleeding (other than intra-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
- External swelling of nose
- Vasovagal response secondary to the procedure
- Change in external shape or appearance of nose

The following two tables list anticipated observations that are expected in and around the treatment area. Table 2 provides the incidence (reported as percentage of treated nostrils) observed in Clinical Study TP258, the nasal valve pivotal study. Table 3 provides the incidence observed in Clinical Study TP220, the rhinitis feasibility study. Anticipated observations will be assessed and recorded at study visits if they occur but, being anticipated as a result of the procedure, will not be considered adverse events unless they require mitigation by the treating physician or are greater in severity, duration or degree of incidence than anticipated. If one of these types of observations is deemed to be an adverse event, it should be recorded on the study Adverse Event CRF.

Table 2. Treatment Area Observations – TP258 Nasal Valve Pivotal Clinical Study

Observation	Post-Procedure (% treated nostrils n = 99)		4-Week Follow-Up (% treated nostrils n = 99)		12-Week Follow-Up (% treated nostrils n = 99)		26-Week Follow-Up (% treated nostrils n = 96)	
Inflammation / redness	Not present Mild Moderate	53 42 5	Not present Mild Moderate	79 17 4	Not present Mild Moderate	89 9 2	Not present Mild Moderate	89 10 1
Swelling, edema	Not present Mild Moderate	45 52 3	Not present Mild Moderate	75 24 1	Not present Mild Moderate	89 9 2	Not present Mild Moderate	89 8 3
Nasal obstruction from tissue edema	Not present Mild Moderate	76 23 1	Not present Mild Moderate	82 13 5	Not present Mild	94 6	Not present Mild Moderate	90 9 1
Disruption of mucosal flow / crusting	Not present Mild Moderate	89 10 1	Not present Mild Moderate	62 34 4	Not present Mild Moderate	84 15 1	Not present Mild Moderate	91 8 1
Blanching	Not present Mild Moderate	29 58 13	Not present Mild	98 2	Not present Mild	98 2	Not present	100
Numbness	Not present Mild Moderate	56 30 14	Not present	100	Not present	100	Not present	100
Soreness, pain	Not present Mild Moderate	70 29 1	Not present Mild	94 6	Not present Mild	99 1	Not present	100
Bleeding at anesthetic injection site (no intervention)	Not present Mild Moderate	51 47 2	Not present	100	Not present	100	Not present	100
Bleeding at treatment site (no intervention)	Not present Mild	85 15	Not present	100	Not present	100	Not present	100
Saddle nose deformity	Not present	100	Not present	100	Not present	100	Not present	100
Bruising around orbital area	Not present	100	Not present	100	Not present	100	Not present	100

Table 3. Treatment Area Observations - TP220 Rhinitis Feasibility Clinical Study

Observation	Baseline (% treated nostrils n = 22)		2-Week Follow-Up (% treated nostrils n = 20)		1-Month Follow-Up (% treated nostrils n = 16)		3-Month Follow-Up (% treated nostrils n = 8)	
Swelling, edema	Not present Mild	9 91	Not present Mild	75 25	Not present Mild Not reported	75 12.5 12.5	Not present Mild	75 25
Blanching / color of mucosa	Pale pink	100	Pale pink Hyperemic	90 10	Pale pink	100	Pale pink Not reported	75 25
Obstruction	Not present Present beyond mid-Meatus	91 9	Not present Present in Ethmoid	90 10	Not present	100	Not present	100
Discharge	Not present Thin Thick	45.4 36.4 18.2	Not present Thin Thick	60 35 5	Not present Thin	87.5 12.5	Not present Thin	87.5 12.5
Scarring / Crusting	Not present Mild	91 9	Not present Mild Severe	35 50 15	Not present Mild	62.5 37.5	Not present	100

12.2 Potential Benefit

Potential benefit, associated with the use of the InSeca System, is to offer a safe, minimally invasive treatment method to alleviate the symptoms of chronic rhinitis.

