CLARITY

CLINICAL INVESTIGATIONAL PLAN (CIP)

PROTOCOL #: CIP-0006

NCT05324397

CIP Dated 12-Apr-2022

CLARITY

CLINICAL INVESTIGATIONAL PLAN (CIP)

PROTOCOL #: CIP-0006

Safety and Efficacy Study of the Neurent Medical NEUROMARK™ System in Subjects with Chronic Rhinitis

A prospective, single-arm, multicenter clinical study

CLARITY Study

Clinical Investigational Plan #: CIP-0006.C / Version: 12APR2022

Sponsor:	Neurent Medical, Ltd. No. 1 Oran Point, Main Street, Oranmore, Galway, Ireland
Investigator(s):	See Master Contact List
Investigational Site(s):	See Master Contact List

PROTOCOL APPROVAL

Approved by (print name): Karen Peterson Title: VP Clinical, Regulatory & Quality

Signature: DocuSigned by: Karen Peterson
Signer Name: Karen Peterson
Signing Reason: I approve this document
Signing Time: 15-Apr-2022 | 11:49:36 AM PDT
5141B3248C2741C2B6BC44A65B5CCE72

Date: 15-Apr-2022

CLARITY Study Investigator Signature Page

Safety and Efficacy Study of the Neurent Medical NEUROMARK™ System in Subjects with Chronic Rhinitis

CLARITY Study

Protocol # / Version Date: CIP-0006.C / 12APR2022

Investigator Attestation of Receipt and Understanding

I, the undersigned, certify that I have reviewed and understand the contents of the Clinical Investigational Plan (CIP) and further agree to abide by the terms described herein. I am in receipt of and understand the contents of the below-listed items, plus all other elements included as part of this CIP.

- Study Protocol
- Investigator Brochure (IB)
- Instructions for Use (IFU)
- Investigator Agreement
- Clinical Trial Agreement
- Case Report Form (CRF)

In addition, I agree to follow FDA abbreviated requirements for NSR, the ethical principles according to the Declaration of Helsinki and The Belmont Report, ISO 14155, Good Clinical Practice (GCP) guidelines as applicable (E6) Consolidated Guidance (R2) and any conditions imposed by the reviewing IRB, national regulations, or other regulatory agency.

Agreed to by (print name): _____

Signature: _____ **Date:** _____

TABLE OF CONTENTS

APPENDICES

1 PROTOCOL SYNOPSIS

Study Title:	Safety and Efficacy Study of the Neurent Medical NEUROMARK™ System in Subjects with Chronic Rhinitis
Short Title:	CLARITY Study
Study Device:	Neurent Medical's NEUROMARK™ System
Device Description:	The NEUROMARK™ System is comprised of two (2) key devices; (1) a hand-held device designed to deliver Radio Frequency (RF) energy to soft tissue in otorhinolaryngological [also known as Ear, Nose and Throat (ENT)] procedures designed to interrupt nasal nerves aimed to reduce symptoms related to Chronic Rhinitis and (2) an algorithmically controlled low power radiofrequency Console (RFG) for delivery of RF energy to the device. Refer to the Investigator's Brochure, provided as **Appendix A**, for additional details.
Study Objective:	The primary objective of this study is to evaluate the safety and efficacy of the Neurent Medical NEUROMARK™ System in patients that suffer from Chronic Rhinitis.
Study Design:	A prospective, single-arm, multicenter clinical Study to evaluate the safety and efficacy of the NEUROMARK™ System in patients with Chronic Rhinitis.
Study Size:	This study aims to evaluate a total of thirty-six (36) study subjects at up to four (4) study centers. All subjects who meet the inclusion and exclusion criteria will receive treatment. It is anticipated that approximately 15 subjects will be enrolled at each site. There is no enrollment maximum per site; however, no investigator may enroll more than 50% of the study population.
Subject Population:	Male and female patients in good general health who experience chronic rhinitis will undergo an initial screening. Those who provide written informed consent and meet eligibility criteria will be considered for enrollment.
Study Procedure:	Subjects that provide informed consent and meet study eligibility requirements will receive undergo treatment. Subjects will have the NEUROMARK™ System applied to both nostrils during a single session. The study procedure will be performed following the NEUROMARK™ System Instructions for Use (IFU), **Appendix B**.

Study Visits:

All subjects will be evaluated at baseline, during treatment, immediately post-treatment, and at 24-48 hours, 1- month, 3- months, 6-months, 9-months and 1-year post treatment.

Refer to Table 1 for an overview of tests, procedures and other activities the subject will undergo as part of this clinical study.

Study Endpoints:

Safety will be evaluated based on frequency of Serious Adverse Events (SAEs) directly attributable to the NEUROMARK™ System at one (1) month post index procedure.

Efficacy will be assessed by the change in Visual Analog Scale (VAS) Nasal Symptom Score (NSS) from baseline through 3 months for rhinorrhea and nasal congestion.

Additional Evaluations:

Additional information, as listed below, will be collected and the resulting data analyzed and reported for each follow-up, as applicable.

- A change in the VAS NSS from baseline.
- A change in reflective Total Nasal Symptom Score (rTNSS) from baseline for rhinorrhea.
- A change in rTNSS from baseline for nasal congestion.
- A change in rTNSS from baseline.
- A change in Postnasal Drip (PND) from baseline.
- A change in Quality of Life (mini-Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) from baseline.
- Procedure tolerability (e.g., discomfort, length of procedure)
- Individual symptoms (e.g., post-nasal drip, nasal itching, sneezing)
- Responder rates.
- Patient satisfaction (e.g., patient reported symptom relief)
- Endoscopic assessment.
- Post-procedure discomfort (e.g., headache, facial pain, ear pain/blockage).
- All adverse events regardless of severity or relatedness.

All subjects who undergo treatment will be followed to 1 year for informational purposes and any study related findings will be reported.

Anticipated Duration:

The study is anticipated to begin enrollment in Q1 of 2022 with enrollment complete in Q2 of 2022. The last patient visit is expected to take place by or during Q2 of 2023.

Study Evaluations: **Table 1** provides an overview of all protocol-related activities the Subject can expect to undergo as part of study participation.

Indications for Use The NEUROMARK™ System is indicated for use in otorhinolaryngology (ENT) surgery for creation of radiofrequency (RF) lesions to disrupt posterior nasal nerves in patients with chronic rhinitis.

Intended Use: The NEUROMARK™ System is intended for the application of Radiofrequency energy to create lesions in mucosal tissue in otolaryngological [also known as Ear, Nose and Throat (ENT)] procedures in patients with chronic rhinitis.

Screening Considerations:

- If data are available at baseline and the information collected per protocol, the existing data may be used to support patient screening. The test/assessment may not need to be redone.
- If Subject is ill or experiencing an exacerbation of symptoms due to illness, the protocol required assessment or follow up visit may be postponed without a protocol deviation. If this occurs, the illness and reason for postponement must be documented in the Subject's study records.
- If a study subject has been exposed to COVID-19 requiring quarantine or isolation or has traveled to a location(s) that may require quarantine, the follow up will be performed outside of the allowable window and the reason documented. This will not be considered a protocol deviation.

Table 1: Study Related Tests, Procedures and Activities ***X = Require O = Optional***

	Screening	Immediately Pre-treatment	Procedure	Immediately Post-Treatment	24– 48 Hour (phone or in-clinic)	1-Month (±7 days)	3-Month (± 14 days)	6- Month Follow-up (± 14 days)	9-Month Follow-up (± 14 days)	1 Year Follow-up (± 14 days)
Informed Consent	X									
History & Demographics	X									
Inclusion/Exclusion Criteria	X									
Pregnancy Test (if	X									
Physical Exam (including Blood Pressure)	X	X								
Computed Tomography (CT) Scan[1,2]	X									
Evaluation of Nasal Cavity by Endoscopic	X	X				X	X			
NEUROMARK Treatment		X								
VAS NSS	X					X	X	X	X	X
rTNSS	X					X	X	X	X	X
Mini-RQLQ	X					X	X	X	X	X
COVID-19 Test for Active Infection [5]	X	O				O	O	O	O	O
Evaluation of Procedure and Anesthesia Tolerability				X	X					
Patient Satisfaction						X	X	X	X	X
Concomitant Medications	X	X			X	X	X	X	X	X
Evaluation of Adverse				X	X	X	X	X	X	X
Study Exit										X

1 *CT scans will be collected should a subject undergo evaluation for sinusitis during the follow up phase. CT scan at baseline is to rule out sinusitis. An existing CT scan may be used for the baseline assessment so long as it was performed within 6 months prior to treatment, and the subject's symptoms have remained stable. It is of note that subjects with sinusitis at baseline are excluded.*

2 *A Lund-Mackay Score should be assigned to each of the 12 sinuses. The sum of all scores is the Lund-Mackay Score.*

3 *A Lund-Kennedy score should be assigned to each nostril.*

4 *Should endoscopy be performed during active screening or at any time during the follow up phase, a recording will be provided to the sponsor.*

5 *A COVID-19 test for active infection is required prior to treatment. The COVID-19 test for active infection will also be performed if the Subject is suspected to be symptomatic for COVID-19 at any point during the study. This requirement is based upon availability of test units assuming there is not a shortage of test units. Should there be a shortage, subjects will be managed for their symptoms per current policy and the suspected infection documented and recorded in their study records.*

1.1 Eligibility Criteria (Inclusion and Exclusion Criteria)

Subjects considered for enrollment must demonstrate eligibility as outlined in the Study Eligibility Criteria Table (**Table 2)** through a review of the Subject's documented medical history and protocol-driven tests and procedures as outlined in **Table 1.**

Documented evidence of eligibility is required and must be housed with the Subject's study records.

