

NEUROMARK RCT

CLINICAL INVESTIGATIONAL PLAN (CIP)

PROTOCOL #: CIP-0010.B

NCT06128200



NEUROMARK® Randomized Controlled Trial (RCT)

CLINICAL INVESTIGATIONAL PLAN (CIP)

PROTOCOL #: CIP-0010

Randomized Controlled Trial Comparing NEUROMARK® System to Sham Control in Patients with Chronic Rhinitis

A prospective, multicenter, randomized, sham-controlled, single-blinded, superiority trial

NEUROMARK RCT

Clinical Investigational Plan #: CIP-0010.B / Version: Apr 2024

Sponsor:	Neurent Medical, Ltd. No. 1 Oran Point, Main Street, Oranmore, Galway, Ireland
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PROTOCOL APPROVAL

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CONTENTS

ii INVESTIGATOR SIGNATURE PAGE 7
iii SPONSOR CONTACT INFORMATION 8
iii INVESTIGATIONAL PLAN SUMMARY 9
1 BACKGROUND AND PURPOSE 12
1.1 Clinical Background 12
1.2 Study Purpose 13
1.3 Neurent Medical's Solution 13
2 PROTOCOL 13
2.1 Study Design 13
2.1.1 Participant Flowchart 14
2.2 Study Objective 15
2.3 Study Endpoints 15
2.3.1 Primary Endpoints 15
2.3.2 Secondary Endpoints 15
2.3.3 Additional Evaluations 15
2.4 Study Size and Duration 15
2.5 Study Hypothesis 15
2.6 Sample Size Estimation 16
2.7 Data Analysis 16
2.8 Study Population 16
2.8.1 Inclusion Criteria 17
2.8.2 Exclusion Criteria 17
2.9 Concomitant Medications 18
2.10 Methods and Procedures 18
2.10.1 Table 1 Study Assessment Schedule 18
2.10.2 Eligibility Assessment 19
2.10.3 Informed Consent 19
2.10.4 Sinonasal medication washout guidelines 19
2.10.5 Screening 20
2.10.6 Enrollment 20

2.10.7 Randomization and Blinding 21
2.10.8 Procedure (Active and Sham) 22
2.10.9 30-Day Follow Up Visit 23
2.10.10 90-Day Follow Up Visit 23
2.10.11 Crossover Procedure and 30-Day Post Crossover Follow-up Visit 24
2.10.12 Screen Failures 24
2.10.13 Study Completion or Premature Withdrawal 24
2.11 Study Assessments 24
2.11.1 Screening Assessments 24
2.11.2 Primary Endpoint Assessment 24
2.11.3 Secondary Endpoint Assessments 25
2.11.4 Additional Assessments 25
3 RISK – BENEFIT ASSESSMENT 25
3.1 Potential Benefits 25
3.2 Potential Risks 25
3.3 Minimization of Anticipated Risks 26
4 DEVICE DESCRIPTION 26
4.1 Device Operation 27
5 DEVICE ACCOUNTABILITY 27
6 SAFETY MONITORING AND ADVERSE-EVENT REPORTING 28
6.1 Adverse Events 28
6.2 Assessment of Relationship 28
6.3 Serious Adverse Events 30
6.4 Contact Details for Reporting Adverse Events 31
6.5 Device Failures and Malfunctions 31
7 PROTOCOL DEVIATIONS 32
8 STUDY MANAGEMENT 32
8.1 Participant Recruitment 32
8.2 Participant Reimbursement 32
8.3 Key Study Contributors 32
8.4 Regulatory Considerations 33
8.5 Approved Informed Consent 33
8.6 IRB 33

8.7 Amendment to the Clinical Investigational Plan (CIP) 33
8.8 Ethical Considerations 33
8.9 Protection of Patient Confidentiality 34
8.10 Study Monitoring 34
8.11 Quality Assurance and Supervision by Authorities 34
8.12 Corrective and Preventative Action 35
8.13 Insurance 35
9 RESPONSIBILITIES 35
9.1 Sponsor Responsibilities 35
9.2 Sponsor Maintenance of Study Records 36
9.3 Investigator Responsibilities 36
9.4 Investigator Reports 37
9.5 Required Documents from the Investigator 37
9.6 Other Investigator Reports 38
10 DATA MANAGEMENT 38
10.1 Data Management Responsibilities 38
10.2 Data Entry 39
10.3 Data Cleaning 39
10.4 Data Retention and Back-up 39
10.5 Confidentiality and Security 39
11 STUDY CLOSE-OUT 39
11.1 Study Suspension or Early Termination 39
11.2 Final Report 40
11.3 Publication Policy 40
12 BIBLIOGRAPHY 40
REVISION HISTORY 41

APPENDICES

Appendix A	Investigator's Brochure
Appendix B	Instructions for Use (IFU)
Appendix C	*Example* Informed Consent Form
Appendix D	*Example* Investigator Agreement
Appendix E	Financial Disclosure and Conflict of Interest Form
Appendix F	Patient Reported Outcome Questionnaires

II INVESTIGATOR SIGNATURE PAGE

NEUROMARK RCT

Investigator Signature Page

Randomized Controlled Trial Comparing NEUROMARK System to Sham Control in Patients with Chronic Rhinitis

NEUROMARK RCT

Protocol # / Version Date: CIP-0010.B / Apr 2024

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 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.

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 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.

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III INVESTIGATIONAL PLAN SUMMARY

Study Title:	Randomized Controlled Trial Comparing NEUROMARK System to Sham Control in Patients with Chronic Rhinitis
Short Title:	NEUROMARK RCT
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.
Study Objective:	To demonstrate that treatment with the NEUROMARK System is superior to a sham procedure in patients with chronic rhinitis
Study Design:	A prospective, multicenter, randomized, sham-controlled, single-blinded, superiority trial
Study Size:	This study aims to evaluate 132 study participants randomized 2:1 to active treatment (88) or sham control (44) at up to 20 clinical sites in the United States. No site may enroll more than 30% (40 participants) of the study population unless approved by Sponsor.
Study Population:	Adults with chronic rhinitis
Study Procedure:	Participants that provide informed consent and meet study eligibility requirements will be randomized 2:1 to receive either active treatment or sham control procedure.
Active Procedure:	The active treatment procedure will be performed following the NEUROMARK System Instructions for Use (IFU), **Appendix B**.
Sham Procedure:	For the sham control procedure, local anesthesia will be administered, the NEUROMARK device will be placed in the nasal cavities, and an audio recording that simulates active treatment will be played, but no RF energy will be delivered.
Study Visits:	Participants will be evaluated at the following visits: • Screening • Randomization and Procedure • 30-day post procedure follow-up • 90-day post procedure follow-up

Additionally, sham control participants will be offered the option to receive active treatment after the 90-day follow-up if they continue to meet eligibility criteria. Those choosing to do so will be followed for 30-days post crossover procedure for AE assessment only.

