Brainomix Limited
℅ Gwilym Owen
Head of Quality and Regulatory
Suite 11-14, Suffolk House, 263 Banbury Road
Oxford, Oxfordshire OX2 7HN
UNITED KINGDOM

February 23, 2023

Re: K221564
Trade/Device Name: Brainomix 360 e-ASPECTS
Regulation Number: 21 CFR 892.2060
Regulation Name: Radiological computer-assisted diagnostic software for lesions suspicious of cancer
Regulatory Class: Class II
Product Code: POK
Dated: January 20, 2023
Received: January 23, 2023

Dear Gwilym Owen:

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,

Jessica Lamb Ph.D.
Assistant Director
Imaging Software Team
DHT8B: Division of Radiological Imaging Devices and Electronic Products
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.

510(k) Number *(if known)*
K221564

Device Name
Brainomix 360 e-ASPECTS

Indications for Use *(Describe)*
Brainomix 360 e-ASPECTS is a computer-aided diagnosis (CADx) software device used to assist the clinician in the assessment and characterization of brain tissue abnormalities using CT image data.

The software automatically registers images and uses an Atlas to segment and analyze ASPECTS regions. Brainomix 360 e-ASPECTS extracts image data from individual voxels in the image to provide analysis and computer analytics and relates the analysis to the atlas defined ASPECTS regions. The imaging features are then synthesized by an artificial intelligence algorithm into a single ASPECTS (Alberta Stroke Program Early CT) Score.

Brainomix 360 e-ASPECTS is indicated for evaluation of patients presenting for diagnostic imaging workup with known MCA or ICA occlusion, for evaluation of extent of disease. Extent of disease refers to the number of ASPECTS regions affected which is reflected in the total score. Brainomix 360 e-ASPECTS provides information that may be useful in the characterization of ischemic brain tissue injury during image interpretation (within 6 hours from time last known well).

Brainomix 360 e-ASPECTS provides a comparative analysis to the ASPECTS standard of care radiologist assessment by providing highlighted ASPECTS regions and an automated editable ASPECTS score for clinician review. Brainomix 360 e-ASPECTS additionally provides a visualization of the voxels contributing to the automated ASPECTS score and the voxels excluded from the automated ASPECTS score.

Limitations:

1. Brainomix 360 e-ASPECTS is not intended for primary interpretation of CT images. It is used to assist physician evaluation.
2. Brainomix 360 e-ASPECTS has been validated in patients with known MCA or ICA occlusion prior to ASPECTS scoring.
3. Brainomix 360 e-ASPECTS is not suitable for use on brain scans displaying neurological pathologies other than acute stroke, such as tumours or abscesses, haemorrhagic transformation and hematoma.
4. Use of Brainomix 360 e-ASPECTS Module in clinical settings other than brain ischemia within 6 hours from time last known well, caused by known ICA or MCA occlusions has not been tested.
5. Brainomix 360 e-ASPECTS has only been validated and is intended to be used in patient populations aged over 21.
6. Brainomix 360 e-ASPECTS has been validated and is intended to be used on Siemens Somatom Definition scanners.
7. Brainomix 360 e-ASPECTS is not intended for mobile diagnostic use. Images viewed on a mobile platform are compressed preview images and not for diagnostic interpretation.

Contraindications/Exclusions/Cautions:

• Patient motion: Excessive patient motion leading to artifacts that make the scan technically inadequate.
• Haemorrhagic Transformation, Hematoma.

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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K221564

510(K) Summary of Safety and Effectiveness

Date of summary:	23rd February 2023
Submitter's name:	Brainomix Limited
Submitter's address:	Brainomix Limited, Suites 11-14 Suffolk House, 263 Banbury Road, Oxford. OX2 7HN. United Kingdom
Submitter's contact:	Gwilym Owen
Telephone number:	+44 (0)1865 582730

Device Proprietary Name:	Brainomix 360 e-ASPECTS
Device Common Name(s):	CADx
Classification Name:	Class II
Product Code:	POK
Regulation No:	21 C.F.R. §892.2060
Classification Panel:	Radiology Devices

Brainomix 360 e-ASPECTS is Substantially Equivalent to the following Legally Marketed device:

Predicate Devices

510(k) Number	Trade Name	Manufacturer
K200760	**Rapid ASPECTS**	**iSchemaView Inc**

Indications for Use

Brainomix 360 e-ASPECTS is a computer-aided diagnosis (CADx) software device used to assist the clinician in the assessment and characterization of brain tissue abnormalities using CT image data.

