Stryker ENT

ClariFix Rhinitis Randomized Controlled Trial

Investigational Plan Number 4666-001-rB

20 August 2019

Stryker ENT

3600 Holly Lane N, Suite 40

Plymouth, MN 55447

This study will be conducted in accordance with the protocol, Good Clinical Practices, and applicable regulatory requirements.

Investigator Signature Page

ClariFix Rhinitis Randomized Controlled Trial

Protocol #4666-001-rB

20 August 2019

1. I have read this protocol and agree to adhere to its requirements.
2. I understand this protocol, including any amendments or associated documents provided with the protocol, contains information that is confidential and proprietary to the sponsor.
3. I will provide this protocol and all pertinent information to the study personnel under my supervision. My study personnel will keep the protocol and associated documents confidential.
4. I will not start enrollment in the study until it is approved by a governing Institutional Review Board (IRB).
5. I understand that the study may be terminated or enrollment suspended at any time by the sponsor, with or without cause, or by me if it becomes necessary to protect the interests of the study participants.
6. I will provide copies of this protocol and all pertinent information to the authorized IRB to ensure they are fully informed regarding the conduct of this study according to this protocol, applicable regulatory requirements (including 21 CFR parts 50 and 56), and IRB requirements.

Read and acknowledge by signature below:

_____
Clinical Site Name

_____
Site Principal Investigator Printed Name

_____ _____
Site Principal Investigator Signature Date

Study Contact Information

Study Sponsor:

Stryker ENT
3600 Holly Lane N, Suite 40
Plymouth, MN 55447

Study Contact:

Stryker ENT Clinical Affairs
3600 Holly Lane North, Suite 40
Plymouth, MN 55447
Phone: (763) 463-1595
Email: robyn.schacherer@stryker.com

Investigational Plan Summary

Short title:	ClariFix Rhinitis Randomized Controlled Trial
Complete title:	A randomized, controlled, single-blinded study comparing outcomes after treatment with the ClariFix cryotherapy device with outcomes after a sham treatment in patients with chronic rhinitis
Study device:	ClariFix® Cryotherapy device
Study design:	A prospective, multicenter, randomized, sham-controlled, single-blinded study
Enrollment:	A total of 128 research participants randomized 1:1 to active treatment or sham control
Treatment:	1. Active: treatment with the ClariFix® device 2. Control: sham procedure with a ClariFix device minus the cryogen cannister
Clinical centers:	Up to 12 US investigational centers
Inclusion criteria:	Participants MUST: 1. Be ≥21 years of age. 2. Has been diagnosed with chronic nonallergic or allergic rhinitis. 3. Have moderate to severe symptoms of rhinorrhea (individual reflective Total Nasal Symptoms Score [rTNSS] symptom rating of 2 or 3), mild to severe symptoms of nasal congestion (individual rTNSS symptom rating of 1, 2, or 3), and a minimum total rTNSS of 4 (out of 12) at baseline. 4. Have an allergy test (by skin prick or intradermal testing or by validated *in vitro* tests for specific Immunoglobin E [IgE]) on file within 12 months of the baseline visit. 5. Be an appropriate candidate for bilateral ClariFix treatment performed under local anesthesia.

6. Be willing and able to comply with all study elements, as indicated by their written informed consent.

Exclusion criteria:

Participants MUST NOT:

1. Have clinically significant anatomic obstructions that in the investigator's opinion limit access to the posterior nose, including but not limited to severe septal deviation or perforation, nasal polyps, and/or sinonasal tumor.
2. Have had previous sinus or nasal surgery within 6 months of study enrollment.
3. Have previously undergone cryotherapy or other surgical interventions for rhinitis.
4. Have an active nasal or sinus infection.
5. Have rhinitis symptoms that are primarily due to seasonal allergies.
6. Have plans to (or otherwise anticipates the need to) undergo an ENT procedure concurrently or within 3 months after the study procedure.
7. Is on prescribed anticoagulants (eg, warfarin, Plavix) or 325 mg aspirin that cannot be discontinued before the procedure (81 mg aspirin and herbal supplements are acceptable).
8. Be unable to discontinue ipratropium bromide (IB) at least 14 days before baseline and through the 90-day follow-up visit.
9. Have a history of chronic epistaxis or experienced a significant epistaxis event (defined as epistaxis requiring medical intervention) in the past 3 months.
10. Have a history of rhinitis medicamentosa.
11. Have had previous head and/or neck irradiation.
12. Have an allergy or intolerance to local anesthetic agents.
13. Have cryoglobulinemia, paroxysmal cold hemoglobinuria, cold urticaria, Raynaud's disease, and/or open and/or infected wounds at or near the target tissue.
14. Have a neurological, medical, psychiatric condition, or social circumstance that would potentially increase risk, interfere with study participation, or confound interpretation of study data.
15. Be participating in another clinical research study.

Objective:

To demonstrate the superiority of treatment with the ClariFix cryotherapy device compared with a sham procedure in patients with chronic rhinitis.

Primary endpoint:

The percentage of responders at 90 days. Responders are defined as participants with a 30% or greater reduction in rTNSS relative to baseline. The active treatment group will be compared with the sham-control group.

Secondary endpoints:

The following secondary endpoints will compare the active treatment group with the sham-control group at 30-day and 90-day follow-ups:

- The mean change from baseline in rTNSS score.
- The mean change from baseline in Standardized Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ(S)) score.

	• Mean change from baseline in EuroQol 5-dimension survey (EQ-5D-5L) scores. • Percent of patient satisfaction at follow-up. • The rate of serious device- and/or procedure-related adverse events. The following secondary endpoints will be assessed at all follow-ups for all participants who receive active treatment (randomized or crossover): • The percentage of responders • The mean change from baseline in rTNSS score • The mean change from baseline in RQLQ(S) score • Mean change from baseline in EQ-5D-5L scores • Percent of patient satisfaction at follow-up Additional exploratory outcomes will be detailed in the Statistical Analysis Plan.
Study assessments	• Screening • Baseline • Randomization and procedure • 30-Day postprocedure follow-up • 90-Day postprocedure follow-up (unblinding of initial treatment) • 180-Day postprocedure follow-up • 270-Day postprocedure follow-up • 365-Day postprocedure follow-up Additionally, sham-control participants will be offered the option to receive active treatment after the 90-day follow-up. Those choosing to do so who continue to meet the eligibility criteria will then complete all the study assessments starting with the new active procedure. Follow-up visits beyond 90 days are only for participants treated with ClariFix (randomized or crossover).
Sponsor:	Stryker ENT, 3600 Holly Lane N, Suite 40, Plymouth, MN 55447 USA
Data management and monitoring:	Stryker ENT, 3600 Holly Lane N, Suite 40, Plymouth, MN 55447 USA

Abbreviations and Acronyms

AE	Adverse event
CFR	Code of Federal Regulations (US)
CI	Confidence interval
eCRF	Electronic case report form
EDC	Electronic data collection
EQ-5D-5L	EuroQol-5-dimension survey (5 level)
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996 (US)
IB	Ipratropium bromide (Atrovent)
ICF	Informed Consent Form
IFU	Instructions for use
IRB	Institutional Review Board
NOSE	Nasal Obstruction Symptom Evaluation scale
PRO	Patient-reported outcome
RQLQ(S)	Standardized Rhinoconjunctivitis Quality of Life Questionnaire
rTNSS	Reflective Total Nasal Symptoms Score
SAE	Serious adverse event
US	United States of America
VAS	Visual analog scale

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1 Background and Purpose

1.1 Background

Rhinitis is a very common condition throughout the world. In the Unites States (US) alone, it affects 10-30% of the adult general population (30-60 million people). The prevalence has been increasing in recent decades, making it the 5th most common chronic disease in the US. Rhinitis is the inflammation of the nasal mucosa affecting patients with at least 1 of the following symptoms: nasal congestion, rhinorrhea, sneezing, and nasal itching.