Measures:

The following efficacy measures will be utilized:

1. Reflective Total Nasal Symptom Score (rTNSS)
2. Mini Rhinoconjunctivitis Quality of Life Questionnaire (mini-RQLQ)
3. Nasal Obstruction Symptom Evaluation (NOSE)
4. Postnasal drip and cough
5. Patient Health Questionnaire-9 (PHQ-9)

Primary Endpoint:

Comparison of the percentage of responders (participants with a 30% or greater reduction in rTNSS relative to baseline) between study arms at 90-days

Secondary Endpoints:

The following secondary endpoints will compare the study arms at 30-day and 90-day follow-ups:

- The mean change from baseline in the rTNSS score
- The mean change from baseline in the mini-RQLQ score
- The mean change from baseline in the NOSE score
- Incidence of device- and/or procedure-related serious adverse events (SAEs)

Additional Evaluations:

The following additional evaluations will compare the study arms at 30-day and 90-day follow-ups:

- The mean change from baseline in rTNSS subscores
- The percent of participants achieving the MCID in mini-RQLQ score (≥0.4 point improvement compared to baseline)
- The percent of NOSE responders (at least one NOSE class improvement or reduction of ≥20% compared to baseline)
- The mean change from baseline in postnasal drip and cough
- The mean change from baseline in PHQ-9 (90-day follow-up only)

Additional outcomes may be assessed per the Statistical Analysis Plan (SAP).

Anticipated Duration:

The study is anticipated to begin enrollment in Q4 of 2023 with enrollment complete in Q4 of 2024. The last patient visit is expected to take place by or during Q1 of 2025.

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.

Inclusion Criteria

Participant **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. Be an appropriate candidate for bilateral NEUROMARK device treatment performed under local anesthesia.
5. Be willing and able to comply with all study elements, as indicated by written informed consent.

Exclusion Criteria

Participant **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 3 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. Be unable to discontinue ipratropium bromide (IB) at least 14 days before screening and through the 90-day follow-up visit.
11. Have a history of chronic epistaxis or experienced a significant epistaxis event (defined as epistaxis requiring medical intervention) in the past 3 months.
12. Have numbness of the soft palate, excessive dry eye, excessive dry nose, or other indication of neuro/nerve compromise in the sinonasal cavity.
13. Have active rhinitis medicamentosa or a history of rhinitis medicamentosa within the past 6 months.
14. Have been diagnosed with atrophic rhinitis.
15. Have had previous head and/or neck irradiation.
16. Have autoimmune disorders which affect the nose such as Sarcoidosis, Wegener's.
17. Be on or be required to be on CPAP.
18. Have an allergy or intolerance to local anesthetic agents.
19. Be pregnant.
20. Have a physical, neurological, medical, psychiatric condition or situation that, in the investigator's opinion, puts the participant at risk, could confound the study results, or may interfere significantly with the participant's participation in the study.
21. Be participating in another clinical research study.

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. The handheld device is connected to a RF Console which provides controlled delivery of energy to the treatment tip.

1.1 Clinical Background

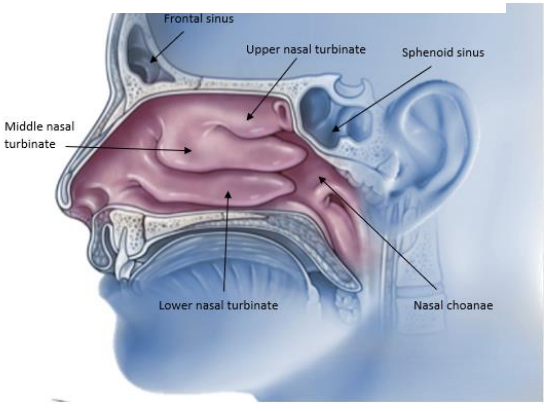
Rhinitis refers to inflammation of nasal mucosa, the tissue that lines the nasal cavity. This inflammation can cause nasal congestion, nasal discharge (rhinorrhea), sneezing, postnasal drainage, and numerous other symptoms adversely affecting quality of life.

The prevalence of allergic rhinitis (AR) and non-allergic rhinitis (NAR) taken together as chronic rhinitis (CR) may be greater than 30% of the US population; over half of these CR patients exhibit both allergic and non- allergic pathology and would be termed 'mixed rhinitis' [1,2].

Chronic rhinitis is associated with direct healthcare costs of up to $8.6 billion per year in the US. More than half of these costs are attributed to prescription medication. The estimated hidden costs stand to be much greater, as there is a direct correlation with the development of rhinitis and progression to both asthma and chronic sinusitis.[3] Chronic rhinitis has a major impact on quality of life, cognitive function, decision-making and self- perception and is associated with decreased work productivity and absenteeism. Indirect costs due to missed days from work, presenteeism, lost leisure activities, and overall quality of life range between $5.5 and $9.7 billion per year.[4]

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 1: Nasal cavity



Treatment options for chronic rhinitis include medications such as systemic or topical antihistamines, topical corticosteroids, decongestants, anticholinergics, mast cell stabilizers, leukotriene receptor antagonists, and nasal saline. Chronic rhinitis can also be treated with immunotherapy, commonly referred to as the allergy shot. Allergen avoidance can also help to prevent chronic rhinitis.[5,6] 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. [7] This is a surgery in which the turbinate size is permanently reduced.

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.[8] Although efficacious, vidian neurectomy may be complicated by persistent dry eye symptoms due to collateral disruption of the parasympathetic innervation of the lacrimal gland arising partially from the vidian nerve. [9,10]

Research has shown that the inflammatory process of the nasal mucosa is driven by branches of the parasympathetic nerves embedded in tissues of the inferior turbinate and the lateral nasal wall. This is the motor supply of the inflammatory cascade, controlling the signaling function and the resulting physiological effects of the sub-mucosal glands (rhinorrhea) and venous sinuses (congestion) within the nasal tissue.[10]

Disruption of the parasympathetic nerves to the lateral nasal wall has been proven to reduce both congestion and rhinorrhea in rhinitis patients.[10]

1.2 Study Purpose

The purpose of this randomized controlled trial is to demonstrate the superiority of treatment with the NEUROMARK system compared to a sham procedure in patients with chronic rhinitis.

1.3 Neurent Medical's Solution

The NEUROMARK System is indicated for use in otorhinolaryngology (ENT) Surgery for creation of radio frequency (RF) lesions to disrupt posterior nasal nerves in patients with chronic rhinitis.

The NEUROMARK System is designed to treat symptoms of chronic rhinitis in the ENT physician's office or operating room with a high degree of patient comfort. The system is engineered to gently apply controlled low-power Radio Frequency (RF) energy to target regions of the nasal cavity to disrupt the parasympathetic nerve signals and halt the inflammatory response and may reduce core symptoms such as congestion and rhinorrhea. Using proprietary algorithms and biofeedback monitoring features, the intelligent system is designed to precisely deliver energy to the target nerve-dense region while restricting energy and minimizing damage to surrounding tissue and improving patient comfort.

The NEUROMARK system is designed with an algorithm control to validate placement check and the RF delivery monitors the tissue composition and limits unnecessary harm to the area. The unique therapy leaflet design enables access to a larger treatment area while accommodating for varying and restricted anatomy. Multiple nerve branches can be treated with a single placement. The procedure has been well tolerated using local anesthetic.[11]