The software automatically registers images and uses an Atlas to segment and analyze ASPECTS regions. Brainomix 360 e-ASPECTS extracts image data from individual voxels in the image to provide analysis and computer analytics and relates the analysis to the atlas defined ASPECTS regions. The imaging features are then synthesized by an artificial intelligence algorithm into a single ASPECTS (Alberta Stroke Program Early CT) Score.

Brainomix 360 e-ASPECTS is indicated for evaluation of patients presenting for diagnostic imaging workup with known MCA or ICA occlusion, for evaluation of extent of disease. Extent of disease refers to the number of ASPECTS regions affected which is reflected in the total score. Brainomix 360 e-ASPECTS provides information that may be useful in the characterization of ischemic brain tissue injury during image interpretation (within 6 hours from time last known well).

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Brainomix 360 e-ASPECTS provides a comparative analysis to the ASPECTS standard of care radiologist assessment by providing highlighted ASPECTS regions and an automated editable ASPECTS score for clinician review. Brainomix 360 e-ASPECTS additionally provides a visualization of the voxels contributing to the automated ASPECTS score and the voxels excluded from the automated ASPECTS score.

Limitations:

1. Brainomix 360 e-ASPECTS is not intended for primary interpretation of CT images. It is used to assist physician evaluation.
2. Brainomix 360 e-ASPECTS has been validated in patients with known MCA or ICA occlusion prior to ASPECTS scoring.
3. Brainomix 360 e-ASPECTS is not suitable for use on brain scans displaying neurological pathologies other than acute stroke, such as tumours or abscesses, haemorrhagic transformation and hematoma.
4. Use of Brainomix 360 e-ASPECTS Module in clinical settings other than brain ischemia within 6 hours from time last known well, caused by known ICA or MCA occlusions has not been tested.
5. Brainomix 360 e-ASPECTS has only been validated and is intended to be used in patient populations aged over 21.
6. Brainomix 360 e-ASPECTS has been validated and is intended to be used on Siemens Somatom Definition scanners.
7. Brainomix 360 e-ASPECTS is not intended for mobile diagnostic use. Images viewed on a mobile platform are compressed preview images and not for diagnostic interpretation.

Contraindications/Exclusions/Cautions:

- Patient motion: Excessive patient motion leading to artifacts that make the scan technically inadequate.
- Haemorrhagic Transformation, Hematoma.

Device Description

Brainomix 360 e-ASPECTS is a stand-alone software device which uses machine learning algorithms to automatically process NCCT (Non-contrast CT scans) brain image data to provide an output ASPECTS score based on the Alberta Stroke Program Early CT Score (ASPECTS) guidelines.

The post-processing image results and ASPECTS score are identified based on regional imaging features and overlayed onto brain scan images. e-ASPECTS provides an automatic ASPECTS score based on the input CT data for the physician. The score includes which ASPECTS regions are identified based on regional imaging features derived from non-contrast computed tomography (NCCT) brain image data. The results are generated based on the Alberta Stroke Program Early CT

Score (ASPECTS) guidelines and provided to the clinician for review and verification. At the discretion of the clinician, the scores may be adjusted based on the clinician's judgment.

Brainomix 360 e-ASPECTS can connect with other DICOM-compliant devices, for example to transfer NCCT scans from a Picture Archiving and Communication System (PACS) to Brainomix 360 e-ASPECTS software for processing.

Results and images can be sent to a PACS via DICOM transfer and can be viewed on a PACS workstation or via a web user interface on any machine contained and accessed within a hospital network and firewall and with a connection to the Brainomix 360° e-ASPECTS software (e.g. a LAN connection)

Brainomix 360 e-ASPECTS notification capabilities enable clinicians to preview images through via e-mail notification with result image attachments.

Images that are previewed via e-mail are compressed, are for preview purposes only, and not intended for diagnostic use beyond notification.

Brainomix 360 e-ASPECTS is not intended for mobile diagnostic use. Notified clinicians are responsible for viewing non-compressed images on a diagnostic viewer and engaging in appropriate patient evaluation and relevant discussion with a treating physician before making care-related decisions or requests.

Brainomix 360 e-ASPECTS provides an automated workflow which will automatically process image data received by the system in accordance with pre-configured user DICOM routing preferences.

Once received, image processing is automatically applied. Once any image processing has completed, notifications are sent to pre-configured users to inform them that the image processing results are ready. User can then access and review the results and images via the Web User Interface case viewer or PACS viewer.

