ARRINEX, INC.

Feasibility Study of Multi-Treatment Posterior Nasal Nerve Modulation for Treatment of Chronic Rhinitis

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1.0	A	30 Oct 2018	Initial Release

ARRINEX, INC.

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STATEMENT OF COMPLIANCE & INVESTIGATOR SIGNATURE PAGE

I acknowledge that the trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 812)

Additionally, as a study Investigator:

1. I understand this protocol contains information that is confidential and proprietary to Sponsor.
2. Any additional information added to this protocol is also confidential and proprietary to Sponsor and must be treated in the same manner as the contents of this protocol.
3. I have read the entire protocol.
4. I understand what the protocol asks me to do as an Investigator.
5. I will conduct this study following this protocol and will make a reasonable effort to complete the study in the time noted.
6. I will provide this protocol to study staff under my supervision. My study staff will keep the protocol and associated documents confidential.
7. I will discuss this information with the study staff to ensure they are fully informed about the study and the ClariFix device.
8. I will not start enrolling in this study until it is approved by a governing Institutional Review Board.
9. I understand the study may be terminated or enrollment suspended at any time by Sponsor, with or without cause, or by me if it becomes necessary to protect the interests of the study subjects.

_____

Name of Investigator

_____ _____

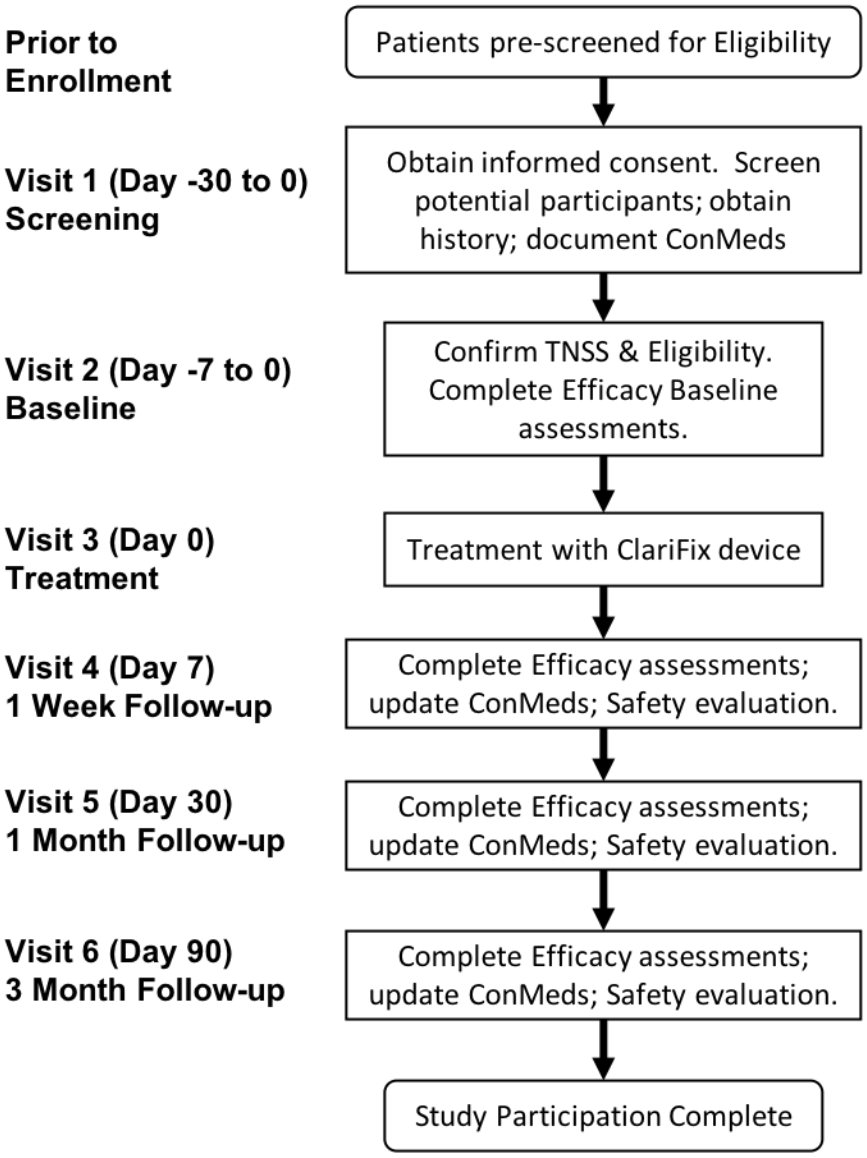
Investigator Signature Date (DD/MMM/YYYY)

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Feasibility Study of Multi-Treatment Posterior Nasal Nerve Modulation for Treatment of Chronic Rhinitis
Study Description:	Prospective, non-randomized, feasibility study of adult patients for treatment to the posterior nasal nerve using cryotherapy at multiple treatment sites within the nasal cavity.
Objectives:	Evaluate the feasibility of treatment to the posterior nasal nerve at both the middle and inferior meatus locations within the nasal cavity. Primary Objective: Evaluate the safety of treatment to the inferior meatus location Secondary Objectives: Evaluate the effectiveness and tolerability of treatment at the inferior meatus location
Endpoints:	Primary Endpoint: Incidence of procedure related Serious Adverse Events (SAEs) and/or Serious Adverse Device Effects (SADE) Secondary Endpoints: • Incidence of procedure-related Adverse Events (AEs) or Adverse Device Effects (ADEs). • Tolerability of treatment via verbal report of pain/discomfort. • Nasal symptoms using rTNSS scale at 30- and 90-Days post-treatment. • Nasal congestion and turbinate hypertrophy as assessed by physician at 30- and 90-Days post-treatment. Exploratory Endpoints: • Physician Evaluation of ease of treatment delivery using study device for inferior meatus location.
Study Population:	Up to 30 adult subjects diagnosed by ENT Physician with chronic rhinitis will be enrolled and treated in-office.
Clinical Site(s)	Up to 5 U.S. sites
Study Device:	Arrinex ClariFix™ Cryotherapy Device
Study Duration:	9 Months
Participant Duration:	Approximately 3.5 months

1.2 SCHEMA


Prior to Enrollment
Patients pre-screened for Eligibility
Visit 1 (Day -30 to 0) Screening
Obtain informed consent. Screen potential participants; obtain history; document ConMeds
Visit 2 (Day -7 to 0) Baseline
Confirm TNSS & Eligibility. Complete Efficacy Baseline assessments.
Visit 3 (Day 0) Treatment
Treatment with ClariFix device
Visit 4 (Day 7) 1 Week Follow-up
Complete Efficacy assessments; update ConMeds; Safety evaluation.
Visit 5 (Day 30) 1 Month Follow-up
Complete Efficacy assessments; update ConMeds; Safety evaluation.
Visit 6 (Day 90) 3 Month Follow-up
Complete Efficacy assessments; update ConMeds; Safety evaluation.
Study Participation Complete