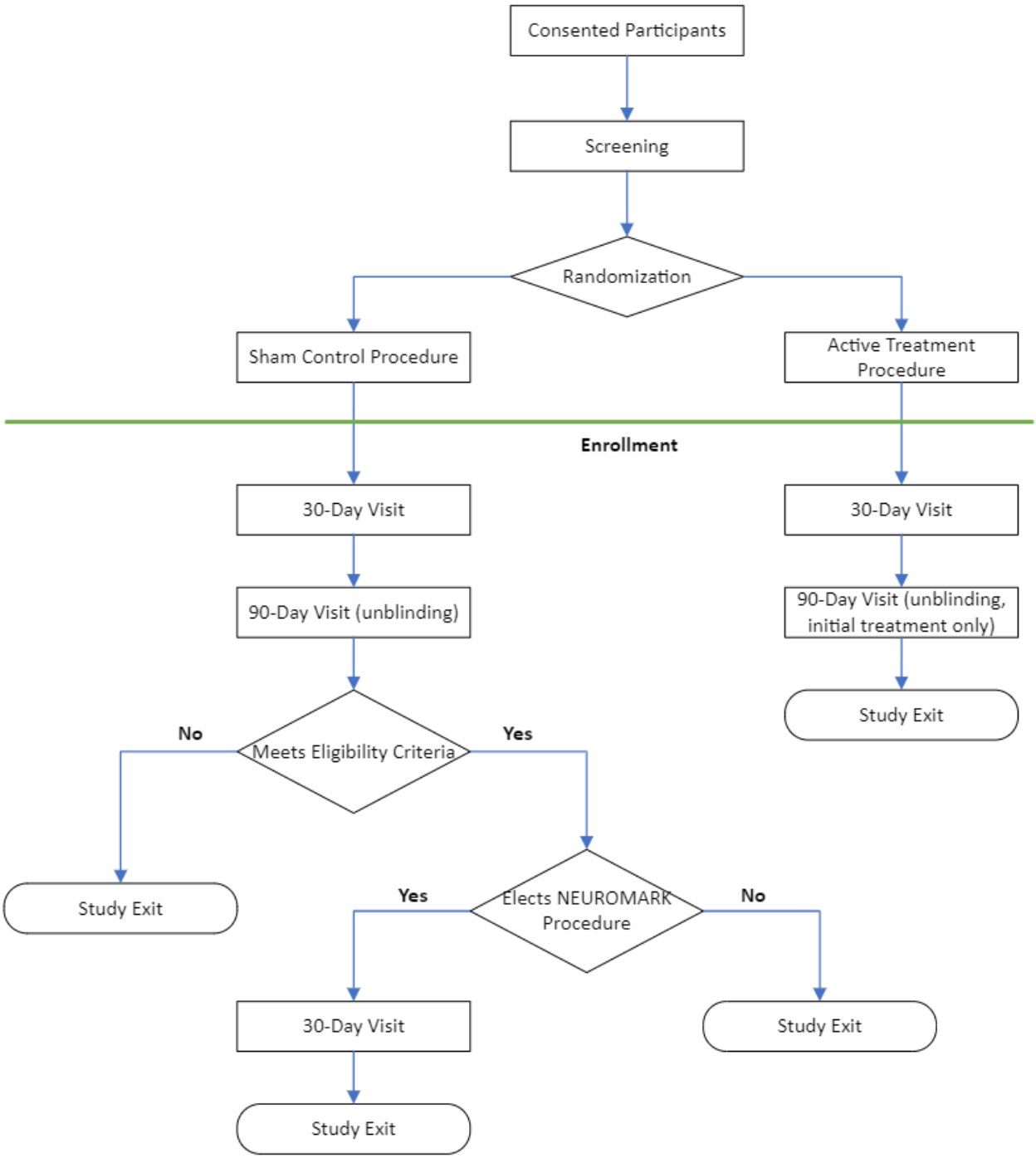
2 PROTOCOL

2.1 Study Design

This study is a prospective, multicenter, randomized, sham-controlled, single-blinded, superiority trial. Eligible participants will be randomized 2:1 to active treatment or sham control. Participants will be blinded to their treatment assignment until completion of the 90-day visit. Active treatment participants will exit the study after the 90-day visit. Sham control participants will be offered the option to crossover to active treatment if they continue to meet eligibility criteria. Those choosing to do so will be followed

for 30-days post crossover procedure for assessment of AEs only. Those electing not to crossover will exit the study after the 90-day visit.

2.1.1 Participant Flowchart



2.2 Study Objective

The objective of this randomized controlled trial is to demonstrate that treatment with the NEUROMARK System is superior to a sham procedure in patients with chronic rhinitis.

2.3 Study Endpoints

2.3.1 Primary Endpoints

The primary endpoint is the comparison of the percentage of responders (participants with a 30% or greater reduction in rTNSS relative to baseline) between study arms at the 90-day follow up visit.

2.3.2 Secondary Endpoints

The following secondary endpoints will compare the study arms at the 30-day and 90-day follow up visits:

- The mean change from baseline in the rTNSS score.
- The mean change from baseline in the mini-RQLQ score
- The mean change from baseline in the NOSE score
- Incidence of device- and/or procedure-related SAEs

2.3.3 Additional Evaluations

The following additional evaluations will compare the study arms at 30-day and 90-day follow up visits:

- The mean change from baseline in rTNSS subscores
- The percent of participants achieving the MCID in mini-RQLQ score (≥0.4 point improvement compared to baseline)
- The percent of NOSE responders (at least one NOSE class improvement or reduction of ≥20% compared to baseline)
- The mean change from baseline in postnasal drip and chronic cough
- The mean change from baseline in PHQ-9 (90-day follow-up only)

Additional outcomes may be assessed as outlined in the SAP.

2.4 Study Size and Duration

This study aims to evaluate 132 study participants at up to 20 clinical sites in the United States. No site may enroll more than 30% (40 participants) of the study population unless approved by Sponsor. The study is anticipated to begin enrollment in Q4 of 2023 with enrollment complete in Q4 of 2024. The last patient visit is expected to take place by or during Q1 of 2025.

2.5 Study Hypothesis

The primary endpoint is the comparison of the percentage of responders (participants with a 30% or greater reduction in rTNSS relative to baseline) between study arms at the 90-day follow up visit. The primary endpoint will be assessed for superiority of active treatment to sham treatment by testing the following 1-sided hypotheses using the Chi-square or Fisher exact test of 2 proportions:

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

Versus

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

where p_{Active} and p_{sham} are the percentages of rTNSS responders in the active treatment and sham control arms, respectively.

2.6 Sample Size Estimation

Sample size estimation was based on comparison of 2 proportions using a Fisher exact test with the following assumptions:

- 90% power
- 2.5% 1-sided type 1 error
- 2:1 randomization allocation
- Responder rate of 75% in active treatment arm
- Responder rate of 44% in sham control arm

The estimated active response rate is based on prior clinical results for the NEUROMARK device at 3-months post procedure. The estimated sham response rate is based on published 3-month results from RCTs of RhinAer device (41%),[12] ClariFix device (36.5%),[13] and placebo rate reported by Benninger et all for review of rhinitis pharmaceutical studies (25%).[14] To ensure an adequate sample size, the anticipated placebo rate was slightly increased from these values.

Under the assumptions outlined above, a total sample size of 120 randomized participants is adequate to test the hypothesis. To account for 10% attrition at 90 days, a total of 132 participants (88 in active treatment arm and 44 in sham control arm) will be enrolled in the study.

2.7 Data Analysis

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

2.8 Study Population

The study population is comprised of adults with chronic rhinitis. Participants considered for enrollment must meet all the inclusion criteria and none of the exclusion criteria.

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

2.8.1 Inclusion Criteria

Participants **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. Be an appropriate candidate for bilateral NEUROMARK device treatment performed under local anesthesia.
5. Be willing and able to comply with all study elements, as indicated by written informed consent.

