

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Cranial electrotherapy stimulator to treat depression
Device Trade Name: Flow FL-100

Accessories: Flow Clinic Patient Platform (FL-CPP), Headset pads (FL-PADS)

Device Procode: JXK

Applicant's Name and Address:
Flow Neuroscience AB
Södra Tullgatan 3,
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Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P230024

Date of FDA Notice of Approval: December 8, 2025

Breakthrough Device: Granted breakthrough device status on May 31, 2022, because of a reasonable expectation that the device can provide more effective treatment of a life threatening disease or condition, and availability would be in the best interest of patients if the device is effective.

II. INDICATIONS FOR USE

Flow FL-100 is intended for the treatment of moderate to severe major depressive disorder (MDD) in the current episode, either as monotherapy or as an adjunctive treatment, in patients 18 years and older who are not considered treatment refractory to medication.

III. LIMITATIONS

In FDA's evaluation of the effectiveness of the Flow FL-100 device, based on the Empower study, there is a moderate level of uncertainty of benefit due to unblinding, lack of a prespecified clinically significant change in HDRS-17 scores, and conflicting results from the literature. See Section X.V. for more information regarding how these uncertainties were addressed.

IV. CONTRAINDICATIONS

- Open wounds, broken skin, or damaged skin at the electrode site.

- Metallic skull reconstruction at the electrode site.

V. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Flow FL-100 labeling.

VI. DEVICE DESCRIPTION

The device trade name is Flow FL-100 (aka “Flow-100”, “FL-100” or “Flow”).

FL-100 is a cranial electrotherapy stimulator (CES) for the treatment of depression using transcranial direct



Figure 1. The Flow FL-100 and Headset Pads.

current stimulation (tDCS). A tDCS device delivers low-intensity direct electrical current to specific areas of the brain via electrodes placed on the scalp. The electrical current may modulate neuronal activity by altering the resting membrane potential of cortical neurons, thereby influencing brain excitability.

FL-100 includes the following components:

- (1) A Bluetooth-enabled tDCS **headset** with electrodes delivering 2.0 mA stimulation. The headset communicates with a smartphone through Bluetooth low energy (BLE). A rechargeable Lithium Polymer battery of 250 mAh drives the headset, which allows for about 10-15 sessions before recharge. The headset is rechargeable with a Micro-USB cord. The Micro-USB connector is located on the inside of the headset to make sure it can't be connected while the headset is on the head.
- (2) A pair of single-use disposable **Headset Pads**. Each pad is a cellulose sponge soaked with saline to improve electrical conductivity by lowering skin impedance to ensure a strong, uniform electrical signal. These pads are attached to the electrodes

using two medical-grade silicone rings and are circular with a diameter of 5 cm that touches the skin. Headset Pads are for one-time use and are packaged in pairs in aluminum foil bags.

- (3) A **smartphone app** that guides the user, controls the headset, and monitors headset usage. The App lets the user register or login, presents a stimulation schedule to the user (i.e., how many sessions the user should do per week or how many sessions have been missed or finished), gives instructions for how to prepare the headset for stimulation, and controls the stimulation (start/pause/resume). The headset has a unique identifier that is accessible from the smartphone app. This is used to track the usage of each individual device, to send reminders/notifications of planned stimulation sessions to the user's phone, and to ensure that the user has not already stimulated more than the daily and weekly stimulation limits.

Each week the user answers a Montgomery-Åsberg Depression Rating Scale Self-report (MADRS-s) questionnaire to track their depression symptoms.

- (4) **Main server:** The main server is the central processing hub of the device software system and manages the core functions, data storage, and processing logic as the backend for the frontends, the smartphone app and CPP.
- (5) **Clinic patient platform (CPP),** a web interface that can be used by a clinician to monitor a patient's headset usage and set the stimulation parameters.

The product is intended to be used in a home environment by a patient diagnosed with MDD. Guided by the instructions in the app, the patient can use the product by themselves or in the presence of a clinician.

Users should complete 5 stimulation sessions per week for the first 3 weeks, followed by completion of up to 3 stimulation sessions per week. Each session is 30 minutes long.

This medical device software has functions subject to FDA premarket review, as well as functions that are not subject to FDA premarket review. For this application, if the product has functions that are not subject to FDA premarket review, FDA assessed those functions only to the extent that they either could adversely impact the safety and effectiveness of the functions subject to FDA premarket review or they are included as a labeled positive impact that was considered in the assessment of the functions subject to FDA premarket review.

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

FL-100 has been marketed for the treatment of MDD in the European Union and the United Kingdom since 2019, and in Brazil and Australia beginning in 2020 and 2025, respectively.

FL-100 has not been withdrawn from marketing for any reason related to safety or effectiveness.

IX. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device observed in the clinical study supporting this approval:

- Dry skin, skin irritation or redness at the site of stimulation
- Stinging, tingling, numbness or burning sensation during stimulation
- Trouble concentrating during stimulation
- Headache
- Tinnitus
- Skin burn
- Sleepiness
- Acute mood change / Worsening depression

For the specific adverse effects that occurred in the clinical study, please see Section XI.D.1 below.

In addition, other studies using FL-100¹⁻⁹ report the following potential adverse effects:

- Accelerated heart rate
- Acute mood change / Sudden mood swings / Mood worsening / Nervousness / Increased anxiety
- Altered breathing
- Blurred / Blurry vision
- Bruise
- Buzzing / Vibration
- Dizziness / Nausea
- Fatigue / Sleepiness / Somnolence
- Hot flashes
- Migraine
- Neck pain / Neck ache
- Skin Pain
- Vivid dreams

Based on the published literature of tDCS treatment of MDD using other devices, a potential adverse effect also includes:

- Mania/Hypomania¹⁰

X. SUMMARY OF NON-CLINICAL STUDIES

A. Biocompatibility

Flow FL-100 and the Headset Pads are only used on intact skin with prolonged exposure. The exposure is only up to 30 minutes per day, but the device can be used for more than 48 days in total, resulting in more than 24 hours of exposure. However, these 24 hours will be spaced out over several months. The device and pads are made of materials common in medical devices that are deemed low risk, such as acrylonitrile-butadiene-styrene (ABS) plastic, medical-grade silicone, and cellulose sponge. The biocompatibility evaluation followed the policy outlined in Attachment G: Biocompatibility of Certain Devices in Contact with Intact Skin of Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" Guidance for Industry and Food and Drug Administration Staff.

B. Electromagnetic Compatibility and Electrical Safety

The device was tested for and found to comply with the following standards for electromagnetic compatibility, electrical and thermal safety:

- IEC 60601-1 Medical electrical equipment - Part 1: General requirements for safety and essential performance.
- IEC 60601-1-2 Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral standard: Electromagnetic compatibility - Requirements and tests.
- IEC 60601-1-11 Medical electrical equipment - Part 1-11: General requirements for basic safety and essential performance - Collateral standard: Requirements for

medical electrical equipment and medical electrical systems used in the home healthcare environment.

C. Software & Cybersecurity

Software for the device consisted of proprietary software marketed by Flow Neuroscience and consists of the Flow app, clinic patient portal (CPP), and the server backend. The software and cybersecurity were reviewed when the PMA was submitted, and the provided documentation was found adequate and consistent with a ‘Major’ level of concern given the Class III status of the device.

D. Shelf life

The validated shelf life for the FL-100 Headset and Pads is three (3) years.

E. Performance Testing

Each device is verified during manufacturing to generate a stimulation current of 2.0 ± 0.05 mA.

XI. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of at-home transcranial direct current stimulation (tDCS) with FL-100 for monotherapy or adjunctive treatment of moderate to severe major depressive disorder (MDD) in the current episode, in the US and the United Kingdom under IDE G210328.¹¹ Data from this clinical study, (aka “Empower”, “the Empower study”) were the basis for the PMA approval decision.

A summary of the clinical study is presented below.

A. Study Design

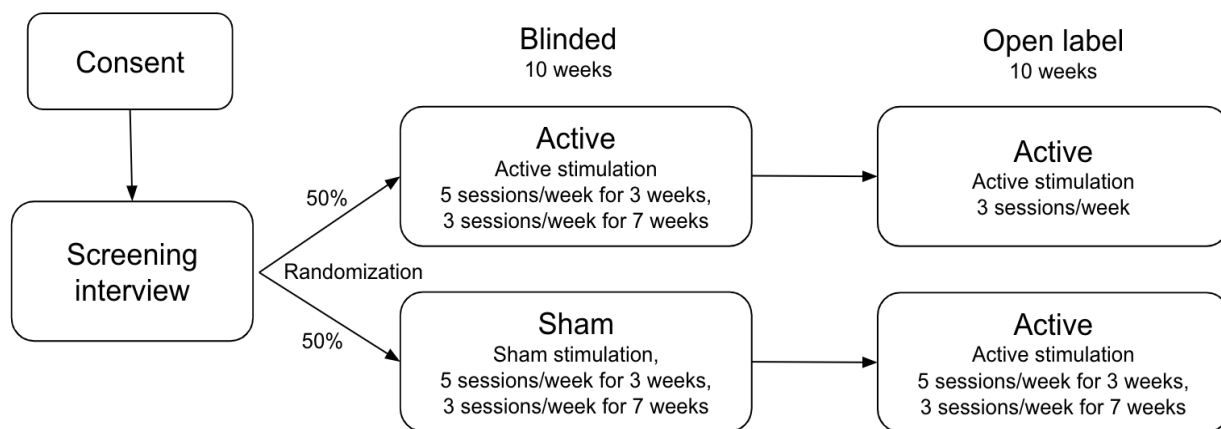
Patients were treated between June 2022 and August 2023. The database for this PMA reflected data collected through August 2023 and included 174 subjects. There were 2 investigational sites.

