

PARAGON

CLINICAL INVESTIGATIONAL PLAN (CIP)

PROTOCOL #: CIP-000

NCT05591989



PARAGON

CLINICAL INVESTIGATIONAL PLAN (CIP)

PROTOCOL #: CIP-0007

Clinical Evaluation of Safety and Efficacy for the NEUROMARK® System in Subjects with Chronic Rhinitis

A prospective, single-arm, multicenter clinical study

PARAGON Study

Clinical Investigational Plan #: CIP-0007.B / Version: 13SEP2022

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

PROTOCOL APPROVAL

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II INVESTIGATOR SIGNATURE PAGE

PARAGON Study Investigator Signature Page

Clinical Evaluation of Safety and Efficacy for the NEUROMARK® System in Subjects with Chronic Rhinitis

PARAGON Study

Protocol # / Version Date: CIP-0007.B / 13SEP2022

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:

Investigator Name	Signature	Date

III SPONSOR CONTACT INFORMATION

Neurent Medical's sponsor contact information is provided below. This information is subject to change during the course of the clinical study. Periodic updates to study contact information will be sent to the sites as needed; however, personnel changes do not necessitate a clinical investigational plan (CIP) amendment.

Annalise Sorensen *Primary Sponsor Contact, AE Reporting* Director of Clinical Operations 303-881-1757 annalise@neurentmedical.com	**Lauren Yeager, PhD** *Study, Monitoring &* *AE Reporting Contact* Clinical Research Specialist 612-730-6790 lauren@neurentmedical.com
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III INVESTIGATIONAL PLAN SUMMARY

Study Title: Clinical Evaluation of Safety and Efficacy for the NEUROMARK® System in Subjects with Chronic Rhinitis

Short Title: PARAGON Study

Study Device: 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: To demonstrate treatment with the NEUROMARK® System is safe and effective in adults with chronic rhinitis

Study Design: A prospective, single-arm, multicenter, non-significant risk (NSR) clinical study

Study Size: This study aims to evaluate a total of eighty (80) study subjects at up to fifteen (15) clinical sites in the United States (U.S.).

It is anticipated that approximately 10 subjects will be enrolled at each site. No site may enroll more than 50% of the study population.

Subject Population: Adults who suffer from chronic rhinitis

Study Procedure: Subjects that provide informed consent and meet study eligibility requirements will receive 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 the following visits:

- Screening, Baseline, Procedure
- 1-, 3-, 6-, 9-, 12-, 15-, 18-, 21-, and 24-month post procedure follow-up

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

Primary Endpoints:

Safety, as assessed by the incidence of device- and/or procedure related serious adverse events (SAEs)

Efficacy, as assessed by the mean change from baseline in nasal symptoms using the 4-symptom rTNSS (reflective Total Nasal Symptom Score) at 6-month follow-up (FU)

Secondary Endpoints:

The following secondary endpoints will be assessed at relevant follow-ups:

- The mean change from baseline in rTNSS total score (except 6-month FU)
- The mean change from baseline in rTNSS subscores
- The mean change from baseline in Mini Rhinoconjunctivitis Quality of Life Questionnaire (mini-RQLQ) score
- The mean change from baseline in Clinical Global Impression – Improvement (CGI-I) score
- Percent of subject satisfaction at follow-up

The following will be assessed at the procedure visit:

- Tolerability of treatment via verbal report using the Numeric Rating Scale (NRS) score

Additional Evaluations:

The following additional evaluation will be assessed at relevant follow-ups:

- The percent of responders in the rTNSS score (subjects with a 30% or greater reduction in rTNSS relative to baseline)
- The percent of subjects achieving the minimal clinically important difference (MCID) in rTNSS relative to baseline (≥1 point on the rTNSS)
- The percent of subjects achieving the MCID in mini-RQLQ score (≥0.7 point on the mini-RQLQ)
- The mean change from baseline in postnasal drip and cough
- The mean change from baseline in the Nasal Obstruction Symptom Evaluation (NOSE) score
- The mean change from baseline in the Eustachian Tube Dysfunction Questionnaire (ETDQ-7)
- The change in rhinitis medications from baseline (at 12- and 24-month follow-up visits)

Additional outcomes may be assessed as outlined in the Statistical Analysis Plan (SAP)

Anticipated Duration:

The study is anticipated to begin enrollment in Q3 of 2022 with enrollment complete in Q2 of 2023. The last patient visit is expected to take place by or during Q2 of 2025.

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.