12.3 Minimization of Anticipated Risks

Risks associated with the InSeca ARC System are minimized by design. In addition, risks will be minimized through the use of an Investigator with a high degree of experience in nasal surgical and minimally invasive procedures. The Investigator will receive sponsor-led training in proper use of the device prior to study initiation and as warranted throughout the study. The sponsor will monitor the study for any trends that would indicate a safety issue.

12.4 Potential Risks to Patient 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 collecting personally identifying information on Case Report Forms (CRFs) or other study-related documentation to be provided to the study sponsor.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Design

This study is a prospective, multicenter, nonrandomized, nonsignificant risk (NSR) study of the Aerin Medical InSeca ARC Stylus when used to treat tissue in the posterior nasal nerve area to improve symptoms in those diagnosed with chronic rhinitis. Each subject serves as their own control for comparing baseline condition with postintervention condition.

The design encompasses a 2-phase enrollment. Up to 10 subjects will be enrolled in the first phase. Further enrollment will be suspended until all initial subjects have completed their 4-week evaluation. Information from these patients will be used to assure the safety of the procedure as well as the adequacy of treatment settings and treatment locations. The standard deviation of the change in TNSS score will be used to gauge the appropriateness of the assumption of standard deviation used for study sample size estimation.

13.2 Study Hypothesis

The primary endpoint of the study is change in mean rTNSS score from baseline to the 12-week evaluation. Improvement in the rTNSS score is represented by a decrease from baseline in the 12-point score. The minimum clinically important difference (MCID) for change in mean TNSS score derived from anchor-based methodologies has been shown to be 0.23 - 0.28 units and by distribution-based methodology the MCID was 0.59 units.[20] A less rigorous expert panel-based estimate of the MCID was 30% of the maximum score of 12, which is 3.6 units.[21] The evidence-based thresholds for MCID have been recommended to supersede the panel-based method.[22,23] An MCID of 1 unit, or 2 to 4 times the more rigorously derived MCIDs, was set for this study.

The hypothesis is that the improvement (decrease) in rTNSS mean score, measured as change from baseline at 12 weeks (12 weeks - baseline), exceeds the MCID (1 unit).

13.3 Sample Size Estimate

Sample size estimation was based on a paired t-test for change from baseline at 12 weeks using the following assumptions:

- Significance level $\alpha = 0.05$ (one-sided)
- Power = 90%
- MCID = 1-point decrease in mean change score = the minimum clinically important difference
- μ_d = -2-point decrease in mean change score = the minimum expected observed difference
- SD = 2 = the expected standard deviation of the observed mean difference
- 10% dropout and nonevaluable.

The minimum number of subjects to achieve 90% power is 36 (G-Power, paired t-test).

The overall planned study sample size is 50 subjects. Fifty subjects allows for the possibility that findings from the review of the phase-1 initial subjects, with respect to the planned protocol treatment parameters, leads to significant protocol modifications to the procedure parameters for the remainder of the subjects. Significant modifications would exclude the initial subjects from the primary endpoint analysis, but a sufficient number of subjects would remain for analysis of the primary study hypothesis.

The sample size estimate will be re-evaluated after the standard deviation of the mean change for the phase-1 initial subjects has been obtained. If the observed standard deviation is larger than the assumed standard deviation, the sample size may be recalculated to assure adequate study size to evaluate the study hypothesis. This evaluation will not be an efficacy evaluation and will not be used to halt the study based on an early determination of success or to decrease the planned sample size.

13.4 Definition of Populations

Enrolled Population – all subjects enrolled in the study.

Evaluable Population – all subjects that are enrolled in the study and have received the study procedure. If a protocol revision is required after review of the initial subjects that substantially alters the treatment settings, a subgroup of the evaluable population will be defined to include only those subjects enrolled and treated under the revised protocol (revised protocol population). Results will be summarized for the evaluable population, the initial protocol population, and the revised protocol population (used for primary endpoint analysis).