Empower was a fully remote 20-week clinical study that included a prospective, multi-center, double-blinded, randomized, two-arm (active/sham control) phase followed by a 10-week open-label phase. Empower was designed to evaluate the safety and effectiveness of at-home treatment with FL-100 in patients at least 18 years old in the current episode of moderate to severe MDD.

As shown below in **Figure 2.**, during the Blinded Phase of the Empower study, patients used FL-100 at home for 5 sessions per week for 3 weeks, followed by 3 sessions per week for 7 weeks, for a total of 36 sessions over 10 weeks. Research

staff directly supervised patients' initial device use. Thereafter, research staff monitored patients' device use via the clinic patient portal (CPP) and provided assistance as needed. Upon completion of the Blinded Phase, patients were offered the opportunity to participate in the 10-week Open-label Phase.

Figure 2. Study Design Overview



The Sham (control) group received stimulation using the same device as the Active group according to a standard protocol for sham tDCS.¹² At the beginning of each 30-minute stimulation session, the current was gradually ramped up to 1 mA, over 30 seconds. However, upon reaching the 1 mA maximum threshold, the current reached was gradually ramped down over 15 seconds to 0 mA. Forty-five seconds before the end of each session, the current was again ramped up to 1 mA over 30 seconds and then ramped down over 15 seconds to 0 mA.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the Empower study was limited to patients who met the following inclusion criteria:

1. Be ≥ 18 years.
2. Have a diagnosis of Unipolar MDD with a current depressive episode as defined by the diagnostic criteria in the Diagnostic and statistical manual of mental disorders – 5th edition (DSM-V)
3. Have a Hamilton Depression Rating Score (HDRS-17) of ≥ 16 .
4. For 6 weeks prior to enrollment, are either:
 - a. not taking antidepressant medication or;
 - b. are taking a stable antidepressant regimen with a stable medication source and agree to continue the same regimen throughout study participation

5. If in psychotherapy, have maintained stable psychotherapy for at least 6 weeks prior to enrollment.
6. Have access to a stable internet connection through which the treatment will be received.
7. Have access to a smartphone or other device running Android 5.0+ or iPhone Operating System (iOS) 12+ (e.g., reasonably new iPhone/iPad or Android phone), used to using the device in their everyday life, and can capably use the study application on the device, as determined by the investigator.
8. Are currently living in England/Wales (UK) or Texas (US).
9. Subject is currently under the care of a psychiatrist or a primary care physician, agrees to be evaluated at regular intervals by a psychiatrist or primary care physician for the duration of study participation, and agrees to promptly inform the study staff of any change of psychiatric or mental health providers during study participation.
10. Subject agrees to allow any and all forms of communication between the investigators/study staff and any healthcare provider who currently provides and/or has provided service to the patient/subject within at least two years of study enrollment.
11. Subject agrees to provide the name and verifiable contact information (email and mailing addresses, mobile and land-line phone numbers, as applicable) of at least two persons \geq age 18 who reside within a 60-minute drive of the patient's residence and whom the research staff is at liberty to contact, as they deem necessary, for the duration of study participation.
12. Be able to give voluntary, written informed consent to participate and have signed an Informed Consent Form specific to this study.
13. Be willing and able to comply with all study procedures.
14. Subject agrees to meet all of the inclusion criteria throughout their participation in the study. Otherwise, the subject will be discontinued from the study.
15. Subject agrees to a Safety/Suicide Risk Management Protocol, which is intended to reduce the reduce the risk of suicide during study participation.

Patients were not permitted to enroll in the study if they met any of the following exclusion criteria:

1. Are in a current state of mania, as determined by the Young Mania Rating Scale (YMRS) or psychosis, as determined by the Mini International Neuropsychiatric Interview (MINI).
2. Are diagnosed with vitamin or hormonal deficiencies that may mimic mood disorders, as determined by the investigator.
3. Are currently receiving any other interventional therapy for MDD other than a stable regimen of antidepressants or psychotherapy as defined in the inclusion criteria.
4. Considered to have treatment-resistant depression (TRD) as defined by inadequate clinical response to 2 or more trials of antidepressants at an adequate dose and duration.

5. Have a history of electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), cranial electrotherapy stimulation (CES), transcranial direct current stimulation (tDCS), deep brain stimulation (DBS), or other brain stimulation.
6. Patient answers Yes to Questions 4, 5 or 6 on the Columbia Suicide Severity Rating Scale (C-SSRS) Triage and Risk Identification Screener.
7. Any previous hospitalization for suicidal behavior.
8. Have chronic severe insomnia (< 4 hours of sleep each night), or depression secondary to chronic insomnia or sleep apnea
9. Have any structural lesion (e.g., any structural neurological condition, or more subcortical lesions than would be expected for age or have had a stroke that affects stimulated area or connected areas) or any other clinically significant abnormality that might affect safety, study participation, or confound interpretation of study results, as determined by the investigator.
10. Have any implant in the brain (e.g., DBS) or neurocranium, or any other active implantable medical device.
11. Have any neurocranial defect.
12. Have a history of epilepsy or seizures (including history of withdrawal / provoked seizures).
13. Have shrapnel or any ferromagnetic material in the head.
14. Have any disorder that would impair the ability to complete the study questionnaires.
15. Have been diagnosed with autism spectrum disorder.
16. Are actively abusing substances (<1 week prior to enrollment).
17. Have a cognitive impairment (including dementia).
18. Have a history of mania or psychosis.
19. Are currently using any medications that affect cortical excitability (e.g., benzodiazepines, epileptics, etc.).
20. Are currently experiencing symptoms of withdrawal from alcohol or benzodiazepines.
21. Have been diagnosed with Parkinsonism or other movement disorder as determined by the investigator to interfere with treatment.
22. Have ever taken esketamine / ketamine for treatment of depression.
23. Have ever been admitted to hospital for depression.
24. Have ever been diagnosed with obsessive-compulsive disorder (OCD) or bipolar type 1 or 2 disorder.
25. Is diagnosed with an active primary anxiety disorder, or post-traumatic stress disorder (PTSD), agoraphobia, anorexia or bulimia, panic or personality disorder with active symptoms.
26. Have a history of psychosurgery for depression.
27. Have any history of myocardial infarction, coronary artery bypass graft (CABG), coronary heart failure (CHF), or history of other cardiac issues.
28. Are currently experiencing or have a history of intractable migraines.
29. Are a chronic tobacco smoker, as defined by smoking by smoking >100 cigarettes (including hand-rolled cigarettes, cigars, cigarillos, etc.) in their lifetime and have smoked every day for the last 7 days.

30. If female and of child-bearing potential, currently pregnant or breastfeeding or planning to become pregnant or breastfeed any time during the study.
31. Are currently a prisoner.
32. Are participating concurrently in another clinical investigation or have participated in a clinical investigation within the last 90 days or intend to Participate in another clinical investigation during the study, and where the participation in the other investigation might interfere with the results of this trial as deemed by the PI.
33. Have any medical condition or other circumstances, in the judgment of the investigator, that might interfere with the ability to complete follow-up visits and the self-reported MADRS-s in the app.
34. Have any condition which, in the judgment of the Investigator, would preclude adequate evaluation of the device's safety and performance.
35. A Subject who meets any of the exclusion criteria during study participation will be discontinued from the study

2. Follow-up Schedule

Table 1. Schedule of Procedures shows the procedures that occurred during each study Phase: Pre-Treatment (Weeks -3 to -1), Blinded (Weeks 0 to 10), Open-Label (Weeks 10 to 20), and Early Termination (Weeks 1 to 20).

Table 1. Schedule of Procedures.

