February 2, 2023

Prolira B.V.
% Dr. Paul Manberg
Corolla Clin/Reg Consulting
481 Spindrift Trail #696
Corolla, North Carolina 27927

Re: K222680
Trade/Device Name: DeltaScan Monitor R2
Regulation Number: 21 CFR 882.1440
Regulation Name: Neuropsychiatric Interpretive Electroencephalograph Assessment Aid
Regulatory Class: Class II
Product Code: NCG
Dated: December 16, 2022
Received: January 3, 2023

Dear Paul Manberg:

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,

Jay R. Gupta -S

Jay Gupta
Assistant Director
DHT5A: Division of Neurosurgical,
Neurointerventional
and Neurodiagnostic Devices
OHT5: Office of Neurological
and Physical Medicine Devices
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)*
K222680

Device Name
DeltaScan Monitor R2

Indications for Use *(Describe)*
The DeltaScan Monitor provides the binary DeltaScan Output based on a technical index of polymorphic delta (PMD) waveshape detections made in the EEG from the bipolar Fp2 and Pz channel on adult patients (over 60 years of age) to aid in the diagnosis of acute encephalopathy.

DeltaScan should only be used by a healthcare provider as a component of a complete clinical evaluation or as support for the clinician's decision to pursue further testing. The device is NOT to be used as a stand-alone method in the evaluation or diagnosis of acute encephalopathy.

The intended patient is a hospitalized, awake adult, who is at risk of acute encephalopathy and delirium as decided by the responsible licensed healthcare physician or a medical professional working under the responsibility of a licensed healthcare physician.

The use environment is in hospitals:
• non-sterile environments;
• ICUs, wards, and other patient evaluation locations;

The DeltaScan Monitor is intended to be used in combination with the DeltaScan Patch (K222671) through a proprietary connector design.

Please refer to the Instructions for Use and the Instructions for Use on the Primary packaging of the DeltaScan Patch for more information.

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.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 79 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

510(k) Summary

This summary of 510(k) safety and effectiveness information is being submitted in accordance with 21 CFR 807.92.

I. SUBMITTER

Prolira BV
Padualaan 8
Utrecht, The Netherlands NL-3584CH
Phone Number: +31 6 47762936
Email: r.vanmerkerk@prolira.com

Contact Person: Rutger van Merkerk
Date Prepared: February 2nd, 2023

II. DEVICE

Name of Device: DeltaScan Monitor
Common or Usual Name: DeltaScan Monitor R2
Classification Name: Neuropsychiatric interpretive electroencephalograph assessment aid (21 CFR 882.1440)
Regulatory Class: II
Product Code: NCG

III. PREDICATE DEVICE

Name	Manufacturer	De novo #
NEBA system	NEBA HEALTH, LLC	DEN110019

IV. DEVICE DESCRIPTION

Acute encephalopathy and delirium are extremely common in hospitalized patients, for example, one third of general medical patients aged 70 years or older has delirium (Marcantonio *et al.*, 2017, NEJM). Acute encephalopathy and delirium are, by definition, the consequence of the same underlying medical condition (Slooter *et al.*, 2020, Intensive Care Med). Acute encephalopathy can present as subsyndromal delirium, or delirium. Acute encephalopathy can be assessed with EEG (Palanca *et al.*, 2017, BJA). Delirium is determined by clinical examination (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition). Acute encephalopathy and delirium occur in the same patient. Many patients with acute encephalopathy (i.e., EEG alterations) develop delirium (i.e., behavioral changes). Patients with acute encephalopathy and/or delirium should therefore also be seen as the same

patient population. Clinically, there is a clear relation between the two, which is important to understand. The figure below presents the relationship between underlying conditions, acute encephalopathy, and delirium.

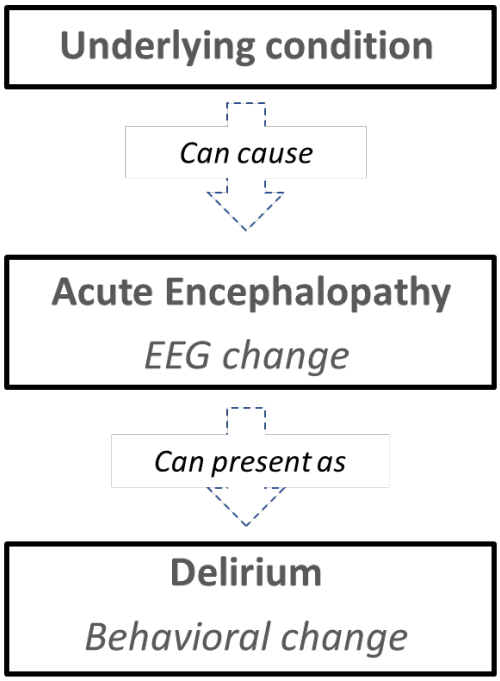


Figure 5-1: the relation between acute encephalopathy and delirium

In everyday care, standard 21-lead EEG as well as delirium expert assessments are not routinely feasible. Therefore, checklists were developed for routine screening. The diagnostic performance in routine care settings, however, is found to be low as these tests have subjective elements. Patient can be best cared for when acute encephalopathy is assessed with an objective tool that helps to detect acute encephalopathy as early as possible, followed by further clinical assessment.

