

**Clinical Evaluation of Safety and Efficacy for the
ClariFix™ Cryotherapy Device in Subjects with Chronic Rhinitis
(FROST)**

Investigational Plan

Sponsor: Arrinex, Inc.
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Protocol Summary of Changes

CIP Version	Rev.	CIP Date	Summary of Changes
1.0	A	16 Jan 2017	Initial Protocol
1.1	B	25 Sep 2017	<ul style="list-style-type: none"> • Expanded enrollment from 75 to 100 • Updated regulatory information to include current 510(k) reference • Update inclusion criteria to include minimum congestion score of 1 and minimum overall TNSS of 4. • Clarify that subject must have or is willing to take an allergy test prior to study exit. • Clarify exclusion criteria for sinus or nasal surgery that “significantly alters the anatomy of the posterior nose”. • TNSS description for mild, moderate and severe symptoms. • Update study contact information.
1.2	C	23 Feb 2018	Addition of Extended Follow-up through 24-Months
2.0	D	04 Dec 2018	Administrative Clarifications and the following changes/updates: <ul style="list-style-type: none"> • Update sponsor contact • Addition of Investigator Protocol Signature Page • Clarification of Follow-Up Visit study activities • Correction of rTNSS reflective time period • Clarification of physician evaluation data collection at Follow-up visits • Addition of Concomitant Medication section • Addition of Subject Treatment Questionnaire and corresponding unscheduled visit • Removal of criteria for Extended Follow-up eligibility • Allowance for Extended Follow-up visits to be completed via phone • Addition of references for study assessments • Overall restructuring of protocol sections and ordering

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1. Protocol Summary

Title	Clinical Evaluation of Safety and Efficacy for the ClariFix™ Cryotherapy Device in Subjects with Chronic Rhinitis (FROST)
Purpose	A multi-center, prospective, non-randomized, interventional clinical trial to assess the safety and effectiveness of the ClariFix™ device when used to ablate unwanted tissue in the nose of subjects with chronic rhinitis.
Design	Prospective, non-randomized, multi-center interventional cohort
Sponsor	Arrinex, Inc.
Study Device	ClariFix™ Cryotherapy Device
Enrollment	Up to 100 subjects
Clinical Site(s)	Up to 7 sites
Study population	Subjects that suffer from chronic rhinitis symptoms
Primary Endpoints	<ul style="list-style-type: none"> • Safety as assessed by the incidence of procedure- or device-related serious adverse events (SAEs) and unanticipated adverse device effects (UADEs) • Effectiveness as assessed by the change in nasal symptoms using the four-symptom rTNSS (reflective Total Nasal Symptom Score) at 90 days post-treatment
Secondary Endpoints	<ul style="list-style-type: none"> • Incidence of device or procedure related adverse events • Impact on quality of life assessed by the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) at 90 days post-treatment

Investigator Protocol Signature

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.

Read and acknowledged by signature below:

Name of Investigator

Investigator Signature

Date

1. Introduction

1.1. Background

Rhinitis is a very common condition throughout the world. In the United 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 at least one of the following distressing 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 turbineoplasty, radiofrequency ablation, subtotal turbinectomy, total inferior turbinectomy, and submucosal resection. These procedures 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 have been reported in the literature.^(1,2,3,4,5,6,7,8,9,10,11) Target nasal passageway locations that were 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 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.

Arrinex, Inc. has developed a novel cryotherapy device designed specifically to facilitate a transnasal approach to allow cryoablation of unwanted tissue in the nasal passageway.

1.2. Report of Prior Investigations

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 a non-significant risk study 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. Treatments were successfully completed bilaterally with no complications in 100% of subjects (n=27) using injected or topical anesthesia in the office. 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. Nasal symptoms assessed by rTNSS were significantly reduced 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 at least a one-point improvement of 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 were no device or procedure-related serious adverse events or unanticipated adverse device effects reported during the course of the study.

In this pilot study of 27 subjects, 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.

1.3. Device Description

The ClariFix device 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 sterile device is provided with two 10-ml non-sterile cryogen cannisters. The cryogen canisters are provided separately. The canisters contain enough cryogen for 60 seconds (10-ml) of ablation time.