[Note: X within a blue cell – procedure performed by research clinician; X within a red cell – procedure performed by subject]

Study Phase	Pre-Treatment	Blinded					Open-Label		Early Termination
Procedure	Week -3 to -1 (± 3 days)	Week 0	Week 1 (± 3 days)	Week 4 (± 3 days)	Week 7 (± 3 days)	Week 10 (± 3 days) Final blinded visit ¹	Week 10 (± 3 days) Open Label Start	Week 20 (± 3 days)	Weeks 1-20
Informed Consent	X								
Screening and baseline Video Call	X								
Diagnostic Assessment for MDD	X ⁹								
Intervention Kit Shipped to subject	X ⁵								
Randomization ⁶		X							
Technical onboarding		X							
Initial Visit		X							
Video call	X	X	X	X	X	X		X	X
MINI	X								
HDRS-17	X		X	X	X	X		X	X
MADRS	X		X	X	X	X		X	X
MADRS-s		X ⁴	X	X	X	X		X	X
C-SSRS	X		X	X	X	X		X	X
YMRS	X		X	X	X	X		X	X
HAM-A	X					X		X	X
EQ-5D-3L	X					X		X	X
RAVLT	X					X		X	X
SDMT		X ²				X ²		X ²	
TAQ	X					X		X	X
AEQ						X		X	X
Healthcare Visit Survey ³						X		X	X
FLOW FL-100 use ⁷		X	X	X	X	X	X	X	
Record/Review Concomitant Medications	X	X	X	X	X	X		X	X
Record/Review Adverse Events		X	X	X	X	X		X	X

Abbreviations: AEQ (Adverse Events Questionnaire), C-SSRS (Columbia–Suicide Severity Rating Scale), EQ-5D-3L (EuroQol 5-Dimension 3-Level Questionnaire), HAM-A (Hamilton Anxiety Rating Scale), HDRS-17 (17-item Hamilton Depression Rating Scale), MADRS (Montgomery–Åsberg Depression Rating Scale), MADRS-S (Montgomery–Åsberg Depression Rating Scale – Self-rated), MINI (Mini International Neuropsychiatric Interview), RAVLT (Rey Auditory Verbal Learning Test), SDMT (Symbol Digit Modalities Test), TAQ (Treatment Acceptability Questionnaire), YMRS (Young Mania Rating Scale).

¹The week 10 visit includes the study Primary endpoint. This will be the final blinded visit and will be the start of the open label phase of the study. Participants in the Sham arm will be informed of their assignment and will restart with active stimulation for 10 weeks; participants in the Flow FL-100 arm will be allowed to continue maintenance treatment for 10 more weeks at 3 sessions per week. The unblinding will occur after the primary end-point data has been recorded.

¹The week 10 visit includes the study Primary endpoint. This will be the final blinded visit and will be the start of the open label phase of the study. Participants in the Sham arm will be informed of their assignment and will restart with active stimulation for 10 weeks; participants in the Flow FL-100 arm will be allowed to continue maintenance treatment for 10 more weeks at 3 sessions per week. The unblinding will occur after the primary end-point data has been recorded.

²Optional

³Participants will be surveyed about the number of times he/she has sought healthcare due to depression during the previous 10 weeks.

⁴Participants will be required to answer the nine questions of the MADRS-s form in the app to start the first stimulation session during the technical onboarding.

⁵Participants will be required to start treatment within 24 days from completing the baseline surveys.

⁶Completed after eligibility is confirmed by the investigator; when the participant signs up with their email in the trial app they will automatically be randomized to the sham or active treatment arm (with 50% probability).

⁷Five sessions per week for 3 weeks, followed by three sessions per week for 7 weeks. In total, thirty-six sessions during 10 weeks during the blinded phase. Please refer to Table 2 and Table 3 below for more details.

⁸In case there is an early termination the research staff can request to have an early termination interview, if the subject agrees.

⁹Diagnostic Assessment for MDD will be performed by Investigator-Psychiatrist according to the most recent APA Practice Guideline for treatment of MDD.

3. Clinical Endpoints

With regards to safety, the tDCS Adverse Effects Questionnaire (AEQ)¹³ was administered at weeks 10 and 20.

With regards to effectiveness, the following primary and secondary endpoints were defined.

Primary Endpoint

The primary effectiveness endpoint is the change in adjusted mean group difference in the HDRS-17 scores between 10 weeks and baseline between subjects randomized to the active study device (active group) relative to those subjects randomized to the sham device (sham group).

Secondary Endpoints

There were nine secondary effectiveness endpoints, all at Week 10:

1. Arm difference in HDRS-17: (a) response rate and (b) remission rate;
2. Arm difference in MADRS: (a) average score change, (b) response rate, and (c) remission rate;
3. Arm difference in (a) MADRS-s average score change, (b) response rate, and (c) remission rate; and
4. Quality of life improvement as measured by EQ-5D-3L in the active compared to sham arm.

Three of the nine secondary endpoints were pre-specified for multiplicity control: 1(a), 1(b), and 4.

The primary and three of the secondary effectiveness endpoints were pre-specified to be evaluated in the modified intent-to-treat (mITT) population, defined as the participants in the ITT subjects who receive at least one treatment session of the study device (Active or Sham). Therefore, the mITT population has n=173. The difference between the arms was assessed using a mixed model for repeated measures. If the p-value of the difference between the arms was less than one-sided $p = 0.025$, then the endpoint was declared a success.

The response rate was pre-specified as the proportion of patients with a <50% reduction in score from the baseline to Week 10. Remission was pre-specified as: HDRS-17 score ≤ 7 , MADRS score ≤ 10 , MADRS-s score ≤ 12 , at Week 10.

With regard to success/failure criteria, the primary effectiveness endpoint was the change in adjusted mean group difference in the HDRS-17 scores between 10 weeks and baseline between subjects randomized to the active study device relative to those subjects randomized to sham. The formal statistical hypothesis is as follows:

$$H_0: d_{\text{flow}} - d_{\text{sham}} \leq 0$$

$$H_a: d_{\text{flow}} - d_{\text{sham}} > 0$$

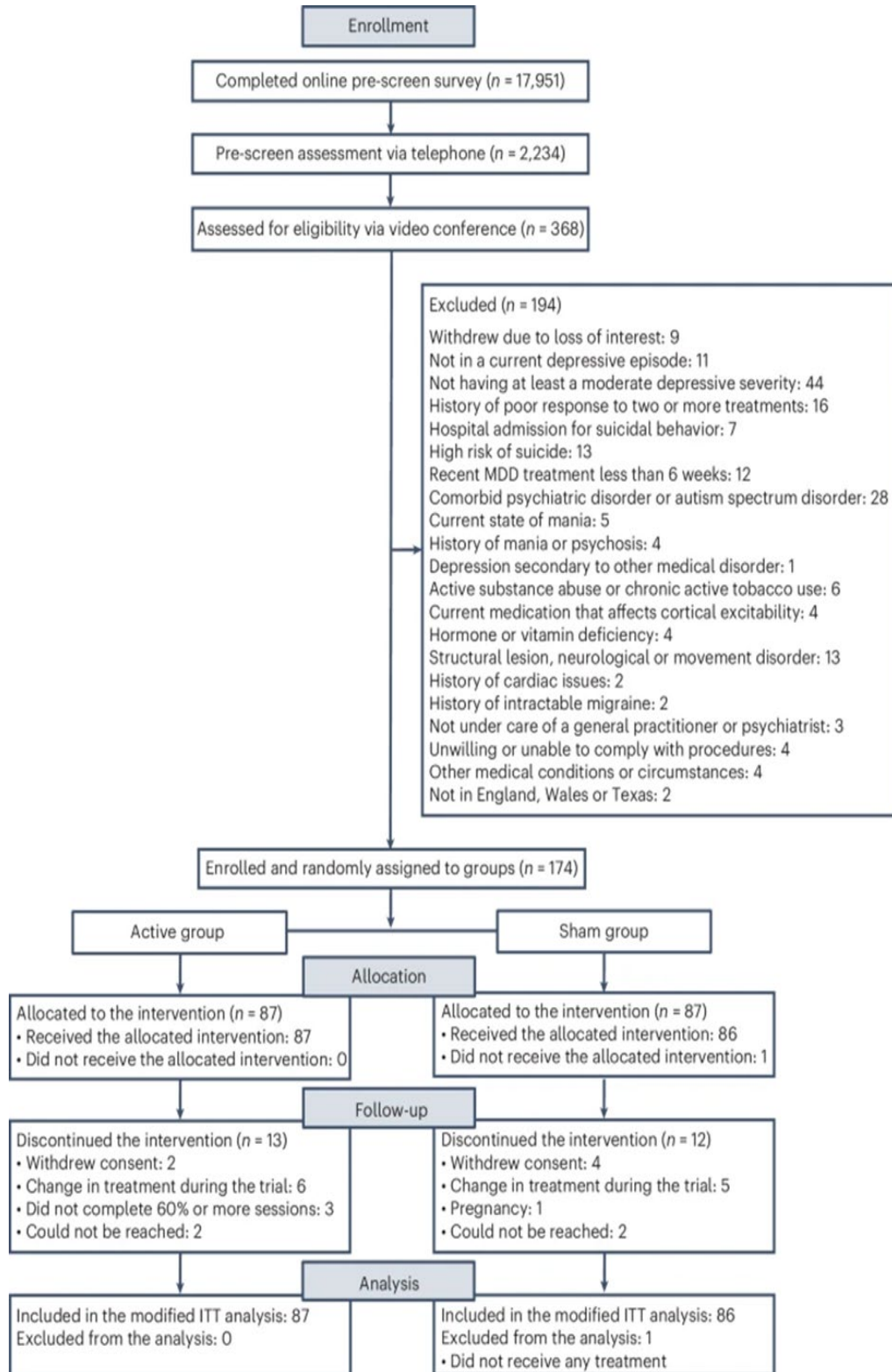
Where d_{flow} and d_{sham} are the adjusted mean group difference in HDRS-17 scores in subjects randomized to Active and Sham groups, respectively.

