SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Cranial electrotherapy stimulator to treat depression

Device Trade Name: Proliv™Rx external Combined Occipital and Trigeminal Afferent Stimulation (eCOT-AS) which will be abbreviated to Proliv™Rx

Device Procode: JXK

Applicant's Name and Address:

Neurolief Ltd.
12 Giborei Israel
Netanya, Israel, 4250412

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P250010

Date of FDA Notice of Approval: December 31, 2025

Breakthrough Device: Granted breakthrough device status on August 3, 2020, because of a reasonable expectation that the device could provide more effective treatment of a life-threatening disease or condition, namely Major Depressive Disorder, and the assessment that availability of an at-home noninvasive neuromodulation treatment option would be in the best interest of patients if the device were to be effective.

II. INDICATIONS FOR USE

Proliv™Rx provides focal external Combined Occipital and Trigeminal Afferent Stimulation (eCOT-AS) treatment. It is intended as an adjunctive treatment for Major Depressive Disorder (MDD) in adults who failed to achieve satisfactory improvement from at least one previous antidepressant medication, for use at home or in clinic.

The device is a prescription only device.

III. LIMITATIONS

In FDA's evaluation of the effectiveness of the Proliv™Rx System device, based on the MOOD study, there is a moderate level of uncertainty of benefit due to: lack of consensus in the medical literature regarding what constitutes a clinically significant or meaningful between-group difference in Hamilton Depression Rating Scale 17-question version

(HDRS17) scores and the absence of a pre-specified clinical significance threshold in the primary study success criterion. In addition, because the blinding assessment was conducted at baseline rather than after trial completion, the degree to which study participants guessed their study arm assignment during the treatment phase is not known. Finally, there is uncertainty about durability of effect due to the study being unblinded at 8 weeks. See Section X.V for more information regarding these sources of uncertainty.

IV. CONTRAINDICATIONS

Proliv™Rx is contraindicated for use in patients with:

- A history of intracranial surgery
- Recent traumatic brain injury (TBI) (less than three months)
- A metal implant or shrapnel in their head, except for dental implants
- An implanted neurostimulator or electronic device in the head such as a cochlear implant or brain pacemaker.
- A cardiac pacemaker or an implanted or wearable defibrillator
- Skin lesions, scars, or inflammation at the region of the stimulating electrodes

V. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Proliv™Rx System labeling.

VI. DEVICE DESCRIPTION

The device trade name is Proliv™Rx external Combined Occipital and Trigeminal Afferent Stimulation (eCOT-AS) (aka "Proliv™Rx").

Proliv™Rx provides focal external Combined Occipital and Trigeminal Afferent Stimulation (eCOT-AS) treatment. It is intended as an adjunctive treatment for Major Depressive Disorder (MDD) in adults who failed to achieve satisfactory improvement from at least one previous antidepressant medication, for use at home or in clinic.

Proliv™Rx consists of embedded software and a headset with integrated electrodes that contact the patient's forehead and scalp in a manner that is intended to enable stimulation of both the trigeminal (supraorbital & supratrochlear, bilaterally) and the greater occipital nerve branches.

A. Proliv™Rx System Components

The Proliv™Rx System includes the following components:

(1) The Proliv™Rx **Device** (Figure 1)
(2) The Proliv™Rx **Charger**
(3) Proliv™Rx **Electrode Pads** (6)
(4) Spray bottle
(5) Proliv™Rx **Quick Guide**
(6) Proliv™Rx **Carrying Case**
(7) Proliv™Rx App, a **mobile application** that guides the user, controls the device, and monitors device use. This application is required to operate Proliv™Rx. Therefore, the Proliv™Rx mobile application should be downloaded from the iOS App Store/Google Play store prior to the first use of the Proliv™Rx device. The Proliv™Rx Mobile Application includes:

- An interface for pairing the device with the user's smartphone.
- Onboarding videos to guide the user through the setup process.
- Treatment management interface, including starting, pausing, resuming, and ending sessions, as well as adjusting treatment intensity. The app also displays the current intensity level and treatment duration.
- Real-time device status, including battery status, connectivity, electrode contact.
- Bi-weekly self-report depression assessment questionnaires for tracking progress.
- Comprehensive treatment statistics, including questionnaire results, session compliance, duration, and average intensity level. Users can export these statistics to a PDF report for sharing with their healthcare provider.
- Access to user manual and video tutorials

(8) Proliv™Rx **cloud-based environment** that enables patients to share device treatment data, compliance, and periodic MDD self-report questionnaires with the treating healthcare professional. The Proliv™Rx cloud-based environment communicates with the Proliv™Rx Mobile Application (and the device via the app) via secured web protocol.

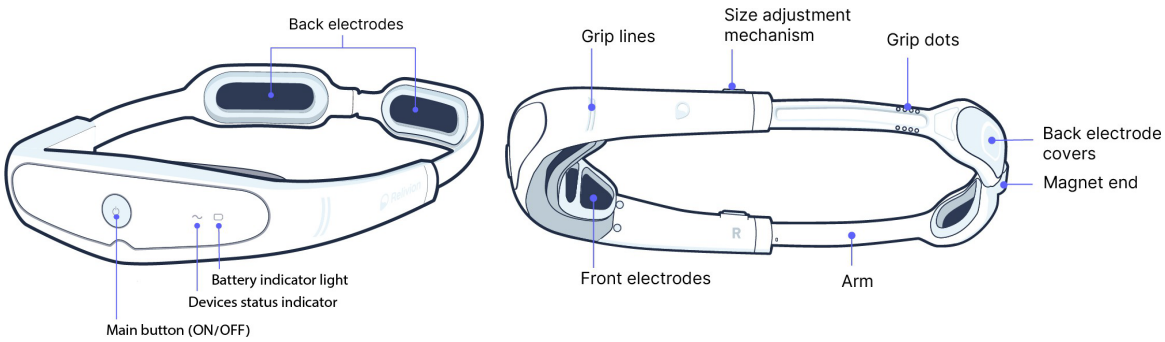

Figure 1: Proliv TM Rx device. Front view (left), and side view (right).

B. Technological Characteristics

The Proliv™Rx external combined occipital and trigeminal afferent stimulator (eCOT-AS) device integrates three (3) pairs of output electrodes that contact the patient's scalp, with two (2) pairs of output electrodes at the forehead and one (1) pair at the back of the

head. When the device is worn, each electrode pair is intended to be positioned above a nerve branch. Each forehead pair is intended to align with a trigeminal nerve branch; the pair at the back is intended to align with the greater occipital nerve branches. The device's onboard stimulation circuit is adapted to deliver electrical pulse patterns to trigger action potentials in the target nerves. Stimulation intensity can be adjusted by the user; all other parameters are fixed and cannot be adjusted by the user or the clinician.