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

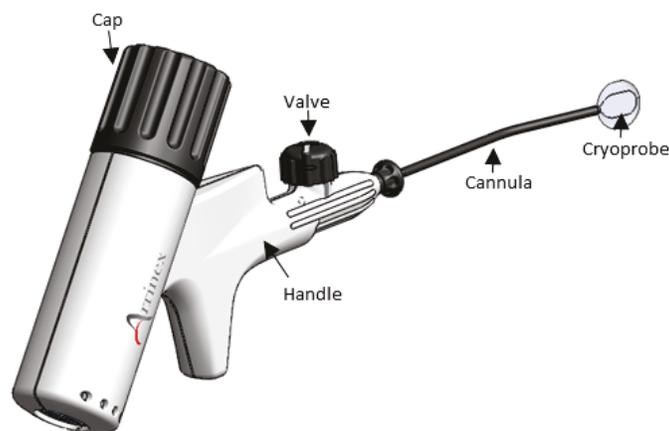


Figure 1. ClariFix™ Device

1.4. Regulatory Status

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.

2. Risk/Benefit Analysis

The Sponsor has undertaken a comprehensive risk-benefit analysis.

2.1. 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.

2.2. Risks

The study 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

In addition, the specific nature of cryosurgery using the ClariFix Device results in a known potential for adverse events related to the cold application, including but not limited to:

- Bleeding
- Crusting and/or tissue sloughing

- Swelling
- Pain/discomfort and/or facial pain
- Sensory alterations (numbness, tingling) in the face/mouth
- Increase in nasal congestion, Intranasal scarring/nasal obstruction
- Headache
- Dry nose
- Ear blockage
- Septal perforation
- Dry eyes, optical changes or orbital damage
- Vasovagal reaction
- Infection

3. Study Protocol

3.1. Design

Prospective, non-randomized, multi-center interventional cohort.

3.2. Study Duration and Timeline

Enrollment and follow-up is expected to take 36 months. The anticipated timeline is:

- Actual start date: March 2017
- Anticipated end date: March 2020

3.3. Physician Participants

Study investigators must be practicing physicians in otolaryngology.

3.4. Site Requirements

Site investigators must have at least one study coordinator with experience in conducting clinical research and with sufficient time to conduct the study.

3.5. Subject Recruitment

Subjects who seek treatment of chronic rhinitis will be recruited from the general population.

3.6. Sample Size

The target sample size is 100 treated subjects.

3.7. Subject Eligibility

To be eligible to participate, subjects must meet all of the inclusion criteria and none of the exclusion criteria listed in **Table 1**.

Table 1. Eligibility Criteria

<p>Inclusion Criteria</p> <ul style="list-style-type: none"> a) Subject is ≥ 21 years of age b) Subject has moderate to severe symptoms of rhinorrhea (individual symptom rating of 2 or 3), mild to severe symptoms of congestion (individual symptom rating of 1, 2 or 3) and a minimum rTNSS score of 4 (out of 12) at the time of the treatment visit. These symptoms shall have been present for > 6 months. c) 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. d) Subject has been dissatisfied with medical management, defined as usage of intranasal steroids for a minimum of 4 weeks without adequate symptom relief by the subject's assessment e) Subject has signed IRB-approved informed consent form
<p>Exclusion Criteria</p> <ul style="list-style-type: none"> a) Subject has clinically significant anatomic obstructions that in the investigator's opinion limit access to the posterior nose, including but not limited to septal deviation or perforation, nasal polyps, sinonasal tumor. b) Subject has had any prior sinus or nasal surgery that significantly alters the anatomy of the posterior nose. c) Subject has active nasal or sinus infection d) Subject has moderate to severe ocular symptoms e) Subject has a history of nosebleeds in the past 3 months f) Subject has a history of rhinitis medicamentosa g) Subject has had prior head or neck irradiation h) Subject has active coagulation disorder or is receiving anti-coagulants which cannot be safely stopped for 4 weeks (excluding aspirin) i) Subject is pregnant j) Subject is participating in another clinical research study k) Subject has an allergy or intolerance to anesthetic agent

- l) Subjects with cryoglobulinemia, paroxysmal cold hemoglobinuria, cold urticaria, Raynaud's disease, and/or, open and/or infected wounds at or near the target tissue
- m) Any physical condition that in the investigator's opinion would prevent adequate study participation or pose increased risk

3.8. Screening Procedures (Visit 1)

The screening evaluation will take place up to 30 days prior to the study procedure. Potential study subjects will be pre-screened against study eligibility criteria, including confirmation of prior allergy test (if none, an allergen-specific IgE antibody blood test will be required). Endoscopic assessment will be performed to evaluate anatomic suitability, and photographic and/or video documentation will be obtained if possible.

A member of the site's Research Team will explain the study to the subject and seek the subject's written informed consent. The subject must sign the consent form prior to enrollment. This form must have prior approval of the Institutional Review Board (IRB).

All female subjects of childbearing potential will be asked if they are pregnant at the screening visit. If the subject is pregnant, they will be excluded from participation.