The success/failure criteria for individual patient success was pre-defined as response and remission on the HDRS-17.

B. Accountability of PMA Cohort

At the time of database lock, a total of 174 subjects were enrolled in the PMA study, 115 in the UK and 59 in the US. All eligible subjects were treated according to their randomized allocation and comprised the ITT population (n=174). The mITT population included all ITT subjects who received at least 1 treatment with the study device (Active or Sham); one subject was randomized but never received any stimulation, therefore, the mITT population has n=173. At the Week 10 time point, 149 patients remained in the study (14.3% attrition). Thirteen (13) subjects discontinued the treatment in the active group and 12 in the sham group. At week 20, after the open label phase, 111 subjects remained in the study.

Figure 3. Subject Disposition and Reasons for Discontinuation through Week 10



C. Study Population Demographics and Baseline Parameters

The baseline demographics of the study population are typical for a MDD study performed in the US in terms of gender, where the highest prevalence of depression is in females. No interaction effect was found between the treatment outcome and geography (US vs. UK), sex, age, race, or baseline HDRS-17. Baseline demographics are listed below:

Table 2. Baseline Demographic - Continuous Variables. ITT Analysis Set (N=174)

	Active						Sham						Group Difference			
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	Δ^1	LB	UB	p^2
All																
Age (years)	87	37.1	11.1	36.0	20.0	75.0	87	38.3	10.9	39.0	19.0	64.0	-1.2	-4.5	2.1	0.463
Female																
Age (years)	54	35.4	10.5	32.5	20.0	56.0	66	37.2	10.8	35.0	20.0	64.0	-1.9	-5.7	2.0	0.339
Male																
Age (years)	33	39.9	11.7	40.0	20.0	75.0	21	41.7	11.0	41.0	19.0	56.0	-1.8	-8.1	4.5	0.568
Clinical scores																
HDRS-17	87	19.2	2.8	18.0	16.0	30.0	87	18.9	2.6	18.0	16.0	25.0	0.3	-0.6	1.1	0.524
MADRS	87	24.7	4.7	24.0	11.0	39.0	87	23.9	5.5	24.0	7.0	36.0	0.9	-0.7	2.4	0.273
MADRS-s	87	26.8	6.9	27.0	4.0	43.0	87	25.7	6.3	26.0	9.0	42.0	1.1	-0.9	3.1	0.273
HAM-A	87	15.4	4.6	15.0	4.0	27.0	87	14.3	4.6	13.0	4.0	26.0	1.2	-0.2	2.6	0.088
YMRS	87	2.1	1.7	2.0	0.0	8.0	87	1.9	1.6	2.0	0.0	7.0	0.2	-0.3	0.7	0.463
¹ 95% Student's t Confidence Interval.																
² Nominal p-values. Without multiplicity adjustment.																

Table 3. Baseline Demographic - Categorical Variables. ITT Analysis Set (N=174)

	Active		Sham		p-value ¹
	n	%	n	%	
Gender (all)					
Male	33	38%	21	24%	0.071
Female	54	62%	66	76%	
Gender 18-21 years old					
Male	1	1%	1	1%	0.417
Female	6	7%	1	1%	
Ethnicity					
Hispanic or Latino	7	8%	13	15%	0.378
Not Hispanic or Latino	77	89%	70	80%	
Not reported	3	3%	3	3%	
Missing	0	0%	1	1%	

	Active		Sham		p-value ¹
	n	%	n	%	
Race					
Asian	9	10%	2	2%	0.012
Black or African American	3	3%	1	1%	
Native Hawaiian or Other	0	0%	0	0%	
White	72	83%	73	84%	
Other	3	3%	11	13%	
Missing	0	0%	0	0%	
Educational Level					
Less than High School/Secondary School	1	1%	0	0%	0.972
Some college	18	21%	19	22%	
Diploma	9	10%	7	8%	
Bachelor's or Professional Degree	37	43%	37	43%	
Master's or Doctoral Degree	22	25%	23	26%	
Prefer not to answer/Missing	0	0%	1	1%	
Adjunctive treatment					
Antidepressant ²	56	64%	53	61%	0.647
Psychotherapy ²	12	14%	14	16%	
No adjunctive treatment (monotherapy)	25	29%	32	37%	
¹ Nominal p-values. Without multiplicity adjustment.					
² Not mutually exclusive					

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the mITT cohort of 173 subjects available for the 10-week randomized controlled trial (RCT), and the 111 subjects completing the additional 10-week open-label phase. Flow FL-100 was well-tolerated in all 173 RCT subjects. There were no serious adverse events (SAEs) attributed to use of the device (Table 7).

As shown in Table 4, the most frequent AEs (active % vs. sham %), based on the Adverse Events Questionnaire (AEQ) included: Skin redness (63.5% vs. 18.5%), Itching (50.6% vs. 43.2%), Burning sensation (43.5% vs. 38.3%), Headache (42.4% vs. 35.8%), and Scalp pain (21.2% vs. 12.3%).

At Week 10, the percentage of active vs. sham subjects reporting at least one AE was 70.1% vs. 59.3%, respectively (Table 5). According to Table 5, headache and tinnitus were reported with similar frequency in the active and sham groups. Two

active group subjects suffered first-degree skin burns. Each subject reported having used dried out headset pads. The burns resolved, and treatment resumed, after a few days.

During Weeks 10 - 20 (Open-label phase), 9% (6/67) of original active group subjects vs. 16.9% (12/ 71) of original sham group subjects, reported at least one AE (Table 6). Notably, dry skin was reported by 4 subjects, all originally randomized to the sham group. No SAEs were reported during the Open-label phase.

Table 4. Anticipated Adverse Events Based on the AEQ [N (%)]

Adverse event category	Active (N = 87)				Sham (N = 86)			
	Total	Mild	Moderate	Severe	Total	Mild	Moderate	Severe
Headache	36 (42.4)	24 (28.2)	11 (12.9)	1 (1.2)	29 (35.8)	18 (22.2)	9 (11.1)	2 (2.5)
Neck pain	2 (2.4)	0 (0)	2 (2.4)	0 (0)	4 (4.9)	1 (1.2)	3 (3.7)	0 (0)
Scalp pain	18 (21.2)	14 (16.5)	3 (3.5)	1 (1.2)	10 (12.3)	7 (8.6)	3 (3.7)	0 (0)
Itching	43 (50.6)	37 (43.5)	3 (3.5)	3 (3.5)	35 (43.2)	28 (34.6)	7 (8.6)	0 (0)
Burning sensation	37 (43.5)	32 (37.6)	4 (4.7)	1 (1.2)	31 (38.3)	25 (30.9)	6 (7.4)	0 (0)
Skin redness	54 (63.5)	42 (49.4)	11 (12.9)	1 (1.2)	15 (18.5)	13 (16.0)	2 (2.5%)	0 (0)
Sleepiness	10 (11.8)	5 (5.9)	4 (4.7)	1 (1.2)	12 (14.8)	9 (11.1)	2 (2.5)	1 (1.1)
Trouble concentrating during stimulation	12 (14.1)	8 (9.4)	3 (3.5)	1 (1.2)	3 (3.7)	2 (2.5)	1 (1.2)	0 (0)
Acute mood change	7 (8.2)	3 (3.5)	3 (3.5)	1 (1.2)	6 (7.4)	5 (6.2)	1 (1.2)	0 (0)

An adverse event was present if the participant rated that it was at least remotely possible that it was associated with the intervention. Participants rated the severity of the adverse events as mild, moderate or severe.