Brainomix 360 e-ASPECTS principal workflow for NCCT includes the following key steps:

- NCCT Image Loading.
- Automated image analysis and processing to identify and visualize the voxels which have been included in the ASPECTS score and the voxels which have been excluded from the ASPECTS score (Also referred to as a 'heat map').
- Automated image analysis and processing to register the subject image to an atlas to segment and highlight ASPECTS regions and to display whether or not each region is qualified as contributing to the ASPECTS score.
- Notifications and alerts to users.
- Generation of a summary results report.
- Presentation of results for review and analysis by users.

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Once the physician has been notified of availability of the ASPECTS score, the system requires that the physician confirms that the case in question is for an ICA or MCA occlusion. The ASPECTS results, including the ASPECTS score, indication of affected side, affected ASPECTS regions and voxel-wise analysis (shown as a heatmap of voxels 'contributing to e-ASPECTS score' and a heat map of voxels 'excluded from e-ASPECTS score') can be exported as a report and/or sent to the Picture Archiving and Communications System (PACS).

Technological Characteristics

Brainomix 360 e-ASPECTS is a machine learning implementation using the processing pipeline below. Brainomix 360 e-ASPECTS provides an automatic ASPECT score based on the case input file for the physician. The score includes which ASPECT regions are identified based on a voxel-wise analysis of non-contrast computed tomography (NCCT) brain image data based on the random forest machine learning technique. The results are generated based on the Alberta Stroke Program Early CT Score (ASPECTS) guidelines and provided to the clinician for review and verification.

ASPECTS regions are generated as an overlay by registering the subject NCCT scan to an atlas. The Brainomix 360 e-ASPECTS algorithm analyses the voxels in the subject NCCT scan to identify voxels contributing to, or excluded from, the e-ASPECTS score. The regions then contribute towards the determination of an ASPECTS score which must be reviewed by the physician.

ASPECTS regions identified as contributing to the ASPECTS score are highlighted and labelled for the physician. The voxel-wise analysis is visualized for the physician as shaded heat maps showing voxels contributing to the e-ASPECTS score and voxels excluded from the e-ASPECTS score.

Physicians can, at their discretion and depending on their level of agreement with the processing results, manually edit the ASPECTS score by manually selecting ASPECTS regions to be included or excluded from the calculation of the ASPECTS score.

The following figure provides the general layout of the ASPECTS display as presented by Brainomix 360 e-ASPECTS

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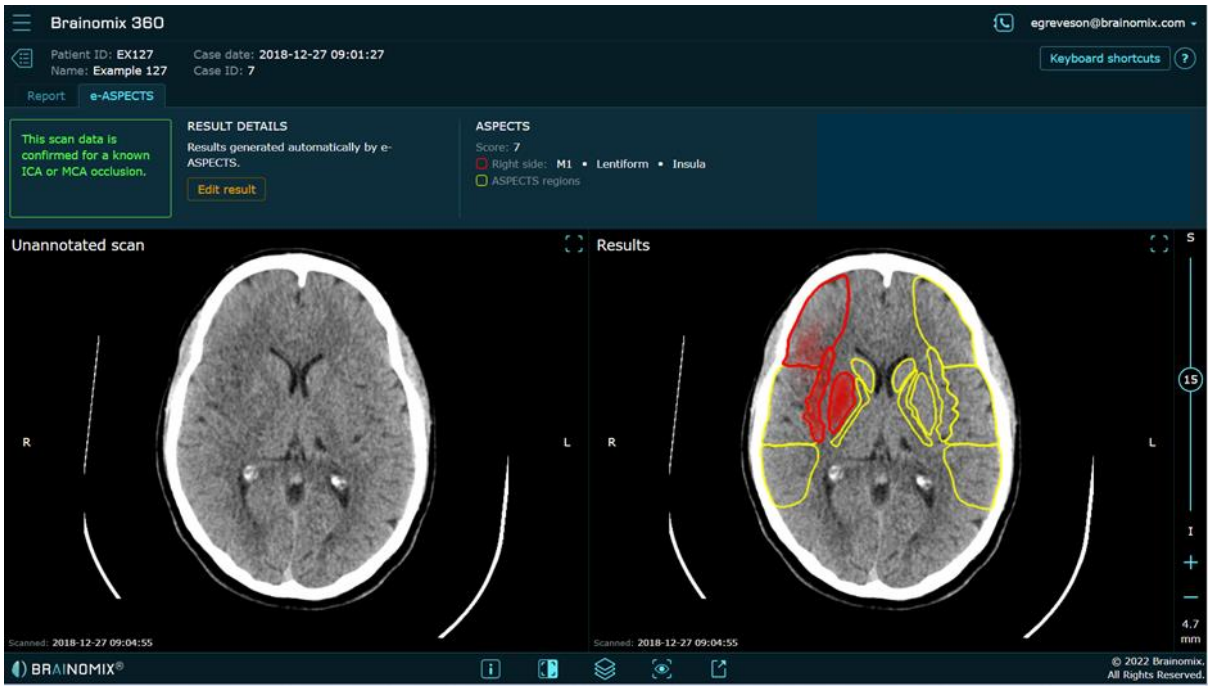