The investigator and/or designee will document the subject's medical information and endoscopic observations on the Screening Case Report Form (CRF), as well as subjective assessment of nasal symptoms using the rTNSS (reflective Total Nasal Symptom Score) described in Section 3.11.3.

At the time of the screening visit, subjects will report any prior and/or ongoing use of any nasal sprays. Subjects will also be instructed not to take nasal anticholinergic sprays (e.g., Atrovent) beginning a minimum of 3 days prior to the procedure and throughout their study participation (See Section 3.12). Subjects may continue to use other nasal medications, but will be instructed not to introduce any new category of nasal sprays into their medication regimen for the duration of their study participation (changes in medication brand are acceptable).

Subjects will be instructed not to take anti-coagulant medications for 2 weeks prior to the procedure, and 2 weeks after the procedure.

3.9. Study Treatment (Visit 2)

The study treatment is described below. Further details can be found in the instructions for use document.

3.9.1. Pre-Procedure Evaluation

The baseline evaluation will take place on the day of the study procedure. All female subjects of childbearing potential will be asked to take a pregnancy test (urine). If the subject is pregnant,

they will not be considered eligible to participate in the study. If a subject becomes pregnant after the study treatment, during the study follow-up period, the subject shall be withdrawn from the study and will not undergo any further testing. The subject will be asked to rate their nasal symptoms using the rTNSS. If the subject does not meet the minimum symptom score requirement (**Table 1**, Inclusion criterion b), the subject will not be considered eligible to participate in the study.

If all the eligibility criteria are met, and the subject has signed the IRB-approved informed consent document, the subject shall be considered enrolled. The investigator and/or designee will document the subject's medical information on the Baseline CRF. Subjects will also complete the quality of life questionnaire (RQLQ) described in Section 3.11.4. Subjects shall then undergo treatment with the study device.

3.9.2. Preparation for Procedure

The subject will be positioned in an upright or partially reclined sitting position. The subject will then undergo appropriate local anesthesia procedure, per physician preference. Baseline images of the intended treatment sites will be collected endoscopically whenever possible.

3.9.3. Cryotherapy Procedure

Video documentation including recording of intra-procedural endoscopic visualization as well as external video documentation of the procedure may be performed. Subject pain/discomfort during each treatment will be assessed using Wong-Baker FACES pain scale (See Section 3.11.2).

Details of use of the ClariFix device are provided in the IFU (Instructions For Use). Use of the device in the nasal passageway for the purpose of this study involves the following:

- a. Prepare the device per the IFU. Insert cryogen canister into handle.
- b. An endoscope will be placed into the nasal cavity to allow visualization of the cryotherapy procedure.
- c. Insert the cryoprobe into the nasal cavity, and advance until the cryoprobe is located at the posterior aspect of the middle turbinate meatus.
- d. Place the cryoprobe against the mucosal surface. Visually inspect that the probe is against the lateral wall and the lower 1/3 of the cryoprobe is laying on the inferior turbinate at the desired location in the treatment zone. Ensure the cryoprobe is in firm contact by gently rotating the device cannula toward the lateral wall (clockwise for the subject's left nasal cavity treatment, counterclockwise for the right).

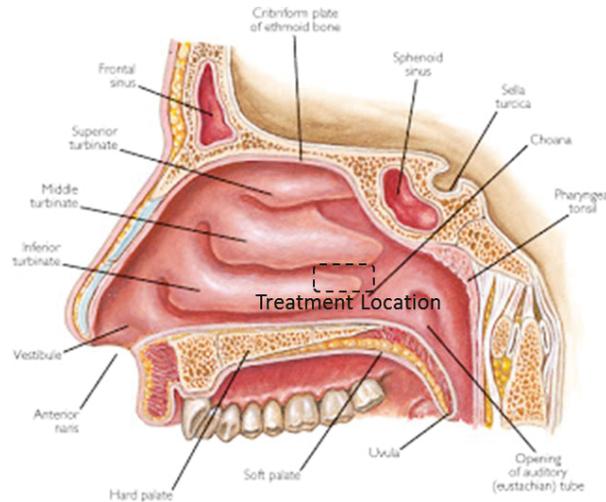


Figure 2. Treatment Location

- e. Obtain photographic and/or video documentation if available.
- f. Activate cryotherapy delivery via the valve on the device handle.
- g. Maintain the device in position for the duration of the cooling cycle (up 1 minute for the 10-ml and 2 minutes for the 21-ml).
- h. Once cooling cycle is complete, allow cryoprobe to thaw and then withdraw the cryoprobe from the nasal cavity.
- i. Evaluate the treatment site with the endoscope and obtain photographic and/or video documentation if possible.
- j. If a second cooling cycle is desired, replace the cryogen canister per the device IFU and repeat steps a to i. Up to two cooling cycles may be performed in each nasal cavity.
- k. Rotate cannula and perform the identical procedure in the contralateral nasal cavity.