Table 5. All Adverse Events by AE Code, Weeks 0-10, Regardless of Device Relatedness

	Active (N=87)			Sham (N=86)			Group Difference [†]		
	Events	Subjs	%*	Events	Subjs	%*	Δ	LB	UB
All Events	118	61	70.1%	89	51	59.3%	10.8%	-3.6%	25.0%
Blood and lymphatic system disorders	1	1	1.1%	0	0	0.0%	1.1%	-3.3%	6.4%
Lymphadenopathy	1	1	1.1%	0	0	0.0%	1.1%	-3.3%	6.4%
Ear and labyrinth disorders	2	2	2.3%	2	2	2.3%	0.0%	-6.2%	6.0%
Tinnitus	2	2	2.3%	2	2	2.3%	0.0%	-6.2%	6.0%
Eye disorders	4	3	3.4%	1	1	1.2%	2.3%	-3.3%	8.9%
Photopsia	2	2	2.3%	1	1	1.2%	1.1%	-4.5%	7.0%
Vision blurred	2	1	1.1%	0	0	0.0%	1.1%	-3.3%	6.4%
Gastrointestinal disorders	8	6	6.9%	1	1	1.2%	5.7%	-0.4%	13.6%
Diarrhea	1	1	1.1%	0	0	0.0%	1.1%	-3.3%	6.4%
Irritable bowel syndrome	2	2	2.3%	0	0	0.0%	2.3%	-2.2%	8.1%
Nausea	3	2	2.3%	1	1	1.2%	1.1%	-4.5%	7.0%
Vomiting	2	1	1.1%	0	0	0.0%	1.1%	-3.3%	6.4%
General disorders and administration site conditions	3	3	3.4%	4	4	4.7%	-1.2%	-8.5%	5.7%
Chest pain	0	0	0.0%	1	1	1.2%	-1.2%	-6.5%	3.3%
Fatigue	1	1	1.1%	1	1	1.2%	0.0%	-5.5%	5.3%
Malaise	1	1	1.1%	0	0	0.0%	1.1%	-3.3%	6.4%
Pain	1	1	1.1%	2	2	2.3%	-1.2%	-7.2%	4.4%
Infections and infestations	25	22	25.3%	25	19	22.1%	3.2%	-9.8%	16.1%
Bacterial infection	0	0	0.0%	1	1	1.2%	-1.2%	-6.5%	3.3%
COVID-19	6	6	6.9%	5	5	5.8%	1.1%	-7.0%	9.3%
Cystitis	1	1	1.1%	0	0	0.0%	1.1%	-3.3%	6.4%
Gastroenteritis viral	1	1	1.1%	1	1	1.2%	0.0%	-5.5%	5.3%
Influenza	4	3	3.4%	6	6	7.0%	-3.5%	-11.5%	3.7%
Lower respiratory tract infection	1	1	1.1%	1	1	1.2%	0.0%	-5.5%	5.3%
Nasopharyngitis	12	11	12.6%	8	7	8.1%	4.5%	-5.1%	14.5%
Pneumonia	0	0	0.0%	1	1	1.2%	-1.2%	-6.5%	3.3%
Sinusitis	0	0	0.0%	1	1	1.2%	-1.2%	-6.5%	3.3%
Viral infection	0	0	0.0%	1	1	1.2%	-1.2%	-6.5%	3.3%

	Active (N=87)			Sham (N=86)			Group Difference [†]		
	Events	Subjs	%*	Events	Subjs	%*	Δ	LB	UB
Injury, poisoning and procedural complications	4	4	4.6%	0	0	0.0%	4.6%	0.1%	11.4%
Burns first degree	2	2	2.3%	0	0	0.0%	2.3%	-2.2%	8.1%
Head injury	1	1	1.1%	0	0	0.0%	1.1%	-3.3%	6.4%
Limb injury	1	1	1.1%	0	0	0.0%	1.1%	-3.3%	6.4%
Metabolism and nutrition disorders	1	1	1.1%	0	0	0.0%	1.1%	-3.3%	6.4%
Gout	1	1	1.1%	0	0	0.0%	1.1%	-3.3%	6.4%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	1	1.1%	0	0	0.0%	1.1%	-3.3%	6.4%
Acrochordon	1	1	1.1%	0	0	0.0%	1.1%	-3.3%	6.4%
Nervous system disorders	40	31	35.6%	41	30	34.9%	0.7%	-13.7%	15.1%
Burning sensation	1	1	1.1%	1	1	1.2%	0.0%	-5.5%	5.3%
Dizziness	5	3	3.4%	2	2	2.3%	1.1%	-5.2%	8.0%
Dysgeusia	0	0	0.0%	1	1	1.2%	-1.2%	-6.5%	3.3%
Headache	26	25	28.7%	29	24	27.9%	0.8%	-12.7%	14.6%
Hyperaesthesia	0	0	0.0%	1	1	1.2%	-1.2%	-6.5%	3.3%
Migraine	4	3	3.4%	0	0	0.0%	3.4%	-1.0%	9.8%
Migraine with aura	1	1	1.1%	0	0	0.0%	1.1%	-3.3%	6.4%
Ophthalmic migraine	0	0	0.0%	1	1	1.2%	-1.2%	-6.5%	3.3%
Paraesthesia	2	2	2.3%	3	3	3.5%	-1.2%	-8.0%	5.1%
Somnolence	1	1	1.1%	3	3	3.5%	-2.3%	-9.1%	3.3%
Psychiatric disorders	5	4	4.6%	4	4	4.7%	-0.1%	-7.5%	7.3%
Aggression	0	0	0.0%	1	1	1.2%	-1.2%	-6.5%	3.3%
Anxiety	1	1	1.1%	1	1	1.2%	0.0%	-5.5%	5.3%
Depressed mood	1	1	1.1%	0	0	0.0%	1.1%	-3.3%	6.4%
Insomnia	1	1	1.1%	2	2	2.3%	-1.2%	-7.2%	4.4%
Panic attack	1	1	1.1%	0	0	0.0%	1.1%	-3.3%	6.4%
Tension	1	1	1.1%	0	0	0.0%	1.1%	-3.3%	6.4%
Reproductive system and breast disorders	0	0	0.0%	1	1	1.2%	-1.2%	-6.5%	3.3%
Heavy menstrual bleeding	0	0	0.0%	1	1	1.2%	-1.2%	-6.5%	3.3%
Respiratory, thoracic and	1	1	1.1%	2	1	1.2%	0.0%	-5.5%	5.3%

	Active (N=87)			Sham (N=86)			Group Difference [†]		
	Events	Subjs	%*	Events	Subjs	%*	Δ	LB	UB
mediastinal disorders									
Asthma	0	0	0.0%	1	1	1.2%	-1.2%	-6.5%	3.3%
Dyspnea	0	0	0.0%	1	1	1.2%	-1.2%	-6.5%	3.3%
Oropharyngeal pain	1	1	1.1%	0	0	0.0%	1.1%	-3.3%	6.4%
Skin and subcutaneous tissue disorders	20	17	19.5%	8	8	9.3%	10.2%	-0.4%	21.4%
Acne	1	1	1.1%	1	1	1.2%	0.0%	-5.5%	5.3%
Alopecia	1	1	1.1%	0	0	0.0%	1.1%	-3.3%	6.4%
Dry skin	9	9	10.3%	4	4	4.7%	5.7%	-2.5%	14.8%
Pain of skin	1	1	1.1%	1	1	1.2%	0.0%	-5.5%	5.3%
Pruritus	0	0	0.0%	1	1	1.2%	-1.2%	-6.5%	3.3%
Rash	1	1	1.1%	1	1	1.2%	0.0%	-5.5%	5.3%
Skin irritation	7	6	6.9%	0	0	0.0%	6.9%	1.9%	14.5%
Vascular disorders	3	2	2.3%	0	0	0.0%	2.3%	-2.2%	8.1%
Hot flush	1	1	1.1%	0	0	0.0%	1.1%	-3.3%	6.4%
Hypertension	2	1	1.1%	0	0	0.0%	1.1%	-3.3%	6.4%

Abbreviations: Subjs =subjects, LB=lower bound, UB= upper bound
Δ % difference between active and sham
*Percentage of subjects experiencing the specific event.

Table 6. All Adverse Events by AE Code Weeks 10-20, Regardless of Device Relatedness

	Originally in Active (N=67)			Originally in Sham (N=71)			Group Difference [†]		
	Events	Subjs	%*	Events	Subjs	%*	Δ	LB	UB
All Events	6	6	9.0%	14	12	16.9%	-7.9%	-20.1%	3.7%
Blood and lymphatic system disorders	0	0	0.0%	1	1	1.4%	-1.4%	-7.7%	4.4%
Anemia	0	0	0.0%	1	1	1.4%	-1.4%	-7.7%	4.4%
Ear and labyrinth disorders	1	1	1.5%	1	1	1.4%	0.1%	-6.3%	6.9%
Tinnitus	1	1	1.5%	1	1	1.4%	0.1%	-6.3%	6.9%
Gastrointestinal disorders	0	0	0.0%	1	1	1.4%	-1.4%	-7.7%	4.4%
Nausea	0	0	0.0%	1	1	1.4%	-1.4%	-7.7%	4.4%
General disorders and administration site conditions	0	0	0.0%	2	2	2.8%	-2.8%	-10.0%	3.1%
Asthenia	0	0	0.0%	1	1	1.4%	-1.4%	-7.7%	4.4%
Illness	0	0	0.0%	1	1	1.4%	-1.4%	-7.7%	4.4%
Immune system disorders	1	1	1.5%	0	0	0.0%	1.5%	-3.8%	8.2%