Substantial Equivalence Discussion

Both proposed and predicate devices have the same intended use. Both devices are computer-aided diagnosis (CADx) software devices used to assist clinicians in the assessment and characterization of brain tissue abnormalities using CT image data.

Both devices use an atlas to segment and identify ASPECTS regions and use artificial intelligence algorithms to analyse image data to facilitate the evaluation of extent of disease and to identify and count the affected ASPECTS regions to generate an ASPECTS score. Both devices display and highlight the affected ASPECTS regions along with the automatically generated ASPECTS score

Both devices are not intended for primary interpretation of CT images and both require that cases processed meet pre-requisite criteria such that a primary diagnosis of ICA or MCA occlusion has already been made by clinicians prior to accessing the processing results and the resulting ASPECTS score.

Both devices are indicated for cases within 6 hours from time last known well.

Both devices include a gating condition requiring users to confirm that the case in question is for a confirmed ICA or MCA occlusion before processing results are made available.

Both devices include pre-processing steps to straighten NCCT scans and to register the NCCT scans to an atlas of ASPECTS regions in order to identify and segment ASPECTS regions on the subject NCCT scan.

In both cases, the algorithms identify signs indicative of ischemic damage and relate these to the segmented ASPECTS regions in order to determine whether or not individual ASPECTS regions are included as contributing to a reduced ASPECTS score.

In both cases, the segmented ASPECTS regions are labelled and presented to users in the software User Interface with the regions highlighted depending on whether they have been determined to affect the e-ASPECTS score or not. In both cases, users can manually edit and override the automated result for one or more ASPECTS regions by selecting the regions.

Both predicate and proposed devices use trained machine learning AI algorithms to analyse NCCT scans to identify signs indicative of ischemic damage. Both devices use a random forest machine learning technique to classify tissue in brains scans to identify both early/acute ischemic changes and old/non-acute ischemic changes to differentiate old or prior signs of stroke from the acute stroke for which the ASPECTS methodology is intended. In both devices, signs of non-acute ischemic change are masked to ensure that these do not contribute towards the determination of the output ASPECTS score.

The following principal difference exists between Brainomix 360 e-ASPECTS and the predicate device:

In addition to highlighting affected ASPECTS regions which is a common technical characteristic of both subject and predicate devices, the Brainomix 360 e-ASPECTS device includes the visualization of the analysis of individual voxels underlying the scoring of ASPECTS regions and the overall ASPECTS score as a heat map.

Characteristic/Parameter	Brainomix 360 e-ASPECTS – Proposed Device	iSchemaView Rapid ASPECTS - Predicate Device (K200760)
Product Code	POK	POK
Regulation	21 C.F.R. §892.2060	21 C.F.R. §892.2060