1.3 SCHEDULE OF ACTIVITIES (SOA)

Study Activity	Screening (V1) Day -30 to 0	Baseline (V2) Day -7 to 0	Treatment (V3) Day 0	1-Week Follow-up (V4) Day 7 (±3 days)	1-Month Follow-up (V5) Day 30 (±7 days)	3-Month Follow-up (V6) Day 90 (±14 days)	Unscheduled[b]
Informed Consent	X						
Demographics Questionnaire	X						
Medical History	X						
Concomitant Medication	X	X				X	X
Physical/Endoscopic Nasal Exam	X			X[c]	X	X	X
Reflective Total Nasal Symptom Score (rTNSS)	X	X			X	X	X
Inclusion/Exclusion Criteria	X	X					
Nasal Obstruction Symptom Evaluation (NOSE) Instrument		X			X	X	
Sino-Nasal Outcome Test (SNOT-22)		X			X	X	
Visual Analog Scales – Nasal Symptoms		X			X	X	
Mini Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ)		X			X	X	
Clinical Global Impression – Improvement (CGI-I)					X	X	
Treatment with ClariFix			X				
Pain Numeric Rating Scale			X				
Adverse Event review and evaluation[a]			X			X	X
Study Exit						X	

a. AEs to be collected beginning at treatment timepoint. Any AEs experienced between Consent to Treatment timepoints should be evaluated for continued eligibility and suitability for study participation and may be documented as medical history, if applicable.
b. Unscheduled Visit activities to be completed based on reason for Visit and discretion of the Investigator.
c. Physical/Endoscopic Nasal Exam may be performed at the discretion of the Investigator in the event of a new or continuing AE.

2 INTRODUCTION

2.1 STUDY RATIONALE

Anatomic dissections have demonstrated that parasympathetic nerve fibers innervate the nasal cavity within the inferior meatus as well as the middle meatus. In studies to date (see Section 2.3), interruption of these nerve signals in the middle meatus has demonstrated a response rate of ~80% with reduction in rhinorrhea and congestion symptoms by approximately 50%. Extending this interruption of the nasal nerve fibers in the inferior meatus may improve the symptom reduction and/or response rate in patients with chronic rhinitis.

2.2 BACKGROUND

Rhinitis is a very common condition throughout the world. In the Unites States alone, it affects 10-30% of the adult general population. This accounts for 30-60 million people in the United States and the prevalence has been increasing in recent decades, making it the fifth most common chronic disease in the US. Rhinitis is the inflammation of the nasal mucosa affecting patients with distressing symptoms of at least one of the following symptoms: nasal congestion, rhinorrhea, sneezing, and nasal itching.

The current standard of care to control this disease starts with pharmacologic interventions, typically beginning with over the counter medications. Nasal steroids (i.e. Flonase, Nasonex) and oral anti-histamines (i.e. Claritin, Allegra, Zyrtec) are the mainstays of medical management. They have their challenges, however, as they require daily use and have limited effectiveness, especially against non-allergic rhinitis. Sedating anti-histamines such as Benadryl are used intermittently but the somnolent side effects are not usually well tolerated.

Prescription medications are used when OTC medication management fails. Oral steroids can be effective in the short term but carry more severe long-term side effects including immunosuppression, osteoporosis, Cushing syndrome and diabetes. Adrenergic agents such as Afrin are effective but quickly result in tolerance and “rebound” (recurrence and sometimes worsening of symptoms when off the medication).

When pharmacological treatments do not provide adequate response, surgical techniques have also been developed to treat rhinitis. These techniques include electrocautery, chemocautery, laser cautery, microdebrider turbinoplasty, radiofrequency ablation, subtotal turbinectomy, total inferior turbinectomy, and submucosal resection. These primarily seek to address the nasal obstructive component through reduction of the inferior turbinate.

Use of various cryosurgical tools for destruction of tissue in the nasal passageway to treat nasal obstruction or symptoms of rhinitis has been reported in the literature.[1,2,3,4,5,6,7,8,9,10,11] Target tissue in the nasal passageway that was subjected to cryosurgery included the nasal soft tissue covering the turbinates, which included nasal nerves. All studies included patient-reported outcomes of nasal symptoms, which is a commonly accepted method for demonstrating the effectiveness outcomes in the nasal passageway. Physicians also performed visual assessments of nasal congestion and recorded the presence of complications including resolution of any adverse symptoms. Although these published reports reflect improvement in symptoms and a low rate of complications, endoscopic cryotherapy techniques and tools have not been fully optimized to achieve consistent outcomes.

The ClariFix Cryoablation clinical study evaluated cryosurgical tools[12]. In this study, the safety and effectiveness of cryosurgical posterior nasal tissue ablation for the treatment of rhinitis using the ClariFix Device was assessed. The initial clinical findings demonstrated a significant reduction in rhinorrhea and nasal congestion with minimal to no adverse events (see section 2.3). In this study, the cryotherapy was applied to unwanted tissue including postganglionic branches of the vidian nerve (referred to as Posterior Nasal Nerves PNN) along the lateral wall in the posterior region of the middle meatus just inferior to the sphenopalatine foreman (SPF).

Upon further investigation, Dr. Benjamin Bleier et al. noted that additional postganglionic fibers may project from the pterygopalatine ganglion via multiple individual postganglionic rami to supply the nasal mucosa[13]. Anatomic dissections showed that accessory posterolateral nerves were noted in 87.5% of specimens (14 of 16). Of the 25 additional posterolateral nerves identified, the most common location (40%, 10/25) was within 1 cm posterosuperior to the horizontal attachment of the inferior turbinate; however, 28% (7/25) were noted within 5 mm anteroinferior to this attachment (see Figure 1). The initial clinical studies demonstrated that the posterosuperior location had a clinical effect in roughly 80% of patients, so the intent of this study is to evaluate the safety and effectiveness of Cryoablation along the lateral wall in the middle meatus (as done in previous studies) as well as the inferior meatus in patients that suffer from Chronic Rhinitis.

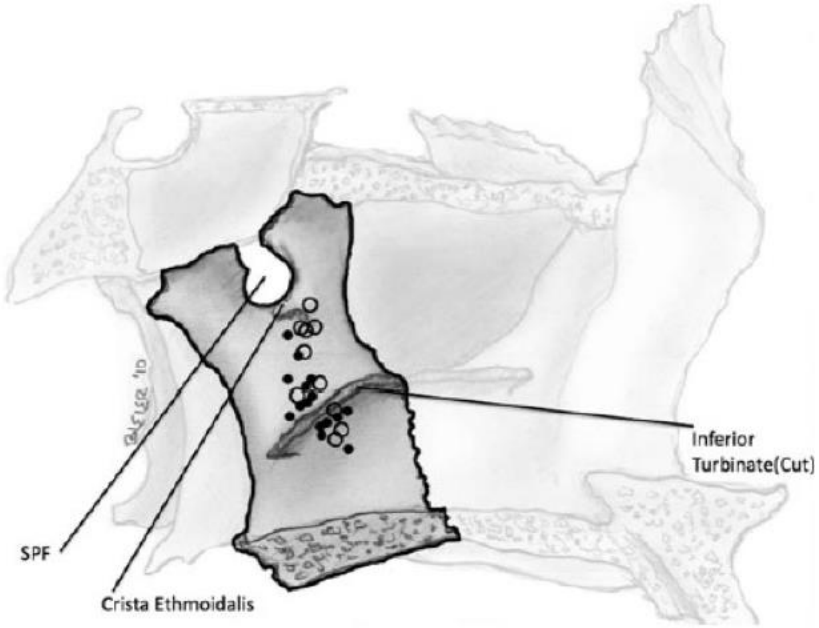


Figure 1. Illustration of medical aspect of the left palatine bone indicating the location of all 25 accessory posterolateral nerves identified. The closed dots represent nerves traversing directly through the bone whereas the open circles represent nerves that were associated with distinct foramina.