Specific delta activity (PolyMorphic Delta activity; PMD) occurs in the EEG of patients with acute encephalopathy and delirium (i.e., PMD waves are a known characteristic of acute encephalopathy and delirium). PMD is considered a sensitive and specific biomarker for acute encephalopathy and delirium in awake adults (over 60 years of age) without dementia, neurological trauma, or other causes of PMD in the awake state.

The DeltaScan Monitor provides EEG signal acquisition and analysis technology intended for use as an adjunct to clinical judgment. The DeltaScan Monitor provides support in clinical decision-making by providing an assessment for a patient having acute encephalopathy or not, based on a measure of the detected polymorphic delta (PMD) waves in the EEG.

The DeltaScan Monitor consists of (see Figure 5-2 below):

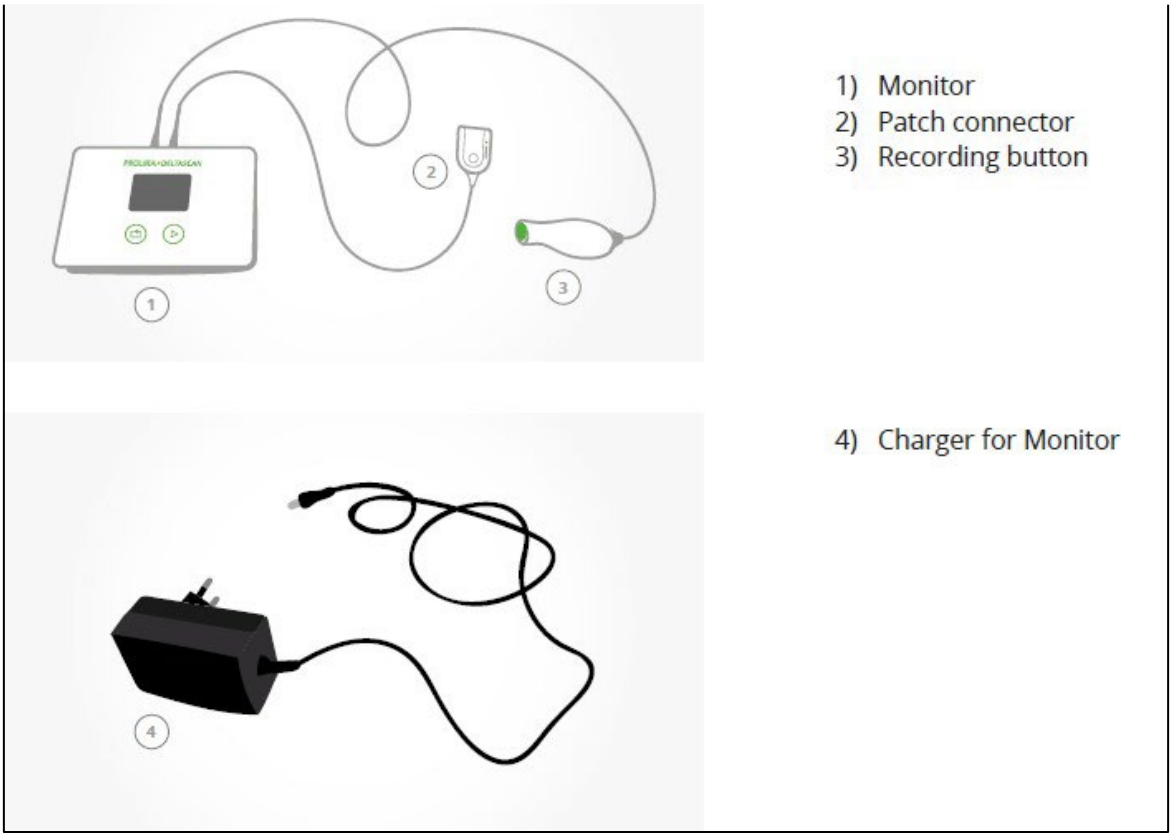


Figure 5-2 DeltaScan Monitor components

The Patch connector contains the EEG amplifier hardware. The Monitor contains electronics for galvanic isolation to the EEG cable with Patch connector, storage of EEG recording and log files (eMMC memory chip), processing capacity to run software (DeltaScan Monitor Application, or DMA), user interface elements (e.g., screen, keys, recording button), battery (FEY PA-IEC-LNB162Q.R001), and the charging circuitry.