2.8.2 Exclusion Criteria

Participants **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 3 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. Be unable to discontinue ipratropium bromide (IB) at least 14 days before screening and through the 90-day follow-up visit.
11. Have a history of chronic epistaxis or experienced a significant epistaxis event (defined as epistaxis requiring medical intervention) in the past 3 months.
12. Have numbness of the soft palate, excessive dry eye, excessive dry nose, or other indication of neuro/nerve compromise in the sinonasal cavity.
13. Have active rhinitis medicamentosa or a history of rhinitis medicamentosa within the past 6 months.
14. Have been diagnosed with atrophic rhinitis.
15. Have had previous head and/or neck irradiation.
16. Have autoimmune disorders which affect the nose such as Sarcoidosis, Wegener's.
17. Be on or be required to be on CPAP.
18. Have an allergy or intolerance to local anesthetic agents.
19. Be pregnant.
20. Have a physical, neurological, medical, psychiatric condition or situation that, in the investigator's opinion, puts the participant at risk, could confound the study results, or may interfere significantly with the participant's participation in the study.
21. 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.

Participants taking nasal anticholinergic sprays (eg, IB) must discontinue use at least 14 days before the screening visit and through the 90-day visit. Participants will also be instructed not to change their baseline concomitant medications (start/stop or change of dose) before the 90-day follow up, unless required to treat an adverse event.

2.10 Methods and Procedures

2.10.1 Table 1 Study Assessment Schedule

Study evaluation	Study Visit (window)					
	Screening (up to 30 days pre-procedure) [a,b]	**Randomization & procedure** (day 0)	**30-Day** (± 7 days)	**90-Day** (-0 days, + 21 days)	**Crossover procedure** (up to 30 days post-90-day visit) [c]	**30-Day post crossover procedure** (± 7 days) [d]
Informed consent	✓					
Demographics and medical history	✓					
Eligibility assessment	✓			✓[f]		
Urine pregnancy test [e]	✓					
Endoscopic assessment	✓					
Randomization & Procedure (active or sham)		✓				
Crossover Procedure					✓	
Adverse events		✓	✓	✓	✓	✓
Concomitant medications	✓	✓	✓	✓	✓	
rTNSS, postnasal drip and cough	✓		✓	✓		
mini-RQLQ	✓		✓	✓		
NOSE	✓		✓	✓		
PHQ-9	✓			✓		

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

[b] The participant must discontinue use of ipratropium bromide (IB) at least 14 days before screening visit.

[c] Sham control participants will be offered the option to receive active treatment after the 90-day follow-up if they continue to meet eligibility criteria. Crossover procedure must take place within 30 days of 90-day visit.

[d] Participants will be followed 30 days post crossover procedure to assess AEs only. Visit can be completed via phone/virtual.

[e] Urine pregnancy tests are required for all women of childbearing potential.

f Only for sham control participants who elect to receive active treatment.

2.10.2 Eligibility Assessment

Adult patients 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. Patients whose records support potential eligibility may be approached regarding the study and, if interested, the potential participant will be asked to provide written informed consent before protocol-driven evaluations 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 patient. The background of the proposed study and the benefits and risks of the procedures and study will be explained to the patient. The patient 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 participant 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 participants and the authorized study personnel obtaining informed consent must sign and date the ICF. A copy must be given to the participant.

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

Once written consent has been obtained, the participant will be entered on a site-specific screening log. All participants *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 participants throughout the duration of the study.

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

If a participant 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 Sinonasal medication washout guidelines

The participant must discontinue the use of ipratropium bromide (IB) at least 14 days before the screening visit. The participant must be willing to discontinue IB through the 90-day follow up visit.

2.10.5 Screening

The Screening Visit can be performed up to 30 days before the procedure. Note: The Screening Visit can be performed on the same day as the procedure. However, be aware that the participant may not meet all eligibility requirements, and then the procedure would need to be cancelled.

The following must be completed at the screening visit:

- Informed Consent
- Collect and review demographics, medical history and concomitant medications.
- Eligibility Assessment: participant should meet all of the inclusion and none of the exclusion criteria.
- Urine pregnancy test: a negative urine pregnancy test is required for all women of childbearing potential.
- Endoscopic Assessment
- The participant will complete Screening/Baseline rTNSS, postnasal drip and cough questionnaire, mini-RQLQ, NOSE, and PHQ-9.

2.10.6 Enrollment

The participant will be considered enrolled once the informed consent is obtained, they meet the study eligibility criteria, and receive the procedure (active or sham).

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

Definition of Enrollment: Participants will be considered enrolled once they are consented, meet eligibility criteria, and have received the procedure (active or sham).

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

Unique Study ID Assignment

At the time of enrollment, a unique study identification (ID) will be assigned to the participant and the unique ID entered. The site will maintain a study participant name log which will link the unique study Subject ID code to the participant. 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 participant 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 participant for the entire study.

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

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

Site # + Participant Sequence Number + Name Code

___ ___ + _7_ ___ ___ + ___ ___ ___ ___ ___

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 participant's unique study identification code.

Example = Site 01

Participant Sequence #: These numbers should be assigned in sequential order. Each site will begin with 01 and assign sequentially within their study center.

Example = Site 01's third (3rd) → Participant Sequence # is: 01- 703

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

Should characters not be available (e.g., participants' 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 third participant whose name is John Smith

Unique Subject ID Code Example: 01-703-HNITH

2.10.7 Randomization and Blinding

Randomization will occur the day of the procedure and after all screening data have been collected and eligibility criteria have been confirmed. The randomization treatment assignments will be generated by SMART-TRIAL electronic data capture (EDC) randomization module using a variable block size distribution by site with a 2:1 allocation to active or sham treatment. Sites will be trained at site initiation to follow detailed randomization instructions to assure strict adherence to the randomization process.

This is a single-blind study; participants will be blinded to the randomization assignment. The following will be incorporated during the procedure to support patient blinding:

- Participants will receive local anesthesia regimens per physician preference.
- Participants will wear blindfolds during the procedure to limit any visual clues that could suggest the treatment assignment.
- A standard script for the physician/staff will be used during both active and sham procedure to promote blinding.

Upon completion of the 90-day follow-up visit, each participant will be unblinded. Sham control participants will be offered the opportunity to crossover and receive active treatment if they continue to meet eligibility criteria.

2.10.8 Procedure (Active and Sham)

Randomization should occur just prior to perfoming the procedure but allowing enough time for preparation of the assigned treatment (active procedure or sham procedure). The blinding guidelines listed in **Section 2.10.7** will be followed.

Below is a high-level description of the procedure steps for both the active and sham procedures:

Study procedure

1. Ensure all required supplies are present for the procedure, including NEUROMARK System, blindfold, standard script, and audio recording as necessary.
2. Perform endocsopic rhinoscopy to plan target device placement in nasal cavity.
3. Administer local anesthesia regimen for the procedure per physician preference.
4. Have the participant put on the blindfold.
5. If assigned to **active treatment**, perform treatment procedure following the NEUROMARK System Instructions for Use (IFU) found in **Appendix B**.
6. If assigned to **sham control treatment**, ensure the console is turned off to ensure no energy is delivered to the participant. Place the NEUROMARK device in the first nasal cavity and play the audio recording that simulates active treatment. Repeat these steps for the contralateral side.

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 participant's identity will be concealed and patient confidentiality will be maintained.

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

- Randomization assignment (active or sham)
- Type of anesthesia
- Procedure duration
- Treatment received (active or sham)
- Assessment for any adverse events
- Review of concomitant medications

The NEUROMARK System device is intended for use by appropriately trained medical 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 by a trained medical professional.

Reminder: Device Accountability
Once opened, each NEUROMARK device must be documented on the study's Device Accountability Log.

Post-Treatment Pain Medications

Both active and sham participants should receive the post-procedure regimen per each sites standard practice. Participants 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 participant's file and any potential related risk will be discussed with the participant.

2.10.9 30-Day Follow Up Visit

Participants will undergo clinical evaluations according to **Table 1 in Section 2.10.1** at approximately 30-days post-procedure.