Safety Population – all subjects that have received the study procedure

13.5 Missing Data

All efforts will be made to collect all data points in this study. The study hypothesis will be tested using all available data for the subjects in the evaluable patient population. If the primary endpoint is not available for all such subjects, then sensitivity analysis will be performed to assess the potential effect of missing data on the study conclusion. The sensitivity analysis will be performed by imputing all missing data points for the primary endpoint as no (0) improvement. If the study conclusion is upheld using this type of worst-case scenario, no other analysis will be performed. However, if the conclusion using imputed data is different, a multiple imputation approach may be used to gain further insight to the results.

13.6 Multicenter Study - 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 13.3). Pooling is generally justified because the study will be conducted such that: 1) the same protocol will be used at each site; 2) site investigators and personnel will receive uniform training; and 3) central data management and monitoring will be consistent and applied with equal rigor at all sites. Primary endpoint results, demographics and baseline characteristics will be summarized by site and evaluated for comparability among study sites.

13.7 Subject Disposition

A detailed description of subject disposition will be provided using a CONSORT diagram and summaries of subjects falling in various subgroups of interest, such as, enrolled but not treated, discontinued, deaths, and withdrawals. Follow-up by visit will be presented, showing theoretical, expected, and actual follow-up visits.

13.8 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized using frequencies and percentages for categorical factors and mean, median, standard deviation, minimum and maximum for continuous factors.

13.9 Primary Efficacy Endpoint Analysis

The mean change in the rTNSS score from baseline to 12 weeks will be tested using a paired t-test for a significant decrease greater than the MCID under the one-sided null (H_0) and alternative (H_A) hypotheses:

H_0: $\mu_d \geq -1$

H_A: $\mu_d < -1$

where μ_d = the mean change of the paired differences of the 12-week score - the baseline score.

A p-value for the test statistic ≤ 0.05 will indicate that the mean decrease is statistically significantly greater than 1 point. The upper limit of the one-sided 95% confidence interval on the mean decrease will also be calculated.

13.10 Other Efficacy Outcome Measures

13.10.1 Responder Rate

Subjects will be considered to have responded to treatment if they show a decrease of at least 1 point in the rTNSS score at 12 weeks compared to baseline score. An overall responder rate of at least 55% is expected for the study.

13.10.2 rTNSS scores over time

Summary descriptive statistics (mean, SD, median, range) for the rTNSS scores and change from baseline will be summarized at baseline and for each follow-up evaluation.

13.10.3 rTNSS individual nasal symptom scores

The distribution of responses (frequency, percentage) and the mean (SD, median, range) response, based on the 4-point response scale, for each of the survey questions will be summarized at baseline and for each follow-up evaluation.

13.10.4 QOL Questionnaire

The distribution of responses (frequency, percentage) for each of the 9 questions will be summarized at baseline and for each follow-up evaluation at which the survey is administered.

13.10.5 Subject Satisfaction Survey

The distribution of responses (frequency, percentage) and the mean (SD, median, range) response, based on the 10-point response scale, for each of the survey questions will be summarized for each follow-up evaluation at which the survey is administered.

13.11 Primary Safety Endpoint Analysis

Safety will be assessed by characterizing the type and frequency of adverse events reported at or following the study procedure, and throughout the follow-up period. Event types include:

- Serious Adverse Events, including Deaths
- Serious Adverse Device Effects
- Unanticipated Adverse Device Effects
- Device Related Serious Adverse Events

The number of events as well as the percentage of subjects experiencing each event type will be calculated.

All adverse events will be analyzed for all enrolled subjects. Adverse events will be coded using a standardized 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 subjects, number of adverse events, and the proportion of subjects reporting each adverse event will be summarized. Seriousness and severity of adverse events and their relationship to the device and/or procedure will be summarized. A time course of adverse events will be presented using the intervals:

- 0 days to 2 weeks
- 2 weeks to 4 weeks
- 4 weeks to 12 weeks
- 12 weeks to 26 weeks
- 26 weeks to 52 weeks

Narratives will be presented for all deaths, serious adverse events, serious adverse device effects, unanticipated adverse device effects, and subjects withdrawn due to an adverse event.

