The Vivaer® Procedure for Treatment of the Septal Swell Bodies for Airway Obstruction - A Prospective Open-Label Multicenter Study (SWELL)

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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 Institutional Review Board, Ethics Committee, U.S. FDA or other regulatory agency.

Site Name: _____

Print Name: _____

Signature: _____ Date: _____

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Protocol Summary

Title:	The Vivaer® Procedure for Treatment of the Septal Swell Bodies for Airway Obstruction - A Prospective Open-Label Multicenter Study (SWELL)
Purpose:	The purpose of this study is to assess the clinical use of the Vivaer ARC Stylus to treat Septal Swell Bodies (SSB) to improve symptoms in adults diagnosed with nasal obstruction attributed to SSB.
Indications for Use:	The Vivaer 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 (NAO) by shrinking submucosal tissue, including cartilage in the internal nasal valve area. 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.
Study Objectives:	The primary objective of this study is to determine the efficacy of treating the nasal septal swell body area with temperature-controlled radiofrequency (RF) using the Vivaer system for the treatment of NAO. The secondary objective is to evaluate the durability of the treatment effect in an extended follow-up period of 36 months. .
Study Design:	The study is designed as a multicenter, prospective, open-label, single-arm study. All participants will be evaluated prior to treatment and following treatment at week 1 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 26 weeks (6 months), 52 weeks (12 months), 104 weeks (24 months) and 156 weeks (36 months) to provide additional information on longer-term efficacy and duration of treatment effect. A subset of study sites will be selected to participate in a substudy of the use of computed tomography (CT) imaging to assess changes in the SBB after treatment.
Vivaer Treatment:	The Vivaer procedure will be performed in the study clinic using the Vivaer ARC Stylus and Aerin Console. The Vivaer ARC 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 undergo bilateral treatment of the nasal airway in a single study procedure session. Each side of the nose will be treated as follows:

- Two (2) to six (6) nonoverlapping applications of RF energy are performed at the SSB per nostril.

The default treatment settings will be used for the study: temperature 60° C, power 4 watts, treatment time 18 seconds, and cooling time 12 seconds. No repeat ("touch up") procedures will be permitted after the initial procedure through the end of the study (36 months).

Primary Endpoint:

The primary endpoint is improvement in self-reported Nasal Obstruction Symptom Evaluation (NOSE) Scale score from baseline recorded at the screening evaluation to 13 weeks after the procedure.

Secondary Endpoints:

- Responder percent: A responder is defined as at least 1 NOSE Scale class improvement or an improvement (decrease) in NOSE Scale score of 20% or more from baseline to 13 weeks after the procedure.
- Frequency of device-related and procedure-related serious adverse events, including frequency of septal perforation during the procedure, through the 3-month evaluation.

Study Hypotheses

Primary hypothesis: mean improvement in NOSE Scale score from screening to 13 weeks will exceed 25 points.

Other hypothesis: the treatment effects will be maintained through the extended follow-up period of 36 months.

Other Outcome Measures:

Adverse Events - Incidence (type and category) of adverse events overall and by follow-up interval.

Nasal Assessment - The target SSB within each nostril will be visually assessed at screening, prior to the procedure, immediately after the procedure, and 3 months after the procedure. The use of an endoscope for visual assessment is required. Representative endoscopic video of each nasal passage will be captured for each assessment. Endoscopic nasal assessment will include assignment of an SSB grading score.[36] CT Assessment - A subset of study sites will be selected to participate in a substudy of the use of computed tomography (CT) imaging to assess changes in the SBB after treatment. Radiographic changes, including change in size of the SSB, will be assessed using CT imaging prior to the procedure and at 3 months after the procedure.

NOSE Scale Score:

- Mean and mean change from screening at the 3-, 6-, 12-, 24- and 36-month follow-up evaluations.
- Distribution of NOSE Scale score severity categories (mild, moderate, severe, extreme) at the 3-, 6-, 12-, 24- and 36-month follow-up evaluations.

- Mean, change from screening in mean, and response distribution of the 5 components of the NOSE Scale score (nasal congestion, nasal blockage, trouble breathing, trouble sleeping, and getting enough air during exercise) at the 3-, 6-, 12-, 24- and 36-month follow-up evaluations.
- Proportion of responders based on improvement in NOSE Scale score at the 3-, 6-, 12-, 24- and 36-month follow-up evaluations.

Visual Analog Scale (VAS) for nasal pain - perception of pain associated with the procedure on a 0 to 100 mm scale (0 indicating no pain and 100 indicating the worst pain ever) assessed immediately after treatment and at 1 week.

Numerical Rating Scale (NRS) for ease of breathing through the nose - perception of the ability to breathe through the nose over the past week on a 0 to 10 scale (0 indicating no difficulty and 10 indicating severe difficulty) assessed at screening, 3, 6, 12, 24 and 36 months.

Sino-Nasal Outcome Test (SNOT-22) - Participant-reported outcome measure for the prior 2 weeks of 22 symptoms related to both nasal and general health on a score of 0 (no problem) to 5 (problem as bad as it can be) and indicate up to 5 items they consider the most important items affecting their health. Scores range from 0 to 110, with higher numbers representing a significant problem for the participant.

Participant Satisfaction Assessment - Five-question self-reported survey of satisfaction with the procedure and recommendation to others administered at the 3-, 6-, 12-, 24- and 36-month follow-up evaluations.

Medications - Medication used for relief or treatment of NAO symptoms will be documented at screening and updated as necessary with new associated medications at each postprocedure evaluation through the End of Study visit. An increase, decrease, no change, starting new or stoppage of medication use compared to the first recorded use will be documented.

Length of Study: The primary outcome will be evaluated at 3 months. In addition, evaluations at 6, 12, 24 and 36 months after treatment will extend follow-up to 3 years for evaluation of longer-term efficacy. Enrollment is anticipated to be completed within 6 months. Therefore, total study duration is anticipated to be approximately 42 months.

Study Centers: up to 10

Participants: up to 70

Inclusion Criteria:

1. Age 22 to 85 years (inclusively).
2. Seeking treatment for nasal obstruction and willing to undergo an office-based procedure.

3. Baseline NOSE score ≥ 55.
4. Presence of SSB hypertrophy limiting visualization of the middle turbinate (MT) by more than 50%.
5. Reduction in size of the SSB after application of topical decongestant on a cotton plug directly to the SSB region.
6. Improvement in the symptoms of nasal obstruction after SSB decongestion suggesting that the SSB may play a role in nasal obstruction.
7. Willing and able to withhold anticoagulant medications during the perioperative period (3-day window on either side).
8. Willing and able to provide informed consent.
9. Willing and able to comply with the participant-specific requirements outlined in the study protocol.

Exclusion Criteria:

1. Rhinoplasty, septoplasty, inferior turbinate (IT) reduction, or other surgical nasal procedures within the preceding 6 months.
2. Severe case of any of the following: septal deviation, turbinate hypertrophy, polyps, or ptotic nose tip believed to be the primary contributor to the participant's nasal obstruction symptoms and warranting surgical intervention.
3. Any adjunctive surgical nasal procedure planned on the same day or within 3 months after the Vivaer procedure.
4. Known or suspected allergies or contraindications for any general or local anesthetic agents.
5. Known or suspected to be pregnant or is lactating.
6. Participating in another clinical research study.
7. Other medical conditions which in the opinion of the investigator would predispose the participant to poor wound healing or increased surgical risk, or poor compliance with the requirements of the study.
8. Known or suspected regular use of oxymetazoline (Afrin) nasal decongestant or oral steroids.
9. For sites participating in the CT substudy only: Active sinus condition (eg, significant sinus diseases, infection or polyp formation) identified by CT.

SCHEDULE OF EVENTS

Activity / Assessment	Screening	Treatment			Follow-up (in-office)		Extended Follow-up (remote)			
		Preprocedure	Procedure	Immediate Postprocedure	1 Week	3 Months (13 weeks)	6 Months (26 weeks)	12 Months (52 weeks)	24 Months (104 weeks)	36 months (156 weeks)
Window (days)	**(-30)**	**(0)**			**(± 3)**	**(± 14)**	**(± 30)**	**(± 30)**	**(± 30)**	**(± 30)**
Eligibility	X									
Consent	X									
Demographics / Medical History	X									
Physician Evaluations										
Nasal Assessment (visual, endoscopic)	X	X[1]		X	X	X				
CT imaging of SSB	X[2]					X				
Current medication use (study relevant)	X			X[3]	X	X	X	X	X	X
Participant Evaluations										
NOSE Scale	X[4]					X[5]	X	X	X	X
VAS nasal pain				X	X					
NRS ease of breathing	X					X	X	X	X	X
Participant Satisfaction Survey						X	X	X	X	X
SNOT-22	X					X	X	X	X	X
Study Procedure (includes anethesia)			X							
Adverse Events	X			X	X	X	X	X	X	X

[1] Nasal Assessment do not need to be repeated if Screening and Treatment visits occur on the same day.
[2] CT should only be performed if your site was selected for the CT substudy and only after all other screening procedures and participant eligibility is confirmed.
[3] Add any postprocedure medications to the medication log.
[4] Baseline NOSE Scale Score for analysis is defined as the Screening score.
[5] Primary analysis endpoint evaluation.