The current standard of care to control rhinitis starts with pharmacologic interventions. Over the counter nasal steroids (ie, Flonase, Nasonex) and oral antihistamines (ie, Claritin, Allegra, Zyrtec) are the mainstays of medical management. The disadvantages of these medications are that they require daily use and have limited effectiveness, especially against nonallergic rhinitis. Sedating antihistamines such as Benadryl are used intermittently but the somnolent side effects are not usually well tolerated.

Prescription medications are used when over the counter 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).

Surgical treatments are performed when pharmacological treatments do not provide an adequate response. These treatments include electrocautery, chemocautery, laser cautery, microdebrider turbinoplasty, 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.

A variety of 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 for cryosurgery have included the nasal soft tissue that covers the turbinates and includes nasal nerves. All of the studies have included patient-reported outcomes (PRO) 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. (now part of Stryker ENT) has developed a novel cryotherapy device, the ClariFix 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 at 3 investigational sites in the US to evaluate the performance of the ClariFix device as a cryosurgical tool to treat patients with chronic rhinitis. This study was a prospective, multicenter, single-arm interventional, nonsignificant risk study of the ClariFix device.

A total of 27 participants were enrolled and bilateral treatments were successfully completed with no complications in 100% of participants using injected or topical anesthesia in the office. All participants completed the 30-day follow-up and 24 of the 27 participants (88.9%) completed the 90-day follow up (3 participants were lost-to-follow-up) and participated in the extended follow-up. Nasal symptoms, assessed by the reflective Total Nasal Symptom Scale (rTNSS), were significantly reduced at each follow-up interval compared with baseline. The average rTNSS score was reduced by 58% from 6.2 at baseline to 2.6 at 30 days and the reduction was maintained at 2.7 at 90 days (56% reduction). Extended follow-up showed sustained improvements: average rTNSS of 2.3 at 180 days post treatment. Eighty-one percent (22/27) of participants had at least a 1-point improvement of rTNSS scores at 30 days and 79% (19/24) of participants had improved rTNSS scores at 90 days. The visual analog scale (VAS) scores 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 (SAEs) reported during the study. This pilot study demonstrated that office-based treatment using the ClariFix device was safe, well-tolerated, and effective in reducing nasal symptoms in participants with chronic rhinitis.

1.3 Purpose

This study will build on previous results and is designed to demonstrate the superiority of treatment with the ClariFix cryotherapy device compared with a sham procedure in patients with chronic rhinitis.

2 Protocol

2.1 Study design

This is a prospective, multicenter, randomized, sham-controlled, single-blinded study. Eligible participants will be randomized 1:1 to active treatment or sham-control. Participants will be blinded to their treatment assignment until the 90-day follow-up visit, at which time, the participants will be informed of their treatment and sham-control participants will be offered the opportunity to crossover to active treatment if they still meet the inclusion and exclusion criteria. Active treatment participants and crossover control participants will be followed through 365 days after the procedure.

Figure 1 presents the study design and participant flow.

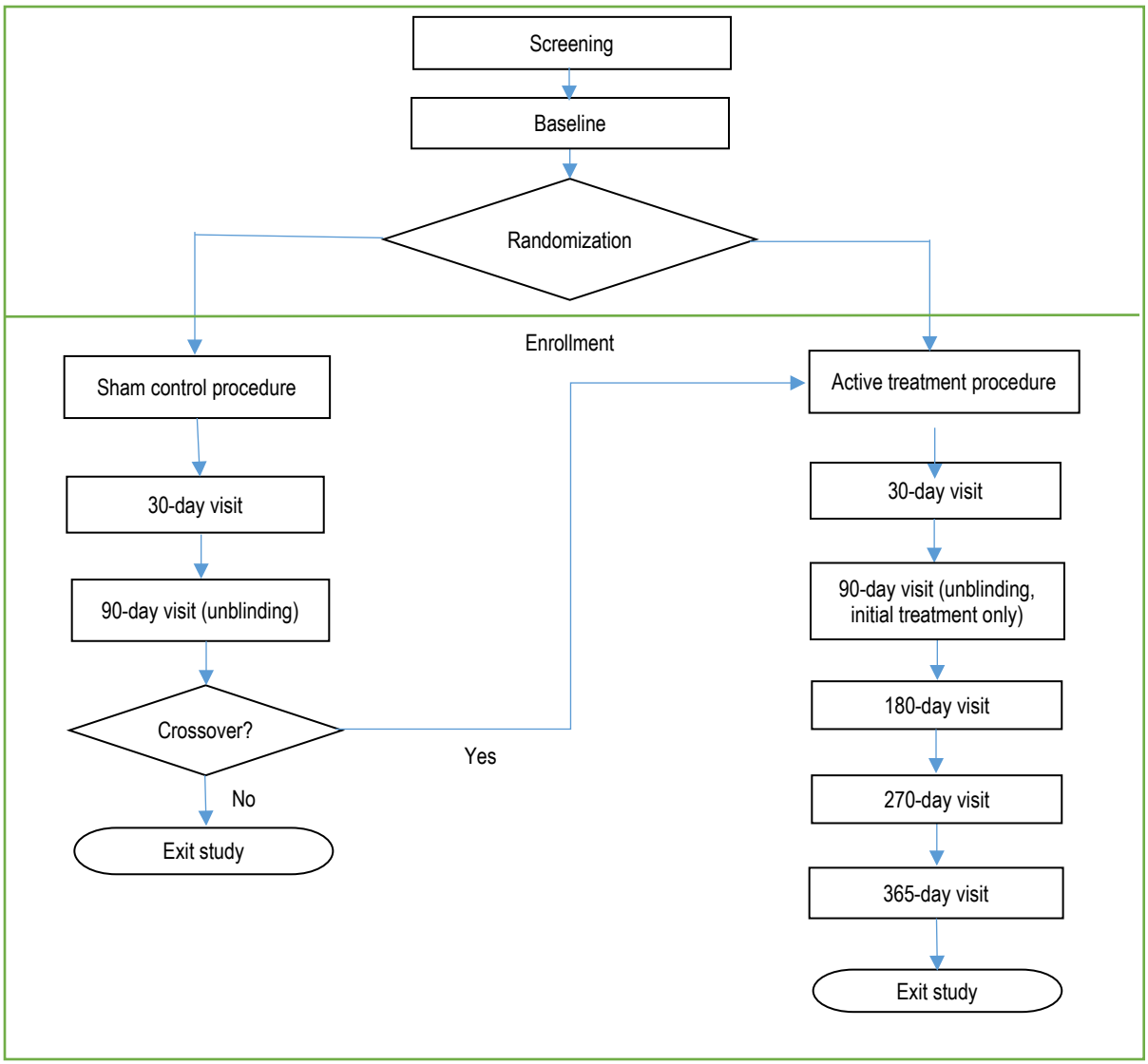

Figure 1. Study Design and Participant Flow

2.2 Study objective

2.2.1 Primary objective

To demonstrate that treatment with the ClariFix cryotherapy device is superior to a sham treatment in patients with chronic rhinitis.