Inclusion Criteria

Subjects **Must**:

1. Be ≥18 years of age.
2. Have been experiencing rhinitis symptoms for a minimum of 6 months.
3. Have moderate to severe symptoms of runny nose (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 score of 5 (out of 12) at baseline.
4. Have an allergy test (by skin prick or intradermal testing, or by a validated *in vitro* Immunoglobin E [IgE test]) on file within 5 years of the baseline visit or is willing to have one performed during the study prior to 6-month visit.
5. Be an appropriate candidate for bilateral NEUROMARK® device treatment performed under local anesthesia.
6. Test negative for active COVID-19 at the start of the study screening and continue to be free of COVID-19 symptoms until the time of enrollment/treatment.
7. Be willing and able to comply with all study elements, as indicated by written informed consent.

Exclusion Criteria

Subjects **Must Not:**

1. Have clinically significant anatomic obstruction 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 RF, cryotherapy, or other surgical interventions for rhinitis.
4. Have an active nasal or sinus infection.
5. Have nasal mucosal erosion/ulceration.
6. Have rhinitis symptoms that are due to seasonal allergies only.
7. Have plans to (or otherwise anticipates the need to) undergo an ENT procedure concurrently or within 6 months after the study procedure.
8. Have started a new sinonasal medication regimen within 4 weeks prior to treatment that, according to the manufacturer's labelling, has not yet stabilized.
9. Be on prescribed anticoagulants (eg, warfarin, Plavix) or ≥ 325 mg aspirin that cannot be held for an appropriate time before the procedure.
10. Have a history of chronic epistaxis or experienced a significant epistaxis event (defined as epistaxis requiring medical intervention) in the past 3 months.
11. Have numbness of the soft palate, excessive dry eye, excessive dry nose, or other indication of neuro/nerve compromise in the sinonasal cavity.

12. Have an active rhinitis medicamentosa or a history of rhinitis medicamentosa within the past 6 months.
13. Have been diagnosed with atrophic rhinitis.
14. Have had previous head and/or neck irradiation.
15. Have an allergy or intolerance to local anesthetic agents.
16. Be pregnant.
17. Have a physical, neurological, medical, psychiatric condition or situation that, 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.
18. Be participating in another clinical research study.

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 Assessment Schedule

Study evaluation	Study Visit (window)											
	Screening (up to 30 days pre-procedure) [a]	Baseline (up to 7 days pre-procedure) [b]	Procedure (day 0) [b]	1-Month (± 7 days)	3-Month (± 14 days)	6-Month (± 21 days)	9-Month (± 21 days) Virtual/Phone Visit	12-Month (± 21 days)	15-Month (± 21 days) Virtual/Phone Visit	18-Month (± 30 days)	21-Month (± 30 days) Virtual/Phone Visit	24-Month (± 30 days)
Informed consent	✓											
Demographics and medical history	✓											
Eligibility assessment	✓	✓										
Urine pregnancy test[c]	✓											
Endoscopic assessment[d]	✓		✓	✓	✓							
COVID-19 test for active infection[e]	✓											
Allergy testing[f]	✓											
Procedure			✓									
NRS scale (procedure tolerability)			✓									
Adverse events			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant medications	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
rTNSS, postnasal drip and cough[g]	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
Mini RQLQ		✓			✓	✓		✓		✓		✓
CGI-I					✓	✓		✓		✓		✓
NOSE		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
ETDQ-7		✓				✓		✓				✓
Subject satisfaction				✓	✓	✓	✓	✓	✓	✓	✓	✓

[a] The procedure must take place within 30 days of the screening visit.

[b] The subject must discontinue use of ipratropium bromide (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] Urine pregnancy tests are required for all women of childbearing potential before the procedure.

[d] A Lund-Kennedy score should be assigned to each nostril. Endoscopy recordings should be provided to the sponsor.

[e] A COVID-19 test for active infection is required prior to treatment. The COVID-19 test will also be performed if the subject is suspected to be symptomatic for COVID-19 at any point during the study.

[f] Allergy test required before 6-month visit if no allergy test on file within 5 years of baseline visit.

[g] Only rTNSS is required to be completed at the screening visit.

1 BACKGROUND AND PURPOSE

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.

1.1 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**).