13.12 Other Safety Analyses

13.12.1 Nasal Status Assessment

Each component of the assessment will be summarized as frequency and percentage for each level of the categorical variable at baseline and each follow-up evaluation.

13.12.2 VAS Pain Scores

VAS pain scores will be summarized descriptively (mean, median, standard deviation, minimum, and maximum) at the immediate post-treatment evaluation and at the 2-, 4-, and 12-week follow-up evaluations.

13.12.3 Medications

Medications and indications will be summarized and reviewed for significant trends. Full detailed listings will be provided by subject.

14.0 SAFETY RELATED STOPPING RULES

The study sponsor will be charged with monitoring the study for safety and for auditing the quality of the data. If there are any perceived safety concerns related to the InSeca ARC System or procedure, the trial may be terminated.

15.0 QUALITY ASSURANCE AND SUPERVISION BY AUTHORITIES

This study will be conducted in accordance with elements of the Good Clinical Practice E6(R2): Integrated Addendum to ICH E6(R1) (March 2018), abbreviated requirements of 21 CFR 812.2(b) for Non-significant Risk (NSR) device studies, the Declaration of Helsinki, the Belmont Report, and IRB/EC requirements.

All documents and data shall be produced and maintained in such a way to assure control of documents and data to protect the patient's privacy as far as reasonably practicable. The Sponsor and representatives of the FDA or other regulatory authorities are permitted to inspect the study documents (e.g., study protocol, CRFs, and original study-relevant medical records/files) as needed. All attempts will be made to preserve patient confidentiality.

All clinical sites are subject to audit by study sponsor personnel or designee for protocol adherence, accuracy of CRFs and compliance with applicable regulations. Any evident pattern of non-compliance with respect to these standards will be cause for corrective action.

The study protocol, data-recording procedures, data handling as well as study reports are subject to an independent clinical Quality Assurance audit by the study sponsor, its designee, or health authorities.

16.0 STUDY MANAGEMENT

This study will be conducted in accordance with elements of the Good Clinical Practice E6(R2): Integrated Addendum to ICH E6(R1) (March 2018), Abbreviated Requirements of 21 CFR 812 for NSR 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 Principal Investigator. The study sponsor and Principal Investigator will ensure that the study is conducted according to all applicable regulations. All personnel to participate in the conduct of this clinical trial will be qualified by education and / or experience to perform their tasks.

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

17.0 DEVICE MANAGEMENT

Devices used in this study will be labeled with the study protocol number and controlled in a manner consistent with investigational devices. The investigator shall maintain adequate records of the receipt and disposition of all study devices. When study enrollment is complete, the investigator shall return any unused devices to the sponsor or their designee. The device will only be used as part of this study in eligible patients and will be used according to its intended use. A copy of the Instructions for Use (IFU) accompanies each study device.

18.0 REQUIRED DOCUMENTS FROM THE INVESTIGATOR (PRIOR TO STUDY START)

At a minimum, the following documents will be provided by the study site to the study sponsor:

- Clinical Trial Agreement signed by the Investigator or responsible party at the Investigator's facility
- Signed Investigator Agreement
- Signed Clinical Protocol Signature Page
- IRB Site Approval Letter
- IRB Site Approved Informed Consent Form (ICF)
- Current Curriculum Vitae (initialed and dated) from all investigators and study coordinators
- Current Medical Licenses from all investigators and licensed study coordinators
- Evidence of GCP training (for all investigators and study coordinators)
- Financial disclosure from all investigators
- Delegation of Authority log

A site may not begin study participation until all the above listed documents have been provided to the study sponsor.

19.0 TRAINING

The InSeca ARC System is intended for use by experienced medical personnel. Any site personnel who will perform the procedure (i.e., the Investigator and appropriate sub-investigators) will be provided training by the study sponsor to familiarize them with the use of the InSeca ARC System prior to their participation in the clinical study.

