Neurolief

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	The MOOD study – external Combined Occipital and Trigeminal Nerve Stimulation (eCOT-NS) for the treatment of Major Depressive Disorder (MDD)
Clinical Investigation Plan Identifier	SP-201-MOOD
Study Product Name	Relivion®$_{DP}$
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Confidentiality Statement

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1. Investigator Statement

Study product Name	Relivion®$_{DP}$
Sponsor	Neurolief Ltd.
Clinical Investigation Plan Identifier	SP-201-MOOD
Version Number/Date	Rev. 3 / 09 June 2021

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.
I agree to comply with 21 CFR Parts 50, 54, 56 and the relevant section of Part 812, as well as ISO 14155 and local laws and regulation for the conduct of clinical studies with medical devices. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Neurolief.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Neurolief. I will discuss this material with them to ensure that they are fully informed about the products and the study.

Investigator's Signature:	
Investigator's Name:	
Institution:	
Date:	

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2. Glossary

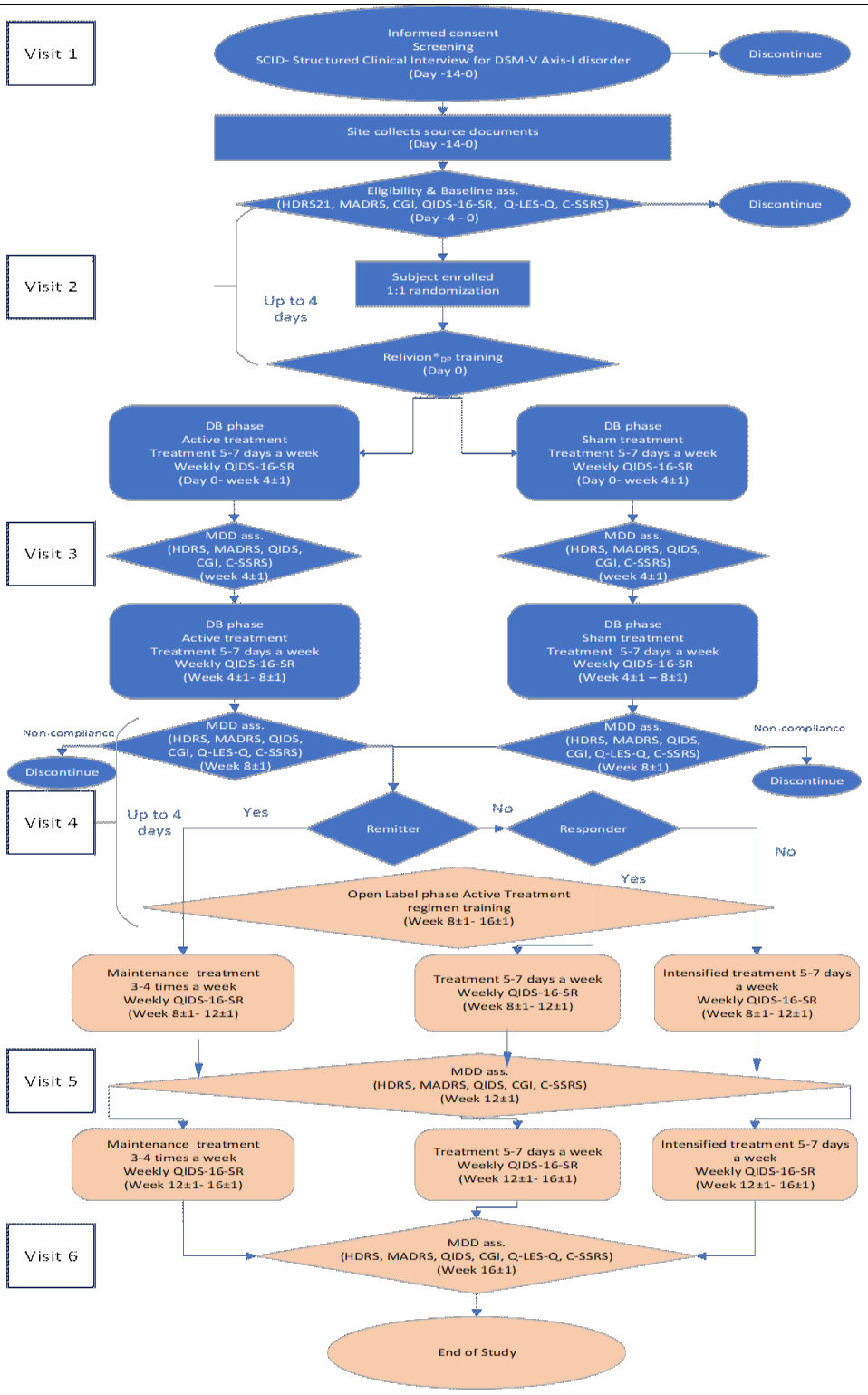
Term	Definition
ADE	Adverse Device Effect
AE	Adverse Event
ADHD	Attention Deficit Hyperactivity Disorder
ATRF	Antidepressant Treatment Resistance Form
ATIF	Antidepressant Treatment Intolerance Form
C-SSRS	Columbia – Suicide Severity Rating Scale
CAPA	Corrective and Preventive Action
CFR	Code of Federal Regulation
CGI-S	Clinical Global Impression scales - Severity
CGI-I	Clinical Global Impression scales – Improvement
CIP	Clinical Investigation Plan
CP	Conditional Power
CRF	Case Report Form
EC	Ethics Committee
DBS	Deep Brain Stimulation
DSM-V	Diagnostic and Statistical Manual of Mental Disorders- V
eCRF	Electronic Case Report Form
eCOT-NS	external Combined Occipital and Trigeminal Nerve Stimulation
ECT	Electroconvulsive Therapy
EDC	Electronic Data Capture
EOS	End of Study
FDA	Food and Drug Administration
HDRS	Hamilton Depression Rating Scale
IEC	International Electrotechnical Commission
IRB	Institutional Review Board
ISO	International Organization of Standardization
ITL	Israel Testing Laboratories
ITT	Intent to Treat
MBS	Most Bothersome Symptom
MDD	Major Depressive Disorder
MDRS/MADRS	Montgomery-Asberg Depression Rating Score
mITT	modified Intent to Treat
MOH	Ministry of Health
NSR	Non-Significant Risk
OCD	Obsessive Compulsive Disorder
ONS	Occipital Nerve Stimulation
OUS	Outside United States
P/N	Part Number
PNS	Peripheral Nerve Stimulation
PTSD	Post-Traumatic Stress
QIDS	Quick Inventory of Depressive Symptomatology

Term	Definition
Q-LES-Q	Quality of Life Enjoyment and Satisfaction Questionnaire
RDC	Remote Data Capture
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SCID	Structured Clinical Interview for DSM-V
TENS	Transcutaneous Electrical Nerve Stimulation
TMS	Transcranial Magnetic Stimulation
TNS	Trigeminal Nerve Stimulation
UM	User Manual
US	United States
U(S)ADE	Unanticipated (Serious) Adverse Device Effect
VAS	Visual Analogue Scale

3. Synopsis

Title	The MOOD study - Safety and efficacy of external Combined Occipital and Trigeminal Nerve Stimulation (eCOT-NS) for the treatment of Major Depressive Disorder (MDD)
Clinical Study Type	Pivotal, Pre-market, Non-Significant Risk (NSR) Device Study
Product Name	**Relivion®$_{DP}$** (Device version PLV3; SW version 0.1.0.2; App Version 1.2)
Sponsor	Neurolief Ltd.
Indication under investigation	The Relivion®$_{DP}$ external Combined Occipital and Trigeminal Nerve Stimulator (eCOT-NS) is intended as an adjunctive treatment to pharmaceutical management of Major Depressive Disorder (MDD) in adults who failed to achieve satisfactory improvement from previous Antidepressant medication treatment. The Relivion®$_{DP}$ is a prescription device for patient at home, self-use.
Investigation Purpose	The MOOD Study will evaluate the safety and efficacy of a self-administered treatment for MDD using an external combined occipital and trigeminal nerve stimulator (Relivion®$_{DP}$). This pivotal clinical investigation is intended to support future marketing applications (US FDA and CE) for Neurolief's Relivion®$_{DP}$ device.
Product Status	Pre-market
Patient Population	Male and female; 18 – 70 years of age; Primary diagnosis by the DSM-V criteria for MDD
Primary Objectives	To assess the change in depressive symptoms, from baseline to 8 weeks post treatment initiation when using active external combined occipital and trigeminal nerve stimulation (Relivion®$_{DP}$), compared to sham stimulation (Relivion®$_{DP}$-Sham), in subjects suffering from MDD. Depressive symptoms severity will be assessed by the HDRS$_{17}$ depression scale total score.
Secondary Objectives	• To assess the proportion of subjects achieving at least 50% improvement ("responders") in the HDRS$_{17}$ score from baseline to 8 weeks post treatment initiation when using the Relivion®$_{DP}$ device compared to sham stimulation (Relivion®$_{DP}$-Sham), in subjects suffering from MDD. • To assess the proportion of subjects achieving remission (HDRS$_{17}$ score ≤7) at the 8 weeks post treatment initiation when using the Relivion®$_{DP}$ device compared to sham stimulation (Relivion®$_{DP}$- Sham), in subjects suffering from MDD. • To assess the change in depressive symptoms, from baseline to 8 weeks post treatment initiation when using the Relivion®$_{DP}$ device compared to sham stimulation (Relivion®$_{DP}$-Sham), in subjects suffering from MDD. Depressive symptoms severity will be assessed by the MADRS depression scale total score.
Safety Objective	To demonstrate the safety of the Relivion®$_{DP}$ device in subjects suffering from Major Depressive Disorder (MDD).

Exploratory Objectives	• To assess the change on the Clinical Global Impression (CGI) scale for Improvement (CGI-I) and change on the CGI-Severity scale (CGI-S) from baseline to 8 weeks post treatment initiation when using the Relivion®$_{DP}$ device compared to sham stimulation (Relivion®$_{DP}$-sham), in subjects suffering from MDD. • To assess the changes in total score on the 16-Item Quick Inventory of Depressive Symptomatology Self-Rated (QIDS-SR-16) score from baseline to 8 weeks post treatment initiation when using the Relivion®$_{DP}$ device compared to sham stimulation (Relivion®$_{DP}$-Sham), in subjects suffering from MDD. • To assess the change in depressive symptoms from baseline to 8 weeks post treatment initiation when using the Relivion®$_{DP}$ device compared to sham stimulation (Relivion®$_{DP}$-Sham) in subjects suffering from MDD. Depressive symptoms severity will be assessed by the $HDRS_{21}$ depression scale total score.
Planned Study Duration	Each subject will participate in the study for up to 20 weeks (including the screening period). The duration of the treatment protocol for each subject will be 8±1 weeks of a double blind active or sham treatment phase, followed by 8±1 weeks of an active open label treatment. The overall enrollment period is expected to last approximately 18 months.
Study Design	This is a prospective, multi-center, 2-arm randomized, parallel group, double-blind sham-controlled study followed by an open label active treatment phase.



Study design Flowchart

	The study will include the following study visits & phases: • **Visit 1**- Screening (Day (-14)-0) - Screening & Preliminary Eligibility Assessment. • **Visit 2**- Baseline (Day (-4)-0) – Eligibility, baseline assessment, Randomization to Relivion®$_{DP}$ vs. Sham control (1:1 randomization) and training. • **Double blind phase** (Day 0 to day 56±7)- 5-7 days a week treatment: Active/Sham treatment protocol. • **Visit 3**- Follow Up Visit (day 28±7)- MDD assessment. • **Visit 4**- End of Double-Blind phase (day 56±7)- MDD assessment. • **Open label phase**– Active treatment period: According to HDRS response in DB phase, in between Maintenance treatment 3-4 times a week and up to 5-7 days a week of intensified treatment (Day 56±7 to day 112±7) • **Visit 5**- follow up visit (day 84±7) - MDD assessment. • **Visit 6**- End of study (day 112±7)- MDD assessment and end of study. After completion of the open label period the subject's participation in the study will be over.
Randomization	Eligible subjects will be randomly allocated (with a 1:1 ratio) to one of the following 2 treatment groups based on a randomization scheme using the permuted block method stratified by center: • Active stimulation • Sham stimulation The randomization scheme will be prepared by the study statistician using the SAS (version 9.4.) random number procedure. The block size will be random, and all study personnel will be therefore blinded to the randomization block size.
Sample Size	The overall calculated sample size is up to 124 randomized subjects aged 22-70 to allow for 53 evaluable subjects per treatment group, anticipating a 15% drop-out, plus an additional up to 36 randomized subjects aged 18-21 to allow 15 evaluable subjects per treatment group. The study will follow a sample size adaptive design with one interim analysis planned to allow for sample size increase, completion per original sample size, stop for futility or stop for efficacy. One interim analysis is planned after 86 (~80% of the calculated adult sample size) evaluable subjects have been accrued.
Inclusion Criteria	1. Males and females 18-70 years of age: a. Up to 124 randomized subjects aged 22-70 b. Up to 36 randomized subjects aged 18-21 2. Primary diagnosis of unipolar major depressive disorder by DSM-V criteria. 3. Current MDD episode lasts up to three years. 4. Score on the Hamilton Depression Rating Scale ($HDRS_{21}$) $\geq$ 20

	5. Symptoms of current major depressive episode that, as determined by the Investigator, for the current episode and according to the Antidepressant Treatment Resistance Form (ATRF) or Antidepressant Treatment Intolerance Form (ATIF): • Did not respond or have insufficiently responded by less than 50% improvement; dose and duration defined & rated at minimum confidence level 3 on the ATRF; • Did not respond or has insufficiently responded to at least one but no more than four adequate trials of antidepressant medications (4 ≥ ATRF ≥1) or • Did not respond or has insufficiently responded due to poor tolerability to at least two inadequate antidepressant medication trials (ATIF ≥2). 6. Subject must be on at least one (1) antidepressant medication (minimum therapeutic dose not required if tolerability precluded further dose titration) and is willing to remain on the same daily dose of antidepressant medication(s) for a minimum of 28 days prior to randomization and thereafter for the duration of the study. 7. For subjects receiving current depression focused psychotherapy: psychotherapy initiated at least 1 month prior to baseline visit with a stable frequency of visits regimen, in the opinion of the Investigator. 8. Subject is able to provide written Informed Consent and is capable of complying with the specified study requirements, as determined by the Investigator. 9. Subject has cognitive and/or motor skills needed to operate a smartphone and can be contacted by phone, as determined by the Investigator.
Exclusion Criteria	1. History of intracranial surgery. 2. Current denervation in one or more of the following: the supraorbital or supratrochlear branches of the trigeminal nerve, or the greater occipital branch of the occipital nerve. 3. An implanted neurostimulators or any implanted metallic or electronic device in the head, a cardiac pacemaker or an implanted or wearable defibrillator, except for dental implants. 4. Skin lesion, scars, or inflammation at the region of the stimulating electrodes. 5. Subjects with a history of traumatic brain injury (TBI), defined as a disruption in the normal function of the brain that can be caused by a bump, blow, or jolt to the head, or penetrating head injury, within 3 months of study enrollment. 6. Pregnancy or Lactation. 7. Women of reproductive age not using a reliable contraceptive method as determined by the Investigator. 8. In the opinion of the Investigator, subjects with a psychiatric history consistent with, suspicious for, or diagnostic of, bipolar depression or depression associated with psychosis. 9. Borderline personality disorder, defined by DSM-V criteria, that in the judgement of the Investigator is likely to complicate the assessment of clinical response to study treatments or limits the patient's ability to comply with study procedures.

	10. Subjects who, within one (1) year of study enrollment, have a history consistent with, suspicious for or diagnostic of, any of the following: psychosis, psychotic disorder, schizophrenia or schizoaffective disorder, in the opinion of the Investigator. 11. Subjects who demonstrate or have a history of any cognitive disorder or impairment, memory loss, dementia, confusion or delirium that, in the opinion of the Investigator, may compromise the integrity of the study data or impact the ability of the subject to comply with the study requirements. 12. Past 12 months active suicidal intent or plan as defined by a "yes" answer to Q4 or Q5 on the Columbia-Suicide Severity Rating Scale, (C-SSRS) or with a history of suicide attempt in the past twelve months. 13. Subjects currently (past month) meeting diagnostic criteria for Obsessive-Compulsive Disorder or post-traumatic stress disorder and that is their primary diagnosis. 14. Subjects meeting the DSM-V criteria for alcohol use disorder or other substance use disorder (not including tobacco/nicotine) within six (6) months prior to study enrollment. 15. The subject has any past or present medical condition, disease, illness, disorder or injury that, in the opinion of the Investigator, may reduce or hinder the subject's ability to fully comply with all study requirements for the duration of the study or may confound the integrity of the study data. 16. Participation in a previous study with the Relivion®$_{DP}$ or the Relivion® device. 17. Treatment with Transcranial Magnetic Stimulation (TMS) in the past 6 months. 18. Current treatment with any other approved or investigational brain stimulation therapies (i.e. Vagus or trigeminal nerve Stimulation, tDCS, TES). 19. Failure to receive clinical benefit from an adequate trial of ECT in the current or a past depressive episode in the opinion of the Investigator. 20. Subject having received Botox treatment in the head or neck region within 90 days prior to study enrollment. 21. Subject having received supraorbital or occipital nerve blocks within 1 month prior to enrollment. 22. Head circumference smaller than 51 centimeters or larger than 60 centimeters. 23. Current neurological condition or disease which, in the opinion of the investigator, is likely to manifest a depressive syndrome or symptoms that would substantially confound the diagnosis or serial assessment of major depressive disorder. 24. Subjects participating in other clinical trials evaluating experimental treatments or procedures.
Primary Efficacy Endpoint	Mean change in depressive symptoms, measured by HDRS17 total score, from baseline to week-8 post treatment initiation.

Secondary Efficacy Endpoints	• Proportion of responder subjects- defined as the percent of subjects achieving at least 50% reduction from baseline in their $HDRS_{17}$ total score, 8 weeks post Relivion®$_{DP}$ treatment initiation. • Proportion of subjects achieving remission- defined as the percent of subjects with $HDRS_{17}$ score≤7 at 8 weeks post Relivion®$_{DP}$ treatment initiation. • Mean change in depressive symptoms, measured by MADRS total score, from baseline to week-8 post treatment initiation.
Safety Endpoint	Safety of the study device following study treatment: Incidence of adverse events and serious adverse events related or unrelated to the study device [Time Frame: up to 18 weeks post treatment initiation].
Exploratory Endpoints	• Mean Change in the severity and improvement scores - Clinical Global Impression scales (CGI-S and CGI-I) at 8 weeks post treatment initiation. • Mean Change from baseline in total score of the Quick Inventory of Depressive Symptomatology self-rated (QIDS-SR-16) score at 8 weeks post treatment initiation. • Mean change in depressive symptoms, measured by $HDRS_{21}$ total score, from baseline to week-8 post Relivion®$_{DP}$ treatment initiation.
Statistical Considerations	**Study Hypothesis:** **Null hypothesis:** Mean change from baseline in $HDRS_{17}$ to 8 weeks post treatment initiation in subjects suffering from Major Depressive Disorder (MDD) in the active Relivion®$_{DP}$ arm = Mean change from baseline in $HDRS_{17}$ to 8 weeks post treatment initiation in the sham arm. **Alternative hypothesis:** Mean change from baseline in $HDRS_{17}$ to 8 weeks post treatment initiation in subjects suffering from Major Depressive Disorder (MDD) in the active Relivion®DP arm ≠ Mean change from baseline in $HDRS_{17}$ to 8 weeks post treatment initiation in the sham arm. **Statistical Analysis:** **Study Analysis Sets** Each of the following analysis sets will be evaluated for the principal statistical analysis: Intent-to-treat Analysis Set (ITT) The intent-to-treat (ITT) population will include all subjects enrolled in the study, aged 22 to 70, as randomized. This population will include all subjects who receive at least one active/sham treatment. According to the ITT principle all subjects will be analyzed in the treatment group as assigned by randomization. Modified Intent-to-treat Analysis Set (mITT) The modified intent-to-treat (mITT) population will include all subjects from the ITT set enrolled in the study, who completed the minimal stimulation time required by the protocol and have no post randomization exclusion criteria. The mITT analysis set will be analyzed in the treatment group as treated. Per-Protocol Analysis set (PP) All subjects from mITT set that complete the 8-week treatment period (without withdrawal) and without any major protocol deviations. Modified Younger Intent-to-Treat (mYITT) Analysis Set The modified younger intent-to-treat (mYITT) population will include all subjects from the ITT set enrolled in the study including subjects aged 18-21, who completed the minimal

stimulation time required by the protocol and have no post randomization exclusion criteria. The mYITT analysis set will be analyzed in the treatment group as treated.