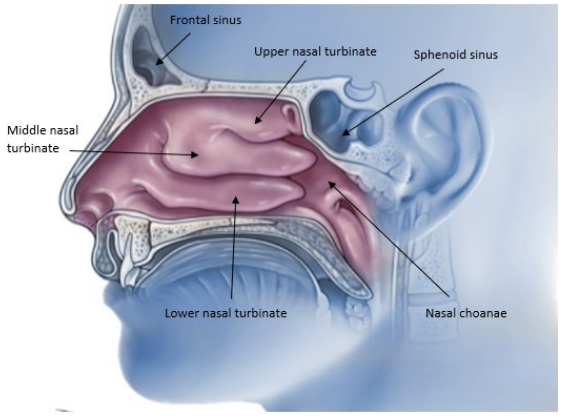


Figure 1: Nasal cavity

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 modern surgical options: the delivery of thermal energy

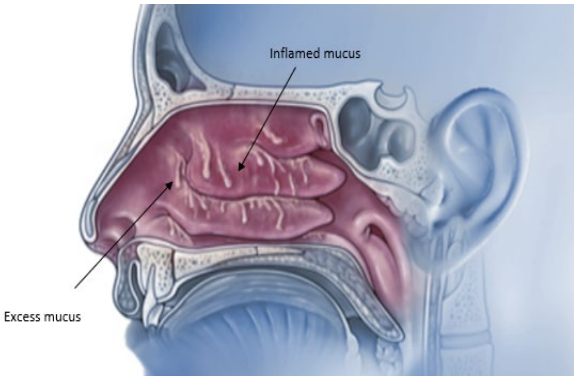


Figure 2: Nasal cavity with inflamed turbinates

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.

1.2 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**.

1.3 Study Purpose

The purpose of this study is to evaluate the safety and efficacy of the NEUROMARK® System in subjects with chronic rhinitis. To assess safety, the primary endpoint will evaluate the incidence of device- and/or procedure related serious adverse events (SAEs). To assess efficacy, the primary endpoint will evaluate the mean change from baseline in nasal symptoms using the 4-symptom rTNSS (reflective Total Nasal Symptom Score).

2 PROTOCOL

2.1 Study Design

The PARAGON study is prospective, single-arm, multicenter, non-significant risk (NSR) clinical study.

2.2 Study Objective

The objective of the PARAGON study is to demonstrate treatment with the NEUROMARK® System is safe and effective in adults with chronic rhinitis

2.3 Study Endpoints

2.3.1 Primary Endpoints

The primary safety endpoint will be assessed by the incidence of device- and/or procedure related serious adverse events.

The primary efficacy endpoint will be assessed by the mean change from baseline in nasal symptoms using the 4-symptom rTNSS at 6-month follow-up (FU).

2.3.2 Secondary Endpoints

The following secondary endpoints will be assessed at relevant follow-ups:

- The mean change from baseline in rTNSS total score (except 6-month FU)
- The mean change from baseline in rTNSS subscores
- The mean change from baseline in Mini Rhinoconjunctivitis Quality of Life Questionnaire (mini-RQLQ) score
- The mean change from baseline in Clinical Global Impression – Improvement (CGI-I) score
- Percent of subject satisfaction at follow-up

The following will be assessed at the procedure visit:

- Tolerability of treatment via verbal report using the Numeric Rating Scale (NRS) score

2.3.3 Additional Evaluations

The following additional evaluation will be assessed at relevant follow-ups:

- The percent of responders in the rTNSS score (subjects with a 30% or greater reduction in rTNSS relative to baseline)
- The percent of subjects achieving the minimal clinically important difference (MCID) in rTNSS relative to baseline (≥1 point on the rTNSS)
- The percent of subjects achieving the MCID in mini-RQLQ score (≥0.7 point on the mini-RQLQ)
- The mean change from baseline in postnasal drip and cough
- The mean change from baseline in the Nasal Obstruction Symptom Evaluation (NOSE) score
- The mean change from baseline in the Eustachian Tube Dysfunction Questionnaire (ETDQ-7)
- The change in rhinitis medications from baseline (at 12- and 24- month follow-up visits)

Additional outcomes may be assessed as outlined in the Statistical Analysis Plan (SAP)

2.4 Study Size and Duration

This study aims to evaluate a total of eighty (80) study subjects at up to fifteen (15) clinical sites in the United States (U.S.). It is anticipated that 10 subjects will be enrolled at each site. No site may enroll more than 50% of the study population. The study is anticipated to begin enrollment in Q3 of 2022 with enrollment complete in Q2 of 2023. The last patient visit is expected to take place by or during Q2 of 2025.

2.5 Study Hypothesis

This is a prospective, single-arm, multicenter safety and efficacy study. The primary endpoint is the mean change in the total rTNSS at 6 months compared to baseline. The primary endpoint will be assessed by testing the following 2-sided hypotheses using the student's *t*-test for paired differences

H_o: Mean change from baseline = 0

H_a: Mean change from baseline ≠ 0

2.6 Sample Size Estimation

The sample size was calculated using PASS 2019 Power Analysis and Sample Size Software (2019). Based on the Neurent Meridien and Relieve clinical studies, the change in rTNSS at 6 months is expected to be -2.5 ±2.6.