Per the standard definition of rhinitis and for the purposes of this study, Subjects are enrolled if they are experiencing long term chronic rhinitis. Subjects must be experiencing symptoms of rhinitis for at least 6 months to be considered for enrollment defined as:

- Rhinorrhea, anterior runny nose
- AND
- Congestion, blockage (stuffy nose, obstruction)

Table 2: Study Eligibility Criteria

ID:	INCLUSION CRITERIA – Subject must meet all of the following to be enrolled.
I-A	Subject provides written informed consent, including authorization to release health information.
I-B	Subject is 18 years of age or older at the time of consent.
I-C	Subject has provided a negative pregnancy test (if Subject is a woman of childbearing potential (WOCBP).
I-D	Subject WOCBP must be practicing and willing to continue an effective method of birth control during the course of the study.
I-E	Confirmation of moderate to severe symptoms of rhinorrhea. (VAS NSS score for runny nose ≥ 5.0 and rTNSS score for runny nose ≥ 2)
I-F	Confirmation of mild to severe symptoms of nasal congestion. (VAS NSS score ≥ 2.5 for stuffy nose (congestion) and rTNSS score of ≥ 1)
I-G	Confirmation that the total combined VAS NSS score is ≥ 10 for nasal congestion and runny nose.
I-H	Subjects stated willingness to comply with all study procedures, post- treatment care and availability for the duration of the study follow up of 1 year.
I-I	Subject tests negative for active COVID-19 at the start of study screening and continues to be free from COVID-19 symptoms until the time of enrollment/treatment.
I-J	Subject understands and agrees to follow local COVID-19 restrictions (social distancing, face mask, etc.)
I-K	Nasal anatomy appropriate to receive the NEUROMARK™ System.
I-L	Subject is experiencing long term chronic rhinitis. Subject has been experiencing symptoms of rhinitis for at least 6 months prior to enrollment, defined as: rhinorrhea, anterior runny nose AND congestion, blockage (stuffy nose, obstruction).
ID:	EXCLUSION CRITERIA – Subject meeting any of the following to be excluded.
E-A	Subject has clinically significant anatomic obstruction that limits access to the posterior nose as determined by the Study Investigator such as severe septal deviation, prior surgical considerations, cleft palate, nasal polyps, or sino-nasal tumor.
E-B	Subject has an active nasal or sinus infection at the time of treatment.

E-C	Subject has a diagnosis of Atrophic Rhinitis.
E-D	Subject has a Lund-Mackay score >3 during the screening phase, an active history of chronic sinusitis (within the last year).
E-E	Subject has a septal perforation or nasal mucosal erosion/ulceration.
E-F	Subject experiences numbness of the soft palate, excessive dry eye, excessive dry nose, or other indication of neuro/nerve compromise in the sino-nasal anatomy.
E-G	Subject has had prior sinus or nasal surgery that may prevent access or proper placement of the NEUROMARK™ System.
E-H	Subject has had prior head or neck irradiation (head/neck cancer therapy).
E-I	Subject has an allergy or intolerance to anaesthetic agent or other study-required materials.
E-J	Subject is taking anticoagulant medication or 325 mg aspirin that cannot be discontinued before the procedure and for the length of the study.
E-K	Subject has a history of nasal manifestation of rheumatic disease.
E-L	Subject has started a new sino-nasal medication regimen within 4 weeks prior to treatment (i.e. antihistamines, cromolyn, leukotriene receptor antagonists, inhaled or systemic steroids, anticholinergics, expectorants, decongestants) that, per the manufacturer's labelling, has not yet stabilized.
E-M	Subject has uncontrolled Hypothyroidism.
E-N	Subject has uncontrolled Hypertension (stage 2 or higher).
E-O	Subject is an active smoker or has been a smoker within the last 6 months (patient reported).
E-P	Any physical condition that in the Investigator's opinion would prevent adequate study participation or pose increased risk to the study Subject.
E-Q	Subject is pregnant, nursing or plans to become pregnant during the study, or is a WOCBP, but is not willing to use an effective method of birth control.
E-R	Patient is enrolled in an investigational drug or device study or has participated in such a study within the last 30 days prior to screening that in the opinion of the Investigator would interfere with the study results
E-S	Patient presents with any condition or situation which, in the Investigator's opinion, puts the Subject at risk, could confound the study results, or may interfere significantly with the Subject's participation in the study.
E-T	Subject presents with acute sinusitis at time of treatment or other sino-nasal related illness other than rhinitis.
E-U	Subject has history of chronic epistaxis or nosebleed episodes within the last 12 months
E-V	Subject has rhinitis symptoms due to seasonal allergies only.
E-W	Subject has received previous procedure or surgery for chronic rhinitis and/or to disrupt the posterior nasal nerve

2 INTRODUCTION AND BACKGROUND

The NEUROMARK™ System has been developed by Neurent Medical for the treatment of chronic rhinitis through the application of radio frequency (RF) current to disrupt the parasympathetic nerve supply to the nasal cavity. The device consists of a handheld therapeutic device which will be introduced into the nasal cavity under local anesthetic to access the treatment area. In clinical use, the device will be connected to a RF Console which will provide controlled delivery of energy to the treatment tip.

2.1 Clinical Background

Rhinitis refers to inflammation of nasal mucosa, the tissue that lines the nasal cavity. This inflammation can cause nasal congestion, nasal discharge (rhinorrhea), sneezing, postnasal drainage, and numerous other symptoms adversely affecting quality of life.

There are two types of Rhinitis, Allergic Rhinitis (AR) and Nonallergic Rhinitis (NAR). AR is triggered by an allergen, such as pollen or dust. The cause for NAR is not always known, however some common causes are viral infections such as a cold or flu, or environmental irritants such as smoke or chemical fumes. Rhinitis is reported to affect 30% of the population, 21% suffering from AR and 7% from NAR. It is the most common chronic disease in children and also the fifth most common chronic disease in the United States (US) overall.

Inferior turbinate hypertrophy is the main anatomic cause of nasal obstruction and rhinitis is the main non-infectious cause of turbinate hypertrophy. Nasal turbinates are structures located within the nasal cavity (Figure 1). They are made of bone and are covered by soft tissue (mucosa). Their function is to regulate airflow and humidify the air you breathe in through your nasal passages. In patients with Rhinitis, these turbinates swell, leading to nasal congestion and secretion (**Figure 2**).

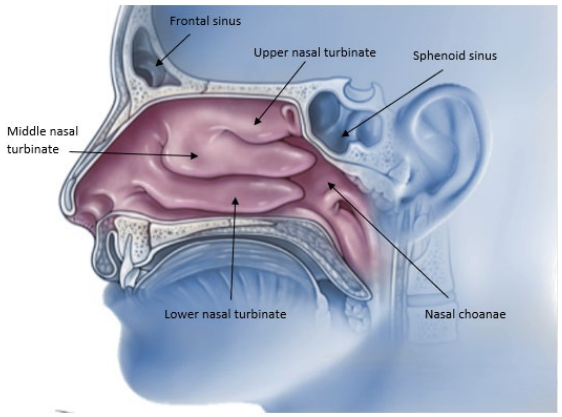

Figure 1: Nasal cavity

Treatment options for Rhinitis include medications such as systemic or topical antihistamines, topical corticosteroids, decongestants, anticholinergics, mast cell stabilizers, leukotriene receptor antagonists, and nasal saline. Rhinitis can also be treated with immunotherapy, commonly referred to as the allergy shot. Allergen avoidance can also help to prevent Rhinitis.