VII. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of MDD. These alternatives include:

- Psychotherapy: Commonly used types of psychotherapy for MDD include cognitive behavioral therapy (CBT), interpersonal psychotherapy (IPT), and problem-solving therapy (PST). Psychotherapy is often combined with another MDD treatment alternative (below).

- Pharmacotherapy (Antidepressant medication): FDA has approved medication for MDD from each of the following major classes of antidepressants: selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), atypical antidepressants, tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), serotonin modulators, and N-methyl-D-aspartate receptor antagonists (NMDA antagonists).

- FDA-approved or -cleared medical devices that deliver transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS), electroconvulsive therapy (ECT), or an interactive cognitive-emotional and behavioral intervention via a smartphone app-based digital therapeutic.

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VIII. MARKETING HISTORY

The Proliv™Rx System has not been marketed in the United States or any other country.

IX. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Proliv™Rx has the potential for certain adverse reactions, including:

- Unpleasant sensation during treatment (e.g., pressure sensation at the stimulation position).

- A sensation of scalp numbness (paresthesia) during and after treatment.
- Persistent tingling, stinging, itching, or burning sensation after the treatment ends.
- Pain or discomfort.
- Skin reaction (e.g., irritation, lesion, or burn) beneath the electrodes. In such cases, treatment should be temporarily discontinued.
- Redness of the skin under or around the electrodes. Skin redness usually disappears within several hours after treatment.
- Sleepiness (somnolence), fatigue, or disruption in sleep patterns. Sedative effect during or after treatment.
- Dizziness during or after treatment.
- Headache/migraine.
- Depression-related adverse events (AEs):
  - Mania
  - Suicidal ideation
  - Worsening depression

For the specific AEs that occurred in the clinical study, please see Section XI. below.

X. SUMMARY OF NON-CLINICAL STUDIES

The company conducted non-clinical and bench studies to evaluate the safety and effectiveness of the Proliv™Rx System. Key non-clinical testing included:

- **Biocompatibility Testing**: The device's patient-contacting components, including the device headset and water-absorbing foam electrodes that are integrated into the headset, are only used on intact skin with prolonged exposure. Each exposure to the device is limited, but because the device is intended to be used repeatedly over time, this results in more than 24 hours of exposure. The skin-contacting device components were evaluated for cytotoxicity, sensitization, and intracutaneous reactivity in compliance with FDA biocompatibility guidance (2023) and ISO 10993-1: 2018. Based upon the information provided in the submission, Neurolief Ltd has provided an acceptable biocompatibility evaluation for the Proliv™Rx system.

- **Electromagnetic Compatibility (EMC) and Electrical Safety Testing**: The Proliv™Rx System was tested per international standards, including IEC 60601 series, IEC 62366-1 Ed. 1.1, and IEC 62304 Ed. 1.1. All tests confirmed compliance with electrical safety and EMC requirements. Immunity from other electromagnetic emitters (RFID, WPT, and 5G) was assessed by performance testing. The device labeling is appropriate for the intended use environment.

- **Software and Cybersecurity**: Software underwent verification and validation

according to IEC 62304:2015 and FDA guidance documents on "Content of Premarket Submissions for Device Software Functions" and "Off-The-Shelf Software Use in Medical Devices" (2023). Cybersecurity risks were also identified and mitigated. Basic level of documentation is appropriate because the software does not manage life-sustaining functions or deliver potentially harmful energy; therefore, it does not present a hazardous situation with a probable risk of death or serious injury.

- **Shelf Life:** The Proliv™Rx device is intended for repeat use by a single user. It is supplied and used non-sterile, and it is not intended to be sterilized or processed by the user prior to use. The Proliv™Rx device does not have a labeled shelf-life as the packaging does not maintain sterility and the device is composed of hardware that is not expected to degrade under the recommended storage conditions. Further, the device is cleaned as part of its maintenance only with a wet cloth (moistened with tap water). The user is specifically instructed not to use solvents of any kind (acetone, petrolatum and so on) on the device. Water is not expected to degrade the device as it meets the requirements of sealing per IP54 and is fully protected against solid objects and splashing of water from any angle. The Proliv™Rx electrode pads are made from Medisponge® 30W TDI foam and are limited to single use. Thus, there is no potential degradation from repeated use over time because the pads are replaced for every treatment day.

- **Performance testing:** Testing verified that Proliv™Rx stimulation parameters and output characteristics comply with design specifications. All measured output parameters are within ±10% of the expected value, or within the defined range if a range is specified.

XI. SUMMARY OF PRIMARY CLINICAL STUDIES

The clinical assessment of the Proliv™Rx System consisted of two clinical studies: a feasibility study and the company's pivotal MOOD study. In total, 141 patients were assessed clinically including patients in the feasibility study, those in the active arm of the pivotal study, and the crossover group in the pivotal study. The feasibility study is described in **Section XIII. Supplemental Studies**. A summary of the pivotal study is presented below.

Neurolief conducted the pivotal MOOD clinical study entitled, "External Combined Occipital and Trigeminal Nerve Stimulation (eCOT-NS) for the treatment of Major Depressive Disorder (MDD)".

A. Study Design

The MOOD study was a prospective, multi-center, 2-arm, parallel-group, randomized,

double-blind (DB), sham-controlled trial followed by an active open-label (OL) phase that used the Hamilton Depression Rating Scale (HDRS17) score as an outcome measure. The study was conducted at 13 sites across the US (12 sites) and Israel (1 site). Enrolled subjects had a diagnosis of unipolar MDD according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria and had failed 1-4 antidepressant trials during the current episode.

Subjects participated in the study for up to 20 weeks, with 8±1 weeks in a DB, randomized phase (active vs. sham treatment) followed by 8±1 weeks in an OL active treatment-only phase. For the DB phase, subjects were randomly assigned (1:1) to either active stimulation or sham stimulation:

- *Active stimulation*: Symmetrical biphasic waveform with trigeminal stimulation intensity up to 6.7mA and occipital stimulation intensity up to 18mA.
- *Sham stimulation*: Reduced stimulation parameters (e.g., lower intensity, pulse frequency of 0.33 Hz) to mimic active stimulation without therapeutic effects.

  Both active and sham treatments were administered to 60±20 minutes per day, 5-7 days per week, over 8±1 weeks. After the DB phase, all subjects received OL active treatment. Based on their HDRS17 scores from the DB phase, subjects were assigned to either maintenance treatment (3-4 times per week for 40±10 minutes) or daily treatment (5-7 days a week for 60±20 minutes).