Each study center will undergo study initiation including but not limited to a review of the following:

- Study Protocol
- Procedures for obtaining Informed Consent
- Procedures for completing Informed Consent Form
- Reporting requirements, including those associated with the handling of adverse events
- CRF completion and correction procedures

- InSeca ARC System overview / Device usage instructions
- Good Clinical Practices (GCP) overview
- Protection of patient confidentiality

20.0 ETHICAL CONSIDERATIONS

The rights, safety and wellbeing of clinical study subjects shall be protected consistent with the ethical principles outlined in the Declaration of Helsinki. This shall be understood, observed and applied at every step in this clinical study.

It is expected that all parties will share in the responsibility for ethical conduct in accordance with their respective roles in the study. The Sponsor and the Investigator shall avoid improper influence or inducement of the patient, study monitor, clinical investigator or other parties participating in or contributing to the study.

21.0 PROTECTION OF PATIENT CONFIDENTIALITY

At all times throughout the clinical study, confidentiality will be observed by all parties involved. All data shall be secured against unauthorized access. Privacy and confidentiality of information about each patient shall be preserved in the reports and in any publication. Each patient participating in this study will be assigned a unique identifier. All CRFs will be tracked, evaluated, and stored using only this unique identifier.

The study site will maintain a confidential study patient list (paper or electronic) identifying all enrolled patients. This list will contain the assigned study patient's unique identifier and name. The Site Principal Investigator (PI) 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 center.

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

NOTE: The patient's name, medical record number or address will NOT be recorded in the monitor's visit report or the database; demographic data that may be recorded includes age, race, and gender.

Any source documents copied for monitoring purposes by the Sponsor will have patient identifiable information redacted and be identified by using the assigned patient's unique identifier to protect patient confidentiality.

22.0 DATA COLLECTION

Study data will be collected using standardized Case Report Forms (CRFs). The CRFs are designed to accommodate the specific features of the trial design. Modification of CRFs will only be made if deemed necessary by the study sponsor.

23.0 SOURCE DATA VERIFICATION

At a minimum, source data verification will be performed on all primary endpoint, outcome measures, and safety data for each patient enrolled in this study.

24.0 STUDY SUSPENSION OR EARLY TERMINATION

The study can be discontinued at the discretion of the Site PI or Sponsor for reasons including, but not limited to, the following:

- Occurrence of adverse events unknown to date in respect to their nature, severity, or duration, or the unexpected incidence of known adverse events
- Obtaining new scientific knowledge that shows that the study is no longer valid or necessary
- Insufficient recruitment of patients
- Unanticipated adverse device effect (UADE) presenting an unreasonable risk to patients (Sponsor may terminate the study immediately)
- Persistent non-compliance with the protocol
- Persistent non-compliance with IRB/EC or regulatory requirements

If the study is discontinued or suspended prematurely, the Sponsor shall promptly inform all clinical investigator(s) / study center(s) of the termination or suspension and the reason(s) for this. The IRB/EC shall also be informed promptly and provided with the reason(s) for the termination or suspension by the Sponsor or by the Site PI / study center(s). Regulatory authorities and the personal physicians of the patients may also need to be informed if deemed necessary.

25.0 SITE CLOSE-OUT

At the time of the site close-out visit, the site monitor or designee will collect all outstanding study documents, ensure that the Investigator's files are accurate and complete, review record retention requirements with the Investigator, make a final accounting of all study supplies, and ensure that all applicable requirements are met for the study. The observations and actions made at this visit will be documented in a final closeout report.

26.0 RESPONSIBILITIES

Aerin Medical Inc. is the manufacturer of the InSeca ARC System and the Sponsor of this study. The study sponsor has the overall responsibility of the study and will work to ensure compliance with the Study Plan, elements of Good Clinical Practice E6(R2): Integrated Addendum to ICH E6(R1) (March 2018), signed study agreements and 21 CFR 812.2(b), *Abbreviated Requirements*.