List of Abbreviations

ADE – Adverse Device Effect

AE – Adverse Event

BMI – Body Mass Index

CFR – Code of Federal Regulations

CPAP – Continuous Positive Airway Pressure

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

CT (CAT)– Computed Tomography (Computed Axial Tomography)

CTA – Clinical Trial Agreement

DICOM – Digital Imaging and Communication in Medicine

EDC – Electronic Data Capture

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

FDA – Food and Drug Administration

FDAAA – Food and Drug Administration Amendments Act

FOV – Field of View

FWA – Federal Wide Assurance for the Protection of Human Participants

GCP – Good Clinical Practice

HIPAA – Health Insurance Portability and Accountability Act

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

ICMJE – International Committee of Medical Journal Editors

IFU – Instructions for Use

IRB – Institutional Review Board

ISO – International Organization for Standardization

IT – Inferior Turbinate

KVp – kilovotage peak

MPR – Multiplanar reformation

MRI – Magnetic Resonance Imaging

MT – Middle Turbinate

NAO – Nasal Airway Obstruction

NOSE – Nasal Obstruction Symptom Evaluation Scale

NRS – Numeric Rating Scale

SSB – Septal Swell Body

OTC – Over-The-Counter (nonprescription)

QOL – Quality of Life

RF – Radiofrequency

RFTR – Radiofrequency turbinate reduction

SAE – Serious Adverse Event

SADE – Serious Adverse Device Effect

SD – standard deviation

SNOT-22 – Sino-Nasal Outcomes Test 22

UADE – Unanticipated Adverse Device Effect

ULC – Upper Lateral Cartilage

US – United States

VAS – Visual Analog Scale

1.0 Introduction and Background

Nasal airway obstruction (NAO) is a highly prevalent disorder that affects the upper airway system causing restriction in normal airflow into the nasal cavity. Chronic nasal obstruction can elicit many symptoms, including congestion, stuffiness, headache, fatigue, sleep disturbance, daytime sleepiness, snoring and impairment of various daily and social activities leading to an overall decline in health-related quality of life (QOL).[1-3] Given its high prevalence, treatment of NAO can be costly, with expenditures for prescriptions, over-the-counter (OTC) medications, and doctor's visits.

NAO can be mediated by a diversity of mucosal and structural disorders in the nasal cavity, including acute or chronic mucosal inflammation from infection, allergenic or non-allergenic irritants, or structural factors such as nasal masses or polyps, turbinate or septal swell body (SSB) hypertrophy, nasal septal deviation, and nasal valve angle changes, narrowing or collapse.[1,4-8]

Treatment strategies for NAO have included both noninvasive management and surgical treatment with recent focus on treatment of the nasal valve region. The nasal valve is defined by the caudal cartilaginous nasal septum, the anterior head of the inferior turbinate (IT), and the caudal end of the upper lateral cartilage (ULC). This region is critical in the development of nasal obstruction and represents the narrowest part of the nasal airway.[3,8-10] As described by Poiseuille's law, minute changes in the diameter of a tube will result in exponential changes in airflow[11]. Thus, any narrowing in the nasal valve region, such as that associated with septal deviation, turbinate hypertrophy, congestion of SSB, ULC collapse or insufficiency, nasal polyps, or structural changes after rhinoplasty, will change nasal breathing.[11]

Multiple devices designed to increase the size of the nasal passage at the nasal valve area are available OTC for noninvasive management of NAO. These products are marketed to people with poor nasal breathing, snoring difficulties, and those with increased breathing demands, such as athletes. These devices include adhesive external nasal dilator strips and internal nasal dilators. Both internal and external dilators have been found to effectively dilate the nasal airway and reduce airway resistance.[12-15] However, nasal dilating devices require significant patient involvement and compliance to be effective.

Surgical treatment most commonly consists of repair of a deviated nasal septum and reduction of the IT. Surgical treatments may involve various suturing techniques used alone or in conjunction with grafting techniques using autologous cartilage typically harvested from the nasal septum or ear or synthetic biomaterials.[9,16-19] A new minimally invasive surgical procedure has also been introduced that uses an absorbable polymer blend nasal implant to support the upper and lower cartilage inside the lateral nasal wall similar to more traditional cartilage and nonabsorbable polymer grafts.[20] Surgical treatments are efficacious, but may require significant recovery periods with complication risks such as bleeding, intranasal adhesions, scarring, infection, and graft migration, resorption or extrusion.[16,19]

Radiofrequency (RF) energy has been used for decades in the fields of otorhinolaryngology (ENT), neurosurgery, cardiology, urology, and general surgery.

ENT surgeons currently use radiofrequency energy in several nasal therapies. Numerous studies have demonstrated that radiofrequency therapy applied to tissue of the nasal passage can be safe and effective in improving nasal obstruction while preserving nasal function.[21] 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 to create heat within the submucosal tissue of the turbinate, reducing tissue volume with minimal impact on surrounding tissues. Radiofrequency turbinate reduction differs fundamentally from traditional surgical methods by using low-power radiofrequency energy to provide a relatively quick and painless treatment for tissue coagulation and/or ablation.[22,23] There have been multiple studies analyzing the safety and outcomes of RFTR treatment. A systematic literature review of the RF ablation technique concluded that the technique is well tolerated and effective.[24]

Targeted radiofrequency heating of the lateral cartilaginous nasal wall has also been used in patients with inspiratory nasal valve collapse. [25,26] The Seren procedure[25] used an incisional approached to apply RF heating to the target tissue with the intent to produce tissue retraction and volume reduction. Significant improvement in Nasal Obstruction Symptom Evaluation (NOSE) Scale score was seen at 16 weeks. The Vivaer procedure[26] applies radiofrequency energy along with outward pressure to the mucosa at the region of the caudal end of the weakened ULC to induce mechanical deformation and potentially change the shape of the lateral nasal wall. At 6 months, mean NOSE Scale score improved to 24.7 (SD 20.4, range 0-90) with an average decrease of 54.5 (68.6%). Improvement in mean NOSE Scale score was maintained through the 12-, 18-, and 24-month evaluations (27.6, 32.7, and 26.8, respectively).[27]

As discussed above, typical medical, surgical, or radiofrequency treatments of nasal obstruction target the nasal septum, IT or nasal valve cartilage. However, SSBs also lie within the nasal airflow pathway and may be contributors to obstructed flow.[10,28,29], but only minimal attention has been paid to them historically and few studies describe them. The SSB have also been referred to as septal turbinate, nasal swell bodies, Kiesselbach's ridge, septal body, and septal tumescence since first being described by Wustrow.[30] The SSB can be identified on rhinoscopy, endoscopy, and by computed tomography (CT) and magnetic resonance imaging (MRI), appearing as a widened portion of the anterior nasal septum. The SSB contains both glandular and vasoerectile tissues although the function of the SSB is not well described.[10] A study of MRI brain studies from 54 patients with nonsinonasal complaints provided measures of the average length, width, and height of the SSB and further described them as a normal 2x3-cm fusiform structure located anterior to the middle turbinate (MT) and superior to the IT approximately 2.5 cm above the nasal floor[31] The study also concluded that the proximity of the SSB to the nasal valve region in conjunction with its composition of a large number of venous sinusoids suggested a role in nasal airflow regulation. The SSB has been found to be more prominent contralateral to a septal deviation[32] and to be significantly larger among patients with allergic rhinitis and rhinosinusitis than in

control patients without those conditions.[33] The SSB are known to swell in the presence of histamine.[34] A decrease in the size of the anterior nasal septum after application of a topical decongestant has been observed through MRI.[35] Preliminary studies indicate that radiofrequency energy can be used to reduce swell body size.[36,37]

2.0 Purpose

The purpose of this study is to assess the clinical use of the Vivaer ARC Stylus to treat Septal Swell Bodies (SSB) to improve symptoms in adults diagnosed with nasal obstruction.

2.1 Device and Regulatory Status

The Vivaer procedure will be performed in the study clinic using the Vivaer ARC Stylus and Aerin Console. The Vivaer ARC Stylus is a disposable handheld device capable of delivering bipolar radiofrequency energy to tissue when connected to the Aerin Console radiofrequency generating device with temperature control capable of delivering very low doses of energy.

The Vivaer ARC Stylus was cleared for use in the United States (U.S.) by the Food and Drug Administration (FDA) under 510(k) K172529 and the Aerin Console was cleared under 510(k) K162810.

2.2 Indications for Use

The Vivaer 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 (NAO) by shrinking submucosal tissue, including cartilage in the internal nasal valve area.

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 Rational

Patients suffering from symptoms attributed to NAO primarily due to internal nasal valve dysfunction, rather than hypertrophied turbinates, have treatment options ranging from OTC devices and 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 NAO. The Vivaer 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 when treating the SSB tissue.

3.0 Device and Procedure Description

The Vivaer ARC 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 Vivaer ARC 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, treatment parameters, usage timestamp data, and a count of the remaining treatment cycles (based upon preset maximum).