In more severe cases, where allergen avoidance, medication, or immunotherapy failed, or are not an option, Rhinitis may be treated surgically by inferior turbinate reduction. This is a surgery in which the turbinate size is permanently reduced. There are two

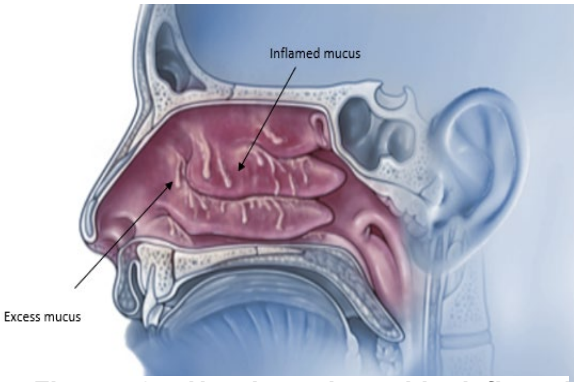

Figure 2: Nasal cavity with inflamed turbinates

modern surgical options: the delivery of thermal energy to the inflamed soft tissue, resulting in the temporary volumetric reduction of the tissue to improve nasal airflow; and microdebrider resection of the inflamed soft tissue, which has a higher degree of efficacy however requires general anesthetic and is associated with a higher degree of complications.

Research has shown of another potentially effective surgical technique, posterior nasal neurectomy. Vidian neurectomy surgical procedure is a base of skull procedure that severs neural pathways to the eye, mouth and the nose. It is an imbalance in this neural pathway that initiates the inflammatory cascade in effected rhinitis patients and is responsible for mucus production and submucosal engorgement that routinely manifest as congestion and rhinorrhea. A number of published studies have concluded that vidian neurectomy procedures show significant improvement on patient outcomes reported over traditional turbinate surgical interventions at a three-year time point which, in turn, have as significant an improvement over those treated with medical therapy.

2.2 Neurent Medical's Solution

Neurent Medical has developed a novel device-based therapy to treat Rhinitis that leverages the well-published efficacy and durability of vidian neurectomy surgical procedures. The Neurent Medical device aims to treat Rhinitis through localized application of radiofrequency (RF) thermal energy in the nasal cavity to disrupt the parasympathetic nerve supply. Using this method, Neurent Medical envisages that the efficacy of vidian neurectomy can be achieved in an office setting without the associated side effects caused by the transection of the ocular as well as the nasal parasympathetic nerves during a vidian neurectomy procedure. The design of the Neurent Medical device is described in **Section 3**.

3 DEVICE DESCRIPTION

Neurent Medical has received regulatory clearance for the NEUROMARK™ System in the USA under an FDA Class II device designation. The NEUROMARK System used in this clinical investigation is identical to the NEUROMARK System cleared by FDA. The NEUROMARK™ System comprises 2 key elements which are described in this section:

1. The NEUROMARK™ device and
2. The NEUROMARK™ RF Console

3.1 NEUROMARK™ Device

The NEUROMARK™ device comprises a handle, shaft and treatment tip. The treatment tip, which is referred to as the end effector (EE), consists of an array of micro electrodes. These electrodes deliver bipolar RF energy whilst monitoring and providing feedback on the tissue bio-impedance changes to tailor the optimal RF energy level delivery. The shaft of the device is pre-shaped for optimal access and delivery to the nasal cavity. The outer sheath of the shaft constrains and protects the EE during delivery. The NEUROMARK™ device is operated via an ergonomically designed handle, slider and activation button. Once in position within the nasal cavity, the operator engages and moves the slider proximally which retracts the outer sheath, thus deploying the EE.

The NEUROMARK™ device **(Figure 3)** is connected, via a flexible cable, to the NEUROMARK™ RF Console **(Section 3.2).**

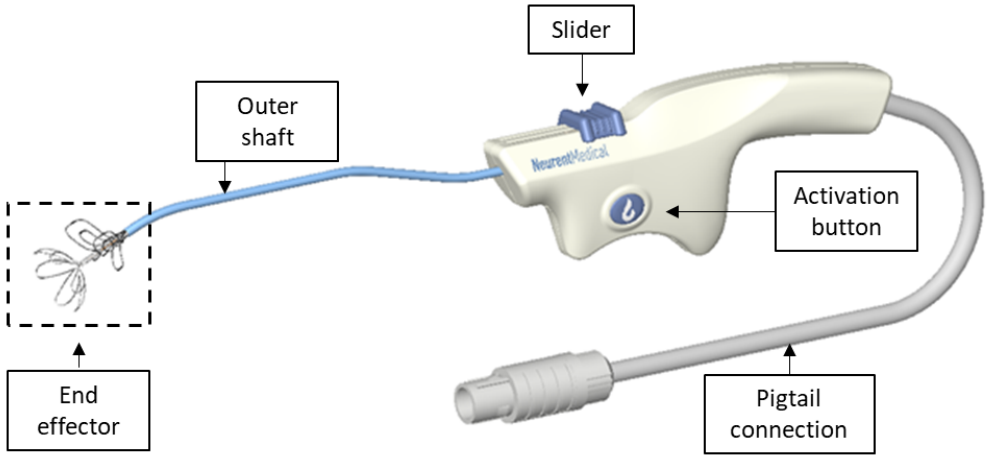

Figure 3: NEUROMARK™ Device

3.2 NEUROMARK™ RF Console

The NEUROMARK™ Console delivers, monitors and controls RF energy to the device.

The NEUROMARK™ Console algorithm ensures a controlled delivery of RF energy to the EE. The NEUROMARK™ System monitors the tissue properties during the procedure and the algorithm controls the location of the energy delivery, the power delivered and the duration of energy delivery. In doing so, the algorithm will direct energy to the EE electrodes that require energy while restricting energy delivery to EE electrodes that have reached the desired endpoint state change, thus minimizing collateral damage. The algorithm is designed to deliver and control power to the device EE in a specific manner to create micro lesions that penetrate the mucosal tissue to disrupt the nerves.

The Console is mounted on an ergonomic mobile stand for ease of use. The Graphical User Interface (GUI) (**Figure 4**), the interface between the device and the user, is designed to ensure simplicity and control during procedure. The GUI will provide operational instructions for the procedure; directs user to select which nasal cavity to treat, indicates when the device is primed to start treatment, provides status of therapy and indicates when the procedure is complete.

Figure 4: RF Console/Graphical Operator Interface

3.3 Device Operation

The device will be connected to the Console via a flexible electrical cable. The patient will sit in the surgery chair and local anesthetic is administered. The device is inserted into the nasal cavity under endoscopic guidance. For this part of the procedure, the end effector is constrained with only the shaft of the device tracking to the target position (**Figure 5**).

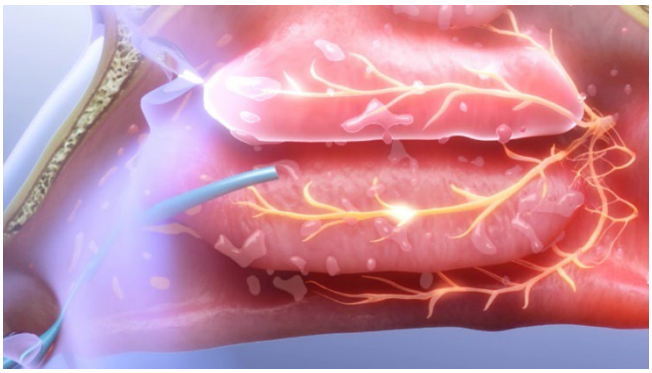

Figure 5: Introduction of the device into the nasal cavity - the end effector is not yet deployed.

Under endoscopic guidance, the physician will advance the device towards the posterior superior/inferior region of the nasal cavity. The visual shaft markings on the top and bottom of device shaft are aligned to ensure superior orientation within the nasal cavity during delivery. The physician will align the inter stage marker on the shaft at the lateral attachment of the middle turbinate thus ensuring that the device is correctly positioned prior to initiating deployment of the end effector (see **Figure 6**)

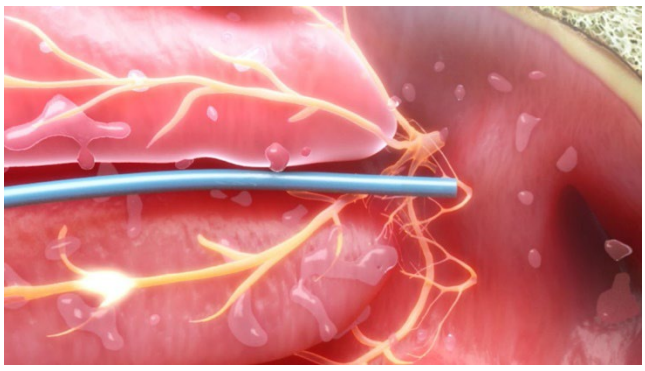

Figure 6: Device positioned in the correct target position prior to deployment of the end effector

Once in position, with the surgical landmark of the lateral attachment of the middle turbinate, the physician will move the slider proximally on the handle to the deployed position, thereby deploying the end effector in the nasal cavity (Figure 7: Device in position with end effector deployed. **Figure 7**).