In this study, the targeted treatment regimen is:

- Application of cold in each treatment cycle for up to 120 seconds
- Treatment to approximately -20°C at a depth of 3 millimeters and -60 to -80 °C at the surface of the cryoprobe)

The investigator or study coordinator will record treatment data on the Procedure CRF. Additionally, physicians' feedback on device usability and ease of treatment delivery will be recorded at the time of the Procedure Visit.

Note: All subjects should have bilateral treatment. Unilateral treatment will be considered incomplete. Subjects who receive an incomplete treatment will receive all follow up evaluations per protocol.

3.9.4. Post-Procedure

After the procedure, the treatment area will be evaluated endoscopically. The subject will be instructed in post-treatment care. The subject will also be told to report any adverse events to the Investigator.

3.10. Follow-up Procedures

Subjects will be evaluated immediately post-treatment, at 1-day post-treatment by phone, and at 7, 30, 90, 180, 270, and 365 days post-treatment by office visit, (see **Table 2**). In addition, subjects participating in the Extended Follow-up (See Section 3.10.5) will be evaluated at 15, 18, 21 and 24 months post-treatment by office visit or via phone.

3.10.1. 1-Day Phone Evaluation (Visit 3)

A study team member will telephone the subject one (1) day (+2 days) following the procedure visit. The 1-day phone evaluation will consist of assessment of any study-related adverse events.

3.10.2. 7-Day Follow-Up (Visit 4)

Subject will return to the office seven (7) days (\pm days) following the procedure visit.

The subject will be assessed for Adverse Events and Concomitant Medications will be updated.

If deemed necessary by the Investigator, an endoscopic exam may be performed (See Section 3.11.1).

3.10.3. 30- and 90-Day Follow-Ups (Visits 5 & 6)

Subject will return to the office at thirty (30) days (± 7 days) and ninety (90) days (± 14 days) following the procedure visit.

Any adverse events will be documented, and concomitant medications will be reviewed and updated, if applicable. Overall health information will be reviewed and documented, and subject reported nasal symptoms will be recorded.

The investigator will perform an endoscopic assessment of the treatment sites (left and right) will be performed and findings documented (See Section 3.11.1).

At the 90-day office visit, a subject satisfaction questionnaire and a quality of life questionnaire (RQLQ) will be administered.

3.10.4. 180-, 270- and 365-Day Follow-Ups (Visits 7, 8 & 9)

Subject will return to the office at 180 days (± 21 days), 270 days (± 30 days), and 365 days (± 30 days) following the procedure visit.

Any adverse events will be documented, and concomitant medications will be reviewed and updated, if applicable. Overall health information will be reviewed and documented, and subject reported nasal symptoms via rTNSS scale will be recorded.

At the 180-Day office visit, the investigator will perform an endoscopic assessment of the treatment sites (left and right) and findings will be documented.

At the end of the 365-day office visit, the subject will be given the option to continue through the 24-month timepoint. If the subject does not consent to the extended follow-up, the subject's participation in the study will be complete and will be exited.

3.10.5. Extended Follow-Up: 15-, 18-, 21- & 24-Month Follow-Ups (Visits 10, 11, 12, 13)

Subjects who have consented to continue into the Extended Follow-up will complete study visits at the 15-, 18-, 21- and 24-Month (all ± 30 days) timepoints following the procedure visit. The 15-, 18-, 21- and 24-Month Follow-up visits may be complete in-office or via phone.

Any adverse events will be documented, and concomitant medications will be reviewed and updated, if applicable. Overall health information will be reviewed and documented, and subject reported nasal symptoms via rTNSS scale will be recorded.

At the 18- and 24-Month visits, the RQLQ will be administered.

At the completion of the 24-Month visits, study participation will be complete.

3.10.6. Subject Treatment Questionnaire Phone Visit (Visit 14)

The Subject Treatment Questionnaire Phone Visit (See Section 3.11.6) will be conducted via phone for subjects that are both currently enrolled and that have completed the study. The Phone Visit will be completed by independent consultant.

The Visit should be completed within three (3) months of the CIP v2.0 IRB approval. If the Visit cannot be completed in that timeframe, no further efforts will be made to complete the Visit. Non-completion of the Visit will not be deemed a protocol deviation.

The following procedures will be completed:

- Independent Consultant will follow IRB-approved script to explain purpose of the call and obtain verbal consent from the Subject.
- Upon receipt of Subject's verbal consent to participate, consent will be documented.
 - Note: If consent is not given, no further activities to be completed for this visit.
- Subject will be asked questions in the IRB-approved Subject Treatment Questionnaire.