Statistical Analysis of Cohorts Analysis Sets

Safety assessments will be performed on the ITT and mYITT analysis sets.

The mITT cohort will serve as the principal data analysis set for the primary and secondary statistical efficacy endpoints. The primary, secondary and exploratory efficacy assessment will also be performed on the per protocol (PP) analysis set for descriptive purposes and to show consistency of study results. Primary and secondary efficacy analysis will be performed on the mYITT set as well.

Interim Analysis

An interim analysis will be performed by an independent statistician once about 80% of the required number of subjects aged 22-70 have been randomized and completed the 8-week post treatment initiation visit.

Depending on the outcome of the interim analysis, the study will either continue to the originally planned sample size, stop for futility, stop for efficacy, or continue with an increased sample size. These decisions will be made based on the conditional power (CP), which is defined as the conditional probability that the result will exceed a critical value at the interim given the observed effect size.

Note that the interim analysis will be conducted on all populations (ITT, mITT, PP and mYITT analysis sets), and the study will be stopped due to futility only if the interim effects in all populations fall below the threshold.

Handling of the Type I Error

The overall significance level for this study is 5% using two-tailed tests, except for treatment by site interaction that will be tested at a significance level of 10%.

Controlling the Overall Type I Error:

The hierarchy approach will be adopted for the primary and secondary endpoints to control type I error due to multiple endpoint testing. It is recognized that the ordering is important only with regard to rejection or non-rejection of the null hypothesis. Thus, the first endpoint will first be analyzed and only if $p \leq 0.05$, will the second endpoint be analyzed, and so on.

General

Data will be analyzed using SAS ® version 9.4 or higher (SAS Institute, Cary North Carolina). All statistical tests will be two-sided.

Study data will be summarized with descriptive statistics and presented in tables and figures. Continuous variables will be summarized by a mean, standard deviation, minimum, median and maximum and categorical variables by a count and percentage. For comparison of means (continuous variables), the two-sample t-test or the Wilcoxon rank sum test will be used as appropriate. For comparison of proportions (categorical variables), the chi-squared test or Fisher's exact test will be used as appropriate. If multiple measurements are taken in a single subject, statistics described below will be appropriately modified to accommodate the within subject correlation.

Primary Endpoint Analysis

The primary efficacy endpoint is the change from baseline to 8 weeks post treatment initiation in $HDRS_{17}$ score.

	The change in HDRS17 from baseline to 8 weeks post treatment initiation will be compared between the treatment groups using a repeated measures analysis of covariance (ANCOVA, SAS® MIXED procedure). The model will include the following fixed effects: treatment group, visit, treatment group by visit interaction with Baseline $HDRS_{17}$ and center entered as covariates. Baseline $HDRS_{17}$ scores will be entered as a continuous variable so that the potential for co-linearity problems will be minimized. The treatment group by center will be evaluated as well, but not as part of the principal statistical evaluation. Additionally, the center variable will be grouped by country as US versus out of US (OUS) and the analyses for center will repeated on this new variable. **Safety analysis** The primary safety variable, the cumulative incidence (and 95% CI) of device related adverse events (AEs) throughout the study, will be presented in tabular format and will include incidence tables by severity. Adverse event rates will be compared between the study groups with a Fisher's exact test.

4. Introduction

Background

Major Depressive Disorder (MDD)

Major Depressive Disorder (MDD) is a common, disabling and undertreated condition associated with significant morbidity. MDD affects approximately 350 million people of all ages globally. It was classified by the World Health Organization (WHO) as the 4th leading cause of disability worldwide and it has been estimated that by 2020, it would be the second leading cause [1]. During 2020, with the global outbreak of the COVID-19 virus, depression prevalence has undergone a major increase in the US and globally [2]. In fact, Bueno-Notivol et al. (2020) report that compared with a global estimated prevalence of depression of 3.44% in 2017, they found a 7 times higher pooled prevalence of 25%, thus suggesting the immergence of a global mental health crisis [2].

MDD is a clinical condition characterized by depressive episodes that alternate with periods of normal mood. These episodes are marked with depressed mood, anhedonia (lack of pleasure in previously pleasurable activities) and accessory symptoms like alterations in sleep, appetite, psychomotricity, pessimistic thoughts, and even attempts of suicide. Half of the episodes are recurrent, and in one-third of them, treatment refractoriness occurs (symptoms persist despite adequate use of antidepressants) [3].

If depression is not treated, it can become chronic (long-lasting). Treatment can shorten the length and severity of a depressive episode [4], [5]. Currently, the most common treatments for MDD are medications, psychotherapy, attending support groups or a combination of these treatments. It has been

reported that patients show an improvement in their depression symptoms generally within four to six weeks from the beginning of treatment [6]. However, it has been estimated that around 40% of patients do not respond adequately to the common treatments, including pharmacotherapy and psychotherapy [7]. The lack of adherence to medication, the presence of adverse effects (e.g. weight gain, sexual dysfunction, insomnia, dizziness, nausea, constipation) and high refractoriness rates altogether generate an ultimate need for alternative non-drug antidepressive therapies, such as neurostimulation technologies [3]. With demand for therapeutic solutions which can be self-administered at home and remotely controlled by health-care providers due to the Covid-19 outbreak, neurostimulation technologies which can satisfy such needs are acutely needed to bring relief to billions of depressed patients globally.

Neurostimulation Technologies

Different nonpharmacological techniques for neuromodulation have been used in clinical neurology and psychiatry, such as electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), transcranial direct current stimulation (tDCS), deep brain stimulation (DBS) and stereotactic surgery and trigeminal nerve stimulation (TNS). Theoretically, such techniques present different mechanisms of action. For instance, ECT nonspecifically increases brain activity and excitability through controlled, electrically induced seizures; rTMS through an electromagnetic field induces intracortical electric currents which may modulate neuronal activity focally; and tDCS modifies brain excitability through weak, direct electric currents.

Out of these methods, peripheral nerve stimulation (PNS) has gained much interest, as it presents both high therapeutic value, on one hand, and promising progress in becoming non-invasive on the other. Indeed, the use of PNS for psychiatric and neurological indications has been studied extensively. Evidence has been reported for successful treatment of symptoms of MDD as well as Parkinson's disease, Neuropathic pain, Stroke rehabilitation, Smoking Cessation, OCD, PTSD, ADHD and other pending indications [8]. Several technologies have been approved by the FDA and European notified bodies for neurological and psychiatric applications. MDD is one of the most recurrent indications, consistently showing great therapeutic potential [8].

Neurolief's Treatment - An External Combined Occipital and Trigeminal Nerve Stimulation (eCOT-NS)

Relivion®DP, an external Combined Occipital and Trigeminal Nerve Stimulation (eCOT-NS) is proposed as a novel treatment for MDD. The combination of neuromodulation of both the occipital and the trigeminal nerve branches non-invasively is made possible for the first time, after having been successfully performed either separately or in invasive procedures.

A. Trigeminal Nerve Stimulation (TNS)

Trigeminal Nerve Stimulation (TNS) is a noninvasive technology, reported to be well-tolerated, with no severe adverse effect and with impressive results for MDD treatment [8]. Despite repeated reports of

efficacy for this treatment, the full mechanism by which TNS works is still under debate. Neuroanatomically, the trigeminal nerve is the largest cranial nerve and thus is considered a high-bandwidth pathway for conveying information to the central nervous system [8]. It has three major sensory branches over the face, all of which are bilateral. The trigeminal ganglion, located in the Meckel cave ('cavum trigeminale'), projects to the trigeminal nucleus which makes reciprocal projections to the nucleus tractus solitarius (NTS), locus coeruleus (LC), and reticular formation [9]. Neuroimaging studies of TNS show associated neuronal activity changes in certain sites of the brain, such as the amygdala, insula, precentral gyrus, hippocampus, and thalamus. It is hypothesized that by a mechanism operating on a 'bottom-up' principle, the stimuli propagate from the cranial nerves in the direction of the brainstem and central brain areas [8].

The stimulation of the trigeminal nerve was at first described for treatment-resistant epilepsy patients in a randomized controlled trial (DeGiorgio et al., 2013)[10]. The TNS was performed at home, in an eight-hour session, during sleep and for eight weeks, with clinical improvements observed for the refractory epilepsy. Following the studies on epilepsy, Schrader et al (2011)[11] demonstrated findings on drug-resistant recurrent MDD and PTSD patients, first from a pilot study with five patients and then from an open-label trial with 12 patients. In the later study, patients underwent TNS by a nocturnal protocol for 55 sessions during eight weeks, yielding impressive positive results (response rates of 75% and 54.5% in the HDRS-17, respectively). Following these studies, Shiozawa et al (2014, 2015)[9], [12] investigated the use of TNS for MDD with changes to the stimulation protocol. The TNS was performed for ten sessions during two weeks. The on/off cycle used in the previous studies was changed to a continuous stimulation for 30 minutes. Firstly, an open-label trial was performed with eleven patients in order to observe the effect of the reduced session of TNS, and the authors reported promising results, with a mean reduction of 5.72 points in the Hamilton depression rating scale (HDRS-17), and with all patients presenting a reduction of at least 50% of the depressive symptoms, and ten patients (90.9%) presenting remission of depressive symptoms as defined by less than eight points in HDRS-17 [9]. In sequence, the same group conducted a randomized, sham-controlled double-blinded study with 40 patients with 20 patients in each group, performing the same 10-session protocol. The authors reported that despite a substantial placebo effect, a significant difference of 6.36 points in HDRS-17 between the sham and the active group was obtained. This effect was found to be sustained in a one month follow up evaluation [12].

Trevizol et al. (2016)[13] later evaluated the safety and efficacy for elderly patients in an open-label trial with ten patients (mean age 73 years), reproducing the results observed in previous studies, with 80% response rate and 40% of remission rate by the HDRS-17. The TNS was well tolerated with no severe adverse effects reported even for this population [13]. Due to common pathways involved in anxiety symptoms, depressive symptoms and trauma-related disorders, Cook et al. (2016) and Trevizol et al. (2016) performed studies on TNS for comorbid MDD and Post-traumatic Stress Disorder (PTSD) with twelve and five patients, respectively [13], [14]. Both groups reported their positive findings on depression, anxiety and the core symptoms of PTSD, expanding the possibilities of uses in neuropsychiatric disorders.

B. Occipital nerve stimulation

Another targeted peripheral nerve is the occipital nerve. Stimulation of the occipital nerve may modulate the locus coeruleus and facilitate the release of norepinephrine to mediate the brain's response to environmental threats and stress [15]. It may also indirectly affect the mesolimbic dopaminergic system and thereby affect mood [16]. The occipital nerve converges with the trigeminal nerve at the trigemino-cervical complex (TCC) from which both nerves have mutual afferent projections to higher cerebral regions such as the insular cortex and the anterior cingulate cortex (ACC) [17]. Invasive neurostimulation of the occipital nerve is widely used for treatment of chronic migraine [18], [19] and was also shown effective for mood enhancement [20].

Due to the challenge of transferring current through the hair, stimulation of the occipital nerve is mostly performed with implanted [18], [19], [21], [22] and percutaneous [23] nerve stimulators. However, due to its superficial anatomic location at the level of the external occipital protuberance [24], [25]. once the electrodes are placed under the hair and close enough to the scalp, it can be stimulated transcutaneously [23], thereby providing similar clinical benefits without the risks associated with an invasive procedure.

C. Combined Non-Invasive Trigeminal and Occipital Stimulation

Combined trigeminal and occipital neurostimulation (COT-NS) has initially evolved as a treatment for migraine. This multi-focal stimulation was termed by Reed and colleagues (2015) 'concordant paresthesia' following pioneering successful operative procedures initiated in 2009 [26], and suggested a clinically promising approach for pain modulation [27]. Similar evidence for successful eradication of headache following invasive concurrent trigemino-occipital stimulation has been reported since repeatedly [26]–[33]. These reports, when taken together, suggest the possible superiority of multi-focal PNS over uni-focal PNS. However, high complication rates appear across these reports, which highlight the obstacle in making this potent, yet invasive, stimulation technology widely accessible, and further emphasize the need for a similar non-invasive approach.

The underlying neural mechanism by which COT-NS alleviates migraine pain directly implies that this therapeutic impact may be extended to MDD as well. The proposed mechanism of action, detailed in section 6.2 ('proposed mode of action'), points towards a neuro-chemical cascade which involves neural pathways associated with depression. Indeed, results obtained in a prospective, single group, feasibility clinical trial which assessed the safety and efficacy of the Relivion®$_{DP}$ in 23 MDD patients, confirms eCOT-NS efficacy for the treatment of depression. High rates of treatment efficacy, as measured on the HDRS-17, were found in the sample group following treatment. Additionally, anxiety reduction was found as well. No serious adverse events were observed. The study and results are further described in section 7.6.2 ('clinical evaluation'). Based on its novel technology and these promising open label clinical results, the Relivion®$_{DP}$ system was granted Breakthrough Device designation by the U.S. Food and Drug Administration (FDA) for major depressive disorder in August 2020.

Summary and conclusions

In summary, major depressive disorder is one of the leading causes of disability worldwide. However, treatment options are still limited, therefore new approaches are needed to enhance clinical improvement. The non-invasive combined neuromodulation of both the occipital and trigeminal nerve branches is a, safe, self-administered novel technology with high potency for treating MDD patients.

Based on this rationale, Neurolief developed the Relivion®$_{DP}$, a neuro-stimulator applying combined occipital and trigeminal nerve stimulation for treatment of major depressive disorder (MDD). Following completion of an early clinical study showing promising results, Neurolief designed the proposed clinical trial to evaluate the safety and efficacy of the Relivion®$_{DP}$ in a two-arms controlled, double blinded randomized study.

Purpose

The MOOD Study will evaluate the safety and efficacy of a self-administered treatment for MDD using an external combined occipital and trigeminal nerve stimulator (Relivion®$_{DP}$).

This pivotal clinical investigation is intended to support future marketing applications (US FDA and CE) for Neurolief's Relivion®$_{DP}$ device.

5. Objectives and Endpoints

Objectives

5.1.1. Primary Objective

To assess the change in depressive symptoms, from baseline to 8 weeks post treatment initiation when using active external combined occipital and trigeminal nerve stimulation (Relivion®$_{DP}$) compared to sham stimulation (Relivion®$_{DP}$-Sham), in subjects suffering from MDD. Depressive symptoms severity will be assessed by the HDRS$_{17}$ depression scale total score.

5.1.2. Secondary Objectives

1. To assess the proportion of subjects achieving at least 50% improvement ("responders") in the HDRS$_{17}$ score from baseline to 8 weeks post treatment initiation when using the Relivion®$_{DP}$ device compared to sham stimulation (Relivion®$_{DP}$-Sham), in subjects suffering from MDD.
2. To assess the proportion of subjects achieving remission (HDRS$_{17}$ score ≤7) at the 8 weeks post treatment initiation when using the Relivion®$_{DP}$ device compared to sham stimulation (Relivion®$_{DP}$-Sham), in subjects suffering from MDD.

3. To assess the change in depressive symptoms, from baseline to 8 weeks post treatment initiation when using the Relivion®$_{DP}$ device compared to sham stimulation (Relivion®$_{DP}$-Sham), in subjects suffering from MDD. Depressive symptoms severity will be assessed by the MADRS depression scale total score.

5.1.3. Safety Objective

To demonstrate safety in using the Relivion®$_{DP}$ device in subjects suffering from Major Depressive Disorder (MDD).

5.1.4. Exploratory Objectives

1. To assess the change on the Clinical Global Impression (CGI) scale for Improvement (CGI-I) and change on the CGI-Severity scale (CGI-S) from baseline to 8 weeks post treatment initiation when using the Relivion®$_{DP}$ device compared to sham stimulation (Relivion®$_{DP}$-sham), in subjects suffering from MDD.
2. To assess the changes in total score on the 16-Item Quick Inventory of Depressive Symptomatology Self-Rated (QIDS-SR-16) score from baseline to 8 weeks post treatment initiation when using the Relivion®$_{DP}$ device compared to sham stimulation (Relivion®$_{DP}$-Sham), in subjects suffering from MDD.
3. To assess the change in depressive symptoms from baseline to 8 weeks post treatment initiation when using the Relivion®$_{DP}$ device compared to sham stimulation (Relivion®$_{DP}$-sham) in subjects suffering from MDD. Depressive symptoms severity will be assessed by the HDRS$_{21}$ depression scale total score.

Endpoints

5.1.5. Primary Efficacy Endpoint

Mean change in depressive symptoms, measured by HDRS17 total score, from baseline to week-8 post treatment initiation.

5.1.6. Secondary Efficacy Endpoints

1. Proportion of responder subjects- defined as the percent of subjects achieving at least 50% reduction from baseline in their HDRS17 scale 8 weeks post Relivion®$_{DP}$ treatment initiation.
2. Proportion of subjects achieving remission- defined as the percent of subjects with HDRS$_{17}$ score≤7 at 8 weeks post Relivion®$_{DP}$ treatment initiation.
3. Mean change in depressive symptoms, measured by MADRS total score, from baseline to week-8 post treatment initiation.

5.1.7. Safety Endpoint

Safety of the study device following study treatment: Incidence of adverse events and serious adverse events related or unrelated to the study device [Time Frame: up to 18 weeks post treatment initiation].

5.1.8. Exploratory Endpoints

1. Mean Change in the severity and improvement scores - Clinical Global Impression scales (CGI-S and CGI-I) at 8 weeks post treatment initiation.
2. Mean Change from baseline in total score of the Quick Inventory of Depressive Symptomatology self-rated (QIDS-SR-16) score at 8 weeks post treatment initiation.
3. Mean change in depressive symptoms, measured by $HDRS_{21}$ total score, from baseline to week-8 post Relivion®$_{DP}$ treatment initiation.

6. Product Description

6.1. General

The Relivion®$_{DP}$ is an external neurostimulator designed for transcutaneous electrical nerve stimulation. The headset integrates three pairs of output electrodes which come in contact with the subject scalp at the forehead (two pairs) and occiput (1 pair). The electrodes deliver the stimulation pulses produced by the stimulation unit to the subject's scalp. The frontal electrodes stimulate the trigeminal (supraorbital & supratrochlear) nerve branches and the posterior electrodes stimulate the occipital nerve branches (**Figures 1** and **2** below). Stimulation intensity can be adjusted by the user.

The Relivion®$_{DP}$ is a prescription device that will be self-used in a home environment.

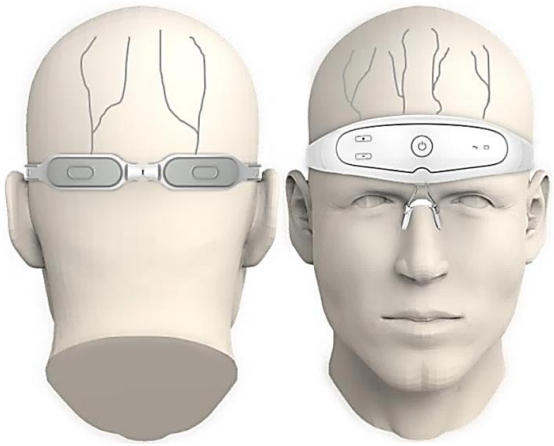


Figure 1: Relivion®$_{DP}$ and its target nerves

Figure 2: Relivion®$_{DP}$ on a user

The device is comprised of a headset with integrated electrodes, designed to enable stimulation of the target nerves. The on-board stimulation circuit is adapted to deliver stimulation patterns to enhance proper nerve activation. The headset adjusts to various head sizes and contours and can be worn comfortably. Each time the headset is worn, the six electrodes are placed over the underlying nerves. Four anterior forehead electrodes are aligned with branches of the trigeminal nerve (supraorbital &

supratrochlear) and two posterior electrodes are aligned with the greater occipital nerve branches. The headset includes two flexible arms that penetrate under the hair layers while the headset is donned. A size adjustment mechanism is located at both sides of the headset. It enables adjustment of the headset size to the head of the user before first use. The Relivion®$_{DP}$ includes six replaceable electrode pads that are positioned above the integrated headset electrodes. The pads consist of a water absorbing foam and should be wetted by the user before each use to provide proper conductivity between the electrodes and the scalp. Water releasing covers are located on the outer side of each occipital electrode. After positioning the headset on the head, the user press once on the water release covers to release moisture from the electrode pads onto the scalp, thereby maintaining conductivity between the electrodes and the scalp. The Relivion®$_{DP}$ incorporates an on-board interface that enables the user to activate/deactivate the device and to adjust the stimulation intensity. It also provides visual and auditory indications such as whether the device is active/non-active and when there is a low battery.