2.3 REPORT OF PRIOR INVESTIGATIONS

CT-0001 ClariFix Cryoablation Study

A pilot clinical study was performed to evaluate the performance of the ClariFix device as a cryosurgical tool to treat subjects with chronic rhinitis. This study was a prospective, multi-center, single-arm interventional study of the ClariFix device. The study protocol was reviewed and approved as non-significant risk (NSR) by Quorum Review IRB. Three investigational sites were selected in the United

States. All treatments were performed on consented awake subjects in an office setting by experienced otolaryngologists. Subjects were seen in the office at 7, 30, and 90 days post-treatment for follow-up assessments. Extended follow-up to a maximum of one-year post-treatment was conducted to assess the durability of treatment outcomes. The primary safety endpoint for the study was the frequency of serious device or procedure-related adverse events (SAEs). The primary efficacy endpoint was the change in subject reported nasal symptoms at the follow-up intervals relative to baseline. Nasal symptoms were assessed using the reflective Total Nasal Symptom Scale (rTNSS) and a Visual Analog Scale (VAS).

A total of twenty-seven (27) subjects were enrolled and received bilateral treatments. Twenty-seven (27) subjects completed 1-month follow-up and twenty-four (24) subjects completed 90-day follow up (3 subjects were lost-to-follow-up). Twenty-four (24) subjects participated in extended follow-up. Treatments were successfully completed bilaterally with no complications in 100% of subjects (n=27) using injected or topical anesthesia in the office. Nasal symptoms assessed by rTNSS were reduced significantly at each follow-up interval compared to baseline. The average rTNSS score was reduced by 58% from 6.2 at baseline to 2.6 at 30 days and maintained at 2.7 at 90 days (56% reduction). Extended follow-up data showed sustained improvements, with an average rTNSS of 2.3 at 180 days post-treatment. Eighty-one percent (22/27) of subjects had improved rTNSS scores at 30 days and 79% (19/24) of subjects had improved rTNSS scores at 90 days. The VAS symptom data similarly demonstrated significant reductions in nasal symptoms. The average total VAS score was reduced by 50% and 53% at 30 and 90 days, respectively. There was no device or procedure-related serious adverse events or unanticipated adverse device effects reported during the course of the study.

CT-0003 ClariFix Cryotherapy Device in Subjects with Chronic Rhinitis "FROST" Study
A post-market clinical study was initiated to evaluate the safety and efficacy of the ClariFix device in subjects with chronic rhinitis. The "FROST" study was a prospective, multi-center, single-arm interventional study. The study protocol was deemed NSR by Quorum Review IRB (as central IRB) and by Advarra IRB (formerly Chesapeake IRB) for an individual site. Seven (7) investigational sites were selected and initiated, with six of the seven enrolling subjects. Subjects that were consented and met eligibility criteria received treatment in an office setting by Otoloaryngologist. All subjects were followed-up with via phone at 1-day post, and were seen in-office at 7-, 30-, 90-, 180-, 270- and 365-days post-treatment. Subjects that had an improvement in their overall rTNSS score at both the 270- and 365-day post-treatment were offered participation in an extended follow-up that includes office visits at 15-, 18-, 21-, and 24-months post-treatment. The rTNSS scale was administered at all in-office study visits and the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was administered at 90-days and 18- and 24-months post-treatment.

A total of one hundred (100) subjects were enrolled and received bilateral treatment with the ClariFix device at the middle meatus location within the nasal cavity. At this time, all 100 subjects completed the 30-day follow-up, ninety-eight (98) have completed through 90-day follow-up with two (2) subjects having exited the study at that timepoint, and data analysis has been completed through this timepoint. The study is still currently in follow-up with visits completed as follows: 180-day n=89, 270-day n=77, 365-day n=56, 15-month n=12, and 18-month n=1. As of the 90-day timepoint, the average per subject rTNSS score was reduced by 48.4% from 6.15 at baseline to 3.06 at 30-days and to 3.02 at 90 days (46.5% reduction), with the largest improvements in the individual symptom scores for rhinorrhea (change from baseline of 2.42 to 1.05 at 90-days) and congestion (change from baseline of 2.07 to 1.05 at 90-days). The RQLQ data at 90-days showed a 45.8% reduction from an overall score of 3.12 at baseline to 1.63 at 90-days. A total of 29 adverse events were reported at the 90-day timepoint, with

one (1) probable adverse device effect and procedure-related, two (2) procedure related adverse events, and two (2) serious adverse events (one not related, and one possible device related).

Summary

In both the 27 subject pilot study and 100 subject FROST study, office-based treatment using the ClariFix device was demonstrated to be safe, well-tolerated, and effective in reducing nasal symptoms in subjects with chronic rhinitis. This study will build on those results and is designed to assess the safety and effectiveness of the ClariFix device when used to ablate unwanted tissue in the nasal passageway of subjects with chronic rhinitis.

2.4 DEVICE DESCRIPTION

The ClariFix™ device (K162608) is an FDA 510(k) cleared Class II cryosurgical tool indicated for the destruction of unwanted tissue during surgical procedures, including in adults with chronic rhinitis.

The ClariFix device (Figure 2) is a handheld cryosurgical device which provides focal, controlled freezing to the target tissue. In order to deliver treatment, a nitrous oxide canister is inserted into the device. The device's cryoprobe is placed in contact with the target tissue, under direct visualization. The low profile semi-flexible cannula allows the user to maintain visibility of the cryoprobe and apply pressure to target tissue with the cryoprobe to ensure contact throughout the treatment. Once the cryoprobe is in the desired position, the physician manually initiates the flow of cryogen and ablates unwanted tissue. The nitrous oxide gas is contained within the cryoprobe and allowed to exit the device at the handle away from the subjects.

The ClariFix device consists of a Cryoprobe, Cannula, On/Off valve, Handle, & Cap. The device is provided sterile and designed for single patient use.

The device is provided with 10-ml cryogen canisters. The cryogen canisters are provided separately. The canisters are provided non-sterile and each canister contains enough cryogen for approximately 60 seconds (10-ml) of ablation time.

