ABRIDGED STATISTICAL ANALYSIS PLAN

NEUROLIEF LTD – COMBINED OCCIPITAL AND SUPRAORBITAL TRANSCUTANEOUS NERVE STIMULATION FOR TREATMENT OF MIGRAINE (SP-302-RIME)

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
CI	Confidence Interval
FA	Full Analysis
ITT	Intent to Treat
mITT	Modified Intent to Treat
PP	Per Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

1 INTRODUCTION

This Statistical Analysis Plan (SAP) is a more detailed companion to the Statistical Methods section of the study protocol SP-302-RIME (Rev. 2 / June 11, 2019) and provides a comprehensive description of the analysis sets, efficacy endpoints, methods and data analyses to be used. When differences exist in descriptions or explanations provided in the protocol and this SAP, the SAP prevails .

This SAP was finalized before any analysis was performed on the study's clinical data (e.g. interim or final analysis).

Overall, the company has enrolled approximately 187 subjects.

During the initial phase of the study and after a through technical investigation a device issue was identified which may have caused ineffective device treatments. To overcome this technical issue, the sponsor performed corrective and preventive actions. Upon resolution, it was decided to exclude from the study data analysis all study treatments performed up to May 31, 2019; these data will still be analyzed separately for safety. As a result of the exclusion of these treatments approximately 50 randomized subjects' efficacy data were lost. To ensure sufficient efficacy evidence, the sponsor communicated the above issue to all ethical committees and received their approval to randomize up to 50 additional subjects to reach the original planned study sample size.

On 02 July 2020 study enrollment was stopped, unfortunately, due to COVID-19; formal notice was sent out to the sites and ethical committees. Even though the company implemented all measures possible to ensure continued screening and randomization, subject retention and minimize loss to follow-up, but found that the completion of the originally planned randomized sample size was impossible .

Therefore, approximately 130 subjects for efficacy analysis were enrolled with 109 that have data for the primary endpoint, but that data remains blinded and has not yet been analyzed.

The approved study analysis plan utilizes a "sample size adaptive design" which calls for a single interim analysis for purposes of sample size adjustment, which was designed to occur when approximately 144 subjects had reached the primary endpoint. Due to the impact of the COVID-19 situation, the company would like to

modify the statistical plan while it remains blinded. The study has been stopped but the interim analysis has not been performed so that only one analysis - the final analysis - will be completed after data lock.

Based on the "Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency" June 2020 FDA Guidance, and the fact that the Sponsor remains blinded to the treatment assignment and since no interim analysis was performed, no penalty to the alpha level is required. We shall address further analysis strategies in this revised SAP.

2 EFFICACY ENDPOINTS

2.1 Primary Efficacy Endpoints

The primary endpoint is the proportion (%) of patients reporting reduction in their pain level 2 hours post-treatment without rescue medications, from severe or moderate to mild or no pain, or from mild to no pain, in their first treated eligible migraine attack (excluding the "self-practice" treatment).

An eligible treatment is defined as a treatment meeting these basic criteria:

- no analgesics or other pain relief drugs or cannabis within 4 hours period before the treatment initiation; and
- no more than 30 minutes passed from the start of the migraine episode; and
- more than 48 pain free hours have passed since subject's previous Migraine episode; and
- subject did not wake up with a Migraine headache; and
- treatment with total stimulation time of at least 30 minutes of a "pass" session on the device log timeline, where pass is defined as a minimal stimulation of 2mA delivered).

2.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

1. Proportion of subjects reporting improvement in their most bothersome migraine-associated symptom (MBS) other than a headache, 2 hours post-treatment initiation (if rescue therapy was not used), in their first eligible

treated migraine attack. MBS may be nausea, photophobia, phonophobia as defined by each subject prior to beginning of the treatment.

2. Proportion of subjects reporting reduction of migraine headache pain 1-hour post treatment initiation (if rescue therapy was not used), from severe or moderate to mild or no pain, or from mild to no pain, in their first eligible treated migraine attack.
3. Proportion of subjects who are pain free at 2 hours post treatment initiation (if rescue therapy was not used), in their first eligible treated migraine attack.

2.3 **Additional efficacy endpoints**

1. Proportion of subjects reporting freedom from their MBS other than a headache, 2 hours post-treatment initiation (if rescue therapy was not used), in their first eligible treated migraine attack.
2. Proportion of subjects who are pain free at 1-hour post treatment initiation (if rescue therapy was not used), in their first eligible treated migraine attack.
3. Proportion of subjects rating the subjects positive (score of 4 or 5) Global Impression of Effect of study device at the end of the study, defined as satisfied or very satisfied using a simple Likert-type scale whereas 1 = Very dissatisfied, 2 = dissatisfied, 3 = unsure, 4 = satisfied, 5 = Very satisfied.
4. Proportion of subjects reporting 2-24h headache relief, defined as headache relief at 2 hours without rescue medications, then no moderate to severe headache in the next 22 hours, and no use of rescue medication or additional stimulation.

