January 11, 2024

Darmiyan, Inc.
℅ John Doucet, Ph.D.
Vice President, Neurology Regulatory Affairs
MCRA, LLC
803 7th Street NW, 3rd Floor
Washington, District of Columbia 20001

Re: DEN220066
Trade/Device Name: BrainSee
Regulation Number: 21 CFR 882.1454
Regulation Name: Prognostic assessment software of mild cognitive impairment
Regulatory Class: Class II
Product Code: QWT
Dated: September 26, 2022
Received: September 29, 2022

Dear Dr. Doucet:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your De Novo request for classification of the BrainSee, a prescription device under 21 CFR Part 801.109 with the following indications for use:

> "BrainSee is a software application indicated as a prognostic tool to aid in the clinical assessment of how likely patients aged between 55 and 95 years old who are diagnosed with amnestic mild cognitive impairment (aMCI) are to progress to clinical Alzheimer's disease (AD)-dementia within 5 years of assessment. BrainSee analyzes inputs of brain magnetic resonance imaging (MRI), patient demographic information, and cognitive assessment scores to produce a similarity score between 0 and 100 reflecting the degree of similarity between the patient and two reference populations of aMCI patients who either did not progress to clinical AD-dementia within 5 years (non-converters) or progressed to clinical AD-dementia within 5 years (converters). Clinical AD-dementia is defined as probable Alzheimer's disease established according to the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Alzheimer's Criteria.
>
> - Similarity scores less than 50 indicate that a patient's inputs are more similar to those of the non-converter population.
> - Similarity scores greater than 50 indicate that a patient's inputs are more similar to those of the converter population.
> - Patients with a similarity score close to 50 have inputs that are similar to both the converter and non-converter aMCI patient populations used to develop and train the BrainSee device.

> The similarity score output is provided along with information to assist in the interpretation of the output to aid in evaluating the prognosis of patients diagnosed with aMCI to progress to clinical AD-dementia within 5 years.
>
> The BrainSee analysis is intended to provide supplemental information for interpretation in conjunction with a standard neurological assessment. Patient management decisions should not be made solely on the results of the BrainSee analysis. BrainSee is not indicated as a stand-alone diagnostic or prognostic tool. BrainSee should not be used to diagnose aMCI."

FDA concludes that this device should be classified into Class II. This order, therefore, classifies the BrainSee, and substantially equivalent devices of this generic type, into Class II under the generic name Prognostic assessment software of mild cognitive impairment.

FDA identifies this generic type of device as:

> **Prognostic assessment software of mild cognitive impairment**. Prognostic assessment software of mild cognitive impairment is a prescription-only device that combines information from multiple clinical data sources to produce an output indicative of the likelihood that a patient diagnosed with mild cognitive impairment will progress to more severe forms of cognitive impairment, or will develop dementia, such as Alzheimer's disease dementia, within a specified period of time. This device is intended for adjunctive use and not intended as a stand-alone diagnostic or prognostic tool.

Section 513(f)(2) of the Food, Drug and Cosmetic Act (the FD&C Act) was amended by section 607 of the Food and Drug Administration Safety and Innovation Act (FDASIA) on July 9, 2012. This law provides two options for De Novo classification. First, any person who receives a "not substantially equivalent" (NSE) determination in response to a 510(k) for a device that has not been previously classified under the Act may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act. On December 13, 2016, the 21st Century Cures Act removed a requirement that a De Novo request be submitted within 30 days of receiving an NSE determination. Alternatively, any person who determines that there is no legally marketed device upon which to base a determination of substantial equivalence may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act without first submitting a 510(k). FDA shall, within 120 days of receiving such a request, classify the device. This classification shall be the initial classification of the device. Within 30 days after the issuance of an order classifying the device, FDA must publish a notice in the Federal Register announcing the classification.