	Originally in Active (N=67)			Originally in Sham (N=71)			Group Difference [†]		
	Events	Subjs	%*	Events	Subjs	%*	Δ	LB	UB
Seasonal allergy	1	1	1.5%	0	0	0.0%	1.5%	-3.8%	8.2%
Infections and infestations	1	1	1.5%	4	4	5.6%	-4.1%	-12.5%	3.1%
COVID-19	0	0	0.0%	2	2	2.8%	-2.8%	-10.0%	3.1%
Lower respiratory tract infection	0	0	0.0%	2	2	2.8%	-2.8%	-10.0%	3.1%
Sinusitis	1	1	1.5%	0	0	0.0%	1.5%	-3.8%	8.2%
Musculoskeletal and connective tissue disorders	1	1	1.5%	0	0	0.0%	1.5%	-3.8%	8.2%
Pain in extremity	1	1	1.5%	0	0	0.0%	1.5%	-3.8%	8.2%
Nervous system disorders	1	1	1.5%	0	0	0.0%	1.5%	-3.8%	8.2%
Headache	1	1	1.5%	0	0	0.0%	1.5%	-3.8%	8.2%
Psychiatric disorders	1	1	1.5%	0	0	0.0%	1.5%	-3.8%	8.2%
Mood Altered	1	1	1.5%	0	0	0.0%	1.5%	-3.8%	8.2%
Reproductive system and breast disorders	0	0	0.0%	1	1	1.4%	-1.4%	-7.7%	4.4%
Pelvic pain	0	0	0.0%	1	1	1.4%	-1.4%	-7.7%	4.4%
Skin and subcutaneous tissue disorders	0	0	0.0%	4	4	5.6%	-5.6%	-13.8%	0.2%
Dry skin	0	0	0.0%	4	4	5.6%	-5.6%	-13.8%	0.2%

Abbreviations: Subjs=subjects, LB=lower bound, UB=upper bound, p= p-value.
Δ % difference between active and sham
*Percentage of subjects experiencing the specific event.
† 95% Confidence Interval.

Table 7. All Serious Adverse Events Weeks 0-10.

All Serious Adverse Events by AE Code mITT Analysis Set (N= 173)										
	Active (N=87)			Sham (N=86)			Group Difference [†]			
	Events	Subjs	%*	Events	Subjs	%*	Δ	LB	UB	p
All Events	1	1	1.1%	0	0	0.0%	1.1%	-3.3%	6.4%	0.999
Vascular disorders	1	1	1.1%	0	0	0.0%	1.1%	-3.3%	6.4%	0.999
Hypertension	1	1	1.1%	0	0	0.0%	1.1%	-3.3%	6.4%	0.999

Abbreviations: Subjs= subjects, LB=lower bound, UB=upper bound, p=p-value.
Δ % difference between active and sham
*Percentage of subjects experiencing the specific event.
† 95% Confidence Interval.

2. Effectiveness Results

The analysis of effectiveness was based on the 173 evaluable patients at the 10-week time point. The prespecified primary and secondary endpoint results are shown in Table 8.

A fully Conditional Specification (FCS) approach was used to produce 20 multiply imputed completed data sets. The FCS approach accommodates nonmonotonicity in the pattern of missing data and requires regression models to be specified for each variable with missing values needing imputation. All models included age, sex, in psychotherapy at baseline, use of any antidepressants at baseline, and treatment group. The resulting completed datasets were combined using Rubin's Rule.

Given that the primary endpoint was statistically met, the secondary endpoints were tested. As pre-specified (see Table 9.), a Hochberg approach was used for controlling multiplicity. The 2-sided p-values (and conversion to 1-sided) are provided along with the corresponding Hochberg-adjusted p-values. After correcting for multiplicity, the secondary endpoints Week 10 HDRS-17-based Remission and Week 10 HDRS-17-based Response are statistically significant based on the covariate-adjusted multiple-imputation-based multiplicity-adjusted 1-sided p-values (Table 8). The Week 10 EQ-5D-3L endpoint is not statistically significant before or after multiplicity correction.

Table 8. Prespecified Primary and Secondary Endpoint Results at Week 10

Endpoint (10 weeks)	Active	Sham	Delta	OR/Cohen's d	p-value ^{2,3}
N (mITT)	87	86	-	-	-
<i>HDRS-17 (baseline)</i>	19.2	19.0	-	-	-
- Mean change	-9.4	-7.1	-2.3	0.37	0.012
- Response rate	54.4%	26.9%	27.5%	3.25	0.001 ³
- Remission rate	44.9%	21.8%	23.1%	2.93	0.004 ³
MADRS (baseline)	24.7	23.9	-	-	-
- Mean change	-11.3	-7.7	-3.6	0.41	0.006 ³
- Response rate	63.0%	31.6%	31.4%	3.70	<0.001 ³
- Remission rate	57.5%	29.4%	28.1%	3.26	0.002 ³
<i>MADRS-s (baseline)</i>	26.8	25.8	-	-	-
- Mean change	-9.9	-6.2	-3.7	0.41	0.009 ³

Endpoint (10 weeks)	Active	Sham	Delta	OR/Cohen's d	p-value ^{2,3}
N (mITT)	87	86	-	-	-
- Response rate	49.1%	24.0%	25.1%	3.06	0.004 ³
- Remission rate	53.8%	23.4%	30.4%	3.83	0.002 ³
EQ-5D-3L (baseline)	0.75	0.75	-	-	-
- Mean change¹	0.08	0.06	0.02	-	0.326 ³

Abbreviations: OR=odds ratio ¹Higher is better ²Two-sided
³Nominal p-values. Without multiplicity adjustment.

Table 9. Multiplicity Analysis

Endpoint	2-sided p-values	1-sided p-values	1-sided Hochberg adjusted p-values
Week 10 HDRS response	0.001	0.0005	0.0015
Week 10 HDRS remission	0.004	0.0020	0.0040
Week 10 EQ-5D-3L	0.326	0.1630	0.1630

- For the primary endpoint (see Figure 4), the Active/Sham between-group mean difference in HDRS-17 scores is -2.3 points in favor of the Active group (p=0.012). This result is statistically significant.
- For the secondary endpoint using the HDRS-17: the Active/Sham between-group difference in response rates is 27.5% higher in favor of the Active group (p=0.001); the between-group difference in remission rates is 23.1% in favor of the Active group (p=0.004). These results are statistically significant.
- For the secondary endpoint using the MADRS: the Active/Sham between-group mean difference in MADRS scores is -3.6 points in favor of the Active group (p=0.006); the between-group difference in response rates is 31.4% higher in favor of the Active group (p=<0.001) the between-group difference in the remission rates is 28.1% higher in favor of the Active group (p=0.002). These results are statistically significant.
- For the secondary endpoint using the EQ-5D-3L, the Active/Sham mean change from baseline to Week 10 is: 0.08 - 0.06 = 0.02 (p=0.326), indicating there was no benefit in Active group subjects compared to Sham group subjects.

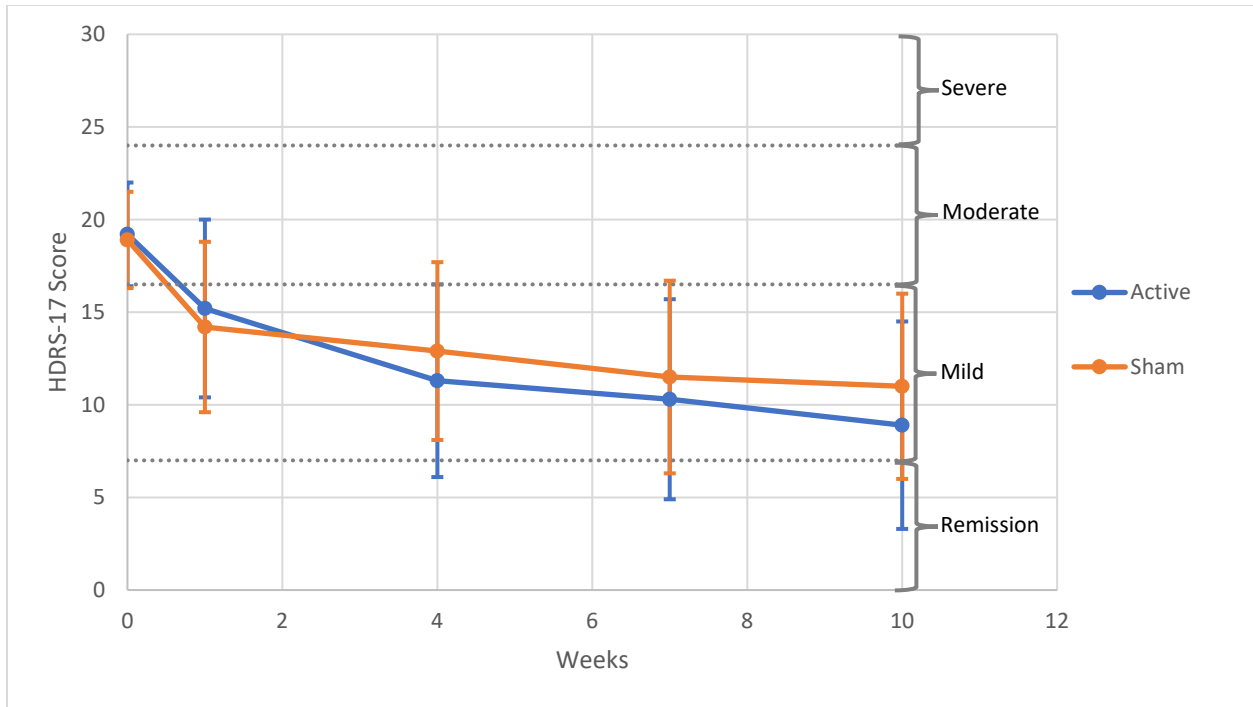


Figure 4. Change in Mean HDRS-17 Scores between Baseline and 10 Weeks, Overlaid with HDRS-17 Depression Symptom Severity Levels

3. Subgroup Analyses

Subgroup analyses showed no interaction between site- gender-, age-, race- and treatment effect, suggesting that the data is poolable. No subgroup analysis was performed for ethnicity.