EEG data is collected by the DeltaScan Monitor using a DeltaScan Patch (see Figure 5-3). The DeltaScan Patch requires separate 510(k) clearance as a Class II device under Classification Name Cutaneous electrode (21 CFR 882.1320).

In designing the DeltaScan Patch, the International 10-20 System was used as a basis for electrode placement. Two recording electrodes are placed on the scalp at the Fp2 and Pz locations, and the reference electrode is placed at the Fpz location. The electrodes are individually packaged and pre-gelled. The DeltaScan Monitor should only be used in combination with a DeltaScan Patch.

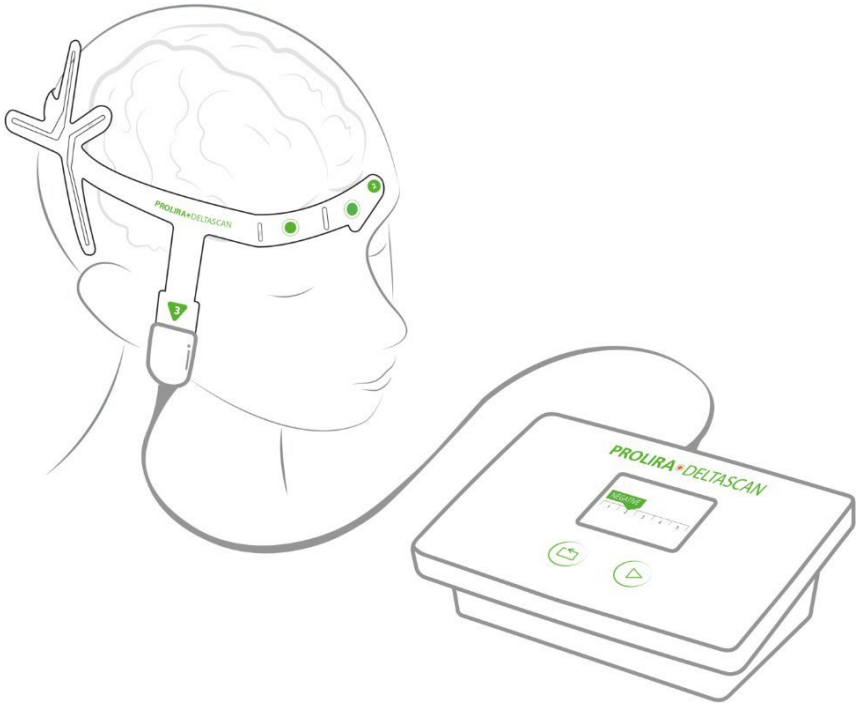


Figure 5-3 Artist impression of the DeltaScan Monitor used with a DeltaScan Patch

Collected EEG signals are amplified, digitized, and then processed by the software algorithms to provide the user with the DeltaScan Output. The DeltaScan Monitor Application is stand-alone software running on an Embedded Linux OS.

To understand Prolira's technology, first the basic concept of EEG power spectrum analysis is explained. Kooi *et al.* (2015, Chest) explain that a relative delta measure presents the relative amount of energy that is present in the EEG spectrum between 0.5Hz and 4Hz, divided by the energy in the whole spectrum of interest that lies between 0.5Hz and 30Hz. Kooi *et al.* used EEG segments that are handpicked by the researcher and that are relatively free of artefacts to perform their analysis. But, as with any automatically derived parameter, artefacts and poor signal quality may lead to inappropriate results. For example, eye movements are commonly present in a typical EEG segment (even in eyes closed EEG data). Furthermore, eye movements can present as waveshapes in the same frequency range as the waveshapes that are characteristic of acute encephalopathy and delirium (i.e., energy in the delta frequency band). Therefore, a general relative delta measure will also count the energy of eye movements when automated algorithms provide the result in a clinical setting.

To deal with this situation, Prolira's technology specifically detects EEG waveshapes that are characteristic for acute encephalopathy and delirium, allowing to calculate a specific (rather than general) measure based on the amount of detected PMD waves in the EEG. In this, Prolira uses several artifact detection and segregation approaches:

1. State-of-the-art signal conditioning and signal quality quantification technology are applied to minimize the disturbance of artefacts, removing as many artefacts as possible, for example due to poor skin contact (high impedance), muscle activity or rigidity, head and body motion, improper sensor placement, and unusual or excessive electrical interference.
2. Specific EEG waveshapes in the delta frequency range (polymorphic delta waves; PMD) are detected. Using advanced waveshape recognition technology, the chance of detecting the target waveshapes is increased, and the chance to include artefacts in the resulting measure is reduced. In addition, the algorithm also specifically detects eye artifact, which allows for additional scrutiny of detected PMD waves in the case that eye artifact and PMD waves are situated close together (see Figure 5-4 for an example of PMD wave and eye artifact detections in the EEG).