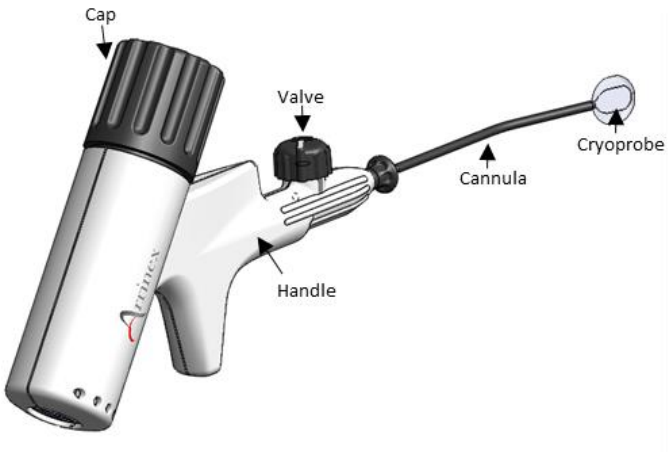


Figure 2. ClariFix™ Device

2.5 RISK/BENEFIT ASSESSMENT

2.5.1 KNOWN POTENTIAL RISKS

The study cryotherapy procedure involves transnasal placement of the ClariFix device under endoscopic visualization and use of local anesthesia. In order to minimize risks associated with the study, the procedure will be performed by practicing otolaryngologists experienced in transnasal procedures. Further, subjects with known allergies to local anesthetic agents shall be excluded from participation in the study.

While nasal endoscopy is generally known to be safe, anticipated risks may include, but are not limited to:

- Temporary pain, discomfort or irritation
- Bleeding
- Cerebrospinal fluid (CSF) leak

Similarly, while generally known to be safe, submucosal placement of a needle and delivery of local anesthesia may be additionally associated with the following risks, not limited to:

- Minor bleeding
- Pain with injection
- Facial numbness or tingling
- Sedation
- Tachycardia, nervousness, anxiety
- Lightheadedness, dizziness, confusion,
- Muscular twitching, tremors
- Infection
- Allergic reaction
- Lidocaine or Tetracaine toxicity with overdose
- Visual disturbance
- Vomiting
- Headache
- Tinnitus
- Seizures
- Hypotension, bradycardia
- Unconsciousness
- Respiratory arrest
- Cardiac arrest

While generally considered safe, cryotherapy has known potential risks[14] including, but not limited to:

- Postoperative bleeding
- Epistaxis
- Nasal obstruction
- Nasal crusting
- Ear blockage

In addition, the specific nature of cryosurgery using the ClariFix Device results in a known potential for adverse events related to the cold application. Potential risks and complications are outlined in the IFU (See Appendix I).

2.5.2 KNOWN POTENTIAL BENEFITS

Use of the ClariFix device as a tool during cryosurgery may reduce the symptoms of chronic rhinitis. Improvement in rhinitis symptoms may improve patients' quality of life and may improve work or school productivity.

This study may provide valuable information as to the underlying mechanisms of rhinitis, which may enable the development of more effective devices in the future.

2.5.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Potential risks are typically transient and resolve, however potential improvement in quality of life and symptoms associated with rhinitis have been shown to be durable through at least one-year post-treatment.

3 OBJECTIVES AND ENDPOINTS

The study overall objective is to evaluate the feasibility of treatment to the posterior nasal nerve at both the middle and inferior meatus locations within the nasal cavity for improvement in the symptoms of chronic rhinitis.

OBJECTIVES	ENDPOINTS
Primary	
Evaluate the safety of treatment to the inferior meatus location	Incidence of procedure related Serious Adverse Events (SAEs) and/or Serious Adverse Device Effects (SADE)
Secondary	
Evaluate the effectiveness and tolerability of treatment at the inferior meatus location	1. Incidence of procedure-related Adverse Events (AEs) or Adverse Device Effects (ADEs). 2. Tolerability of treatment via verbal report of pain/discomfort. 3. Nasal symptoms using rTNSS scale at 30- and 90-Days post-treatment.
Tertiary/Exploratory	
Physician Evaluation of ease of treatment delivery using study device for inferior meatus location.	Physician-reported ease-of-use rating.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Prospective, non-randomized, open-label, multi-center, interventional feasibility study.

4.2 END OF STUDY DEFINITION

A subject is considered to have completed the study if he or she has completed all phases of the study including the last visit shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit shown in the SoA in the trial for all subjects.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Subject is ≥18 years of age.
2. Subject has had presence of moderate to severe rhinorrhea symptoms and mild to severe nasal congestion symptoms for >3 months.
3. At the Baseline Visit, subject has, as determined by rTNSS, moderate to severe symptoms of rhinorrhea (individual symptom score of >1), mild to severe symptoms of nasal congestion (individual symptom score >0).
4. Subject has had documented allergy test within the last 10 years that defines whether or not subject has allergies to perennial and seasonal allergens, or is willing to have one performed prior to study exit.
5. Subject is able to provide informed consent and willing to complete study activities and visits per protocol.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Subject has clinically significant anatomic obstructions that limit access to the posterior nose including severe septal deviation, nasal polyps, and sinonasal tumor.
2. Subject has had prior sinus or nasal surgery that significantly alters the anatomy of the posterior nose.
3. Subject has moderate to severe ocular symptoms as determined.
4. Subject has a history of epistaxis in the past 3 months.
5. Subject has a history of rhinitis medicamentosa.
6. Subject has had prior head or neck irradiation.
7. Subject has active or chronic nasal or sinus infection.
8. Subject is pregnant.
9. Subject has an allergy or intolerance to anesthetic agent.
10. Subjects with cryoglobulinemia, paroxysmal cold hemoglobinuria, cold urticaria, Raynaud's disease, and/or, open and/or infected wounds at or near the target tissue.
11. Subject is currently participating in another clinical research study.
12. Subject has any physical condition that, in the investigator's opinion, would prevent adequate study participation or pose increased risk.

5.3 SCREEN FAILURES

Screen failures are defined as subjects who consent to participate in the clinical trial but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants. Minimal information includes demography, screen failure details, and eligibility criteria.

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

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

It is anticipated that up to 5 U.S. based sites will participate in this study. A sufficient number of potential subjects will be screened to be able to complete targeted enrollment of up to thirty (30) subjects within three (3) months of study initiation.

Targeted study population will be pre-screened based on eligibility criteria and recruited from patients within the practice of otolaryngology practices. Additionally, subjects may be recruited into the practice by means of IRB approved recruitment materials, that may include, but are not limited to, web postings, posters, and mailers.

While there is no known risk to pregnant or lactating females, as there is no need to evaluate the safety and efficacy of the study device in this population, they will be excluded from study participation.

Participants will receive a stipend in the form of a pre-paid gift card for their participation in the study. The gift cards will be provided after the completion of each study visit's activities. A schedule of stipends to be paid for each visit will be outlined in each site's IRB-approved Informed Consent Form (ICF) document.

6 STUDY TREATMENT

6.1 STUDY TREATMENT ADMINISTRATION

All subjects will receive bilateral cryoablation treatment with the ClariFix device per Instructions for Use (IFU) (See Appendix I).

Each side of the nasal cavity will be treated in two locations (see Figure 3): (a) middle meatus and (b) inferior meatus. Each location will receive approximately thirty (30) seconds of cryoablation treatment.