Using 90% power with a 2-sided alpha of 0.05, a sample size of 17 subjects using one-sample Student's *t*-test will be adequately powered. Allowing a conservative attrition rate of up to a 10%, a minimum of 19 subjects would need to be enrolled to achieve 17 subjects with paired data at 6 months.

Out of desire to test this same hypothesis in subgroups of interest, the sample size will be inflated. The smallest group of interest is allergic rhinitis with an expected incidence of 30% and is expected to have similar performance as the entire population. Using a conservative approach and allowing that it might be as low as 24%, the sample size of 19 will be increased by a factor of 4.2 (19*4.2) and thus, a total of 80 subjects will be enrolled in the study.

2.7 Data Analysis

Primary Effectiveness Endpoint

The primary efficacy endpoint is the mean change from baseline in the rTNSS at the 6-month follow-up period. The rTNSS is a PRO used to describe symptoms of rhinitis. The assessment consists of 4 nasal symptom domains (nasal congestion, runny nose, nasal itching, and sneezing). 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.

Descriptive statistics including mean, standard deviation, and median for the change from baseline to the 6-month follow-up in the total rTNSS will be calculated for the change in rTNSS (paired observations) along with 95% confidence intervals. Testing whether this change is statistically different from zero will be assessed using a paired 2-sided *t*-test and a p-value < 0.05 will be considered statistically significant. If the data are not normally distributed, a Wilcoxon signed rank test will be conducted in place of the *t*-test and the median and interquartile range will be presented instead of the mean ± SD. Normality will be assessed by the Shapiro-Wilk test, where a p-value <0.05 indicates the non-normality of the data.

Primary Safety Endpoint

The primary safety endpoint is the proportion of subjects that experienced a serious adverse event that was related to the device/procedure. The count and percentage of subjects that experienced a device/procedure related SAE will be summarized and may include a 95% confidence interval.

General

Continuous data will be summarized using descriptive statistics and will include mean, standard deviation, median and possibly 95% confidence intervals for endpoints. Changes from baseline will be calculated where applicable and will include the same descriptive statistics plus statistical testing for change from baseline to see if difference was statistically different from zero (using student's *t*-test as appropriate). Categorical data will be summarized using counts and percentages and may include 95% confidence intervals may be calculated for certain categories (e.g., percent improved / satisfied). An alpha level of 0.05 will be considered statistically significant, and no adjustments will be made for multiple hypotheses testing.

2.8 Study Population

Subjects considered for enrollment must demonstrate eligibility as outlined in the Study Eligibility Criteria 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.

2.8.1 Inclusion Criteria

Subjects **Must**:

1. Be ≥18 years of age.
2. Have been experiencing rhinitis symptoms for a minimum of 6 months.
3. Have moderate to severe symptoms of runny nose (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 score of 5 (out of 12) at baseline.
4. Have an allergy test (by skin prick or intradermal testing, or by a validated *in vitro* Immunoglobin E [IgE test]) on file within 5 years of the baseline visit or is willing to have one performed during the study prior to 6-month visit.
5. Be an appropriate candidate for bilateral NEUROMARK® device treatment performed under local anesthesia.
6. Test negative for active COVID-19 at the start of the study screening and continue to be free of COVID-19 symptoms until the time of enrollment/treatment.
7. Be willing and able to comply with all study elements, as indicated by written informed consent.

2.8.2 Exclusion Criteria

Subjects **Must Not:**

1. Have clinically significant anatomic obstruction 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 RF, cryotherapy, or other surgical interventions for rhinitis.
4. Have an active nasal or sinus infection.
5. Have nasal mucosal erosion/ulceration.
6. Have rhinitis symptoms that are due to seasonal allergies only.
7. Have plans to (or otherwise anticipates the need to) undergo an ENT procedure concurrently or within 6 months after the study procedure.

8. Have started a new sinonasal medication regimen within 4 weeks prior to treatment that, according to the manufacturer's labelling, has not yet stabilized.
9. Be on prescribed anticoagulants (eg, warfarin, Plavix) or ≥ 325 mg aspirin that cannot be held for an appropriate time before the procedure.
10. Have a history of chronic epistaxis or experienced a significant epistaxis event (defined as epistaxis requiring medical intervention) in the past 3 months.
11. Have numbness of the soft palate, excessive dry eye, excessive dry nose, or other indication of neuro/nerve compromise in the sinonasal cavity.
12. Have an active rhinitis medicamentosa or a history of rhinitis medicamentosa within the past 6 months.
13. Have been diagnosed with atrophic rhinitis.
14. Have had previous head and/or neck irradiation.
15. Have an allergy or intolerance to local anesthetic agents.
16. Be pregnant.
17. Have a physical, neurological, medical, psychiatric condition or situation that, 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.
18. Be participating in another clinical research study.