1. Clinical Inclusion and Exclusion Criteria

   Inclusion criteria were as follows:

   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-5 criteria.
   3. Current MDD episode lasts up to three years.
   4. Score on the Hamilton Depression Rating Scale 21-item version (HDRS21) > 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):
      a. 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;
      b. Did not respond or have insufficiently responded to at least one but no more than four adequate trials of antidepressant medications (4 ≥ ATRF ≥1) or
      c. Did not respond or have 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.

Exclusion criteria were as follows:

1. History of intracranial surgery.
2. Current denervation of one or more of the following
   a. the supraorbital or supratrochlear branches of the trigeminal nerve
   b. the greater occipital branch of the occipital nerve.
3. An implanted neurostimulator 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-5 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 (OCD) or post-traumatic stress disorder (PTSD) and that is their primary diagnosis
14. Subjects meeting the DSM-5 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, Transcranial Direct Current Stimulation (tDCS), Transcranial electric stimulation (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.

2. Follow-up Schedule

The duration of the treatment protocol for each subject was 8±1 weeks of double blind (DB) active or sham treatment phase, followed by 8±1 weeks of active open

label (OL) phase. See Figure 2, MOOD Study Flowchart.

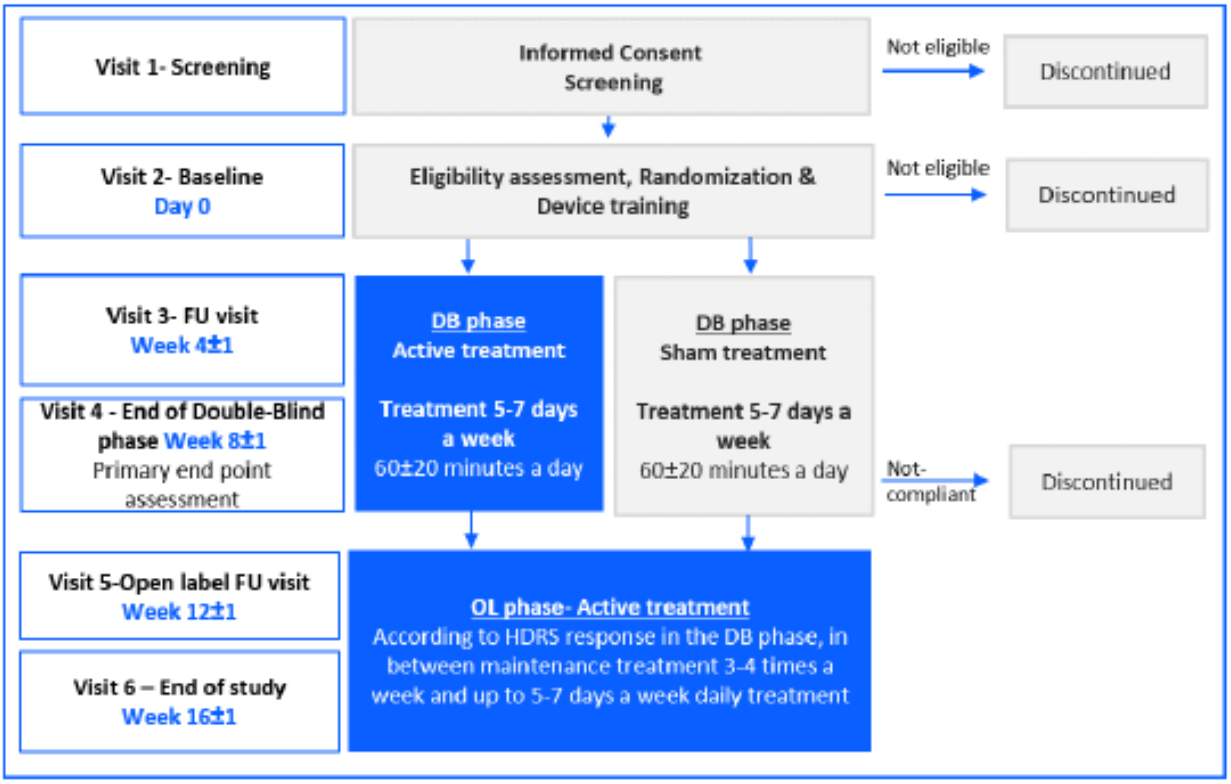

Figure 2: MOOD Study Flowchart

The study included 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 Proliv™Rx 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, subject's participation was considered

complete.

3. Clinical Endpoints

The primary objective was to assess the change in depressive symptoms from baseline to 8 weeks post-treatment initiation when using the Proliv™Rx System compared to a sham control in individuals with MDD. Effectiveness was measured via the change in HDRS17 score from baseline to week 8 post-Proliv™Rx treatment and was statistically evaluated through a repeated measured Analysis of Covariance (ANCOVA) model. The model was adjusted for baseline HDRS17 scores and study center effects, with success defined as a statistically significant difference between groups with a p-value <0.05 with mean change in HDRS17 scores higher in the Proliv™Rx group compared to the sham group.

Secondary effectiveness endpoints included:

- *Proportion of responders*: Defined as the percentage of subjects who achieved a reduction of 50% or more in their HDRS17 total score, measured at 8 weeks post-treatment initiation.
- *Proportion of subjects achieving remission*: Defined as the percentage of subjects with HDRS17 total score ≤ 7 at 8 weeks post-treatment initiation.
- *Change from baseline to week 8 post-treatment initiation in depressive symptoms*, as measured by Montgomery-Åsberg Depression Scale (MADRS) score.

Tertiary effectiveness endpoints included:

- *Change from baseline to week 8 post-treatment initiation in depressive symptoms*, as measured by HDRS17 total score.
- *HDRS17 total score at week 8* post-treatment initiation.
- *Proportion of subjects achieving clinically substantial improvement in HDRS17 total score:* Defined as the percentage of subjects who achieved a reduction of at least 7 points in HDRS17 total score, measured at 8 weeks post-treatment initiation.
- *Proportion of subjects with HDRS17 category shift from baseline to week 8 post-treatment initiation*: Defined as the percentage of subjects who experienced a category change, defined by HDRS17 total score, from baseline to 8 weeks; HDRS17 categories: Very severe = 26-52; Severe = 20-25; Moderate = 14-19; Mild = 8-13; Remission = 0-7.