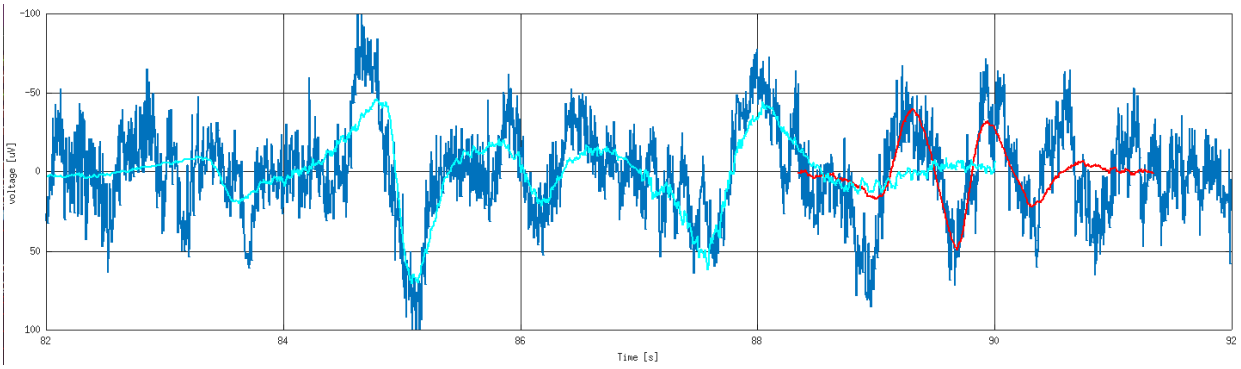


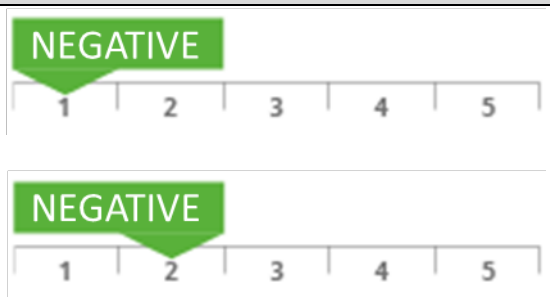
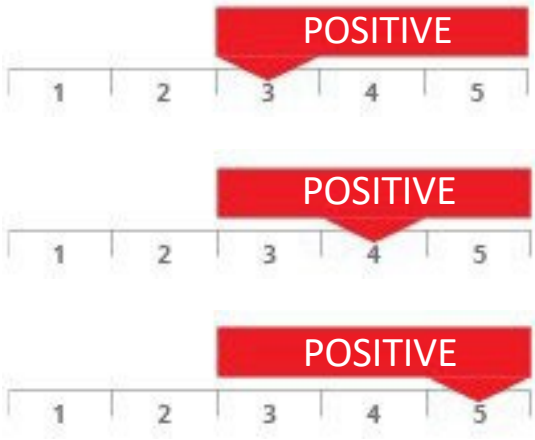
Figure 5-4: examples of a polymorphic delta (PMD) wave detection (red line) and eye artifact detections (turquoise line)

The detected and analyzed PMD waveshapes in the EEG are then translated into the 5-point DeltaScan Score, which is the DeltaScan's calibrated technical index.

The DeltaScan Output is NEGATIVE for acute encephalopathy for DeltaScan Score 1 or 2.
The DeltaScan Output is POSITIVE for acute encephalopathy for DeltaScan Score 3, 4 or 5.
See below in the section Clinical Studies for details on the clinical validation thereof.

Table 5-1 below indicates the clinical meaning of the DeltaScan Output and the technical meaning of the 5-point DeltaScan Score.

Table 5-1 Technical and clinical meaning of a DeltaScan result

DeltaScan result	***Clinical meaning of DeltaScan Output***	***Technical meaning of DeltaScan Score***
	NEGATIVE test for acute encephalopathy	For Score 1 and 2, PMD waveshapes are not or hardly detected in the EEG
	POSITIVE test for acute encephalopathy	For Score 3, 4 and 5, the amount of detected PMD waveshapes in the EEG increases

The technical 5-point scale and clinical threshold for acute encephalopathy are calibrated based on a previous clinical calibration dataset (the dataset is presented in Numan *et al.*, 2019, BJA) containing of 321 EEG recordings with expert labels for acute encephalopathy and delirium. The following calibration steps were performed:

- For each recording in the calibration dataset, the number of PMD detections and the PMD power (detected PMD waveshapes / unit time) was calculated.
- The clinical threshold for acute encephalopathy, NEGATIVE (score 1-2) and POSITIVE (score 3-5), is determined on the calibration dataset by finding an optimum for sensitivity, specificity and NPV using the expert labels for acute encephalopathy and delirium.