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 participant will complete the rTNSS, postnasal drip and cough questionnaire, mini-RQLQ and NOSE.

2.10.10 90-Day Follow Up Visit

Participants will undergo clinical evaluations according to **Table 1 in Section 2.10.1** at approximately 90-days post-procedure.

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 participant will complete the rTNSS, postnasal drip and cough questionnaire, mini-RQLQ, NOSE, and PHQ-9.

At the end of this visit, and after all the above participant patient reported outcomes (PROs) are completed, participants will be unblinded to their treatment assignment.

- **Active Procedure Arm:** Participants who received the active procedure will exit the study. See **Section 2.10.12** for study completion guidelines**.**
- **Sham Control Arm:** Sham control participants will be offered the option to receive active treatment after the 90-day follow-up provided they still meet all eligibility criteria. If the participant does not elect to receive the crossover procedure, they will exit the study per **Section 2.10.13**.

2.10.11 Crossover Procedure and 30-Day Post Crossover Follow-up Visit

The crossover procedure must take place within 30 days of the 90-day visit. The procedure will be conducted according to the IFU. The participant will be assessed for adverse events approximately 30-days post-crossover procedure. This visit can be completed via phone/virtual.

2.10.12 Screen Failures

Participants 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

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

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

- Loss to follow-up (following 3 documented attempts to reach participant).
- In the physician's opinion, it is not in the best interest of the participant to continue study participation.
- Participant withdrawal, meaning that participant voluntarily chooses not to participate in the study.

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

2.11 Study Assessments

Enrolled participants will be required to complete all assessments listed in the Study Assessment schedule (Table 1) in **Section 2.10.1.**

2.11.1 Screening Assessments

Demographics and medical history

Information on the participant'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.

Urine Pregnancy Test

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

Endoscopic Assessment

An endoscopic assessment should be performed to confirm eligibility criteria.

2.11.2 Primary Endpoint Assessment

Reflective Total Nasal Symptom Score (rTNSS)

The rTNSS is a validated PRO used to describe symptoms of rhinitis. The participant will be asked to rate their nasal symptoms over the 12 hours prior to questionnaire completion. The participant 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.

2.11.3 Secondary Endpoint Assessments

Mini-Rhinoconjunctivitis Quality of Life Questionnaire (mini-RQLQ)
The participant 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.

Nasal Obstruction Symptom Evaluation (NOSE) score
The participant 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.

Serious Adverse Events
The participant will be assessed for SAEs. SAEs that are related to the device-and/or procedure will be evaluated as part of the secondary endpoint.

2.11.4 Additional Assessments

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

Patient Health Questionnaire-9 (PHQ-9)
The participant will be asked how often they have been bothered by problems related to depression over the past 2 weeks prior to questionnaire completion. Responses range from 0=not at all to 3 = nearly every day.

3 RISK – BENEFIT ASSESSMENT

3.1 Potential Benefits

It is anticipated that the NEUROMARK procedure may provide some benefit to the participant by improving their chronic rhinitis symptoms. However, there may be no direct benefits of study participation.

3.2 Potential Risks

Refer to the IFU for details concerning potential hazards/adverse events associated with the use of the device during the procedure or immediately post-procedure. These risks or potential adverse events are included here for completeness:

Potential adverse effects related to the use of radiofrequency energy on tissue in the nasal airway include infection, bleeding (mild or severe), mucosal trauma, mucosal perforation, superficial burns, temporary pain/discomfort, temporary headache, scar formation with increased obstruction, cosmetic deformity, sensory (olfactory) changes at treatment site, septal perforation, worsened eustachian tube function, atrophic rhinitis or dry nose.

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

Risks associated with the NEUROMARK System are minimized as the device has received FDA clearance.

4 DEVICE DESCRIPTION

Neurent Medical has received FDA clearance to market the NEUROMARK System in the USA under a Class II device designation.

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

The NEUROMARK Device (**Figure 2**) 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).

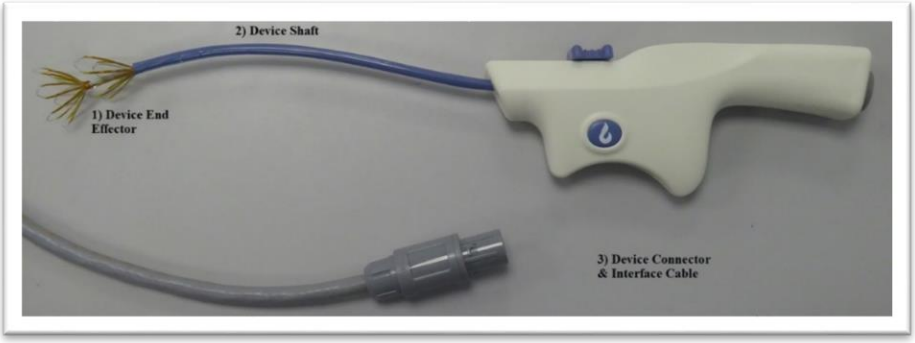


Figure 2: NEUROMARK Device

The NEUROMARK Console (**Figure 3**) 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 3: RF Console/Graphical Operator Interface

4.1 Device Operation

Refer to the IFU in **Appendix B** for device operation and device use details.

5 DEVICE ACCOUNTABILITY

Neurent Medical anticipates using one device per participant who is enrolled in the active treatment arm (88) and two devices per participant who are randomized to the sham control arm (44) and elect to have the crossover procedure for a total of approximately 176 devices.

Device inventory will be managed using a Device Accountability Log that will include details concerning device use during the study.

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, device identification number, expiration date, date of use, participant 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 procedure or during the follow-up phase. 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 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 device and/or study 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 Participant's usual activity or is transient, resolved without treatment **and** → no sequelae
Moderate	→ interferes with the Participant's usual activity **and/or** → requires symptomatic treatment
*Severe	→ symptom(s) causing severe discomfort **and** → significant impact of the Participant'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 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.
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** → Participant'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 Participant'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** → Participant's condition or concomitant therapy could have caused the AE

Relationship	Description
Probable	→ temporal sequence is relevant **or** → event abates upon procedure completion **or** → event cannot be reasonably explained by the Participant'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 should be reported to the Sponsor within 24 hours 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 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 ☎ (+1) 303-881-1757 ✉ Annalise@neurentmedical.com OR An An Hua ☎ (+1) 808-205-1865 ✉ AnAn@neurentmedical.com OR Karen Peterson ☎ (+1) 651-398-4341 ✉ Karen@neurentmedical.com	Annalise Sorensen ☎ (+1) 303-881-1757 ✉ Annalise@neurentmedical.com OR An An Hua ☎ (+1) 808-205-1865 ✉ AnAn@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 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 Participant'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 Participant 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., Participant 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 participant in an emergency will be reported to the study Sponsor in a timely manner and documented in a Protocol Deviation CRF. Participant specific deviations will be reported on the Protocol Deviation CRF. Non-Participant specific deviations, (e.g. unauthorized use of a device outside the study, unauthorized use of a 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 may 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 Participant Recruitment

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

8.2 Participant Reimbursement

Participants 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 participant'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; 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 the elements required by the study sponsor. Therefore, each study 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 study site for monitoring, and a copy provided to the participant.

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 participants 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 participant, 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 participant shall be preserved in the reports and in any publication. Each participant 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 participant list identifying all enrolled participants. This list will contain the assigned study participant'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 participant list and other personally identifying information of study participants 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 participant's name, address, date of birth, gender, race and medical record number.

The participant'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 participant confidentiality. Any participant identifiers will be blacked or scratched out and replaced with the participant's study identification code.