Additional exploratory and post-hoc analyses were conducted to assess changes in depressive symptoms throughout the OL phase of the study. These analyses were performed separately for subjects who were initially randomized to Proliv™Rx

treatment during the DB phase, and for subjects initially randomized to the sham treatment and later crossed over to Proliv™Rx treatment during the OL phase (post hoc). The following assessments were performed:

The following OL phase outcome measures were evaluated in the Proliv™Rx active treatment group for the modified intent-to-treat (mITT) analysis set:

- Change from Baseline to 16 weeks post Proliv™Rx treatment initiation in HDRS17 (Visit 6).
- Proportion of HDRS17 responder subjects to week 16 visit.
- Proportion of subjects achieving clinically substantial improvement in HDRS17 scores to week 16 visit, defined as the percent of subjects with reduction in HDRS17 score of at least 7 points at 16 weeks post Proliv™Rx treatment initiation.
- Proportion of subjects achieving remission to week 16 visit - defined as the percent of subjects with HDRS17 score≤7 at 16 weeks post Proliv™Rx treatment initiation in the original active group.
- HDRS17 Category Shift from Baseline to week-16 Visit - defined as the category change from baseline to week-16 post Proliv™Rx treatment initiation in HDRS17; Categories definition: 5: Very severe 26-52, 4: Severe 20-25, 3: Moderate 14-19, 2: Mild 13-8 and 1: 0-7 Remission.
- Proportion of new responder subjects - defined as the percent of subjects who did not have a response (per HDRS17) at the week 8 visit, achieving at least 50% reduction from baseline (Visit 2) in HDRS17 total score 16 weeks post Proliv™Rx active treatment initiation (Visit 6).
- Proportion of new subjects achieving remission - defined as the percent of subjects who did not have a remission (per HDRS17) at the week 8 visit, achieving a HDRS17 total score≤7 points 16 weeks post Proliv™Rx active treatment initiation (Visit 6).

Post-hoc analyses of selected exploratory efficacy endpoints during the OL phase were conducted to evaluate the impact of transitioning from sham to active treatment on depressive symptoms in the mITT analysis set. These analyses were conducted for subjects originally treated in the original Sham treatment group after crossing over to active treatment. The following assessments were performed:

- Change from Baseline to 16 weeks in HDRS17 total score
- Proportion of HDRS17 Responder Subjects From Week 8 to Week 16
- Proportion of HDRS17 Remission Subjects From Week 8 to Week 16
- Proportion of HDRS17 Clinically Substantial Reduction Rate Subjects From

Week 8 to Week 16

- HDRS17 Category Shift from week 8 to week 16

Safety was assessed through the incidence of adverse events (AEs) and serious AEs (SAEs) related or unrelated to the Proliv™Rx System at 16 weeks post-treatment initiation (end of OL phase).

4. Study Analysis Sets

The MOOD study results were analyzed in different analysis populations (different ways of grouping participants for analysis), as follows:

Intent-to-treat Analysis Set (ITT)

The intent-to-treat (ITT) population included all subjects who were randomized and attempted any use of the investigational device, regardless of significant protocol deviations or lack of follow-up data. According to the ITT principle, all subjects were analyzed in the treatment group as assigned by randomization.

Modified Intent-to-treat Analysis Set (mITT)

The modified intent-to-treat (mITT) population included all subjects from the ITT set enrolled in the study, who completed the minimal 1680 minutes of stimulation time required by the protocol and had no post-randomization exclusion criteria. The mITT analysis set was analyzed in the treatment group as treated. **The primary success criterion for this study was a statistically significant difference between treatment and sham groups in this analysis set.**

Per-Protocol Analysis set (PP)

The per-protocol population included all subjects from the mITT set who completed the 8-week treatment period without withdrawal and without any major protocol deviations.

Statistical Analysis of Cohorts Analysis Sets

Safety assessments were performed on the ITT analysis set.

The mITT cohort served as the principal data analysis set for the primary, secondary, and tertiary statistical effectiveness outcome measures. The primary and secondary effectiveness assessments were also performed on the PP and the ITT analysis set to assess the consistency of study results.

B. Accountability of PMA Cohort

126 eligible and consenting subjects were enrolled in the study and randomized. Two (2) of these subjects were under the age of 22 and were only included in reporting of safety data, leaving 124 subjects to be included in the ITT analysis set. See Figure 3 below for a detailed flow diagram illustrating the subject disposition and tolerability throughout the study.