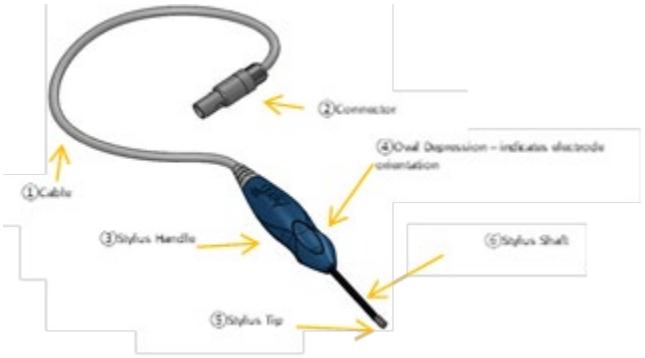


Figure 1. Vivaer ARC Stylus

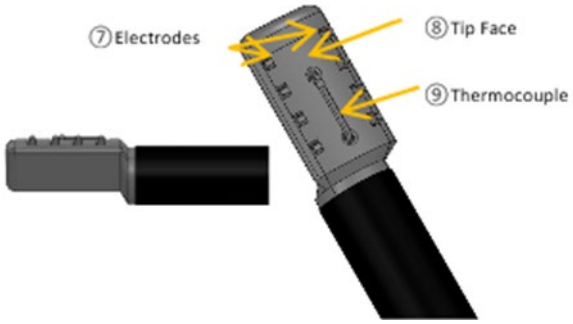


Figure 2. Vivaer ARC Stylus Tip

Figure 3. Aerin Console with Vivaer ARC Stylus

The Vivaer ARC Stylus is temporarily inserted into the nose to access the treatment area. The Stylus requires the application of conductive media (eg, saline gel) to the 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 Aerin Console. The Vivaer ARC Stylus improves nasal breathing by modifying the tissues of the nasal airway using low doses of radiofrequency energy. The low-power RF energy generates heat within the tissue and creates a coagulation lesion. As the lesion heals, the tissue retracts and stiffens, thereby decreasing NAO and improving airflow.

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 participant.

4.0 Study Objectives

4.1 Primary Objective

The primary objective of this study is to determine the efficacy of treating the nasal septal swell body area with temperature-controlled radiofrequency (RF) using the Vivaer system for the treatment of NAO.

The primary objective will be assessed through evaluation of the primary endpoint, defined as change in mean participant NOSE Scale score at 3 months after the procedure, and the secondary endpoints of responder percent at 3 months and frequency of septal perforation, and other device-related and procedure-related serious adverse events through 3 months.

4.2 Secondary Objective

The secondary objective is to evaluate the durability of the treatment effect in an extended follow-up period of 36 months.

In addition to the primary and secondary endpoints, both the primary and secondary objectives will be supported by assessment of several other effectiveness and safety measures that will include:

- Adverse events - Incidence (type and category) of adverse events overall and by follow-up interval.
- Nasal Assessment - The target SSB within each nostril will be visually assessed at screening, prior to the procedure, immediately after the procedure, and 3 months after the procedure. The use of an endoscope for visual assessment is required. Representative endoscopic video of each nasal passage will be captured for each assessment. Endoscopic nasal assessment will include assignment of an SSB grading score.[36]
- CT Assessment – A subset of study sites will be selected to participate in a substudy of the use of CT imaging to assess changes in the SBB after treatment. Radiographic changes, including change in size of the SSB, will be assessed using CT imaging prior to the procedure and at 3 months after the procedure.
- NOSE Scale score:
    - Mean and mean change from screening at the 3-, 6-, 12-, 24- and 36-month follow-up evaluations.
    - Distribution of NOSE Scale score severity categories (mild, moderate, severe, extreme) at the 3-, 6-, 12-, 24- and 36-month follow-up evaluations.
    - Mean, change from screening in mean, and response distribution of the 5 components of the NOSE Scale score (nasal congestion, nasal blockage, trouble breathing, trouble sleeping, and getting enough air during exercise) at the 3-, 6-, 12-, 24- and 36-month follow-up evaluations.
    - Proportion of responders based on improvement in NOSE Scale score at the 3-, 6-, 12-, 24- and 36-month follow-up evaluations.
- Visual Analog Scale (VAS) for nasal pain - perception of pain associated with the procedure on a 0 to 100 mm scale (0 indicating no pain and 100 indicating the worst pain ever) assessed immediately after treatment and at 1 week.
- Numeric Rating Scale (NRS) for ease of breathing through the nose - perception of the ability to breathe through the nose over the past week on a 0 to 10 scale with 0 indicating no difficulty and 10 indicating extreme

difficulty assessed at screening and the 3-, 6-, 12-, 24- and 36-month follow-up evaluations.

- Sino-Nasal Outcome Test (SNOT-22) - Participant-reported outcome measure for the prior 2 weeks of 22 symptoms related to both nasal and general health on a score of 0 (no problem) to 5 (problem as bad as it can be) and indicate up to 5 items they consider the most important items affecting their health. Scores range from 0 to 110, with higher numbers representing a significant problem for the participant.
- Participant Satisfaction Assessment - Five-question self-reported survey of satisfaction with the procedure and recommendation to others administered at the 3-, 6-, 12-, 24- and 36-month follow-up evaluations.
- Medications - Medication used for relief or treatment of NAO symptoms will be documented at screening and updated as necessary with new associated medications at each postprocedure evaluation through the End of Study visit. An increase, decrease, no change, starting new or stoppage of medication use compared to the first recorded use will be documented.

5.0 Study Plan

5.1 Study Design

The study is designed as a multicenter, prospective, open-label, single-arm study involving up to 10 sites in the US.

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

Participants will have an extended follow-up with evaluations conducted remotely at 6 months (26 weeks), 12 months (52 weeks) 24 months (104 weeks) and 36 months (156 weeks).

A subset of study sites will be selected to participate in a substudy of the use of computed tomography (CT) imaging to assess changes in the SBB after treatment.

5.2 Study Population

The target population for this study is adults suffering from symptoms attributed to NAO with evidence of SSB obstruction of the airway which may or may not include hypertrophied turbinates. This study requires severe or extreme symptoms demonstrated by a NOSE Scale score $\geq$55 and determination by the investigator that the SSBs are the primary or significant contributor to the nasal obstruction.

Participants who have had previous surgical treatment of the nasal valve in the past 6 months are not eligible to enroll in this study; however, it is anticipated that many participants will have already undergone rhinoplasty, septoplasty, IT reduction or other surgical procedures prior to being approached for participation in this study. Therefore, a history of those types of procedures does not exclude a participant from enrolling in this study. However, to ensure that changes in NOSE Scale score over

the course of follow-up are the result of the Vivaer procedure, prior surgical procedures must have been performed at least 6 months before the participant is enrolled in this study and no additional procedures should take place on the day of the Vivaer procedure or in the next 3 months.

Participants must meet all inclusion and no exclusion criteria listed below for participation in the study.

5.2.1 Inclusion Criteria

1. Age 22 to 85 years (inclusively).
2. Seeking treatment for nasal obstruction and willing to undergo an office-based procedure.
3. Baseline NOSE score ≥ 55.
4. Presence of SSB hypertrophy limiting visualization of the middle turbinate (MT) by more than 50%.
5. Reduction in size of the SSB after application of topical decongestant on a cotton plug directly to the SSB region.
6. Improvement in the symptoms of nasal obstruction after SSB decongestion suggesting that the SSB may play a role in nasal obstruction.
7. Willing and able to withhold anticoagulant medications during the perioperative period (3-day window on either side).
8. Willing and able to provide informed consent.
9. Willing and able to comply with the participant-specific requirements outlined in the study protocol.

5.2.2 Exclusion Criteria

1. Rhinoplasty, septoplasty, inferior turbinate (IT) reduction, or other surgical nasal procedures within the preceding 6 months.
2. Severe case of any of the following: septal deviation, turbinate hypertrophy, polyps, or ptotic nose tip believed to be the primary contributor to the participant's nasal obstruction symptoms and warranting surgical intervention.
3. Any adjunctive surgical nasal procedure planned on the same day or within 3 months after the Vivaer procedure.
4. Known or suspected allergies or contraindications for any general or local anesthetic agents.
5. Known or suspected to be pregnant or is lactating.
6. Participating in another clinical research study.

7. Other medical conditions which in the opinion of the investigator would predispose the participant to poor wound healing or increased surgical risk, or poor compliance with the requirements of the study.
8. Known or suspected regular use of oxymetazoline (Afrin) nasal decongestant or oral steroids is exclusionary.
9. For sites participating in the CT substudy only: Active sinus condition (eg, significant sinus diseases, infection, or polyp formation) identified by CT.

5.3 Study Entry and Enrollment

Participants will be considered entered into the study upon signature of the informed consent document. All participants must provide written informed consent before undergoing any study-related procedures. Participants must be diagnosed with NAO prior to entry into the study and it is expected that participants will have undergone standard evaluations for the diagnosis of NAO as part of their regular care. Participants will be considered enrolled in the study upon introduction of anesthetic into the nasal cavity for the purpose of the study procedure.

5.4 Outcome Measures

5.4.1 Nasal Assessment

The targeted nasal area within each nostril will be visually assessed for this study. The use of both visual and endoscope assessment is required. Observations are categorized as not present, mild, moderate, or severe. Representative endoscopic video of each nasal passage will be captured for each assessment.

General assessments include:

- Saddle nose deformity
- Bruising around orbital area
- Soreness, pain
- Numbness.