On September 29, 2022, FDA received your De Novo requesting classification of the BrainSee. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the BrainSee into class I or II, it is necessary that the proposed class have sufficient regulatory controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use. After review of the information submitted in the De Novo request FDA has determined that, for the previously stated indications for use, the BrainSee can be classified in class II with the establishment of special controls for class II. FDA believes that class II (special) controls provide reasonable assurance of the safety and effectiveness of the device type. The identified risks to health are shown in the table below. The identified risks and mitigation measures associated with the device type are summarized in the following table:

Identified Risks to Health	Mitigation Measures
Device failure or incorrect analysis leading to: • False positives or falsely high prognostic outputs resulting in inappropriate patient treatment and delayed diagnosis of non-Alzheimer's disease conditions • False negatives or falsely low prognostic outputs resulting in delayed diagnosis and/or patient treatment	Clinical performance testing Postmarket surveillance Software verification, validation, and hazard analysis Labeling
Use error or misinterpretation of results leading to: • A false positive or falsely high prognostic outputs • A false negative or falsely low prognostic outputs • Overreliance on device output for follow-up	Human factors/usability assessment Labeling

In combination with the general controls of the FD&C Act, the Prognostic assessment software of mild cognitive impairment is subject to the following special controls:

(1) Data obtained from premarket clinical performance validation testing and postmarket surveillance acquired under anticipated conditions of use must demonstrate that the device performs as intended when used to analyze data from the intended patient population, unless FDA determines based on the totality of the information provided for premarket review that data from postmarket surveillance is not required.
   (i) Data provided from (1) must demonstrate the accuracy, precision, and reproducibility of the device for predicting progression of patients with mild cognitive impairment to more severe forms of cognitive impairment or to dementia, such as Alzheimer's disease dementia, based on a clinically relevant reference standard for the diagnosis of such disease states or conditions. The test data set must include data acquired from a patient population that is representative of the intended patient population normally seen in clinical practice. The test data set must be independent from data used in training/development of the device.
   (ii) Objective performance measures (e.g., sensitivity, specificity, positive predictive value, and negative predictive value) must be reported with relevant descriptive or developmental performance measures.

(2) Software verification, validation, and hazard analysis must be provided. Software documentation must include a detailed, technical description of the model/algorithm(s), and algorithm inputs and outputs.

(3) Human factors/usability assessment must demonstrate that the intended user(s) in the intended use environment can correctly use the device and interpret the device output(s).

(4) Physician labeling must include:
   (i) A detailed summary of the clinical performance testing methods, including results of the performance testing for tested performance measures/metrics, selection criteria, and the patient demographics;
   (ii) A description of the patient population that was used in development or training of the device algorithm/model;

(iii) Device limitations or subpopulations for which the device may not perform as expected or for whom the device has not been validated;
(iv) A statement that the device is not a stand-alone diagnostic or prognostic tool and that the device output should only be interpreted in the context of all available clinical information, including patient history, medications, and comorbidities; and
(v) Information for interpretation of the device outputs detailing the risks associated with misinterpretation of the device outputs.

(5) Patient labeling must include information explaining the device output(s) and the associated risks if the device output is incorrect.

In order to satisfy special control (1) above, FDA has determined that you must collect and report postmarket surveillance data acquired under anticipated conditions of use to demonstrate that the device performs as intended when used to analyze data from the intended patient population. Specifically, you must conduct postmarket clinical validation performance testing of the BrainSee device in patients from demographic groups representative of the United States (U.S.) population, to include patients of diverse race, socioeconomic status, levels of education, who are from community-based care settings, and having comorbidities which may impact the effectiveness of the device.

FDA expects that the postmarket clinical validation performance testing will include a statistically justified study sample size of aMCI patients, with at least 50% of patients from community-based healthcare settings, and adequate to allow for inclusion of patients with diverse demographics to include race, socioeconomic status, and education levels representative of the intended use population in the U.S. The study should enroll at least 50% of patients who are non-Caucasian, including Black, Hispanic, Asian, or other minority populations in the U.S. The study should record patient comorbidities, age, sex, education level, socioeconomic status, race, and cognitive test scores using the Mini Mental State Examination (MMSE) and Clinical Dementia Rating (CDR), and assess their impact on the device's effectiveness as measured by sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The study should use probable Alzheimer's disease as defined by the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Alzheimer's Criteria to determine the presence or absence of clinical AD-dementia.