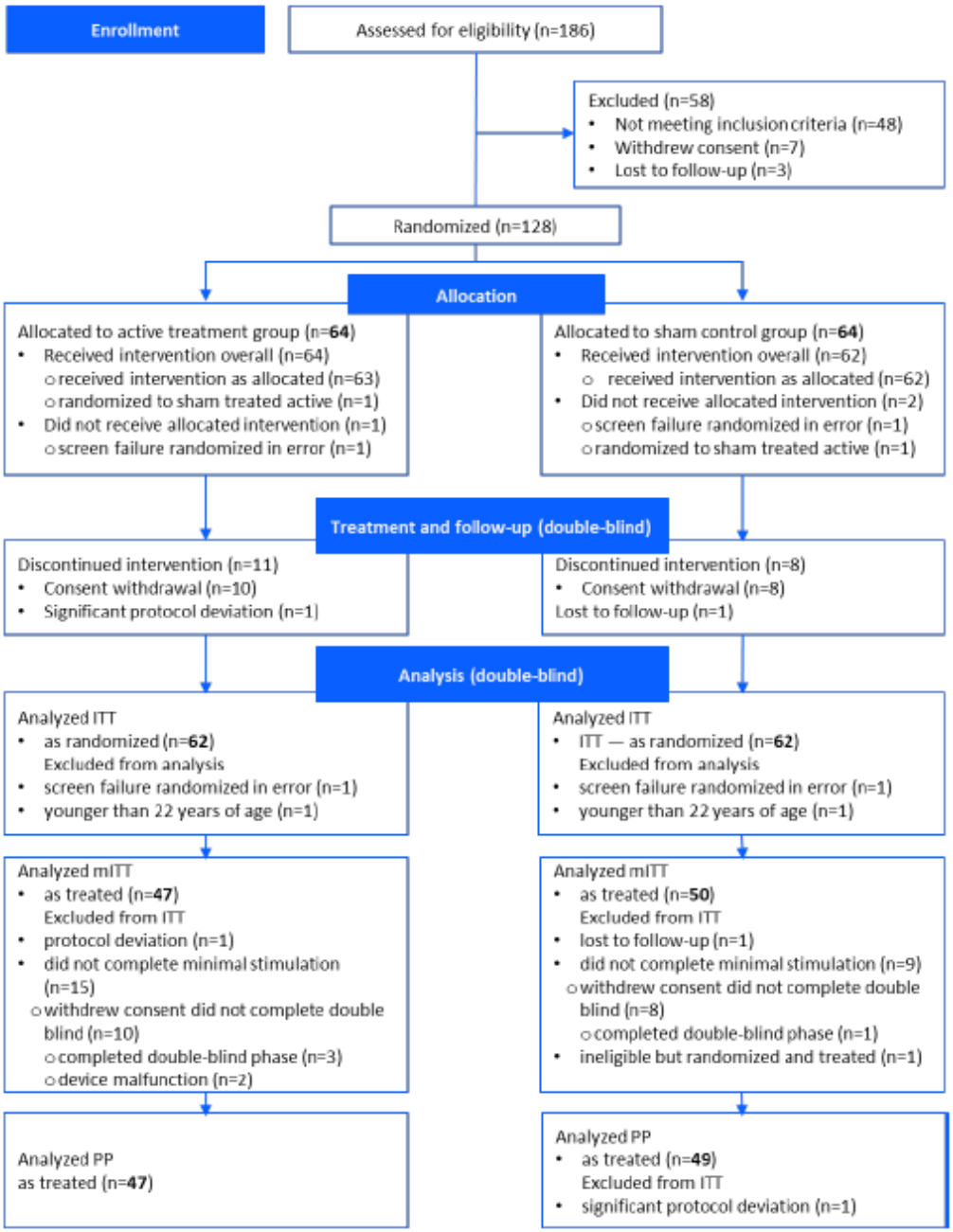

Figure 3: Consolidated Standards of Reporting Trials (CONSORT) Flow Diagram

C. Study Population Demographics and Baseline Parameters

Table 1 summarizes the total number of subjects in the three analysis populations.

Table 1. Number of subjects in each analysis population

	Total	Study arm as randomized		Study arm as treated	
		Active	Sham	Active	Sham
ITT analysis set	124	62	62	63	61
mITT analysis set	97	46	51	47	50
PP analysis set	96	46	50	47	49

Demographic characteristics and depression history in the mITT population are provided in Table 2 and Table 3, respectively, stratified by treatment group. There were no statistically significant differences from the ITT and mITT groups in any demographic or depression history variables.

Table 2. Demographic Characteristics at Baseline (mITT Population)

		Active Treatment (n = 47)	Sham Control (n = 50)	Total (n = 97)	P-value
Gender (n, %)	Male	12 (25.5)	13 (26.0)	25 (25.8)	0.9580 (@)
	Female	35 (74.5)	37 (74.0)	72 (74.2)	
Race (n, %)	American Indian or Alaska Native	-	1 (2.0)	1(1.0)	0.8887 (#)
	Asian	2 (4.3)	1 (2.0)	3 (3.1)	
	African or African-American	2 (4.3)	2 (4.0)	4 (4.1)	
	Caucasian [and white Israelis]	36 (76.6)	35 (70.0)	71 (73.2)	
	Not reported	-	1 (2.0)	1 (1.0)	
	Other	7 (14.9)	10 (20.0)	17 (17.5)	
Age (years)	Mean (SD)	48.8 (13.05)	47.1 (12.95)	47.9 (12.96)	0.5056 (*)
	Median [Range]	51.3 [24.6;70.0]	50.6 [22.3;69.6]	50.6 [22.3;70.0]	
Body mass index	Mean (SD)	29.11 (7.85)	28.15 (6.94)	28.61 (7.37)	0.5235 (*)
	Median [Range]	27.46 [17.23;45.73]	26.36 [18.66;48.56]	26.97 [17.23;48.56]	
Education (years)	Mean (SD)	15.7 (2.09)	16.3 (3.90)	16.0 (3.15)	0.4162 (*)
	Median [Range]	16.0 [12.0;21.0]	16.0 [12.0;27.0]	16.0 [12.0;27.0]	
Employment status (n, %)	Other	5 (10.6)	1 (2.0)	6 (6.2)	0.4552 (#)
	Full-time employment	16 (34.0)	18 (36.0)	34 (35.1)	
	Part-time employment	5 (10.6)	5 (10.0)	10 (10.3)	
	Unemployed	11 (23.4)	16 (32.0)	27 (27.8)	
	Self-employed	3 (6.4)	6 (12.0)	9 (9.3)	
	Homemaker	2 (4.3)	2 (4.0)	4 (4.1)	
	Retired	5 (10.6)	2 (4.0)	7 (7.2)	
Head circumference (cm)	Mean (SD)	56.84 (1.90)	56.60 (2.04)	56.72 (1.96)	0.5567 (*)
	Median (Range)	57.0 [53.0;60.0]	56.5 [53.0;60.0]	56.7 [53.0;60.0]	

(*) t-test
(@) χ^2 test
(#) Fisher's exact test

Table 3. Depression History at Baseline (mITT Population)

		Active Treatment (n = 47)	Sham Control (n = 50)	Total (n = 97)	P-value
Number of antidepressant medications with none or insufficient response in the current episode	Mean (SD)	1.7 (0.89)	1.9 (0.89)	1.8 (0.89)	0.2269 (*)
	Median [Range]	1.0 [1;4]	2.0 [1;4]	2.0 [1;4]	
Number of inadequate antidepressant medications in the current episode	Mean (SD)	0.1 (0.49)	0.1 (0.50)	0.1 (0.49)	0.9025 (*)
	Median [Range]	0.0 [0;3]	0.0 [0;3]	0.0 [0;3]	
Age in which the first episode occurred	Mean (SD)	25.3 (13.40)	26.5 (13.91)	25.9 (13.60)	0.6574 (*)
	Median [Range]	20.0 [11;60]	24.0 [8;67]	22.0 [8;67]	
Number of episodes since initial diagnosis	Mean (SD)	9.2 (8.47)	10.1 (9.24)	9.7 (8.84)	0.6006 (*)
	Median [Range]	6.0 [2;35]	7.0 [1;34]	6.0 [1;35]	
Current episode duration (months)	Mean (SD)	13.8 (8.25)	14.2 (7.45)	14.0 (7.81)	0.7915 (*)
	Median [Range]	14.0 [1;34]	13.0 [2;30]	13.0 [1;34]	
Medication treatment in current episode	(n, %)	47 (100)	50 (100)	97 (100)	1.0000 (@)
Device treatment in current episode	(n, %)	1 (2.1)	6 (12.0)	7 (7.2)	0.1126 (#)
Psychotherapy treatment in current episode	(n, %)	30 (63.8)	31 (62.0)	61 (62.9)	0.8521 (@)
Other treatment in current episode	(n, %)	1 (2.1)	3 (6.0)	4 (4.1)	0.6178 (#)

(*) t-test
(@) χ^2 test
(#) Fisher's exact test

D. Safety and Effectiveness Results

1. Safety Results

In total, 74 AEs were reported among 39 "as treated" ITT subjects. 19 of these subjects were in the Proliv™Rx arm, resulting in an AE incidence of 30.16% (19/63). 20 subjects in the sham arm experienced at least one AE, resulting in an incidence of 32.79% (20/61).

During the open-label phase, 48 AEs were reported in 29 ITT subjects, resulting in an incidence of 29.90% (29/97).