Endoscopic assessments:

- Inflammation / generalized redness
- Swelling, edema
- Blanching (generalized whiteness)
- Bleeding at anesthetic injection site (not requiring physician intervention) immediately postprocedure only
- Bleeding at treatment site (not requiring physician intervention) immediately postprocedure only
- Nasal obstruction from tissue edema

- Disruption of mucosal flow / crusting
- SSB endoscopy grading score. The SSB endoscopy grading scale was developed by Catalano et al.[36] to complement the more subjective NOSE Scale for the purpose of evaluating the degree of reduction of the SSB as seen clinically and is based on the ability to see the middle turbinate from the most anterior nares during endoscopy. Scores are assigned as:

  1 = visualization of >50% of the ipsilateral middle turbinate
  2 = visualization of <50% of the middle turbinate
  3 = no visualization of the middle turbinate.

5.4.2 CT Assessment – Substudy – Selected Sites Only

A subset of study sites will be selected to participate in a substudy of the use of CT imaging to assess changes in the SBB after treatment.

CT imaging will be conducted prior to the procedure and at 3 months after the procedure using the following specifications:

- 120 kilovoltage peak (KVp)
- Dose reduction technique according to manufacturer
- Anatomical Scan Range: paranasal sinus
- Slice thickness 0.4mm minimum
- Scan Field of View (FOV) – 15cm
- Reformat technique – Multiplanar reformation (MPR)
- Contrast – none
- Save file identified with participant ID and date of scan to DICOM format
- Upload DICOM images to the designated secure cloud content management system.

SSB measurement adapted from Gelera et al.[33] Thickness of 3 segments of the SSB will be measured by an independent board certified radiologist:

- the anterior part located anterior and superior to the IT,
- the middle or widest part located anterior to middle turbinate and superior to IT, and
- the posterior part located within the anterior 1/3 of the middle turbinate not going beyond the crista galli.

The posterior part of septum will be measured at the area of horizontal attachment of middle turbinate to the lateral nasal wall and superior turbinate to represent the less vasoactive part of the septum.

Other structures or anatomy that may contribute to nasal airway passage compromise at or about the SSB such as nasal septal deviation, turbinate hypertrophy/concha bullosa, polyp/cyst, will be entered into electronic Case Report Form (eCRF).

All CTs will be reviewed by a central reviewer. The central reviewer is a board-certified radiologist.

5.4.3 Nasal Obstruction Symptom Evaluation (NOSE) Scale

Evaluation of NAO is based on clinical observations of signs and symptoms with no easily obtained, reproducible objective measurement techniques of the airway.[3] Poor correlation and uncertainty between more objective measures of nasal patency (eg, nasal inspiratory peak flow, acoustic rhinometry, rhinomanometry, CT scans, physician assessment of anatomy) and participantive measures have generally been reported.[38-42] Since participant symptoms and perception of condition are the factors leading an individual to seek treatment, participant-reported participantive measures are cited as the most important determinates of treatment outcome.[3,38,39]

To evaluate the significance of a participant's nasal obstruction both before and after the procedure, this study will use the well-known participant-reported NOSE Scale for determining the primary endpoint of the study. The NOSE Scale is a validated disease-specific health status instrument used by clinicians to measure the outcome of participants treated for nasal obstruction.[43] The NOSE Scale consists of 5 items, each scored using a 5-point Likert scale to make a total score range of 0 through 100, where higher scores indicate worse obstruction. Severity of symptoms can be classified as mild (range, 5-25), moderate (range, 30-50), severe (range, 55-75), or extreme (range, 80-100) nasal obstruction, based on responses to the NOSE Scale survey.[44]

Treatment responder based on NOSE Scale score improvement:

A responder is defined as 1 NOSE Scale class improvement (eg, going from a score in the severe range (55-75) at preprocedure to a score in the moderate range (30-50) at the 3-month evaluation), or an improvement (decrease) in NOSE Scale score of 20% or more from screening at the 3-month evaluation.

5.4.4 Visual Analog Scale (VAS) for Nasal Pain

A horizontal 100 mm VAS[45] 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 vertical slash placed by the participant to indicate their current level of pain in and around the nose.

5.4.5 Ease of Breathing Through the Nose – Numeric Rating Scale (NRS) Breathing Score

Participants will be asked to describe their perception of their ability to breathe through the nose over the past week on a NRS from 0 to 10 where 0 is defined as "No Difficulty Breathing" and 10 is defined as "Extreme Difficulty Breathing".

5.4.6 Sino-Nasal Outcomes Test 22 (SNOT-22)

The SNOT-22 is a disease-specific, 22-item, participant-reported outcome measure of the prior 2 weeks of symptoms originally developed and validated specifically for rhinosinusitis[46] that has also been described and used in the context of NAO.[47,48] participants rate 22 different symptoms related to both nasal and general health on a 6-point Likert scale of no problem (0), very mild problem (1), mild or slight problem (2), moderate problem (3), severe problem (4), and problem as bad as it can be (5) and indicate up to 5 items they consider the most important items affecting their health. Scores on the SNOT-22 are scaled from 0 to110, with higher numbers representing a significant problem to a participant's life. Individual studies have consistently shown that SNOT-22 scores improve after endoscopic sinus surgery in adults with chronic rhinosinusitis with the minimal clinically important difference commonly considered to be a change of 8.9 points; however, the magnitude of changes across studies is quite variable.[49]

The SNOT-22 has also been shown to measure 5 underlying domains, each of which may be impacted differently depending on the therapy or intervention involved.[50]. The domains are 3 sinus-specific symptom domains (Rhinologic, Extra-nasal rhinologic and Ear/Facial symptoms) and 2 general health-related QOL domains (Psychological and Sleep dysfunction). The domains are defined by grouping individual items from the 22 total items:

- Rhinologic symptoms - Items 1, 2, 3, 6, 21, 22 (0-30 score)
- Extra-nasal rhinologic symptoms - Items 4, 5, 6 (0-15 score)
- Ear/Facial symptoms - Items 2, 7, 8, 9, 10 (0-25 score)
- Psychological dysfunction - Items 14, 15, 16, 17, 18, 19, 20 (0-35 score)
- Sleep dysfunction - Items 11, 12, 13, 14, 15 (score 0-25).

Reporting individual domain scores may help improve the sensitivity and usefulness of the SNOT-22 for the specific procedure in this study.

5.4.7 Participant Satisfaction Assessment

Five-question self-reported survey of satisfaction using a 5-point scale to assess tolerability of the procedure, ease of recovery, change in breathing through nose, overall satisfaction with the procedure, and recommendation to others.

5.4.8 Medications for Symptoms of Nasal Obstruction

Medication used for relief or treatment of NAO symptoms will be documented at screening and updated as necessary with new associated medications at each postprocedure evaluation through the End of Study visit. An increase, decrease, no change, starting new or stoppage of medication use compared to the first recorded use will be documented.

5.4.9 Adverse Events

Adverse events will be documented according to Section 8.1.

5.5 Success/Failure Criteria

Determinations of the overall success of treatment will be based on 2 levels: (1) the individual participant level and (2) the overall treatment success. Each level has its own criteria for success.

5.5.1 Participant Success

The primary outcome success measure for a participant in this study is based on an improvement (decrease) in the NOSE Scale score after the procedure compared to the baseline (screening) score. The improvement must reflect at least one category improvement or ≥ 20% decrease in score at the 3-month evaluation for the participant to be considered a success (responder). A participant will be considered a nonresponder (failure) at the 3-month evaluation if neither success criterion has been attained.

5.5.2 Study Success

The study will be considered a success if the mean improvement in NOSE Scale score from baseline (screening) to 13 weeks exceeds 25 points.

5.6 Duration of the Study

The primary endpoint will be evaluated at 3 months. In addition, evaluations at 6, 12, 24 and 36 months after treatment will extend follow-up to 3 years for evaluation of longer-term efficacy. Study enrollment is anticipated to be completed within 6 months. Therefore, total study duration is anticipated to be approximately 42 months.

5.7 Site Staffing and Responsibilities of Study Personnel

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

- Investigator/Treating Physician - The Investigator/Treating Physician will perform the procedure and postprocedure assessments. The treating physician must be a medical doctor with experience in ENT procedures and trained on study procedures, including the administration of the Vivaer procedure for treatment of SSB.
- 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.

5.8 Risk/Benefit Analysis

5.8.1 Risks

Potential risks associated with the use of the Vivaer ARC Stylus do not differ from commonly used devices and treatments for nasal obstruction and snoring, 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 such as RF turbinoplasty, septoplasty, or functional rhinoplasty.

Potential risks associated with the use of the Vivaer ARC 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.

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

- 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
- External deformity
- Sensory changes at treatment site
- Bruising including around the orbital area (black eyes)

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

- Inflammation / generalized redness
- Temporary swelling, edema
- Blanching (generalized whiteness)
- 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 events above 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 Report electronic case report forms (eCRF).

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

5.8.2 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 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 21 CRF 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 resign the eCRF, thereby protecting the integrity of the data collection process and the data.

5.8.3 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:

- 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 Vivaer ARC 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 and are CE-marked in the European Union.
- 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.
- Careful consideration has been given to the inclusion/exclusion criteria in order to select appropriate candidates for treatment.
- Participants 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 Vivaer ARC

Stylus for performing the Vivaer procedure will be permitted to participate in the study.