- The cut-offs between score 3 and 4, and score 4 and 5, were chosen to maximize repeatability of the score points. The number of patients from the calibration dataset with a POSITIVE result are equally divided over the score bins 3, 4, and 5. This sets the boundaries in terms of the PMD power.
- The cut-off between score 1 and 2 is determined by the number of detections; none or one detection always leads to DeltaScan Score 1, two detections always lead to DeltaScan Score 2, regardless of the power in those detections.

Note: the measure based on the detected PMD waveshapes underlying the 5-point scale is non-linear.

V. INDICATIONS FOR USE

The DeltaScan Monitor provides the binary DeltaScan Output based on a technical index of polymorphic delta (PMD) waveshape detections made in the EEG from the bipolar Fp2 and Pz channel on adult patients (over 60 years of age) to aid in the diagnosis of acute encephalopathy.

DeltaScan should only be used by a healthcare provider as a component of a complete clinical evaluation or as support for the clinician's decision to pursue further testing. The device is NOT to be used as a stand-alone method in the evaluation or diagnosis of acute encephalopathy.

The intended patient is a hospitalized, awake adult (over 60 years of age), who is at risk of acute encephalopathy and/or delirium as decided by the responsible licensed healthcare physician or a medical professional working under the responsibility of a licensed healthcare physician.

The use environment is in hospitals:
- in non-sterile environments;
- in departments like ICUs, wards, and other patient evaluation locations;

The DeltaScan Monitor is intended to be used in combination with the DeltaScan Patch (K222671) through a proprietary connector design.

Please refer to the Instructions for Use and the Instructions for Use on the Primary packaging of the DeltaScan Patch for more information.

VI. COMPARISON OF TECHNOLOGICAL CHARACTERISTICS WITH THE PREDICATE DEVICE

The DeltaScan Monitor is an EEG acquisition device with an integrated computer module that runs the DeltaScan Monitor Application (DMA) to provide the User Interface and runs automated processing modules to determine the DeltaScan Output on an EEG recording. Although standard EEG devices could also be used by a trained physician to detect elevated slow wave activity (high relative delta measure), the DeltaScan Monitor has been designed to provide a more practical, consistent, and easy to interpret measure of elevated low frequency waveforms associated with acute encephalopathy. In recognition of this more focused clinical application, a standard EEG device may not be the most appropriate predicate device for a 510(k) regulatory pathway.

Instead, the NEUROPSYCHIATRIC EEG-BASED ASSESSMENT AID FOR ADHD (NEBA) SYSTEM with De Novo # DEN110019 is suggested as the most appropriate predicate device.

A technology comparison between the DeltaScan Monitor and the NEBA System is provided in Table 5-2 below.

Table 5-2 Technology comparison

NEBA System	**DeltaScan Monitor**
Intended Use	
Neuropsychiatric Interpretive Electroencephalograph Assessment Aid. The Neuropsychiatric Interpretive Electroencephalograph Assessment Aid is a prescription device that uses a patient's electroencephalograph (EEG) to provide an interpretation of the patient's neuropsychiatric condition. The Neuropsychiatric Interpretive EEG Assessment Aid is used only as an assessment aid for a medical condition for which there exists other valid methods of diagnosis.	Neuropsychiatric Interpretive Electroencephalograph Assessment Aid. The Neuropsychiatric Interpretive Electroencephalograph Assessment Aid is a prescription device that uses a patient's electroencephalograph (EEG) to provide an interpretation of the patient's neuropsychiatric condition. The Neuropsychiatric Interpretive EEG Assessment Aid is used only as an assessment aid for a medical condition for which there exists other valid methods of diagnosis.
Indications for Use	

NEBA System	**DeltaScan Monitor**
The Neuropsychiatric EEG-Based ADHD Assessment Aid (NEBA®) uses the theta/beta ratio of the EEG measured at electrode CZ on a patient 6-17 years of age combined with a clinician's evaluation to aid in the diagnosis of ADHD. NEBA should only be used by a clinician as confirmatory support for a completed clinical evaluation or as support for the clinician's decision to pursue further testing following a clinical evaluation. The device is NOT to be used as a stand-alone in the evaluation or diagnosis of ADHD.	The DeltaScan Monitor provides the binary DeltaScan Output based on a technical index of polymorphic delta (PMD) waveshape detections made in the EEG from the bipolar Fp2 and Pz channel on adult patients (over 60 years of age) to aid clinicians in the diagnosis of acute encephalopathy. DeltaScan should only be used by a clinician as a component of a complete clinical evaluation or as support for the clinician's decision to pursue further testing. The device is NOT to be used as a stand-alone method in the evaluation or diagnosis of acute encephalopathy. The intended patient is a hospitalized, awake adult (over 60 years of age), who is at risk of acute encephalopathy and/ or delirium as decided by the responsible licensed healthcare physician or a medical professional working under the responsibility of a licensed healthcare physician. The use environment is in hospitals: • in non-sterile environments; • in departments like ICUs, wards, and other patient evaluation locations; The DeltaScan Monitor is intended to be used in combination with the DeltaScan Patch (**K222671**) through a proprietary connector design. Please refer to the Instructions for Use and the Instructions for Use on the Primary packaging of the DeltaScan Patch for more information.