The Relivion®$_{DP}$ can communicate via a low energy Bluetooth link with a mobile application on the user's smartphone. The dedicated mobile app is used to support the user during treatment (i.e. provides usage guidance, indicates treatment duration and intensity, assists with trouble shooting and uploads the data from the device to the secured cloud database). The Relivion®$_{DP}$ device cannot be controlled (activate, adjust intensity, etc.) by the mobile application. The patient treatment compliance can be monitored remotely using a dedicated secured cloud interface.

Further details, images and specifications are provided in the User Manual.

6.2. Proposed Mode of Action

As explained, the Relivion®$_{DP}$ is a neurostimulator headset designed for external Combined Occipital and Trigeminal Nerve Stimulation (eCOT-NS). The headset integrates three pairs of output electrodes which come in contact with the skin at the forehead and occiput. The electrodes deliver the stimulation pulses produced by the stimulation unit to the subject's scalp. The frontal electrodes stimulate the trigeminal (supraorbital and supratrochlear) nerve branches and the occiput electrodes stimulate the occipital nerve.

Once signals from the trigeminal and occipital nerves enter the brain, they converge at the Trigeminocervical complex and projects to key structures in the brainstem, thalamus, and cortex [27]. Important connections in the brainstem include the nucleus tractus solitarius (NTS) and locus coeruleus (LC). The NTS is a key regulator of the parasympathetic nervous system. The LC is an important component of the sympathetic, or "fight and flight" nervous system, and has been implicated in neurologic and psychiatric conditions including major depressive disorder (MDD). The LC produces much of the brain's supply of norepinephrine (NE) which is involved in mood and anxiety disorders [34].
After the signals from these nerves pass through the brainstem, they travel to higher brain regions via the thalamus, and then to the primary sensory cortex and the anterior cingulate gyrus, an area thought to be involved in the regulation of attention and mood. Other signals may be passed from NTS to the thalamus and to the amygdala, an area involved in anxiety [3].

Neuroimaging studies demonstrated that trigeminal nerve stimulation increases blood flow in brain regions such as the anterior cingulate gyrus, that are frequently underactive in people with depression and anxiety disorders [8], [35], [36].

6.3. Dosage Form

6.3.1. Double Blind Phase

For purposes of this study double blind phase, the Relivion®$_{DP}$ will be provided in therapeutic and non-therapeutic modes, to accommodate for the Active and Sham groups:

- Active Treatment: For the therapeutic mode the device will be preset to the following parameters: stimulation waveform- symmetrical biphasic, phase duration 130-300 microseconds, pulse frequency 80Hz, trigeminal stimulation intensity – up to 6.7mA, Occipital stimulation intensity– up to 18mA.
- Sham Control: For the non-therapeutic mode the device will be preset to the following parameters: Stimulation waveform- symmetrical biphasic, phase duration 100 microseconds, pulse frequency 0.33 Hz, trigeminal stimulation intensity up to 5mA, occipital stimulation intensity up to 10mA for 3 minutes, then gradually decrease to 0.2 mA and stays constant throughout the remaining treatment duration.

Both Active and Sham stimulation devices are packaged and labeled identically to maintain blinding of both the subject and study staff.

Double blind Relivion®$_{DP}$ treatment will last 60±20 minutes (preferably in two equal sessions of 30±10 minutes each) per day for 5-7 days a week (intensity level up to 50) for a period of 8±1 weeks.

6.3.2. Open Label Phase

For purposes of the active open label phase, only active treatments will be applied with the Active therapeutic mode device parameters, as detailed above: stimulation waveform- symmetrical biphasic, phase duration 130-300 microseconds, pulse frequency 80Hz, trigeminal stimulation intensity – up to 6.7mA, Occipital stimulation intensity– up to 18mA.

The designated study central trainer will perform (on site or remote) the device conversion to the open label mode (i.e. conversion of the sham devices to active) with the subjects.

Open label phase treatment regimens would be as follows, according to the subject HDRS score at the end of the double-blind phase, for a period of 8±1 weeks:

Maintenance treatment (for HDRS remitter subjects): 40±10 minutes 3-4 times a week (intensity level up to 50).
Daily treatment (for HDRS responder subjects): 5-7 days a week (intensity level up to 50) 60±20 minutes per day (preferably in two equal sessions of 30±10 minutes each).

Intensified treatment regimen (for HDRS non-responder subjects): 5-7 days a week (intensity level - up to 60) 60±20 minutes per day (preferably in two equal sessions of 30±10 minutes each).
The treatment regimen assignment will be re-evaluated according to the subject HDRS score at visit 5 (after 4 weeks of open label treatment).

6.4. Manufacturer & Device Version

Neurolief Ltd, Israel, is the manufacturer of the Relivion®$_{DP}$.

The Relivion®$_{DP}$ to be used in this study is identified as follows:

- Device version PLV3
- SW version 0.1.0.2
- Mobile Application Version 1.2

6.5. Packaging & Supply

6.5.1. Source

The Relivion®$_{DP}$ will be provided by Neurolief Ltd.

6.5.2. Labeling

Labeling of devices will be provided in accordance with local language requirements.

The Relivion®$_{DP}$ package will bear a label with the following information:

- The name of the device
- The model marketing P/N
- Serial number (the randomization scheme will assign each serial number to a numbered subject, such that the device provided will be active or sham, in accordance with the group assignment).
- The name and place of business of the manufacturer.
- Contact phone.
- The statement "Exclusively for SP-201 Clinical Investigation Only".

Additional information for devices distributed in the US:

- The statement, "CAUTION - Investigational device. Limited by Federal (or United States) law to investigational use."

Additional information for devices distributed in Israel:

- Investigator's name
- The statement: "Keep out of reach of children".

Additionally, the label will describe all relevant contraindications, hazards, adverse effects, warnings and precautions, or refer the user to the User Manual.

6.5.3. Storage

The Relivion®$_{DP}$ will be provided to the investigational sites and/or be shipped to the study subjects directly from the sponsor dedicated warehouse. The Relivion®$_{DP}$ will be stored by the investigational site and sponsor in a limited access area, in accordance with the storage conditions specified in the User Manual. At home the subject will be requested to follow the storage requirements described in the User Manual.

6.6. Intended Use & Intended Population

The Relivion®$_{DP}$ external Combined Occipital and Trigeminal Nerve Stimulator (eCOT-NS) is intended as an adjunctive treatment to pharmaceutical management of for Major Depressive Disorder (MDD) in adults who failed to achieve satisfactory improvement from previous Antidepressant medication treatment. The Relivion®$_{DP}$ is a prescription device for patient at home, self-use.

6.7. Equipment

No special equipment is required for use of the Relivion®$_{DP}$. Calibration is not required. The Neurolief App will be installed on a dedicated study smartphone provided to each subject or on the subject personal iPhone, if applicable. Training will be provided as described below.

6.8. Product Use

Once the headset is on, the user may open the accompanying software application on the mobile phone. Upon successful pairing between Relivion®$_{DP}$ and the application, the user follows the instructions on the application.

While holding the headset's arms away from one another, the user places the tips of the arms at the sides of the head (above the ears) and pushes the headset backwards so that the arms penetrate under the hair and lock to each other by the magnets (**Figure 3**).

Figure 3: Device placement

The user then presses on the water release covers located on the occipital electrodes to release moisture towards the scalp. To initiate treatment, the user presses the "+" button on the Relivion®$_{DP}$. The indicator light begins flashing blue and electrical stimulus is applied. To increase the treatment intensity, the user presses the "+" button until he/she feels a tingling sensation over the forehead and occiput.

The user can further fine-tune the treatment intensity level by pressing the "+" or "- "buttons. The treatment automatically ends after 40 minutes or alternatively, the user can stop the treatment by turning the device off.

During use of the Relivion®$_{DP}$ the user can observe usage information via the application on the mobile phone. The mobile application displays the device status and provides indications and alerts such as treatment intensity level, treatment duration, low battery, charging state, etc. The device cannot be controlled (activate, adjust intensity, etc.) by the mobile application.

Detailed instructions for use of the Relivion®$_{DP}$ and the mobile app are provided in the User Manual.

6.9. Product Training Requirements

Investigative sites teams will be trained on the use of the investigational device and the treatment regimen by Neurolief team. Training will be conducted prior to study initiation and throughout the study, as needed, and will be documented.

Subjects will be trained on the use of the device and the treatment regimen by qualified study dedicated sponsor/ designee central trainer/technical support person. Training may be provided in a remote and/or in-clinic training sessions prior to the first use of the device, at the beginning of the open label period and throughout the study, if required.

In addition, subjects will be trained on the self-reported questionnaires (hard copy or electronic) by the investigative site teams.

During the study, technical support will be provided by the qualified study dedicated sponsor/ designee central trainer/ technical support person by a remote and/or in-clinic visits; contact details of the central trainer/ technical support will be detailed in the Study Files. Training and technical support will be documented and maintained on file.

6.10. Product Receipt and Tracking

The Sponsor will initiate shipment of equipment to the site upon receipt of all required documents (e.g., Institutional Review Board (IRB)/Ethics Committee (EC) approval, local regulatory authorities' approval if applicable). The study dedicated central trainer will initiate shipment of study devices to study subjects upon receipt of all required documents (e.g., Institutional Review Board (IRB)/Ethics Committee (EC) approval, local regulatory authorities' approval, if applicable), completion of study site initiation visit activities and only after subject's eligibility criteria were verified by the clinical site, randomization was performed and a dedicated device serial number was assigned to the randomized subject. The Sponsor will maintain tracking for all shipment documentation. Prior to any shipment, the site/study subject will be informed by the Sponsor/delegate/central trainer on the upcoming shipment, expected arrival date, and content of the shipment. The site/subject should confirm receipt of the shipment and maintain shipping receipts.

Device shipments to investigational sites/study patients will be accompanied by delivery note which will be filed in the Study Files. Additionally, product receipt will be documented in a Device Log which will document dates, quantities received, serial numbers.

Each Relivion®$_{DP}$ device dispensed to study subjects, will be documented in the Device Accountability Log and Case Report Form (CRF).

6.11. Product Return

In the event of product malfunction, the subject will be asked to contact the sponsor technical support representative. The representative will verify that the device is indeed non-functional and will approve the device return/replacement to sponsor. The representative will arrange for product collection/replacement and inform Neurolief and the investigational site.

Procedures for device replacement due to device malfunction will be detailed on the study specific randomization and blinding plan.

At the termination of the study, all unused study material must be returned with the corresponding documentation as directed by Neurolief. All returned products from subjects and site will be documented in the Device Accountability Log.

6.12. Product Accountability

Good clinical research practice requires that investigators and research teams ensure accurate accountability for any device used in a research study. It is expected that all devices will be used in the manner intended during the study, that they will be stored under appropriately controlled conditions and that they will be used only by (on) subjects who have consented to participate in the research study. Access to study device storage and handling should be limited to designated study staff only.

The study dedicated central trainer and/or investigator is responsible for the accountability of all used and unused study devices prior to dispensing them to subjects. Device accountability records will be reviewed at the investigative site by the study monitoring team during monitoring visits and in a centralized fashion on the sponsor centralized warehouse. Adequate device accountability records include documentation of all study device received, dispensed to study subjects, returned from subject and returned to sponsor.

At completion of enrollment, all devices, supplies and documentation will be reviewed and verified by the study monitors. The site will be instructed to return to the sponsor all study devices.

Neurolief technical representative/central trainer will maintain records of all devices shipped to and returned by the subjects during the study including devices replaced/returned due to product malfunction. Final device accountability will be performed by the sponsor.

7. Study Design

7.1. General

This is a prospective, multi-center, 2-arm randomized, parallel group double-blind sham-controlled study followed by an active open label treatment phase.

The study will include the following visits & phases:

- **Visit 1**- Screening (Day (-14)-0) - Screening & Preliminary Eligibility Assessment.
- **Visit 2**- Baseline (Day (-4)-0) – Eligibility, baseline assessment, Randomization to Relivion®$_{DP}$ vs. Sham control (1:1 randomization) and training.
- **Double blind phase** (Day 0 to day 56±7)- 5-7 days a week treatment: Active/Sham treatment protocol.
- **Visit 3**- Follow Up Visit (day 28±7)- MDD assessment.
- **Visit 4**- End of Double-Blind phase (day 56±7)- MDD assessment.
- **Open label phase**– Active treatment period: According to HDRS response in DB phase, in between Maintenance treatment 3-4 times a week and up to 5-7 days a week of intensified treatment (Day 56±7 to day 112±7)
- **Visit 5**- follow up visit (day 84±7)- MDD assessment.
- **Visit 6**- End of study (day 112±7)- MDD assessment and end of study.

After completion of the Open label period the subject's participation will be over.

The overall calculated number of subjects is a total of up to 124 aged 22 through 70 and an additional up to 36 subjects ages 18-21. There are no procedures for the replacement of subjects.

The study will be conducted at a maximum of 15 investigational sites in the US and Israel;

Each site will enroll up to 30 subjects.

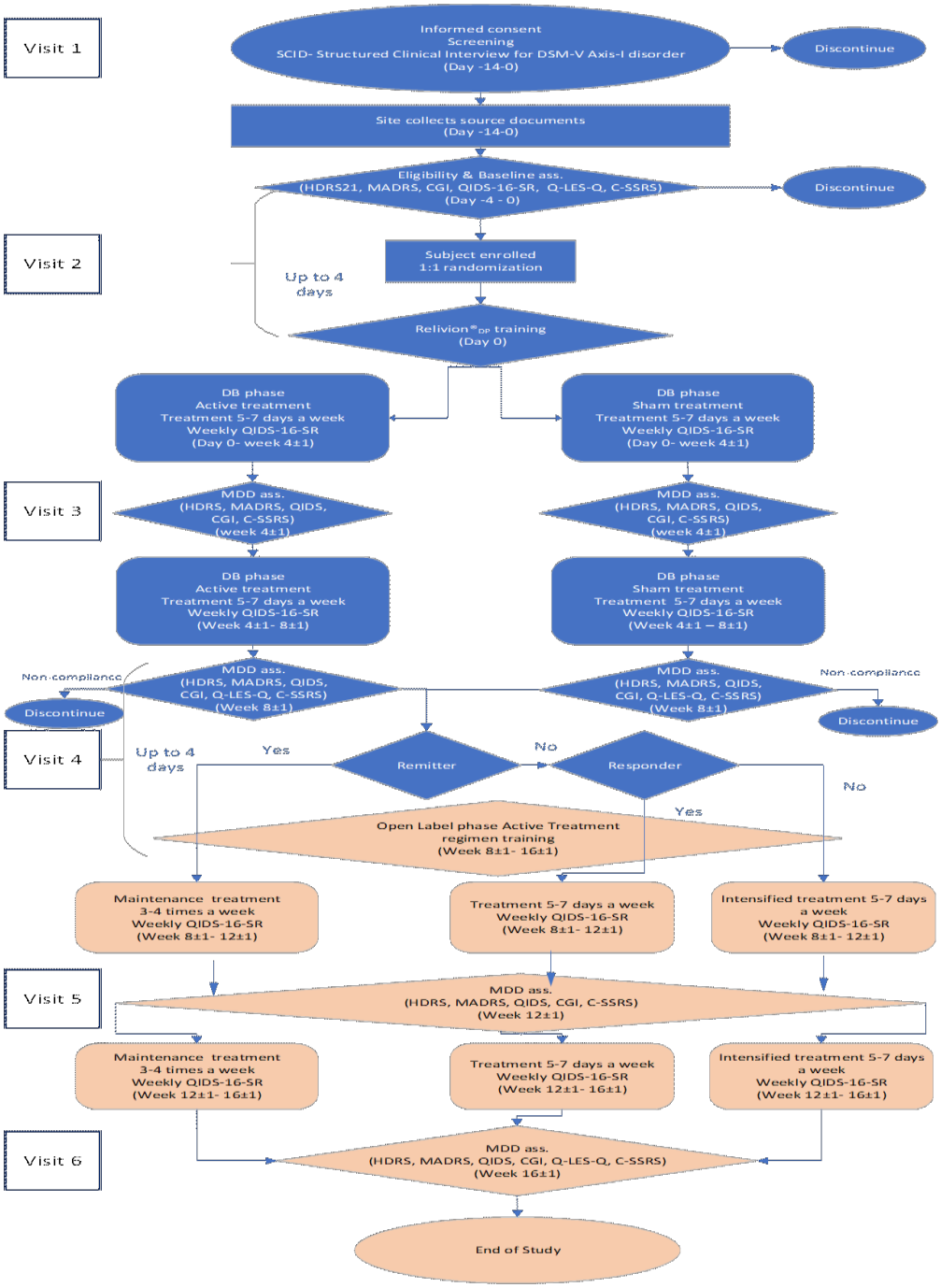


Figure 4 - Study Flowchart

Study flowchart summarized in Figure 4 and details of the assessments to be completed at each period / visit are provided is Section 9.

7.2. Qualifications and Training

The training of investigative site personnel will be the responsibility of Neurolief and site investigator. Training will cover topics such as investigational device, study Clinical Investigation Plan (CIP, with reference to applicable regulations), study execution and data collection/reporting procedures specific to this CIP and efficacy outcome measures rating (i.e. HDRS, MDRS, C-SSRS). Training will be conducted prior to study initiation and throughout the study, as needed, and will be documented.

Experience and training are required in order to accurately fill and assess the Depression symptoms questionnaires (i.e. HDRS, MDRS) and the C-SSRS questionnaire. Efficacy outcome measures and C-SSRS clinical sites raters will be required to pass the study rater training and certification program, which is developed to ensure adequate scoring reliability and rating skills. These clinical sites raters would be blinded to the study treatment sessions data.

It is the responsibility of the Principal Investigator at each participating site to assure any staff performing tasks related to the clinical trial (Study Coordinators, Study Nurses, Sub-Investigators, blinded raters etc.) have been properly trained and included on the Delegation of Authority Log.

7.3. Randomization

Subjects will be prospectively randomized into the clinical study. Randomization will occur only after the subject provides informed consent, completes all required screening and baseline procedures, and satisfies the study eligibility criteria.

7.4. Measures to Minimize Bias

Several measures will be implemented to minimize systematic error/bias:

- Randomization to active treatment vs. sham control.
- Blinding of both study subjects, site study personnel and efficacy outcome measure raters.
- Subjects will be asked for their opinion concerning their group assignment. Their response will be documented in the CRF.
- Depression severity and symptoms would be assessed according to the HDRS/MDRS and additional assessment tools by a qualified blinded rater, with an attempt for one rater to evaluate same subject through study visits.
- Study dedicated central trainer/technical support person would be blinded to the efficacy outcome measure scores throughout the study.
- Study subjects will be instructed not to disclose any details of the treatment sessions to the study blinded raters during rating sessions.
- Study subjects will be instructed to report all adverse events to the clinical site team or the central device trainer/technical support but not to the blinded study rater.
- Screening log will be completed by investigational sites listing all major depression patients consented to the MOOD study. The log will include reasons for exclusion from the study.
- Reported serious adverse events and device related adverse events will be reviewed and adjudicated, if required, by Neurolief and if needed forwarded to the study 'Data Monitoring Committee' (DMC) for further review and assessment. The adjudicated results will be updated in the study CRF and used in all cases for purposes of data analysis.
- The sponsor, the DMC and Principal Investigators will oversee the overall safety of the study. The DMC will periodically review safety data and will make recommendations concerning continuation, modification, or termination of the study.
- Clinical monitors will verify patients' data and ensure compliance with good clinical practice (GCP), CIP and other study requirements.

7.5. Duration

Each subject will participate in the study for up to 20 weeks (including the screening period).
The duration of the treatment protocol for each subject will be 8±1 weeks of 5-7 days a week active or sham treatment, followed by 8±1 weeks of a maintenance treatment and up to daily (5-7 days a week) treatment protocols. The overall enrollment period is expected to last approximately 18 months.