- Study procedures, follow-up, and study monitoring are designed to identify and closely manage adverse events in a timely manner.

5.8.4 Study Justification in Relation to Risk

The 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 nasal obstruction, that may be realized by participation in this study.

5.8.5 Benefits

The potential benefit associated with the Vivaer procedure is to offer a minimally invasive treatment method that has been shown in a previous study to help alleviate symptoms of nasal obstruction and which has been cleared for use by the FDA and is CE-marked in the European Union. The Vivaer ARC Stylus improves nasal breathing by modifying the tissues of the nasal airway using low doses of RF energy. The low-power RF energy generates heat within the tissue and creates a coagulation lesion. As the lesion heals, the tissue retracts and stiffens, thereby decreasing NAO and improving airflow. In addition to symptom relief after correcting nasal obstruction, participants may also experience better sleep function and better psychological function. (eg, concentration, productivity, and frustration). These benefits may last beyond the length of the study.

6.0 Study Schedule and Procedures

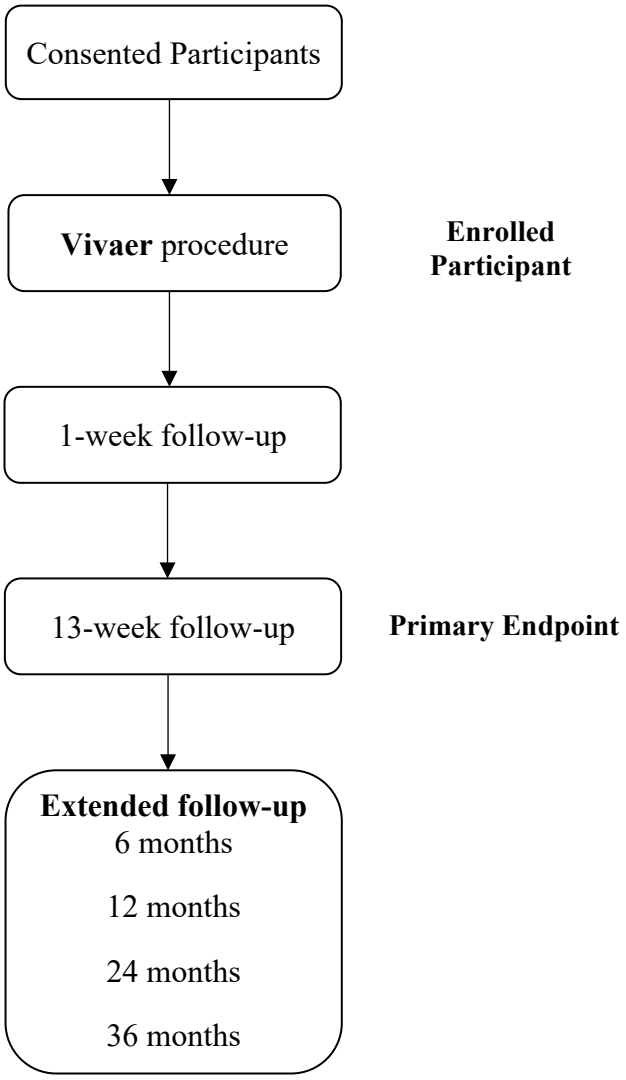
This section provides summaries of the study Schedule of Events and flow of participants through the study, as well as more detailed information on study procedures and processes.

6.1 Schedule of Events

Activity / Assessment	Screening	Treatment			Follow-up (in-office)		Extended Follow-up (remote)			
		Preprocedure	Procedure	Immediate Postprocedure	1 Week	3 Months (13 weeks)	6 Months (26 weeks)	12 Months (52 weeks)	24 Months (104 weeks)	36 months (156 weeks)
Window (days)	**(-30)**	**(0)**			**(± 3)**	**(± 14)**	**(± 30)**	**(± 30)**	**(± 30)**	**(± 30)**
Eligibility	X									
Consent	X									
Demographics / Medical History	X									
Physician Evaluations										
Nasal Assessment (visual, endoscopic)	X	X[1]		X	X	X				
CT imaging of SSB	X[2]					X				
Current medication use (study relevant)	X			X[3]	X	X	X	X	X	X
Participant Evaluations										
NOSE Scale	X[4]					X[5]	X	X	X	X
VAS nasal pain				X	X					
NRS ease of breathing	X					X	X	X	X	X
Participant Satisfaction Survey						X	X	X	X	X
SNOT-22	X					X	X	X	X	X
Study Procedure (includes anethesia)			X							
Adverse Events	X			X	X	X	X	X	X	X

[1] Nasal Assessment do not need to be repeated if Screening and Treatment visits occur on the same day.
[2]CT should only be performed if your site was selected for the CT substudy and only after all other screening procedures and participant eligibility is confirmed.
[3]Add any postprocedure medications to the medication log.
[4]Baseline NOSE Scale Score for analysis is defined as the Screening score.
[5]Primary analysis endpoint evaluation.

6.2 Participant Flowchart



6.3 Enrollment and Screening Assessment

Screening

During screening, the investigator or designated research staff will perform an evaluation of the study candidate for study eligibility, which will include a history and physical examination of the nasal area bilaterally, review of overall medical history, history of allergies, understanding of general health and discussion of any conservative measures used for NAO.

Participants must be diagnosed with NAO prior to entry into the study. 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. A participant will be considered as being entered into the study once informed consent is provided. Once the participant is entered into the study, screening assessments are completed, and the study treatment (preprocedure, procedure and immediate post procedure) should be completed **within 30 days**.

Informed Consent

Informed consent must be obtained in accordance with FDA regulation 21 CFR Part 50 and ISO 14155. The investigator or designated staff member is responsible for ensuring that IRB current and approved informed consent is obtained for each participant prior to participation in the study, or before undergoing any procedure specific to the clinical investigation. The participant must be fully counseled with an explanation of the study background, non-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. Any new information obtained during the course of the study that may affect the health of the participant or their decision to continue in the study will be provided to the participant. This process includes a thorough explanation of the informed consent document that the participant will be asked to sign and date acknowledging that they understand and desire to participate in the study. The explanation and discussion should be conducted in such a way as to:

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

A copy of the signed informed consent document should be provided to the participant.

Evaluation of Inclusion and Exclusion Criteria

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

Screening Data and Assessments

The following data will be obtained at Screening and recorded on the Screening Visit – Demographics, Treatment History and Nasal Exam eCRF:

- Demographics
  - Sex
  - Height (inches)

- Weight (pounds)
- BMI
- Date of birth
- Race / Ethnicity

- Medical history, Nasal Symptoms, History of Treatments, General Nasal Exam
  - History (duration) of nasal obstruction
  - History of nasal trauma
  - Related nasal symptoms
  - History of rhinitis (allergic, nonallergic), sinus disease, and/or obstructive sleep apnea
  - participant-reported, Medication/treatments used to address nasal obstruction and/or related symptoms, including continuous positive airway pressure (CPAP)
  - Evaluation of significant anatomic conditions that could affect treatment outcome (eg, severe septal deviation, turbinate enlargement, nasal polyps, ptotic nasal tip, and/or other external nasal deformity)
- Nasal assessment (visual and endoscopic exam) for each nostril including representative video of each nasal.
- (Selected sites only)CT to assess changes in the SSB after treatment will be collected at a subset of study sites.
- Current use of medication for symptoms of nasal obstruction will be detailed on the Nasal Medication Log
- Current use of devices, or other therapies.
- Screening NOSE Scale score (completed by participant).
- NRS ease of breathing score (completed by participant).
- SNOT-22 (completed by participant).
- Adverse Events.

6.4 Treatment Visit and Procedure (Day 0)

The treatment is summarized below and is comprised of the preprocedure, procedure and postprocedure as indicated on the Schedule of Events (Section 6.1). The treatment visit should occur within 30 days of the Screening Visit (study entry), once all inclusion and exclusion criteria have been met. Consult the Aerin Console Instructions for Use (IFU) for full detail of the standard treatment procedure and step-by-step instructions for preparation and use of the Vivaer ARC Stylus and Aerin Console.

Preparation (preprocedure)

The treatment will be performed in the study clinic within 30 days of study entry. The participant will be seated and positioned in the exam chair according to personal comfort and study physician's preference (eg, upright, reclined or supine). A nasal assessment (visual and endoscopic exam) will be performed on each side of the nose and for each nostril, including endoscopic video. This is to assess the configuration of the structural components of the lateral nasal wall (including the upper and lower lateral cartilage, their junction and the overlying mucosa), location of SSB and the MT to allow the study physician to map out and plan the areas of treatment. If the Screening and Treatment visits occur on the same day, the nasal assessment does not need to be repeated for Preprocedure.

Following the nasal assessment, it is recommended the study physician prepare the treatment area with a topical anesthetic agent (eg, lidocaine, tetracaine, etc.) and applying via spray, gel, or saturated pledget placed within the nose. After an appropriate amount of time, the SSB is then visualized with an endoscope and infiltrated in a submucosal plane with a small amount of local anesthetic to provide adequate tissue analgesia as well as tumescence to facilitate radiofrequency energy transfer. For example, cottonoid pledgets saturated with 4% lidocaine are placed in the nasal passages adjacent to the septum; after 5 minutes, these pledgets are removed and the swell body is injected bilaterally with 0.4 cc of 1% lidocaine with 1:100,000 epinephrine on each side.