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Indications for Use	Brainomix 360 e-ASPECTS is a computer-aided diagnosis (CADx) software device used to assist the clinician in the assessment and characterization of brain tissue abnormalities using CT image data. The software automatically registers images and uses an Atlas to segment and analyze ASPECTS regions. Brainomix 360 e-ASPECTS extracts image data from individual voxels in the image to provide analysis and computer analytics and relates the analysis to the atlas defined ASPECTS regions. The imaging features are then synthesized by an artificial intelligence algorithm into a single ASPECTS (Alberta Stroke Program Early CT) Score. Brainomix 360 e-ASPECTS is indicated for evaluation of patients presenting for diagnostic imaging workup with known MCA or ICA occlusion, for evaluation of extent of disease. Extent of disease refers to the number of ASPECTS regions affected which is reflected in the total score. Brainomix 360 e-ASPECTS provides information that may be useful in the characterization of ischemic brain tissue injury during image interpretation (within 6 hours from time last known well).	Rapid ASPECTS is a computer-aided diagnosis (CADx) software device used to assist the clinician in the assessment and characterization of brain tissue abnormalities using CT image data. The Software automatically registers images and segments and analyzes ASPECTS Regions of Interest (ROIs). Rapid ASPECTS extracts image data for the ROI(s) to provide analysis and computer analytics based on morphological characteristics. The imaging features are then synthesized by an artificial intelligence algorithm into a single ASPECTS (Alberta Stroke Program Early CT) Score. Rapid ASPECTS is indicated for evaluation of patients presenting for diagnostic imaging workup with known MCA or ICA occlusion, for evaluation of extent of disease. Extent of disease refers to the number of ASPECTS regions affected which is reflected in the total score. This device provides information that may be useful in the characterization of early ischemic brain tissue injury during image interpretation (within 6 hours). Rapid ASPECTS provides a comparative analysis to the ASPECTS standard of care radiologist assessment using the ASPECTS atlas definitions and atlas display including highlighted ROIs and numerical scoring.

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Brainomix 360 e-ASPECTS provides a comparative analysis to the ASPECTS standard of care radiologist assessment by providing highlighted ASPECTS regions and an automated editable ASPECTS score for clinician review. Brainomix 360 e-ASPECTS additionally provides a visualization of the voxels contributing to the automated ASPECTS score and the voxels excluded from the automated ASPECTS score.

Limitations:

1. Brainomix 360 e-ASPECTS is not intended for primary interpretation of CT images. It is used to assist physician evaluation.
2. Brainomix 360 e-ASPECTS has been validated in patients with known MCA or ICA occlusion prior to ASPECTS scoring.
3. Brainomix 360 e-ASPECTS is not suitable for use on brain scans displaying neurological pathologies other than acute stroke, such as tumors or abscesses, hemorrhagic transformation and hematoma.
4. Use of Brainomix 360 e-ASPECTS Module in clinical settings other than brain ischemia within 6 hours from time last known well, caused by known ICA or

Limitations:

1. Rapid ASPECTS is not intended for primary interpretation of CT images, it is used to assist physician evaluation.

2. Rapid ASPECTS has been validated in patients with known MCA or ICA Occlusion prior to ASPECTS scoring.

3. Use of the Rapid ASPECTS Module in clinical settings other than early brain ischemia (within 6 hours) caused by known ICA or MCA occlusions has not been tested.

4. Rapid ASPECTS has been validated and is intended to be used on GE Lightspeed VCT Scanners.

Contraindications/Exclusions/Cautions:

• Patient Motion: excessive motion leading to artifacts that make the scan technically inadequate.

• Hemorrhagic Transformation, Hematoma

• Very thin or no Ventricles

Characteristic/Parameter	Brainomix 360 e-ASPECTS – Proposed Device	iSchemaView Rapid ASPECTS - Predicate Device (K200760)
	MCA occlusions has not been tested. 5. Brainomix 360 e-ASPECTS has been validated and is intended to be used on Siemens Somatom Definition scanners. 6. Brainomix 360 e-ASPECTS has only been validated and is intended to be used in patient populations aged over 21 years. 7. Brainomix 360 e-ASPECTS is not intended for mobile diagnostic use. Images viewed on a mobile platform are compressed preview images and not for diagnostic interpretation. Contraindications/Exclusions/Cautions: • Patient motion: Excessive patient motion leading to artifacts that make the scan technically inadequate • Hemorrhagic Transformation, Hematoma	
Environment of use	Clinical/Hospital environment	Clinical/Hospital environment
Energy used and/or delivered	None – software only application. The software application does not deliver or depend on energy delivered to or from patients	None – software only application. The software application does not deliver or depend on energy delivered to or from patients
Primary Users	Neuroradiologist/Clinician	Neuroradiologist/Clinician