7.6. Rationale

Neurolief is planning to conduct the MOOD Study as part of its clinical program assessing use of the Relivion®$_{DP}$ Device. This study is being conducted following successful completion of pre-clinical and early clinical studies, as summarized below. To assess the safety and efficacy of the Relivion®$_{DP}$ for MDD patients, a sham controlled, double blinded randomized study design was chosen as most appropriate for meeting the study objectives. The study includes through screening procedures which include several depression assessment questionnaires assessed by a qualified rater to ensure suitability of study

population. Then, an in-clinic or at-home Relivion®$_{DP}$ training will take place to allow the subject to operate the device by himself in the home environment. A double-blind 5-7 days a week treatment period of 8±1 weeks will take place, followed by an open label 8±1 weeks period. Healthcare professional and self-reported Depression assessment tools would be applied throughout the study to monitor subject's depression status and response to treatment. Adverse events will be assessed and reported throughout the study. This study design will allow sufficient safety and efficacy data collection.

7.6.1. Pre-Clinical Testing

Device Design

The Relivion®$_{DP}$ has been carefully designed to perform safely and effectively its intended use as a self-used device for the treatment of major depression in subjects 18 -70 years of age. The design process was completed in accordance with the Neurolief Quality System and is reflective of the requirements for this class of medical devices.

Device Testing Summary

Neurolief is conducting extensive verification and validation testing of the Device. The device is being tested to ensure that it provides all the capabilities necessary to operate safely and effectively. Testing are performed, where applicable, per guidelines established in relevant international and regulatory standards. Checkup testing is currently ongoing; devices will be released for use in human subjects only after successful completion of relevant design verification testing.

Following is a short outline of the various testing of the device.

Functional testing: The tests ensure that the device meets system requirements and functional specifications. Mechanical durability of the various device components, verification of physical parameters, battery tests, hardware functionality, electrodes tests, and wireless/radio capability are tested.

Biocompatibility testing: The tests ensure that the device is biocompatible. Irritation, sensitization, and cytotoxicity are tested for both the headset and electrode pads. The biocompatibility tests are performed per ISO 10993 (ISO 10993-5: Biological Evaluation of Medical Devices- Part 5: Tests for in Vitro Cytotoxicity; ISO 10993 -10: Biological Evaluation of Medical Devices – Part 10: Tests for Irritation and Delayed-Type Hypersensitivity).

Software validation: Software (SW) validation is performed on the Relivion®$_{DP}$ software to verify that the developed software complies with the defined SW requirements and demonstrates the actual implementation of risk mitigation as analyzed in the risk analysis. SW validation is being performed according to FDA GPSV (Guidance Principles of Software Validation) and IEC62304 Software Development Life Cycle standard. The device SW is a "moderate" level of concern (LOC) as defined in FDA's Guidance

for the Content of Premarket Submission for Software Contained in Medical Devices (May 11, 2005) ("Software Guidance Document").

Electromagnetic compatibility and electrical safety: Electromagnetic testing for the device is conducted by an independent laboratory in accordance with IEC 60601-1-2, Medical electrical equipment - Part 1-2: Collateral Standard: Electromagnetic compatibility – Requirements and tests and IEC 60601-1-11, Medical Electrical Equipment – Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment.

Electrical safety testing of the device is conducted by the same independent laboratory in accordance with IEC 60601-1, Medical Electrical Equipment, Part 1: General requirements for basic safety and essential performance. Further, electrical equipment testing with particular requirements for the safety of nerve and muscle stimulators are conducted in accordance with IEC 60601-2-10, Medical Electrical Equipment: Part 2-10: Particular Requirements for the Safety of Nerve and Muscle Stimulators.

7.6.2. Clinical Evaluation

Overview

Neurolief has gained clinical experience through the conduct of a series of clinical studies during the design and development phases of the Relivion®- a device similar to the Relivion®$_{DP}$, indicated for Migraine, as well as of the Relivion®$_{DP}$ device.
In the following are short summaries of clinical research performed with the Relivion® and the Relivion®$_{DP}$ devices:

First-in-Human Study (study #100CLD): A prospective, randomized, single blind, parallel-group, placebo controlled clinical study to evaluate the short-term effectiveness of eCOT-NS in reducing migraine related pain. Forty subjects were enrolled at a single investigational site in Israel and treated using an earlier design iteration of the Relivion®, out of which 10 were excluded due to protocol exclusion criteria or inability to coordinate an intervention meeting, leaving a total of 30 subjects, 15 who received real stimulation and 15 who received placebo (sham) stimulation.
The average reduction of Pain Visual Analogue Scale (VAS) score, the study's primary endpoint, in the treatment group was 79.2% compared to an increase of 14.9% in the control group, amounting to a 94.1% difference between the two study groups at the end of treatment (P=0.0002). The difference between the groups was substantially greater than anticipated in the original hypothesis which assumed only a 20% difference. The secondary endpoints also revealed substantial differences between the groups with clear superiority of the treatment group. At two hours post treatment, eight subjects (53.3%) in the treatment group were pain free compared to none in the control group (P=0.0031). Twelve subjects in the treatment group (80%) were "Responders" compared to only two in the control group (16.7%; P=0.0018). The number of subjects with "Sustained pain free" and "Sustained responders" at 24 hours post treatment was also substantially higher in the treatment group compared to the control group (P<0.05), reflecting

the efficacy of the treatment in preventing relapse of the migraine episode. At two hours post treatment, only five subjects (33.3%) in the treatment group had functional disability compared to twelve subjects (100%) in the control group (p=0.0004). Only two subjects (13.3%) in the treatment group had photophobia two hours post treatment compared to nine subjects (75%) in the control group (P=0.0020). A superiority of the treatment group was also found in the "Global impression of treatment" (P=0.0192) reflecting patient's satisfaction from the treatment. Nausea and phonophobia showed a favorable trend in the treatment group but did not reach statistical significance due to the relatively small number of subjects who suffered from these symptoms.

Only one mild adverse event (mild dizziness) was reported during the trial and was resolved without any treatment.

Importantly, these results are mostly superior to those reported by clinical trials of Triptans which are the most effective abortive medications presently available for migraine.

Altogether, these results indicate that the Relivion® is a safe and effective abortive treatment for episodic migraine and may prove a superior, fast acting, and adverse-reaction free alternative to medications.

Pivotal Outside-United States (OUS) Study (study #SP301):

In a prospective randomized, parallel-group, sham-controlled clinical trial, 55 subjects with EM or CM were randomized to receive either an active or a sham treatment. The primary endpoint was to assess the change in VAS pain score from baseline to 1-hour post treatment initiation. Pain intensity (VAS) was recorded before treatment and then at 1, 2 and 24-hours post treatment initiation. Following one-hour of treatment, pain decreased significantly more in the treatment group compared to the sham group at all time points (group difference at 1-hour 41%, p=0.0002, at 2-hours 33%, p=0.03, at 24-hours 36%, p=0.02). Headache relief rate (subjects who improved from severe or moderate pain at baseline to mild or no pain) was significantly higher in the treatment group compared to the sham group at 1-hour (66.7% vs. 26.32%, p=0.01) and 2-hours (76.19% vs. 31.58%, p=0.01) test points. Responder rate (≥ 50% pain reduction) was significantly higher in the treatment group than in the sham group at 1-hour (67% vs. 20%, p=0.001), 2-hours (67% vs. 32%, p=0.02) and 24-hours (78% ver. 48%, p=0.04). Pain freedom at 2-hours for subjects with a severe-moderate baseline pain level was significantly higher in the treatment group than in the sham group (43% vs. 11%, p=0.02). Notably, pain freedom at 2-hours regardless of baseline level was more than twice as high in the treatment group compared to the sham group but did not reach statistical significance (41.7% ver. 20%, respectively, p=0.12). No serious adverse events were reported.

Pivotal Study within the US and OUS (study #SP302):

Findings from an additional pivotal, multi-center, placebo-controlled clinical trial (RIME) of the Relivion® system were submitted to the US Food and Drug Administration (FDA) for review in late 2020. This study included 131 patients with migraine and the results further support the findings demonstrated in previous clinical trials.

After the treatment period, the treatment group demonstrated a statistically significant higher improvement rate than the sham group in the study pre-defined end points. Pain relief at 2 hours post-

treatment was found significantly higher in the active group than in the sham group (60% vs. 37%, p-value 0.0180) with a therapeutic gain of 23%. Pain free at 2 hours post-treatment was found significantly higher in the active group than in the sham group (46.0% ver. 11.86%, p-value<.0001) with a therapeutic gain of 34.14%. Improvement in MBS at 2 hours post-treatment was also significantly higher in the active group than in the sham group (80.56% ver. 60.0%, p-value=0.0466) with a therapeutic gain of 20.56%. MBS freedom at 2 hours post-treatment was also statistically significantly higher in the active group than in the sham group (75% ver. 46.67%, p-value=0.0099) with a therapeutic gain of 28.33%. Complete symptoms free (Pain Free and Freedom from MBS) at 2-hours post-treatment was found statistically significantly higher in the active group than in the sham group (47.22% ver. 11.11%, p-value=0.0003) with a therapeutic gain of 36.11%. In terms of rescue medication intake, a statistically significant difference was found between the two study groups, as 29.17% of subjects in the active group consumed rescue medication on their first eligible episode vs. 52.63% in the sham group, p-value=0.0152. In relation to consistency of response, the proportion of subjects who were pain free in at least 50% of their treated episodes 2-hours post-treatment was statistically significantly higher in the active group than in the sham group (44% ver. 15.25%, p-value=0.0009). 2-24 hours pain free rate was statistically significantly higher in the active group than in the sham groups (36% ver. 8.47%, p-value=0.0004) with a therapeutic gain of 27.53%. Adverse event incidence was similar in both study groups and no serious adverse events were reported.

This multi-center pivotal study provides pivotal evidence that migraine abortive treatment with self-administered, combined occipital and trigeminal neurostimulation by the Relivion® device is a safe and effective treatment for migraine.

Major Depression related Clinical Data to Date

A prospective, single group, open label feasibility clinical trial (study #SP200): this study assessed the safety and efficacy of the Relivion®$_{DP}$ in patients with MDD. The study included unipolar MDD patients who had 1-6 antidepressant medication trials fail prior to entering the study. Treatment consisted of 1-2 hours of daily self-administered sessions. The primary endpoint was change in the Hamilton Depression Rating Scale (HDRS-17) score at 6 weeks compared to baseline. During treatment, data from the device was gathered via a mobile app installed on the patients' cellphones and uploaded to a secure cloud database for analysis. In this pilot study, 23 MDD patients ranging in age between 21-65 years, completed the study protocol. Six weeks of daily treatment resulted in a 9-point average improvement in HDRS-17 score ($P<0.05$). 35% (8/23) and 70% (16/23) of the patients improved ≥50% and ≥40% in the HDRS-17 score, respectively. Over one third (35%) of the patients reached remission (8/23). Additional results included a mean improvement of 9 points on the Hamilton Anxiety Rating Scale (HAMA-A) and a mean improvement of 6 points on the Quick Inventory of Depressive Symptomatology (QIDS-SR). No serious adverse events were observed. All participants were able to self-administer the treatment in their home with a high compliance rate.

8. Selection of Subjects

8.1. Study Population

The study will include male and female subjects, 18 to 70 years of age; Primary diagnosis by the DSM-V criteria for MDD.

8.2. Subject Enrollment

The overall calculated number of subjects is a total of 124 aged 22 through 70 and an additional up to 36 subjects ages 18-21. There are no procedures for the replacement of subjects.

Subjects will be assessed, treated and followed as per the requirements listed in **Table 1**.

Adults known to the clinic as suffering from MDD, or subjects referred to the clinic, or subjects who approach the clinic due to study MOOD advertising may be recruited for inclusion in the study. After being informed of the nature of the study, the subject will sign a written or electronic informed consent form (ICF) that has been approved by the Sponsor and the appropriate IRB/ EC of the respective clinical site or the central IRB/EC, during the screening visit. Written or electronic, informed consent will be obtained for all patients who are potential study candidates prior to applying any study specific assessment to the subject or any data collection. See **Section 9.4** for details on subject informed consent procedure.

Refer to **table 1** for a summary of the study schedule of assessment. Specifically, subjects will be evaluated by the site team at Visits 1 and 2 to assess whether they meet study eligibility criteria. Those meeting all the inclusion and none of the exclusion criteria will be enrolled and randomized for the treatment period. A subject is considered enrolled (randomized) in the study when it is determined that all inclusion/exclusion criteria are met during visit 2, the informed consent was signed and all the required depression assessment questionnaires were completed as detailed in section 7.1.2. Enrolled subjects will receive (a) the study device, (b) the device application which may be installed on the subject's phone (or on a dedicated iPhone supplied by the Sponsor) (c) instructions for use including the treatments regimen. Also, at this visit subjects will undergo device and device app, treatment regimen and Patient Reported Outcome (PRO) (hard copy and/or electronic) training and will be asked to complete the self-reported depression questionnaires and blinding assessment questionnaire (hard copy or electronic). Device and device app training will be performed by the study dedicated central trainer. All subject's training activities may be performed by an on-site or remote fashion. In the case of a remote device training the device would be sent by a courier to the subject home and only then the device training would take place. Upon training completion subject would initiate the study daily treatment. During the DB period (8±1 week from device training), Subjects will follow the provided treatment regimen which specifies their recommended daily treatment regimen, recommended stimulation duration and maximal intensity. Subjects will return for follow up visits, which may be performed by an on-site or remote fashion, at 4±1 weeks post visit 2

(visit 3) and at 8±1 weeks post visit 2 (visit 4). During visits 3 and 4 subject's depression symptoms will be assessed by the site team qualified raters using the study questionnaires and the subject self-reported questionnaire. Study visit 4 will be the end of the double-blind phase and the beginning of the open label extension period. At this visit, subject's compliance with the treatment regimen during the DB phase will be assessed. Subjects who would not fulfill the minimum stimulation requirements during the DB phase (non-compliant subjects) will complete their participation in the study. DB phase treatment regimen compliant subjects will be offered to participate in a 8±1 weeks open-label period with an active device. Subjects who choose to continue to the open label phase will be trained as per their recommended treatment regimen (see Figure 5) by the study central trainer in an on-site or remote fashion. (regardless their prior DB treatment assignment) and will follow this treatment regimen for the next 4-8±1 weeks. Subjects will return for follow up visits (on-site or remote) at 4±1 weeks post visit 4 (visit 5) and at 8±1 weeks post visit 4 (visit 6). During visits 5 and 6 subject's depression symptoms will be assessed by study team qualified raters and the PRO (electronic or hard copy) using the study questionnaires. At study visit 5 the subjects response to treatment, according to HDRS, will be re-evaluated and treatment regimen may be amended accordingly (see Figure 5), re-training will be performed by the central trainer, if required. Study visit 6 will be the end of study visit during which the device will be returned, final data will be collected, and the subjects will be exited from the study.

Subjects found ineligible by the procedures required at screening will be marked as 'screen failure' on the screening & enrollment log and will not take part in the study. Screen failure subjects will not be included in the intention-to-treat analysis, nor will they be counted as part of the target subject sample number.

8.3. Inclusion Criteria

In order to be included in the MOOD study patients must fulfill all the inclusion criteria.

1. Males and females 18-70 years of age:
    a. Up to 124 randomized subjects aged 22-70.
    b. Up to 36 randomized subjects aged 18-21.
2. Primary diagnosis of unipolar major depressive disorder by DSM-V criteria.
3. Current MDD episode lasts up to three years.
4. Score on the Hamilton Depression Rating Scale ($HDRS_{21}$) $\geq$ 20
5. Symptoms of current major depressive episode that, as determined by the Investigator, for the current episode and according to the Antidepressant Treatment Resistance Form (ATRF) or Antidepressant Treatment Intolerance Form (ATIF):

- Did not respond or have insufficiently responded by less than 50% improvement; dose and duration defined & rated at minimum confidence level 3 on the ATRF;
- Did not respond or has insufficiently responded to at least one but no more than four adequate trials of antidepressant medications (4 ≥ ATRF ≥1) or
- Did not respond or has insufficiently responded due to poor tolerability to at least two inadequate antidepressant medication trials (ATIF ≥2).

6. Subject must be on at least one (1) antidepressant medication (minimum therapeutic dose not required if tolerability precluded further dose titration) and is willing to remain on the same daily dose of antidepressant medication(s) for a minimum of 28 days prior to randomization and thereafter for the duration of the study.
7. For subject receiving current depression focused psychotherapy: psychotherapy initiated at least 1 month prior to baseline visit with a stable frequency of visits regimen, in the opinion of the Investigator.
8. Subject is able to provide written Informed Consent and is capable of complying with the specified study requirements, as determined by the Investigator.
9. Subject has cognitive and/or motor skills needed to operate a smartphone and can be contacted by phone, as determined by the Investigator.

8.4. Exclusion Criteria

To be included in the MOOD study, patients must fulfill none of the exclusion criteria.

1. History of intracranial surgery.
2. Current denervation one or more of the follows: the supraorbital or supratrochlear branches of the trigeminal nerve, or the greater occipital branch of the occipital nerve.
3. An implanted neurostimulators or any implanted metallic or electronic device in the head, a cardiac pacemaker or an implanted or wearable defibrillator, except for dental implants.
4. Skin lesion, scars, or inflammation at the region of the stimulating electrodes.
5. Subjects with a history of traumatic brain injury (TBI), defined as a disruption in the normal function of the brain that can be caused by a bump, blow, or jolt to the head, or penetrating head injury, within 3 months of study enrollment.
6. Pregnancy or Lactation.
7. Women of reproductive age not using a reliable contraceptive method, as determined by the Investigator.
8. In the opinion of the Investigator, subjects with a psychiatric history consistent with, suspicious for, or diagnostic of, bipolar depression or depression associated with psychosis.
9. Borderline personality disorder, defined by DSM-V criteria, that in the judgement of the Investigator is likely to complicate the assessment of clinical response to study treatments or limits the patient's ability to comply with study procedures.

10. Subjects who, within one (1) year of study enrollment, have a history consistent with, suspicious for or diagnostic of, any of the following: psychosis, psychotic disorder, schizophrenia or schizoaffective disorder, in the opinion of the Investigator.
11. Subjects who demonstrate or have a history of any cognitive disorder or impairment, memory loss, dementia, confusion or delirium that, in the opinion of the Investigator, may compromise the integrity of the study data or impact the ability of the subject to comply with the study requirements.
12. Past 12 months active suicidal intent or plan as defined by a "yes" answer to Q4 or Q5 on the Columbia-Suicide Severity Rating Scale, (C-SSRS) or, with a history of suicide attempt in the past twelve months.
13. Subjects currently (past month) meeting diagnostic criteria for Obsessive-compulsive disorder or post-traumatic stress disorder and that is their primary diagnosis
14. Subjects meeting the DSM-V criteria for alcohol use disorder or other substance use disorder (not including tobacco/nicotine) within six (6) months prior to study enrollment.
15. The subject has any past or present medical condition, disease, illness, disorder or injury that, in the opinion of the Investigator, may reduce or hinder the subject's ability to fully comply with all study requirements for the duration of the study or may confound the integrity of the study data.
16. Participation in a previous study with the Relivion®$_{DP}$ or the Relivion ® device.
17. Treatment with Transcranial Magnetic Stimulation (TMS) in the past 6 months.
18. Current treatment with any other approved or investigational brain stimulation therapies (i.e. Vagus or trigeminal nerve Stimulation, tDCS, TES).
19. Failure to receive clinical benefit from an adequate trial of ECT in the current or a past depressive episode in the opinion of the Investigator.
20. Subject having received Botox treatment in the head or neck region within 90 days prior to study enrollment.
21. Subject having received supraorbital or occipital nerve blocks within 1 month prior to enrolment.
22. Head circumference smaller than 51 centimeters or larger than 60 centimeters.
23. Current neurological condition or disease which, in the opinion of the investigator, is likely to manifest a depressive syndrome or symptoms that would substantially confound the diagnosis or serial assessment of major depressive disorder.
24. Subjects participating in other clinical trials evaluating experimental treatments or procedures.

8.5. Vulnerable Population

No vulnerable population will take part in this study.

9. Study Procedures

9.1. Schedule of Events

The schedule of events is depicted in **Table 1** and **Figure 4**.