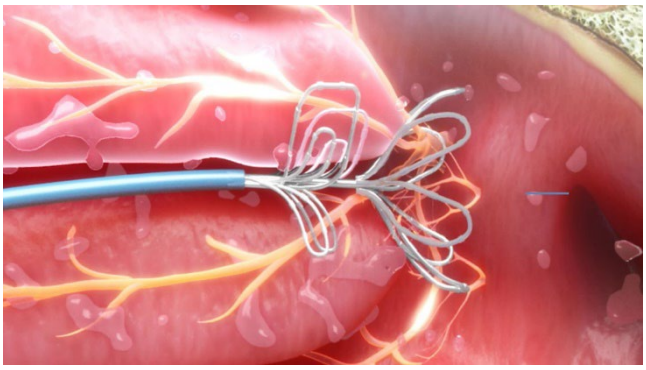

Figure 7: Device in position with end effector deployed.

Once the end effector is deployed, and positioning within the cavity is correct, the electrical activation button on the device handle is pressed to assess the tissue bio-impedance. This impedance check provides confirmation of apposition of the electrodes against the lateral wall.

Upon completion of the impedance check, the NEUROMARK™ Console GUI will confirm to the user that they can initiate treatment. To deliver the therapy, the NEUROMARK™ device is activated by pressing down and holding the activation switch on the handle for 2 seconds. Radiofrequency energy will be delivered through the electrodes to create micro-lesions (**Figure 8**).

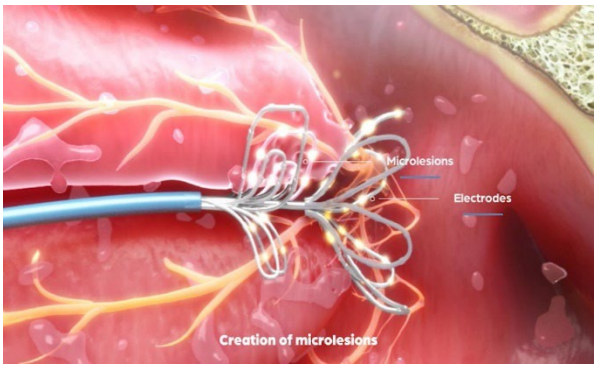

Figure 8: Energy delivery and lesion creation

Energy delivery is algorithmically controlled by the Console based on bioimpedance from the tissue. Once the bioimpedance threshold has been reached the system will automatically stop delivery of energy to that location. The GUI will provide real-time feedback on the progress of the therapy alerting the physician once the therapy has been completed.

Refer to the Investigator's Brochure and the Instructions for Use (IFU) document provided as **Appendix A** and **Appendix B,** respectively, for additional device and device-use details.

4 SUBJECT SCREENING AND ENROLLMENT

4.1 Subject Population

Male or female subjects in good general health who experience chronic rhinitis and meet the study's eligibility criteria as outlined in **Section 1.1, Table 2** will be considered for study participation. Existing medical records may be reviewed to assess the patient for potential eligibility. Subjects whose records support potential eligibility may be approached regarding the study and, if interested, the potential subject will be asked to provide written informed consent before protocol-driven evaluations commence.

4.2 Eligibility Criteria (Inclusion and Exclusion Criteria)

Subjects considered for enrollment must demonstrate eligibility as outlined in the CLARITY Study Eligibility Criteria Table (**Table 2**) through a review of the Subject's documented medical history and protocol-driven tests and procedures as outlined in Study Related Tests, Procedures, and Activities Table (**Table 1**) and further discussed in **Section 4.6.**

Documented evidence of eligibility is required and must be housed with the Subject's study records.

4.3 Subject Recruitment

This study may recruit subjects through in-office, online or other advertising and through existing clients or patients. Any advertising materials to be utilized must be approved by the governing IRB prior to use.

4.4 Subject Reimbursement

Subjects will be compensated for their time and contribution. Compensation is intended to cover any costs associated with travel or other related expenses as well as the Subject's time and contribution. Details concerning reimbursement will be outlined in the site-specific informed consent document, which will undergo IRB/EC review and approval.

4.5 Informed Consent

The Investigator or a designated member of his/her staff should approach the patient to obtain written informed consent. Non-technical language shall be used that is understandable to the Subject. The background of the proposed study and the benefits and risks of the procedures and study will be explained to the Subject. The Subject will be given the plain language study-specific Informed Consent Form (ICF) (example provided as **Appendix C**) which describes all aspects that are relevant to participation. The Subject must sign the consent form prior to study-driven tests or procedures are performed. The informed consent may be provided in hard copy or electronic format. This form or a modification of it must have prior approval of the reviewing IRB or Ethics Committee.

The Subjects and the authorized study personnel obtaining informed consent must sign and date the ICF. A copy must be given to the Subject.

Written informed consent must be obtained prior to performing any protocol-driven tests or procedures.

Once written consent has been obtained, the Subject will be entered on a site-specific screening log. All Subjects *who provide written informed consent* will be entered on the screening log regardless of whether they are enrolled in the study.

As appropriate, important, and new information will be provided to subjects throughout the duration of the study.

It is not expected that a legally authorized representative will provide consent on behalf of study Subject since the Subject must be able to provide active feedback on Quality of Life measures. In addition, this is not an emergent procedure.

If a Subject is unable to read or write, consent shall be obtained through a supervised oral process. The consent process will be appropriately documented.

4.6 Subject Screening

4.6.1 Initial Screening

Prior to obtaining written informed consent, the Subject's existing medical (or other clinic) records may be reviewed by the research staff to determine whether the Subject may be an acceptable candidate for the CLARITY Study. If, upon initial review, there is nothing to indicate that the Subject may not be eligible, the Subject may be approached regarding the study and the informed-consent process may commence.

4.6.2 Active Screening

At any time after the Subject has signed the necessary consent document, but before the NEUROMARK™ procedure subjects will perform eligibility assessments as outlined in **Table 1**. For additional details on the procedures below please refer to the Testing and Evaluation Guidelines document (**Appendix F**) The following must be completed at screening to assess subject eligibility:

- Collect and review medical history, demographics, and concomitant medications.
- Administer Baseline VAS NSS, rTNSS, mini-RQLQ.
- COVID-19 test for active infection.
- Pregnancy test for women of childbearing potential.
- Physical exam (height, weight, blood pressure, respiratory rate, heart rate and temperature).
- Evaluation of the nasal cavity by endoscopic assessment (recorded) to evaluate that the subject is an appropriate candidate for the NEUROMARK™ procedure. A Lund-Kennedy score should be assigned to each nostril.

If the results of the following assessment performed within 6 months prior to treatment are not in the subject's medical record, it must be collected as part of screening:

- Collection and/or review of CT scan of the paranasal sinuses. A Lund-Mackay Score should be assigned to each of the 12 sinuses. The sum of all scores is the Lund-Mackay Score.

4.6.3 Immediately Pre-Treatment

A final eligibility assessment will be conducted immediately pre-treatment to confirm continued eligibility. If the subject meets all eligibility criteria the subject may undergo the NEUROMARK™ procedure on the same day that the screening assessments are performed. Once the subject completes the screening procedures and meets all eligibility criteria, the NEUROMARK™ procedure should be scheduled within 14 days unless otherwise approved by Sponsor. The following evaluations will be performed immediately prior to the study procedure. See Testing and Evaluation Guidelines (**Appendix F**) for evaluation details.

- Confirmation of no indication of COVID-19 infection at the time of treatment.
- Review of concomitant medications.
- Physical exam (height, weight, blood pressure, respiratory rate, heart rate and temperature).
- Endoscopic assessment (recorded).

Once eligibility is confirmed, Subject will be prepared for the treatment following Standard of Care (SOC) for similar procedures and per the manufacturer's IFU (**Appendix B**).

5 ENROLLMENT

Subjects will be considered enrolled once the informed consent is obtained, they meet the study eligibility criteria, and receive treatment.

If for some reason a Subject has consented, but becomes ineligible prior to enrollment, the reason for ineligibility will be documented on the Screening Log and the Subject consent document will be maintained in the site's study records.

Definition of Enrollment: Subjects will be considered enrolled once they are consented, meet eligibility criteria, and have received treatment.

At the time of enrollment, the Subject Sequence Number will be assigned to the Subject.

5.1 Unique Study ID Assignment

At the time of enrollment, a unique study ID will be assigned to the Subject and the unique ID entered on the Screening Log and the Subject Name Log. The site will maintain a Subject name log which will link the unique Subject ID code to the Subject. This log will remain confidential and will not be provided to the Sponsor, but only used for reference when monitoring at the study site.

IMPORTANT: Once a Subject has been assigned a unique study ID code, even if an error is made at the time of assignment, the code should not be changed or fixed. The originally assigned code must remain with the Subject for the entire study.

****ASSIGNMENT OF THE UNIQUE STUDY IDENTIFICATION CODE****

The **unique Subject identification (ID) code** will be made up of

Site # + Subject Sequence Number + Name Code

___ ___ + _3_ ___ ___ + ___ ___ ___ ___ ___

Site #: The Sponsor, at the beginning of the study, will assign each site a number that will be used to identify the site throughout the course of the study. The site number will become part of the Subject's unique study identification code.