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 Good Clinical Practice: Consolidated Guidance.

The sponsor will be responsible for **monitoring the investigation** per Good Clinical Practice: Consolidated Guidance.

The sponsor will be responsible for **reporting** per 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 Good Clinical Practice: Consolidated Guidance. Records must be retained for a minimum of 2 years after the study is completed.

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 participant records are stored for at least 2 years after the study is completed. 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 study 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 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 study 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

Additional study-required documents will be collected 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 ☎ (+1) 303-881-1757 ✉ Annalise@neurentmedical.com

☞ Reports must identify participants 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)
An An Hua ☎ (+1) 808-205-1865 ✉ AnAn@neurentmedical.com

10.2 Data Entry

Participant 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 participants
- Unanticipated adverse device effect (UADE) presenting an unreasonable risk to participants (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)/study 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).

11.2 Final Report

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

11.3 Publication Policy

The NEUROMARK Randomized Controlled Trial will be registered in a publicly accessible database, ClinicalTrials.gov.

At the conclusion of the trial, a multi-center abstract reporting the results may 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.**

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REVISION HISTORY

Version:	Summary of Changes:	Rationale for change
A	N/A – original document	N/A
B	Increase number of sites from 15 to 20. Minor clarifications made to procedure.	Increased number of sites to help with enrollment.

NEUROMARK® RCT / CIP-0010

Statistical Analysis Plan

May 2024

Neurent Medical
No. 1 Oran Point, Main Street,
Oranmore, Galway,
Ireland

Approval:

Name	Title	Signature	Date
Karen Peterson	Vice President Clinical, Regulatory & Quality	DocuSigned by: Karen Peterson Signer Name: Karen Peterson Signing Reason: I approve this document Signing Time: 02-May-2024 | 11:08:26 AM PDT 5141B3248C2741C2B6BC44A65B5CCE72	02-May-2024
Manya Harsch	Consultant, Biostatistics	DocuSigned by: Manya Harsch Signer Name: Manya Harsch Signing Reason: I approve this document Signing Time: 02-May-2024 | 11:13:41 AM PDT C002E81C15BE4FDBB188465EB672ECDA	02-May-2024

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Table of Contents

1 Abbreviations 3

2 Introduction 4

3 Study Design 4

3.1 Study Objectives 4

3.1.1 Study endpoints 4

3.1.2 Statistical hypothesis 5

3.1.3 Sample size calculation and assumptions 5

4 General Analysis Definitions 5

4.1 Study Start and Duration of Follow-up 5

4.2 Randomization and Blinding 6

4.3 Analysis Sets 6

4.4 General Analytical Considerations 7

4.5 Outcome Variables 7

4.5.1 Safety outcome variables 7

5 Demographics and Medical History 7

5.1 Participant Disposition 7

6 Procedure Data 8

7 Efficacy Outcomes 8

7.1 Efficacy Analysis Cohort 8

7.2 Primary and Secondary Efficacy Endpoints 8

7.2.1 Reflective Total Nasal Symptom Score (rTNSS) 8

7.2.2 Mini Rhinoconjunctivitis Quality of Life Questionnaire (mini-RQLQ) 9

7.2.3 Nasal Obstruction Symptom Evaluation (NOSE) Score 9

7.3 Additional Efficacy Assessments 10

7.3.1 Postnasal Drip and Cough 10

7.3.2 PHQ-9 10

8 Safety Outcomes 10

8.1 Safety Analysis Cohort 10

8.2 Safety Secondary Endpoint 11

8.2.1 Device and/or procedure related serious adverse events (SAEs) 11
8.3 Additional Safety Assessments 11
8.3.1 All device and/or procedure related adverse events (AEs) 11
8.3.2 All adverse events 11
9 Protocol Deviations 11
10 Additional Statistical Analyses 11
10.1 Study Termination Criteria 11
10.2 Pooling Assessment 12
10.3 Blinding Assessment 12
10.4 Sensitivity Analyses and Missing Data Imputation 12
10.5 Multiplicity Adjustments 12
10.6 Planned Subgroup Analyses 12
10.7 Interim Analyses 12
11 Changes from Original Statistical Plan 12
12 References 12

1 Abbreviations

AE	Adverse event
CI	Confidence interval
CIP	Clinical Investigational Plan
EDC	Electronic Data Capture
MCID	Minimal clinically important difference
Mini RQLQ	Mini Rhinoconjunctivitis Quality of Life Questionnaire
NOSE	Nasal Obstruction Symptom Evaluation
NRS	Numeric Rating Scale
PHQ-9	Patient Health Questionnaire-9
PRO	Patient-reported outcome
RCT	Randomized Controlled Trial
rTNSS	Reflective Total Nasal Symptom Score
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation

2 Introduction

This statistical analysis plan (SAP) contains the definitions of analysis sets, derived variables, and statistical methods for the analyses of efficacy and safety data from the NEUROMARK Randomized Controlled Trial (RCT).

Participants will be considered enrolled in the study once the informed consent is obtained, they meet the study eligibility criteria, and receive the procedure (active or sham).

3 Study Design

This is a prospective, multicenter, randomized, sham-controlled, single-blinded, superiority trial (Clinical Investigational Plan #CIP-00010.B). Eligible participants will be randomized 2:1 to active treatment or sham control. Participants will be blinded to their treatment assignment until completion of the 90-day visit. Active treatment participants will exit the study after the 90-day visit. Sham control participants will be offered the option to crossover to active treatment if they continue to meet eligibility criteria. Those choosing to do so will be followed for 30-days post crossover procedure for assessment of adverse events (AEs) only. Those electing not to crossover will exit the study after the 90-day visit.

3.1 Study Objectives

The objective of this randomized controlled trial is to demonstrate that treatment with the NEUROMARK System is superior to a sham procedure in patients with chronic rhinitis.

3.1.1 Study endpoints

The primary endpoint is the comparison of the percentage of responders (participants with a 30% or greater reduction in rTNSS relative to baseline) between study arms at the 90-day follow up visit.

The following secondary endpoints will compare the study arms at the 30-day and 90-day follow up visits:

- The mean change from baseline in the rTNSS score.
- The mean change from baseline in the mini-RQLQ score
- The mean change from baseline in the NOSE score
- Incidence of device- and/or procedure-related SAEs

The following additional evaluations will compare the study arms at 30-day and 90-day follow up visits:

- The mean change from baseline in rTNSS subscores
- The percent of participants achieving the MCID in mini-RQLQ score (≥0.4 point improvement compared to baseline)
- The percent of NOSE responders (at least one NOSE class improvement or reduction of ≥20% compared to baseline)
- The mean change from baseline in postnasal drip and chronic cough
- The mean change from baseline in PHQ-9 (90-day follow-up only)

All statistical analyses will be performed using a validated statistical software package like Stata (version 17 or higher) or SAS, unless otherwise noted.

3.1.2 Statistical hypothesis

The primary endpoint is the comparison of the percentage of responders (participants with a 30% or greater reduction in rTNSS relative to baseline) between study arms at the 90-day follow up visit. The primary endpoint will be assessed for superiority of active treatment to sham treatment by testing the following 1-sided hypotheses using the Chi-square or Fisher exact test of 2 proportions:

$$H_0: p_{Active} \leq p_{sham} \quad \text{Versus} \quad H_A: p_{Active} > p_{sham}$$

where p_{Active} and p_{sham} are the percentages of rTNSS responders in the active treatment and sham control arms, respectively.