Within 30 days of receipt of this order, you must submit a complete study protocol for your study as described above. FDA expects to work with you to approve your study protocol within 60 days of this order. Your submission should be clearly labeled as a "De Novo Postmarket Study Protocol" and submitted to the Agency as specified below. Please reference the De Novo number above to facilitate processing. If there are multiple protocols being finalized after granting of this De Novo request, please submit each protocol as a separate submission, identified by their unique study name(s).

From the date of postmarket study protocol approval, you must meet the following timelines:

- First subject enrolled within 6 months
- 20% of subjects enrolled within 12 months
- 50% of subjects enrolled within 18 months
- 100% of subjects enrolled within 24 months

In addition, you must submit separate periodic reports on the progress of the new enrollment postmarket study as follows:

- Postmarket surveillance progress reports every six (6) months until subject enrollment has been completed, and annually thereafter, from the date of the protocol approval letter, unless otherwise specified by FDA.
- If any enrollment milestones are not met, you must begin submitting quarterly enrollment status reports every three (3) months in addition to your periodic postmarket surveillance progress reports, until enrollment has been completed or FDA notifies you otherwise.
- Submit the final postmarket surveillance report three (3) months from study completion (i.e., last subject's last follow-up date).

Each postmarket surveillance report should be submitted to the Agency as specified below, identified as a "De Novo Postmarket Surveillance Report" in accordance with how the study is identified above, and bearing the applicable De Novo reference number.

Be advised that failure to comply with any special control requirement, including the initiation, enrollment, completion, and reporting per the postmarket surveillance data requirements outlined above, may result in the adulteration and misbranding of your device.

In addition, this is a prescription device and must comply with 21 CFR 801.109.

Although this letter refers to your product as a device, please be aware that some granted products may instead be combination products. If you have questions on whether your product is a combination product, contact CDRHProductJurisdiction@fda.hhs.gov.

Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act, if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device type. FDA has determined premarket notification is necessary to provide reasonable assurance of the safety and effectiveness of the device type and, therefore, the device is not exempt from the premarket notification requirements of the FD&C Act. Thus, persons who intend to market this device type must submit a premarket notification containing information on the prognostic assessment software for progression of mild cognitive impairment they intend to market prior to marketing the device.

Please be advised that FDA's decision to grant this De Novo request does not mean that FDA has made a determination that your device complies with other requirements of the FD&C Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the FD&C Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and if applicable, the electronic product radiation control provisions (Sections 531-542 of the FD&C Act; 21 CFR 1000-1050).

A notice announcing this classification order will be published in the Federal Register. A copy of this order and supporting documentation are on file in the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852 and are available for inspection between 9 a.m. and 4 p.m., Monday through Friday.

As a result of this order, you may immediately market your device as described in the De Novo request, subject to the general control provisions of the FD&C Act and the special controls identified in this order.

For comprehensive regulatory information about medical devices and radiation-emitting products, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

All required documents should be submitted, unless otherwise specified, to the address below and should reference the above De Novo number to facilitate processing.

De Novo Postmarket Surveillance
U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Alternatively, documents can be submitted electronically through the CDRH Portal. For more information on the CDRH Portal, please visit https://www.fda.gov/medical-devices/industry-medical-devices/send-and-track-medical-device-premarket-submissions-online-cdrh-portal.

If you have any questions concerning the contents of the letter, please contact Michael McKnight, Ph.D. at michael.mcknight@fda.hhs.gov.

Sincerely,

David P. Mc Mullen -S

Digitally signed by David P. Mc Mullen -S
Date: 2024.01.11 15:56:08 -08'00'

David P. McMullen, MD
Director
OHT5: Office of Neurological
and Physical Medicine Devices
Office of Product Evaluation and Quality
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