2.2.2 Secondary objectives

- To demonstrate durability of the treatment effect through 365 days of follow-up.
- To support peer-reviewed publications on the ClariFix technology.

2.3 Study endpoints

2.3.1 Primary endpoint

The primary endpoint is the percentage of responders at 90 days. Responders are defined as participants with a 30% or greater reduction in rTNSS relative to baseline. The active treatment group will be compared with the sham-control group.

2.3.2 Secondary endpoints

The following secondary endpoints will compare the active treatment group with the sham-control group at 30-day and 90-day follow-ups:

- Mean change from baseline in rTNSS score
- Mean change from baseline in Standardized Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ(S)) score
- Mean change from baseline in EuroQol 5-dimension survey (EQ-5D-5L) scores
- Percent of patient satisfaction at follow-up
- Rate of serious device- or procedure-related adverse events (SAEs)

The following secondary endpoints will be assessed at all follow-ups for all participants who receive active treatment (randomized or crossover):

- The percentage of responders
- The mean change from baseline in rTNSS score
- The mean change from baseline in RQLQ(S) score
- Mean change from baseline in EQ-5D-5L scores
- Percent of patient satisfaction at follow-up

2.3.3 Exploratory endpoints

Additional exploratory outcomes will be detailed in the Statistical Analysis Plan.

2.4 Study size and duration

The study will be conducted at up to 12 investigational centers in the US.

A sufficient number of participants will be screened and consented to reach a total enrollment of 128 participants. Enrollment in the study is anticipated to take approximately 12 months. Participants are considered enrolled at the time of randomization and procedure.

The expected duration of study participation is 13 months for active treatment participants and 16 months for sham-control participants who chose to crossover to active treatment. There is a maximum of a 30-day screening period for all participants. Postprocedure follow-up for active treatment participants is 365 days (12 months). Sham-control participants who meet the criteria may crossover to active treatment after their 90-day follow-up and then complete the same full 365-day postprocedure follow-up as the active participants. Those sham-control participants who

do not meet the original inclusion/exclusion criteria at the 90-day follow-up or elect not to crossover to the active treatment will be exited from the study after their 90-day follow-up.

2.5 Study hypothesis

The primary endpoint is the percentage of participants in each arm who achieve an improvement ≥30% in total rTNSS score at 90 days compared with baseline. The primary endpoint will be compared between treatment groups for superiority of active to sham treatment by testing the following 1-sided hypotheses using the Z-test of 2 proportions:

H_0: $p_{ClariFix} \leq p_{sham}$

versus

H_A: $p_{ClariFix} > p_{sham}$

where $p_{ClariFix}$ and p_{sham} are the percentages of responders in the active ClariFix and sham groups, respectively.

2.6 Sample size estimation

The sample size was calculated using PASS 16 Power Analysis and Sample Size Software (2018), NCSS, LLC., Kaysville, Utah, USA (ncss.com/software/pass). The sample size was calculated with 90% power and a 2.5% 1-sided type 1 error rate based on the following assumptions:

- 1:1 randomization allocation
- Percent of rTNSS responders in active treatment group = 73.5% (95% CI, 63.6% to 81.9%)
- Percent of rTNSS responders in sham control group = 45%

The active response rate is based on the 90-day response rate in FROST.[12] The sham control group rate is based on the placebo rate reported by Benninger et al for a systematic review of rhinitis pharmaceutical studies.[13] In the drug trials evaluated, they reported mean placebo reponse rates of –15.0% (range –7.6% to –40.0%) at 2-week follow-up for seasonal allergic rhinitis and –24.8% (range –14.4% to –37.2%) at 4- to 6-week follow-up for perennial allergic rhinitis. To ensure adequate sample size, the anticipated placebo rate was slightly overestimated from these values.

Additionally, powering the sample size for subgroup analysis of allergic vs nonallergic participant rTNSS responses was considered. However, data from the FROST study (**Table 1**)[12] indicated that there is no difference in response rates between allergic and nonallergic patients and that the groups are poolable at the 90-day follow-up period, so enrollment by allergy subgroup was not incorporated into the sample size calculation. An assessment of poolability by allergy subgroup will be performed during analysis.

Table 1. FROST 90-Day Total rTNSS Responder Rate by Allergy Subgroups

Group	Improved ≥30%
Allergic	73.3% (22/30)
Nonallergic	73.5% (50/68)

Under the assumptions outlined above, a total sample size of 122 randomized participants (61 per arm) is adequate to test this hypothesis. To account for approximately 5% attrition at 90 days, a total of 128 participants will be enrolled in the study.

2.7 Data analyses

Summary statistics will be calculated for all study endpoints. Categorical variables will be summarized using frequency distributions and continuous variables will be summarized with means and standard deviations (normal distributions) or medians and ranges (non-normal distributions). Confidence intervals (95% CI) may be computed for select study endpoint measures. The primary efficacy endpoint will be tested at a 1-sided alpha level of 0.025 using a Chi-square test. The secondary endpoints will be tested at a 2-sided alpha level of 0.05.

Participants who are randomized but drop out before receiving their randomized treatment (active treatment or sham procedure) will not be considered enrolled in the study. Participants who are unblinded before the 90-day visit due to medical necessity will not be included in the analysis of efficacy endpoints. For long-term follow-up analyses, crossover participants will be analyzed with the active treatment participants.

2.7.1 Missing data

Missing data can impact the integrity and credibility of any clinical study. Therefore, all attempts will be made to minimize missing data. These attempts include training of the investigators and site personnel and discussions with the participants during the informed consent process on the importance of accurate and complete data collection. The study sponsor will track issues with sites regarding missing data through the usual monitoring process.

2.8 Study population

The study population is comprised of adults with chronic rhinitis. To be eligible for enrollment in the study the patients must meet all the inclusion criteria and none of the exclusion criteria.

2.8.1 Inclusion criteria

Study participants MUST meet all of the following criteria:

1. Be ≥21 years of age.
2. Has been diagnosed with chronic nonallergic or allergic rhinitis.
3. Have moderate to severe symptoms of rhinorrhea (individual rTNSS symptom rating of 2 or 3), mild to severe symptoms of nasal congestion (individual rTNSS symptom rating of 1, 2, or 3), and a minimum total rTNSS score of 4 (out of 12) at baseline.
4. Have an allergy test (by skin prick or intradermal testing or by validated *in vitro* tests for specific Immunoglobin E [IgE]) on file within 12 months of the baseline visit.
5. Be an appropriate candidate for bilateral ClariFix treatment performed under local anesthesia.
6. Be willing and able to comply with all study elements, as indicated by their written informed consent.