3.1.3 Sample size calculation and assumptions

Sample size estimation was based on comparison of 2 proportions using a Fisher exact test with the following assumptions:

- 90% power
- 2.5% 1-sided type 1 error
- 2:1 randomization allocation
- Responder rate of 75% in active treatment arm
- Responder rate of 44% in sham control arm

The estimated active response rate is based on prior clinical results for the NEUROMARK device at 3-months post procedure. The estimated sham response rate is based on published 3-month results from RCTs of RhinAer device (41%),[1] ClariFix device (36.5%),[2] and placebo rate reported by Benninger et all for review of rhinitis pharmaceutical studies (25%).[3] To ensure an adequate sample size, the anticipated placebo rate was slightly increased from these values.

Under the assumptions outlined above, a total sample size of 120 randomized participants is adequate to test the hypothesis. To account for 10% attrition at 90 days, a total of 132 participants (88 in active treatment arm and 44 in sham control arm) will be enrolled in the study.

4 General Analysis Definitions

4.1 Study Start and Duration of Follow-up

Enrollment and study start is the day of randomization and procedure for each participant. Before enrollment, participants will be assessed at screening. The procedure must take place within 30 days of the screening visit.

All participants will attend follow-up visits at 30 days and 90 days postprocedure. Additionally, sham control participants who opt to receive active treatment after the 90-day follow-up will be followed for 30-days post crossover procedure. All subjects will be followed through end of

study unless they discontinue or are lost to follow-up before that. A listing of subjects who discontinue before the final visit will be provided in the clinical study report with the last visit completed and the reason for discontinuation.

4.2 Randomization and Blinding

Randomization will occur the day of the procedure and after all screening data have been collected and eligibility criteria have been confirmed. The randomization treatment assignments will be generated by SMART-TRIAL electronic data capture (EDC) randomization module using a variable block size distribution by site with a 2:1 allocation to active or sham treatment. Sites will be trained at site initiation to follow detailed randomization instructions to assure strict adherence to the randomization process.

This is a single-blind study; participants will be blinded to the randomization assignment. The following will be incorporated during the procedure to support patient blinding:

- Participants will receive local anesthesia regimens per physician preference.
- Participants will wear blindfolds during the procedure to limit any visual clues that could suggest the treatment assignment.
- A standard script for the physician/staff will be used during both active and sham procedure to promote blinding.

Upon completion of the 90-day follow-up visit, each participant will be unblinded. Sham control participants will be offered the opportunity to crossover and receive active treatment if they continue to meet eligibility criteria.

4.3 Analysis Sets

The planned analysis cohorts are defined below.

Modified intent to treat (mITT): Participants that are randomized and have a procedure attempted will be included in the modified intent to treat analysis cohort. A procedure attempt is defined as the NEUROMARK device attempted to be inserted in the nasal cavity (e.g., a non-missing start time for device insertion on procedure form).

Modified per protocol (mPP): Participants that have no protocol deviations or issues that would impact the integrity of the main endpoint. Examples include inclusion/exclusion criteria violations, medication use violations, sham procedure violations, and unblinding prior to the 90 day visit. These deviations will be documented via a protocol deviation form and categorized by the sponsor as impacting the integrity of the data. Modification is that participants will be evaluated by the treatment that was received regardless of treatment assignment. Efficacy data will use the mPP analysis cohort.

As treated (AT): Participants will be analyzed by the treatment that was received regardless of randomization assignment and regardless of deviations. Safety data will be summarized using the AT cohort, and efficacy data may also be summarized as a sensitivity analysis.

4.4 General Analytical Considerations

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 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. Missing data will not be imputed.

4.5 Outcome Variables

The following outcome variables will be collected and analyzed as primary, secondary or additional efficacy outcomes:

- rTNSS: collected at screening, 30-day, and 90-day follow-up visits
- postnasal drip and cough: collected at screening, 30-day, and 90-day follow-up visits
- mini-RQLQ: collected at screening, 30-day, and 90-day follow-up visits
- NOSE: collected at screening, 30-day, and 90-day follow-up visits
- PHQ-9: collected at screening and 90-day follow-up visit

4.5.1 Safety outcome variables

- Device and/or procedure SAEs
- Device and/or procedure AEs

5 Demographics and Medical History

Demographic information will include collection of participant's age, gender, race and ethnicity.

Active medical history will be collected including chronic rhinitis symptoms, allergic or nonallergic rhinitis, history and response to treatment with ipratropium bromide (IB), allergies, and nicotine smoking status (past, current or never smoker). All past surgeries and cancer history will be recorded. In addition, history of other medical conditions will include migraines, asthma, laryngopharyngeal reflux (LPR) and gastroesophageal reflux disorder (GERD).

5.1 Participant Disposition

A Study Exit form will be completed for all participants upon completion of all planned study requirements or early exit, as applicable. For those participants exiting before completing all the study requirements, the reason for the study exit will be noted. For follow-up visit compliance, once a participant has exited the study, they are no longer included in the denominator for future visits.

6 Procedure Data

Procedure data will include the date of the procedure, treatment assignment (active or control), treating physician, duration (anesthesia start), treatment start on each side (device insertion), and treatment end on each side (device removal). In addition, the ability of the device to deliver energy to the target site and the number of leaflets on each side that were "green" at the end of the procedure will be documented for the active arm.

At the completion of the procedure, the actual treatment participant received will be documented.

The number of devices used (and lot numbers) will be collected as will any reports of device malfunction.

7 Efficacy Outcomes

7.1 Efficacy Analysis Cohort

Efficacy outcomes will be evaluated as a mPP analysis. Participants will be excluded from the efficacy analyses if they have protocol deviations or issues that would impact the integrity of the main endpoint.

All active group participants and control participants not undergoing crossover will be exited at the 90-day visit. No efficacy data will be collected for the crossover participants after the crossover procedure; only 30-day post procedure safety data will be collected.

7.2 Primary and Secondary Efficacy Endpoints

7.2.1 Reflective Total Nasal Symptom Score (rTNSS)

The rTNSS is a patient-reported outcome (PRO) instrument used to capture the symptoms of rhinitis, with 4 symptoms (nasal congestion, runny nose, itching, sneezing) that the participant rates on a scale of 0 (no problem) to 3 (severe problem) over the previous 12-hours. The 4 scores are added to provide the overall score that can range from 0 to 12.[4]

The primary efficacy endpoint is the comparison of active vs sham control groups for the percent of responders at the 90-day follow-up. A responder is defined as a participant having a 30% or greater reduction in total rTNSS compared with baseline. The primary endpoint will be compared between treatment groups for superiority of active to sham treatment using a 1-sided Fishers exact or Chi-square test of 2 proportions.

The mean change from baseline in the rTNSS for both treatment groups will be evaluated and compared as a secondary endpoint at the 30-day and 90-day follow-up periods.

The significance of the change within a group will be assessed using a 1-sample *t*-test. If the data are not normally distributed, a Wilcoxon signed rank test will be conducted in place of the *t*-test. Two-sample *t*-tests will be used to compare treatment arms. If the data are not normally distributed, a Wilcoxon rank sum test will be conducted in place of a *t*-test. Normality will be

assessed by the Shapiro-Wilk test, where a *p*-value <0.05 indicates the non-normality of the data. Statistical significance will be evaluated at a (2-sided) 0.05 alpha level.

Evaluation of individual rTNSS domain scores (rhinorrhea, congestion, itching, and sneezing) will be analyzed as additional evaluations. It is anticipated that changes in the nasal congestion and the runny nose scores of the rTNSS will be more impacted than the itching and sneezing scores and, therefore, will be of more interest for additional analysis.