Table 2. Schedule of Assessments

	Procedure Visit (Visit 2)				1 Day (phone interview) (Visit 3) (Range +2 days)	7-Day (office visit) (Visit 4) (Range ±2 days)	30-Day (office visit) (Visit 5) (Range ±7 days)	90-Day (office visit) (Visit 6) (Range ±14 days)	180-, 270-, and 365-Day (office visits) (Visit 7-9) (Range ±21 days)	15-, 21-month (office visit) (Visit 10-11) (Range ±30 days)	18-, 24-month (office visit) (Visit 12-13) (Range ±30 days)	Subject Treatment Questionnaire Phone visit (Visit 14)
	Screening (Visit 1)	Pre-Procedure	Procedure	Post-Procedure								
Eligibility criteria	X											
Baseline medical history	X											
Clinical evaluation	X	X		X		X	X	X	X	X	X	
Endoscopic assessment	X	X		X			X	X				
Study treatment provided			X									
Physician feedback on device usability			X									
Subject feedback on tolerability of procedure (Wong-Baker Pain Scale)			X									
Medication usage recorded	X	X			X	X	X	X	X	X	X	
Adverse events recorded			X	X	X	X	X	X	X	X	X	
Subject assessment of nasal symptoms (rTNSS)	X	X					X	X	X	X	X	
Subject satisfaction questionnaire								X				
Quality of life questionnaire (RQLQ)		X						X			X	
Concomitant Medications Updated	X	X			X	X	X	X	X	X	X	
Subject Treatment Questionnaire												X

3.11. Assessments

3.11.1. Clinical Evaluation

Investigators will conduct a clinical evaluation of study subjects at each study visit and findings will be documented.

Evaluation may be made by patient interview regarding their symptoms.

At the Screening, Procedure (pre- and post- procedure), 30 Day and 90 Day Visits, the evaluation will include physical exam of the treatment area under endoscope. The treatment

area will be assessed for bleeding, crusting, and swelling using a scale of 0 to 3 (0=None, 1=Mild, 2=Moderate, or 3=Severe). When endoscopic assessment is performed, photographic and/or video documentation will be obtained, if possible. An endoscopic exam may be completed beyond the 90-day time point at the discretion of the Investigator in the event of a study-related adverse event.

When possible, at the 180-, 270- and 365-Day and the 18- and 24-Month Follow-up visits, the clinical documentation will include an investigator’s assessment of improvement of symptoms of rhinitis since time of treatment with ClariFix device using a 7-point Likert¹² scale as follows:

- Very Much Improved
- Much Improved
- Minimally Improved
- No Change
- Minimally Worse
- Much Worse
- Very Much Worse

3.11.2. Wong-Baker FACES Pain Scale

Subject reported pain/discomfort at the time of treatment will be assessed using a 0 to 5-point Wong-Baker FACES pain scale¹³ (Figure 3).

Figure 3. 0 to 5-Point Wong-Baker FACES Pain Scale



3.11.3. Reflective Total Nasal Symptom Score (rTNSS)

The primary effectiveness endpoint will be assessed based on the four-symptom reflective Total Nasal Symptom Score^{14, 15} (rTNSS). 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 to 3 and is based on the subject’s evaluation of symptom severity over the preceding 24 hours at study visits. The four-symptom rTNSS has a possible score of 0-12.

Subjects will be asked to assess their symptoms at baseline (Procedure Visit) and at all follow-up points. The subjects will be asked to assess each symptom individually (runny nose, congestion, nasal itching, sneezing) in the following manner:

Please rate how your <symptom> has been over the past 24 hours

0 = None, no sign / no <symptoms> evident

1= Mild, sign/<symptom> present, but minimal awareness, easily tolerated

2= Moderate symptoms, definite awareness of sign/<symptom> that is bothersome but tolerable

3= Severe, (sign/<symptom> that is hard to tolerate, causes interference with activities of daily living and/or sleeping)

Subject may be reminded of baseline score prior to treatment, as appropriate.

3.11.4. Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)

At baseline (pre-procedure) and post-procedure at the of the 90-day, 18 and 24 Month timepoints, the Rhinoconjunctivitis Quality of Life Questionnaire¹⁶ (RQLQ) will be administered. The RQLQ is a validated tool that measures the functional (physical, emotional, and social) problems associated with rhinitis. At baseline, subjects will select 3 activities and shall use the same 3 activities chosen during baseline RQLQ assessment for all subsequent RQLQ assessments.

3.11.5. Subject Satisfaction Questionnaire

A subject satisfaction questionnaire will be administered at the 90-day visit.