Characteristic/Parameter	Brainomix 360 e-ASPECTS – Proposed Device	iSchemaView Rapid ASPECTS - Predicate Device (K200760)
Clinical Application/Anatomical Region	Stroke/Head	Stroke/Head
Standard of Care Representation	ASPECTS Scoring	ASPECTS Scoring
Design: Modalities for image processing and visualization	CT	CT
Technical Implementation	ML/AI/Random Forest	ML/AI/Random Forest
Image Overlay	ASPECTS regions, highlighted by algorithms. Voxel-wise analysis visualized as a heat map.	ASPECTS Atlas ROIs, highlighted by algorithms.
Gating Conditions	Users must confirm ICA or MCA occlusion prior to accessing Brainomix 360 e-ASPECTS results	Users must confirm LVO prior to accessing Rapid ASPECTS results
Design: PACS functionality	View process and analyze medical images. performs standard PACS functions with respect to querying and listing	same
Design: DICOM compliance	Yes	Yes
Design: Computer Platform	Standard off-the-shelf server or virtual server	same
Design: Data acquisition	Acquires medical image data from DICOM compliant imaging devices and modalities	same
Alters Standard of Care Workflow	In parallel to	In parallel to
Materials	N/A – Software only device	same
Biocompatibility	N/A – Software only device	same
Sterility	N/A – Software only device	same
Electrical Safety	N/A – Software only device	same
Mechanical Safety	N/A – Software only device	same
Chemical Safety	N/A – Software only device	same
Thermal Safety	N/A – Software only device	same
Radiation Safety	N/A – Software only device	same

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Performance Data

The following performance data were provided in support of the substantial equivalence determination.

Software Verification and Validation Testing

Brainomix 360 e-ASPECTS complies with DICOM (Digital Imaging and Communications in Medicine) – Developed by the American College of Radiology and the National Electrical Manufacturers Association. NEMA PS 3.1 - 3.20

Brainomix 360 e-ASPECTS is tested against its user needs and intended use by the successful execution of planned software verification and validation testing included in this submission. Algorithm validation testing has additionally been performed using phantom data with known properties.

The results of software verification and validation and algorithmic testing demonstrate that Brainomix 360 e-ASPECTS has met all design requirements and specifications associated with the intended use of the software.

Stand-alone Performance Testing

Stand-alone performance testing was conducted to comply with special controls for this device type. Stand-alone performance testing demonstrated that the proposed device provides accurate representation of key processing parameters under a range of clinically relevant parameters and perturbations associated with the intended use of the software. The stand-alone performance testing demonstrates the generalized performance for a range of typical patient demographics and a typical range of cases with confounding factors and including radiologically normal cases which is the same as for the predicate device. The standalone performance dataset was additionally enriched to include a greater number of cases within the low ASPECTS and late time-window sub-groups to demonstrate generalizability across these groups.

The stand-alone performance testing dataset comprised 256 non-contrast CT scans from patients with suspected and later confirmed acute ischemic stroke with available follow up imaging at 24 hours, from 8 different USA institutions. Patients were admitted between March 2014 and March 2020. The median age was 71 years, and 45% were female. Median NIHSS was 18 with an interquartile range of 12 to 22. 141 patients presented within 6 hours of time last seen well, 62 presented between 6 and 16 hours and 53 were unknown onset time. 180 patients had a proximal vessel occlusion (internal carotid artery or M1 segment or middle cerebral artery) and 76 were non-proximal. Ground truth ASPECTS score was <7 in 43 patients and >6 in 213 patients.

Overall performance in 256 patients showed an area under the curve of 83% (81-85, 95% CI), with a sensitivity of 68% (57-72) and a specificity of 97% (86-98).

This stand-alone performance testing demonstrates that e-ASPECTS performance generalises to a range of image acquisition and reconstruction parameters encountered in multiple clinical sites and for a range of scanner types and manufacturers.

Stand-alone performance results were generated to demonstrate generalizable performance for a range of typical patient demographics (including patient sex, age, site of occlusion, and ASPECTS score) and within individual ASPECTS regions. Consistent performance was observed in subgroups dichotomised by median age, and subgroups defined by sex. Performance was slightly lower in the non-proximal vessel occlusion subgroup (AUC, 78% versus 84%) although this was not statistically significant. Consistent performance was also observed between the grouped cortical ASPECTS regions compared to grouped basal ganglia ASPECTS regions, although at the level of the individual ASPECTS region performance did vary. Performance was lower in the M4, M6, and internal capsule regions, although this difference was not statistically significant.

Digital phantom testing

Specific validation has been carried out to test the heatmaps. This testing made use of synthetic digital phantom data created to provide a ground truth against which the performance of the heatmaps can be assessed and demonstrated. For clarity, we report that this testing showed a correlation between the volumes of the e-ASPECTS heatmaps and the volumes of synthetic hypodensities generated in the phantom dataset.

The heatmaps are generated and visualized to provide transparency of the basis of the ASPECTS score. The phantom testing results show a correlation (r>=0.95) between the volumes of e-ASPECTS heatmaps and the volume of synthetic hypodensities generated in the 200 digital phantom dataset.