Table 1: Schedule of Events

Visit	Visit 1[1] Day -14-0	Visit 2[1] Day -4 -0	Visit 3 Week 4±1	Visit 4 Week 8±1	Visit 5 Week 12±1	Visit 6 Week 16±1
Event	**Screening**	**Randomization**	**Double blind phase - Daily Treatment**		**open label extension phase**	
Event / Visit window	**Day -14-0**	**Day -4-0**	**Day 28 ±7**	**Day 56±7**	**Day 84±7**	**Day 112±7**
Written/electronic Informed Consent	X					
Preliminary Eligibility Assessment (SCID)	X					
Medical history & Demography	X	X				
Concomitant medication	X	X[2]	X[2]	X[2]	X[2]	X[2]
Suicidal intent assessment (C-SSRS)		X	X	X	X	X
ATRF/ATIF	X					
Eligibility assessment	X	X				
Depression symptoms questionnaires (HDRS, MADRS, QIDS- SR -16, CGI-S&CGI-I)		X	X	X	X	X
Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)		X		X		X
Pregnancy urine test[3]	X					
Enrollment & Randomization		X				
Device training (on site or remote)		X		X[4]	X[4]	
Device conversion (Sham → Active) & OL treatment regimen training				X		
Blinding assessment questionnaire		X				
Device logs verification[5]		X		X		X
Active / sham DB treatment[6]			X	X		
Open label extension treatment[6]					X	X
Subject impression questionnaire						X
Adverse events		X	X	X	X	X
End of study				X[7]		X

1 visit 1 & 2 can be performed same day

2 change in concomitant medications /medical history

3 For women of childbearing potential only

4 Optional

5 Device logs – Remotely

6 weekly QIDS-SR-16

7 For treatment regimen non-compliant patients

9.1.1. Visit 1 – Screening (Day -14- 0) Screening and Preliminary Eligibility Assessment.

Written below are the assessments to be completed at Visit 1 (either on site or remotely):

- Written\Electronic informed consent.
- Assignment of subject ID and EDC registration.
- Preliminary Eligibility Assessment by the Structured Clinical Interview for DSM-IV axis I disorders (SCID).
- Subject's current and past (e.g. if failed) antidepressant medication treatments (including ATIF, ATRF forms)
- Medical history & Demography.
- Urine pregnancy test (for women of childbearing potential).

9.1.2. Visit 2 – Baseline (Day -4 - 0) Eligibility evaluation, Randomization and device training.

Written below are the assessments to be completed at Visit 2 (either on site or remotely):

- Eligibility assessment.
- PRO training for subjects self-reported questionnaire (QIDS-SR-16 and Q-LES-Q) (hard copy and/or electronic)
- Depression symptoms questionnaires:
    - By site qualified rater: HDRS21 (HDRS17- removing 4 last questions from the HDRS21), MDRS, CGI-S & CGI-I
    - By subject: QIDS-SR-16, Q-LES-Q. Subject self-reported questionnaire may be filled in electronically (ePRO) or by hard copy
- Document change in antidepressant medication, if any.
- Documented significant change in health status, if any.
- Suicidal intent assessment by the investigator team (C-SSRS).
- A review the study requirements with the subject to help ensure compliance.
- Randomization to Active Treatment or Sham Control.
- Subject will be provided with the device and the cellular app installed either on their personal iPhone or on a dedicated study iPhone, as applicable. Device and cellular iPhone, if required, may be provided to the subject at the site (in the case of an on-site visit) or by delivery (in the case of a remote visit)
- Device training will be performed by the study central trainer and may be performed during an on-site visit or in a remote fashion.

- Subject will read the User manual, the quick guide and will watch the instructional video and be trained on the device and recommended treatment regimen (detailed on the Relivion®$_{DP}$ Quick guide) by the study central trainer (on-site or remote).
- Device size will be adjusted to subject head circumferences.
- Subject will self-practice the device along with the mobile application to become familiar with its use and with the stimulation sensation.

- Blinding Assessment questionnaire (by hard copy or electronically (ePRO)
- Adverse events occurring during the visit will be documented.

Study visit 2 may occur in between study day -4 to study day 0 to allow for a device shipment to subject home and a remote device training. In any case, the day of the device training would be considered as study day 0.

Telephone numbers and an email address must be obtained from the subject to ensure the ability to contact him/her. This requirement will be described in the Informed Consent Form (ICF).

The study central trainer may contact the subject periodically to remind him/her to follow the recommended daily treatment regimen.

9.1.3. Daily treatment period (Day 0- day 56±7)

- Subjects will operate the device along with the dedicated mobile application independently at home or surrounding, according to the recommended treatment regimen provided by the central trainer and on the "Relivion®$_{DP}$ quick guide" for 8±1 consecutive weeks. The Relivion®$_{DP}$ programmed treatment duration will be 40 minutes. The daily treatment (duration and intensity) will be gradually increased up to a full effective treatment of 60±20 minutes, 5-7 days a week. In general, it is expected that the recommended daily treatment time would be performed in two equal time sessions per day (e.g. morning and evening, each of about 30±10 minutes). During a treatment session, if necessary, treatment can be paused by the subject and then be resumed. Subjects will continue their daily treatment up to their scheduled visit 4 day.
- Subject will self-complete the QIDS-SR-16 once every 7 days starting from day 0 (electronic or hard copy).
- Study central trainer will periodically verify device logs on the study cloud database and may contact the subject for re-training, if required.
- Study team and central trainer will contact the subject periodically to remind him/her to use the device, If necessary.
- The summary of each subject study treatments will be indicated on the subject binder.
- During this period, subject will be asked to schedule 2 follow-up evaluation visits.

9.1.4. Visit 3 – 4 weeks Follow up (Day 28±7)

Written below are the assessments to be completed at Visit 3 (either on site or remotely):

- Depression symptoms questionnaires:

- By site qualified rater: HDRS21 (HDRS17- removing 4 last questions from the HDRS21), MDRS, CGI-S & CGI-I
- By subject: QIDS-SR-16. Subject self-reported questionnaire may be filled in electronically (ePRO) or by hard copy.

- Suicidal intent assessment by the investigator team (C-SSRS)
- Change in concomitant medications, if any.
- Significant change in health status, if any.
- Adverse events will be documented.

9.1.5. Visit 4 – end of the DB phase (Day 56±7)

Written below are the assessments to be completed at Visit 4 (either on site or remotely):

- Depression symptoms questionnaires:
  - By site qualified rater: HDRS21 (HDRS17- removing 4 last questions from the HDRS21), MDRS, CGI-S & CGI-I
  - By subject: QIDS-SR-16, Q-LES-Q. Subject self-reported questionnaire may be filled in electronically (ePRO) or by hard copy.

- Suicidal intent assessment by the investigator team (C-SSRS)
- Change in concomitant medications, if any.
- Significant change in health status, if any.
- Adverse events will be documented.
  - The characteristics of each subject study treatments regimen will be indicated on the subject binder.
  - At the end of the double-blind treatment phase treatment compliance would be verified as follows:
    - A stimulation session marked as "Pass" if a minimal average intensity of 25 on the Relivion®$_{DP}$ app (i.e= Minimal average stimulation of 2.57mA Trigeminal, and 6.92mA Occipital of the active stimulation), was delivered.
    - The first treatment week (Ramp Up) will not be counted for treatment compliance.
    - Expected treatment time for total DB phase: A total of 2400 minutes of "pass" treatment time (calculated as a scenario of 80 min per day, 5 days a week for 6 weeks).
    - Minimal patient compliance for the DB treatment period will be regarded as 70% compliance to the above cumulative "pass" stimulation time recommendation.
- DB treatment regimen compliant subjects will be offered to continue to the open label extension phase for additional 8±1 weeks.
- Treatment regimen non-compliant subjects will exit the study and return the device and iPhone, if provided. For these subjects this study visit would be the "end of study visit".

- Once the OL treatment regimen allocation will be decided, the central trainer will contact the subject (on site or remote) to perform the device conversion to the open label mode (i.e. conversion of all devices to active mode), train the subjects on the assigned treatment regimen and re-train on the device use, if required.
- OL treatment regimens would include:
  - Maintenance treatment (for remitters): 40±10 minutes 3-4 times a week (intensity level up to 50)
  - Daily treatment (for responders): 5-7 days a week (intensity level up to 50) 60±20 minutes per day (preferably in two equal sessions of 30±10 minutes each).
  - Daily Intensified treatment regimen (for non-responders): 5-7 days a week (intensity level up to 60) 60±20 minutes per day (preferably in two equal sessions of 30±10 minutes each).

- Study visit 4 may occur during a 4 days period to allow for the HDRS response, treatment compliance assessments and OL treatment allocation to be finalized and data to be provided to the central trainer who may schedule a remote training session with the subject. In any case, the subject would continue his/her previous treatment regimen up until the day of the device conversion to the open label mode. The device conversion day would be considered as the first day of the OL treatment phase.
- Subjects which completed the minimal stimulation time required by the protocol will be considered as DB phase completers.

9.1.6. Open label extension phase (Day 56±7- day 112±7)

- According to their visit 4 HDRS response assessment, subjects will be assigned into one of three open label treatment groups: Remitters/Responders/Non responders as follows:
  - Remitters: HDRS ≤7 at study visit 4 (week 8±1 post treatment initiation).
  - Responders: 50% ≥ HDRS score improvement from baseline at study visit 4 (week 8±1 post treatment initiation).
  - Non-responders: all other subjects who are not remitters or responders (50% <HDRS score improvement from baseline) at study visit 4 (week 8±1 post treatment initiation).

See Figure 5: Open label phase study flow.

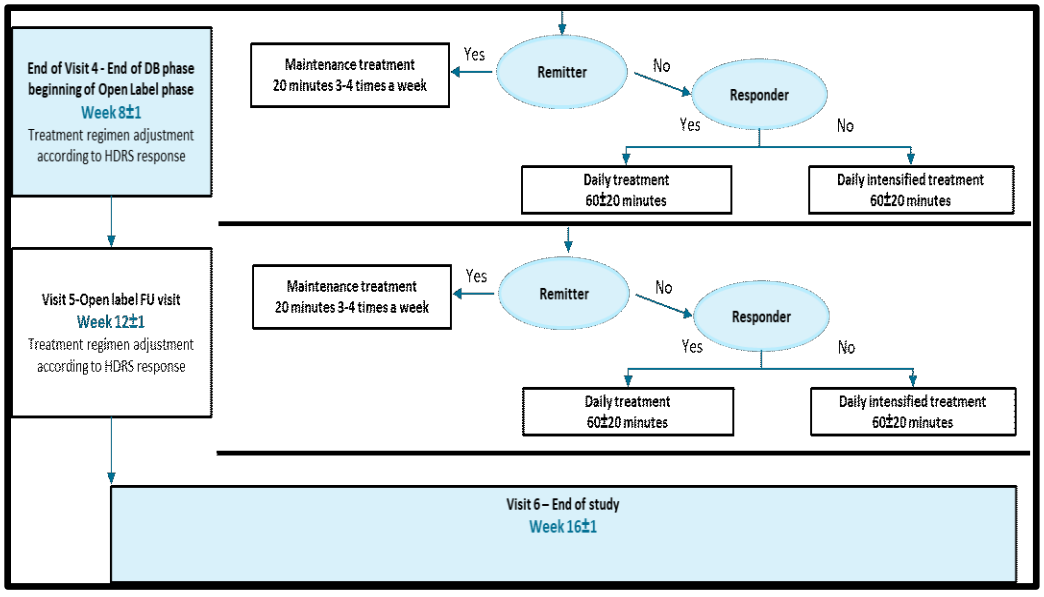


Figure 5: Open label phase study flow

- Subjects will operate the device along with the dedicated mobile application independently at home or surrounding, according to the recommended treatment regimen provided by the central trainer and on the "Relivion®$_{DP}$ quick guide" for 8±1 consecutive weeks. The Relivion®$_{DP}$ device programmed treatment duration will be 40 minutes. If needed, (i.e. for originally sham subjects who are not used to the active stimulation sensation) the daily treatment (duration and intensity) will be gradually increased up to a full effective treatment according to the assigned treatment regimen (i.e. for remitters, responders and non-responders). In general, it is expected that the responders and non-responders' subjects recommended daily treatment time of 60±20 minutes would be performed in two equal time sessions per day (e.g. morning and evening, each of about 30±10 minutes). The remitters subjects would apply the stimulation once a day 3-4 times a week for 40+10 minutes. If necessary, treatment can be paused by the subject and then be resumed. Subjects will continue their assigned treatment regimen up to their scheduled visit 5 day. At study visit 5 the subjects response to treatment, according to HDRS, will be re-evaluated and treatment regimen may be amended accordingly (see Figure 5), re-training will be performed by central trainer, if required. The subjects will continue their assigned treatment regimen up to their scheduled visit 6 day (end of study).
- Subject will continue to self-complete the QIDS-SR-16 once every 7 days.

- The characteristics of each subject assigned study treatments regimen, both from visit 4 and visit 5 (if applicable), will be indicated on the subject binder.
- Study central trainer will periodically verify device logs on the study cloud database and may contact the subject for re-training, if required.
- Study team and central trainer will contact the subject periodically to troubleshoot any issue, If necessary.
- During this period, subject will be asked to schedule 2 follow-up evaluation visits (on-site or remote).

9.1.7. Visit 5 – 12 weeks Follow up (Day 84±7)

Written below are the assessments to be completed at Visit 5 (either on site or remotely):

- Depression symptoms questionnaires:
  - By site qualified rater: HDRS21 (HDRS17- removing 4 last questions from the HDRS21), MDRS, CGI-S & CGI-I
  - By subject: QIDS-SR-16. Subject self-reported questionnaire may be filled in electronically (ePRO) or by hard copy.
- The subjects' response to treatment, according to HDRS, will be re-evaluated and treatment regimen may be amended accordingly as specified in section 9.1.6 and Figure 5.
- The central trainer will provide training to the subjects on the newly assigned treatment regimen, if applicable.
- Clinically significant current suicidal intent re-assessment by the investigator team (C-SSRS)
- Change in concomitant medications will be documented.
- Adverse events will be documented.

9.1.8. Visit 6 – end of study (Day 112±7)

Written below are the assessments to be completed at Visit 6 (either on site or remotely):

- Depression symptoms questionnaires:
    - By site qualified rater: HDRS21 (HDRS17- removing 4 last questions from the HDRS21), MDRS, CGI-S & CGI-I
    - By subject: QIDS-SR-16, Q-LES-Q. Subject self-reported questionnaire may be filled in electronically (ePRO) or by hard copy
- Clinically significant current suicidal intent re-assessment by the investigator team (C-SSRS)
- Change in concomitant medications will be documented.
- Adverse events will be documented.
- Subject Impression will be documented by the Subjects Impression Questionnaire.
- Central trainer will arrange the collection of the device and the iPhone, if applicable, from the subjects and final accountability will be performed.
- The summary of each subject study treatments will be indicated on the subject binder.
- At this point subject's participation in this study will be over.
- Adverse Events that are still ongoing will be followed according to section 9.9

9.2. Activities Performed by Sponsor's Personnel

A sponsor representative, such the study manager/monitor may be present at the clinic for overseeing and guiding the study screening, enrollment and follow up procedures.

The representatives' activities will occur in such a way that they do not influence the conduct of the study, nor do they interfere with any medical decisions or bias the data integrity. Additionally, they will be described in the Informed Consent Form (ICF) and sponsor technical support list.

Device management and training will be conducted on a centralized fashion by the study qualified and dedicated central trainers. The central trainers' responsibilities may include:

- Operational duties such as: Dispensing of the blinded Relivion®$_{DP}$ devices to the subjects according to the randomization scheme and arranging their collection back to sponsor.
- Following up on subject's treatment compliance throughout the study
- Presence at study visits (on site or remotely) for supporting the study participants in device training and operation.
- Presence at the clinic/remotely for observing the use of the device and gathering information and feedback from the site personnel.
- Arrange the conversion of the Sham devices to Active ones at the start of the OL extension.
- Provide device technical support to subject throughout the study conduct.

9.3. Prior and Concomitant Medications

Prior to study enrollment visit, subjects will be on a stable dose of Antidepressant medications (type and dose) for at least four weeks, as per subjects' medical records or subject self-report. During the study period, the subject will continue his/her Antidepressant medication treatment on the same type and dose throughout the study. Please see section 9.7 for additional details. During every study visit, the study team will document patient's Antidepressant medication (type and dose).

9.4. Subject Consent

Informed consent will be obtained before any study-specific procedures are initiated or data collected. Principal Investigator or his/her authorized designee will conduct the informed consent process.

At the screening visit, subjects will be approached to obtain written or electronic informed consent prior to any data collection. Once the ICF is collected, screening of subject will follow. The purpose of the study and the benefits and risks of the procedures will be explained to the subject and the consent process must be documented accordingly in the medical record. Subjects who agree to study participation must sign a Sponsor and IRB/EC-approved ICF. Consent to participate in this study must be given in writing or electronically. Subjects that are unable to give consent will not be included in study.

Informed Consent will be obtained in accordance with the CFR Title 21, Part 50 (US) or ISO14155:2011 (Israel) as well as the Declaration of Helsinki and will follow the FDA guidance for the use of electronic informed consent.

Electronic measures in order to obtain informed consent remotely will be supplied to all study sites and will be implemented in the study EDC system with accordance to the FDA guidelines for the use of Electronic Informed Consent [37]

The Investigator or designee must obtain written/electronic informed consent before any clinical study related activity takes place. Prior to entry into the study, the IRB/EC and Neurolief-approved ICF form, and the Health Insurance Portability and Accountability Act (HIPAA) Authorization Form (US only) will be given to each subject. The Investigator or designee will fully inform the subject of all aspects of the clinical study that are relevant to the subject's decision to participate in the clinical study (e.g. purpose and duration of the study, requirements of the subject during the study, potential risks and possible benefits associated with participation in this study). All items addressed in the Informed Consent Form must be explained. The language used shall be as non-technical as possible and must be understandable to the subjects.

The subject must have ample time and opportunity to read and understand the Informed Consent Form, to inquire about details of the clinical study, and to decide whether or not to participate in the clinical study. All questions about the clinical study should be answered to the satisfaction of the subject. In the case that a subject is unable to read, an impartial witness must also be present and sign the informed

consent to confirm that the research has been clearly explained and all of the subject's questions have been answered.

Neither the Investigator, nor the investigation site staff shall coerce or unduly influence a subject to participate or to continue to participate in the clinical study. The informed consent process shall not waive or appear to waive the subject's rights.

When the subject decides to participate in the clinical study, the HIPAA Form (US only) and the Informed Consent Form must be personally signed and dated by the subject.

After all persons have signed and dated the Informed Consent Form, the Investigator or designee must provide the subject with a copy.

Neurolief will inform the Investigators whenever information becomes available that may be relevant to the subject's confirmed participation in the clinical study. The Investigator or his/her authorized designee should inform the subject in a timely manner.

Neurolief will revise the written Informed Consent Form whenever new information becomes available that may be relevant to the subject's confirmed participation in the clinical study. The revised information will be sent to the Investigator for approval by the IRB/EC. After approval by the IRB/EC, a copy of this information must be provided to the participating subjects, and the informed consent process as described above needs to be repeated.

If the ICF is amended during the course of the study, the IRB/EC will determine:

- Whether or not active subjects should be re-consented at their next visit and
- Whether or not subjects who have completed the study at the time of the amendment should repeat the informed consent process.

Subjects will be informed that qualified personnel from the investigational center, the Sponsor (Neurolief), agencies such as the FDA/local regulatory authority in Israel and/or the IRB/EC may have access to clinic records that reveal their identity.

The investigational center must report the following deviations to their IRB/EC:

- Failure to obtain informed consent from subject.
- Failure to obtain informed consent prior to performing one or more study procedures.
- Failure to maintain ICFs on file for all subjects who have provided informed consent.
- Use of an ICF that has not received approval from the IRB/EC.
- Use of an incorrect version of the ICF.

9.5. Randomization, Treatment Assignment and Blinding

Subjects will be prospectively randomized into the clinical study. Randomization will occur only after the subject provides informed consent, completes all required screening and baseline procedures, and satisfies the study eligibility criteria. Eligible subjects will be randomly allocated (with a 1:1 ratio) to one of the following 2 treatment groups based on a randomization scheme using the permuted block method stratified by center:

- Active stimulation.
- Sham stimulation.

The randomization scheme will be prepared by the study statistician using the SAS (version 9.4.) random number procedure. The block size will be random, and all study personnel will therefore be blinded to the randomization block size. Only the unblinded statistician /sponsor unblinding party and designates will be privy to the masked randomization scheme.

The Relivion®$_{DP}$ Active and Sham devices will look the same and will be provided in the same packaging bearing the same labeling. Hence, both subjects and study personnel will remain blinded to the assigned treatment group.