In order to evaluate changes in the subjects' usage of rhinitis medications, subjects' medication usage will be assessed at baseline and at each follow-up interval.

3.11.6. Subject Treatment Questionnaire

The Subject Treatment Questionnaire (STQ) is intended to better understand the subject's experience at the time of the treatment visit. The results of the STQ will be reviewed by the Sponsor to help understand the subject's experience.

The STQ will be administered via phone by an independent consultant, to ensure unbiased reporting of the patient experience.

The STQ will include a verbal report of subject's recall of occurrence of pain and/or discomfort, pain numeric rating scale (NRS)¹⁷, severity and duration reporting of pain and/or discomfort. 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".

3.12. Concomitant Medications

Concomitant medication will be documented for all subjects for medication usage within thirty (30) days prior to consent and through duration of study participation. Medication collected should include, but is not limited to, medications taken for:

- any ENT, head and neck, respiratory, and/or airway related conditions or systems (i.e., rhinitis, allergies, asthma, migraines, antibiotic for sinusitis, GERD, etc.);
- medications due to a study-related Adverse Event; and
- any medication, as deemed by the investigator, to present a safety risk (i.e., anticoagulants, beta-blockers, etc.).

Subjects will be instructed to not use nasal anticholinergic sprays (e.g., Atrovent) beginning a minimum of 3 days prior to the procedure and throughout their study participation.

Additionally, subjects will be instructed to not take anti-coagulant medications for 2 weeks prior and 2 weeks following the procedure.

4. Adverse Events

4.1. Adverse Events

All adverse device effects (ADE) or procedure-related adverse events (AE) will be documented, including Unexpected Adverse Device Effects (UADE). Additionally, all Serious Adverse Events (SAE), regardless of device- and/or procedure-relatedness, and all ENT, head and neck, respiratory, and/or airway related AEs will be documented.

Adverse events (AE), as defined above, will be assessed continuously throughout the study. An adverse event is defined as any untoward medical occurrence in a subject, regardless of whether the event is related to the device or is a known risk.

Each Investigator shall be responsible for determination of the causal relationship of all adverse events from his/her investigational site to the device and/or procedure, as well as any pre-existing conditions. Each Investigator is responsible for monitoring the safety of the subjects enrolled. The Sponsor is responsible for the ongoing safety evaluation of the product(s) across all sites. The Sponsor shall determine whether an adverse event is reportable and will promptly notify all participating investigators and regulatory authorities, as appropriate, of findings that could affect adversely the safety of subjects, impact the conduct of the trial or alter the IRB's approval opinion to continue the trial.

4.1.1. Adverse Device Effect (ADE)

Any sign, symptom, or disease in a study subject that occurs during the course of a clinical trial that is determined by the investigator to have a causal relationship or possible causal relationship with the device under investigation.

4.1.2. Unanticipated Adverse Device Effect (UADE)

Any serious adverse effect on health and 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, or

any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

4.1.3. **Serious Adverse Event (SAE)**

Any untoward medical occurrence in a subject, regardless of whether the event is related to the device that:

- a. results in death;
- b. results in a life-threatening illness or injury;
- c. results in a permanent impairment of a body structure or body function;
- d. requires in-patient hospitalization or prolongation of existing hospitalization
- e. results in medical or surgical intervention to prevent permanent impairment to body structure or function;
- f. results in fetal distress, fetal death, or a congenital abnormality/birth defect.

4.1.4. **Reportable Incidents**

Serious adverse events (SAEs) and unanticipated adverse device effects (UADEs) must be reported to the Sponsor within 24 hours of study site's knowledge of the event:

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A full reporting of the event shall be provided within five (5) working days of knowledge of the event. The Sponsor is then responsible for notifying the IRB, as required.

5. **Statistical Analysis**

5.1. **Endpoints**

5.1.1. **Primary Endpoints**

- Safety as assessed by the incidence of procedure- or device-related serious adverse events (SAEs) and unanticipated adverse device effects (UADEs).
- Effectiveness as assessed by the mean change in nasal symptoms using the four-symptom rTNSS (reflective Total Nasal Symptom Score) at 90 days post-treatment.

5.1.2. **Secondary Endpoints**

- Incidence of device or procedure related adverse events

- Impact on quality of life assessed by the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) at 90 days post-treatment

5.1.3. Exploratory Endpoints

- Effectiveness as assessed by the change in nasal symptoms using the four-symptom rTNSS (reflective Total Nasal Symptom Score) from baseline at all other follow-up points
- Treatment response as defined by $\geq 25\%$ and $\geq 50\%$ improvement in rTNSS scores
- Change in individual components of the rTNSS score
- Impact on quality of life assessed by the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) at 18 months and 24 months post-treatment

5.2. Statistical Considerations

5.2.1. Statistical Overview

This trial is a prospective, single-arm, open-label, multi-center clinical evaluation of the safety and effectiveness of the ClariFix™ device when used to ablate unwanted tissue in the nose of subjects with chronic rhinitis. Effectiveness will be evaluated by analyzing the 90-day change from baseline in the 4-symptom rTNSS.