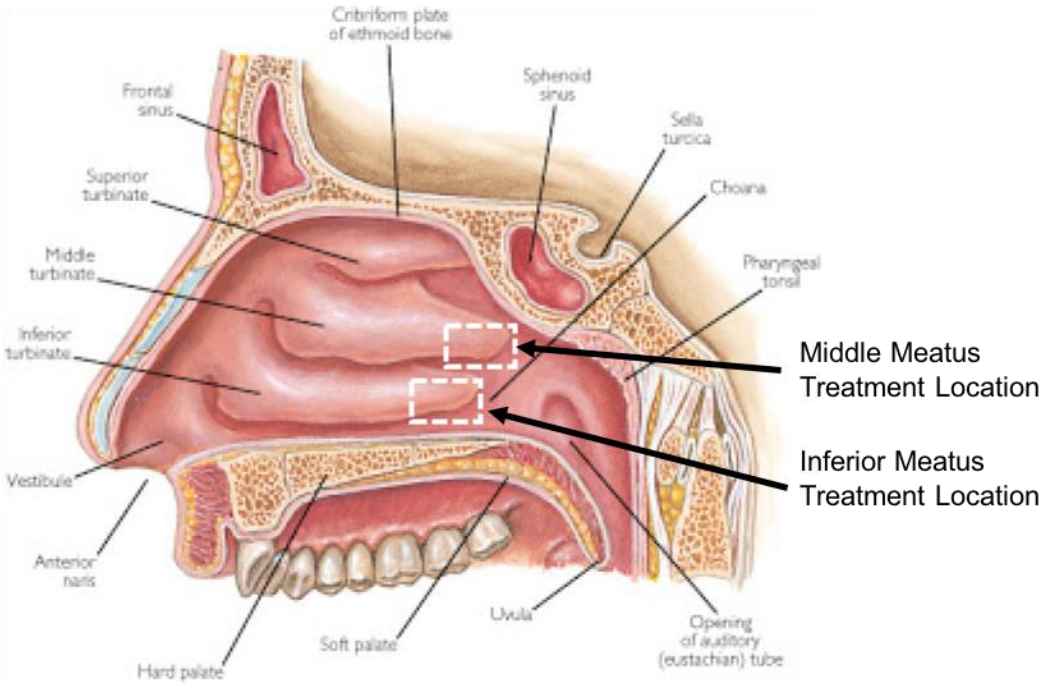


Figure 3: Cryoablation Treatment Locations.

6.2 DEVICE ACQUISITION AND ACCOUNTABILITY

Sponsor will provide the ClariFix devices, at no cost, to be used for the subjects' cryoablation treatments.

Devices will be shipped and designated as study-use only. Device usage will be tracked in site's Regulatory documents and individual device lot numbers will be noted in Source documents and eCRFs. However, as the devices being use are FDA cleared and being used on-label, if necessary, devices may be pulled from site's commercial inventory.

6.3 CONCOMITANT MEDICATIONS

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements.

Medication usage will be documented for medications subject is currently taking at time of Screening Visit, for any medication usage stopped within the previous thirty (30) days, and for medication changes (started, stopped, or change of dose/frequency) through study exit. Medications usage, both prescription and over-the-counter, for the following indications and/or systems will be documented in the Concomitant Medication Log for each subject:

- Allergies
- Nasal, Ear and Throat
- Asthma
- Migraines
- Blood thinners/anti-coagulants

Medications taken in conjunction with time of treatment or post-treatment for pain or anxiety, both prescription and over-the-counter, pain or discomfort will be documented.

Additionally, any medication that is determined by the Investigator to be a potential safety issue or concern, and/or any medication taken in connection with treatment for an Adverse Event will be documented.

Subjects will refrain from the use of ipratropium bromide (i.e. Atrovent) at least 3 days prior to treatment and through the 3-Month timepoint.

At the Investigator's discretion, subjects that have an active coagulation disorder or are receiving anti-coagulants, may be asked to temporarily stop usage prior to treatment.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the Study Exit Case Report Form (CRF). Subjects who sign the informed consent form but do not receive the study treatment may be replaced. Subjects who sign the informed consent form and receive the study treatment, and subsequently withdraw, or are withdrawn or discontinued from the study, may be replaced at the discretion of the Sponsor.

7.2 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 2 or more scheduled visits and is unable to be contacted by the study site staff.

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

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

- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 STUDY PROCEDURES

8.1.1 SCREENING VISIT (VISIT 1) (DAY -30 TO 0)

Potential study subjects will be pre-screened against study eligibility criteria. Those individuals, that meet pre-screening criteria will be offered participation in the study and will be consented (see Section 10.1.1).

The Screening Visit may occur in-office up to 30 days prior to the Treatment Visit (Visit 1). Visit 1 may occur on the same day as the Baseline (Visit 2) and Treatment (Visit 3) Visits.

After obtaining informed consent, the following study activities will be completed:

1. Subject to complete Subject Demographics Questionnaire (See Addendum: Patient Questionnaires). Data collected includes month and year of birth, biological gender, ethnicity and race.
2. Subject will complete rTNSS questionnaire (see Section 8.2.1).
3. Concomitant Medications will be documented (see Section 6.3).
4. Relevant Medical History will be documented. This will include, but not limited to, the following:
    a. History of nasal symptoms including rhinitis, epistaxis and sinusitis;
    b. History of facial pain, TMJ, ocular symptoms, and ear/nose complaints;
    c. Prior allergy testing; and
    d. History of rhinitis medication usage and response to treatment.
5. Physician will complete a Physical Nasal Exam (see Section 8.3.1) and document findings.
6. Investigator will review Inclusion/Exclusion criteria, and subjects meeting criteria will be scheduled for the Baseline Visit (Visit 2).

Note: Due to post-market, on-label use of device, pregnancy exclusion will be based upon self-report. Pregnancy testing will not be required to confirm eligibility.

8.1.2 BASELINE VISIT (VISIT 2) (DAY -7 TO 0)

Subjects meeting eligibility criteria will return in-office for the Baseline Visit (Visit 2). The Baseline Visit may be completed the same calendar day as the Screening (Visit 1) and Treatment (Visit 3) Visits, however it must be completed no earlier than seven (7) calendar days prior to the Visit V3.

At Visit 2, the following study activities will be completed:

1. Subject will complete rTNSS questionnaire.
    Note: If Visit 2 is completed the same calendar day as Visit 1, second rTNSS is not to be completed.
2. Concomitant Medication usage will be updated.

3. Eligibility Criteria will be confirmed.
    a. Subjects meeting criteria will be considered enrolled and continue Visit 2 activities.
    b. Subjects not meeting criteria will be considered a Screen Failure and their study participation will be complete.
4. Subject will complete the NOSE (see Section 8.2.2), SNOT-22 (see Section 8.2.3), VAS for Nasal Symptoms (see Section 8.2.5), and MiniRQLQ (see Section 8.2.4).

Treatment Visit, if on another day, should be confirmed with the Subject.

Additionally, for subjects that do not have confirmation of a prior allergy test within the last 10 years, they will be scheduled for allergy testing prior to study exit.

8.1.3 TREATMENT VISIT (VISIT 3) (DAY 0)

Enrolled subjects will receive bilateral cryoablation treatment in-office. The Treatment Visit (Visit 3) may occur on the same calendar day as Visits 1 and 2 and must be completed within thirty (30) days from Visit 1 and no later than seven (7) calendar days of Visit 2.

Subjects will be begin being assessed for Adverse Events (AEs) starting at Visit 3, with any AEs occurring at Visit 3 or after through study completion (see Section 8.4).