Treatment administration

Once the nasal cavities have been anesthetized, participants will undergo bilateral treatment of the SSB in a single study procedure session. Each side of the nose will be treated as follows

- A nasal speculum is inserted into the nostril and opened to visualize the treatment area. The Vivaer ARC 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.
- Two (2) to six (6) nonoverlapping applications of RF energy are performed at the SSB per nostril.
- For the SSB, Vivaer ARC stylus default settings will be employed. (Figure 4).

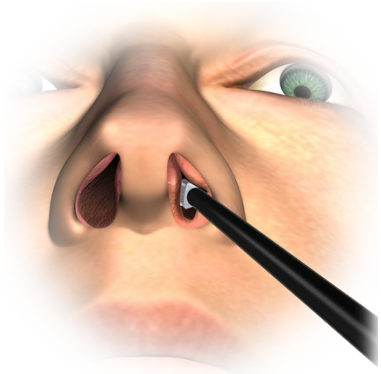


Figure 4. Vivaer ARC Stylus applied at SSB

The default settings for the Vivaer ARC Stylus:

Temperature	60° C
Power	4 Watts
Treatment Time	18 secs
Cooling Time	12 secs

The Aerin Console is activated by depressing the foot pedal. With the Vivaer ARC Stylus pressed against the tissues in the desired treatment locations, the foot pedal is depressed, and the Stylus is gently pressed against the nasal tissues to deliver RF energy to the tissues consistent with the IFU. A tone sounds when the Console is activated, signifying that energy is being delivered through the Stylus. The tone stops when the pedal is released, and RF energy is no longer being delivered.

No repeat ("touch-up") procedures will be permitted during the study follow-up period. Additionally, for the purposes of this study, no other concomitant treatments are permitted during this treatment or the follow-up period.

Procedure data collection

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

- Date of procedure.
- Procedure and postprocedure medications (including anesthesia).
- Aerin Console serial number.
- Procedure start and end times.
- Aerin Console settings.
- Treatment duration and number of sites treated for SSB.
- Occurrence of device malfunctions, protocol deviations, and/or adverse events.

6.5 Postprocedure Assessments and Care

Immediately postprocedure, a nasal assessment (visual and endoscopic exam) for each nostril including endoscopic video will be conducted prior to discharging the participant and reported on the Study Procedure eCRF.

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 on the Pain VAS CRF.

At the discretion of the study physician, the following care may be provided and should be documented:

- Use of nasal saline spray and antibiotic ointment 2 to 3 times daily for 1 week.
- The participant should be instructed not to manipulate the treatment site (i.e., no nose blowing) for 24 hours with the exception of any necessary hemostasis.
- Remind participant to continue to hold all anticoagulants for 3 days post procedure.

Participants should have their first study follow-up visit (1 week +/- 3 days) scheduled within the visit window prior to release.

Participants should not receive other concomitant nasal treatment therapies (other than those specified above) or interventions after the procedure through the 36-month follow-up 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. Should a treatment or procedure be in the best interest of the participant, it must be documented in the source. The participant will remain in the study and be followed through 36 months. Concomitant nasal treatments will be monitored at follow-up evaluations.

6.6 Follow-up Evaluations and Study Exit

Follow-up visit dates will be calculated from the study procedure date (Day 0). Follow-up visits should be scheduled within the specified visit windows described in the Schedule of Events (Section 6.1) and Table 1 (Section 9.3.2). An in-office follow-up evaluation is scheduled for 1 week and 13 weeks (3 months) after the procedure. In addition, follow-up evaluations at 26 weeks (6 months), 52 weeks (12 months), 104 weeks (24 months) and 156 weeks (36 months) after the treatment procedure will be conducted remotely as a 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 non-study visits should be evaluated for possible adverse events and an Adverse Event Report eCRF should be submitted if appropriate.

All participants should be followed through the final follow-up evaluation at 156 weeks (36 months) postprocedure regardless of their earlier success/failure classification. Every effort should be made to avoid having participants withdraw

from the study (Section 10.6). 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 points and recorded on the Follow-up Visit eCRF:

In-office evaluation - 1 Week:

- Nasal assessment (visual and endoscopic exam) for each nostril including endoscopic video.
- Current use and any change in use of medication.
- VAS for pain score (completed by participant).
- Adverse events.

In-office evaluation - 3-month (13 Weeks):

- Nasal assessment (visual and endoscopic exam) for each nostril including endoscopic video.
- Review of current use and change in use of medication for symptoms of nasal obstructions.
- NOSE Scale score (completed by participant).
- NRS ease of breathing score (completed by participant).
- SNOT-22 (completed by participant).
- CT imaging (Substudy – selected sites only).
- Participant Satisfaction Survey (completed by participant).
- Adverse events.

Remote evaluations - 6-month (26 Weeks), 12-month (52-Weeks), 24-month (104-Weeks) and 36-month (156-Weeks) follow-up:

- Current use and participant-reported change in use of medication, and other therapies for symptoms of nasal obstruction and participant-reported changes in frequency of use.
- NOSE Scale score (verbal administration by site personnel).
- NRS ease of breathing score (verbal administration by site personnel).
- SNOT-22 (verbal administration by site personnel).
- Participant Satisfaction Survey (verbal administration by site personnel).
- Adverse events (study staff follow-up required if participant indicates an event).

Study exit:

Participants meeting the study requirements as planned will be exited from the study upon completion of the 36-month follow-up evaluation. If a participant reaches the 36-month follow-up evaluation 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.

Study exit applies to those participants where data is no longer collected for a study participant. A Study Exit form should be completed and entered into the electronic data capture (EDC) Systems in the following cases:

- Completion of 36 month participant questionnaires
- Signed consent but no procedure took place (eg, screen failure)
- Participant was unable to complete the follow-up visits
- Withdrawal of informed consent
- Physician exited participant based on medical or surgical necessity or other reason
- Participant received treatment outside of the study that, in the opinion of the investigator, would affect the study results.
- Lost to follow-up (3 attempts should be made and documented in the participant's record indicating due diligence by the site)
  - If a participant misses a questionnaire window and cannot be contacted, the participant may remain in the study, as contact may be re-established for a future questionnaire window period. (Any missed study assessment is considered a protocol deviation.)Participant withdrawal should be reported within 5 days of site becoming aware. participant death should be reported within 24 hours to Aerin Medical.
- Participant Death

6.7 Product Handling and Accountability

A system that allows tracking of orders, shipping and returns will be used to control the Vivaer ARC Stylus 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 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.

7.0 Statistical Considerations

7.1 Study Design

This is a prospective, multicenter, open-label, single-arm study to assess the Vivaer procedure for treatment of SSB to improve symptoms in those diagnosed with NAO. This study is designed to assess improvement in symptoms from prior to the procedure to a primary endpoint at 3 months after the procedure and out to 36 months.

7.2 Study Hypotheses

The primary endpoint hypothesis for the primary study objective is designed to demonstrate that the mean improvement in participant NOSE Scale score from the baseline assessment at screening to 13 weeks exceeds 25 points. Note that improvement is represented by a decrease in NOSE score. The null hypothesis (H_0) is that the decrease in mean NOSE Scale score will be less than 25 points and the alternative hypotheses (H_1) is that the decrease will be more than 25 points:

$$H_0: \mu_d \geq -25.0$$

$$H_1: \mu_d < -25.0,$$

where μ_d represents the mean change in NOSE Scale score from baseline to 13 weeks (13-week NOSE Scale score − baseline NOSE Scale score). Rejection of the null hypothesis in favor of the alternative hypothesis (H_1) means that there is evidence for a statistically significant reduction in mean NOSE Scale score from baseline to 13 weeks postprocedure.

The secondary endpoint hypothesis for the primary study objective is designed to show that the proportion (percent) of participants meeting the responder definition will exceed 0.55 (55%) at 13 weeks. The null hypothesis (H_0) is that the proportion of responders will be equal to .55 (55%) and the alternative hypotheses (H_1) is that the proportion of responders will exceed 0.55 (55%):

$$H_0: p_0 = 0.55$$

$$H_1: p > 0.55,$$

where p_0 represents the targeted minimum responder proportion at 13 weeks and p represents the expected proportion at 13 weeks.

7.3 Power Analysis and Sample Size Estimate

The study will enroll up to 70 participants. The power analysis was performed such that there is adequate power to reject the null hypothesis for both the primary effectiveness endpoint and for the principal secondary endpoint.

The statistical power (1 – β) for the primary effectiveness endpoint that, on average, there is at least a 25-point improvement in the NOSE Scale score from the pretreatment assessment to the assessment at 13 weeks:

Statistical Hypothesis:	$H_0: \mu_d \geq -25.0$ versus $H_1: \mu_d < -25.0$ where μ_d is the average change from screening (baseline) in the NOSE Scale score at 13 weeks post treatment
Statistical Methodology:	Single-sample paired t-test
Expected μ_d:	-50
Standard Deviation:	20
Significance Level:	One-sided $\alpha = .025$

Minimum Sample Size:	70 Participants
Statistical Power:	0.99

The statistical power (1 – β) for the secondary endpoint is such that at least 55% of the treated participants respond to treatment, defined as either at least one NOSE Scale class improvement, or at least a 20% improvement in the NOSE Scale score, both assessed at 13 weeks posttreatment:

Statistical Hypothesis:	H_0: $\pi \leq 0.55$ versus H_1: $\pi > 0.55$ where π is the proportion of participants responding to treatment 13 weeks posttreatment
Statistical Methodology:	Single-sample chi-square test
Expected π:	0.80
Significance Level:	One-sided $\alpha = .025$
Minimum Sample Size:	70 Participants
Statistical Power:	0.99

With at least 70 treated participants, we can be 95% confident that we will observe at least one unexpected serious device-related event when the underlying incidence of that event is at least 2.3%.