5.2.2. Statement of Hypothesis

The statistical null hypothesis is that the mean 90-day within-subject change is zero; there is no effect of the device on rTNSS.

5.2.3. Analysis Populations

The following subject populations will be created:

Safety (Safety): All subjects enrolled who underwent the device procedure, regardless of outcome.

Efficacy: All subjects enrolled who had at least one follow-up evaluation under this protocol.

Per Protocol (PP): A subset of the Efficacy subjects who underwent the device procedure and do not have major protocol deviations.

5.2.4. General Analytical Considerations

Continuous data will be summarized using descriptive statistics: n, mean, standard deviation, median, minimum and maximum. 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.

5.2.5. Endpoint Analyses

In this single arm, open-label study, the focus of the primary efficacy endpoint analysis is on the magnitude and direction of change over 90 days in the 4-symptom rTNSS. The primary safety endpoint analysis is on the incidence of procedure- or device-related SAEs and UADEs over 90 days post-treatment (however, all AEs will be tracked and reported over the entire duration of the study). The statistical methodology is targeted to employ the paired sample t-test and/or its nonparametric equivalent, the Wilcoxon Signed Rank test. The two-tailed α -level is set at 0.05. No imputation of data will be performed.

All safety analyses will be performed on the Safety Population. All efficacy analyses will be performed on both the Efficacy and PP cohorts, as necessary.

5.2.6. Sample Size Estimation and Assumptions

Assuming a two-tailed α -level of 0.05, and a standard deviation of the within-subject changes from baseline of 2.5, 68 evaluable subjects will yield 90% power to detect a one-point change in the 4-symptom rTNSS. To account for possible dropouts and protocol violations, the enrollment target will be a total sample size of N=100.

5.3. Protocol Adherence

The study investigators are responsible for performing the study in compliance with the protocol. Non-adherence to the protocol will be documented as a protocol deviation. A study site with a large number of violations and/or deviations may be terminated from the study at the Sponsor's discretion.

Protocol deviations that may result in significant additional risk to the subject (e.g., enrollment of a subject who does not meet the study criteria), or non-adherence to Good Clinical Practices (GCP) that may impact patient safety (e.g., failure to obtain proper consent prior to performing study procedures) should be reported to the study Sponsor and the IRB, if applicable, within 5 working days of occurrence.

6. Study Management and Quality Control

6.1. Study Data Collection

Source documentation and Case Report Forms (CRFs) will be provided to all participating sites. CRFs may be completed on paper or via electronic data capture. Data will be reviewed by study staff to identify inconsistent or missing data and to ensure compliance with the study protocol.

Investigators will be responsible for the accurate and timely completion of CRFs during the trial.

6.2. Confidentiality

All information and data concerning study subjects will be considered confidential and handled in compliance with all applicable regulations. Only authorized site staff, the study Sponsor or the Sponsor's designee, IRB, and any relevant regulatory agency will have access to these confidential files. All data used in the analysis, reporting and publication of this clinical trial will be maintained without identifiable reference to the subject. Any data that may be published in abstracts, scientific journals, or presented at medical meetings will reference a unique subject code and will not reveal the subject's identity.

6.3. Safety Data Monitoring

The sites' principal investigators will be responsible for reviewing and adjudicating all adverse events occurring at their sites throughout the course of the study. In addition, an independent medical monitor will assess the safety data at appropriate intervals during the course of the study. Based upon the severity and frequency of adverse events, including any SAEs or UADEs, the medical monitor will determine the continuation or termination of the study based on an evaluation of the risks and benefits of the study.

The study will be terminated if, in the opinion of any of the investigators or the medical monitor, the safety data indicates unacceptable risks to study participants. Unacceptable risk will be identified by the occurrence of adverse events that exceed the anticipated level of severity or frequency.

6.4. Investigator Responsibilities

6.4.1. General Responsibilities

Investigators are responsible for ensuring the investigation is conducted according to all signed agreements, the Protocol, and applicable regulations. The investigator must protect the rights, safety, privacy and welfare of the subjects under the Investigator's care. Investigators will assume overall responsibility and accountability for study site staff and for the clinical data obtained during the study.

6.4.2. Investigator Records

The investigator and study staff must maintain attributable, legible, contemporaneous, original and accurate records relating to the conduct of the investigation. Records must be retained for the period of time defined in the clinical research agreement.