Example = Site 01

Subject Sequence #: These numbers should be assigned in sequential order. Each site will begin with 301 and assign sequentially within their study center.

Example = Site 01's third (3rd) → Subject Sequence # is: 01- 303

Patient Name Code Assignment: The last two letters of the patient's first name and the last 3 letters of the patient's last name. Example: John Smith = HNITH

Should characters not be available (e.g., Subject's last name is only 2 characters in length), an 'X' may be used in lieu of an alpha character. Example: John Do = HNDOX

Example = Site 01 enrolls their 3rd Subject whose name is John Smith

Unique Subject ID Code Example: 01-303-HNITH

6 INVESTIGATIONAL PROCEDURE

The NEUROMARK™ System device is intended for use by appropriately trained personnel. All investigators and support staff will be provided comprehensive training by Neurent Medical (or its designee) in the handling and use of the device. Treatment will be performed in a clinic or doctor's office by a trained medical professional.

6.1 Procedure

The NEUROMARK™ procedure will be performed following the system's Instructions for Use (IFU) found in **Appendix B**.

Immediately prior to system introduction the Subject will have a local anesthetic adminstered to the target site per the clinic's standard practice. The local anesthetic used and related procedure will be documented in the Subject's file. Once the Subject is appropriately anesthetized, the NEUROMARK™ procedure may start. Both nasal cavities will be treated during a single treatment session.

Once both nasal cavities have been treated the system will be removed and the procedure will be considered complete.

The procedure may be photographed or videotaped. The Subject's identity will be concealed and patient confidentiality will be maintained.

6.2 Post-Treatment

Following the procedure, an endoscopic assessment of the treatment area will be performed.

Immediately prior to discharge the following will be performed:

- Evaluation of procedure and anesthesia tolerability.
- Assessment for any adverse events or issues.

Reminder: Device Accountability
Each investigational device must be documented on the study's Device Accountability Log.

6.3 Medications and Subject Care

Study Investigator may prescribe pain and/or other post treatment medication as needed. Subjects may take over-the-counter pain medication per Investigator's judgement. Prescription strength pain medication should not be necessary. Should pain medication be prescribed, it will be documented in the Subject's file and any potential related risk will be discussed with the Subject.

Subjects will be asked to refrain from starting a new allergy medication or changing their existing allergy medication regimen, unless instructed otherwise by the study doctor. All medication will be documented in the Subject's chart and medications related to the Subject's sino-nasal condition and/or post procedure discomfort or pain will be evaluated and reported.

6.4 Follow-up evaluations

Subjects will undergo a brief evaluation at 24-48 hours following treatment. This follow-up evaluation may be performed over the phone or in-person.

The following procedures will be performed:

- Evaluation of procedure and anesthesia tolerability.
- Assessment for any adverse events.

- Review and collection of concomitant medications. Any changes to their medications will be documented.

Subjects will undergo additional follow-up evaluation at 1-month, 3-months, 6-months, 9-months and 1-year post treatment. It is preferred that subjects are seen in person; however, due to COVID-19 considerations, portions of the follow up that can be done remotely, may be performed using an online or by phone mechanism to obtain the necessary study data and information concerning the Subject's safety and well-being.

An overview of the evaluations in a checklist format is provided in **Table 1** above.

6.5 Study Exit or Premature Withdrawal

Subjects will be formally exited from the study through completion of the Study Exit CRF at the time of study completion, provided the Subject has not experienced an AE directly attributable to the study device or procedure *that is ongoing and unstable and/or unexplained*.

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

- Not eligible for treatment.
- Subject starts a medication or treatment that, in the opinion of the Investigator, may skew study results.
- Loss to follow-up (following 3 documented attempts to reach Subject).
- In the physician's opinion, it is not in the best interest of the Subject to continue study participation.
- Subject withdrawal, meaning that Subject voluntarily chooses not to participate in the study.

All subjects enrolled (including those prematurely withdrawn) shall be accounted for and documented.

7 INVESTIGATIONAL DEVICE ACCOUNTABILITY

Neurent Medical anticipates using one device per subject with an estimate of 36 devices total.

Device inventory will be managed using a Device Accountability Log that will include details concerning device receipt and disposition.

Access to device inventory will be controlled and both will be housed in a secure location. Records will be maintained to document the physical location of inventory from shipment/removal from Sponsor facility through use and/or return or disposal.

The site will be responsible for keeping records of receipt, use, and return or disposal of the investigation device, which shall include at a minimum, date of receipt, device identification number, expiration date, date of use, Subject identification code and date of disposition. The Device Accountability Log is provided for this purpose.

If the device is associated with a possible device-related adverse event or device deficiency, it should be prepared for disposition using proper protective procedures and returned to Neurent Medical for evaluation.

In the event of product return, Neurent Medical must be contacted for handling instructions prior to product return.

8 SAFETY MONITORING AND ADVERSE-EVENT REPORTING

8.1 Adverse Events

Adverse events (AEs) may occur during the investigational procedure or during the follow-up phase (see **Section 10** for potential risks). Adverse events occurring prior to the use of the NEUROMARK™ System will be documented in the patient's medical record but will not count as related to the investigational device or procedure.

An Adverse Event may occur in users or other persons. Such Adverse Events will be recorded and reported to the Sponsor.

- Should a user of the device, such as the physician, sustain an injury from the use of the device, the injury would be considered an AE.

Each AE will be judged by the Investigator as to its relationship and level of relatedness to the investigational device and/or investigational procedure. In addition, the Investigator will identify the date of onset, any required treatment or intervention, severity, and duration. All adverse events will be monitored until they are adequately resolved, stabilized and/or explained. Refer to **Table 3** and **Table 4** for Severity and Relationship categories and respective definitions.

The Investigator will use the following **(Table 4)** definitions to rate the severity of each adverse event:

Table 3: Adverse Event (AE) Severity

Severity	Description
Mild	→ awareness of a sign or symptom that does not interfere with the Subject's usual activity or is transient, resolved without treatment **and** → no sequelae
Moderate	→ interferes with the Subject's usual activity **and/or** → requires symptomatic treatment
*Severe	→ symptom(s) causing severe discomfort **and** → significant impact of the Subject's usual activity **and** → requires treatment

*If event is considered to be a Serious Adverse Event (SAE), the Investigator must report to the Sponsor the SAE within 24 hours of knowledge of the event.

8.2 Assessment of Relationship

The Investigator will use the following definitions to assess the relationship of the AE to the use of the NEUROMARK™ System.

The Investigator will determine if the adverse event is related to the study procedure, the investigational device and/or a pre-existing condition as described below (**Table 5**).

Table 4: Adverse Event Relationship

AE Related to:	Description
Study Procedure	An AE that is the result of / or related to the study procedure but not necessarily the NEUROMARK™ System..
Investigational Device	An AE that is a result of / or related to use of the NEUROMARK™ System.
Pre-existing Condition	An AE that is a result of / or related to a pre-existing condition or injury.

The Investigator will then determine the adverse event relationship to the study device and the relationship to the study procedure as described below (**Table 5**) and (**Table 7**).

Table 5: Adverse Event (AE) Device Relationship

Relationship	Description
Not Related	→ not associated with study device → due to an underlying or concurrent illness or effect of another device or drug
Unlikely	→ little or no temporal relationship to the study device **and/or** → a more likely alternative etiology exists
Possible	→ temporal sequence between device application and event → is such that the relationship is not unlikely **or** → Subject's condition or concomitant therapy could have caused the AE
Probable	→ temporal sequence is relevant **or** → event abates upon device application completion/removal **or** → event cannot be reasonably explained by the Subject's condition
Highly Probable	→ temporal sequence is relevant **and** → event abates upon device application completion/removal **or** reappearance of the event on repeat device application
Related	→ temporal sequence is relevant **and** → the adverse event is directly related to the use of the NEUROMARK™ System

Table 6: Adverse Event (AE) Procedure Relationship

Relationship	Description
Not Related	→ not associated with study procedure → due to an underlying or concurrent illness or effect of another device or drug
Unlikely	→ little or no temporal relationship to the study procedure **and/or** → a more likely alternative etiology exists
Possible	→ temporal sequence between procedure and event → is such that the relationship is not unlikely **or** → Subject's condition or concomitant therapy could have caused the AE
Probable	→ temporal sequence is relevant **or** → event abates upon procedure completion **or** → event cannot be reasonably explained by the Subject's condition
Highly Probable	→ temporal sequence is relevant **and** → event abates upon procedure completion/removal **or** reappearance of the event on repeat device application

Relationship	Description
Related	→ temporal sequence is relevant **and** → An adverse event that is not directly related to the use of the NEUROMARK™ System but is directly attributable to the procedure in which Neuromark was used.

8.3 Serious Adverse Events

An adverse event is any undesirable experience associated with the use of a medical product in a patient. The event is serious and reportable to the sponsor within 24 hours of knowledge of the event when the event was unanticipated or unexpected, or the patient outcome is any of the following, making the event "Serious":

- Death

Report if you suspect that the death was an outcome of the adverse event, and include the date, if known.