2.9 Concomitant Medications

All current concomitant medication will be recorded, including those used to treat rhinitis symptoms. All changes in medication use and dosage should be assessed and recorded at each follow-up visit.

Any subject taking nasal anticholinergic sprays (eg, IB) will be instructed at screening to discontinue use at least 14 days before baseline visit and through the 6-month visit. Subjects will also be instructed not to change their baseline concomitant medications (start/stop or change of dose) before the 6-month follow up, unless required to treat an adverse event.

2.10 Methods and Procedures

2.10.1 Eligibility Assessment

Adult subjects who experience chronic rhinitis and meet the study's eligibility criteria as outlined in **Section 2.8** 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.

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

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

2.10.2 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 PARAGON 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.

2.10.3 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.

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.

2.10.4 Active Screening

After the Subject has signed the necessary consent document, but before the NEUROMARK® procedure subjects will perform eligibility assessments as outlined in **Table 1**. The Screening Visit can be performed up to 30 days before the procedure. 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:

- Informed Consent

- Collect and review medical history, demographics and concomitant medications. Medical history should include if the subject is a past, current or never smoker.
- Eligibility Assessment: subject should meet all of the inclusion and none of the exclusion criteria to continue to the baseline visit
- Urine pregnancy test for women of childbearing potential
- Endoscopic Assessment: 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.
- COVID-19 test for active infection
- Allergy Testing required before 6-month visit if no allergy test on file within 5 years of baseline visit
- Administer Screening rTNSS
- If the subject is taking ipratropium bromide, it should be discontinued at least 14 days prior to the baseline visit.

2.10.5 Baseline Visit

The baseline visit will be scheduled no more than 7 days prior to the procedure. The baseline visit and procedure can occur on the same day if all criteria are met. The following must be completed at baseline to assess subject eligibility:

- Eligibility Assessment: subject should meet all the inclusion and none of the exclusion criteria to continue to the procedure
- Review, collect and record concomitant medications
- The subject will complete the rTNSS, postnasal drip and cough assessment, mini-RQLQ, NOSE and ETDQ-7

2.10.6 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.

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

___ ___ + _4_ ___ ___ + ___ ___ ___ ___ ___

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 401 and assign sequentially within their study center.

Example = Site 01's third (3rd) → Subject Sequence # is: 01- 403

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: 01-403-HNITH

2.10.7 Procedure Visit: 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 baseline assessments are performed. Once the subject completes the screening and baseline procedures and meets all eligibility criteria, the NEUROMARK® procedure should be scheduled within 7 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.

- Review of concomitant medications.

- Endoscopic assessment: 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.

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**).

2.10.8 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.

2.10.9 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.

Post-Treatment Assessments

Following the procedure, the following information will be collected:

- Evaluation of procedure tolerability by collecting the NRS score
- Adverse event assessment

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

Post-Treatment Pain Medications

Study Investigator may prescribe pain 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.

2.10.10 1-Month and 3-Month Follow-up Visits

Subjects will undergo clinical evaluations according to **Table 1** at approximately 1- and 3-months post-treatment.

The following procedures will be performed:

- Endoscopic Assessment: Evaluation of the nasal cavity by endoscopic assessment (recorded). A Lund-Kennedy score should be assigned to each nostril.
- Assessment for any adverse events.
- Review and collection of concomitant medications. Any changes to their medications will be documented.
- The subject will complete the rTNSS, postnasal drip and cough assessment, NOSE score and subject satisfaction at the 1-month follow-up visit.
- The subject will complete the rTNSS, postnasal drip and cough assessment, NOSE score, mini-RQLQ and subject satisfaction at the 3-month follow-up visit.
- The CGI-I will be assessed by the investigator at the 3-month follow-up visit.

2.10.11 6-, 9-, 12-, 15-,18-, 21-, 24-Month Follow-up Visits

Subjects will undergo additional follow-up evaluations according to **Table 1** at approximately 6-, 9-, 12-, 15-, 18-, 21- and 24-months post treatment. The 9-month, 15-month and 21-month visits can be completed via phone/virtual.

The following procedures will be performed:

- Assessment for any adverse events.
- Review and collection of concomitant medications. Any changes to their medications will be documented.
- The subject will complete the rTNSS, postnasal drip and cough assessment, NOSE score, and subject satisfaction at all follow-ups.
- The subject will complete the mini-RQLQ at the 6-, 12-, 18-, and 24-month follow-ups.
- The subject will complete the ETDQ-7 at the 6-, 12- and 24-month follow-ups.
- The CGI-I will be assessed by the investigator at the 6-, 12-, 18-, and 24-month follow-ups.