Additional efficacy analyses that will be performed

1. Proportion of subjects reporting improvement in their MBS other than a headache AND reduction in their pain level, 1 and 2 hours post-treatment initiation (if rescue therapy was not used), in their first eligible treated migraine attack.
2. Proportion of subjects reporting freedom from their MBS other than a headache AND pain free, 1 and 2 hours post-treatment initiation (if rescue therapy was not used), in their first eligible treated migraine attack.
3. Rescue medicine usage.
4. Proportion of subjects who had pain relief in at least 50% of their eligible treated attacks at each timepoint.

5. Proportion of subjects who were free of pain in at least 50% of their eligible treated attacks at each timepoint.
6. Proportion (%) of attacks for which patients reporting reduction in their pain level without rescue medications from severe or moderate to mild or no pain, or from mild to no pain, from all treated eligible migraine attack at each timepoint (excluding the "self-practice" treatment).
7. Proportion of attacks for which subjects reporting improvement in their MBS other than a headache (if rescue therapy was not used), from all eligible treated migraine attack at each timepoint. MBS may be nausea, photophobia, phonophobia as defined by each subject prior to beginning of the treatment.
8. Proportion of attacks for which subjects reporting pain free (if rescue therapy was not used), from all eligible treated migraine attack at each timepoint.
9. Proportion of attacks for which subjects reporting freedom of MBS other than a headache (if rescue therapy was not used), from all eligible treated migraine attack at each timepoint. MBS may be nausea, photophobia, phonophobia as defined by each subject prior to beginning of the treatment.
10. Proportion (%) of patients with pain level moderate/severe at baseline reporting reduction in their pain level 1, 2 and 24 hours post-treatment without rescue medications, to mild or no pain, in their first treated eligible migraine attack (excluding the "self-practice" treatment).
11. Proportion (%) of patients with pain level moderate/severe at baseline reporting pain freedom at 1, 2 and 24 hours post-treatment without rescue medications, in their first treated eligible migraine attack (excluding the "self-practice" treatment).

3 SAFETY ENDPOINTS

Safety endpoints include:

- Treatment related Adverse Event (AE)
- Serious Adverse Event (SAE)
- All AE's

4 ANALYSIS SETS

The following analysis sets are defined for this study:

4.1 Full Analysis (FA) set

The Full Analysis (FA) set will include all the subjects randomized, including the subjects treated with the device up to May 31, 2019.

4.2 Intent-to-Treat (ITT) analysis set

The Intent to Treat (ITT) analysis set will include all randomized subjects who were treated with the device after May 31, 2019 (including self-practice). Per ITT principles, all subjects will be analyzed as randomized.

4.3 Modified Intent-to-Treat (mITT) analysis set

The mITT analysis set will include all subjects from the ITT analysis set who treat at least one eligible attack (excluding the "self-practice test"). Subjects in the mITT analysis set will be analyzed as treated.

4.4 Per-protocol (PP) analysis set

The per-protocol (PP) analysis set will include all subjects in the mITT population who completed at least one eligible attack in compliance with the protocol and have no major protocol deviations. Subjects in the PP population will be analyzed as-treated.

Major protocol deviations defined as deviations which may impact subject safety, alter the risk/benefit ratio, compromise the integrity of the study primary end point data include, but are not limited to:

- Study treatment deviation for first eligible attack, e.g. baseline diary reported after treatment initiation, diary reported after treatment start, Baseline diary reported more than 30 minutes prior to the initiation of

treatment.

- PRO report outside of window for first eligible attack.

4.5 Statistical Analysis of Analysis Sets

As discussed in the introduction section to the SAP, a technical issue may have rendered the study device ineffective for those subjects treated prior to May 31, 2019. Since the treatments may not have been therapeutic, including them in the primary safety analysis may lead to under reporting of safety events. Consequently, the ITT data analysis set will serve as the principal data analysis set for the safety analyses.
The safety analyses will also be performed on the Full Analysis set.
The mITT data analysis set will serve as the principal data analysis set for the efficacy analyses.
The primary and secondary efficacy assessments will also be performed on the per protocol (PP) and the ITT analysis sets.