2.8.2 Exclusion criteria

Study participants MUST NOT meet any of the following criteria:

1. Have clinically significant anatomic obstructions that, in the investigator's opinion, limit access to the posterior nose, including but not limited to severe septal deviation or perforation, nasal polyps, and/or sinonasal tumor.
2. Have had previous sinus or nasal surgery within 6 months of study enrollment.
3. Have previously undergone cryotherapy or other surgical interventions for rhinitis.
4. Have an active nasal or sinus infection.
5. Have rhinitis symptoms that are primarily due to seasonal allergies.
6. Have plans to (or otherwise anticipates the need to) undergo an ENT procedure concurrently or within 3 months after the study procedure.
7. Is on prescribed anticoagulants (eg, warfarin, Plavix) or 325 mg aspirin that cannot be discontinued before the procedure (81 mg aspirin and herbal supplements are acceptable).
8. Be unable to discontinue ipratropium bromide (IB) at least 14 days before baseline and through the 90-day follow-up visit.
9. Have a history of chronic epistaxis or experienced a significant epistaxis event (defined as epistaxis event requiring medical intervention) in the past 3 months.
10. Have a history of rhinitis medicamentosa.
11. Have had previous head and/or neck irradiation.
12. Have an allergy or intolerance to local anesthetic agents.
13. Have cryoglobulinemia, paroxysmal cold hemoglobinuria, cold urticaria, Raynaud's disease, and/or open and/or infected wounds at or near the target tissue.
14. Have a neurological, medical, psychiatric condition, or social circumstance that would potentially increase risk, interfere with study participation, or confound interpretation of study data
15. Be participating in another clinical research study.

2.9 Concomitant medications

Concomitant medications that should be documented at screening and throughout the study include the following:

- Medications taken for rhinitis, allergies, asthma, sinusitis, migraines, and GERD (or any other ENT, head and neck, respiratory, and/or airway related conditions or systems), including saline.
- Medications administered to treat a study-related adverse event.

Additionally, any medication, as deemed by the investigator, to present a potential safety risk at the time of the procedure (eg, beta-blockers) should be noted as a concomitant medication.

2.9.1 Prohibited medications

Any participants taking nasal anticholinergic sprays (eg, IB) will be instructed at screening to discontinue use at least 14 days before the baseline visit and through the 90-day follow-up visit.

Participants will also be instructed not to change their baseline concomitant medications (start/stop or change of dose) before the 90-day study follow-up, unless required to treat an adverse event.

2.10 Methods and procedures

Study methods and procedures are described below. An overview of the required study assessments at each follow-up visit is provided in **Table 2**. Each participant's follow-up schedule is based on the procedure date. Control participants who elect crossover after the 90-day visit will undergo a ClariFix procedure and then continue follow-up through 365 days after the active treatment.

Table 2. Study Assessment Schedule

	Study Visit (window)							
Study evaluation	**Screening (up to 30 days preprocedure)[a]**	**Baseline (up to 7 days preprocedure)[b]**	**Randomization & procedure (day 0)[b,c]**	**30-Day (± 7 days) [c]**	**90-Day (± 14 days) [c]**	**180-Day (± 21 days)[c]**	**270-Day (± 21 days)[c]**	**365-Day (± 21 days)[c]**
Informed consent	✓							
Demographics and medical history	✓							
Clinical evaluation	✓							
Eligibility assessment	✓	✓						
Urine pregnancy test[d]			✓					
Randomize to treatment arm			✓					
Procedure (active or sham)			✓					
Record procedure information			✓					
Blinding questionnaire[e]			✓	✓	✓			
Adverse events			✓	✓	✓	✓	✓	✓
Concomitant medications[f]	✓	✓	✓	✓	✓	✓	✓	✓
Quantitative endoscopic rhinoscopy[g]	✓		✓	✓	✓	✓	✓	✓
rTNSS	✓	✓		✓	✓	✓	✓	✓
RQLQ(S)		✓		✓	✓	✓	✓	✓
EQ-5D-5L		✓		✓	✓	✓	✓	✓
NOSE		✓		✓	✓	✓	✓	✓
Participant satisfaction				✓	✓	✓	✓	✓

[a] The procedure must take place within 30 day of the screening visit.
[b] The participant must discontinue use of IB at least 14 days before the baseline visit. The procedure must be scheduled within 7 days of the baseline visit (it can be the same day as baseline if all criteria are met).
[c] Control participants electing to crossover to active treatment will undergo a ClariFix procedure and then continue follow-up through 365 days after the active treatment.
[d] Urine pregnancy tests are required for all women of childbearing potential before the procedure.
[e] Blinding questionnaire is only completed for the initial randomized treatment procedure (active or control), not for crossover treatments.

Study evaluation	Study Visit (window)							
	Screening (up to 30 days preprocedure)[a]	Baseline (up to 7 days preprocedure)[b]	Randomization & procedure (day 0)[b,c]	30-Day (± 7 days)[c]	90-Day (± 14 days)[c]	180-Day (± 21 days)[c]	270-Day (± 21 days)[c]	365-Day (± 21 days)[c]
[f] Concomitant medications include those taken for rhinitis, allergies, asthma, sinusitis, migraines, and GERD (or any other ENT, head and neck, respiratory, and/or airway related conditions or systems), including saline; and medications taken to treat a study-related adverse event. Additionally, any medications deemed to present a potential safety risk at the time of the procedure (eg, beta-blockers) should be documented.								
[g] Quantitative endoscopic rhinoscopy will consist of an assessment of nasal congestion before administration of decongestant and an assessment to include rhinorrhea and nasal congestion after administration of a decongestant.								

2.10.1 Eligibility assessment

Patients are considered eligible for this study if they meet **all** the inclusion criteria and **none** of the exclusion criteria as defined in **Section 2.8**. The principal investigator or subinvestigator at each investigational center will determine patient eligibility based on the inclusion/exclusion criteria. Participants will be considered enrolled at the time of randomization and procedure.

2.10.2 Screening visit

The initial screening visit can occur up to 30 days before the study procedure.

For individuals who have been prescreened for eligibility, the following procedures/assessments will be performed at the screening visit:

1. Informed consent form signed.
2. Participant completes the rTNSS questionnaire.
3. Record demographics and patient medical and surgical history (with focus on nasopharyngeal, ocular, and respiratory conditions; allergies; and rhinitis history).
4. Record concomitant medications (See **Section 2.9**).
5. Clinical evaluation, including visual inspection of eyes, mouth/throat, and ears to confirm participant's overall health and suitability to undergo the study procedure.
6. Perform a quantitative endoscopic rhinoscopy before administration of nasal decongestant to evaluate nasal congestion.
7. Administer nasal decongestant. If the participant is a woman of childbearing potential, use medical judgement to select a decongestant (eg, oxymetazoline) that is safe to use during pregnancy.
8. Repeat quantitative endoscopic rhinoscopy to evaluate nasal structures, treatment site, and assess degree/extent of rhinorrhea and postdecongestant nasal congestion.

9. Determine if an allergy test conducted within 12 months is available and whether participant's rhinitis is allergic or nonallergic. If an allergy test is not on file, a blood allergy test (IgE level) should be scheduled to take place before the baseline visit.
10. Review of study eligibility criteria.

Patients not meeting the screening criteria will be considered screen failures and are not eligible for participation in the study.

Participants continuing in the study will be scheduled for the baseline visit. For participants using IB, they must discontinue IB usage at least 14 days before the baseline visit.

2.10.3 Baseline visit

The following activities are conducted at the baseline visit:

1. Participant completes questionnaires: rTNSS, RQLQ(S), EQ-5D-5L, and Nasal Obstruction Symptom Evaluation (NOSE).
2. Record concomitant medications (confirm discontinuation of IB for at least 14 days prior, if applicable).
3. Review eligibility criteria; if participant continues to meet eligibility criteria, schedule for randomization and procedure. The study procedure must be scheduled within 7 days of the baseline visit (the procedure can occur on the same day as the baseline visit if all criteria are met).