2.10.12 Screen Failures

Subjects who sign an informed consent form but do not meet the eligibility criteria prior to the NEUROMARK® procedure or decline study participation will be considered screen failures.

2.10.13 Study Completion or Premature Withdrawal

Subjects will be formally exited from the study through completion of the Study Exit CRF at the time of study completion. Prior to exiting a subject from the study, it is recommended to follow the subject until all ongoing device-related and/or procedure-related AEs are resolved or unresolved with no further actions planned.

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

- 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.

2.11 Subject Assessments

Enrolled subjects will be required to complete all assessments listed in the Study Assessment schedule in **Table 1.**

2.11.1 Screening Assessments

Allergy Testing

All subjects must have an allergy test (by skin prick or intradermal testing, or by a validated *in vitro* Immunoglobin E [IgE test]) on file within 5 years of the baseline visit or is willing to have one performed during the study prior to 6-month visit.

COVID-19 Test for Active Infection

A negative COVID-19 test for active infection is required prior to treatment. The COVID-19 test will also be performed if the subject is suspected to be symptomatic for COVID-19 at any point during the study.

Demographics and medical history

Information on the subject's age, gender, race and ethnicity will be collected. Active medical history will be collected including chronic rhinitis symptoms, allergies and nicotine smoking status (past, current or never smoker). All past surgeries and cancer history will be recorded.

Endoscopic Assessment

An endoscopic assessment should be performed, and a Lund-Kennedy score should be assigned to each nostril. Endoscopy recordings should be provided to the sponsor.

Urine Pregnancy Test

A negative urine pregnancy test is required for all women of childbearing potential before the procedure.

2.11.2 Primary Endpoint Assessments

Reflective Total Nasal Symptom Score (rTNSS)

The rTNSS is a validated patient-reported outcome (PRO) used to describe symptoms of rhinitis. The subject will be asked to rate their nasal symptoms over the 12 hours prior to questionnaire completion. The subject can rate their symptoms as 0=none, 1=mild, 2=moderate or 3=severe in 4 domains: nasal congestion, runny nose, nasal itching and sneezing.

Serious Adverse Events

The subject will be assessed for SAEs. SAEs that are related to the device-and/or procedure will be evaluated as part of the primary safety endpoint.

2.11.3 Secondary Endpoint Assessments

Clinical Global Impression Improvement (CGI-I)

The investigator will be asked to complete the CGI-I that asks, "compared to the rhinitis symptoms at baseline, how much has the subject's symptoms changed?" 1=very much improved; 2=much

improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse.

Mini-Rhinoconjunctivitis Quality of Life Questionnaire (mini-RQLQ)

The subject will complete the mini-RQLQ rating how their symptoms have impacted their quality of life. The assessment consists of 14 questions related to nose symptoms, eye symptoms, activity limitations, practical problems, and other symptoms. Each item is scored from 0=not troubled to 6=extremely troubled.

Numeric Rating (NRS) scale for procedure tolerability

The subject will be asked to rate the procedure and anesthesia tolerability on a scale of 0 to 10. Zero being no discomfort and 10 being the most discomfort they have ever experienced.

Subject Satisfaction

Subjects will rate their overall satisfaction with the procedure on a satisfaction questionnaire that consists of one statement. The statement is "subject is satisfied with the NEUROMARK® procedure." The subject will rate their satisfaction as: strongly agree, agree, does not agree or disagree, disagree, strongly disagree, unknown.

2.11.4 Additional Evaluations Assessments

Nasal Obstruction Symptom Evaluation (NOSE) score

The subject will be asked to rate the impact of nasal obstruction on their quality of life, using a 5-item survey that rates their symptoms on a range of 0=not a problem to 4=severe problem.

Postnasal drip

The subject will rate their postnasal drip symptoms as none, mild, moderate or severe over the 12 hours prior to questionnaire completion.

Cough

The subject will rate their cough symptoms as none, mild, moderate or severe over the 12 hours prior to questionnaire completion.

Eustachian Tube Dysfunction Questionnaire (ETDQ-7)

The subject will rate their eustachian tube/ear symptoms over the 1-month prior to questionnaire completion on a 7-item survey on a range of 1=no problem to 7=severe problem.

3 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.

3.1 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**.

3.2 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.

3.3 Minimization of Anticipated Risks

The PARAGON Study has been reviewed against the criteria for significant risk devices (21 CFR 812.3(m) and has been classified as a non-significant risk study (NSR).