At Visit 3, the following study activities will be completed:

1. Concomitant Medication usage will be updated.
2. Physician will perform bilateral cryoablation treatment with the ClariFix device, per IFU. See Section 6.
    a. Subject will be asked for a Verbal Pain Numeric Rating Scale (NRS) immediately after cryoablation treatment at each individual treatment location (see Section 8.3.2) and documented.
3. Subject will be monitored and assessed for Adverse Events.
    a. Should post-procedure discomfort or pain be experienced, in addition to an adverse event form, subject will be asked for a Verbal Pain NRS.
4. Subject will be scheduled for 1-Week Follow-up (Visit 4).

8.1.4 7-DAY FOLLOW-UP VISIT (VISIT 4) (DAY 7)

Subjects will return to the office at one (1) week (±3 days) from Visit 3 for the 1-Week Follow-up Visit (Visit 4).

At Visit 4, the following study activities will be completed:

1. Concomitant Medication usage will be updated.
2. Subject will be assessed for any new Adverse Events experienced since Visit 3 and/or review of previously unresolved Adverse Events.
3. If a continuing or new study-related AE, Physician may choose to complete a Physical Nasal Exam (see Section 8.3.1) and document findings.
4. Subject will be scheduled for 1-Month Follow-up visit (Visit 5).

8.1.5 1-MONTH FOLLOW-UP VISIT (VISIT 5) (DAY 30)

Subjects will return to the office at thirty (30) days (±7 days) from Visit 3 for the 1-Month Follow-up Visit (Visit 5).

At Visit 5, the following study activities will be completed:

1. Subject will complete rTNSS, NOSE, SNOT-22, VAS for Nasal Symptoms and MiniRQLQ questionnaires.
2. Concomitant Medication usage will be updated.
3. Subject will be assessed for any new Adverse Events experienced since Visit 4 and/or review of previously unresolved Adverse Events.
4. Physician will complete Physical Nasal Exam and document findings.
5. Investigator will complete Clinical Global Impression—Improvement (CGI-I) scale (see Section 8.2.5).
6. Subject will be schedule for 3-Month Follow-up visit (Visit 6).

8.1.6 3-MONTH FOLLOW-UP VISIT (VISIT 6) (DAY 90)

Subjects will return to the office at ninety (90) days (±14 days) from Visit 3 for the 3-Month Follow-up Visit (Visit 6).

At Visit 6, the following study activities will be completed:

1. Subject will complete rTNSS, NOSE, SNOT-22, VAS for Nasal Symptoms and MiniRQLQ questionnaires.
2. Concomitant Medication usage will be updated.
3. Subject will be assessed for any new Adverse Events experienced since Visit 5 and/or review of previously unresolved Adverse Events.
4. Physician will complete Physical Nasal Exam and document findings.
5. Investigator will complete Clinical Global Impression—Improvement scale (see Section 8.2.5).
6. Investigator will complete the Study Exit form.

Subject participation will be complete at the Visit 6 time point.

8.1.7 UNSCHEDULED VISITS

An Unscheduled Visit (UV) may occur after Visit 3 through the end of the study participation. A UV may occur due to a study-related adverse event.

The following activities will be completed as part of a UV:

- Concomitant Medication usage will be updated.
- Subject will be assessed for any new Adverse Events experienced since previous Visit and/or review of previously unresolved Adverse Events.

Additional data may be collected and documented at the discretion of the Investigator. Activities that may be completed at the Investigator's discretion is as follows:

- Physical Nasal Exam

- Physician completed CGI-I

8.2 EFFICACY ASSESSMENTS

8.2.1 REFLECTIVE TOTAL NASAL SYMPTOM SCORE (RTNSS)

The primary effectiveness endpoint will be assessed based on the four-symptom reflective Total Nasal Symptom Score (rTNSS)[15,16] (See Addendum: Patient Questionnaires). rTNSS is a validated symptom severity scoring system that consists of the sum of four (4) individual subject-assessed symptom scores for rhinorrhea, nasal congestion, nasal itching, and sneezing. Each item is scored on a scale of 0 (No Symptoms) to 3 (Severe Symptoms) and is based on the subject's evaluation of symptom severity over the preceding two (2) weeks at study visits. The four-symptom rTNSS has a possible score of 0-12. The reflective scores will be based on the subject's evaluation of symptom severity over the preceding two (2) week period.

In this study, a modified version of the rTNSS will be utilized that adds two additional questions for rating of post-nasal drip and clearing of throat. However, these will not be included in the analysis of the 4-item rTNSS and will be analyzed separately.

Subjects will be asked to assess their symptoms at the Screening Visit (Visit 1), Baseline Visit (Visit 2) (if on a day other than Screening), and at the 1-Month (Visit 5) and 3-Month Follow-up (Visit 6) Visits. The subjects will be asked to assess each symptom individually (runny nose, congestion, nasal itching, sneezing) (See Addendum: Patient Questionnaires). Subject may be reminded of baseline score prior to treatment, as appropriate.

8.2.2 NASAL OBSTRUCTION AND SEPTOPLASTY EFFECTIVENESS (NOSE) SURVEY

The Nasal Obstruction and Septoplasty Effectiveness (NOSE) survey[17] consists of 5 items, each scored using a 5-point Likert scale to make a total score rant of 0 to 100. The subject completes the survey by circling the response closest to describing their current symptoms over the past 1 month (See Addendum: Patient Questionnaires). The sum of those response is multiplied by a factor of 5 to base the scale out of a possible score of 100 for analysis. Higher scores indicate worse obstruction.

The NOSE survey will be administered at the Baseline (Visit 2), and 1- (Visit 5) and 3-Month (Visit 6) Follow-up Visits.

8.2.3 SINO-NASAL OUTCOME TEST (SNOT-22)

The Sino-Nasal Outcome Test (SNOT-22)[18] is a validated patient-reported questionnaire to assess the impact of nasal symptoms on a patient's quality of life. The questionnaire consists of 22 categories, each scored using a 5-point Likert scale (0 = No Problem to 5 = Problem as base as it can be). The subject completes the survey by circling the response closest to describing "how bad" their current symptoms are in each category over the past two (2) weeks, and then checks up to five (5) categories that are the "Most Important Items" affecting their health (See Addendum: Patient Questionnaires). The sum of the responses produces a total possible score of 0 to 110 for analysis. Higher scores indicate worse obstruction.

The SNOT-22 questionnaire will be administered at the Baseline (Visit 2), and 1- (Visit 5) and 3-Month (Visit 6) Follow-up Visits.

8.2.4 MINI RHINOCONJUNCTIVITS QUALITY OF LIFE QUESTIONNAIRE (MINIRQLQ)

The Mini Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ)[19] is a validated tool that measures the functional (physical, emotional, and social) problems associated with rhinitis (See Addendum: Patient Questionnaires). The MiniRQLQ was adapted from the original 28-item Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)[20], which included 28-items in 7 domains (sleep, non-Rhinoconjunctivitis symptoms, practical problems, nasal symptoms, eye symptoms, activity limitations, and emotional function). The MiniRQLQ, is a 14-item questionnaire that covers 5 domains of activities, practical problems, nose symptoms, eye symptoms, and other symptoms. Subjects are asked to recall impairments experienced during the previous week and to respond to each item on a 7-point scale (0 = no impairment, 6 = maximum impairment). The overall RQLQ score is the mean of all 14 responses and the individual domain scores are the means of the items in those domains.