2.10.4 Randomization and blinding

Randomization assignments will be generated by in independent statisitician using variable block size distribution by site with a 1:1 allocation to active or sham treatment. Randomization will also be stratified by allergy subgroup (allergic, nonallergic). The randomization schedule will be entered into the Medrio electronic data collection (EDC) randomization module. Randomization will occur on the day of the procedure and after all baseline data have been collected and eligibility has been confirmed. All randomized and treated participants will be considered enrolled. Confirmation of randomization assignment from EDC will be printed and filed in the study record.

This is a single-blind study; participants will be blinded to the randomized assignment. To facilitate blinding, control participants will undergo a sham procedure using the ClariFix device without a cryogen cannister. To support blinding, participants will wear blindfolds during the procedure to limit any visual clues that may suggest the treatment assignment. A separate device with a canister held near the participant will be used to provide the sound of the gas release from the cannister. A standardized script for the physician/staff will be used during the procedure to assure blinding. Additionally, local anesthesia regimes will be the same for both treatment groups within each investigational center.

Participants will complete a blinding questionnaire at completion of the procedure and at the 30-day and 90-day follow-up visits to assess the adequacy of the blinding procedures. Upon

completion of their 90-day visit, each participant will be unblinded. Sham control participants will be offered the opportunity to receive active treatment if they wish and still meet eligibility criteria.

Before the 90-day visit, unblinding of participants will only occur when medically necessary. In the event of a device-or procedure-related SAE, the sponsor may authorize the site to unblind the participant in order to adequately assess the event.

2.10.5 Procedure (Active and Sham)

Pregnancy testing

Before the procedure, urine pregnancy tests are required for all women of childbearing potential. In the case of pregnancy, use medical judgement to select appropriate procedural anesthesia medications (eg, low doses of epinephrine and lidocaine) that are safe for use during pregnancy.

Procedure anesthesia

The local anesthesia regimen for the procedure for both active and sham treatments will be performed according to the physician's usual practice. Information regarding the anesthesia regimen will be documented in the study records.

Study procedure

Below is a high-level description of the procedure for both the active and sham procedures. Detailed instructions on the preparation, usage, and storage of the ClariFix device is available in the instructions for use (packaged with the device). To maintain the participant blind during the procedure, the sham devices will be identical to the active devices except the cryogen cannister will not be inserted into the device.

1) Review and update concomitant medications.
2) Perform quantitative endoscopic rhinoscopy before administration of nasal decongestant to evaluate nasal congestion.
3) Administer decongestant. If the participant is a woman of childbearing potential, use medical judgement to select a decongestant (eg, oxymetazoline) that is safe to use during pregnancy.
4) Perform quantitative endoscopic rhinoscopy to assess degree/extent of rhinorrhea and postdecongestant nasal congestion, and plan target treatment placement at the middle meatus.
5) Administer local anesthesia to both sides of the nasal cavity.
6) Have the participant put on the blindfold.
7) Prepare the ClariFix device according to the IFU (for sham treatment, do not insert the cryogen cannister).
8) Place the cryoprobe in firm contact with the targeted middle meatus tissue under visual guidance.

9) For active treatment: initiate the flow of cryogen for a total of 30 seconds and, using endoscopic visualization, ensure the cryoprobe is functioning.
   For sham treatment: turn on the device and leave the cryoprobe in contact with tissue for the 30 seconds, tissue will not freeze with the sham treatment. Use a separate device held near the participant to provide the sound of gas release from the cannister.
   For both treatments, during this time, instruct the participant breathe in and out through their mouth.
10) After the treatment (active or sham) wait at least 60 seconds before removing the cryoprobe to allow the cryoprobe to release from the target tissue (active). **During this time, instruct the participant to breathe in through their mouth and out through their nose.**
11) Remove the device from the target tissue.
12) At the physician's discretion, steps 8 through 11 above may be repeated for a second treatment of up to 30 seconds on the same side.
13) Repeat steps 8 to 12 above for treatment on the contralateral side.

The following data will be collected during the study procedure and documented in the appropriate study records:

- Type of anesthesia, including method of administration, location, and dosage
- Individual freeze (or sham) cycle
- Procedure durations (including time roomed, anesthesia start, procedure start, procedure stop, leaves procedure room/treatment chair, discharge)
- Adverse events
- Active or sham treatment
- Device malfunctions

Postprocedure care

Participant will be monitored at the clinic for a minimum of 30 minutes after the procedure. **During this time, have the participant complete the blinding questionnaire (for initial randomized treatment only – active or control)**.

During the postprocedure waiting period, participants will be asked to rate their postprocedure pain/discomfort on a scale of 0 (no pain/discomfort) to 10 (severe pain/discomfort). Any report of severe pain/discomfort (≥7) during the postprocedure waiting period shall be reported as an adverse event. Anesthesia (eg, lidocaine, marcaine) may be injected at the treatment site to alleviate or minimize participant pain.

Postprocedure nasal saline rinses or sprays may be prescribed, as needed, or in accordance with the physician's standard practice.

Concomitant procedures

Concomitant procedures are not allowed in this study. No additional sinonasal procedures should be scheduled within 3 months after the index procedure.

At the physician's discretion, after the 90-day postprocedure visit, ClariFix retreatment or other surgical interventions for rhinitis may be performed for participants who experience continuing or recurrent symptoms. Such treatments will be documented in the study records. The participants will continue to be followed according to their initial follow-up schedule.

2.10.6 30-Day and 90-day follow-up visits

All randomized and treated participants will attend the following postprocedure study visits (window):

- 30-Day in-office visit (±7 days)
- 90-Day in-office visit (±14 days); all participants will be unblinded to treatment assignment at this visit

The following assessments are required at these follow-up visits (also see **Table 2**):

1. Patient-reported questionnaires: rTNSS, RQLQ(S), EQ-5D-5L, NOSE, and satisfaction
2. Review and update concomitant medications
3. Review and update adverse events
4. Perform quantitative endoscopic rhinoscopy before administration of nasal decongestant to evaluate nasal congestion
5. Administer decongestant and perform quantitative endoscopic rhinoscopy to evaluate treatment site, and assess degree/extent of rhinorrhea and postdecongestant nasal congestion. If the participant is a woman of childbearing potential, use medical judgement to select a decongestant (eg, oxymetazoline) that is safe to use during pregnancy.
6. Blinding questionnaire (only for initial randomized treatment – active or control)

Control participants who elect to undergo crossover to active treatment after their 90-day visit will repeat these visits after the active treatment procedure. All activities for these visits are repeated and documented except for the blinding questionnaire, which is no longer applicable.

2.10.7 180-Day, 270-day, and 365-day follow-up visits

All participants who receive active treatment (as randomized or crossover participants) will continue with the following long-term visits (window):

- 180-Day visit (±21 days)
- 270-Day visit (±21 days)
- 365-Day visit (±21 days)

The following assessments are required at these long-term follow-up visits (also see **Table 2**):

1. Patient-reported questionnaires: rTNSS, RQLQ(S), EQ-5D-5L, NOSE, and satisfaction
2. Review and update concomitant medications
3. Review and update adverse events
4. Perform quantitative endoscopic rhinoscopy before administration of nasal decongestant to evaluate nasal congestion

5. Administer decongestant and perform quantitative endoscopic rhinoscopy to evaluate treatment site, and assess degree/extent of rhinorrhea and postdecongestant nasal congestion. If the participant is a woman of childbearing potential, use medical judgement to select a decongestant (eg, oxymetazoline) that is safe to use during pregnancy.

