DE NOVO CLASSIFICATION REQUEST FOR

BRAINSEE

REGULATORY INFORMATION

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.

NEW REGULATION NUMBER: 21 CFR 882.1454

CLASSIFICATION: Class II

PRODUCT CODE: QWT

BACKGROUND

DEVICE NAME: BrainSee

SUBMISSION NUMBER: DEN220066

DATE DE NOVO RECEIVED: September 29, 2022

SPONSOR INFORMATION:

Darmiyan, Inc.
1425 Berkeley Way
Berkeley, CA 94702

INDICATIONS FOR USE

The BrainSee is indicated as follows:

> "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."

LIMITATIONS

The sale, distribution, and use of BrainSee are restricted to prescription use in accordance with 21 CFR 801.109.

The device is not intended for use as a stand-alone diagnostic or prognostic device but as an adjunct to the diagnostic process.

The device is intended for use in conjunction with patient history, clinical observations, and other clinical evidence the healthcare provider determines are necessary before making clinical decisions. For instance, additional follow-up evaluations at a future time point may be sought, especially when the device similarity score is at or near 50.

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

BrainSee is a software as a medical device (SaMD) intended to aid clinicians in evaluating the prognosis of patients diagnosed with amnestic mild cognitive impairment (aMCI). The software provides the clinician with a score between 0 and 100, which reflects the degree of similarity

between the patient (in terms of cognitive profile and brain magnetic resonance imaging [MRI] features) and two reference aMCI patient populations of converters and non-converters that were used to develop the software. Conversion is defined as progression from aMCI to clinical Alzheimer's disease dementia (AD-dementia) within 5 years, where 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.

To calculate the similarity score, BrainSee uses:

1. Cognitive/behavioral test scores, including scores from the Mini-Mental State Examination (MMSE) and Clinical Dementia Rating Sum of Boxes (CDRSumBox) provided by the clinician.
2. The patient's age and sex.
3. Brain tissue volumes measured from T1-weighted brain MRI.

BrainSee is offered to clinicians through a cloud-based platform. Clinicians access the platform via a web portal, where they can add patient records, enter the required clinical information, upload brain MRI scans, and view, download, and print the output report.

BrainSee uses standard 3-dimensional T1-weighted MRI sequences obtained at 1.5 Tesla (T) or 3 T, and does not require any special MRI scan parameters, contrast agent, or additional hardware.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BrainSee is a SaMD implemented on a general-purpose computing platform. Nonclinical or bench testing was generally not needed to evaluate the hardware that the software is intended to be run on. Software documentation was provided to demonstrate the safety and effectiveness of the device.

SOFTWARE

Software verification and validation testing and documentation was provided according to a MODERATE level of concern and FDA's guidance document, "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices" (May 11, 2005), to demonstrate that the device software performs as intended. Adequate documentation describing the software, software specifications, architecture design, software development environment, traceability, revision level history, and unresolved anomalies conclude that the software will operate in the manner described in the specifications. A hazard analysis characterized the software and cybersecurity risks, including those related to device malfunction, user-related error, and network connectivity. The software verification and validation testing addressed all identified hazards with satisfactory results. The device algorithm was provided describing how the data are collected and analyzed by the underlying model that is applied to produce the final device outputs.

HUMAN FACTORS - USABILITY

A simulated use test was performed in which participants interacted with the device software in realistic use scenarios under simulated clinical conditions. Participants were observed as they completed each task and were asked to provide subjective feedback at the conclusion of each use scenario to gain their perspectives on device use and any problems observed. Objective data was collected by observing task performance during each scenario and any problems were recorded as use errors, close calls, or use difficulties. The testing was performed with a total of 15 participants who had residency or fellowship training that included evaluating and caring for adult patients with cognitive impairment, and who are trained in either neurology, geriatrics, psychiatry, family practice, or internal medicine.

Participants performed critical tasks related to use of the device software interface, input of patient data for analysis, and interpreting the device outputs. Study results indicated that most participants were able to complete all eight critical tasks; however, three use errors occurred where the user either did not understand the meaning of the device outputs or did not understand the device's indications.