In addition, one of the two subjects enrolled but excluded from the ITT due to their age (<22) had one AE: "Sinusitis", which was deemed mild and not related to the study device.

Two AEs were considered severe, of which one (worsening of sciatica) occurred in the active treatment group and was classified as definitely not related to the device and one (worsening depression symptoms) occurred during the open-label phase and

was classified as possibly related to the device.

Across 120 AEs throughout the entire study period (including both DB and OL phases), 91 (75.8%) were considered mild (35 in the Proliv™Rx-treated group, 21 in the sham group, and 35 during the OL phase and 29 (24%) were considered moderate (9 in the active arm, 8 in the sham arm, and 12 in the OL phase).

In the course of the double-blind phase of the study, there were 20 headache adverse events reported over 6 subjects, 3 of whom withdrew from the study for this reason. This was attributed by the sponsor to the subjects' misinterpretation of the instructions provided for increasing stimulation intensity. This led to a revision of the training procedure to clarify the instructions approximately 80% of the way through the trial. Following this change, there were no additional withdrawals due to headaches.

Overall, 51 AEs were considered as definitely, probably, or possibly related to the study device (25 in the Proliv™Rx arm [incidence = 15.87%, 10/63], 6 in the sham arm [incidence = 8.20%, 5/61], and 20 in the OL stage [incidence = 10.31%, 10/97]).

Table 4 below presents the AEs that were considered related to the device, stratified by severity and treatment arms (ITT as treated).

Table 4. AEs by Severity and Treatment – ITT, Possible/Probably/Definitely Related to Device

Severity		Treatment Arm (treated)								
		Active			Sham			Open Label		
		# of reports	# of subjects	Incidence	# of reports	# of subjects	Incidence	# of reports	# of subjects	Incidence
Mild	All	20	6	9.52%	5	5	8.20%	18	8	8.25%
	Cold with a headache	.	.	.	.	.	.	1	1	1.03%
	Erythema	1	1	1.59%	.	.	.	.	.	.
	Headache	18	4	6.35%	2	2	3.28%	11	4	4.12%
	Intermittent headaches and body aches	.	.	.	.	.	.	1	1	1.03%
	Migraine	.	.	.	1	1	1.64%	.	.	.
	Pain and discomfort	.	.	.	.	.	.	1	1	1.03%
	Pressure in ears	.	.	.	1	1	1.64%	.	.	.
	Redness and indentation on forehead	.	.	.	1	1	1.64%	.	.	.
	Scalp itching	1	1	1.59%	.	.	.	.	.	.
	Skin irritation	.	.	.	.	.	.	1	1	1.03%
	Unpleasant sensation during treatment	.	.	.	.	.	.	3	2	2.06%
Moderate	All	5	4	6.35%	1	1	1.64%	1	1	1.03%
	Burning sensation	1	1	1.59%	.	.	.	.	.	.
	Headache	1	1	1.59%	.	.	.	1	1	1.03%
	Migraine	1	1	1.59%	.	.	.	.	.	.
	Pain & discomfort	1	1	1.59%	.	.	.	.	.	.
	Stinging sensation	1	1	1.59%	.	.	.	.	.	.
	Worsening depression symptoms	.	.	.	1	1	1.64%	.	.	.
Severe	All	.	.	.	.	.	.	1	1	1.03%
	Worsening depression symptoms	.	.	.	.	.	.	1	1	1.03%

2. Effectiveness Results

Primary effectiveness outcome measure

The active group (participants who received the real Proliv™Rx treatment) showed an 8.62-point reduction from the baseline following the 8-week-long treatment period, while the sham group showed a corresponding reduction of 6.01 points. This represented a 2.61-point improvement in the Proliv™Rx-treated group over the sham group, a difference that was statistically significant ($p = 0.0196$). As a result, the null hypothesis was rejected, and the study was deemed a success in showing

that adjunctive Proliv™Rx treatment lowered HDRS17 scores compared to sham control treatment in individuals with MDD who previously failed to achieve satisfactory improvement with antidepressant medication who used it as directed. These results demonstrate a statistically significant improvement in the device-treated group compared to the sham group.

Table 5: HDRS17 Total Score Adjusted Mean Model Results Over 8-Week Treatment Period (mITT Population)

		HDRS17 change from baseline			
		Adjusted mean	SE	*P* value	95% CI
Week 4	Active	-6.13	0.7689	<.0001	[-7.66;-4.60]
	Sham	-4.67	0.7498	<.0001	[-6.16;-3.18]
	Difference (active-sham)	-1.46	0.9768	0.1394	[-3.40;0.48]
Week 8	Active	-8.62	0.8476	<.0001	[-10.30;-6.93]
	Sham	-6.01	0.8257	<.0001	[-7.65;-4.37]
	Difference (active-sham)	**-2.61**	1.0959	**0.0196**	[-4.79;-0.43]

ITT (n=124):
All randomized participants

mITT (n=97):
Participants with no enrollment criteria violations who completed the minimal treatment time

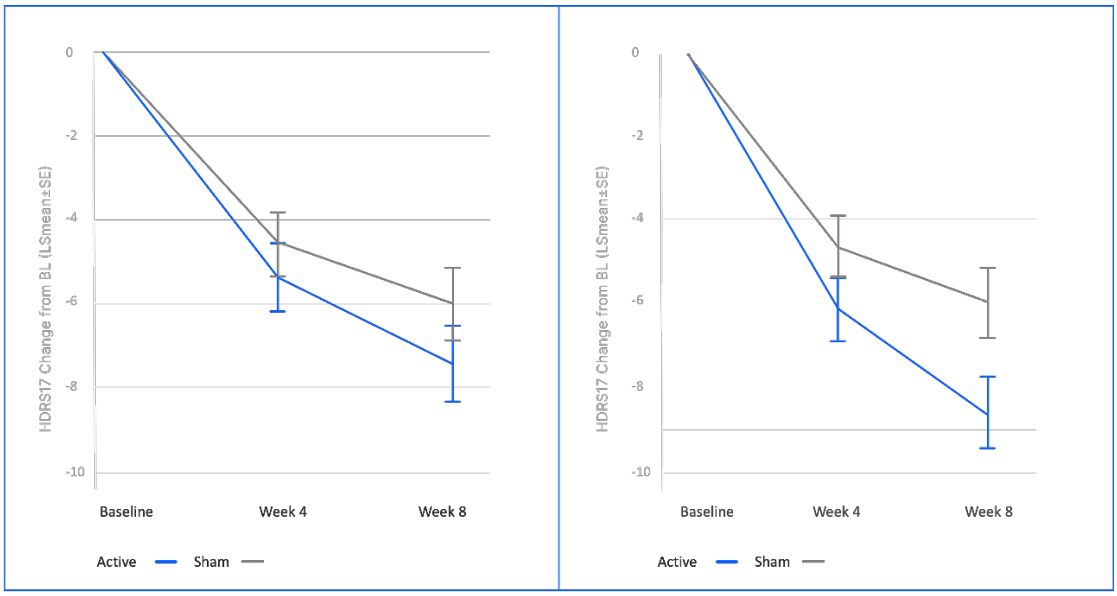

Figure 4 Change from Baseline in HDRS17 Regression Model Results Over 8-Week Treatment Period – ITT (left) and mITT (right) Analysis Sets

Secondary Effectiveness Outcome measures

Given the success of the primary outcome (mean change in HDRS17 score), the statistical analysis proceeded to evaluate the secondary outcomes. A hierarchical analysis was employed, with p-values adjusted using the prespecified Benjamini-

Hochberg method to control for multiplicity. Across the secondary outcomes, the study arm demonstrated a numerical advantage over the sham control arm but did not meet the $p < 0.05$ criterion for statistical significance.