The study is complete for each participant upon completion of their 365-day follow-up.

2.10.8 Early withdrawal and lost to follow-up

Study participants are free to withdraw from the investigation at any time without having to justify their reasons and without affecting their relationship with the investigator. An investigator may also withdraw a participant from the study at any time if it is determined to be in the participant's best interests.

A participant's future management will not be changed by a decision, voluntary or otherwise, to withdraw from the study. All reasonable efforts should be made to retain participants until completion of the clinical study. Reasons for termination or withdrawal include but are not limited to the following:

- Participant death
- Participant request
- Participant lost to follow-up. A participant is considered "lost to follow-up" after a minimum of 3 documented attempts to reach the participant. The last attempt must be by a traceable method (eg, read-receipt email, certified letter)
- Participant's participation terminated by the investigator
- Study terminated by the sponsor

For any participants with early withdrawal or termination, termination information will be recorded in the participant's records and the date of last contact with the participant noted in the study records.

2.10.9 End of study

Participants randomized to the control arm who do not crossover to active treatment are exited upon completion of their 90-day visit. For all other treated participants, the study is considered complete upon completion of the 365-day postprocedure visit.

If a participant has a ClariFix device inserted into their nose but does not undergo either an active or sham treatment, the participant will be contacted by phone approximately 30 days after the procedure to inquire about adverse events (AEs). If the participant has not experienced any device or procedure-related AEs, they can then be exited from the study. If the participant has an ongoing device or procedure-related AE, they will be followed until AE resolution or 90 days after the procedure, whichever comes first.

Study exit will be documented in the study records when the participant has completed their last required follow-up visit or at the time of withdrawal or lost to follow-up, if the participant discontinues the study prematurely.

2.11 Study assessments and data collection

Study data will be collected according to Good Clinical Practices. Source worksheets will be provided to the investigational sites for collection of study data. Data will be entered into the study database by investigational site staff using the Medrio EDC system. The data will be reviewed by Stryker ENT staff, or designee, and any queries will be submitted to the investigational center for clarification. Patient-reported outcome questionnaires may be entered into the EDC directly by study participants or entered by study staff from paper source documents.

The required study assessments for each specified interval are outlined in the **Sections 2.10.6** and **2.10.7**. See **Table 2** for an overview of the required study assessments at each follow-up visit. Each participant's follow-up schedule is based on the date of their study procedure.

2.11.1 Primary endpoint assessments

Reflective Total Nasal Symptom Score (rTNSS)

The reflective Total Nasal Symptom Score (rTNSS) is a validated patient-reported outcome (PRO) used to describe symptoms of rhinitis.[14] The assessment consists of 4 nasal symptom domains (runny nose [rhinorrhea], itchy nose, sneezing, and stuffiness [nasal congestion]). Each item is rated from 0 (absent) to 3 (severe). The 4 domains are added together to provide an overall score ranging from 0 to 12.

The primary efficacy endpoint is the comparison of active vs sham-control groups for the percent of responders at the 90-day follow-up. A responder is defined as a participant having a 30% or greater reduction in total rTNSS compared with baseline.

2.11.2 Secondary endpoint assessments

Reflective Total Nasal Symptom Score (rTNSS)

The rTNSS will be collected at screening, baseline, and all follow-up visits. The mean change from baseline in the rTNSS for both treatment groups will be evaluated and compared between treatment groups as a secondary endpoint at the 30-day and 90-day follow-up periods. Additionally, the mean change from baseline will be accessed at all follow-ups for all participants who received active treatment (randomized or crossover).

Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ(S))

The RQLQ(S) is a validated PRO that measures functional impairments due to allergic or non-allergic rhinoconjunctivitis.[15,16] The assessment consists of 28 questions related to nose symptoms, eye symptoms, non-eye/nose symptoms, sleep problems, practical problems, activity limitations, and emotional function. Each item is scored from 0 (no impairment) to 6 (severely impaired). An overall score is calculated from the mean of the 28 item responses. Domain scores are the mean of the item scores within that domain. The RQLQ(S) differs from the initial RQLQ in that it standardizes the 3 activities reported for the duration of the study.

The RQLQ(S) will be completed at baseline and all follow-up visits. The mean change from baseline in the RQLQ(S) will be evaluated and compared between treatment groups as a secondary endpoint at the 30-day and 90-day follow-up periods. Additionally, the mean change from baseline will be accessed at all follow-ups for all participants who received active treatment (randomized or crossover).

EuroQOL (EQ-5D-5L)

The EQ-5D-5L is a validated, standardized questionnaire used to evaluate general health-related quality of life.[17,18] The questionnaire consists of 5 health dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a visual analog scale (VAS) to indicate overall health on a scale of 0 to 100. Each health dimension has 5 possible responses: no problems, slight problems, moderate problems, severe problems, or extreme problems. The questionnaire is designed to be self-completed by the participant.

The EQ-5D-5L will be completed at baseline and all follow-up visits. The mean change from baseline in the EQ-5D-5L will be evaluated and compared between treatment groups as a secondary endpoint at the 30-day and 90-day follow-up periods. Additionally, the mean change from baseline will be accessed at all follow-ups for all participants who received active treatment (randomized or crossover).

Satisfaction questionnaire

The satisfaction questionnaire consists of 3 questions that the participant answers at each follow-up visit. The questions indicate whether the participant is satisfied with the procedure outcome, whether the participant would undergo the procedure again for similar results, and whether the participant would recommend the procedure to family or friends with a similar condition. For each item the participant indicates agreement/disagreement with each statement.

Serious device- or procedure-related adverse events (SAEs)

The rate of serious device- or procedure-related adverse events (SAEs) will be compared between treatment groups through the 90-day follow-up visit (**Section 6)**. The parameter of interest is the percent of participants who experience 1 or more device- and/or procedure-related SAEs from the time of the index procedure through the 90-day follow-up.

2.11.3 Additional assessments

Blinding questionnaire

The blinding questionnaire is intended to assess the adequacy of participant blinding. Participants are asked to indicate which study arm (active or sham) they believe they were assigned to, the reasons for their belief, and other questions to assess the overall treatment experience. The blinding questionnaire will be completed immediately post procedure and at follow-up visits through 90 days from the initial randomized treatment only (active or sham).

Nasal Obstruction Symptom Evaluation (NOSE) questionnaire

The NOSE scale is a standardized, validated PRO that evaluates the patient's perception of their ability to breathe through their nose.[19] Patient's rate to 5 items (nasal congestion or stuffiness, nasal blockage or obstruction, trouble breathing through the nose, trouble sleeping, and unable to get enough air through the nose during exercise or exertion) on a scale of 0 (not a problem) to 4 (severe problem). The sum of the items is multiplied by 5 to provide an overall score with a possible range of 0 to 100, with higher scores indicating worse symptoms. This is an exploratory outcome measure.

3 Risk/Benefit Analysis

3.1 Benefits

Participation in this study is voluntary. Participants with rhinitis may experience an improvement in their symptoms.

3.2 Potential risks

Study participants will be informed of all known potential side effects and complications associated with study treatment and study assessments before consenting for the study. The risks associated with participating in the study are the same as those that the participant would have if treated with nasal cryotherapy outside of the study.

While endoscopic rhinoscopy 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
- Increase in nasal congestion
- Intranasal scarring/nasal obstruction
- Sensory alterations (numbness, tingling) in the face/mouth
- Headache
- Dry nose
- Ear blockage
- Septal perforation
- Vasovagal reaction
- Infection
- Dry eyes, optical changes or orbital damage

Also refer to the manufacturer's Instructions for Use (IFU) provided with the device.