SUMMARY OF CLINICAL INFORMATION

Study Design

The clinical validation study was a retrospective algorithm performance validation study conducted using data collected at 27 North American sites to evaluate the prognostic capability of the BrainSee algorithm for predicting conversion of aMCI to clinical AD-dementia within 5 years based on a comparison to the clinical reference standard diagnosis. Each patient had at least two clinical visits, and at each clinical visit a neurocognitive clinical diagnosis of either aMCI or AD-dementia was determined by a panel of clinicians trained to perform this task (e.g., geriatrician, neurologist, psychiatrist).

Clinical Reference Standards

The clinical reference standard used to classify converters and non-converters is based on the neurocognitive clinical diagnosis of either aMCI or AD-dementia at each clinical visit.

Amnestic mild cognitive impairment (aMCI) was defined as impaired memory and cognition, with no significant impairment in the instrumental activities of daily living (iADLs). Patients diagnosed with aMCI were defined by having all of the following:

- Presence of a subjective memory concern; AND
- Abnormal memory function documented by the clinician; AND
- Impairments in two or more cognitive domains; AND
- No significant impairment in the iADLs.

AD-dementia was defined as "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, which is also known as clinical Alzheimer's disease.

For prognostic ground truth labeling, aMCI cases who progressed to AD-dementia within 5 years were labeled as a converter, and aMCI cases who did not progress to AD-dementia (remained aMCI) for at least 5 years were labeled as a non-converter. All ground truth labels were reviewed and confirmed by consensus of three physicians with clinical experience evaluating aMCI patients.

Device Converter/Non-converter Classification

For device classification labeling, aMCI cases who received a similarity score output greater than 50 based on the device analysis were labeled as a converter, and aMCI cases who received a similarity score output less than 50 were labeled as a non-converter.

Inclusion Criteria

- Patients in the age between 55-95 years.
- Patients diagnosed with aMCI, defined by having all of the following:
    - Presence of a subjective memory concern; AND
    - Abnormal memory function documented by the clinician; AND
    - Impairments in two or more cognitive domains; AND
    - No significant impairment in the iADLs.
- Availability of a non-contrast, T1-weighted, whole brain MRI scan, with:
    - Field strength between 1.5 T and 3.0 T; AND
    - Voxel resolution < 1.31 mm in all dimensions; AND
    - Good image quality, based on expert visual inspection confirming clear gray matter – white matter (GM-WM) differentiation, and absence of major image artifacts such as distortion, motion, susceptibility, and aliasing.

Exclusion Criteria

- Normal cognition or dementia of any type.
- Parkinson's disease, Huntington's disease, progressive supranuclear palsy.
- Diagnosis of normal pressure hydrocephalus (NPH).
- Brain tumor, seizure disorder, subdural hematoma, multiple sclerosis.
- History of significant head trauma followed by persistent neurologic deficits.
- Brain infection, infarction, or stroke.
- Focal lesions or lacunes in a critical memory structure.
- Poor MRI image quality, or major image artifacts (see inclusion criteria for details).

Objectives

Primary Effectiveness Objectives

- Sensitivity > 70% based on pre-defined classification threshold.
- Specificity > 70% based on pre-defined classification threshold.

Results

Enrollment

A total of 198 aMCI patients meeting all study eligibility criteria and had sufficient follow-up to define the ground truth from 27 different hospitals were identified for retrospective analysis in

the pivotal study. These 198 aMCI subjects' data are used for the validation of the BrainSee device and the data from these subjects are presented in Tables 1-5. An additional 209 patients from these clinical sites met the selection criteria for the study but were not included for analysis because they had an undefined ground truth. Most of these had an undefined ground truth because they did not complete 5 years of follow-up either for reasons unrelated to the cognitive health (e.g., late entry to study) or for reasons that might be attributable to the burdens of such longitudinal follow-up on an elderly population (e.g., consent withdrawn, lost to follow-up, missed visits). The race, sex, and age characteristics of the patient population that was included in this validation data set (N=198) are detailed in Tables 1 through 3 below.