These records must be available and suitable for inspection at any time by Sponsor representatives (monitors), the reviewing IRB, or the relevant regulatory agency. The Investigator will supply access to study-related medical records, original laboratory data, and other records and data as they relate to the trial. The investigator will ensure that both he/she and his/her study staff have adequate time and resources to devote to the study, including study enrollment, subject evaluations, study documentation and site monitoring.

Subject Treatment Questionnaire Visit: Upon completion of the Subject Treatment Questionnaire Visit, the documentation of subject consent and questionnaire source documentation will be transferred to the corresponding site for each subject via a certified shipping method (i.e. FedEx).

6.4.3. Investigator Reports

The investigator is responsible for preparation and submission of the following reports:

- Report of any serious adverse events or unanticipated adverse device effects shall be submitted to the Sponsor within 24 hours of knowledge of the event, and full details of the event will be provided no later than 5 working days after the Investigator first learns of the effect.
- Withdrawal of IRB approval of the investigator's part in the investigation shall be reported to the Sponsor within 5 working days.
- Progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB annually. Alternatively, the Sponsor may prepare the report.
- Protocol deviations and violations shall be reported to the Sponsor
- Failure to obtain informed consent prior to use of a device in a subject shall be reported to the Sponsor and IRB within 5 working days after the use occurs

6.4.4. Device Accountability

The investigator is responsible for maintaining records of receipt, use or disposition of all devices. The Sponsor will maintain records of all shipments and disposition of the study devices.

6.5. Sponsor Responsibilities

6.5.1. General Responsibilities:

The Sponsor assumes overall responsibility for the conduct of the study including assurance that the study satisfies applicable regulatory requirements. Arrinex, Inc. assumes all responsibilities per applicable regulations, and shall:

IRB approval: Ensure IRB approval is secured for the investigation prior to enrolling subjects.

Investigators: Select investigators qualified by training and experience. Providing investigators with the information needed to conduct the study properly. Obtain a signed Investigator Agreement from each participating investigator. Study sites will be evaluated to ensure that they have an adequate subject base and can provide sufficient staff and documentation support to conduct the study properly.

Monitoring: Select monitors qualified by training and experience and ensure proper monitoring of the study.

Data Management and analysis: Ensure data collection, verification, analysis, records storage, etc. Sponsor will assist with presentation(s) and/or publication(s).

Device Provision: The Sponsor will provide all study devices to the site. The Sponsor will deliver study devices only to qualified investigators participating in this trial. The Sponsor will not deliver study devices to any site until evidence of IRB approval has been provided to the Sponsor.

6.5.2. Training

Study Training: To ensure uniform data collection and protocol compliance, Sponsor personnel will provide an educational session to study site personnel as needed, which will cover the Protocol, techniques for the identification of eligible subjects, data collection and form completion, and the device directions for use. The investigator and study staff will be trained on the study device and protocol, applicable regulations and requirements, and expectations of the study, enrollment expectations, subject selection, informed consent, required clinical data and record keeping, etc.

Device Use: Representatives of the Sponsor will train investigators in use of the study device.

6.5.3. Site Monitoring

The Sponsor will ensure that qualified clinical monitors are utilized to monitor and oversee the conduct of the trial and that monitoring is performed in accordance with the Sponsor's approved procedures or third-party procedures approved by the Sponsor, FDA guidance and ICH guidelines.

The clinical monitors will evaluate compliance with the protocol, applicable regulations, any specific recommendations made by the IRB, and the signed Investigator Agreement.

A Clinical Monitoring Plan will be implemented for the study.

6.5.4. Final Report

A final report will be prepared at the conclusion of the trial. Copies of the final report will be provided to each investigator and to the IRB.

6.5.5. Trial Registration

Prior to study initiation, the trial will be registered on Clinicaltrials.gov.

7. Data Ownership

Arrinex, Inc., the study Sponsor, retains ownership of all data generated in this study, and controls the use of the data for purposes of regulatory submissions to the US and/or other governments. Investigator(s) and institution(s) (which shall include their employees, agents, and representatives) may not issue or disseminate any press release or statement, nor initiate any communication of information regarding this study (written or oral) to the communications media or third parties without the prior written consent of Arrinex.

8. Publication Policy

Participating investigators and/or Institutions may publish information or data collected or produced as a result of participation in appropriate scientific conference or journals or other professional publications subject to written permission from Arrinex, provided that drafts of the material are provided to Arrinex for purposes of review and comment at least sixty (60) days prior to the first submission for publication or public release. Investigators may not publish information regarding site-specific data until a multicenter study report has been published.

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