- Life-threatening

Report if suspected that the patient was at substantial risk of dying at the time of the adverse event or use or continued use of the device or other medical product might have resulted in the death of the patient.

- Hospitalization (initial or prolonged)

Report if admission to the hospital or prolongation of hospitalization was a result of the adverse event.

Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening, required intervention to prevent permanent impairment or damage, other serious medically important event).

- Disability or Permanent Damage

Report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, e.g., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.

- Congenital Anomaly/Birth Defect

Report if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.

- Required Intervention to Prevent Permanent Impairment or Damage (Devices)

Report if you believe that medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be because of the use of a medical product.

- Other Serious (Important Medical Events)

Report when the event does not fit the other outcomes but may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

8.4 Contact Details for Reporting Adverse Events

Emergency Contact	AE Reporting Contact
Annalise Sorensen ☎ + 303-881-1757 ✉ Annalise@neurentmedical.com OR David Townley ☎ + 353 87 993 0159 ✉ David@neurentmedical.com	Annalise Sorensen ☎ + 303-881-1757 ✉ Annalise@neurentmedical.com OR Kenny Walsh ☎ + 353 87 947 1202 ✉ Kenny@neurentmedical.com

☞FRIENDLY REMINDER:

The Investigator will report adverse events to the reviewing IRB (as applicable) and according to local reporting requirements.

8.5 Device Failures and Malfunctions

All reported device observations / performance issues, malfunctions, or failures of the NEUROMARK™ System are required to be documented in the CRF. In the event of a suspected observation or device problem (e.g., device failure or malfunction), the investigational device may need to be returned to the manufacturer for analysis. The site must contact the sponsor for instructions. Device failures and malfunctions will be documented in the Subject's study records. Should a return be required, general return instructions and supplies are included in the Study Binder.

NOTE: Device failures or malfunctions are NOT to be reported as adverse events. However, if there is an adverse event that results from a device failure or malfunction, that specific event would be recorded in the usual manner on the AE CRF.

9 PROTOCOL DEVIATIONS

Investigators must obtain prior approval from Neurent Medical and, in some cases where applicable, the reviewing IRB before initiating deviations from the protocol, except when necessary to protect the life or physical well-being of a Subject in an emergency. Such approval shall be documented in writing and maintained in clinical study management and Investigator files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control, (e.g., Subject was not available for scheduled evaluation, etc.); however, the event is still considered a deviation and will be reported on the appropriate CRF.

All deviations regardless of whether medically justifiable, pre-approved by Sponsor, or taken to protect the Subject in an emergency will be reported to the study Sponsor in a timely manner and documented in a Protocol Deviation CRF. Subject specific deviations will be reported on the Protocol Deviation CRF. Non-Subject specific deviations, (e.g. unauthorized use of an investigational device outside the study, unauthorized use of an investigational device by a clinician who has not signed an Investigator agreement or not been trained in the use of the device, etc.), will be reported to Sponsor. Investigators will also adhere to procedures for reporting study deviations to their IRB, in accordance with their specific IRB reporting policies and procedures.

Regulations require that Investigators maintain accurate, complete, and current records, including documents showing the dates of and reasons for each deviation from the protocol.

10 RISK – BENEFIT ASSESSMENT

Refer to risk-benefit details provided in **Appendix A**, the Investigator's Brochure. A summary overview is provided below in this section.

10.1 Potential Benefits

It is expected that the Neurent Medical NEUROMARK™ procedure may provide some benefit to the Subject; however, the actual benefits are not known. There may be no direct benefits of study participation.

A more-comprehensive Risk-Benefit assessment is included in the Investigator's Brochure provided as **Appendix A**.

10.2 Potential Risks

Refer to the manufacturer's labeling for details concerning potential AEs associated with the use of materials, tools or fluid used during the procedure or immediately post-procedure.

Potential risks to the study Subject that may be associated with the use of the NEUROMARK™ System are as follows. Risk of these events is low.

- Allergic or other reaction to device materials or anesthetic (subjects are to be excluded if an allergy/potential allergy is known)
- Trauma to the nasal cavity including

    - Mucosal bleeding
    - Mucosal damage
    - Pain/discomfort
    - Synechiae/Adhesions
    - Perforation
- Infection
- Impaired Nasal Function including:
    - Olfactory change
    - Worsening nasal obstruction
    - Septal perforation
    - Worsened eustachian tube function
    - Cosmetic deformity
- Atrophic rhinitis or dry nose
- Headache
- Bone necrosis
- Burn

There may be additional risks related to the local anesthetic including dermal allergic reactions, itching, rash, erythema, stinging and inflammation. Many of these side effects will subside quickly. Systemic side effects are rare and unexpected. They include arrythmia, hypotension, and a system allergic reaction.

There may be risks related to any post-procedure medication prescribed by the Study Investigator. Those risks can be found on the medication's labeling from the manufacturer.

10.3 Minimization of Anticipated Risks

Neurent Medical has received regulatory clearance for the NEUROMARK™ System in the USA under an FDA Class II device designation. The NEUROMARK System used in this clinical investigation is identical to the NEUROMARK System cleared by FDA. It is used in this study as an unaltered, commercially available medical device that is subject to Quality System Regulations and Good Manufacturing Practices per 21 CFR Part 820. Risks associated with the NEUROMARK™ System are minimized by design. Risks are minimized under this protocol due to:

- Only operators with proper training and experience will use the device
- Extensive non-clinical evaluation of the device (animal and bench-top testing)
- Clinical investigation in a non-therapeutic Clinical Study (non-active evaluation)
- The results of the RELIEVE Study (registry style first in human study) which indicates a positive safety profile
- The use of standard medical-grade materials in the manufacture of the device

11 STATISTICAL ANALYSIS

This is a prospective, single-arm, multicenter, safety and efficacy study.

Summary statistics will be calculated for endpoints and additional evaluations. 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 measures.

Each subject serves as their own comparison of pre-procedure to post-procedure outcome scores. Primary efficacy will be assessed based on a reduction in the VAS Nasal Symptom Score as related specifically to rhinitis (rhinorrhea and nasal congestion) from pre-procedure [baseline] to 3 months post-procedure. The statistical methodology is targeted to employ the paired *t*-test and/or its nonparametric equivalent (the Wilcoxon Signed Rank test) with a 2-sided alpha level of 0.05. Additional Evaluations, as listed in the Protocol Synopsis, will be evaluated in a similar manner.

All subjects treated will be included in the safety analyses. All subjects treated who have at least one follow-up will be included in the efficacy analyses. All subjects treated will be included in the safety analyses.

11.1 Protocol Compliance

As with any clinical investigation, it is critical that one conduct the study per the Clinical Investigational Plan so that the study results are not compromised. Areas of particular criticality are as follows:

- Eligibility criteria (all patients treated must be eligible per the protocol)
- Patients should not be enrolled in another clinical study or be undergoing follow-up for another clinical study that may compromise study results
- Compliance with the protocol follow-up activity
- Thorough, accurate and timely reporting of adverse events
- Thorough, accurate and timely reporting of all clinical trial data

11.2 Sample Size

It has been determined that treatment of 30 subjects is sufficient for assessing the safety and symptom reduction durability. To allow for up to 20% loss to follow-up, 36 subjects will be enrolled (treated) in the study.

12 STUDY MANAGEMENT

For this study, Neurent Medical will have certain direct responsibilities and will delegate other responsibilities to appropriate consultants and contract research organizations (CROs). Together, Neurent, consultants and CROs will ensure that the study is conducted according to the Clinical Investigational Plan and all applicable regulations.

12.1 Key Study Contributors

A Master Contact List will be maintained to include all key study personnel (e.g., monitors, data management personnel), reviewing IRBs and the primary site contacts (investigators, study coordinators). The Master Contact List will be available upon request.

All personnel participating in the conduct of this clinical trial will be qualified by education or experience to perform their tasks.

12.2 Regulatory Considerations

As the study sponsor, Neurent Medical has the overall responsibility for the conduct of the study in accordance with applicable elements of E6 (R2) Good Clinical Practice Consolidated Guidance; FDA abbreviated requirements for NSR; ISO14155, and any conditions imposed by the reviewing IRB(s). The study will not commence until the necessary IRB approvals have been obtained.

12.3 Approved Informed Consent

The reviewing IRB must review and approve an ICF specific to this study. The sponsor will provide each study center with an example ICF (included as **Appendix C**). The study center, to meet specific requirements, may modify this example ICF; however, the ICF to be used for patient consent under this protocol must contain all of the elements required by the study sponsor. Therefore, each investigational site will provide the sponsor with a copy of the IRB-approved ICF and any amendments for the duration of the study. The original signed and dated ICF must be retained by the investigational site for monitoring, and a copy provided to the Subject.