Table 1: Summary of Clinical Validation Data Distribution by Race (N=198)

Subgroup	Converter count (fraction of subgroup)	Non-converter count (fraction of subgroup)	Total aMCI patient count (fraction of total)
White	109 (61.2%)	69 (38.8%)	178 (89.9%)
Black	3 (42.9%)	4 (57.1%)	7 (3.5%)
Asian	3 (42.9%)	4 (57.1%)	7 (3.5%)
Multiracial	3 (60%)	2 (40%)	5 (2.5%)
Unknown	0	1 (100%)	1 (0.5%)

Table 2: Summary of Clinical Validation Data Distribution by Sex (N=198)

Subgroup	Converter count (fraction of subgroup)	Non-converter count (fraction of subgroup)	Total aMCI patient count (fraction of total)
Female	52 (58.4%)	37 (41.6%)	89 (44.9%)
Male	66 (60.6%)	43 (39.4%)	109 (55.1%)
Other	0	0	0

Table 3: Summary of Clinical Validation Data Distribution by Age (N=198)

Subgroup	Converter count (fraction of subgroup)	Non-converter count (fraction of subgroup)	Total aMCI patient count (fraction of total)
Age range 55-65	6 (33.3%)	12 (66.7%)	18 (9.1%)
Age range 65-74	43 (50.6%)	42 (49.4%)	85 (42.9%)
Age range 75-84	56 (70.9%)	23 (29.1%)	79 (39.9%)
Age range 85-94	13 (81.2%)	3 (18.8%)	16 (8.1%)

Effectiveness

Measures of specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV) with associated 95% confidence intervals (CI) were calculated for those patients

meeting study eligibility criteria and with a defined ground truth (N=198). This analysis resulted in specificity of 96% (92%, 100%), sensitivity of 73% (65%, 81%), PPV of 97% (93%, 100%), and NPV of 71% (62%, 79%). The lower 95% confidence interval for sensitivity was below the pre-defined effectiveness performance goal of > 70%. This lower sensitivity was considered acceptable because aMCI patients receiving a false negative output are likely to receive continued follow-up for their aMCI condition. Furthermore, the device algorithm is tuned to favor specificity over sensitivity, to reduce the false positives. The patient population in the clinical validation study were primarily Caucasian as shown in Table 1 that is higher than the representative Caucasian population in the United States (U.S.). This was one of the limitations of the design of the clinical validation study. This raises uncertainty regarding whether the device performance observed in the clinical validation study is the same in more representative non-Caucasian patients in the U.S., and this uncertainty will be studied in the required postmarket study.

Table 4: Results Comparing Device to Reference Standard (N=198)

Total Subjects *n = 198*		**BrainSee Classification**	
		Converter *n = 89*	**Non-converter** *n = 109*
Clinical Reference Standard	**Converter** *n = 118*	True Positives TP = 86	False Negatives FN = 32
	Non-converter *n = 80*	False Positives FP = 3	True Negatives TN = 77

Table 5: Device Performance Metrics Observed in Validation Study (N=198)

Performance metric	Value	95% confidence interval
Specificity (SP)	96.3%	92.1% to 100%
Sensitivity (SN)	72.9%	64.9% to 80.9%
Positive predictive value (PPV)	96.6%	92.9% to 100%
Negative predictive value (NPV)	70.6%	62.1% to 79.2%

Pediatric Extrapolation

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

POSTMARKET EVALUATION

A postmarket study will be conducted to collect data to assess how the BrainSee device performs in aMCI patients in the U.S. who are not adequately represented in the premarket pivotal validation study population, including patients from certain demographic groups (e.g., Black, Asian, Hispanic, other minority populations), with lower levels of education, with co-morbidities, or from community-based settings. This study will evaluate the device effectiveness for predicting progression to AD-dementia within 5 years in the aMCI patient population normally seen in usual clinical practice. The study will also assess the course of treatment and diagnosis, including the frequency of adverse events, in patients who received a false positive or false negative device result.