The MiniRQLQ questionnaire will be administered at the Baseline (Visit 2), and 1- (Visit 5) and 3-Month (Visit 6) Follow-up Visits.

8.2.5 VISUAL ANALOG SCALE – NASAL SYMPTOMS

A Visual Analog Scale (VAS) is a measurement instrument that tries to measure a characteristic or attitude that is believed to range across a continuum of values and cannot easily be measured. It is often used in epidemiologic and clinical research to measure the intensity or frequency of various symptoms. From the subject's perspective, this spectrum appears continuous and does not make discrete jumps, as a categorization of none, mild, moderate and sever would suggest.

In this study, a 100mm scale (see Addendum: Patient Questionnaires) will be used to evaluate the individual symptoms over the last week of rhinitis (runny nose), nasal congestion (stuffiness), and overall nasal symptoms. Subjects will report record their symptoms, based on the last week, on a continuum of 0mm on the left, representing no symptoms, to 100mm on the right, representing severe symptoms.

The VAS for Nasal Symptoms will be administered at the Baseline (Visit 2), and 1- (Visit 5) and 3-Month (Visit 6) Follow-up Visits.

8.2.6 CLINICAL GLOBAL IMPRESSION – IMPROVEMENT (CGI-I)

The Clinical Global Impression--Improvement (CGI-I)[21] rating scales is a clinician completed subject assessment of the changes of symptoms since time of treatment based on their clinical experience. The CGI-I is a 7-point Likert scale that ranges from a scale of 1 being "Very Much Improved" to 7 being "Very Much Worse".

The CGI-I will be completed that the 1- (V5) and 3-Month (V6) Follow-up Visits at the completion of the Physical Nasal Exam (See Section 8.3.1). Additionally, the CGI-I may, at the discretion of the clinician, be administered at an Unscheduled Visit (See Section 8.1.7).

8.3 SAFETY AND OTHER ASSESSMENTS

8.3.1 PHYSICAL NASAL EXAM

A physical nasal evaluation of the treatment area and nasal cavity will be performed by a licensed clinician via endoscope at the Screening (Visit 1), 1-Week (Visit 4 due to AE occurrence or monitoring), 1-Month (Visit 5) and 3-Month (Visit 6).

IMPORTANT: Except for 1-Week (Visit 4), if applicable, subjects are not to be decongested prior to the Physical Nasal Exam.

Prior to decongestant, bilateral endoscopic videos or images are to be collected capturing the head of the inferior and middle turbinates (see Section 8.3.3).

The clinician will assess each side of the nasal cavity for hypertrophy of the middle and inferior turbinates and congestion using a 0 to 3 scale (0=None, 1=Mild, 2=Moderate, or 3=Severe).

After decongestant, a second bilateral endoscopic videos or images are to be collected capturing the head of the inferior and middle turbinates.

At Visit 4 (if applicable), Visit 5 and Visit 6, the clinician will assess each treatment area (left middle meatus, left inferior meatus, right middle meatus and right inferior meatus) for bleeding, crusting, and swelling using the same scale of 0 to 3.

An endoscopic exam may be completed at an Unscheduled Visit at the discretion of the Investigator, in the event of a study-related adverse event.

8.3.2 PAIN NUMERIC RATING SCALE

A pain numeric rating scale (NRS)[22] for pain function best for the patient's subjective feeling of the intensity of pain right now—present pain intensity. The NRS utilizes an 11-point scale of zero to 10. Subjects verbally report pain on the scale of 0 to 10 with zero representing "no pain" and 10 representing "worst pain imaginable".

Pain and/or discomfort during the Treatment Visit (Visit 3) will be collected for each individual freeze treatment location (left middle meatus, left inferior meatus, right middle meatus, and Right Inferior Meatus), and any post-treatment pain and/or discomfort reported immediately following the treatment.

8.3.3 CLINICAL EVALUATION OF NASAL CONGESTION AND TURBINATE HYPERTROPHY

Images, photographic and video, collected at the time of Physical Nasal Exam (See Section 8.3.1) may be evaluated for visible nasal congestion and turbinate hypertrophy by an independent physician reviewer. Images will be collected at the Screening (Visit 1), 1-Month (Visit 5) and 3-Month (Visit 6) Follow-up timepoints.

Images will be of the internal nasal valve only. In the event that only video is collected, still shots will be taken by sponsor showing the internal nasal valve only prior to images being available to physician reviewer. Images to be reviewed are the heads of the inferior and middle turbinate for each side of the nose.

Images will be stored on thumb drives at the individual site, and videos transferred to Sponsor by designated Sponsor representatives via a secure data transfer. Transferred files are not to contain patient health information ("PHI") data (i.e., name, date of birth, etc.). Files will be identified by the subject's study identification number, the study Visit, and pre- or post-decongestant (e.g., 01-001 V1 pre-decongestant).

8.4 ADVERSE EVENTS, ADVERSE DEVICE EFFECTS, SERIOUS ADVERSE EVENTS AND UNEXPECTED ADVERSE DEVICE EFFECTS

In this study, the following types of adverse events will be collected and documented:

- ClariFix Device-related Adverse Device Effects (ADE)
- Cryotherapy procedure-related Adverse Events (AE)
- Head, ear, nose, throat, and breathing/lung related AEs, including anticipated AEs
- All Serious Adverse Events (SAE)
- Unanticipated Adverse Device Effects (UADE)

Anticipated adverse events are identified in the ClariFix IFU (See Appendix I).

8.4.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event (AE) is any untoward medical occurrence in a subject who receives treatment with the study device, which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the treatment with the study device, whether or not related to the treatment or device.

All AEs must be reported to the study sponsor.

8.4.2 DEFINITION OF ADVERSE DEVICE EFFECT (ADE)

Any adverse event related to the use of the study device. An adverse event is an untoward medical occurrence, unintended disease or injury, or untoward clinical sign in subjects.

8.4.3 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.4.4 DEFINITION OF UNEXPECTED ADVERSE DEVICE EFFECT (UADE)

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, the study 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 well-being of subjects.

8.4.5 CLASSIFICATION OF AN ADVERSE EVENT

8.4.5.1 SEVERITY OF EVENT

For all adverse events (AEs), the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.4.5.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to both the study device and study procedure assessed by the clinician who examines and evaluates the subject based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship to either the study device or the study procedure, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study device or the study procedure and cannot be explained by concurrent disease or other drugs or chemicals. The event must be phenomenologically definitive.
- **Probably Related** – There is evidence to suggest a causal relationship to either the study device or the study procedure, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals.
- **Potentially Related** – There is some evidence to suggest a causal relationship to either the study device or the study procedure (e.g., the event occurred within a reasonable time after study procedure). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events).
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to either the study device or the study procedure makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after study procedure) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of either the study device or the study procedure, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.4.5.3 EXPECTEDNESS

Sponsor will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.4.6 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE), adverse device effect (ADE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it may be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Study site will record all reportable events with start dates occurring any time from treatment with the study device until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.]