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.

7.4 Timing of Analysis

The primary evaluation phase of the study lasts until all participants have reached the primary endpoint at 13-weeks (3-month) 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 may be 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 36-month follow-up evaluation of the extended follow-up phase of the study.

7.5 Analysis Populations

All enrolled participants entered in the study will comprise the safety population and will be subject to all safety analyses. All enrolled participants undergoing the procedure (initiation of anesthesia) represent the evaluable study population. For some evaluations, summaries will be presented by nostril. The per-protocol population is defined as all participants who received treatment, with 13-week (3-month) follow-up data and no major protocol deviations.

7.6 Missing Data

Every effort will be made to obtain complete follow-up data for all participants, and it is anticipated that analysis of the primary and secondary endpoint hypotheses will be conducted using all available complete data. The effect of missing data will be examined by imputing missing NOSE scores as no change from baseline and as nonresponders.

Other outcome measures will be analyzed by using available data only.

7.7 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 7.3). Comparability between study sites may be shown using summary statistics calculated by site.

7.8 Participant Disposition

A detailed description of participant disposition will be provided using a CONSORT diagram and summaries of participants falling in various subgroups of interest, such as, consented but not treated, discontinued, major protocol deviations, deaths, and withdrawals. All study population exclusions and reasons will be summarized. All 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.

7.9 Demographics and Baseline Characteristics

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

7.10 Primary Endpoint Analysis

The primary endpoint hypothesis of change from baseline to the 13-week endpoint will be analyzed using a paired t-test at the 1-sided alpha .025 level and presented as the mean change with associated 1-sided lower confidence bound.

7.11 Secondary Endpoint Analysis

The secondary endpoint hypothesis will be tested only after the primary endpoint of the study is met. The secondary hypothesis will be evaluated using the proportion of responders on the primary outcome measure at 13 weeks. A responder is defined as having improvement in NOSE Scale score of ≥ 20% from baseline or at least one NOSE Scale class improvement.

The hypothesis will be tested at the 1-sided alpha .025 level with a single proportion binomial test. The responder proportion (percent) will be presented with the associated 95% confidence interval. The secondary endpoint will be met if the lower bound of the confidence interval exceeds 0.55 (55%).

The frequency (proportion) of septal perforation will be calculated along with the 95% confidence interval along with a summary of each event.

The frequency (proportions) of serious device-related adverse events and procedure-related adverse events will be calculated along with the 95% confidence interval along with a summary of each serious event.

7.12 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, SD, minimum and maximum for continuous factors. Statistical comparisons will either not be performed or used for information purposes. Proportions may be compared using exact tests, chi-square tests, or general linear models. Continuous outcomes may be compared using t-tests or nonparametric equivalents. Repeated measures linear mixed models may be used for longitudinal analysis across evaluations.

Other outcome measures include:

- Nasal Assessment - The visual 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 screening, just prior to procedure (if screening and procedure occur on different days), immediately after procedure and at 3 months. The distribution of SSB grades prior to the procedure and at each follow-up will be summarized along with the mean scores and change from screening.
- Radiographic Imaging - A subset of study sites will be selected to participate in a substudy of the use of CT imaging to assess changes in the SBB after treatment. SSB measures from CT scans will be summarized and presented as means at screening and at 3 months and as the mean change from screening to 3 months.
- NOSE Scale score - Categorical responses and scores on the NOSE Scale and its individual components will be subject to multiple summary methods and analyses including the:
    - Mean and mean change from preprocedure at the 3-, 6-, 12-, 24- and 36-month follow-up evaluations.
    - Distribution of NOSE Scale score severity categories (mild, moderate, severe, extreme) at the 3-, 6-, 12-, 24- and 36-month follow-up evaluations for each group.
    - Mean, change from preprocedure in mean, and response distribution of the 5 components of the NOSE Scale score (nasal congestion, nasal blockage, trouble breathing, trouble sleeping, and getting enough air during exercise) at the 3-, 6-, 12 24- and 36-month follow-up evaluations for each group.

- Proportion of responders based on improvement in NOSE Scale score at the 3-, 6-, 12-, 24- and 36-month follow-up evaluations for each group.

- VAS for nasal pain- Summary will include mean NRS pain scores assessed postprocedure.
- NRS for ease of breathing - Summary will include mean and mean change from baseline (screening) of ease of breathing scores assessed at screening and at each follow-up evaluation.
- SNOT-22 - mean and change from baseline (screening) in mean SNOT-22 score and individual domain scores will be summarized at the 3-, 6-, 12-, 24- and 36-month follow-up evaluations.
- Participant Satisfaction Assessment - mean response for each of the 5 survey questions will be summarized at the 3-, 6-, 12-, 24- and 36-month follow-up evaluations.
- Medications - Medication, and other therapies associated with relief or treatment of NAO symptoms will be documented at screening and updated as necessary with changes to any treatment and any new associated medications at each postprocedure evaluation. An increase or decrease in frequency of use or dose, no change, starting new or stoppage of medication use compared to the first recorded use will be documented.

7.13 Subgroup Analysis

A subgroup analysis of primary and secondary efficacy measures based on allergic or nonallergic classification will be performed for the 3-month endpoint using a 2-sample t-test to compare changes in mean NOSE Scale score between the 2 groups and a 2 sample binomial or exact test to compare the responder percents between the 2 groups.

Other exploratory subgroup analyses may be performed based on demographic, procedural, or other identified characteristics. Potential baseline covariates with possible impact on outcomes at 3 months are:

- Age
- Race
- Sex
- BMI

7.14 Safety Analysis

All adverse events, collected from the time of study consent (study entry) until the end of the study will be analyzed for all participants. Adverse events may occur during the treatment phase or during the follow-up phase. AEs occurring after the screening assessment but before the procedure (application of anesthesia) will be

documented in the participant's medical record and EDC but will not count as related to the study device or procedure. 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.

7.15 Follow-up Phase Analysis

The follow-up 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.

7.16 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 evaluation.

8.0 Adverse Events and Product Complaints / Device Deficiencies

8.1 Adverse Events

All adverse events, collected from the time of study consent (study entry) until the end of the study will be analyzed for all participants. Adverse events may occur during the treatment phase or during the follow-up phase. AEs occurring after the screening assessment but before the preprocedure (application of anesthesia) will be documented in the participant's medical record and EDC but will not count as related to the study device or procedure.

8.1.1 Definitions

Following are definitions associated with AEs:

Adverse Event - any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory or image findings) in participants, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated (per ISO 14155)

Note: This definition includes events related to the investigational medical device or the comparator. This definition also includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to the use of investigational medical devices.

Serious Adverse Event (SAE) - an adverse event that led to any of the following (per ISO 14155)

a) death,

b) serious deterioration in the health of the participant, users or other persons as defined by one or more of the following:

1) a life-threatening illness or injury, or

2) a permanent impairment of a body structure or a body function including chronic disease, or

3) in-patient or prolonged hospitalization, or

4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) fetal distress, fetal death, or a congenital abnormality, or birth defect including physical or mental impairment.

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

Adverse Device Effect (ADE) – adverse event related to the use of an investigational medical device.

Note: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition also includes any event resulting from use error or from intentional misuse of the investigational medical device. This includes comparator if the comparator is a 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 (per ISO 14155).

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 participants (21 CFR 812.3(s)).

Relationship to device and procedure
The potential relationship of the event to the device or procedure will be categorized by the investigator as follows:

- 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 procedure.

- Unlikely

  The relationship with the use of the device or procedure seems not relevant and/or the adverse event can be reasonably explained by another cause, but additional information may be obtained.

- 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, and an alternative etiology is unlikely or significantly less likely.

- 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- 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.

8.1.2 Documentation and Reporting of Adverse Events

All adverse events will be monitored from the time of study entry through study exit. All adverse events must be reported on the Adverse Event Report eCRF. A description of the event, including onset date, resolution date, action taken, and the outcome should be provided. All adverse events will be followed until they are adequately resolved or reach a chronic, stable state. If a participant reaches the 36-month follow-up visit and is experiencing a new or ongoing adverse event, the 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 or if the event lasted longer in duration than 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 must be reported to the sponsor within 24 hours of learning of the event.

Sponsor Contact: Anais Laborde
Phone: 650-518-9624
Email: alaborde@aerinmedical.com

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

8.2 Product Complaints / Device Deficiencies

8.2.1 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 21 820.3(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).

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

- US FDA (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

Device Deficiency – inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance.

Note: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labeling. This definition includes device deficiencies related to the investigational medical device or the comparator (per ISO 14155).

