January 8, 2018

Combinostics Oy
% Lennart Thurfjell
CEO
Hatanpään valtatie 24
Tampere FI 33100
FINLAND

Re: K171328
Trade/Device Name: cNeuro cMRI
Regulation Number: 21 CFR 892.2050
Regulation Name: Picture archiving and communications system
Regulatory Class: II
Product Code: LLZ
Dated: December 6, 2017
Received: December 8, 2017

Dear Lennart Thurfjell:

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. 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); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820);

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 http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/) and CDRH Learn (http://www.fda.gov/Training/CDRHLearn). 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 (http://www.fda.gov/DICE) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

For

Robert Ochs, Ph.D.
Director
Division of Radiological Health
Office of In Vitro Diagnostics
and Radiological Health
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: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*

K171328

Device Name

cNeuro cMRI

Indications for Use *(Describe)*

cNeuro cMRI is intended for automatic labeling, quantification and visualization of segmentable brain structures from a set of MR images. The software is intended to automate the current manual process of identifying, labeling and quantifying the segmentable brain structures identified on MR images.

The intended user profile covers medical professionals who work with medical imaging. The intended operational environment is an office-like environment with a computer.

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.

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Combinostics Oy
Hatanpään valtatie 24
33 100 Tampere
Finland

Section 5. 510(k) Summary

5.1 Submitter

Name:	Combinostics OY
Address:	Hatanpään valtatie 24, FI 33 100 Tampere, Finland
Contact Person:	Lennart Thurfjell
Telephone number:	+46 730 699057
Fax Number:	N.A.
E-mail:	lennart.thurfjell@combinostics.com
Consultant:	Allison Komiyama, PhD, RAC
Date prepared:	January 2, 2018

5.2 Device

Trade Name:	cNeuro cMRI
Common Name	Medical Image Processing Software
Classification Name	System, Image processing, Radiological
Regulation Number	892.2050
Product Code	LLZ
Classification Panel	Radiology

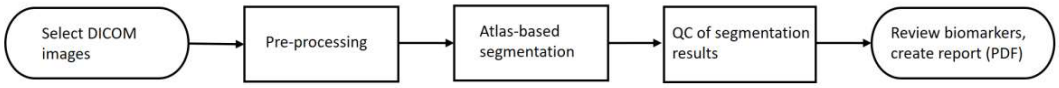
5.3 Predicate Device

Primary predicate device	
Device	NeuroQuant
510(k) #	K061855
Manufacturer	CorTechs Labs, Inc. 4690 Executive Drive, Suite 250 San Diego, CA 92121 USA
Secondary predicate device	
Device	icobrain
510(k) #	K161148
Manufacturer	Icometrix, Kolonel Begaultlaan 1b / 12 3012 Leuven, Belgium

5.4 Device Description

cNeuro cMRI is intended for automatic labeling, quantification and visualization of segmentable brain structures from a set of MR images. The software is intended to automate the current manual process of identifying, labeling and quantifying the segmentable brain structures identified on MR images.

The flowchart below outlines the workflow and main steps in the usage of cNeuro cMRI.



As input, cNeuro cMRI uses T1-weighted (T1) and fluid-attenuated inversion recovery (FLAIR) DICOM MR images from a single time point. The T1 image is mandatory but the FLAIR image is optional. The user selects images through connection with a Picture Archiving and Communication System (PACS) or by selecting DICOM files from a folder. cNeuro cMRI displays the selected images together with information extracted from the DICOM headers.

Image processing starts with a pre-processing stage with bias-field correction and brain extraction before the actual segmentation and calculation of MRI biomarkers begins. When the processing has completed, the user can review the images with brain segmentations displayed as an overlay. cNeuro cMRI presents computed biomarkers corresponding to volumes of structures and FLAIR white matter hyperintensities. The computed biomarkers are corrected for the subject's head size, gender and age and are compared to corresponding biomarkers from a healthy reference population using a statistical model.

5.5 Indications for Use

cNeuro cMRI is intended for automatic labeling, quantification and visualization of segmentable brain structures from a set of MR images. The software is intended to automate the current manual process of identifying, labeling and quantifying the segmentable brain structures identified on MR images.

The intended user profile covers medical professionals who work with medical imaging. The intended operational environment is an office-like environment with a computer.

5.6 Comparison and substantial equivalence statement

cNeuro cMRI is substantially equivalent to the NeuroQuant device by Cortechs Labs, cleared in K061855 with regards to processing of T1 images and it is substantially equivalent to the icobrain device by icometrix, cleared in K161148 with regards to processing of FLAIR images. K061855 is the primary predicate and K161148 is the secondary predicate.

A comparison of the subject device and predicate devices (K061855 and K161148) is provided below.

	SUBJECT DEVICE	***Primary Predicate Device***	***Secondary Predicate Device***	***Conclusion/ Comparison***
Device	**cNeuro cMRI**	**NeuroQuant**	**icobrain**	---
510(k) Number	K171328	K061855	K161148	
Manufacturer	**Combinostics OY**	**CorTechs Labs, Inc**	**icometrix**	---
Device Classification Name	Picture archiving and communication system	Picture archiving and communication system	Picture archiving and communication system	Identical
Deployment	Cloud based	Cloud based or installed	Cloud based	cNeuro cMRI and icobrain are identical. NeuroQuant is available either cloud based or installed.