The sponsor will be responsible for, but not limited to, conducting the following tasks:

- Select qualified Investigators
- Select qualified monitors and other contract study personnel
- Provide the Study Plan and any subsequent amendments
- Sign the protocol signature page (and any amendments as applicable)
- Provide appropriate information and device training to Investigators and study site staff
- Promptly inform the Investigators and where applicable any regulatory authorities and institutional review boards if the study is prematurely terminated or suspended and the reason for the termination or suspension
- Provide study initiation training to include review of the InSeca ARC System instructions for use, the Study Plan, CRF completion guidelines, and guidelines for obtaining informed consent
- Coordinate ongoing communication with CRO(s), consultants and study sites to resolve any problems concerning the protocol or data collection. Every effort will be made to ensure compliance with the protocol.
- Retain ownership of all clinical data generated in this study, and control the use of the data for purposes of regulatory submissions to the US and other regulatory agencies
- Protect patient confidentiality
- Collect, store and keep secure, at a minimum, the following documents:
    - A current Curriculum Vitae and medical license of each Investigator
    - The name of the institutions where the study will be conducted
    - The IRB/EC opinion and / or approval, in writing, and relevant correspondence
    - Correspondence with authorities (as required)
    - Investigator Agreement
    - Financial Disclosure
    - Protocol Signature Page
    - Appropriate insurance certificates (as necessary)
    - IRB/EC approved informed consent form
    - Names / contact information for study monitor(s)
    - Copies of signed and dated CRFs
    - Records of any adverse events and adverse device effects
    - Statistical analyses and underlying supporting data
    - Final report

27.0 SPONSOR MAINTENANCE OF STUDY RECORDS

The Sponsor will be responsible for **maintaining study records** per 21 CFR 812.140(b) and Good Clinical Practice E6(R2): Integrated Addendum to ICH E6(R1) (March 2018), Section 8.

The Sponsor will be responsible for **monitoring the study** per 21 CFR 812.46 and Good Clinical Practice E6(R2): Integrated Addendum to ICH E6(R1) (March 2018), Section 5.18.

The Sponsor will be responsible for **reporting** per 21 CFR 812.50(b).

28.0 INVESTIGATOR MAINTENANCE OF STUDY RECORDS

The Site PI will be responsible for **maintaining study records** per 21 CFR 812.140(a) Good Clinical Practice E6(R2): Integrated Addendum to ICH E6(R1) (March 2018), Section 4.9.

The Site PI will allow auditing of their clinical procedure(s).

Each investigator will provide a completed Financial Disclosure prior to study initiation and upon request at later time points in the study.

The Investigator is responsible for maintaining medical and study records for every patient participating in the clinical study (including information maintained electronically such as digital imaging). The study center will also maintain ***original*** source documents from which study-related data are derived, which may include, but are not limited to:

- Clinic progress notes recording patient's medical history and medications
- Medical records regarding AEs, including treatment and clinical outcome
- Results of diagnostic examinations
- Notes of phone calls and/or correspondence indicating study site's attempts to contact and follow a study patient at the required follow-up visits until such time a subject is determined to be lost-to-follow-up.

The Investigator must ensure that all study patient records are stored for at least 2 years after the latter of the following two dates: The date on which the study is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol. To avoid error, the study site should contact the study sponsor prior to the destruction of study records to ensure that they no longer need to be retained. In addition, the study sponsor should be contacted if the Investigator plans to leave the study site so that arrangements can be made for the handling or transfer of study records.

29.0 INVESTIGATOR REPORTS

The Site PI will be responsible for reporting per 21 CFR 812.150(a) and according to applicable IRB/EC requirements and Good Clinical Practice E6(R2): Integrated Addendum to ICH E6(R1) (March 2018), Sections 4.10, 4.11 and 4.13.

NOTE: Reports must identify patients using the study's unique identifier to protect patient's confidentiality.

The primary responsibility of the investigator is to protect the welfare of the study subjects. Other responsibilities, including adherence to the protocol, are defined in the Investigator Agreement.

30.0 DATA MANAGEMENT

Data will be handled as applicable, per Good Clinical Practice E6(R2): Integrated Addendum to ICH E6(R1) (March 2018), Section 5.5. To ensure proper tracking of Case Report Forms, a tracking system will be utilized.

30.1 Data Entry

Qualified personnel assigned by the principal investigator and/or the sponsor will perform data entry.