LABELING

The labeling is sufficient and satisfies the requirements of 21 CFR 801.109 for prescription devices.

The labeling includes a detailed description of the device. The labeling also describes the patient population for whom the device should be used, details the requirements for device inputs, and discusses how to interpret the device outputs. The labeling includes summary information regarding the population used for algorithm development, as well as a summary of the retrospective clinical validation performed to evaluate the device algorithm performance or effectiveness. These discussions have been provided in a user manual for physicians detailing use of the software, an interpretation guide for physicians describing the interpretation of the device outputs, and a guide to facilitate patients and caregivers understanding of the device benefits, limitations, and risks.

The labeling cautions against use of the device in patients who are not eligible for analysis with the device software, such as in patients with certain other coexisting medical conditions. The labeling also indicates that the device is not a standalone diagnostic or prognostic software and cautions the physicians against using the device if they have concerns about the reliability of the inputs. The labeling cautions the users regarding interpretation of device scores close to 50, as patients with such scores may have inputs similar to both converter and non-converter aMCI patient populations.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of a prognostic assessment software of mild cognitive impairment and the measures necessary to mitigate these risks.

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

SPECIAL CONTROLS

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.

BENEFIT-RISK DETERMINATION

The risks of the device are based on software verification and validation, human factors-usability evaluations, and data evaluated in a retrospective clinical study described above.

The number of patients in the retrospective clinical validation study who received a false negative based on a similarity score cut-off of 50 was moderate (n=32). Risks associated with patients who receive a false negative are mitigated by the device labeling, which states that a false negative assessment, or scores that under-estimate a patient's similarity to converters, may delay timely action for clinical work-up, delay early treatment and proper life and care planning, and provide a false reassurance to the patient and their family members. Similarly, the number of patients in the study who received a false positive classification based on a similarity score cut-off of 50 was low (n=3). Risks associated with patients who receive a false positive are mitigated by the device labeling, which states that a false positive assessment, or scores that over-estimate a patient's similarity to converters may cause undue stress to patients, expose the patient to hazards from unnecessary diagnostic procedures, and expose the patient to side effects from unnecessary treatments.

The probable benefits of the device are also based on software verification and validation, human factors-usability evaluations, and data evaluated in a retrospective clinical study described above.

The benefit of BrainSee is that it can aid in the prediction of the likelihood that a diagnosis of aMCI may or may not convert to AD-dementia within 5 years' time. The high specificity of 96% (95% CI: 92%, 100%) observed in the retrospective clinical validation study based on a pre-determined similarity score cut-off of 50 indicates that there are few false positive results. Therefore, the device can accurately identify most patients who will not progress to AD-dementia over 5 years. Furthermore, the positive predictive value of 97% (95% CI: 93%, 100%) observed in the retrospective clinical validation study supports that most positive device results based on a similarity score cut-off of 50 are likely to convert to AD-dementia within 5 years. There is a moderate level of uncertainty associated with the probable benefits because the clinical validation study had certain limitations. Notably, some sociodemographic groups of aMCI patients were under-represented in the validation study. This uncertainty is mitigated through product labeling, which describes the patients included in both the training and validation data sets and will be further addressed in the planned postmarket study.

For the reasons described above, the probable benefits of the BrainSee outweigh the probable risks when considering the listed special controls and general controls.

PATIENT PERSPECTIVES

This submission did not include specific information on patient perspectives for this device.

BENEFIT/RISK CONCLUSION

In conclusion, given the available information above, for the following indication statement:

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.

The probable benefits outweigh the probable risks for the BrainSee. The device provides benefits and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo for the BrainSee is granted and the device is classified as follows:

Product Code: QWT

Device Type: Prognostic assessment software of mild cognitive impairment

Regulation Number: 21 CFR 882.1454

Class: Class II