September 14, 2023

Combinostics Oy
℅ Erin Gontang
Senior Consultant
Rqm+
2251 San Diego Avenue, B-257
San Diego, California 92110

Re: K231576
Trade/Device Name: cNeuro cPET
Regulation Number: 21 CFR 892.1200
Regulation Name: Emission Computed Tomography System
Regulatory Class: Class II
Product Code: KPS, LLZ
Dated: May 31, 2023
Received: May 31, 2023

Dear Erin Gontang:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the 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 Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, 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).

Sincerely,

Daniel M. Krainak, Ph.D.
Assistant Director
Magnetic Resonance and Nuclear Medicine Team
DHT8C: Division of Radiological Imaging
and Radiation Therapy Devices
OHT8: Office of Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2023
See PRA Statement below.

Submission Number *(if known)*

k231576

Device Name

cNeuro cPET

Indications for Use *(Describe)*

cNeuro cPET aids physicians in the evaluation of patient pathologies via assessment and quantification of PET brain scans.

The software aids in the assessment of human brain PET scans enabling automated analysis through quantification of tracer uptake and comparison with the corresponding tracer uptake in normal subjects. The resulting quantification is presented using volumes of interest and voxel-based maps of the brain. cNeuro cPET allows the user to generate information regarding relative changes in PET-FDG glucose metabolism.

cNeuro cPET additionally allows the user to generate information regarding relative changes in PET brain amyloid load between a subject's images and a normal database, which may be the result of brain neurodegeneration.

PET co-registration and fusion display capabilities with MRI allow PET findings to be related to brain anatomy.

cNeuro cPET aids physicians in the image interpretation of PET studies conducted on patients being evaluated for cognitive impairment, or other causes of cognitive decline.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

510(k) Summary
(K231576)

DATE PREPARED
August 17, 2023

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DEVICE INFORMATION

Proprietary Name/Trade Name:	cNeuro cPET
Common Name:	System, Image Processing, Radiological System, Tomography, Computed, Emission
Regulation Number:	892.2050 892.1200
Class:	Class II
Product Code:	LLZ KPS
Premarket Review:	Radiology
Review Panel:	Office of Radiological Health (OHT8) Div. of Imaging Devices and Electronic Products (DHT8B)

PREDICATE DEVICE IDENTIFICATION
The cNeuro cPET is substantially equivalent to the following predicate:

510(k) Number	*Predicate Device Name / Manufacturer*	*Primary Predicate*
K141074	CortexID Suite / GE Medical Systems, LLC	✓

The predicate device have not been subject to a design related recall.

DEVICE DESCRIPTION

cNeuro cPET has been developed to aid clinicians in the assessment and quantification of pathologies derived from PET scans. The software enables the display, co-registration, and fusion of PET images with those from MRI. Additionally, cPET enables automated quantitative and statistical analysis of tracer uptake by registration of a volume-of-interest atlas to the PET images and by comparing voxel and region-based uptake with corresponding uptake in healthy, amyloid-negative subjects. There are two quantification pipelines, one when the patient's MRI is not available (PET-only) and one when the patient's MRI is available (PET-MR). Quantification results are presented using volumes of interest, voxel-based or 3D stereotactic surface projection maps of the brain.

INDICATIONS FOR USE

cNeuro cPET aids physicians in the evaluation of patient pathologies via assessment and quantification of PET brain scans.

The software aids in the assessment of human brain PET scans enabling automated analysis through quantification of tracer uptake and comparison with the corresponding tracer uptake in normal subjects. The resulting quantification is presented using volumes of interest and voxel-based maps of the brain. cNeuro cPET allows the user to generate information regarding relative changes in PET-FDG glucose metabolism.

cNeuro cPET additionally allows the user to generate information regarding relative changes in PET brain amyloid load between a subject's images and a normal database, which may be the result of brain neurodegeneration.

PET co-registration and fusion display capabilities with MRI allow PET findings to be related to brain anatomy.

cNeuro cPET aids physicians in the image interpretation of PET studies conducted on patients being evaluated for cognitive impairment, or other causes of cognitive decline.

COMPARISON OF TECHNOLOGICAL CHARACTERISTICS

Combinostics believes that the cNeuro cPET is substantially equivalent to the predicate device based on the information summarized here:

The subject device and predicate device are software for the automated quantification, visualization, and reporting of PET FDG and amyloid brain scans. Both devices compute standard uptake value ratios (SUVR) where the value in a target region or voxel is divided with the value in a reference region. In addition, both devices provide comparison to tracer specific

reference data with results presented as region and voxel-based Z-scores and with results summarized in a report.