Table 10. Results for FL-100 Users without any Adjunctive Treatment (FL-100 as Monotherapy)

HDRS-17	Active vs Sham, Week 10, OC (mITT)			
Subgroup	Mean score change	Response rate	Remission rate	N
<i>Monotherapy</i> ¹	-9.7 vs -5.9, delta: -3.8, Cohen's d: 0.56, p=0.0027.	47.8% vs 13.8%, OR=5.76, p<0.0001	34.8% vs 13.8%, OR=3.29, p=0.0027	23 vs 29, 52 (35%)

¹Observed cases (subjects with complete week 10 data. Only 4 subjects with FL-100 as monotherapy did not reach Week 10

Table 11. Results for FL-100 Users on an Antidepressant (AD)

HDRS-17	Active vs Sham, Week 10, mITT			
Subgroup	Mean score change	Response rate	Remission rate	N
<i>On AD</i>	-10.6 vs -7.8, delta: -2.8, Cohen's d: 0.46, p=0.019	63.2% vs 35.4%, OR=3.14, p=0.010	53.1% vs 25.5%, OR=3.33, p=0.009	56 vs 53

4. Blinding

A blinding assessment was conducted at Week 10: Prior to subjects unblinding through the system they were asked to respond to the question “Which treatment arm do you think you are in?” (answers: sham/active), followed by the question “How certain are you of this?”, with the options 1 to 5 where 5 is very certain and 1 is very uncertain.

In the active group, 77.6% correctly guessed they received active treatment, while in the sham group 40.7% correctly guessed they received sham treatment (Table 12). This constitutes a statistically significant difference (p=0.012).

Table 12. Post-treatment Blinding Assessment Results

Real arm	Gessed active [N (%)]	Gessed sham [N (%)]
Active	66 (77.6%)	19 (22.4%)
Sham	48 (59.3%)	33 (40.7%)

Note: Seven withdrawn subjects did not perform the blinding assessment. Therefore, the total N is 166.

Table 13 shows the change in HDRS-17 score, response rate and remission rate at Week 10 were, respectively, highest in the Active/Gessed Active group (-11.14, 61.4%, 50.9%) and lowest in the Sham/Gessed Sham group (-6.66, 15.6%, 15.6%). Comparing the Week 10 outcomes between the Active/Gessed Sham and Sham/Gessed Active groups, the Sham/Gessed Active Group had a greater reduction in HDRS-17 score (-8.58 versus -7.24), higher response rate (37.2% versus 35.3%) and lower remission rate (27.9% versus 29.4%).

Table 13. Mean HDRS-17 Change, Response/Remission Rates at Week 10, Guessed Arm with any Certainty, 1 to 5

HDRS-17	Guessed arm, with any certainty (options 1 to 5, where 5 is very certain and 1 is very uncertain)							
N = 149	Guessed Active				Guessed Sham			
Real arm	Change	Response	Remission	N	Change	Response	Remission	N
Active	-11.14	61.4%	50.9%	57	-7.24	35.3%	29.4%	17
Comparison	delta: -2.56	OR: 2.66, p: 0.014*	OR: 2.65, p: 0.017	-	delta: -0.58	OR: 2.87, p: 0.11	OR: 2.21, p: 0.22	-
Sham	-8.58	37.2%	27.9%	43	-6.66	15.6%	15.6%	32

Table 14 shows the change in HDRS-17 score, response and remission rates at Week 10 were, respectively, highest in the Active/Guessed Active group (-11.78, 68%, 56.0%) and lowest in the Sham/Guessed Sham group (-6.52, 14.3%, 14.3%). Comparing the Week 10 outcomes between the Active/Guessed Sham and Sham/Guessed Active groups, the Sham/Guessed Active group had a greater reduction in HDRS-17 score (-9.0 versus -7.46), higher response rate (44.4% versus 38.5%) and higher remission rate (33.3% versus 30.8%).

Table 14. Mean HDRS-17 change, response/remission rates at Week 10, Guessed Arm with certainty ≥ 3 *

HDRS-17	Guessed arm, with certainty ≥ 3							
N = 120	Guessed Active				Guessed Sham			
Real arm	Change	Response	Remission	N	Change	Response	Remission	N
Active	-11.78	68.0%	56.0%	50	-7.46	38.5%	30.8%	13
Comparison	delta: -2.78	OR: 2.62, p: 0.0248*	OR: 2.52, p: 0.031	-	delta: -0.94	OR: 3.59, p: 0.12	OR: 2.59, p: 0.23	-
Sham	-9.0	44.4%	33.3%	36	-6.52	14.3%	14.3%	21

To estimate what the results would have been if the active guesses for both arms were balanced, the adjusted HDRS-17 mean changes was calculated. Table 15 shows that the balanced guesses resulted in a between-group difference of -2.12 points, which is 0.35 points below the original results.

The analysis in Table 15 was also complemented by a similar method; Correct Guess Rate (CGR) adjustment¹⁵. CGR estimates the distribution of score changes for the $2 \times 2 = 4$ subgroups based on the real and guessed arm and then resamples

(with replacement) the data so as to create a dataset where guesses are perfectly balanced. After adjustment, CGR yields a between-group mean change of -2.0 points on HDRS-17.

Table 15. Adjusted HDRS-17 Mean Change Score (Observed Cases) Based on Balanced Blinding Guesses

<i>Real arm</i>	<i>Guessed active</i>	<i>Guessed sham</i>	<i>Original results</i>	<i>Adjusted results</i>
<i>Active</i>	-11.14 (77.6% ¹)	-7.24	-10.27	-10.27
<i>Sham</i>	-8.58 (59.3% ¹)	-6.66	-7.80	-8.15 ²
<i>Difference</i>			-10.27 - 7.80 = -2.47	-10.27 - 8.15 = -2.12

¹Percentage of the group that guessed active.

²Rebalanced sham result at 77.6% active guesses: $-8.58 \times 0.776 - 6.66 \times (1 - 0.776) = -8.15$

5. Open-label Phase Results

In the active group, a total of 55 (55/87=63.2%) participants completed the additional 10-week open-label phase (Table 16). 30 of the 31 participants (97%) who showed a treatment response (HDRS-17) during the 10-week blinded phase continued to show a treatment response at Week 20. Of the 24 participants in the active group who did not show a treatment response during the blinded phase, 9 participants (38%) showed a treatment response at Week 20.

In the sham group, 10 of the 12 participants (83%) who showed a treatment response in the 10-week blinded phase continued to show a treatment response at Week 20. Of the 44 sham group participants who did not show a treatment response in the blinded phase, 22 (50%) showed a treatment response at Week 20.

Table 16. Responders (HDRS-17) at Week 20 Based on Response at Week 10.

Active group	N at Week 10	Responders at Week 20 [N (%)]
<i>Week 10 responders</i>	31	30 (97%)
<i>Week 10 nonresponders</i>	24	9 (38%)
<i>Total</i>	55	39 (71%)
Sham group		
<i>Week 10 responders</i>	12	10 (83%)
<i>Week 10 nonresponders</i>	44	22 (50%)
<i>Total</i>	56	32 (57%)

6. 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 2 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

Flow FL-100 was the subject device in a single-center, 3-arm, randomized, double-blind, sham-controlled clinical trial conducted at Hospital Universitário in São Paulo, Brazil (NCT04889976).³ The study, titled “Portable Transcranial Electrical Stimulation and Internet-Based Behavioral Therapy for Major Depression Study (PSYLECT)”, was designed to evaluate the efficacy, safety, tolerability and usability of: (1) active tDCS (Flow FL-100) with active internet behavioral therapy (iBT) (“double active”); (2) active tDCS (Flow FL-100) with sham iBT (“tDCS only”); and (3) sham tDCS (sham Flow FL-100) + sham iBT (“double sham”) in adults with MDD with a HDRS-17 score ≥ 17 at baseline, during 6 weeks. No antidepressant washouts were performed during the trial.