Proportion of Subjects Achieving Remission

The proportion of remitters (subjects with HDRS17 score ≤ 7) at the 8-week visit was higher in the Proliv™Rx-treated group (10/47, 21.3%) compared to the sham group (3/50, 6.0%).

Proportion of Responder Subjects

At the 8-week visit, the proportion of responders (subjects with ≥ 50% reduction in HDRS17 score) was higher in the active treatment group (15/47, 31.9%) compared to the sham group (9/50, 18.0%).

Change from Baseline to Week 8 in MADRS Total Score

Both active and sham groups in the mITT population exhibited improvement in MADRS total scores over the 8-week period ($p < 0.0001$ for both groups). However, the Proliv™Rx-treated group showed a 2.09-point improvement over the sham group, though this difference did not reach statistical significance at the $p < 0.05$ level. The observed mean (SD) changes in MADRS total score were -10.3 (8.07) and -8.3 (8.03) for the active treatment and sham control groups, respectively.

Tertiary Effectiveness Outcome Measures

Statistically significant differences between sham and control were not observed at the $p < 0.05$ level for any of the tertiary outcomes. Favorable trends were observed for the following tertiary outcomes:

Proportion of Subjects Achieving Clinically Substantial Reduction Rate in HDRS17 at Week 8

The proportion of subjects achieving clinically substantial improvement in HDRS17 scores (subjects with reduction of ≥7 points from baseline to week 8) was higher in the Proliv™Rx-treated group (29/47, 61.7%) compared to the sham group (16/50, 32.0%).

HDRS17 Depression Severity Category Shift from Visit 2 to Visit 4

While none of the participants were considered Mild or in Remission at baseline, after 8 weeks of treatment, 51% (24/47) of the participants in the active group were considered Mild or in Remission, compared to only 26% (13/50) in the sham group.

3. Blinding

Subjects in the MOOD Study were blinded to their treatment allocation during the double-blind phase of the study. To assess the robustness of the blind, subjects completed a survey immediately after performing the training session (Visit 2) with their assigned device, which asked the subjects to guess which treatment group they had been assigned ("active", "sham/placebo", or "don't know"). In the Proliv™Rx group, after training, 15% of subjects correctly guessed the treatment they received, while in the sham group 6% of the subjects guessed correctly, attesting to the effectiveness of blinding before treatment start. When subject impression of treatment assignment at Visit 2 was added as an additional covariate to the primary endpoint model, the main study outcome was unchanged.

4. Open Label Phase Results

96% (93/97) of subjects in the mITT analysis set continued to the Open Label (OL) phase of the study in which all subjects received the active device. 95.7% (45/47) of subjects originally randomized to the active group and 96% (48/50) of subjects originally randomized to the sham group participated in this stage.

Participants who continued from the active group to the open label phase of the study, for a total of 16 active treatment weeks, showed continued improvement and benefits with increasing rates of response and remission up to the end of the study. Furthermore, participants who transitioned from the sham group to the active group after completing the double-blind phase improved significantly over the eight weeks treatment of the open-label phase. Although these results are difficult to interpret due to the absence of sham control for placebo effects in this extension of the study, the open-label phase provided additional information regarding the Proliv™Rx treatment.

5. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

XII. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 22 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XIII. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Feasibility Study

The initial feasibility study was an outside the United States, open label, single-arm, single-center investigation designed to assess the safety and feasibility of the Proliv™Rx System. The study enrolled 29 patients, aged 21 to 65, diagnosed with depression, who had not responded to treatment with at least one but no more than four (average = 1.8) antidepressant medications in the current episode. Of the 29 participants, 24 completed the study. The primary effectiveness outcome of the trial was the change in depression symptoms from study baseline (initial score before treatment) to the end of 6 weeks of daily Proliv™Rx treatment. This change was assessed by each participant's physician using the Hamilton Depression Rating Scale (HDRS21). Participants experienced improvement in symptoms, with an average HDRS21 reduction of 10 points, representing a 40% average improvement in depression scores. In total, 67% (16/24) of the participants improved by 40% or more, and 42% (10/24) of the participants improved by 50% or more. Regarding safety, there were no serious AEs reported during the study, and all AEs were mild to moderate, suggesting a favorable safety profile for the studied therapy.

The feasibility trial was used to assess safety and could not be used to determine treatment effectiveness due to the lack of control group.

XIV. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Neurological Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XV. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Effectiveness of the Proliv™Rx System was assessed in the prospective, multicenter, randomized, sham-controlled, double-blind pivotal MOOD study (Carpenter et al. 2025). One-hundred-twenty-six (126) subjects were randomized to active stimulation therapy or sham control. The main analysis population was the modified intent-to-treat (mITT) population. This analysis group comprised 97 subjects (47 active, 50 control) who used the device for at least 40 minutes per day, 5 days per week, over 8 weeks (a total of at least 1,680 minutes) and had no major protocol deviations.

The MOOD study met the primary effectiveness outcome pre-specified in the study protocol. This outcome was a statistically significant improvement in HDRS17 scores at 8 weeks compared to sham control in the mITT group. An 8.62-point mean reduction from baseline following the 8-week-long treatment period was observed in the Proliv™Rx-treated group, and a 6.01-point reduction in the sham control group. This group difference of 2.61 points was statistically significant ($p = 0.0196$).

Given the success of the primary outcome measure, the secondary outcome measures were evaluated. A hierarchical analysis was employed, with p-values adjusted using the prespecified Benjamini-Hochberg method to control for multiplicity. Across all secondary endpoints, the treatment arm demonstrated a numerical advantage over the sham control arm but did not meet the $p < 0.05$ criterion for statistical significance. The proportion of participants achieving remission in the active treatment group was 3.5-fold greater than its sham control group counterpart at the end of the double-blind phase (21.3% and 6.0%, respectively). At baseline, by inclusion criteria, none of the subjects had depression classified as normal or at mild severity, but by the end of the double-blind phase, 51% of the Proliv™Rx group had depression severity that was classified as normal or mild, compared to 26% in the sham group.