Clinical Studies

A multiple reader multiple case (MRMC) cross-over study was conducted to assess performance of Brainomix 360 e-ASPECTS. The MRMC study evaluated the performance of 10 clinical readers (4 neurologists and 6 radiologists) when scoring the ASPECTS for 54 clinically representative NCCT retrospective scans with and without the aid of Brainomix 360 e-ASPECTS. Data truthing was performed by three expert neuroradiologists with access to clinical data and follow up imaging.

The MRMC study dataset comprised 54 non-contrast CT scans from patients with acute ischemic stroke affecting the middle cerebral artery territory and eligible for acute reperfusion therapy. Patients must have had no evidence of intracranial hemorrhage and imaging data had to be of adequate quality with associated demographic and follow up imaging available. Patients aged 21 years and younger were excluded. The median age was 72 years, and 48% were female. Median NIHSS was 17 with an interquartile range of 12 to 21. 36 patients presented within 6 hours of time

last seen well, 10 presented between 6 and 16 hours and 8 were unknown onset time. 40 patients had a proximal vessel occlusion (internal carotid artery or M1 segment or middle cerebral artery) and 14 were non-proximal. Ground truth ASPECTS score was <7 in 12 patients and >6 in 42 patients.

Comparison of the area under the curve (AUC) for each reader with and without the support of the e-ASPECTS tool showed a statistically significant improvement of 0.02 from 0.81 to 0.83 (p=0.028) which was the primary endpoint for the study. When comparing reader performance with the ground truth, the improved AUC in the primary endpoint was driven by an increase in both the sensitivity (positive percentage agreement, from 66 to 70%) and a small improvement in specificity (negative percentage agreement, 96%) when assisted by e-ASPECTS compared to unassisted reading. Overall percentage agreement (accuracy) also improved in line with the AUC result from 93 to 94%. Subgroup analysis based on the clinical training of the reader (radiologist versus neurologist) demonstrates a consistent impact of Brainomix 360 e-ASPECTS across reader groups. Analysis of individual reader ROC curves showed greater magnitude of increases in AUC were observed in users with lower unassisted performances ("lower performers"), and smaller changes in readers with higher unassisted performance ("high performers"). The overall ASPECTS score was more consistent between readers with use of e-ASPECTS. The range in AUC between users was also narrower with Brainomix 360 e-ASPECTS than unassisted indicating a reduction in the variation of performance between different readers when Brainomix 360 e-ASPECTS outputs are available.

Subgroup analysis of the individual regions within the ASPECTS scoring system showed that the impact of e-ASPECTS is consistent in both deep and cortical ASPECTS regions.

As the study used retrospective data, there were no specific safety endpoints in the reader study.

This study demonstrates substantial equivalence of the Brainomix 360 e-ASPECTS software for improving reader accuracy, compared to the predicate device. The results showed statistically significant improvement in the agreement between the readers and a reference standard when using the Brainomix 360 e-ASPECTS software compared to routine clinical practice.

Risk Benefit Analysis

Risk Benefit Summary	
Summary of Benefits	This device provides a systematic, automated analysis of NCCT scans of the head to provide a standardized, automated ASPECT score for Stroke workup. The clinical reader study, which included 4 neurologists and 6 neuroradiologists,

	demonstrated a statistically significant improvement in the readers' AUC (0.02 increase, with 0.04 sensitivity improvement and 0.01 specificity improvement) when scoring was performed in conjunction with the e-ASPECTS output. In a subgroup analysis, the benefit of the software was most substantial among the "lower performers" (clinical readers with a lower unaided performance compared to the ground truth) whereas "high performers" were minimally affected by the device output. Both cohorts included a mix of US board certified neurologist and neuroradiologist readers, indicating potential benefit for less experienced clinicians evaluating NCCT for ASPECTS. It is important to note that ASPECTS evaluations can be challenging, particularly for less experienced clinicians, and studies have shown varying levels of interobserver agreement for ASPECTS evaluation. Overall, the system should provide more consistent and timely benefit of aided reads for less-experienced or less confident users in the evaluation of overall ASPECTS. Timely, consistent and accurate assessments of acute ischemic patients with *known* MCA and ICA occlusions can help ensure that physicians determine appropriate patient management at the right time. ASPECTS may be used in the assessment of patients for consistency with patient selection for neurothrombectomy and other acute stroke therapeutic interventions. Proper and timely patient selection increases the likelihood for successful therapeutic interventions proven to reduce long term disability. The duration of the effect is lifetime. Based on the data provided it is not possible to accurately predict the exact likelihood of