30.2 Data Cleaning

All CRF pages will be subject to initial inspection for omitted data, gross data inconsistencies, illegible data and deviations. Any deficiencies or deviations will be reviewed, and any necessary action determined (e.g., data query, communication to the study center).

Intermittent data review will be performed, and any discovered errors will be reported to the study site using the data correction and query process (as necessary). The study site will be expected to review the query, make any necessary corrections or comments, and return to Data Management where the correct response will be entered. The data cleaning cycle will be repeated until all data are considered clean.

30.3 Data Back-up

Incremental computer data backup will be performed on a regular basis. All hard copies of Case Report Forms and media will be stored in a secure location.

30.4 Confidentiality and Security

Passwords will be issued to appropriate personnel to insure confidentiality and protection of data.

30.5 Final Report

A final report will be completed, even if the study is prematurely terminated.

30.6 Publication Policy

At the conclusion of the trial, the results may be prepared and presented at a major meeting(s). The publication of results from any center experience within the trial is not allowed, unless there is written consent from the study sponsor.

31.0 DEFINITIONS AND ACRONYMS

Adverse Events

Adverse Event (AE) – any untoward medical occurrence in a subject (ISO 14155).

NOTE: This definition does not imply that there is a relationship between the adverse event and the device under investigation.

Serious Adverse Event (SAE) – an adverse event that (ISO 14155):

- led to a death,
- led to a serious deterioration in the health of the subject,
- resulted in a life-threatening illness or injury,
- resulted in a permanent impairment of a body structure or a body function,
- required hospitalization or prolongation of existing hospitalization,
- resulted in medical or surgical intervention to prevent permanent impairment to body structure or function,
- led to fetal distress, fetal death, a congenital abnormality, or birth defect.

Adverse Device Effect (ADE) – any untoward and unintended response to a medical device (ISO 14155)

NOTE: This includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device. This definition also includes any event that is a result of user error.

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 (ISO 14155).

Anticipated Adverse Device Effect (AADE) – an adverse device effect which by its nature, incidence, severity or outcome has been previously identified in the previously identified in nature, severity, or degree of incidence in the investigational plan or application

Unanticipated Adverse Device Effect (UADE) – any 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 (21CFR812.3.s and ISO 14155).

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 or device-related.

Adverse Device Effect (ADE)
See Adverse Events.

Case Report Form (CRF)
Printed, optical or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject

Confidentiality
Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or a subject's identity (GCP Consolidated Guidance).

Ethics Committee (EC) / **Institutional Review Board** (IRB)
Synonyms. An independent body constituted of medical, scientific and nonscientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trials, of protocols and amendments, and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects (GCP Consolidated Guidance).

Good Clinical Practice (GCP)
An international quality standard for conducting clinical trials that is provided by International Conference on Harmonisation (ICH) to protect trial subjects' rights, safety, and welfare, as well as provide integrity to the overall study data.

Informed Consent
The process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated consent form (GCP Consolidated Guidance).

Informed Consent Form (ICF)
A document disclosing the risks, benefits, and alternatives of a clinical trial and documents the subject's voluntary willingness to participate in a clinical trial.

Monitoring
The act of overseeing the progress of a trial, and of ensuring that it is conducted, recorded and reported in accordance with the protocol, standard operating procedures (SOPs), and the applicable regulatory requirements.

Serious Adverse Device Effect (SADE)
See Adverse Events.

Serious Adverse Event (SAE)
See Adverse Events.

Source Data
All information in original and identified records and certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation. Source data are contained in source documents (ISO 14155 and GCP Consolidated Guidance).

Source Documents
Original documents, data and records (ISO 14155).

NOTE: This may be, for example, hospital records, laboratory notes, pharmacy dispensing records, copies or transcriptions certified after verification as being accurate copies, photographic negatives, radiographs, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical investigation.

Standard Operating Procedure (SOP)
Detailed, written instructions to achieve uniformity of the performance of a specific function

Unanticipated Adverse Device Effect (UADE)
See Adverse Events.

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