9.6. Unblinding

9.6.1. Planned Unblinding

Subjects and study personnel may be unblinded to each subject's group assignment at the end of the study. Blinding will be opened, and the subject will be notified about his/her treatment assignment, if requested.

9.6.2. Unplanned Unblinding

The investigator, sponsor or regulatory authorities may initiate unplanned unblinding procedures in the interest of patient safety.

In case of medical emergency, the Investigator will contact the Sponsor's on call unblinded biostatistician and the specific patient's code will be broken. In case the sponsor's on-call unblinded biostatistician cannot be reached, the investigator will contact the unblinded sponsor representative and the specific patient's code will be broken. The Investigator will promptly document the reason for breaking the code.

9.7. Medication Compliance

For the double-blind phase duration, subjects will be asked to maintain on a stable type and dose of antidepressant medications (any psychotropic medications with CNS effects that are prescribed or taken for MDD symptoms).

A change of up to 25% (increase or decrease) in dose of an ongoing psychotropic medication would be considered as "no change" i.e stable dose.

A change in the type of an ongoing psychotropic medications and/or discontinuation of medication regimen or a change of dose over 25% (decrease or increase) of an ongoing psychotropic medication throughout the study, would be considered as a "change" i.e. non stable-dose.

If necessary (i.e. In the case of emergence or worsening of insomnia), benzodiazepines ≤3mg lorazepam (or equivalent dose of another benzodiazepine) may be used for agitation/anxiety or insomnia up to 3 times per week. Partial benzodiazepine agonists, including zolpidem 5 to 10 mg/day, zaleplon 5 to 10 mg/day, and eszopiclone 2-3 mg/day, may be used on an exceptional basis for insomnia/sleep disturbance within the prescribing doses for insomnia. Any equivalent short half-life non-benzodiazepine hypnotic may be substituted if zolpidem, zaleplon, or eszopiclone are not available.

During the open label phase ineffective antidepressant doses may be decreased, as per investigator discretion.

9.8. Assessment of Efficacy

Efficacy parameters including Hamilton Depression Rating Scale -HDRS17 and HDRS21; Montgomery-Asberg Depression Rating Score (MDRS); Quick Inventory of Depressive Symptomatology -QIDS-SR-16; and Clinical Global Impression scales -CGI-S and CGI-I; will be performed and documented at each visit.

The study questionnaires will be documented by a qualified rater (HDRS, MDRS), C-SSRS, CGI-S and CGI-I using the hard copy questionnaires and thereafter will be documented in the subject' CRF.

The study questionnaires that are self- reported by the subjects (QIDS-SR-16, Q-LES-Q, SIQ) will be completed using the study EDC ePRO tool or hard copy.

The treatment duration and intensity will be documented automatically in the device logs.

9.9. Assessment of Safety

Safety will be assessed by the collection of adverse events information from Enrollment through study exit. Type, incidence, severity, duration, and procedure/device relationship of adverse events (AEs) will be collected throughout the study. Subjects with AEs at study exit will be followed for 14 days or until event resolves, whichever comes first. Adverse event data will be collected and reported on eCRFs.

Additionally, at baseline and during each visit (from randomization throughout the study) and whenever there is a suspect for increased suicidal intent, the investigator team will perform the Columbia-Suicide Severity Rating Scale (C-SSRS) questionnaire with the subject for the assessment of suicidality. At baseline, subjects that in the past 12 months reported active suicidal intent or plan as defined by a "yes" answer to

Q4 or Q5 on C-SSRS questionnaire or had a history of suicide attempt in the past twelve months will be excluded (according to exclusion criteria # 12). Throughout the study, an answer of "yes" to Q 4 or Q5 would serve as an immediate need for re assessment with the principal investigator. Upon principal investigator assessment of the “yes” answer to Q4 or Q5, the patient would be excluded from the study and the event will be reported as an AE.

9.10. Data Capture

Data will be collected using a hard copy CRF and/or Electronic Data Capture (EDC) System for all site reported information.

Data points not collected and/or recorded will be considered deviations unless otherwise specified. Procedures used for data review, database cleaning, and issuing/resolving data queries will be included in the data management plan.

The Principal Investigator must ensure the accuracy and completeness of the recorded data and then provide his/her signature on the appropriate CRF/eCRFs. The Investigator’s electronic signature for specific eCRFs will be documented in compliance with local regulations.

Visual and/or computer data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the site for appropriate response. The site staff will be responsible for resolving all queries in the database.

This study will be using a 21 CFR Part 11 compliant electronic data capture. All system level validation documentation is retained within the Information Systems group. See **Section 14.4**, Data Management.

9.11. Deviation Handling

A deviation is defined as an event where the exact instructions contained in this protocol or the applicable regulations have not been followed. Deviations are classified by occurrence (*i.e.*, sporadic vs. repeated) and seriousness (*i.e.*, major vs. minor). Major deviations may impact subject safety, alter the risk/benefit ratio, compromise the integrity of the study primary end point data. Minor deviations do **not** impact subject safety, compromise the integrity of the primary end point study data.

No changes to the protocol will be permitted. Investigators are required to obtain prior approval from the sponsor or designee and their respective IRB/EC and Regulatory Authority, if required, before initiating deviations from the protocol, except where necessary to protect the rights, safety and well-being of human subjects in an emergency. Such approval will be documented in writing and maintained in study files. The investigator must notify Neurolief and the reviewing IRB/EC of any deviation, which will be recorded in the eCRF, from the CIP when specific to the protection of the life or physical well-being of a subject in an emergency. Such notice must be given as soon as possible, but in no event later than 5 working days after the emergency has occurred. Prior approval is generally not expected in situations

where unforeseen circumstances are beyond the investigator's control, (*e.g.*, subject did not attend scheduled follow-up visit); however, the event is still considered a deviation and must be recorded in the subject eCRF.

Deviations shall be reported to the sponsor regardless of whether medically justifiable, pre-approved by Neurolief, IRB/EC and Regulatory Authority, if required, or taken to protect the patient in an emergency. If these deviations affect the scientific soundness of the CIP or the rights, safety, or welfare of human subjects the IRB/EC will also be notified. All other deviations will be reported per the site's IRB/EC deviation policy. All protocol deviations will be reported in the eCRF. Non-subject specific deviations (*e.g.*, unauthorized use of an investigational device outside the study, unauthorized use of an investigational device by a non-certified physician) must also be reported by the investigator to the sponsor in writing. Investigators must also adhere to procedures for reporting study deviations to their EC/IRB in accordance with their specific EC/IRB reporting policies and procedures.

The monitor will discuss deviations with relevant site personnel and will document them on monitoring visit reports.

Neurolief will review records of deviations and will consider the need for corrective and preventive action and further external reporting to regulatory authorities. Deviations will be summarized and included in the study report. Assessment and discussion of their potential impact / lack of impact on study results will be addressed.

If the deviation is performed without written approval from all parties, the investigator may be terminated from the study. Corrective and preventive actions and principal investigator disqualification will be included in the Clinical Study Management Plan and/or Monitoring Plan. If further escalation is needed, it may result in Corrective and Preventive Action (CAPA), suspension, or termination. If it is determined that there is investigator fraud, or strong evidence of fraud, the course of action may include, but is not limited to: potential exclusion from analyses, site closure, notification of the responsible IRB/EC of the actions to be taken, notification of key stakeholders and/or study team of the actions to be taken, notification of appropriate regulatory authority(ies) and/or restrictions on future participation in clinical studies.

9.12. Subject Withdrawal or Discontinuation

The reason for study exit, including screen failure, will be documented on the applicable CRF/eCRF and in the subject file. The Sponsor must be informed of each withdrawal case.

Once a subject has been enrolled in the study, he/she may withdraw his/her consent to participate in the study at any time without prejudice. Participation in this clinical investigation is entirely voluntary.

In the event the subject withdraws consent during the study, the date of withdrawal will be documented. Individual subjects will not be replaced.

The investigator may prematurely discontinue the participation of any subject in the study.

If the Investigator voluntarily removes a subject from further study participation, supporting documentation must be in place for the rationale and date of removal. The Investigator may withdraw a subject from the study at any time for the following reasons:

- Severe side effects clearly related to the study procedures.
- Presence or appearance of exclusion criteria
- Clinically significant current suicidal intent as assessed by the investigator team: a "yes" answer to Q4 or Q5 on C-SSRS questionnaire.
- Appearance of accompanying diseases rendering further participation in the study impossible
- A significant protocol deviation, as determined either by the Sponsor or the Investigator.
- Subject noncompliant with procedures
- Subject noncompliant with visits
- At the specific reasonable request of the Investigator

Attempts will be made to conduct an exit/final visit prior to a subject terminating participation in the study. The reason for early discontinuation will be documented in the source documents and eCRF. Data collected up to the point of withdrawal or premature discontinuation will be included in the data analysis, unless specifically requested not to.

9.13. Subject Missed Contact / Visit

Every attempt will be made to contact subjects that are noncompliant with study visits. If a subject does not show for a visit and cannot be contacted to collect follow-up information, he/she will be counted as a 'missed visit' for that specific schedule. Prior to counting the subject as a 'missed visit' the following will be performed:

- Repeated attempts to contact the subject via all available means. Each attempt should be clearly documented in the source documents and the response or lack thereof should be captured.
- Repeated, documented attempts to contact the subject's general practitioner or referring physician.
- If a visit cannot be arranged, obtain as much information as possible through all communication means with the subject and/or his/her treating physician.

If still unsuccessful to obtain information, attempts shall be made to contact the subject for the next scheduled visit. A subject will be considered 'lost' only after a period of two (2) weeks after the last scheduled visit for that subject. If a subject is lost, the methods used to attempt to contact the subject should be noted. At least three attempts should be made to contact the subject and/or his/her treating physician via all available routes, and a certified letter should be sent to the permanent address on file. A copy of the letter and return or delivery receipts should be retained in the subject's source document. The Sponsor should be notified and the End of Study (EOS) form should be completed.

10. Risks and Benefits

Risk management is performed as per ISO 14971, complete documentation is maintained on quality management file (Neurolief document # QAD-222).

10.1. Potential Risks

Technical characteristics and electrical output of the Relivion®$_{DP}$ are similar to other known external transcutaneous devices applying electrical stimulation for psychiatric purpose. Safety of the Relivion®$_{DP}$ has been extensively tested and confirmed through bench performance testing as well as throughout Neurolief's early clinical study. No serious device related adverse events were recorded during the early studies, and treatment was well tolerated by participants.

Current study design does not require application of electrical stimulation for exceptionally prolonged periods, or other circumstances where the use of the device has not yet been validated. Hence this protocol presents minimal risks to the subjects and adverse events are not anticipated beyond those reported for other electrical neurostimulation devices. Potential expected device side effects are summarized below. See **Section 11.2**.

No information is available for use of the Relivion®$_{DP}$ during pregnancy or lactation, so women who are pregnant or lactating are not eligible for inclusion in this study.

Participating in this study DB phase means that the subject has a 50% chance of receiving a sham treatment, which may lead to worsening of the subject Depression state (including suicidal intent).
The above mentioned risk is mitigated by the following: study patients continue using their prescribed antidepressant medications during the study duration and are closely followed up by the study team as to their mental state, including the continued assessment of their MDD severity on the HDRS score, weekly QIDS-SR-16 and the C-SSRS suicidality assessment. In the case of worsening depression symptoms, the study team will be able to unblind the subject arm and/or respond immediately with treatment change and if required study exit. In the case of worsening depression symptoms, a process for emergency unblinding is implemented during study conduct. In addition, subjects and family members would be instructed to contact the study doctor if symptoms get worse.

The risk for suicide is reduced by the study exclusion criteria by which subjects with a current suicidal intent or plan would not be randomized to the study (exclusion criteria #12: Past 12 months active suicidal intent or plan as defined by a "yes" answer to Q4 or Q5 on the Columbia-Suicide Severity Rating Scale, (C-SSRS) or with a history of suicide attempt in the past twelve months). In addition, at every follow up visit the suicidal intent will be re-assessed and documented by the study team. Throughout the study, an answer of "yes" to questions Q4, or Q5 would exclude the subject from the study.

There may be additional risks related to this study (other than those listed here) that are not yet known. Risks must be continuously monitored, assessed, and documented by the Investigator.

10.2. Potential Benefits

Neurolief's feasibility clinical study demonstrates a significant improvement effect of the Relivion®$_{DP}$ in subject's who suffers from MDD by an average reduction of 9 points on the HDRS score over the six weeks of treatment period. Moreover, 35% of the patients showed symptoms remission and 85% experienced a decrease in their HDRS score with no serious adverse effects over the six weeks of treatment period. It is anticipated that patients will experience similar effect under the setting of the current study.

Another known benefit to patients participating in such a study is the ability to learn more about their medical condition through the assessments that will be performed throughout the course of the study. Additionally, patients will be closely observed by the study staff throughout their participation in the study and therefore their treating physicians may be able to make more informed decisions in their medical care. Last, all assessments associated with the study, as well as the study device, are provided at no charge to the participants.

The information from this study may benefit other subjects with Major depression in the future.

10.3. Risk Control and Mitigation

The following efforts will minimize risks to subjects in the study:

- Conduct of the study following successful completion of extensive bench performance testing and careful risk analysis.
- Selection of investigators who are experienced and skilled in management of patients with MDD.
- Establishment of a training program for study staff members (investigators and coordinator) and use of tools that will ensure proper training to the subjects for home use of the device.
- Clearly defining the inclusion and exclusion criteria such that only appropriate patients are enrolled in the study.
- Close monitoring of worsening of depression symptoms and suicidal intent

10.4. Risk-Benefit Rationale

Assessing the risks against the potential benefits of the use of the Relivion®$_{DP}$ for improvement of MDD symptoms, Neurolief and the principal investigators have determined that there is a high likelihood that the expected benefit may outweigh the risk in patients fulfilling the study eligibility criteria.

11. Adverse Events and Device Deficiencies

Adverse event definitions used in this study are based on ISO 14155:2020 (Clinical Investigation of Medical Devices for Human Subjects -- Good Clinical Practice).

Adverse Events will be collected for all enrolled subjects with the point of enrolment (Visit #2 upon randomization) and end at the study termination visit (visit #6). Subjects with AEs at termination visit will be followed for 14 days or until event resolves, whichever comes first.

During the course of the study, all AEs will be collected and reported on the CRF/eCRF including:

- All AEs related to Relivion®$_{DP}$ device and/or procedure.
- All AEs not related to Relivion®$_{DP}$ device and/or procedure.
- All device deficiencies that may lead to a SAE.
- All Deaths

11.1. Definitions

Safety definitions are provided below. Clinical events to be considered and reported as AE or SAE include but are not limited to those listed in Section 11.2.

Adverse Event (AE): Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated.

NOTE 1 This definition includes events related to the investigational medical device or the comparator.

NOTE 2 This definition includes events related to the procedures involved.

NOTE 3 For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

Adverse Device Effect (ADE): Adverse event related to the use of an investigational medical device.

Note 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Serious Adverse Event (SAE): An adverse event that led to any of the following:

- death;
- a serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
  - a life-threatening illness or injury;
  - a permanent impairment of a body structure or a body function including chronic diseases; or

- in-patient or prolong hospitalization; or
- medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function;
- fetal distress, fetal death, a congenital abnormality or birth defect including physical or mental impairment.

Note: A planned hospitalization for pre-existing condition, or a procedure required by the clinical protocol, without a serious deterioration in health, is not considered to be a serious adverse event.

Serious Adverse Device Effect (SADE): Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated (Serious) Adverse Device Effect (U(S)ADE): Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

11.2. Relivion®$_{DP}$ Anticipated Adverse Events

Possible risks and adverse events that may be associated with the Relivion®$_{DP}$ device are based on adverse events reports of similarity devices include, but are not limited to the following:

- Unpleasant sensation during treatment
- Scalp Numbness sensation during and after treatment
- Persistent tingling sensation after the treatment ends
- Pain in the head and neck area
- Skin reaction (for example, irritation, lesion, burn) beneath the stimulation electrodes. In this case, treatment should be temporarily discontinued.
- Redness of the skin under or around the electrodes. Skin redness usually disappears within several hours after treatment.
- Sleepiness, fatigue or sleep disorders
- Sedative effect during or after treatment
- Dizziness during or after treatment
- Tension type headache after treatment

11.3. Reporting of Adverse Events

11.3.1. Reportable Adverse Events

The definition of AE applies to any underlying diseases, present at baseline, that exacerbate in severity post intervention. Therefore, an underlying disease that was present at the time of enrollment is not reported as an AE, but any increase in the severity of the underlying disease is to be reported as an AE.

All AEs including laboratory abnormalities that are deemed clinically significant by the investigator must be recorded in the source document and eCRF, irrespective of attribution to device or procedure. All clearly related signs, symptoms, and abnormal findings should be grouped under one diagnosis. A description of the event, including the start date, resolution date, action taken, and the outcome should be provided, along with the investigator's assessment of the severity, the seriousness and the relationship between the AE and the study device and/or procedure. If any radiological imaging or other testing are taken, which are related to the event, these will be added to the eCRF of the subject.

11.3.2. Hospitalizations

Any adverse event that results in inpatient hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, nor surgery are reported as an adverse event under the following circumstances:

- Hospitalization for diagnostic or elective surgical procedures for a preexisting condition.
- Emergency department visits, unless meeting the SAE definition under another criterion.
- Social admission (e.g., patient has no place to sleep).
- Administrative admission (e.g., for yearly physical exam).
- Optional admission not associated with a precipitating clinical adverse event (e.g., for elective cosmetic surgery).
- Nursing home admission, admission to custodial care, or admission to a rehabilitation facility.

11.3.3. Reporting Procedures

The investigator shall submit to the sponsor and to its representative all associated information and documentation related to each AE. Notification to local authorities should follow local requirements.

AEs will be categorized according to severity and relatedness.

Adverse Event Severity Classification

Severity of AEs will be determined using the following scale:

- Mild: The subject is aware of a sign or symptom, but it is easily tolerated.
- Moderate: Discomfort or interference with usual activity.
- Severe: Incapacitating, with inability to engage in usual activity.

Relatedness: The investigator will determine the relationship of each adverse event to the use of the device / procedure.

Adverse Event Relationship Classification

Causality assessments define the relationship between the use of the medical device (including the medical procedure) and the occurrence of each adverse event. During causality assessment activity, clinical judgment shall be used and the relevant documents, such as the Clinical Evaluation Report and the Risk Management Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

Each AE will be classified according to five different levels of causality. The Sponsor and the Investigators will use the following definitions to assess the relationship of the serious adverse event to the medical device or procedures:

Relationship to study product administration will be determined as follows:

Not related: relationship to the device or procedures can be excluded when:

- the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has no temporal relationship with the use of the device or the procedures;
- the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
- the event involves a body-site, or an organ not expected to be affected by the device or procedure;
- the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the device used for diagnosis, when applicable;
- harms to the subject are not clearly due to use error;
- In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

Possible: the relationship with the use of the device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.

Probable: the relationship with the use of the device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.

Causal relationship: the serious event is associated with the device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with device use/application or procedures;
- the event involves a body-site or organ that
  - the device or procedures are applied to;
  - the device or procedures have an effect on;
- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the device used for diagnosis, when applicable;
- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

The Sponsor and the Investigators will distinguish between the AEs related to the device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the device. Complications of procedures are considered not related if the said procedures would have been applied to the subjects also in the absence of device use/application.

In some particular cases the event may be not adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The Sponsor and the Investigators will make the maximum effort to define and categorize the event and avoid these situations. Where the

Sponsor remains uncertain about classifying the serious event, it should not exclude the relatedness and classify the event as "possible".

Adverse Event Outcome Classification

Adverse Event Outcome Classification will be defined according to the following:

Resolved: The event has fully resolved at the end of the study.

Resolved with sequel: The event has resolved, but retained pathological conditions resulting from the prior disease or injury.

Continuing: The event is ongoing at the end of the study.

Death: This event is determined to be the cause of death.

11.3.4. Reporting of Adverse Events

Please refer to **Table 2** for a list of the minimum AE reporting requirements for Investigators. If local regulations or IRB/EC require faster reporting, then the Investigator will adhere to those requirements. Reporting of all safety events to the Sponsor will be completed through Investigator submission of the AE CRF by e-mail and/or eCRF in the remote data capture (RDC) system. In case of emergency only for SAEs (ex. RDC system is unavailable), the sponsor site representative may be contacted directly; this will not serve as a substitute for proper reporting on the appropriate eCRF.