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

The mini Rhinoconjunctivitis Quality of Life Questionnaire (mini-RQLQ) is a validated PRO to evaluate functional impairments that are most troublesome to adult patients as a result of their rhinoconjunctivitis.[5,6] The questionnaire has 14 items covering 5 domains: activity limitations (standardized), practical problems, nose symptoms, eye symptoms, and other symptoms. Each of the 14 items is scored from 0 (no impairment) to 6 (severely impaired). An overall score is calculated from the mean of the 14 item responses. Domain scores are the mean of the item scores within that domain. The MCID for the mini-RQLQ has been established as 0.4.[7]

The mini-RQLQ will be completed at baseline and all follow-up visits. The mean change from baseline in the mini-RQLQ will be evaluated and compared between treatment groups as a secondary endpoint at the 30-day and 90-day follow-up periods.

The significance of the change within a group will be assessed using a 1-sample *t*-test. If the data are not normally distributed, a Wilcoxon signed rank test will be conducted in place of the *t*-test. Two-sample *t*-tests will be used to compare treatment arms. If the data are not normally distributed, a Wilcoxon rank sum test will be conducted in place of a *t*-test. Normality will be assessed by the Shapiro-Wilk test, where a *p*-value <0.05 indicates the non-normality of the data. Statistical significance will be evaluated at a (2-sided) 0.05 alpha level.

Individual mini-RQLQ domain scores and percent of participants achieving MCID will be analyzed as additional evaluations.

7.2.3 Nasal Obstruction Symptom Evaluation (NOSE) Score

The NOSE scale is a validated PRO instrument that allows participants to quantify their perception of nasal obstruction.[8] The tool measures the severity of 5 symptoms (nasal congestion or stuffiness, nasal blockage or obstruction, trouble breathing through the nose, trouble sleeping, and difficulty breathing through the nose during exercise or exertion) on a Likert scale from 0 (no problem) to 4 (severe problem). The sum of the 5 symptom scores is multiplied by 5 to give a score range from 0 to 100.

Lipan and Most developed a clinically relevant classification system for NOSE scores: mild (5-25 points), moderate (30-50 points), severe (55-75 points), or extreme (80-100 points).[9] This system has been used to define treatment responders. In previous clinical studies, responders were defined as participants who had at least 1 NOSE class improvement or a NOSE score reduction of at least 20% from baseline.

The NOSE score will be completed at baseline and all follow-up visits. The mean change from baseline in the NOSE score will be evaluated and compared between treatment groups as a secondary endpoint at the 30-day and 90-day follow-up periods.

The significance of the change within a group will be assessed using a 1-sample *t*-test. If the data are not normally distributed, a Wilcoxon signed rank test will be conducted in place of the *t*-test. Two-sample *t*-tests will be used to compare treatment arms. If the data are not normally distributed, a Wilcoxon rank sum test will be conducted in place of a *t*-test.

Individual NOSE scores and responder rates will be analyzed as additional evaluations.

7.3 Additional Efficacy Assessments

7.3.1 Postnasal Drip and Cough

The participant will rate their postnasal drip symptoms and cough symptoms on a scale of 0 (no problem) to 3 (severe problem) over the previous 12-hours prior to questionnaire completion.

Postnasal drip and cough will be completed at baseline and all follow-up visits. The mean changes from baseline will be evaluated and compared between treatment groups as additonal evaluations at the 30-day and 90-day follow-up periods.

The significance of the changes within a groups will be assessed using a 1-sample *t*-test. If the data are not normally distributed, a Wilcoxon signed rank test will be conducted in place of the *t*-test. Two-sample *t*-tests will be used to compare treatment arms. If the data are not normally distributed, a Wilcoxon rank sum test will be conducted in place of a *t*-test.

7.3.2 PHQ-9

The participant will be asked how often they have been bothered by problems related to depression over the past 2 weeks prior to questionnaire completion. Responses range from 0=not at all to 3 = nearly every day.

The PHQ-9 will be completed at baseline and the 90-day follow-up visit. The mean change from baseline will be evaluated and compared between treatment groups as an additonal evaluation.

The significance of the change within a groups will be assessed using a 1-sample *t*-test. If the data are not normally distributed, a Wilcoxon signed rank test will be conducted in place of the *t*-test. Two-sample *t*-tests will be used to compare treatment arms. If the data are not normally distributed, a Wilcoxon rank sum test will be conducted in place of a *t*-test.

Individual PHQ-9 scores may be analyzed as additional evaluations.

8 Safety Outcomes

8.1 Safety Analysis Cohort

Safety outcomes will be analyzed on all enrolled participants from randomization through study completion or early exit, whichever comes first. Safety outcomes will be evaluated using the AT cohort. Control participants will be analyzed in the control arm for all visits before the crossover

procedure for comparisons to the treatment arm. Summaries of these control subjects that have the crossover procedure will be summarized separately and identified as crossover participants.

8.2 Safety Secondary Endpoint

8.2.1 Device and/or procedure related serious adverse events (SAEs)

A secondary safety endpoint is the incidence of device and/or procedure related (active or sham) serious adverse events (SAEs). The investigator will determine the adverse event relationship to the NEUROMARK device and the relationship to the procedure. SAEs categorized as possible, probable, highly probable, or related, will be considered related.

The count and percentage of participants that experienced a device and/or procedure related SAE will be summarized and may include 95% confidence interval for percentage of subjects with an AE.

8.3 Additional Safety Assessments

8.3.1 All device and/or procedure related adverse events (AEs)

An additional safety assessment is the incidence of device and/or procedure related non-serious adverse events (AEs). The investigator will determine the adverse event relationship to the device and the relationship to the procedure. AEs categorized as possible, probable, highly probable, or related, will be considered related.

The count and percentage of participants that experienced a device and/or procedure related AE will be summarized and may include 95% confidence interval for percentage of subjects with an AE.

8.3.2 All adverse events

A summary of all adverse events by relatedness will be provided. The summary will include the number and percentage of participants and the number of events as related or unrelated to the device and/or procedure.

A listing by participant of all SAEs and AEs will be provided.

9 Protocol Deviations

Protocol deviations will be summarized by deviation type, and overall using counts. A listing of all protocol deviations by participant will also be provided.

10 Additional Statistical Analyses

10.1 Study Termination Criteria

There are no preset criteria for study termination of this study.

10.2 Pooling Assessment

No pooling analyses are planned.

10.3 Blinding Assessment

No blinding assessments are planned.

10.4 Sensitivity Analyses and Missing Data Imputation

Sensitivity analyses will be completed for the primary efficacy endpoint on the mITT and AT cohorts.

A tipping point analysis may be performed if there are significant missing data (>15% for the primary outcome) as a sensitivity analyses. No missing data will be imputed.

10.5 Multiplicity Adjustments

No multiplicity adjustments are planned.

10.6 Planned Subgroup Analyses

Subgroup analyses may be conducted to evaluate efficacy outcomes between participants with allergic versus nonallergic rhinitis. Additional subgroup analyses of efficacy that may be evaluated include: baseline rTNSS score (5-6, 7-10, 10-12), previous response to ipratropium bromide (yes, no, unknown), medical history variables (history of smoking, migraines, GERD, and laryngopharyngeal reflux, etc.). Additional ad hoc subgroup analyses may be performed.

10.7 Interim Analyses

No interim analyses are planned.

11 Changes from Original Statistical Plan

Version:	Summary of Changes:
Feb 2024	N/A – original document
May 2024	Updated CIP to Rev b. Clarified efficacy analyses to be performed on mPP basis.

12 References

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