There is also a possible risk of a loss of confidentiality. The sponsor will take all reasonable efforts to prevent the release of confidential participant information in accordance with the local and national privacy laws.

3.3 Risk mitigation

The protocol has been developed to minimize the risks for the participant in a number of ways. Sample size was calculated to expose the smallest number of participants while still being able to adequately test the study hypothesis. The procedure will be performed by practicing otolaryngologists experienced in transnasal procedures and trained on the use of the ClariFix device. Investigators are expected to comply with the manufacturer's IFU for the ClariFix device. The participant selection criteria have been designed to minimize risk by excluding patients who have comorbidities or conditions that may put the patient at higher risk for cryotherapy. Specifically, patients with known allergies to local anesthetic agents are excluded from participation in the study. Women of childbearing potential will be required to take a urine pregnancy test before the procedure to allow for appropriate selection of procedure anesthesia medications that are safe to use during pregnancy.Concomitant procedures that could increase risk and confound study results are not permitted during the study. Finally, the participants will be closely monitored by frequent follow-up visits during the study.

4 Device Information

4.1 Investigational device description

The study device is the ClariFix® Cryotherapy device (ClariFix). The device is currently a Class I, 510(k)-cleared, commercially available device for chronic rhinitis. Use in this study is on-label with the cleared indications for use.

The ClariFix device is a handheld, single patient-use, disposable cryosurgical device used for the destruction of tissue during surgical procedures. The device consists of a handle attached to a

cannula with a cryoprobe at the distal end. The ClariFix device is provided sterile to the user. See the IFU packaged with the device for further information.

4.2 Investigational device management

ClariFix devices will be provided to the investigational centers specifically labeled "for study use only". Active and sham devices will be identical. The cryogen cannister will not be inserted in the device for the sham procedures.

The sponsor will monitor use of the study devices by the following activities:

- Shipping or hand-carrying devices only to approved investigators who are participating in the study
- Maintaining records of shipment and distribution of the devices
- Maintaining records of devices used on participants and returned devices

4.3 Device malfunctions

A device malfunction is defined as a failure of a device to meet its performance specifications or otherwise to perform as intended. A malfunction may be a result of any of the following: failure, malfunction, improper or inadequate design, manufacturing, labeling, or user error.

All device malfunctions must be reported to the sponsor. All attempts should be made to return malfunctioning devices to Stryker ENT for evaluation. Contact the clinical monitor for instructions on used device preparation and return procedures.

5 Monitoring Procedures

Stryker ENT personnel or qualified designees will monitor the clinical study in a manner consistent with 21 CFR 812, Subpart C, Responsibilities of Sponsor. Contact information will be provided separately.

5.1 Investigators

The clinical monitors will ensure investigators are selected based on their qualifications and ability to fulfill the investigator responsibilities as outlined in **Section 9.6**.

The Lead Investigator for the study is Dr. Anthony DelSignore of the Icahn School of Medicine, Mount Sinai, New York, NY.

5.2 Investigational center monitoring

A risk-based approach to monitoring of the study will be utilized and outlined in a Clinical Monitoring Plan. Monitoring visits to the investigational centers will be conducted at a frequency sufficient to ensure that all aspects of the current approved protocol and any amendment(s) are followed. Source documents will be reviewed for verification with data in the eCRFs and all regulatory documents will be checked for accuracy including but not limited to IRB approvals,

study-related correspondence, and participant informed consent. The investigator and/or investigational center staff must be available to meet with the sponsor during monitoring visits.

Upon reasonable notice, the investigator and institution agree to provide the sponsor representatives or designees and applicable regulatory authorities with direct access to source documents relevant to the study for sponsor quality assurance audits or inspections by the regulatory authorities.

6 Adverse Event Definitions and Reporting

6.1 Adverse events and serious adverse events

An adverse event (AE) is any undesirable clinical occurrence experienced by the participant during the follow-up period regardless of the event's relationship to either the study device or procedure. An underlying disease that was present at the time of enrollment is not an AE; however, any increase in the severity of an underlying disease is an AE.

A serious adverse event (SAE) is an event that results in any of the following:

- Death
- Life-threatening
- Hospitalization or prolongation of an existing hospitalization
- Invasive surgical intervention to correct or prevent further injury
- Persistent or significant disability or incapacity
- An important medical event

An important medical event that may not meet one of the above definitions might be considered as an SAE if it jeopardizes the health of the participant or requires surgical intervention to prevent one of the outcomes listed in the above definition.

An elective hospitalization/intervention that was planned before the participant enrolled in the study is not considered an SAE as defined above.

6.2 Assessing, recording, and reporting of adverse events

For the purposes of this study, all serious adverse events (regardless of relationship) must be reported. Only nonserious adverse events that are related to the device, procedure, or the participant's ENT condition(s) should be reported. Nonserious adverse events that are not related to the device, procedure, or ENT conditions should not be reported.

An adverse event may be volunteered spontaneously by the participant or discovered by the investigator or study staff upon questioning or physical examination of the participant. The following information should be reported for all reportable adverse events and updated as needed until the event resolves:

- Adverse event (diagnosis associated with the main complaints or symptoms)
- Date the adverse event occurred
- Date the investigator (or staff) became aware of the adverse event

- Adverse event details (main complaints or symptoms)
- Relationship to study device
- Relationship to the study procedure
- Seriousness of the adverse event
- Interventions undertaken
- Status of the adverse event (ongoing, resolved, unresolved but stable, death)
- Date of event resolution, if applicable

Source documents (eg, procedural notes, treatment notes, clinical summary) may be required as supporting documentation for an adverse event.

Any serious device- or procedure-related adverse events should be reported to the sponsor as soon as possible (preferably within 24 hours) after the investigator or clinic staff become aware of the event. Initial report of the event can be by email and/or telephone call to a sponsor representative.

During the study, **all** participant deaths must be reported to the sponsor within **24 hours** of the investigator's (or designated staff's) knowledge of the death. Deaths should be reported as the reason for study exit and the cause of the death should be reported as an adverse event. A copy of death records, medical records for the event(s) that led to the participant's death, death certificate (if available), and an autopsy report (if performed) should be deidentified and sent to the sponsor as soon as they become available for any death deemed related to the device and/or procedure.

7 Protocol Deviations

Investigators are required to adhere to the study protocol, applicable national or local laws and regulations, and any conditions required by the applicable IRB or regulatory authority.

A protocol deviation is used to describe situations in which the protocol was not followed (including all required activities at each scheduled visit or activities occurring outside of the study windows).

An investigator must notify the sponsor and the applicable IRB of any deviation from the study protocol done to protect the life or physical well-being of a participant (medical emergencies). Such notice should be given within 24 hours. The sponsor will determine if the participant affected is eligible to continue in the study.

Deviations identified by the investigational center, the monitor, or other sponsor representative(s) will be documented in the study records for tracking compliance with the protocol. The investigational centers will be required to document actions taken to prevent recurrence of deviations. The sponsor representative may initiate corrective actions based on individual deviations or trending reports, as appropriate.

8 Labeling

An additional sticker will be added to the existing FDA-cleared labeling (package labels) for the ClariFix device to indicate the device is “for study use only”.