Table 2: AE Reporting Requirements

Type	Report to	Reporting Timeframe (from time of learning of event)
Adverse Event (AE)	Sponsor	Within 10 working days
	IRB/EC	Per EC reporting requirements
Serious Adverse Event (SAE)	Sponsor	Within 24 hours
	IRB/EC	Per/IRB/ EC reporting requirements
Adverse Device Effect (ADE), Serious Adverse Device Effect (SADE) and Unanticipated Serious Adverse Device Effect (USADE/UADE)	Sponsor	Within 24 hours
	IRB/EC	Per EC reporting requirements
	Sponsor	Within 48 hours

Type	Report to	Reporting Timeframe (from time of learning of event)
Device Deficiency	IRB/EC	If SAE occurs due to the device deficiency, within 24 hours of learning of the event and per EC reporting requirements
	EC	Per EC reporting requirements

Events will be reviewed by the Sponsor to determine any reporting obligations to the FDA or Regulatory Authorities as well as IRB/EC. Reporting will occur within the timelines per local regulations and requirements. The Principle Investigator is responsible to report the events to the IRB/EC.

The sponsor shall immediately conduct an evaluation of any unanticipated events if determines that the event presents an unreasonable risk to subjects, report the results of such evaluation to the Regulatory authority and to reviewing IRB/EC and participating investigators within 10 working days after the sponsor first receives notice of the event.

11.3.5. Notification to Authorities

The following events are generally considered reportable during the course of this study and should be reported to the Sponsor:

- any SAE
- any Device Deficiency that might have led to an SAE if
  - suitable action had not been taken or
  - intervention had not been made or
  - if circumstances had been less fortunate
- new findings/updates in relation to already reported events.
- deaths

Events will be reviewed by the Sponsor for reporting obligations to Regulatory Authorities. Reporting to the sponsor or its designated CRO is responsible for relaying adequate information on reportable events to the regulatory authorities per country's applicable reporting requirements.

11.3.6. Device Deficiencies

Device deficiency is an inadequacy with respect to the device's identity, quality, durability, reliability, usability, safety, or performance, such as a malfunction, failure, use error and inadequacy in the information supplied by the manufacturer including labeling. Device deficiencies may or may not be associated with an adverse event.

All device deficiencies will be entered in the eCRF. Device deficiencies that were associated with an SAE or that could have led to an SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstance had been less fortunate, will be documented within **24 hours** of knowledge. If possible, the device(s) associated with a malfunction or failure should be retained until arrangements for its collection are made by Neurolief.

Device deficiencies are NOT to be reported as AEs. However, if there is an AE that results from a device deficiency, that specific event would be recorded on the appropriate eCRF.

A device deficiency must be reported to Neurolief (technical support) within 48 hours after the investigator is made aware of the event.

Device deficiencies will be summarized and reported in the clinical study report and will be reported to the regulatory authorities per country's applicable reporting requirements.

11.3.7. Safety Monitoring and Adjudication of Adverse Events

The sponsor will review submitted AE information and may request supplemental information if needed. For SAE, U(SA)DE and ADE (as classified by the investigator) a narrative will be prepared and adjudicated for assessing the relatedness, seriousness and possible action items required. The sponsor may ask for further information or clarification from the investigator. A summary of the adjudication results will be issued; if different than investigator's report, PI will be notified, and the information will be forwarded to Neurolief medical advisor for final adjudication. All the safety data including any adverse events or side effects related to the treatment will be reported periodically to the independent data monitoring committee (DMC) as indicated in section 14.1. The DMC will provide recommendations to sponsor about stopping or continuing the trial or making modifications to enhance safety of trial participants to protect the integrity of the study.

Adjudicated events will serve as a basis for reporting AE/SAE. Differences between site-reported events and adjudicated events will also be presented and discussed in the report.

12. Statistical Considerations

12.1. Study Design and Objectives

12.1.1. Objectives

The MOOD Study will evaluate the safety and efficacy of a self-administered treatment for MDD using an external combined occipital and trigeminal nerve stimulator device (Relivion®$_{DP}$).

12.1.2. Study Design

This is a prospective, randomized, double-blind, parallel-group, sham controlled, multi-center clinical investigation followed by an active open label extension period. All enrolled patients are those treated with the Relivion®$_{DP}$ device either by active treatment or sham treatment. The treatment will be done according to the IFU. Patients duration in the study will be up to 20 weeks (including the screening period).

One interim analysis is planned after 86 (~80% of the calculated sample size) evaluable subjects have been accrued, mainly for sample size re-assessment. The primary, as well as the safety endpoints will be assessed in the ITT, mITT, PP and mYITT analysis sets.

After the last treated patient will complete full study duration, a final clinical study report will be generated with conclusions relating back to original objective(s) and hypothesis/hypotheses.

12.2. Study Endpoint Variables

12.2.1. Primary endpoint variable

The primary endpoint is the change in HDRS17 total score from baseline to 8 weeks post treatment initiation, in each of the study groups. This variable will be calculated by subtracting the subject's baseline HDRS17 score from the score at visit 4.

12.2.2. Secondary and exploratory endpoint variables

The secondary endpoints of responder and remission will be represented in the form of binary variables which will be assigned the value of "1" if the subject is a "responder" or a "remitter" per specific secondary endpoint, and "0" otherwise. Other exploratory binary endpoints will be defined in a similar manner.

Secondary and exploratory endpoints described as changes from baseline, such as QIDS-SR-16, CGI-S and CGI-I and MDRS will be calculated by subtracting the subject's baseline score from the score at each visit.

12.2.3. Safety endpoint variables

Incidence of all adverse events and complications by severity and relationship to study device.

12.3. Study Hypothesis

Null hypothesis:

Mean change from baseline in HDRS17 total score to 8 weeks post treatment initiation in subjects suffering from Major Depressive Disorder (MDD) in the active Relivion®$_{DP}$ arm = Mean change from baseline in $HDRS_{17}$ to 8 weeks post treatment initiation in the sham arm.

Alternative hypothesis:

Mean change from baseline in $HDRS_{17}$ total score to 8 weeks post treatment initiation in subjects suffering from Major Depressive Disorder (MDD) in the active Relivion®$_{DP}$ arm ≠ Mean change from baseline in HDRS17 to 8 weeks post treatment initiation in the sham arm.

12.4. Sample Size Estimation

Sample size estimation is driven by the hypothesis testing of the primary endpoint and will be calculated using the sample size equation for a two-sample t-test, even though for the final analysis we may employ a statistically more powerful model such as repeated measures ANOVA.

An effect size of 0.5 (Cohen's d- Cohen, J. (1988). Statistical power analysis for the behavioral sciences (2nd ed.) Hillsdale, NJ: Lawrence Earlbaum Associates.) is considered a moderate effect size, and is lower than effect sizes seen for similar studies, thus 0.55 will be considered in this study for sample size estimation as the minimally important clinical effect size to be detected.

In a company feasibility study of the Relivion®$_{DP}$ device we evaluated the mean change from baseline up to weeks 3 and 6 in HDRS-17 score. The 3 week results were a (baseline adjusted) mean change of -5.95 points (95% CI:[-8.1,-3.8]) and the standard deviation of 4.2 points. The 6 week results were a (baseline adjusted) mean change of -8.4 points (95% CI:[-10.6,-6.26]) and the standard deviation of 5.6 points. This study had no control arm thus considering a minimally important effect size (Cohen's D) of 0.5 (and assuming equal group variances rounded up to 5 and 6 at 3 and 6 weeks respectively) we would expect an HDRS17 score reduction in the sham group of about 3.45 points at 3 weeks and 5.4 points at 6 weeks unless the treatment arm has a greater reduction.

In planning their study, Levkovitz et al (Brainsway ltd.) assumed that effect size of 0.5 and a difference of 3.75 points between active to sham subjects treated with TMS will provide a significant clinical effect. The final results show a significant reduction in HDRS21 of 6.39 points in the TMS group compared to 3.28 in the sham group with an effect size of 0.76. Neuronetics Inc. reported an HDRS17 score reduction of 5.2 points in the active TMS group compared with a 3.3 point reduction in the sham group (ES>0.5), with a

minimal considered effect size of 0.4. Moreover, in a large analysis of the FDA database of antidepressant medications, Khan et al reported that the mean percentage reduction from the baseline in HDRS17 score was 40.7% for active treatment and 30.9% for placebo.

We use conservative estimates of a 3.3-point difference with a standard deviation of 6 points. Calculations show that a sample size of 53 subjects per group (total 106) would provide 80% power at a 5% level of significance (two-sided) to detect the difference between treatment and sham groups.

Given our preliminary results, together with other companies clinically relevant data, we hypothesize that our statistical assumptions are aligned with competitive treatments for MDD.

The company anticipates that after randomization, but before the endpoint can be observed, up to 15% of the subjects will drop out from the study irrespective of study arm and success of treatment; thus, an adjustment for this drop-out rate is made and a sample size of 124 is required at the point of randomization.

We shall randomize an additional up to 36 subjects (30+15% dropout) in the age range 18-21 to assess efficacy in this age range as well.

12.5. Interim Analysis

Planning one interim analysis that permits an increase in the sample size as described below does not additionally inflate the type I error [38]–[41]. In addition, the final analysis is performed using the conventional test as appropriate for the statistical hypothesis.

An interim analysis will be performed by an independent statistician once about 80% of the required number of subjects aged 22-70 have been randomized and completed the 8-week post treatment initiation visit. Depending on the outcome of the interim analysis, the study will either continue to the originally planned sample size, stop for futility, stop for efficacy, or continue with an increased sample size. These decisions will be made based on the conditional power (CP), which is defined as the conditional probability that the result will exceed a critical value at the interim given the observed effect size.

Note that the interim analysis will be conducted on the ITT, mITT, PP and mYITT analysis sets, and the study will be stopped due to futility only if the interim effects in all populations fall below the CP threshold.

12.5.1. Procedure

After all the relevant data will be entered into the database, and the database cleaned, a soft lock to the database will be performed. An independent un-blinded statistician (not the study statistician) will perform the assessments described below. A designated data monitoring team will recommend whether to stop the study once the interim results are available.

At the interim analysis, the data of the evaluable subjects in the ITT, mITT, PP and mYITT sets will be analyzed.

12.5.2. Blinding

Only the unblinded statistician and members of the data monitoring committee (DMC) will be exposed to the interim report. The members of the data monitoring team may also have access to the unmasked information of the interim analysis. Investigators and company directors will only be informed of a decision to continue or to discontinue the trial, or to implement modifications in trial procedure. The un-blinded statistician who is responsible for conducting the interim analyses should ensure that the unmasked data is not available to any unauthorized person within or outside the company.

12.5.3. Decision Rules

The study will either continue to the originally planned sample size if the result is "favorable", stop for futility if the result is "unfavorable", stop for success if the result is "overwhelming" or an increase will be made to the sample size if the result is "promising". These decisions will be made based on the conditional power (CP), defined as the conditional probability that the result will exceed a critical value at the interim given the observed effect size $\widehat{\delta_1}$ = difference between mean change in HDRS17 scores for the active versus sham groups at the interim look.

Notation:

n1= sample size at interim analysis.

n2= original sample size calculated based on assumed effect size.

nmax = the highest sample size the company is willing to use, nmax = 250 subjects and is based on a more conservative estimate of the effect size of 0.356.

CPmin=is the calculated minimum CP based on the ratios nmax/n2, n1/n2 and the target study power (80%).

The following are the decision rules for the interim analysis which will be performed upon accrual of ~80% of the sample size, 86 evaluable subjects:

- If the result is "Unfavorable", i.e. CP < CPmin = 29.14% (interim result is so disappointing that it is not worth increasing the sample size to retrieve conditional power), then stop the trial for futility.
- If the result is "Promising", i.e. 29.14% ≤ CP < 80% the sample size is increased recover the targeted power of 80%. The sample size used will be either the new calculated sample size based on the conditional power (as described in Sample size re calculation using conditional power Jonathan S. Denne Statist. Med. 2001; 20:2645–2660) or the predetermined maximum sample size of 250 subjects.

- If the result is "Favorable", i.e. CP ≥ 80% the interim results are sufficiently favorable, and the trial continues to the original sample size planned of 106 (before allowance for dropouts) without the need to adaptively increase the sample size.
- If the result is "overwhelming" i.e. primary endpoint at the interim analysis is statistically significant at a 0.04108 level of significance, then stop the study for success. This was calculated based on an adaptive design with one interim analysis planned to either stop the study for futility or early success at the interim with a Lan-DeMets alpha spending approach using a Pocock type function, where at the interim the study will be stopped for success if the null hypothesis is rejected at an alpha level of 0. 04108.

Note that the interim analysis will be conducted on all populations (ITT, mITT, PP and mYITT analysis sets, see **Section 12.7**), and the study will be stopped due to futility only if the interim effects in all populations fall below the threshold.

The un-blinded statistician will also calculate the sample size required to test the null hypothesis to achieve 80% power at 4.108% level of significance given the current trend.

12.5.4. Controlling the Alpha Level for the Primary Endpoint

The overall alpha level for this study is 5%. According to [Müller 2001; Jonathan 2001 Broberg 2013 and Siu 2001], planning an interim analysis that permits an increase in the sample size as described above does not inflate the type I error.

12.6. Randomization

Eligible subjects will be randomly allocated (with a 1:1 ratio) to one of the following 2 treatment groups based on a randomization scheme using the permuted block method stratified by center:

- Active (Relivion®$_{DP}$) stimulation
- Sham stimulation

The randomization scheme will be prepared by the study statistician using the SAS (version 9.4.) random number procedure. The block size will be random, and all study personnel will be therefore blinded to the randomization block size.

12.7. Study Analysis Populations

12.7.1. Intent-to-Treat (ITT) Population:

The intent-to-treat (ITT) population will include all subjects aged 22 through 70 enrolled in the study as randomized. This population will include all subjects who receive at least one active/sham treatment.

According to the ITT principle all subjects will be analyzed in the treatment group as assigned by randomization.

12.7.2. Modified Intent-to-Treat (mITT) Population:

The modified intent-to-treat (mITT) population will include all subjects from the ITT set enrolled in the study, who completed the minimal stimulation time required by the protocol and have no post randomization exclusion criteria. The mITT analysis set will be analyzed in the treatment group as treated.

12.7.3. Per-Protocol Population:

All subjects from mITT set that complete the 8-week treatment period (without withdrawal) and without any major protocol deviations.

12.7.4. Modified Younger Intent-to-Treat (mYITT) Population:

The modified younger intent-to-treat (mYITT) population will include all subjects from the ITT set enrolled in the study including subjects aged 18-21, who completed the minimal stimulation time required by the protocol and have no post randomization exclusion criteria. The mYITT analysis set will be analyzed in the treatment group as treated.

12.7.5. Statistical Analysis of Analysis Sets

Safety assessments will be performed on the ITT and mYITT analysis set.

The mITT cohort will serve as the principal data analysis set for the primary and secondary statistical evaluation of the efficacy endpoints. The primary, secondary and exploratory efficacy assessment will also be performed on the per protocol (PP) analysis set as a sensitivity analysis and to show consistency of study results. The primary and secondary efficacy analyses will also be performed on the mYITT analysis set.

12.8. Statistical Analysis

12.8.1. General Considerations

Statistical analyses will be performed using SAS® v9.4 (SAS Institute, Cary NC, USA). Statistical analyses and reporting will be performed in compliance with FDA Guidance E6 GCP, 21 CFR part 812, E9 and ISO 14155.

Study data will be summarized with descriptive statistics and presented in tables and figures. Continuous variables will be summarized by a mean, standard deviation, minimum, median and maximum and

categorical variables by a count and percentage. For comparison of means (continuous variables), the two-sample t-test or the Wilcoxon rank sum test will be used as appropriate. For comparison of proportions (categorical variables), the chi-squared test or Fisher's exact test will be used as appropriate. If multiple measurements are taken in a single subject, statistics described below will be appropriately modified to accommodate the within subject correlation.

Deviations from the planned analysis will be described, with proper justification, in the clinical study report.

12.8.2. Significance Level and Handling of Type I Error

Type I Error:

The overall significance level for this study is 5% using two-tailed tests, except for treatment by site interaction that will be tested at a significance level of 10% and the test for early efficacy at the interim look.

Controlling the Overall Type I Error:

The hierarchy approach will be adopted for the primary and secondary endpoints to control type I error due to multiple endpoint testing. Thus, the primary endpoint will first be tested and only if $p \leq .05$, will the secondary endpoints be tested. For the three secondary performance endpoints, the Benjamini–Hochberg step-up method will be used to adjust the p-values.

12.8.3. Demographic and Other Baseline Characteristics

Demographic and baseline condition related characteristics will be tabulated and compared between the study groups by data type. Continuous variables will be summarized by a mean, standard deviation, minimum, median and maximum and categorical variables by a count and percentage. The statistical evaluation of baseline characteristics will include all available data from the ITT population.

These data will include:

- Demographic data
- Medical history
- Psychiatric history
- Previous and Current Psychotropic Medication
- Type, dose and frequency of concomitant medications

12.8.4. Disposition of Subjects

The number of subjects who entered the study and completed each stage of the study will be provided and compared between the study groups, as well as the reasons for all post randomization discontinuations, grouped by major reason, e.g., lost to follow-up, adverse event, poor compliance, did not administer any treatment (with reasons). A list of discontinued patients, protocol deviations and subjects excluded from the efficacy analysis will be provided as well.

Time to withdrawal will also be assessed and presented by Kaplan-Meier curves and will be compared using the Log-Rank test if relevant.

12.9. Efficacy Analysis

12.9.1. Primary Efficacy Analyses

The primary efficacy endpoint is the change from baseline to 8 weeks post treatment initiation in $HDRS_{17}$ score.

The change in $HDRS_{17}$ from baseline to 8 weeks post treatment initiation will be compared between the treatment groups using a repeated measures analysis of covariance (ANCOVA, SAS® MIXED procedure). The model will include the following fixed effects: treatment group, visit, treatment group by visit interaction with Baseline $HDRS_{17}$, and center entered as covariates. Baseline $HDRS_{17}$ scores will be entered as a continuous variable so that the potential for co-linearity problems will be minimized. The treatment group by center interaction will be evaluated as well, but not as part of the principal statistical evaluation. Additionally, the center variable will be grouped by country as US versus out of US (OUS) and the analyses as for center will repeated on this new variable.

The unstructured covariance matrix structure will be used. If the model does not converge, then either the compound symmetry or autoregressive (whichever model has the lower AIC statistic) covariance matrix structure will be used instead. At this time point (up to 8 weeks) we do not expect a high proportion of dropouts, as a placebo effect of the sham treatment is expected and was taken into consideration in the design of the study. Thus, any missing data at 8 weeks post treatment initiation can be considered missing at random. Therefore, since repeated measures ANOVA is also an imputation method, for this evaluation no other method of imputation of missing data is considered beyond the model estimates. Nevertheless, should the missing at random assumption prove to be incorrect, a sensitivity analysis using methods for data imputation mentioned in section 12.9.5 will be performed.

The principal statistical analysis will be a comparison between the treatment groups, derived from the visit by treatment group interaction term from the model. The adjusted mean change from baseline in $HDRS_{17}$ scores at 8 weeks post treatment initiation will be estimated from the model (LS Means) interaction term for each group as well as the difference between the adjusted means and presented together with 95% confidence intervals.

The null hypothesis will be rejected in favor of the alternative hypothesis and the study deemed successful if the p-value is <0.05 and the mean change $HDRS_{17}$ in the active group is higher than that of the sham group.

Cohen's D will be calculated and presented as well as a measure of the clinical effect size of the change from baseline HDRS17 at week 8. An effect size can also be calculated using methods described in "Effect sizes for growth-modeling analysis for controlled clinical trial in the same metric as for classical analysis", *Psychol Methods*. 2009 March; 14(1): 43-53), where ES = difference between LSmeans / Pooled SD of baseline $HDRS_{17}$ score.

Subset Analyses of Primary Endpoint:

Significant or important variables, such as demographic or other baseline patient characteristics or concomitant medications (depending on use), will be entered as additional covariates in the primary efficacy endpoint ANCOVA model to evaluate their effect on the change from baseline $HDRS_{17}$ score.

- Use of concomitant medications.
- Blinding assessment
- US vs. OUS sites

The effect of potential unblinding will be evaluated as a sensitivity analysis, where an additional binary variable identifying subjects unblinded versus those not un-blinded will be added to the ANCOVA model as a covariate.