Participants from the active group who continued treatment in the open-label phase of the study showed increasing rates of response and remission. Improvements in HDRS17 scores observed at 8 weeks were sustained after 16 weeks of active treatment. Depressive symptoms continued to improve between weeks 8 and 16, leading to a mean reduction in HDRS17 scores of nearly 10 points from baseline for participants who received active treatment throughout the 16-week period. Furthermore, among the participants who received active treatment for 16 weeks, both response and remission rate continued to nominally improve during the open-label phase, with almost 32% eventually achieving remission by week 16. Importantly, without a control group in the open-label phase, the impact of device use cannot be distinguished from a potential placebo effect.

Participants who transitioned from the sham group to the active group after completing the double-blind phase improved over the eight weeks of the open-label phase. These participants had an average reduction of 9.6 points from their baseline HDRS17, with a decrease in HDRS17 scores from the point of crossover to the end of the open-label phase. For this patient cohort, the remission rate rose fourfold following the switch from the sham control to active treatment, reaching 22%. In addition, transitioning from the sham to active treatment significantly reduced the proportion of participants with depression categorized as severe or very severe (from 20.9% to 7.3%) and markedly increased the proportion of remitted patients (from 6.3% to 22%). However, since this was an open label phase and this patient population is susceptible to placebo effects, the benefit of device use during this time is uncertain.

Thus, device use appeared to benefit patients who completed the minimum usage time, as demonstrated during the randomized, controlled portion of the pivotal trial. The lack of a control group during the open-label period lends significant uncertainty to the benefits shown during this study phase.

B. Safety Conclusions

The risks of the device were evaluated from published scientific studies, nonclinical testing, and clinical data collected in the MOOD study. In the MOOD study, 74 adverse events (AEs) were reported among 39 “as treated” ITT subjects. 19 of these subjects were in the Proliv™Rx arm, resulting in an AE incidence of 30.16% (19/63). 20 subjects in the sham arm experienced at least one AE, resulting in an incidence of 32.79% (20/61). During the study, only two AEs were considered severe, of which one (worsening of sciatica) occurred in the active treatment group

and was assessed to be definitely not related to the device and one (worsening depression symptoms) occurred during the open-label phase and was assessed to be possibly related to the device. In the course of the double-blind phase of the study, there were 20 headache adverse events reported across 6 subjects. This led to a revision of the training procedures to clarify the instructions approximately 80% of the way through the trial. All other AEs were anticipated, mild to moderate, and transient.

The changes made to the instructional procedures provided to participants during the study, while they may have reduced the incidence of headache AEs, also had the effect of increasing uncertainty in understanding the risks associated with device use. In addition, during the study, AEs were asked about only at study visits and not between visits, increasing the likelihood that AEs might not be remembered, and further adding to the uncertainty regarding risks. Despite the uncertainties, the overall risk of device use appears to be low.

C. Benefit-Risk Determination

The totality of the evidence demonstrated that Proliv™Rx provides a probable benefit to adults with major depressive disorder (MDD), that, while modest, is sufficient to outweigh its probable risk. The Proliv™Rx presents some probable risks, but these probable risks are low. The risks are, in general, mild and transient. The main risk of the device is transient headache. Stinging, burning, or itching sensations at the stimulation site were also common.

In FDA's evaluation of the effectiveness of the Proliv™Rx System device, based on the MOOD study, sources of uncertainty of benefit included:

- Absence of a pre-specified clinical significance threshold in the primary study success criterion, and a lack of consensus in the medical literature regarding what would constitute such a threshold (Fountoulakis & Möller 2011, Hengartner & Plöderi 2018, Kirsch et al 2008, Kirsch et al 2002, Luan et al 2018, Montgomery 2011, Montgomery et al 2011, Rush et al 2003).
- Use of an outcome in the modified intent to treat (mITT) group (Abraha 2010, Montedori 2011) as the primary success criterion for the MOOD study.
- Uncertainty of blinding in the MOOD study due to blinding assessment having been conducted at baseline rather than after trial completion (Hrobjartsson et al 2007, Sackett 2007).
- Uncertainty about durability of effect due to unblinding of participants at 8 weeks.

Additional factors that were considered in determining probable risks and benefits for the Proliv™Rx device included:

- The suitability of the device for home use facilitates access to the treatment and provides an alternative to patients with low tolerance to pharmacological treatments.
- The probable risks are well-characterized due to the presence of similar devices on the market.

The population of patients who do not respond to an antidepressant are exposed to greater risks from additional medications. Although many patients are helped by changing or adding an antidepressant medication, relief is not experienced by a high proportion of these patients, and the risk of suicidality may increase with each failed medication. Furthermore, patients may not be able to tolerate multiple medications, which can limit adherence to the treatment. By contrast, the MOOD study of Proliv™Rx showed primarily mild, transient risks for adverse events, and showed that the device could be added safely to an existing antidepressant medication. The MOOD Study showed high patient adherence to the Proliv™Rx: among the 104 ITT subjects who finished the double-blind phase, 96% (100/104) completed the minimal device treatment regimen, and 96% (93/97) of the mITT analysis set both completed the minimal treatment regimen and elected to continue to the open-label phase. In the open-label phase, 3.2% (3/93) ended the study early due to failure to adhere to the treatment regimen.

Overall, the evidence is adequate to demonstrate a reasonable assurance that Proliv™Rx is safe and effective under the conditions of use described in the indications for use.

D. Patient Perspective

While no formal patient preference study was conducted, patients in the pivotal study were informally questioned on their thoughts regarding use of the Proliv™Rx. The home-based, self-operated treatment was deemed convenient by 85% of participants, with only 4% finding it inconvenient to some extent. Additionally, 89% of questionnaire responders found the device easy or very easy to use. Compliance was high, with 96% (100/104) of participants completing the 8-week double-blind treatment regimen and 96% (93/97) of the mITT analysis set continuing to the open-label phase. In the open-label phase, 97% (90/93) of participants adhered to protocol requirements.

E. Overall Conclusions

The data in this application constitute valid scientific evidence within the meaning of 21 CFR 860.7. These data support a reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The data support the intended use of the Proliv™Rx System as an adjunctive treatment for Major Depressive Disorder (MDD) in adults who failed to achieve satisfactory improvement from previous antidepressant medication.

XVI. CDRH DECISION

CDRH issued an approval order on December 31, 2025.

The applicant's manufacturing facilities have been found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XVII. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

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