Risks associated with the NEUROMARK® System are minimized by design and additional risk assessment and testing has been conducted to assess the modifications to the cleared device thus ensuring that 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 modified device (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

4 DEVICE DESCRIPTION

Neurent Medical has received clearance to market the NEUROMARK® System in the USA under an FDA Class II device designation. The NEUROMARK® System used in this PARAGON clinical investigation includes modifications to the device cleared by FDA (these modifications are pending market clearance from FDA). These modifications are made to ensure a sustained supply chain, improve manufacturability of the device and are not intended to change the safety or effectiveness profile of the device.

The NEUROMARK® System is composed of the NEUROMARK® Device and the NEUROMARK® Radiofrequency (RF) Console.

The NEUROMARK® Device (**Figure 3**) is a hand-held single-use bipolar radiofrequency device which comprises a handle, shaft, and treatment tip. The treatment tip, which is referred to as the End Effector, consists of an array of bipolar electrodes that deliver bipolar RF energy while monitoring feedback on tissue bio-impedance changes allowing for controlled RF energy delivery. The shaft of the device is pre-shaped to aid access and delivery to the nasal cavity but is malleable to allow the user to bend or shape the shaft to accommodate variations in anatomy to access the desired treatment area. The NEUROMARK® Device is operated via handle, slider and activation button. Once in the desired position within the nasal cavity, the operator moves the slider backwards which retracts the outer sheath, deploying the End Effector. Using the activation button, the user initiates a bio-impedance check to assess and confirm contact between the End Effector and the treatment area. Once the System confirms contact has been achieved, a subsequent press of the activation button initiates the RF energy delivery cycle. The NEUROMARK® Device is intended for single use and provided sterile (EtO).

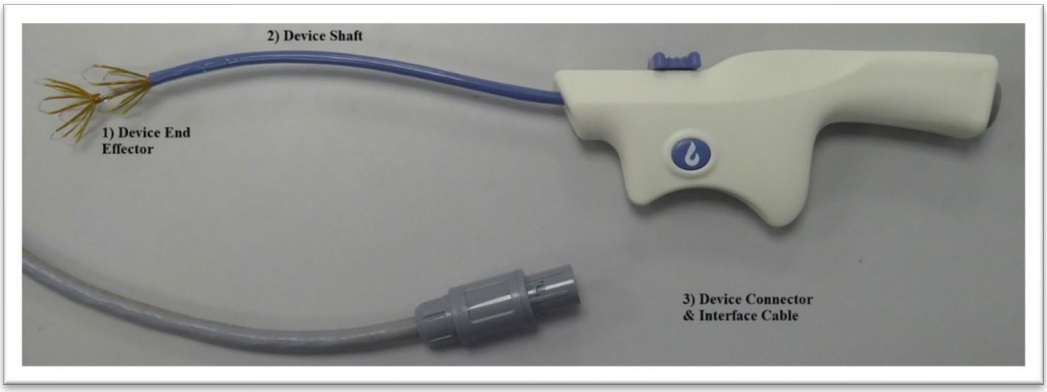


Figure 3: NEUROMARK® Device

The NEUROMARK® Device is designed for use with the NEUROMARK® Radiofrequency (RF) Console; it includes features to allow compatibility and authentication once connected, via a flexible cable, to the Console.

The NEUROMARK® Console (**Figure 4**) delivers, monitors and controls RF energy to the Device. The Console is mounted on an ergonomic mobile stand for ease of use. The Console includes a Graphical User Interface (GUI) which provides operational instructions for the procedure, directs the user to select nasal cavities for treatment, indicates when the device is in contact with tissue and ready to start treatment, provides status of therapy and indicates when the procedure is complete. The NEUROMARK® Console works in conjunction with software.



Figure 4: RF Console/Graphical Operator Interface

4.1 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**).

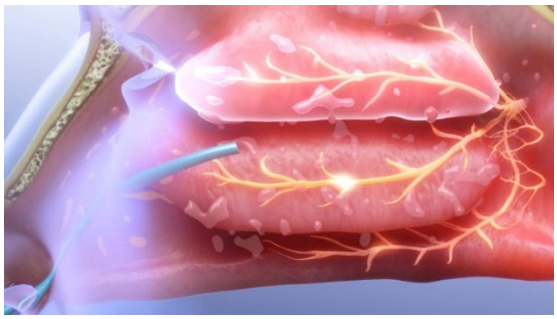


Figure 3: Introduction of the device into the nasal cavity - the end effector is not yet deployed.

Under endoscopic guidance, the physician will advance the device towards the posterior superior/inferior region of the nasal cavity.