8.2.2 Documentation and Reporting of Complaints / Device Deficiencies

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

9.0 Study Administration

This study will be conducted in accordance with elements of ICH E6 Guideline for GCP, Abbreviated Requirements of 21 CFR 812 for nonsignificant risk device studies, the European Standard ISO 14155, the Declaration of Helsinki, the Belmont Report, and any applicable regional or national regulations.

The sponsor has the overall responsibility for the conduct of the study according to all applicable regulatory requirements. The sponsor will have certain direct responsibilities and will delegate other responsibilities to the investigator and study site. The 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 sponsor, treating physician, or any person acting for or on behalf of the sponsor or investigator shall act in accordance the applicable standards, guidelines and regulations.

This study is funded by Aerin Medical. The Clinical Trial Agreement (CTA), mutually signed by the study site and Aerin Medical, describes the agreement between sponsor and site with respect to study financing.

9.1 Investigator Training

Site initiation training will occur prior to the first procedure at a site. Investigators will be trained on the procedure and use of the Vivaer ARC 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, monitoring logistics, and regulatory requirements.

9.2 Study Monitoring

Study monitoring will be carried out in compliance with FDA regulations, ISO 14155, and Good Clinical Practice (GCP) guidelines. 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. The study monitors will oversee the conduct of the study either on-site or remotely and evaluate compliance with the protocol, any specific recommendations made by the site's IRB and the signed Investigator Agreement. During the study, phone contacts and site visits will be conducted to ensure protocol compliance. Monitoring will include a verification the informed consent was properly obtained for all study participants, a review of clinical records for accuracy and completeness, resolution of missing or inconsistent results, a review of source documents, and ensuring adverse events, protocol deviations and device usage are properly documented. The monitor will conduct source data verification by verifying eCRFs are consistent with source documents. The investigator will make available to the monitor for review the informed consent forms, source documents, and any other relevant records for all study participants at the site. The investigator and other site personnel will be accessible to the monitor during visits whether on-site or remote and sufficient time is provided to conduct the visits and address questions. If the monitor becomes aware of any deficiencies during the course of the study, the monitor will discuss with the sponsor and investigator to ensure compliance is maintained. A final close-out monitoring visit will occur when the study has been completed or terminated.

9.3 Documentation of Study Findings

9.3.1 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. Investigators are responsible for accurate completion and timely submission of the data collected during the study. Sites will be trained in the use of the system for entering study data and uploading supporting documents and will be given access for this purpose. Data monitoring will be performed to identify missing data, verify data accuracy, and ensure queries are resolved. Any data issues are to be promptly addressed with the investigator. Quality assurance procedures will be established to ensure that complete, accurate and timely data are submitted, protocol requirements are followed, and that complications, adverse events and adverse device effects are correctly reported and investigated as appropriate. The management and retention of these data will be compliant with applicable regulatory requirements.

9.3.2 Case Report Forms

Standardized electronic case report forms (eCRFs) will be used at all participating study sites to collect complete and accurate records of the clinical data. All study data will be entered by study personnel through eCRFs for each participant screened in the study. A unique ID number will be assigned to each participant.

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

- Screening Visit / Study Eligibility (01)
- ICF Checklist (01A)
- Screening Visit – Demographics, Treatment History & Nasal Exam (02)
- CT Settings Checklist (02A) (selected sites only)
- NOSE Scale (03)
- NRS Ease of Breathing– Participant form (04)
- SNOT-22 (05)
- Preprocedure (06A)
- Anesthesia and Procedure (06B)

- Immediate Postprocedure (06C)
- VAS for nasal pain – Participant form (07A)
- VAS for nasal pain – Site form (07B)
- Follow-up Visit (08)
- Participant Satisfaction Survey (09)
- Study Exit (10)
- Device Malfunction Report (11)
- Protocol Deviation (12)
- Adverse Event Report (13A) (reference AE Code List [13B])
- Serious Adverse Event / Unanticipated Adverse Device Effect
- (SAE / UADE) Report (14)
- Medication Log (15)
- Unscheduled Visit (16)

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

Visit	Visit Window (days)	eCRF	Other
Screening	n/a	01, 01A,02, 02A*,03, 04, 05, 15	Informed Consent Nasal assessment images† CT imaging*
Study Procedure (preprocedure/anesthesia/treatment)	within 30 days of Screening	06A, 06B,	Nasal assessment images† Nasal assessment does not get repeated Preprocedure if the Screening and Treatment visits occur on the same day
Postprocedure	0	06C, 07A, 07B, 15	Nasal assessment images†
1-Week (In-office)	+3	07A, 07B, 08, 15	Nasal assessment images†
13-Week (In-office)	±14	02A*,03, 04, 05, 08, 09, 15	Nasal assessment images† CT imaging*
6-Month (Remote)	±30	03, 04, 05, 08, 09, 15	
12-Month (Remote)	±30	03, 04, 05, 08, 09, 15	
24-Month (Remote)	±30	03, 04, 05, 08, 09, 15	
36-Month (Remote)	±30	03, 04, 05, 08, 09, 10, 15	
As Needed	n/a	10, 11, 12, 13A, 13B, 14, 16	

†Copy de-identified endoscopic video/images collected for study records to USB flash drive and provide to Sponsor.

*Sites selected for substudy only

9.3.3 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 informed consent and 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), or other documentation as required by the IRB and national regulations.

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. 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.
3. Study protocol, amendments, and documentation (dates and reasons) of any deviations from the protocol.
4. IRB records, including original and ongoing study approvals, all correspondence, and the approved informed consent form(s).
5. IRB membership list, Federal Wide Assurance for the Protection of Human participants (FWA) as applicable, statement of compliance and written procedures pertaining to AE and Protocol Deviation reporting (if available).
6. Study agreement, curricula vitae of investigator(s), financial disclosure, signature authorization log (delegation of responsibility), protocol signature page, and participant screening/enrollment log.
7. Reports (including safety reports, progress reports and a final report from the investigator).
8. 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. In the event of an adverse experience that is serious or unanticipated, 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 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. Unanticipated 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 s/he 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 reported 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/EC 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.

9.3.4 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 study participants through final follow-up), or the date that the records are no longer required by the study site record retention policy or per applicable regulatory requirements. 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.

9.3.5 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.

9.3.6 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 investigator is responsible 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 participant 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.

9.3.7 Publication Policies

The 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 now and in the future for presentation or publication at the sponsor's discretion or for submission to governmental agencies. Publication authorship will be established according to the International Committee of Medical Journal Editors (ICMJE) guidelines and Aerin Medical policy. Clinical study design will be publicly disclosed on ClinicalTrials.gov, and summary results posted per FDAAA 801 Requirements, and in accordance with national regulations as required by other regulatory agencies. Additionally, an investigator may only publish data generated by this trial in accordance with the terms of the CTA.

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.

9.4 Study Suspension or Early Termination

The study can be suspended or 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 participants.

- Unanticipated adverse device effect presenting an unreasonable risk to participants.
- Persistent noncompliance with the protocol and/or IRB or regulatory authority requirements.

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. The investigator shall promptly inform screened participants at his/her study site, if appropriate. Regulatory authorities and the personal physicians of the participants may also need to be informed if deemed necessary. All applicable study documents will be participant to the same retention policy as detailed in Section 9.3.3

10.0 Ethics

10.1 Institutional Review Board

This study may not be initiated at a site until applicable Institutional Review Board, or regulatory authority approval/favorable opinion 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. Any additional requirements or conditions imposed by the IRB or regulatory authority shall be followed, if appropriate.

To assure proper review and study oversight, the IRB must comply with the responsibilities, functions, and records requirements defined in U.S. FDA regulations (21 CFR Part 56) or per their regulatory authority.

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

10.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, 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 and the rights, safety and well-being of study participants shall be protected consistent with these principles.

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.

10.3 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, the FDA under applicable federal regulations, or other regulatory authority as required per national regulations. No public reporting or publications of the results of this study will contain identifiable references to individual participants in the study.

10.4 Participant Insurance

It is the responsibility of the sponsor to provide insurance covering the cost of treatment of participants in the event of clinical-investigation-related injuries, in accordance with the national regulations, as applicable.

10.5 Participant Reimbursement

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

10.6 Participant Withdrawal

Participants may voluntarily withdraw from the study at any time for any reason without impact to their future medical care at the study site. In addition, the investigator may withdraw a participant from the study, if in the investigator's opinion, it is not in the best interest of the participant to continue in the study. 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 or designee will make all possible efforts to collect and report the final visit observations. If the investigator has made 3 documented attempts to contact the participant and received no response, the participant may be considered to be lost to follow-up. A participant who misses a study visit but attends a subsequent visit will no longer be considered lost to follow-up. 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.

10.7 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 before implementation.

10.8 Protocol Adherence and Deviations

10.8.1 Definition

Deviation – instance of failure to follow, intentionally or unintentionally, the requirements of the protocol (per ISO 14155).

10.8.2 Documentation and Reporting of 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 agreement by the sponsor and 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. Deviations will also be reported to the regulatory authority as required per national regulations.

Deviations must be reported to the sponsor regardless of whether medically justifiable, preapproved, or performed to protect the participant in an emergency. The investigator will document and explain the reason for the deviation. participant deviations will be reported using the Protocol Deviation eCRF.

11.0 References

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