The subject device and predicate device achieve their intended use based on a similar principle, which is the quantification system relies on fitting a volume-of-interest atlas to the data, and through statistical comparison to reference data. The main difference being that the subject device performs the analysis in PET native space whereas the predicate device performs the analysis in a standardized template space.

A comparison of the subject device and predicate device is provided below.

	Subject Device	***Predicate Device***
	Combinostics OY cNeuro cPET K231576	GE Healthcare CortexID Suite K141074
Indications for Use	cNeuro cPET aids physicians in the evaluation of patient pathologies via assessment and quantification of PET brain scans. The software aids in the assessment of human brain PET scans enabling automated analysis through quantification of tracer uptake and comparison with the corresponding tracer uptake in normal subjects. The resulting quantification is presented using volumes of interest and voxel-based maps of the brain. cNeuro cPET allows the user to generate information regarding relative changes in PET-FDG glucose metabolism. cNeuro cPET additionally allows the user to generate information regarding relative changes in PET brain amyloid load between a subject's images and a normal database, which may be the result of brain neurodegeneration. PET co-registration and fusion display capabilities with MRI allow PET findings to be related to brain anatomy. cNeuro cPET aids physicians in the image interpretation of PET studies conducted on patients being evaluated for	CortexID software has been developed to aid physicians in the evaluation of patient pathologies via assessment and quantification of PET brain scans. The software aids in the assessment of human brain PET scans enabling automated analysis through quantification of tracer uptake and comparison with the corresponding tracer uptake in normal subjects. The resulting quantification is presented using volumes of interest, voxel-based or 3D stereotactic surface projection maps of the brain. The package allows the user to generate information regarding relative changes in the PET-FDG glucose metabolism. CortexID Suite additionally allows the user to generate information in PET brain amyloid load between a subject's images and a normal database, which may be the result of brain neurodegeneration. PET co-registration and fusion display capabilities with CT and MR allow PET findings to be related to brain anatomy and offers visualization of structural abnormalities, which may result from brain injury, trauma, disorder, disease or

	cognitive impairment, or other causes of cognitive decline.	dysfunction, such as subdural hematoma, tumor, stroke, or cerebrovascular disease, etc. CortexID Suite may aid physicians in the image interpretation process of PET studies conducted on patients being evaluated for cognitive impairment, or other causes of cognitive decline, and is an adjunct to other diagnostic evaluations.
Product Code(s)	LLZ – System, Image Processing, Radiological KPS – System, Tomography, Computed, Emission	KPS – System, Tomography, Computed, Emission
Regulation Number/ Description	21 CFR 892.2050 / Medical image management and processing system 21 CFR 892.1200 / Emission computed tomography system	21 CFR 892.1200 / Emission computed tomography system
Import of PET and MRI Images	Upload DICOM files from folder or through connection to PACS. PET images are mandatory, but MRI images are optional.	Upload DICOM files from folder or through connection to PACS. PET images are mandatory, but MRI images are optional.
Supported tracers	Supports FDG, Flutemetamol, Florbetaben and Florbetapir.	Supports FDG, Flutemetamol, Florbetaben and Florbetapir, and the research tracer C11 PIB.
Volumes of interest (VOIs)	A VOI-template is defined outlining VOIs corresponding to the different brain lobes, anterior and posterior cingulate, as well as reference VOIs corresponding to cerebellar gray matter, whole cerebellum and pons. There is also a cortical composite VOI defined by merging all the cortical VOIs.	A VOI-template is defined outlining VOIs corresponding to the different brain lobes, anterior and posterior cingulate, as well as reference VOIs corresponding to cerebellar gray matter, whole cerebellum and pons. There is also a cortical composite VOI defined by merging all the cortical VOIs.
Method for quantification	Fully automated registration to establish the transformation between the PET image and a standard template space. A VOI-template is then transformed to PET native space and is used to quantify tracer uptake.	Fully automated registration to establish the transformation between the PET image and a standard template space. The PET image is then transformed standard space and a VOI-template is used to quantify tracer uptake.
Comparison to tracer specific reference data	Provides reference data for all supported tracers. The reference data is used to compute regional and voxel-based Z-scores.	Provides reference data for FDG and Flutemetamol. The reference data is used to compute regional and voxel-based Z-scores.
Output from quantification	Results are presented as SUVR images, Z-score images, regional SUVR and Z-scores and 3D SSP Z-score images. For amyloid tracers, results include	Results are presented as SUVR images, Z-score images, regional SUVR and Z-scores and 3D SSP SUVR and Z-score images.