9 Administrative Information

9.1 Investigational center selection

The study will be conducted at up to 12 investigational centers in the US. Centers will be evaluated to ensure each center has the capacity and capability to obtain informed consent and comply with all protocol requirements. The investigators and investigational center personnel are required to comply with the principles of Good Clinical Practices (GCP) as described in the FDA regulations.

9.2 Training

The training of investigational center personnel will be the responsibility of the sponsor or sponsor-authorized representatives. All treating physicians must be proficient in the use of endoscopic techniques. All physicians will be trained on the preparation and use of the ClariFix device before participant enrollment in this study.

To ensure uniform data collection and protocol compliance, the sponsor or sponsor-authorized representatives will review all components of the study with the study coordinator(s)/study staff at each investigational center. The review will include the study protocol, techniques for the identification of eligible patients, instructions for data collection during the procedure, schedules for follow-up, and training on the EDC system.

9.3 Informed consent process

Informed consent must be obtained in accordance with US regulation 21 CFR 50. The participants must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the participant is otherwise entitled and also informed that withdrawal from the study will not jeopardize their future medical care. The standard institutional patient consent form does not replace the study informed consent form (ICF).

The sponsor will provide a study-specific ICF template to the central IRB and to each investigational center under jurisdiction of a local IRB. For sites under the jurisdiction of a local IRB, the template may be modified to suit the requirements of the individual investigational center; however, the sponsor must preapprove all changes to the ICF before initial submission to the IRB. The IRB-approved consent form must be sent to and approved by the sponsor before the first device shipment. All investigational centers must retain one copy of the IRB-approved ICF in the study files along with the other investigational forms.

Each enrolled participant must be given a copy of their signed consent form and the original

must be retained in the investigational center study file for that participant. A copy may also be sent to medical records, if required by institutional policy. Informed consent documents must be available for review by the sponsor during monitoring visits.

Modifications to the study-specific ICF and/or any other written information distributed to participants must be preapproved by the sponsor and the IRB, as necessary.

9.4 Confidentiality

All information and data sent to the sponsor concerning participants or their participation in this study will be considered confidential. Participants will be identified by a study-specific identification code. All data used in the analysis and reporting of this investigation will use the study-specific codes and will not include identifiable references to individual participants. Any source documentation must be deidentified by the investigational center before being sent to the sponsor.

The investigator will allow visits by the sponsor representatives and the US FDA inspectors or any other local governmental body to review the study participants' medical records.

9.5 Institutional Review Board (IRB)

It is the investigator's responsibility to obtain and maintain written approval of the final investigational plan and ICF from the applicable IRB. The investigator is responsible for submitting and obtaining initial and continuing review of the study by the IRB. It is also the investigator's responsibility to notify the IRB of any amendments to these documents. Written IRB approval must identify the study by title and version, document the date of review, and be forwarded to the sponsor before the first device shipment.

The investigator must keep all study-related correspondence with the IRB on file and forward copies of such correspondence to the sponsor.

It is anticipated that the central IRB listed below will be used for most, if not all, investigational sites. The sponsor may help facilitate submissions to the central IRB on behalf of the investigators.

Advarra IRB
6940 Columbia Gateway Dr. Suite 110
Columbia, MD 21046

9.6 Investigator responsibilities

The investigator for each investigational center is responsible for ensuring the study is conducted according to:

- All signed agreements
- The study protocol
- IRB guidelines
- Applicable local and federal regulations

The investigator for each center may not begin enrollment until the sponsor has provided written approval to do so. The sponsor will not provide approval until it has received and approved (when necessary) all required documents, including the IRB approvals of the investigational plan and ICF.

It is acceptable for the investigator to delegate 1 or more of the above functions to a subinvestigator or trained study coordinator; however, the investigator remains responsible for the proper conduct of the clinical investigation, including obtaining informed consent, collecting all required data, and submitting accurate and complete eCRFs.

At each investigational center, appropriate procedures must be followed to maintain participant confidentiality according to HIPAA (Health Insurance Portability and Accountability Act) regulations. Each center may have its own internal procedures or requirements for use and release of participant medical information in research studies. Each investigator is responsible for obtaining appropriate approvals, consents, or releases of medical information as dictated by their relevant patient privacy laws.

The study is not transferable to other centers/facilities attended by the investigator unless preapproval is obtained from the applicable IRB and the sponsor.

9.7 Sponsor responsibilities

The sponsor's responsibilities for this study are to:

- Select all clinical investigators, investigational centers and other consultants, including study monitors, who participate in the study
- Provide sufficient training to participating investigational centers to support study activities according to the agreements executed with the centers
- Provide financial support to each center according to the agreements executed with each center
- Follow/promote all regulatory standards according to local/federal regulations for the investigational centers, core laboratories, and other participants, and ensure regular investigational center monitoring to assure compliance with the regulations
- Retain ownership of all clinical data generated in this study and control the use of the data for appropriate purposes only
- Review and approve publication of study results in the literature
- Ensure timely and appropriate study registration in a public clinical trial database (eg, www.clinicaltrials.gov), if applicable

9.8 Criteria for terminating study

The sponsor reserves the right to terminate the study early but intends only to exercise this right for valid scientific or administrative reasons or reasons related to the protection of study participants. Investigators and applicable IRBs will be notified in writing in the event of study termination. Reasons for study termination include but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the study participants
- A decision on the part of the sponsor to suspend or discontinue commercial distribution of the device

9.9 Criteria for terminating an investigational center

The sponsor reserves the right to stop enrollment of participants at a particular investigational center at any time after the study initiation visit for any of the following reasons:

- Repeated failure to complete eCRFs in a timely manner
- Failure to obtain appropriate informed consent
- Failure to report any study participant deaths, SAEs, within the appropriate timeframes (See **Section 6.2**)
- Loss of or unaccounted product inventory
- Repeated protocol deviations
- Lack of study enrollment or study activity

10 Reports and Records

10.1 Records

All records pertaining to the clinical study will be kept for a minimum of 10 years following the date on which the study is terminated or completed. If an investigator wishes to withdraw from the responsibility of maintaining these study records, they may transfer the responsibility to a person at the institution who is willing to accept the responsibility. Such a transfer must be reported to the sponsor not more than 10 days after the transfer occurs. Alternatively, the investigator may transfer the study records to the sponsor after the study is terminated or completed.

10.2 Reporting requirements

Investigators are responsible for the following reporting requirements to the applicable IRB and the sponsor:

- Reporting failure to obtain informed consent before study procedures
- Progress reports
- Deviations due to emergency or participant safety

In addition to this list, individual IRB may add additional reporting requirements. The principal investigator at each investigational center is responsible for ensuring any additional local IRB/EC reporting requirements are met, if applicable.

Investigators are also responsible for the following reporting requirements to the sponsor:

- Withdrawal of IRB/EC approval
- Participant withdrawal

The sponsor will be responsible for reporting any device recalls to the IRBs within 30 days of the request. Additionally, the sponsor will provide a final study report to the Investigators and IRBs within 6 months of the study completion or termination. The sponsor will also be responsible for registration and posting results on www.clinicaltrials.gov.

11 Publications

It is expected that the results of the multicenter study will be submitted for publication. Investigators may not publish site-specific data until the multicenter results have been published. The multicenter study results may be published as early outcomes (procedure through 90 days) and late outcomes. (180 days through 365 days).

Upon publication of the multicenter results, participating Investigators and/or Institutions may submit their site-specific results for publication in appropriate scientific conference or journals or other professional publications as outlined in the study contract/agreement.

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