12.4 IRB

IRB approval is required prior to study commencement. The investigator must also obtain renewal of IRB approval for any protocol amendments or as dictated by local requirements during the entire duration of the study. The investigator is responsible for fulfilling any conditions of approval imposed by the reviewing IRB, such as regular reporting. The investigator will provide the study sponsor with copies of such approvals and reports.

12.5 Amendment to the Clinical Investigational Plan (CIP)

The sponsor is responsible for management, processing, and approval of any amendment to the CIP. Should the site consider an amendment to be necessary, the sponsor will work with the site to make the appropriate changes. The sponsor will manage documentation of such changes through the existing document management or control system. Document history will be maintained per the applicable quality system procedures. The proposed CIP amendment will be submitted to the reviewing IRBs or other governing agency, as applicable. Any necessary approvals will be received in writing before the requested change is implemented.

12.6 Ethical Considerations

The rights, safety and well-being of clinical investigation subjects shall be protected consistent with the ethical principles that have their origin in the Declaration of Helsinki. These principles shall

prevail over interests of science and society, and shall be understood, observed, and applied at every step in this clinical investigation.

It is expected that all parties will share responsibility for ethical conduct in accordance with their respective roles in the investigation. The sponsor and the investigator(s) shall avoid improper influence or inducement of the subject, monitor, the clinical investigator(s) or other parties participating in or contributing to the clinical investigation.

12.7 Protection of Patient Confidentiality

At all times throughout the clinical investigation, confidentiality will be observed by all parties involved. All data shall be secured against unauthorized access. Privacy and confidentiality of information about each subject shall be preserved in the reports and in any publication. Each subject participating in this study will be assigned a unique identifier. All CRFs or other study-related data (such as imaging) will be tracked, evaluated, and stored using only this unique identifier.

The investigator will maintain a confidential study subject list identifying all enrolled subjects. This list will contain the assigned study subject's unique identifier and name. The investigator bears responsibility for keeping this list confidential. This list will not be provided to the study sponsor and is only to be used at the study center. Should the list be provided to the sponsor, all names MUST be blacked or scratched out, rendering the patient's name illegible.

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

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

Any source documents copied for monitoring purposes by the sponsor will be identified by using the assigned patient's unique identifier to protect subject confidentiality. Any subject identifiers will be blacked or scratched out and replaced with the subject's study identification code.

Photographs of the procedure and treatment areas will not include Subject faces or any other personally identifying features. Subject images will be tracked using the unique study ID.

12.8 Study Monitoring

The study will be monitored, as outlined in the monitoring plan, to ensure the rights and well-being of human subjects are protected, the reported trial data are accurate, complete, and verifiable from source documents and that the conduct of the study is in compliance with the approved protocol and applicable regulations and standards. Refer to the Monitoring Plan for details on the monitoring procedures.

12.9 Quality Assurance and Supervision by Authorities

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

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

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

12.10 Corrective and Preventative Action

Aside from an official site audit, non-compliance may be discovered through other means such as monitoring, site management, general communication, or site visits. Any evident pattern of non-compliance with respect to applicable elements of E6 Good Clinical Practice Consolidated Guidance, ISO 14155, the ethical principles of the Declaration of Helsinki or conditions imposed by the reviewing IRB(s), the CIP or other governing requirements may be cause for corrective action. Such corrective action may range from communication of the non-compliance to the site being placed on probation until corrective action is taken. In more-serious circumstances, enrollment may be terminated at the site. Corrective actions will be followed through to resolution and any resulting documentation surrounding the corrective and preventative action will be housed in the central study files.

12.11 Insurance

The sponsor will maintain the appropriate and necessary insurance coverage for the duration of the study.

13 RESPONSIBILITIES

13.1 Sponsor Responsibilities

Neurent Medical Ltd. is the sponsor of this study. The study sponsor has the overall responsibility for the study and will work to ensure compliance with the Investigational Plan, applicable elements of Good Clinical Practice: Consolidated Guidance, signed study agreements and ISO 14155. The sponsor will be responsible for, but not limited to, the following:

- Selecting qualified investigators, monitors and contract study personnel
- Providing the Investigational Plan and any subsequent amendments

- Signing the protocol
- Providing appropriate information and training to investigators and study-site staff
- Promptly informing the investigators and, where applicable, any regulatory authorities and IRBs/ECs if the study is prematurely terminated or suspended and the reason for the termination or suspension
- Providing protocol initiation training to include review of the instructions for use, the Investigational Plan, CRF completion guidelines and guidelines for obtaining informed consent
- Each study center undergoing Protocol Initiation that will include, but is not limited to, a review of the following by key study personnel (investigators, coordinators):
    - → Clinical Investigational Plan (CIP)
    - → Consenting procedures
    - → Instructions for Use (IFU)
    - → Reporting requirements
    - → CRF completion procedures
    - → Device-handling and accountability procedures
    - → Protection of patient confidentiality
- Coordinating ongoing communication with CRO(s), consultants and study sites to resolve any problems concerning the protocol or data collection. Every effort will be made to ensure compliance with the protocol
- Retaining ownership of all clinical data generated in this study, and controlling the use of the data for purposes of regulatory submissions to the U.S. and other governments
- Protecting patient confidentiality
- Collecting, storing, and keeping secure, at a minimum, the following documents:
    - → Curriculum vitae of each investigator
    - → The name of the institution where the study will be conducted
    - → The IRB/EC opinion and/or approval, in writing, and relevant correspondence
    - → Correspondence with authorities (as required)

- → Investigator Agreement for each investigator (example provided as **Appendix D**)
- → Financial Disclosure and Conflict of Interest Form for each investigator (refer to **Appendix E**)
- → CIP Signature Page
- → Insurance certificates (as necessary)
- → IRB/EC Approved ICF
- → Names/contact information for study monitor(s)
- → Records of any adverse events
- → Statistical analyses and underlying supporting data
- → Final report

13.2 Sponsor Maintenance of Study Records

The sponsor will be responsible for **maintaining study records** per FDA abbreviated requirements for NSR and Good Clinical Practice: Consolidated Guidance.

The sponsor will be responsible for **monitoring the investigation** per FDA abbreviated requirements for NSR and Good Clinical Practice: Consolidated Guidance.

The sponsor will be responsible for **reporting** per FDA abbreviated requirements for NSR and local IRB requirements.

13.3 Investigator Responsibilities

The investigator(s) shall be responsible for the day-to-day conduct of the investigation and the safety and well-being of the human subjects involved in the clinical investigation.

To ensure proper execution of the study protocol, each investigator should identify a study coordinator for this study. Working with and under the authority of the investigator, the study coordinator ensures that all study requirements are fulfilled and serves as the contact person at the site for all aspects of study administration.

The investigator(s) will be responsible for maintaining study records per FDA abbreviated requirements for NSR and Good Clinical Practice: Consolidated Guidance. Records must be retained for a minimum off 2 years following FDA approval or, if no application is filed or if the application is not approved, then 2 years after the investigation is discontinued.

The investigator is responsible for maintaining medical and study records for every patient participating in the clinical study (including information maintained electronically, such as digital

imaging). The study center will also maintain original source documents from which study-related data are derived, and that may include, but is not limited to:

- Progress notes recording patient's medical history and medications
- Medical records regarding AEs, including treatment and clinical outcome
- Notes of phone calls and/or correspondence concerning the patient

The investigator must ensure that all study subject records are stored for at least 2 years after the date that a marketing application is approved for the device for the indication for which it is being investigated or, if no application is to be filed, until 2 years after the applicable agency(ies) has been notified (if applicable). To avoid error, the study site should contact Neurent Medical prior to the destruction of study records to ensure that they no longer need to be retained. In addition, Neurent Medical should be contacted if the investigator plans to leave the investigational site, so that arrangements can be made for the handling or transfer of study records.

The investigator(s) will allow auditing of their clinical investigation procedure(s).

13.4 Investigator Reports

The investigator(s) will be responsible for reporting per FDA abbreviated requirements for NSR and according to applicable IRB/EC requirements and Good Clinical Practice: Consolidated Guidance.

Type of Notification	Time Constraints
Adverse event	If SAE, verbal report within 24 hours, followed by a written report within 5 working days If AE, written report within 5 working days
Device deficiency	verbal report within 24 hours, followed by a written report within 5 working days.

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

13.5 Required Documents from the Investigator

At a minimum, the following documents will be provided by the investigational site to the study sponsor prior to study start (consent of the first patient):

- Signed Investigator Agreement (example provided as **Appendix D**)
- Signed Clinical Investigational Plan signature page
- IRB approval
- IRB-approved ICF
- *Investigator and co-investigator's current curriculum vitae

* The study may begin once the CV of the site PI has been received. No additional investigators may participate until a copy of their CV and a signed Investigator Agreement has been provided to the study sponsor.

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

Additional study-required documents will be collected, as applicable, and maintained, as necessary.