NEBA System	**DeltaScan Monitor**
LIMITATIONS For prescription use only. The NEBA cannot be used in an individual for whom an EEG recording is not valid, specifically a patient with: • a history of EEG abnormalities; • a history of a seizure disorder; • on anticonvulsant medication(s); • a metal plate in the head; or • a metal device in the head. The NEBA system cannot be used in subjects who are unable to remain still for a minimum of 30 seconds for EEG recording. The NEBA system should only be used by medical professionals qualified to assess psychiatric disorders and experienced in diagnosing ADHD. To ensure proper device performance, the user must first perform a diagnostic evaluation per the standard of their practice. NEBA interpretations are based on the clinician's initial diagnostic evaluation, the subject's age and the EEG results. The device should not be used as a stand-alone diagnostic device. PLEASE REFER TO THE LABELING FOR A MORE COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.	LIMITATIONS For prescription use only. The DeltaScan Monitor cannot be used in an individual for whom an EEG recording is not valid, specifically a patient: • on sedation (RASS -4 or -5); • persons under 60 years of age; • with a history of brain injury; • using Lithium/Clozapine; • with a metal or plastic implant in the upper hemisphere of the head; • with an active medical device in the head The DeltaScan system cannot be used in subjects who are unable to follow three measurement instructions; the patient should (1) be awake, (2) be relaxed, and (3) keep the eyes closed. For patients on sedatives with a RASS -3, with dementia (MMSE≤24), and with (acute) brain injury, the DeltaScan Output can be higher than expected. For more severe and/or acute cases (i.e., of sedation, dementia and brain injury), it becomes less likely that a POSTIVE DeltaScan Output relates to an acute encephalopathic brain state. The meaning of NEGATIVE DeltaScan Output for these patients is most likely not altered. The DeltaScan Output for these patients should be interpreted accordingly. The DeltaScan Monitor should only be used by licensed healthcare physicians or medical professionals qualified to assess inpatient disorders and who are experienced in diagnosing acute encephalopathy and/ or delirium, or by other medical professionals working under the responsibility of a licensed healthcare physician. To ensure proper device performance, the user must perform a diagnostic evaluation per the standard of their practice. DeltaScan interpretations are based on the clinician's initial diagnostic evaluation, the subject's response to questioning and the EEG results. The device should not be used as a stand-alone diagnostic device. PLEASE REFER TO THE LABELING FOR A MORE COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.
Primary EEG Feature/Electrode position	
Theta/Beta Ratio	A binary DeltaScan Output based on a technical index of polymorphic delta (PMD) waveshape

NEBA System	**DeltaScan Monitor**
	detections made in the EEG
CZ	Fp2 and Pz
Software	
Software for the device consisted of both proprietary software and off-the- shelf (OTS) software. The software was reviewed and the provided documentation was found adequate and consistent with a 'MODERATE' level of concern., as discussed in the FDA document, "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices," issued May 11, 2005.	DeltaScan Monitor Application developed according to "EN 62304:2006+A1:2015 Medical device software - Software life-cycle processes". Software class according to EN62304:2006+A1:2015: Class B. The software was reviewed and the provided documentation was found adequate and consistent with a 'MODERATE' level of concern., as discussed in the FDA document, "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices," issued May 11, 2005.
Device output	
Three categories LOW TBR = Strongly Recommend Further Clinical Testing (other conditions) MODERATE TBR = Suggest Further Clinical Testing (other conditions) HIGH TBR = Confirmatory Support for ADHD as primary diagnosis	Two categories based on a threshold of the amount of PMD waveshapes detected in the EEG: - NEGATIVE for acute encephalopathy - POSITIVE for acute encephalopathy

VII. PERFORMANCE DATA

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

Biocompatibility testing

The biocompatibility evaluation for the DeltaScan Monitor was assessed in accordance with the FDA's guidance document titled, "Use of International Standard ISO 10993-1, 'Biological Evaluation of Medical Devices Part 1: Evaluation and testing within a risk management process'", June 16, 2016.

The DeltaScan Monitor, its EEG cable, the Recording button, and the medical-grade Power adapter have ***transient contact with the patient's and/ or user intact skin*** (i.e., finger contact while setting up and using the device).

If there is contact between the patient and a part of the DeltaScan Monitor at all, this would be with the Patch connector, see Figure 5-2 above.

None of the components are “attached” to skin, all contact is handling contact. The material of DeltaScan Monitor is generally used in combination with intact skin of the user, and the materials used are identical as in widespread use applications.

Based on the above, there is ***no biocompatibility testing needed for the DeltaScan Monitor***.