	SUBJECT DEVICE	***Primary Predicate Device***	***Secondary Predicate Device***	***Conclusion/ Comparison***
Device	**cNeuro cMRI**	**NeuroQuant**	**icobrain**	---
510(k) Number	K171328	K061855	K161148	
Manufacturer	**Combinostics OY**	**CorTechs Labs, Inc**	**icometrix**	---
Indications for Use	cNeuro cMRI is intended for automatic labeling, quantification and visualization of segmentable brain structures from a set of MR images. The software is intended to automate the current manual process of identifying, labeling and quantifying segmentable brain structures identified on MR images. The users are trained healthcare professionals who work with medical imaging. The product is used in an office-like environment.	NeuroQuantTM is intended for automatic labeling, visualization and volumetric quantification of segmentable brain structures from a set of MR images. This software is intended to automate the current manual process of identifying, labeling and quantifying the volume of segmentable brain structures identified on MR images.	icobrain is intended for automatic labeling, visualization and volumetric quantification of segmentable brain structures from a set of MR images. This software is intended to automate the current manual process of identifying, labeling and quantifying the volume of segmentable brain structures identified on MR images. icobrain consists of two distinct image processing pipelines: icobrain cross and icobrain long. icobrain cross is intended to provide volumes from images acquired at a single timepoint icobrain long is intended to provide changes in volumes between two images that were acquired on the same scanner, with the same image acquisition protocol and with same contrast at two different timepoints The results of icobrain cross cannot be compared with the results of icobrain long.	Functionally identical. cNeuro cMRI lists "quantification" while NeuroQuant lists "volumetric quantification". Since cNeuro cMRI makes a volumetric quantification, these expressions can be considered identical. Furthermore, icobrain has the added description of two distinct processing pipelines: icobrain cross and icobrain long. Results of icobrain cross cannot be compared with the results of icobrain long. cNeuro cMRI and NeuroQuant provides only one processing pipeline. Finally, cNeuro cMRI lists intended users and intended use environment whereas NeuroQuant and icobrain does not.

Subject device and predicate devices are software for automatically identifying and quantifying volumes of brain structures, labeling and visualization. Both subject and predicate devices take 3D MR images of the brain as input and generate an electronic report with similar quantitative information. The output values are for all devices compared to a normative data based on MRI data from healthy control subjects.

Subject device and the primary predicate device segments cortical and subcortical structures from MRI T1 images based on a similar principle, where the quantification relies on pre-processing with skull stripping (brain extraction) followed by multi-atlas segmentation. The main difference is that different atlases are used. The subject device uses atlases with 133 brain structures, while the primary predicate uses atlases with 34 brain structures. Similarly, the subject device and the secondary predicate device segments white matter hyperintensities from FLAIR MR images based on a similar principle. Furthermore, for volumes derived from T1 images, the subject device and the predicate devices provide statistical comparison of normalized values with a normative dataset from a healthy reference population. In addition, subject device compares normalized volumes of FLAIR white matter hyperintensities to a normative dataset from a reference population. The secondary predicate device does not provide such a comparison.

The primary predicate device uses an index computed based on the deviation of the image volumes from normal atlas space as a quality control measure. The subject device does not employ such an index, but provides functionality where the user interactively can review the quality of the segmentations by checking color coded overlays on the original MR slices.

Subject device provides a gray matter concentration map, i.e., an overlay on MR T1 images highlighting regions where the local gray matter concentration of the patient is smaller than the gray matter concentration in the reference population normalized for age, sex and head size. This overlay, which can be toggled on and off, provides a means for the user to locate regions that are atypical compared to the reference population. The predicate devices do not provide such a gray matter concentration map. Subject device's gray matter concentration map provides a visual complement to the quantitative volume measurements and it does not affect safety and effectiveness of the device.

5.7 Performance testing

Support for the substantial equivalence of cNeuro cMRI to the predicate devices was provided as a result of risk management and testing. The design verification activities consist of code review and static code analysis, unit tests, integration tests, system tests (including safety related tests from risk analysis) and regression testing after modifications

To demonstrate the performance of cNeuro cMRI, the computed volumes of brains structures were validated for accuracy and reproducibility. Test data included data from healthy subjects, and patients with neurodegenerative diseases such as Alzheimer's disease, mild cognitive impairment, fronto-temporal lobe degeneration, vascular dementia as well as Multiple Sclerosis patients. In the accuracy experiments, cNeuro cMRI fully automated brain segmentation was compared to manually labeled ground truth data. In the reproducibility experiments, the volumes were compared using test-retest data. The experiments included data from 1399 subjects in total.

A literature review was performed to set relevant acceptance criteria for each type of experiment. All experiments passed the acceptance criteria. Averaged over all experiments, the similarity index (or Dice index) were 0.88 for the hippocampus, 0.91 for the thalamus and 0.88 for the whole cortex. Furthermore, intraclass correlation coefficient for the test-retest reproducibility measurements averaged over all 133 structures was 0.96 and the correlation coefficient between the computed FLAIR white matter hyperintensities and the manually labelled data was 0.97.

The verification and performance testing demonstrate that cNeuro cMRI is safe and effective to use.

5.8 Conclusion

Combinostics OY believes that cNeuro cMRI has the identical indication for use and that there are no new types of questions regarding safety and effectiveness for cNeuro cMRI as compared to the cleared predicate devices. Combinostics OY has conducted the risk analysis and performed the necessary verification and validation activities to demonstrate that the design outputs meet the design inputs and the applicable process standards. Combinostics OY has concluded that the performance data for the cNeuro cMRI shows that it is substantially equivalent to the primary predicate device, NeuroQuant (K061855), for processing of MRI T1 images and to the secondary predicate device, icobrain (K161148), for processing of MRI FLAIR images.

This document is reviewed and approved by Lennart Thurfjell, CEO of Combinostics.

DocuSigned by:

Signer Name: Lennart Thurfjell
Signing Reason: I approve this document
Signing Time: 2018-01-02 | 21:10 CET

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