Interventions: tDCS was administered in 2-mA, 30-minute prefrontal sessions for 15 consecutive weekdays (1-mA, 90-second duration for sham) and twice-weekly sessions for 3 weeks. The digital intervention consisted of 46 sessions based on behavioral therapy. Digital placebo was internet browsing.

Main Outcomes and Measures: Change in HDRS-17 score at Week 6.

Results: Of 837 volunteers screened, 210 participants were enrolled (180 [86%] female; mean [SD] age, 38.9 [9.3] years) and allocated to double active (n = 64), tDCS only (n = 73), or double sham (n = 73). Of the 210 participants enrolled, 199 finished the trial. Linear mixed-effects models did not reveal statistically significant group differences in treatment by time interactions for HDRS-17 scores, and the estimated effect sizes between groups were as follows: double active vs tDCS only (Cohen d, 0.05; 95%CI, -0.48 to 0.58; P = .86), double active vs double sham (Cohen d, -0.20; 95%CI, -0.73 to 0.34; P = .47), and tDCS only vs double sham (Cohen d, -0.25; 95%CI, -0.76 to 0.27; P = .35). Skin redness and heat or burning sensations were more

frequent in the double active and tDCS only groups. One nonfatal suicide attempt occurred in the tDCS only group.

Conclusions and Relevance: Unsupervised home-use tDCS combined with a digital psychological intervention or digital placebo was not found to be superior to sham for treatment of a major depressive episode in this trial.

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

The effectiveness data from the Empower RCT study are based on the cohort of 173 randomized subjects that received at least one stimulation session (mITT) with the Flow FL-100 device (1 subject was randomized but never used the device). Subjects were randomized in a 1:1 ratio to either receive active or sham stimulation for 10 weeks (blinded period). All assessments were completed by blinded personnel.

1. The effectiveness outcomes at Week 10 are summarized as follows:

- Clinically meaningful between-group differences for the primary and secondary outcomes were not prespecified.
- The Active/Sham 2.3-point between-group difference in HDRS-17 scores at Week 10 meets a pre-specified statistical primary endpoint. The medical literature lacks consensus regarding what constitutes a clinically significant or meaningful between-group difference in HDRS-17 scores. As such, the clinical significance or meaningfulness of the between-group difference of -2.3 points on the HDRS-17 scale has not been established. Nevertheless, the 2.3 point between-group difference helps support the view that FL-100 provides probable benefit.
- The prespecified HDRS-17 secondary endpoint (adjusted for multiplicity) analyses demonstrate statistically significant between-group differences in: (a) response rates = 27.5% (54.4% in the Active arm compared to 26.9% in the Sham arm, OR=3.25) and (b) remission rates = 23.1% (44.9% in the Active arm compared to 21.8% in the Sham arm, OR=2.93);

- The primary and secondary HDRS-17 results are further supported by the Active versus Sham between-group difference in response and remission rates (secondary endpoints, not adjusted for multiplicity), respectively, on the MADRS (31.4%, OR=3.70; 28.1%, OR=3.2) and the MADRS-s (25.1%, OR=3.06; 30.4%, OR=3.83). These differences are statistically significant.
- The EQ-5D-3L measures a person's health-related quality of life by assessing five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. There was no between-group statistical difference in EQ-5D-3L scores at Week 10. The EQ-5D-3L frequently fails to detect mild depressive symptoms, as individuals with subclinical depression often select "no problems" on the anxiety/depression dimension. The insensitivity of EQ-5D-3L is documented in the literature.¹⁴
- Monotherapy vs. Adjunctive FL-100 Use
 - In the subgroup (N=52) who used the FL-100 as monotherapy (i.e., no adjunctive treatment): HDRS-17 response rate was 47.8% in the active group compared to 13.8% in the sham group (delta=34%, OR=5.76); the HDRS-17 remission rate was 34.8% in the active group compared to 13.8% in the sham group (delta=21.0%, OR=3.33).
 - In the subgroup who used FL-100 adjunctively (i.e., with antidepressant medication): HDRS-17 response rate was 63.2% in the active group compared to 35.4% in the sham group (delta=27.8%, OR=3.14); the HDRS-17 remission rate was 53.1% in the active group compared to 25.5% in (delta=27.6%, OR=3.33).
 - Data were not provided regarding FL-100 used adjunctively with psychotherapy or with psychotherapy and antidepressant medication.
- The blinding assessment showed that 77.6% of active subjects correctly guessed their group whereas 40.7% of sham subjects correctly guessed their group (Table 12), constituting a significant difference (p=0.012) that raised uncertainty about the adequacy of blinding due to study bias. This uncertainty was heightened when comparing the data in Tables 13 and 14 between the Sham – Guessed Active and the Active – Guessed Sham groups.

A post-hoc device blinding study was conducted to determine whether the active and sham devices were indistinguishable, in order to validate the sham. Additional analyses performed showed the adjusted mean change score based on balance blinding guesses would have been a slight decrease in group difference. Therefore, the post-hoc device blinding study and blinding analyses adequately addressed the earlier uncertainty associated with the unbalanced blinding assessment results.

- Patients who previously had an inadequate clinical response to two or more antidepressants at an adequate dose and duration were excluded from the study, limiting the evidence for use of the FL-100 in a more treatment resistant population.

2. Outcomes from Weeks 10-20 (Open-label phase)

At Week 20, a total of 55 participants from the original active group completed the 10-week open-label phase. 30 of the 31 participants (97%) who were responders at Week 10 (HDRS-17 reduction $\geq 50\%$), were responders at Week 20. Of the 24 participants in the original active group who were not HDRS-17 responders at Week 10, 9 participants (38%) showed a treatment response at Week 20. Open-label data does not account for a device placebo effect and cannot be used to determine device effectiveness.

At Week 20, 10 of the 12 original sham group participants (83%) who showed a treatment response at Week 10 continued to show a treatment response at Week 20. Of the 44 sham group participants who did not show a treatment response at Week 10, 22 (50%) showed a treatment response at Week 20.

B. Safety Conclusions

The risks of the device are based on data collected in the clinical study conducted to support PMA approval as described above.

When comparing the device-related adverse events between the active and sham group, only Skin and subcutaneous tissue disorders display a difference greater than 5% (Table 5), which is expected because longer exposure to the stimulation current causes skin irritation and dry skin in some subjects. This difference is also represented in the AEQ for Skin redness related to the device.

Two cases of mild, superficial skin burns (first-degree burns) were reported. The burns healed without sequelae. In both cases, the participant used dried-out electrode pads, a known cause of skin burns. Treatment was resumed after a few days.

Notably, headaches were reported in both groups at almost equal rates. Headaches were generally mild in severity. Consistent with the medical literature^{10,13}, the most frequent adverse events (AEs) (active % vs. sham %) were skin redness (63.5% vs. 18.5%), itching (50.6% vs. 43.2%), burning sensation (43.5% vs. 38.3%), headache (42.4% vs. 35.8%), and scalp pain (21.2% vs. 12.3%). No serious adverse events, including hypomania, mania, or suicidality, were observed in the study.

In conclusion, the FL-100 presents some probable risks, but the probable risks are low.

C. Benefit-Risk Determination

The totality of the evidence demonstrates FL-100 provides probable benefit to persons at least 18 years of age with major depressive disorder (MDD), that, while modest, is sufficient to outweigh its probable risk. Uncertainty of benefit due to unblinding, lack of a prespecified clinically significant change in HDRS-17 scores, and conflicting results from the literature was evaluated. The FL-100 presents some probable risks, but the probable risks are low. The risks are, in general, mild and transient. The main risks of the device are skin dryness, skin irritation or redness after prolonged use and transient headache. Stinging, burning, or itching sensations at the stimulation site are also common. Skin burns have been reported in cases of electrode pad reuse or use of dried-out electrode pads.

Overall, the evidence is adequate to demonstrate a reasonable assurance that FL-100 is safe and effective under the conditions of use described in the indications of use.

Additional factors that were considered in determining probable risks and benefits for the FL-100 device include:

- The clinical study had high compliance with less than 15% attrition.
- The randomized controlled trial had two sites in distinct geographic locations (UK and US, Texas) supporting the generalizability of the results.
- The FL-100 showed a probable clinical benefit as a standalone treatment in the clinical study and as an adjunctive treatment with antidepressant medication.
- The ability for home use of the device 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 long presence of the device on the European market.

D. Patient Perspective

This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

E. Overall Conclusions

In conclusion, given the available information above, the data support that for the indication for use of the FL-100 device, the probable benefits outweigh the probable risks.

XVI. CDRH DECISION

CDRH issued an approval order on December 8, 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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