Electrical safety and electromagnetic compatibility (EMC)
Electrical safety and EMC testing were conducted on the DeltaScan Monitor. The DeltaScan Monitor complies with the IEC 60601-1:2005+A1:2012 standard for safety and the IEC 60601-1-2:2014 standard for EMC.

Software verification and validation testing
Software verification and validation testing were conducted, and documentation was provided as recommended by FDA’s Guidance for Industry and FDA Staff, “Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices” and “Content of Premarket Submissions for Management of Cybersecurity in Medical Devices”. The software for this device was considered a “moderate” level of concern, since a failure or latent flaw in the software could lead to a delay in delivery of appropriate medical care that could lead to minor injury.

Performance bench testing
Thorough bench testing is provided in the file which are considered adequate. This included, but is not limited to:

- Usability testing demonstrated compliance to EN 62366-1:2015+A1:2020
- The labeling was tested to be legible, durable, compliant with regulations, and compatible with the packaging.
- The packaging was tested to verify it is compatible with the labeling and can be shipped without damage.
- Mechanical Strength testing demonstrated compliance to IEC 60601-1:2005+A1:2012 (cl.15.3).
- Bench testing showed >95% reliability for the technical 5-point DeltaScan Score for increasing amounts of polymorphic delta activity (PMD) present in sample EEGs.

These verification and validation activities all show that the device complies to the preset requirements.

Clinical Studies
Diagnostic Performance testing of DeltaScan was done in the multi-center DeltaStudy, which ran between Q1 2018 and Q3-2021.

The study has been designed to comply with ISO 14155:2011 Clinical investigation of medical devices for human subjects - Good clinical practice, and in the European Medical Device Regulation (MDR)

2017/745 Annex XV Chapter II, and to comply with the United States Food and Drug Administration's special control 21 CFR 882.1440.

In respect to 21 CFR 812.28(a)(1) Good Clinical Practice. Although the rule does not identify a specific GCP standard, by following ISO 14155:2011 in the conduct of clinical investigations the requirement in § 812.28(a)(1) of this rule (as well as the local laws and regulations of the countries where the investigations are conducted) are met.

SUMMARY OF CLINICAL TESTS

DeltaScan was developed based on clinical datasets described in 1) Kooi et al. (2015, Chest) and 2) Numan *et al.* (2019, BJA; clinicaltrials.gov # NCT02404181).

Registration study: clinical study design

The objective of the study presented here, called DeltaStudy (clinicaltrials.gov # NCT03966274), was to evaluate the diagnostic performance of the DeltaScan Monitor according to the Indications for Use and to evaluate repeatability.

The clinical investigation included the collection of EEGs with DeltaScan and clinical data on ICUs and wards. An EEG expert panel reviewed the DeltaScan EEGs and a clinical expert panel reviewed the clinical data to determine consensus diagnosis (majority vote) for acute encephalopathy and delirium, respectively.

For acute encephalopathy, the reference standard was defined by the assessment by 3 separate EEG experts of 4-minutes of EEG data recorded with DeltaScan. The EEG data was visually assessed by the EEG experts, for the presence of polymorphic delta activity to determine acute encephalopathy.

For delirium, the reference standard was defined by the assessment of clinical data by 3 clinical delirium experts separately. Clinical data included a researcher's interview based on DSM-5 criteria A-C through an extensive test battery, Electronic Health Record data, and description of the behavior of the patient. Clinical data were assessed on individual DSM-5 criteria, the presence of delirium, and the probability of delirium.

All EEG and clinical assessments were blinded to DeltaScan Output, prospectively planned, and performed as reviews of anonymized patient data. As the estimated diagnosis of acute encephalopathy and delirium we used the majority vote of 3 EEG experts, and 3 clinical delirium experts, respectively.

Subjects were adults on the ICU (avg. age 64 years; std = 13) and elderly on wards (avg. age 80 years; std = 7) in geographically distinct clinics (6 ICUs and 15 wards) in the Netherlands. It shall be noted that some Study Data in the ICU population does contain patients in the 18-60 range; however, the majority of the study population was 60, or above.
In total, 606 patients were enrolled in the study of whom 434 patients (195 on ICUs and 239 on wards) fulfilled inclusion, but not exclusion, criteria. Due to COVID-19 restriction, the number of patients on ICUs is less than aimed for and that resulted in larger confidence bounds than anticipated.

A DeltaScan Output for each subject was determined from the DeltaScan EEG recording in the locked databases (ICUs and wards). To evaluate performance, the DeltaScan Outputs were compared with the estimated diagnosis of the two expert panels (references for acute encephalopathy and delirium).

Results: diagnostic performance of DeltaScan
The diagnosis of acute encephalopathy (EEG reference standard) was based upon the best estimate diagnosis results by consensus of the expert panel and was blinded to the DeltaScan Output.