	Centiloids for a cortical composite region.	
Co-registration with MRI	If the patient's MRI is available, this is co-registered with the PET for display purposes, and it is also used during image quantification.	If the patient's MRI is available, this is co-registered with the PET for display purposes.
Report	Provides a PDF report that can be sent to PACS. The report summarizes region-based SUVR and Z-scores and shows 3D stereotactic surface projections of voxel-based Z-scores as well as Centiloids for a cortical composite region for amyloid tracers.	Provides a PDF report that can be sent to PACS. The report summarizes region-based SUVR and Z-scores and shows 3D stereotactic surface projections of voxel-based Z-scores.

SUMMARY OF PERFORMANCE TESTING

Summary of Non-Clinical Testing

The cNeuro cPET software complies with NEMA PS 3.1 - 3.20 (2021) Digital Imaging and Communications in Medicine (DICOM) Set (Radiology) standard.

cNeuro cPET employs the same fundamental scientific technology as its predicate device, CortexID Suite. cNeuro cPET uses the equivalent DICOM image data input requirements. It has equivalent display, formatting, archiving and visualization technologies compared to the predicate device. cNeuro cPET utilizes essentially the same methodology to quantify and assess uptake of FDG and amyloid tracers. The information is presented using volumes of interest or voxel-based maps of the brain. cNeuro cPET utilizes existing PET co-registration and fusion technologies and provides for PET & MR co-registration and fusion capabilities. Thorough testing of these capabilities has not raised any safety or effectiveness issues.

The following quality assurance measures were applied to the development of the system:

- Risk Analysis
- Requirements Reviews
- Design Reviews
- Integration testing (System verification)
- Performance testing (Bench testing, verification)
- Safety testing (Verification)

The substantial equivalence determination is based on the software documentation for a MODERATE level of concern device.

Combinostics performed testing of cNeuro cPET using PET images from 2,275 subjects. Data were from all tracers supported by cNeuro cPET, i.e., Flutemetamol, Florbetapir, Florbetaben and FDG. The performance evaluation included a comparison with the predicate device,

assessment of robustness using a large dataset from the Alzheimer's Disease Neuroimaging Initiative (ADNI), evaluation of test-retest variability, and comparison with Standard of Truth (SoT) based on majority/consensus visual read and histopathology using Florbetaben Phase III data. Centiloids for amyloid tracers were validated according the methods described by W. E. Klunk et al., The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET. Alzheimers. Dement. 11, 1–4 (2015).

Results showed agreement with the predicate device with correlations (R) ranging from 0.98 – 0.99 depending on cohort. Furthermore, a similar strong correlation (R=0.98 – R=0.99) was obtained for the comparison with a FreeSurfer based PET-MR quantification method used in ADNI. Evaluation of the consistency of cNeuro cPET quantification showed low test-retest variability (TRT) in the quantification of repeat scans. For Flutemetamol, the best results were obtained using Pons as the reference region (TRT = 1.2% for PET-MR, TRT = 1.7% for PET-only), and for Florbetapir, the lowest variability was obtained by using the whole cerebellum as the reference region (TRT = 1.3% for PET-MR, TRT = 1.8% for PET-only).

Categorization of Florbetaben scans into positive and negative based on cNeuro cPET quantification showed agreement with SoT based on histopathology (94.4% for PET-only and 96.3% for PET-MR). The agreement in the comparison of cNeuro cPET categorization with SoT based on majority visual read (5 readers) gave similar agreement (94.8% for PET-only and 92.8% for PET-MR). When excluding all scans where readers had different opinions, i.e., there was unanimous categorization by the readers of the scans into negative or positive, the agreement with cNeuro cPET categorization was 98.8% for PET-only and 98.2% for PET-MR.

The correlation of cNeuro cPET Centiloids for Flutemetamol, Florbetaben and Florbetapir with the corresponding values produced by the Centiloid Project ranged from R^2 = 0.85 – 0.99 depending on tracer and reference region.

The results show that cNeuro cPET is accurate and robust, as well as effective and safe, and is suitable for its intended use. cNeuro cPET is substantially equivalent to the predicate device.

CONCLUSION

Based on performance testing, it can be concluded that the subject device does not raise new issues of safety or effectiveness compared to the predicate device. The similar indications for use, technological characteristics, and performance characteristics for the proposed cNeuro cPET are assessed to be substantially equivalent to the predicate device.