	patient benefit. The study demonstrates improvement in the assessment for readers interpreting NCCT scans for overall ASPECTS assessment. This device additionally also provides transparent AI processing enabling users to understand how the automated output has been determined and enables users to perform a more technically informed review of the automated output. This is a significant benefit which may help mitigate risks related to false negatives or false positives in the automated output, particularly for more challenging cases.
Summary of the Risks	There are minimal potential risks associated with the use of the device.
	Incorrect scoring which may result in false positive results and result to incorrect patient management with possible adverse effects such as, unnecessary additional medical imaging and/or unnecessary additional diagnostic workup.
	Incorrect scoring which may result in false negative results may lead to complications, including incorrect diagnosis and delay in disease management.
	The device could be misused to analyze images from an unintended patient population or on images acquired with incompatible imaging hardware or incompatible image acquisition parameters, leading to inappropriate diagnostic information being displayed to the user.
	Device failure could lead to the absence of results, delay of results or incorrect results, which could likewise lead to inaccurate patient assessment.

Summary of additional factors	However, based on the performance data and the application of mitigating measures (including but not limited to general controls and special controls established for this device type), use of the device is unlikely to decrease diagnostic performance of the user and possible misuse of the device does not present additional risks compared with misuse of other types of radiological image processing devices. The device includes a gating condition in software to help ensure that the software is not used on stroke mimics or the incorrect patient population. The physician may either confirm or overrule the device Heatmap provides additional transparency on regions evaluated by the ASPECTS, which may be used by the clinician to qualify or correct device outputs The study was enriched to cover the range of ASPECT scores; and, the readers in practice may not experience a significant improvement in determining ASPECTS. This device may improve the diagnostic accuracy of less experienced or less confident physicians in rating NCCT for the ASPECT score in the context of acute ischemic stroke caused by ICA or MCA occlusion (confirmed using vascular imaging such as CTA or MRA).
Conclusion	This device shows positive improvement in diagnostic accuracy in comparison to the reference standard. Although some performance data may suggest that sensitivity for some ASPECTS regions may be diminished or inconsistent in comparison to other region however, sample size limitations

	limit conclusions in this regard. The clinical reader study evidence provided demonstrates improvement in the overall performance of aided readers compared to the unaided readers. The greatest benefit was observed for the "lower performers" – bringing them to the level of the "higher performers" while avoiding adversely impacting "high performers" accuracy. The software gating conditions and other warnings integrated in the software UI are expected to be helpful in ensuring appropriate use of the device and directing clinician attention to particular regions which may be more difficult to interpret, both for users and for the device.

Prescriptive Statement

Caution: Federal law restricts this device to sale by of on the order of a physician.

Conclusion

In conclusion, the predicate device has the same intended use and substantially similar indications for use and technological characteristics as Brainomix 360 e-ASPECTS. Performance data demonstrates that Brainomix 360 e-ASPECTS performs as intended within the same clinically relevant parameters for the intended use as the predicate device.

The predicate device was cleared based in part on the results of clinical studies, therefore a clinical study was required to support substantial equivalence. The clinical data demonstrates that Brainomix 360 e-ASPECTS shows a significant improvement in the agreement between the readers and a reference standard when using the Brainomix 360 e-ASPECTS software compared to routine clinical practice. Brainomix 360 e-ASPECTS is intended to improve reader performance in estimating an overall ASPECTS score but may be less sensitive for some ASPECTS regions such as the IC and M4-M6 regions based on the performance data disclosed. The risk/benefit profile of Brainomix 360 e-ASPECTS remains favorable based on the favorable impact on readers' overall aided performance in calculating an ASPECTS score (as measured in the reader study), and the inherent inter-reader variability in identifying individual affected ASPECTS regions.

Brainomix 360 e-ASPECTS has been designed, verified and validated in compliance with 21 CFR Part 820.30 requirements and has been designed to meet the requirements associated with ANSI AAMI

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ISO 14971:2007/(R)2016. Software verification and validation, performance testing and risk management demonstrates that Brainomix 360 e-ASPECTS is safe and effective for use as intended and described in its indications for use.

We propose that Brainomix 360 e-ASPECTS is substantially equivalent to the Rapid ASPECTS predicate.