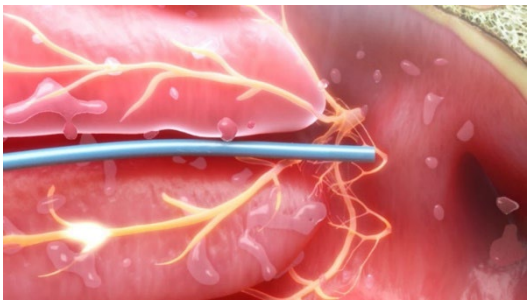
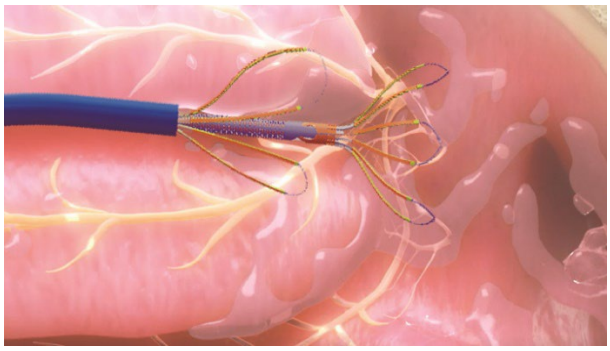


Figure 4: Device positioned in the correct target position prior to deployment of the end effector

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**).



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.

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.

5 INVESTIGATIONAL DEVICE ACCOUNTABILITY

Neurent Medical anticipates using one device per subject with an estimate of 80 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 along with the console and device accountability log. 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.

6 SAFETY MONITORING AND ADVERSE-EVENT REPORTING

6.1 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 2** and **Table 3** for Severity and Relationship categories and respective definitions.

The Investigator will use the following **(Table 2)** definitions to rate the severity of each adverse event:

Table 2: 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.

6.2 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 3**).

Table 3: 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 4**) and (**Table 5**).

Table 4: 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 5: 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
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.

6.3 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.

6.4 Contact Details for Reporting Adverse Events

Emergency Contact	AE Reporting Contact
Annalise Sorensen ☎ + 303-881-1757 ✉ Annalise@neurentmedical.com OR Lauren Yeager ☎ + 612-730-6790 ✉ Lauren@neurentmedical.com OR Karen Peterson ☎ + 651-398-4341 ✉ Karen@neurentmedical.com	Annalise Sorensen ☎ + 303-881-1757 ✉ Annalise@neurentmedical.com OR Lauren Yeager ☎ + 612-730-6790 ✉ Lauren@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.

6.5 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.

7 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.

8 STUDY MANAGEMENT

For this study, Neurent Medical will have certain direct responsibilities and will delegate other responsibilities to appropriate consultants and/or 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.

8.1 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.

8.2 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.

8.3 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.

8.4 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.

8.5 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.

8.6 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.

8.7 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.

8.8 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.

8.9 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.

8.10 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.

8.11 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.

8.12 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.

8.13 Insurance

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

9 RESPONSIBILITIES

9.1 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 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 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 Approved ICF
  - → Names/contact information for study monitor(s)
  - → Records of any adverse events
  - → Statistical analyses and underlying supporting data
  - → Final report

9.2 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.

9.3 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 of 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).

9.4 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.

9.5 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.

9.6 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 6: 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 6**:**

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.

10 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.

10.1 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 Management 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)
Lauren Yeager ☎ + 612-730-6790 ✉ Lauren@neurentmedical.com

10.2 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.

10.3 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).

10.4 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.

10.5 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.

11 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.

11.1 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.

11.2 Final Report

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

11.3 Publication Policy

The PARAGON 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.**

12 DEFINITIONS AND ACRONYMS

Adverse Event (AE)
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 Global Impression – Improvement (CGI-I)

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)

Eustachian Tube Dysfunction Questionnaire (ETDQ-7)

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.

Mini Rhinoconjunctivitis Quality of Life Questionnaire (mini-RQLQ)

Nasal Obstruction Symptom Evaluation score (NOSE)

Numeric Rating Scale (NRS)

Patient Reported Outcomes (PRO)

Reflective Total Nasal Symptom Score (RTNSS)

Serious Adverse Event (SAE)

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, patient source worksheets, 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.

REVISION HISTORY

Version:	Summary of Changes:	Rationale for change
A	N/A – original document	N/A
B	• Addition of the cough assessment to screening, baseline and follow-up visits • Addition of the ETDQ-7 to baseline, 6-,12-and 24-month follow ups • Update anticipated study duration.	• Additional evaluations to measure symptom improvements • Study duration updated based on enrollment projections