8.4.7 ADVERSE EVENT REPORTING

AEs should be documented in the source documents at time of identification, and initial entry of all AEs into the EDC should be completed within 72 hours of identification. Initial EDC entry may be pending additional information, but known information should be entered. Source and EDC entry should be updated as new information becomes available and upon resolution of the AE.

Additionally, Sponsor must be notified of SAE, SADE and UADE within 24-hours of identification via phone or email.

8.4.8 SERIOUS ADVERSE EVENT REPORTING

The study investigator shall complete an Adverse Event source form and email a copy of the form to sponsor within 24-hours of identification, in addition the AE reporting in section 8.4.7 should be followed. If IRB notification is required, this should be completed as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

In the event of an unanticipated adverse device effect, the study sponsor is responsible for conducting an evaluation of any and shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as FDA requests.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Efficacy Endpoints:

H0: Change from Baseline (Delta) in rTNSS = 0
H1: Change from Baseline (Delta) in rTNSS ≠ 0

Secondary Efficacy Endpoints:

H0: Change from Baseline (Delta) = 0
H1: Change from Baseline (Delta) ≠ 0

9.2 SAMPLE SIZE DETERMINATION

Inasmuch as this is a feasibility study with N=30, no formal power and/or sample size estimations were performed. The proposed sample size is comparable to those in other trials of this nature in this discipline.

9.3 POPULATIONS FOR ANALYSES

There are two key populations for analyses:

- The Safety Population is comprised of those subjects who received treatment by the ClariFix device
- The Efficacy Population is comprised of those subjects in the Safety Population who also had at least one valid follow-up assessment.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

All statistical analyses will be performed using a two-sided hypothesis test at the overall 5% level of significance. P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "< 0.001." If a p-value is greater than 0.999 it will be reported as "> 0.999." No adjustments for multiplicity are planned.

Continuous data will be summarized using descriptive statistics: n, mean, standard deviation or standard error, median, minimum and maximum. The decision to use either standard deviation or standard error will be based upon the objective of the presentation: standard deviation will be used when the interest is the natural variability of the data; standard error will be used when comparing two or more means. Continuous variables that are recorded using approximate values (e.g., < or >) will be replaced by the closest exact value for the calculation of summary statistics.

Categorical variables will be summarized using frequency counts and percentages.

For ordinal-scaled variables, a combination of the above may be employed as appropriate: frequency and percentage of observations within a category and means and standard deviations of the scores of the categories.

For categorical and ordinal variables, percentages will be calculated based on non- missing data.

All analyses will be based on available data; no imputation for missing data will be conducted.

Baseline is defined as the last measurement for the outcome of interest obtained before the exposure to the study device.

Duration variables will be calculated using the general formula: [(end date – start date) +1]

Within-subject changes will be calculated as visit value minus baseline value such that a negative change reflects a decrease and a positive change signifies an increase. No judgment ("better" or "worse") is associated with the sign of the change, only direction. The Wilcoxon Signed Rank test will be used to test the null hypothesis that the mean (or median) within-subject change is equal to zero.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

For the purposes of formality, rTNSS has been designated as the primary efficacy endpoint. However, since this is, in fact, a feasibility study, any of the secondary endpoints described below may be promoted in the next study to primary status. Therefore, the analytical approach for all efficacy endpoints will be identical.

The objective of these analyses is to present the changes from baseline for a small sample size in a manner that is statistically sound and intuitively comprehensible. To that end the tables will present summary statistics for the Baseline, 7-Day, and 1- and 3-Month timepoints, as well as serial changes from baseline.

The statistical null hypothesis is that the deltas are distributed around zero change. Wilcoxon Signed Rank tests will be employed to evaluate whether the deltas are distributed around zero or shifted either positively or negatively away from zero. No adjustments for multiplicity are planned since this is a feasibility or proof of concept study.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The secondary endpoints are changes over time in:

- NOSE Survey
- SNOT-22
- MiniRQLQ
- VAS – nasal symptoms
- CGI-I
- Physician Assessment of congestion
- Physician Assessment of turbinate hypertrophy

The analytical approach is described in the section above for the Primary Endpoint.

9.4.4 SAFETY ANALYSES

The overall incidence (i.e., number and percent of subjects with 1 or more adverse event) of adverse events, serious adverse device events, serious adverse events, and device and/or procedure related events (e.g., possibly, probably or definitely related) will be calculated from time of treatment through the entire duration of follow-up. The overall incidence of mild, moderate and severe events will be calculated by considering the most severe event for each subject.

In addition, the overall incidence for each adverse event type will be calculated. The adverse event types will be classified as defined in Section 8.4.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics, including demographic characteristics, medical history, patient-reported outcomes and physical measurements will be summarized using descriptive statistics.

9.4.6 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Listings of adverse events may be produced.

9.4.7 EXPLORATORY ANALYSES

Visual severity of nasal congestion and turbinate hypertrophy will be evaluated for each side of the nasal cavity separately. Screening, 1- and 3-Month timepoint scores will be cross-tabulated, and the proportion with improvement will be calculated.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT DOCUMENTS PROVIDED TO PARTICIPANTS

An Informed Consent Form (ICF) describing in detail the study treatment and study device, study procedures, and risks are to be given to each participant and written documentation of informed consent is required prior to initiating any study-related activities.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator, or qualified designee, will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

The sponsor may choose to temporarily suspend or prematurely terminate study or a study site with or without cause. Written notification, documenting the reason for study suspension or termination, will be provided by the sponsor, as applicable, to the investigator and IRB.

If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform, as applicable, study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study and/or study site may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored with the sponsor. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Arrinex research staff will be secured and password protected.

10.1.4 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

A risk-based approach to monitoring will be utilized and details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP). The CMP will describe in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports. An increased level of monitoring may be utilized either at an individual site or for the study as a whole in the event of, but not limited to, data quality issues or increased incidence of AEs.

10.1.5 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.]

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.6 DATA HANDLING AND RECORD KEEPING

10.1.6.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) will be entered into Medrio (https://medrio.com), a 21 CFR Part 11-compliant data capture system provided by the Sponsor. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.6.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the close-out of the study and until there are no pending or contemplated marketing applications. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.7 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within five (5) working days of identification of the protocol deviation, or within five (5) working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the Sponsor.

Protocol deviations must be sent to the reviewing Institutional Review Board (IRB), when applicable per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.8 FINANCIAL DISCLOSURE

Investigators shall provide financial disclosure according to applicable regulations.

10.2 ABBREVIATIONS

AE	Adverse Event
ADE	Adverse Device Effect
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression--Improvement
CMP	Clinical Monitoring Plan
CRF	Case Report Form
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MiniRQLQ	Mini Rhinoconjunctivitis Quality of Life Questionnaire
MOP	Manual of Procedures
NOSE	
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
rTNSS	Reflective Total Nasal Symptom Score
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAP	Statistical Analysis Plan
SNOT-22	Sino-nasal Outcome Test
SOA	Schedule of Activities
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect
US	United States
UV	Unscheduled Visit
VAS	Visual Analog Scale
NRS	Numeric Rating Scale

11 REFERENCES

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12 APPENDIX I