13.6 Other Investigator Reports

The investigator for each study center is responsible for generating the following reports to the sponsor according to the following schedule. All reporting timelines are "within knowledge of the occurrence."

Table 7: Overview of Other Incident Reporting Timelines, Investigator/Site to Sponsor

Type of Notification	Time Constraints
Withdrawal of IRB Approval	verbal report within 24 hours, followed by a written report within 5 working days
Informed Consent NOT Obtained	verbal or written report within 5 working days

Withdrawal of IRB approval and reports of informed consent not obtained must be reported to the study sponsor according to the timelines reflected in Table 7**:**

Reporting Contact
Annalise Sorensen ☎ + 303-881-1757 ✉ Annalise@neurentmedical.com

☞ Reports must identify subjects using the study's unique identifier to protect patient's confidentiality.

14 DATA MANAGEMENT

Study data will be collected using a standardized Case Report Form (CRF). The CRF may be in electronic form, referred to as an eCRF, or in a paper-based format. The CRF will be designed to accommodate the specific features of the trial design. Modification of the CRF will only be made if deemed necessary to support the study design and by the study sponsor.

14.1 Data Management Responsibilities

The Data Management group will be responsible for managing the database and resulting study data. Conventional data verification routines will be performed. Data management will be performed

according to the study's *Data Handling Plan.* The study sponsor will manage directly or outsource data management to a qualified data management group.

Verification, validation, security measures, and locking/finalizing of an electronic clinical data system (if utilized) will be performed following the EDC/Data Management group's standard operating procedures and processes.

Data Management (Primary Contact)
Annalise Sorensen ☎ + 303-881-1757 ✉ Annalise@neurentmedical.com

14.2 Data Entry

Subject data will be recorded on case report forms and entered into a limited-access secure database. The software and database will be compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures.

Changes made to the clinical data will be captured in an audit trail and available for review.

14.3 Data Cleaning

Data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created and the resulting Data Clarification Form (DCF), or equivalent, issued to the clinical site(s) for appropriate resolution (as applicable).

14.4 Data Retention and Back-up

System backups are performed regularly. The database will be managed on a secure server and computer-access password-controlled. The secure server will be backed up periodically. Upon study completion, the data will be archived.

14.5 Confidentiality and Security

Passwords will be utilized by data entry, data verification and other personnel who have database access to ensure confidentiality and protection of data.

15 STUDY CLOSE-OUT

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

Once all sites are considered closed, the study may be closed. Study closeout will include a Final Report that will be submitted to each participating investigator, IRB and other governing agency, as required.

15.1 Study Suspension or Early Termination

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

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

If the study is discontinued or suspended prematurely, the sponsor shall promptly inform all clinical investigator(s)/investigational center(s) of the termination or suspension, and the reason(s) for it. The IRB shall also be informed promptly and provided with the reason(s) for the termination or suspension by the sponsor or by the clinical investigator/investigation center(s). Regulatory authorities and the personal clinician(s) of the subjects may also need to be informed, if deemed necessary.

15.2 Final Report

A Final Report will be prepared even if the study is prematurely terminated.

15.3 Publication Policy

The CLARITY study will be registered in a publicly accessible database.

At the conclusion of the trial, a multi-center abstract reporting the results will be prepared and may be presented at a major meeting(s). A multi-center publication may also be prepared for publication in a reputable scientific journal. **The publication of results from any single-center experience within the trial is not allowed until the aggregate study results have been published unless there is written consent from the study sponsor.**

16 DEFINITIONS AND ACRONYMS

Adverse Event

An adverse event is any undesirable experience associated with the use of a medical product in a patient. The event is serious when the patient outcome is:

- Death

Report if you suspect that the death was an outcome of the adverse event, and include the date, if known.

- Life-threatening

  Report whether it is suspected that the patient was at substantial risk of dying at the time of the adverse event or use or continued use of the device or other medical product might have resulted in the death of the patient.

- Hospitalization (initial or prolonged)

  Report if admission to the hospital or prolongation of hospitalization was a result of the adverse event.

  Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening, required intervention to prevent permanent impairment or damage, other serious medically important event).

- Disability or Permanent Damage

  Report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, e.g., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.

- Congenital Anomaly/Birth Defect

  Report if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.

- Required Intervention to Prevent Permanent Impairment or Damage (Devices)

  Report if you believe that medical or surgical intervention was necessary to preclude permanent impairment of a body function, or to prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.

- Other Serious (Important Medical Events)

  Report when the event does not fit the other outcomes, but it may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

Audit

Systematic independent examination of activities and documents related to clinical investigation to determine whether these activities were conducted, and the data recorded, analyzed and accurately reported according to the CIP and applicable regulatory requirements.

Case Report Form (CRF)

Set of printed, optical or electronic documents for each subject, on which information to be reported to the sponsor is recorded as required by the CIP.

Clinical Investigational Plan (CIP)

Document that states the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation.

eCRF – Electronic CRF (See CRF)

Hypertension (per the American Heart Association)

BLOOD PRESSURE CATEGORY	SYSTOLIC mm Hg (upper number)		DIASTOLIC mm Hg (lower number)
NORMAL	LESS THAN 120	and	LESS THAN 80
ELEVATED	120 – 129	and	LESS THAN 80
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1	130 – 139	or	80 – 89
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 2	140 OR HIGHER	or	90 OR HIGHER
HYPERTENSIVE CRISIS (consult your doctor immediately)	HIGHER THAN 180	and/or	HIGHER THAN 120

Informed Consent Form (ICF)

Provides the subject with adequate information to allow for an informed decision about participation in the clinical investigation.

Instructions for Use (IFU)

Provides information on the device description, indications for use, contraindications, warnings, procedure, potential hazards/adverse events, device preparation, local anesthetic delivery, NEUROMARK™ procedure and EMC specifications.

Serious Adverse Event (SAE)

See Adverse Events.

Source Data
All information in original and identified records and certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation (ISO 14155).

Source Documents

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

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

SOP - Standard Operating Procedure

Unexpected Adverse Event

An adverse event is considered “unexpected” if it is not listed in the protocol or is not listed at the specificity or severity that has been observed, and/or is not consistent with the risk information described in the general investigational plan.

Unanticipated Adverse Device Effect (UADE)

Unanticipated adverse device effect is any serious adverse effect on health or safety, 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 application, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.

VAS Nasal Sinus Symptoms of Rhinitis

Runny nose and/or post-nasal drip and nasal blockage.

REVISION HISTORY

Version:	Summary of Changes:	Rationale for change
A	N/A – original document	N/A

B	1. Table 1: Rows: Evaluation of Procedure and Anesthesia Tolerability and Evaluation of Adverse Events, added "X" to "Immediately Post-Treatment" column. 2. Table 1: Rows: Physical Exam and Concomitant Medications added “X” to “Immediately Pre-Treatment” column. 3. Table 1: Row: COVID-19 Test for Active Infections added “O” to “Immediately Pre-Treatment” column. 4. Table 2: Added inclusion criterion I-L: Subject is experiencing long term chronic rhinitis. Subject has been experiencing symptoms of rhinitis for at least 6 months prior to enrollment, defined as: rhinorrhea, anterior runny nose AND congestion, blockage (stuffy nose, obstruction). 5. Emergency contacts: Removed Cathal McLaughlin from Emergency Contacts and added “or” between contacts 6. Table 2: Exclusion criterion R: Removed "(this does not apply to the sham to treatment crossover under this study)" 7. Page 12, Section 2 grammatical update	1. These procedures are outlined in the body of the CIP, the "X" was inadvertently missed in Version 1. 2. These procedures are outlined in the body of the CIP, the "X" was inadvertently missed in Version 1. 3. This procedure is outlined in the body of the CIP, the "O" was inadvertently missed in Version 1. 4. This criterion is stated above - added as an inclusion criterion to the table for clarity. 5. Role is not an emergency contact, administrative update 6. This is not applicable for this study 7. Grammatical correction
C	1. Additional Evaluations (page 7): Cleaned up the language for consistency and clarity 2. Table 1, page 7 & page 23: Added 9-Month follow-up 3. Statistical Analysis (page 31): Added details on the summary statistics to be calculated and the targeted statistical tests to be performed on the endpoints and additional evaluations 4. Study Size (page 6, 31): Clarified 36 subjects will be enrolled (treated) 5. Enrollment (page 20): Clarified that a subject will be considered enrolled when they are consented, meet eligibility criteria, and are treated 6. Page 6, 31, & 43: Removed ITT, mITT, and PP language 7. Minor administrative and grammatical updates throughout	1. Edits made for clarity only 2. 9-Month follow-up will enhance data collection and patient compliance to follow-up at 12-months 3. Added more details to the Statistical Analysis section for completeness 4. Desire to have all 36 subjects enrolled (treated) 5. Simplifies study management and analyses 6. No longer needed as all subjects enrolled (treated) will be analyzed