12.9.2. Secondary Efficacy Analyses

- Proportion of responder subjects- defined as the percent of subjects achieving at least 50% reduction from baseline in their HDRS17 total score, 8 weeks post Relivion®$_{DP}$ treatment initiation- will be summarized by a count and percentage and compared between the groups with a chi-squared test and a Fisher's exact test. As an additional measure of effect size the NNT will be presented.
- Proportion of subjects achieving remission- defined as the percent of subjects with HDRS17 score≤7 at 8 weeks post Relivion®$_{DP}$ treatment initiation- will be summarized by a count and percentage and compared between the groups with a chi-squared test and a Fisher's exact test. As an additional measure of effect size the NNT will be presented.
- Mean Change in depressive symptoms, measured by MADRS total score, from baseline to week-8 post treatment initiation - will be compared between the groups using a similar model as the primary endpoint.

12.9.3. Exploratory Analyses

- Mean Change in the severity and improvement scores - Clinical Global Impression scales (CGI-S and CGI-I) at 8 weeks post treatment initiation– will be compared between the groups using a similar model as the primary endpoint.
- Mean Change from baseline in total score of the Quick Inventory of Depressive Symptomatology self-rated (QIDS-SR-16) score at 8 weeks post treatment initiation– will be compared between the groups using a similar model as the primary endpoint.
- Mean change in depressive symptoms, measured by $HDRS_{21}$ total score, from baseline to week-8 post Relivion®$_{DP}$ treatment initiation will be compared between the groups using a similar model as the primary endpoint.

12.9.4. Safety Analysis

Descriptive statistics will be presented per study group for all safety parameters.

The primary safety variable, the cumulative incidence (and 95% CI) of device related adverse events (AEs) throughout the study, will be presented in tabular format and will include incidence tables by severity.

Adverse event rates will be compared between the study groups with a Fisher's exact test.

Serious adverse events will be listed and discussed individually.

The incidence of potentially clinically significant vital signs measurements will be presented at each relevant visit by treatment group. Descriptive statistics, as well as changes from baseline, will also be presented by study group at each scheduled visit.

Treatment tolerability will be compared between the study groups. The number and percent of subjects who fail to complete the study and the number and percent of subjects who fail to complete the study because of Adverse Events will be presented as well.

12.9.5. Handling of Missing Data

The study outcome will not be evaluated for patients who drop out prior to randomization. The primary endpoint will be analyzed using a repeated measures ANCOVA model which can handle data missing at random and we do not expect a high proportion of dropouts until the primary endpoint is measured. Therefore, for this evaluation no imputation of missing data is considered beyond the model estimates. Additionally, imputation of data such as by LOCF may harm linearity in such models, therefore, for this evaluation no imputation of missing data is considered beyond the model estimates. Nevertheless, a sensitivity analysis based upon last observed values (LOV) may be performed. The Last Observed Value (LOV) is defined as the last available post baseline visit data up to and including the last treatment visit or termination visit.

For categorical variables (such as response and remission rates at week 8) the LOCF concept will be applied.

Baseline characteristics of patients who drop out will be evaluated by study group to evaluate the potential reason for differential drop out.

12.9.6. Pooling

Subgroup analysis of the primary efficacy endpoint by comparing US vs OUS centers, will be used to evaluate the poolability of the results. Treatment by center interaction will be tested in the primary analysis model at a significance level of 10%. If the interaction is not significant, it will be removed from the model. If the interaction is found significant, it will also be removed from the model and the reason for this interaction will be further explored and rationalized. This evaluation may include demographic features, symptoms at presentation, and clinical and treatment history, and center comparability in the features found to be associated with the primary efficacy variable.

In the case that poolability is questionable, the reasons for differential treatment effect, such as subject and clinical characteristics, will be investigated and reported.

13. Ethics

13.1. Statement(s) of Compliance

This study will be conducted in compliance with the protocol (after being approved by the local EC/IRB and, if required, by the local RA), 21 CFR Parts 50, 54, 56 and 812 (as applicable for NSR device study), ISO 14155, and the ethical principles that have their origin in the Declaration of Helsinki.

The Informed Consent Form (ICF), patient's information material, and advertising material (if applicable) must be submitted and approved by the IRB/EC (and RA when needed), and any request by the IRB/EC or RA will be followed. Written approval of the protocol, ICF, patient's information material, and any advertising material (if applicable) must be obtained from the EC/IRB and if applicable the corresponding RA prior to any patient enrollment.

Adequate insurance policy will be held valid for the entire study duration as well as for the discovery period required per local regulation.

Information regarding the study and study data will be made available via publication on clinicaltrials.gov. Additionally, the results of this study will be submitted for publication in an appropriate journal.

14. Study Administration

14.1. Data monitoring committee

An independent data monitoring committee (DMC) will be responsible for safeguarding the interests of trial participants by assessing the safety and efficacy of the interventions during the trial. The DMC will

provide recommendations to sponsor about stopping or continuing the trial or making modifications to enhance safety of trial participants and/or the value of the information collected, or to protect the integrity of the study.

The data reviewed by the DMC will include a summary of the following topics:

• Safety monitoring: data related to the safety of the subjects, including any adverse events or side effects related to the treatment

• Efficacy monitoring: interim efficacy analysis and recommendations

14.2. Monitoring

Monitoring will be conducted to ensure the protection and safety of human subjects, the quality and integrity of the clinical data, and compliance with the protocol.

The sites will be monitored, in-person and/or remotely, by sponsor employees and/or Contract Research Organizations (CROs) who have received appropriate training, in accordance with the monitoring procedures set forth by Neurolief. The selected monitors and qualification, extent of SDV, timing and frequency of monitoring visits, the essential documents to be reviewed, and other study-specific monitoring requirements will be addressed in the monitoring plan that will be developed by Neurolief and/or the monitoring CRO. Monitoring may be performed with in person visits or remotely, when applicable. Quality documents will be followed for the conduct of all activities related to monitoring for this study.

Site Qualification and Initiation Visits will be completed prior to enrollment of the first subject.

14.2.1. Initiation Visit

The sponsor and a qualified monitor will conduct an initiation visit at the beginning of the study to ensure that the PI and the site personnel:

- Have been trained on the use of the Relivion®$_{DP}$.
- Understand the requirements and/or contents of the protocol, CRF/eCRF, the Relivion®$_{DP}$ User Manual, questionnaires, applicable regulations, and the Clinical Trial Agreement (CTA).
- Are familiar with the responsibilities of the PI.

14.2.2. Monitoring Visits

In order to comply with the applicable regulations concerning the conduct of clinical studies, to assure the accuracy of the study database, and to assure the overall quality and consistency of the study, a qualified monitor will visit the sites during the course of the study in order to review the study records.

The monitor will:

- Compare study data with any relevant source documents, such as patient's medical records, data tracings/printouts, etc.
- Check the consent form for each patient.
- Check the general study records, including device accountability.
- Check the occurrence of possible adverse events.
- Check compliance with the protocol, CTA, and applicable regulations.

All monitoring visits to the investigational center will be recorded using the Monitoring Visit Log. The log will be kept in the site regulatory binder and a copy will be collected and submitted to the Sponsor.

The Study Investigator and the investigating site will permit authorized clinical research personnel and clinical monitors from Neurolief and/or designee(s) employed by Neurolief to review completed CRF/eCRFs, IRB/EC decisions, and clinical site records, and facilities relevant to this study at regular intervals throughout the study per the monitoring plan. Additionally, subject charts and clinical records will be requested and reviewed so that protocol adherence and source documentation can be verified. In instances where data protection regulations prohibit the direct examination of hospital records by the study Sponsor or designee(s), the Investigator will cooperate in a system of source data verification with the Sponsor.

To ensure the rights, safety, and welfare of study subjects are being maintained, the monitor will review training records to ensure all study staff are adequately trained on the study protocol and use of the study devices. If the monitor discovers that an Investigator is not complying with the signed Investigator Agreement, the investigational plan, applicable laws, or any conditions of approval imposed by the reviewing IRB/EC, the monitor will report to the Sponsor and take such steps necessary to promptly secure compliance. If compliance cannot be secured, device shipments to the Investigator may be discontinued and the Investigator's participation in the investigation terminated. The monitor shall also require such an Investigator to dispose of or return the device, unless this action would jeopardize the rights, safety, or welfare of a subject.

14.2.3. Data Queries

During monitoring visits, the Monitor will perform a source verification of required data points that comprise the CRF/eCRF for each subject. Discrepancies will be queried by Neurolief and must be resolved by the investigational site staff and PI in a timely manner, and as requested by Neurolief. Manual and/or automatic queries will be created in the CRF/EDC system and will be issued to the site for appropriate response. The site staff will be responsible for responding to all queries in the database. In the event of data discrepancies, investigational sites will be asked to resolve queries electronically in the EDC system; otherwise, irresolvable data-related issues will be routed to the Sponsor for review and final disposition.

14.2.4. Close-Out Visit

Upon completion of the clinical study, the sponsor or designee will notify the site of closeout and a study closeout visit will be performed. All study devices and any unused study materials will be collected and returned to the sponsor, if not done earlier. The monitor will ensure that the investigator's regulatory files are up-to-date and complete, and that any outstanding issues from previous visits have been resolved. Other issues which will be reviewed at this visit include discussing retention of study files, possibility of site audits, publication policy, and notifying the EC/IRB of study closure.

14.3. Audits and Inspections

The sites may be subject to quality assurance audits by Neurolief staff and other sponsor designees, as well as inspections by the representatives of regulatory agencies.

In the event that an audit is initiated by Neurolief or a designee, the investigator shall allow access to the original medical records and provide all requested information. In the event that an inspection is initiated by a regulatory authority, the investigator shall immediately notify Neurolief of the impending inspection and allow the regulatory body access to the medical records and other information as required by applicable laws and regulations.

14.4. Direct Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents. Examples of these original documents and data records include, but are not limited to: hospital records, clinical and office charts, laboratory notes, memoranda, patients' evaluation checklists, patient's diary, recording media such as DVD and video tapes, x-rays, patient files, subject PRO (electronic or hard copy) and records kept at the laboratories, and at other departments involved in the clinical trial.

Source documents will be used:

- For verification of the data documented in patient CRF/eCRFs during monitoring visits, audits and inspections.
- For the adjudication of adverse events.

During monitoring visits, audits, and inspections, the PI will guarantee direct access to the study files, patient CRF/eCRFs, and patient medical records to Neurolief staff and other sponsor designees, as well as representatives of regulatory agencies. It is important that the investigators and the relevant site personnel are available during monitoring visits and possible audits and inspections and that sufficient time is devoted to the process.

14.5. Data Management

All data will be collected using a paper CRF or Remote Electronic Data Collection (RDC/EDC) system. The clinical sites will use hard copy or electronic case report forms (eCRFs) to document the information required by the study protocol.

The EDC allows for the secure collection, transmission, validation, monitoring and real-time administration of study data gathered at investigative sites. The system allows password-restricted access to clinical trial information based on individuals' roles and responsibilities. The EDC are compliant with *21 CFR Part 11* and FDA's "*Guidance: Computerized Systems Used in Clinical Trials.*"

Data reported on the CRF/eCRF should be driven from source documents (**Section 14.3**) and be consistent with these source documents. Editing of data is done under full audit trail. Paper CRF worksheets may be provided to the investigational site to assist with data collection for the required fields.

Required data will be recorded on CRF/eCRFs by authorized site personnel as indicated on the Delegation of Authority Log. The Investigator will ensure that all eCRFs are completed promptly, completely, and accurately. Information on case report forms must conform to the information in the source documents.

The Sponsor will oversee and/or perform all data management functions. Data management functions include database development, system maintenance, data queries, and report generation.

Investigators must ensure that clinical records clearly indicate that the subject has been enrolled in a clinical investigation. Regulations require that Investigators maintain information in the study subject's medical records to corroborate data collected on the CRF/eCRF. In order to comply with these regulatory requirements, the study site will manage the following information, and retain/manage it as required to make it available to monitors, auditors and/or regulatory bodies. Complete hospital and clinical medical records for all study subjects should include all study required procedures, labs and assessments as noted in Study schedule and Site Collection Data.

14.5.1. Direct Data Entry

For several CRF fields Source Data Verification (SDV) may not be possible as entries may not be found in source documents. Therefore, it is allowed to use the CRF/eCRF for direct data entry, but only for pre-defined fields.

14.5.2. Data Quality Assurance

To ensure the quality of clinical data across all subjects, a clinical data management review will be performed on subject data submitted in the CRF/eCRF. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and relevant regulations. To resolve any questions arising from the clinical

data management review process, data queries and/or site notifications will be issued. Discrepancy resolution will be documented within the database audit trail.

The development of the primary database for the study will be managed by Neurolief. Neurolief will also be responsible for the quality control of the database and confirming the overall integrity of the data.

Corresponding queries will be issued to site coordinator. Effort will be made to resolve such queries as close as possible to real time.

14.5.3. Electronic Signatures

The PI will hand write/electronically sign each individual CRF/eCRF after the data has been cleaned, monitored and reviewed. The hand write/electronic signature asserts that the investigator inspected or reviewed the data on the eCRF, the data queries, and the site notifications, and agrees with the content. Any changes made to the data after PI signature has been applied will result in invalidation of the original signature, and the PI will be required to re-sign the data after reviewing the change(s).

14.6. Confidentiality

Subject confidentiality will be maintained throughout the clinical study in a way that ensures the information can always be tracked back to the source data. For this purpose, each subject will be identified by a dedicated study code. Records, including investigator site file, will remain on site in secure areas. Possible review and photocopying of the subject's records by regulatory agencies could occur during inspections. Additionally, Neurolief and its representatives may review and photocopy the subject's records. In such cases and in the event subject's data are used for educational, presentation, and/or publication purposes, subject identity will be masked to protect the subject's confidentiality.

The subjects will be informed in writing that representatives of the Sponsor, IRB or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

Subjects will also be informed that information regarding the study that does not include subject identifiers will be posted on clinicaltrials.gov and the mytrails.com Israeli MOH website.

If the results of the study are published, the subject's identity will remain confidential. The Investigator will maintain a list to enable subjects' records to be identified.

Regulatory agencies and Neurolief are required to maintain the privacy of all records they review in connection with this study.

14.7. Liability

Neurolief has taken out an insurance policy for the total duration of the study covering the subjects and investigators in respect of the risks involved in conducting this study according to this protocol. The insurance policy will be filed in the study file and can be made available to the investigator and to the EC/IRB upon request.

14.8. CIP Amendments

CIP amendments, except where necessary to eliminate an immediate hazard to patients, will be issued by Neurolief. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent document. The IRB/EC must be informed of all amendments and give written approval, which must be provided to Neurolief. Notification to the relevant Competent Authorities will take place as required locally. IRB/EC approval, site training and a new acknowledgement form will be signed and returned before any new procedures take place.

14.9. Record Retention

Essential study documents will be maintained both on-site (within the investigator site file) and in-house (both study and site records).

The sponsor and PI shall maintain the study documents as required by the applicable regulatory requirement(s). Documents should not be destroyed without the permission of the sponsor. In the event of the PI leaving the clinical site, it is the PI's responsibility to notify the sponsor in writing and to designate which study material will be transferred from / maintained at the clinical site.

Subject files and other source data must be kept for a period of not less than 2 years after the latter of the following two dates: the date on which this investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket application. Records may need to be maintained by the Investigator for a longer duration if national regulations require or if agreed to in writing with Neurolief.

14.10. Publication and Use of Information

It is the policy of Neurolief to publish the results of clinical studies. Specifics of the arrangements of study publication will be addressed in the clinical trial agreement.

Information regarding the study and study data will be made available via publication on clinicaltrials.gov and the Israeli MOH web site.

Investigators must submit a copy of all manuscripts and/or abstracts to Neurolief for review and comment 30 days prior to planned submission. Neurolief acknowledges that its right to review and comment shall

relate solely to the proprietary, licensing, and/or confidential rights Neurolief may have in such proposed publication, rather than whether such results and/or opinions are favorable to Neurolief.

The publication of sub-studies, post-hoc analyses, regional results, or single-center experiences based on multicenter clinical studies should not precede that of the primary multicenter publication, and should cite the primary publication whenever possible, as required by specific journal and scientific meeting guidelines.

14.11. Funding

The study is funded by Neurolief Ltd., Israel.

14.12. Suspension or Early Termination

The final sample size will be determined following completion of the interim analysis and the study will be considered completed when the last patient completes the final study visit. Premature termination of this clinical study may occur for statistical reasons due to insufficient effectiveness of the investigational device (see Section 12.5). Additionally, early termination may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or at the discretion of sponsor or the PI.

Neurolief will monitor the progression of the clinical investigation. If warranted, the clinical investigation may be suspended or discontinued early if there is an observation of serious adverse reactions presenting an unreasonable risk to the clinical investigation population.

Neurolief may terminate investigator and site participation in the clinical investigation if there is evidence of failure to maintain adequate clinical standards, failure to comply with the clinical investigational plan, fraud or any other forms of misconduct.

Last, Neurolief reserves the right to discontinue the clinical trial/investigation at any stage, with suitable written notice to the investigator. Possible reason(s) include:

- Per medical advisor's recommendation (such as higher frequency of anticipated adverse device effects, endpoint is met, or futility).
- Further product development is cancelled.

In the event of clinical investigation premature termination or suspension, Neurolief will send a report outlining the circumstances to the corresponding ethics committee, regulatory body and all investigators. The appropriate ethics committees will be notified of discontinuation of the study for any reason no later than 5 working days after the Sponsor makes this determination. A suspended or terminated clinical investigation may not be re-initiated without approval of the corresponding EC/IRB and relevant competent authority (as applicable). In the event of clinical investigation premature termination or suspension, enrolled subjects will be followed up as per the institution's standard of care.

Similarly, investigators may withdraw from the study at any time, subject to providing written notification to Neurolief 30 days prior to the date they intend to withdraw. However, Neurolief and investigators will be bound by their obligation to complete the follow-up of subjects already participating in the study. The subjects must be followed according to the clinical protocol, and information obtained during subject follow-up shall be reported to Neurolief on the appropriate eCRF.

Suspension or termination of a site may include but is not limited to:

- Ethics Board approval expiration
- Consistent non-compliance to the protocol (e.g. failure to follow subjects, etc.)
- Lack of enrollment
- Non-compliance to regulations and the terms of the Agreement with Neurolief
- Ethics Board suspension of the site

If the site terminates or suspends participation without prior agreement of Neurolief:

- The site must promptly inform Neurolief and provide a detailed written explanation of the termination or suspension.
- The site must promptly inform the institution (where required per regulatory requirements)
- The site must promptly inform the Ethics Board, if applicable

If the Ethics Board terminates or suspends its approval:

- The site must promptly inform Neurolief and provide a detailed written explanation of the termination or suspension within 5 working days.
- Patient enrollment must stop until the Ethics Board suspension is lifted.
- Subjects already enrolled should continue to be followed in accordance with the Ethics.
- Board policy or its determination that an overriding safety concern or ethical issue is involved.
- The site must inform his/her institution (where required per local requirements)
- The site must promptly inform the patients, if applicable

The PI should notify the IRB/EC in writing of the study's completion or early termination and provide a copy of the notification to Neurolief.

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16. Version History

Version	Summary of Changes	Author(s)/Title
1.0	new issue	Keren Ron Clinical study manager, Neurolief
2.0	Updated inclusion/exclusion criteria, secondary and exploratory endpoints, adding an OLE stage and study flow. added the central trainer role and the sites raters training.	Yaron Gruper Clinical study manager, Neurolief
3.0	• updated inclusion/exclusion criteria, • updated assessment of safety (section 9.9) • the length of the DB and OL treatments stages were prolonged to 8 weeks each. Updated "Expected treatment time for total DB phase" as a result of DB period time extension • Re-evaluation of the assigned treatment regimens according to the subjects' MDD assessment was added to visit 5 procedures • Up to 36 additional subjects ages 18-21 are added to the study overall sample size. Analyses sets and statistical analysis sections update accordingly. • Updated sections 9.9, 9.12 & 10.1 to withdraw subjects with a "yes" answer to c-SSRS Q4 and Q5 • Device and dedicated app SW versions updated to support users with IOS12 and above. • Updated maximum sample size upon IA results to 250 (instead of 200) and the respective IA decision rules.	Yaron Gruper Clinical study manager, Neurolief

17. Appendixes