Table 5-3 tabulates the primary objectives and the results. We see that the pre-specified values for the lower bound of the CI for the ICU (≥0.8) and on wards (≥0.85) are just missed The main reason is that the found prevalence of AE on the ICU was 44% (vs. the expected 35% in the study protocol) and on the ward was 39% (vs. the expected 25% in the study protocol), which resulted in lower values for the lower bound of the CI for NPV than anticipated.

A sensitivity analysis that adjusts the prevalence to the expected prevalence showed that under these conditions, the end-points would have been met (see Table 5-3 for details). When pooling the ICU and ward patients, we see the same result when adjusting the prevalence to the expected prevalence for the ICU.

So, the main reason why the end-point for NPV was missed is clear: the prevalence estimates were too low in the power calculation, resulting in too high pre-specified criteria.

Specifically for the ICU, the included number of patients (n) was less than aimed for due to COVID-19 restriction, resulting in larger confidence intervals.

Table 5-3 Results on primary hypothesis on acute encephalopathy (EEG labels) for adults on the ICU and elderly patients on wards. We are also showing the results when pooling the ICU and ward patients.

Department	Pre-specified criteria	Study result	Pass/Fail on pre-specified criteria	Discussion and Sensitivity analysis	Rationale for safety and effectiveness
ICU	Null hypothesis: NPV < 0.80 (lower bound of CI ≥ 0.8)	NPV = 0.85 CI = [0.77, 0.92]	**Fail**	**The reasons why the end-point for NPV was missed is clear**: 1) due to COVID-19 restriction, the number of patients on ICUs is less than aimed for, resulting in larger confidence intervals, and 2) the prevalence estimates were too low in the power calculation, resulting in too high pre-specified criteria.	We conclude that reasons for the missed end-point on NPV are clear and understood. Overall, NPV values are reasonably high, while NPV+PPV values exceed the pre-specified criterium. Both NPV and PPV results are robust for some variation in study assumptions (sensitivity analysis).
	NPV + PPV ≥ 1	NPV + PPV = 1.62 CI = [1.50, 1.72]	**Pass**		

				A **sensitivity analysis** that adjusts the prevalence to the study protocol estimate for prevalence (35%) shows that: NPV = 0.89 [0.85, 0.94] PPV = 0.69 [0.61, 0.77] NPV+PPV = 1.59 [1.47, 1.70] **Under these conditions, the end-points would have been met.**	**When considering both NPV and PPV, the performance shows safety and effectiveness**
Ward	Null hypothesis: NPV < 0.85 (lower bound of CI ≥ 0.85)	NPV = 0.83 CI = [0.76, 0.89]	**Fail**	**The reason why the end-point for NPV was missed is clear**: the prevalence estimates were too low in the power calculation, resulting in too high pre-specified criteria. A **sensitivity analysis** that adjusts the prevalence to the study protocol estimate for prevalence (25%) shows that: NPV = 0.90 [0.87, 0.93] PPV = 0.71 [0.62, 0.82] NPV+PPV = 1.62 [1.50, 1.74] **Under these conditions, the end-points would have been met.**	We conclude that reason for the missed end-point on NPV are clear and understood. Overall, NPV values are reasonably high, while NPV+PPV values exceed the pre-specified criterium. Both NPV and PPV results are robust for some variation in study assumptions (sensitivity analysis). **When considering both NPV and PPV, the performance shows safety and effectiveness**
	NPV + PPV ≥ 1	NPV + PPV = 1.66 CI = [1.55, 1.75]	**Pass**		
ICU + Ward (pooled)	Null hypothesis: NPV < 0.80 (lower bound of CI ≥ 0.8)	NPV = 0.84 CI = [0.79, 0.88]	**Fail**	**The reason why the end-point for NPV was missed is clear**: the prevalence estimates were too low in the power calculation, resulting in too high pre-specified criteria. A **sensitivity analysis** that adjusts the prevalence to the study protocol estimate for prevalence on the ICU (35%) shows that: NPV = 0.87 [0.84, 0.90] PPV = 0.75 [0.69, 0.81] NPV+PPV = 1.62 [1.53, 1.70] **Under these conditions, the end-points would have been met.**	We conclude that reason for the missed end-point on NPV are clear and understood. Overall, NPV values are reasonably high, while NPV+PPV values exceed the pre-specified criterium. Both NPV and PPV results are robust for some variation in study assumptions (sensitivity analysis). **When considering both NPV and PPV, the performance shows safety and effectiveness**
	NPV + PPV ≥ 1	NPV + PPV = 1.63 CI = [1.55, 1.71]	**Pass**		

Suggested clinical interpretation

The clinician will typically have a DeltaScan Output and his/her clinician's evaluation for clinical signs (behavioral changes) that could indicate delirium. Table 5-4 indicates how the additional information from the DeltaScan Monitor can be used with other existing clinical information.

Table 5-4 Suggested clinical interpretation for combined clinician's evaluation and DeltaScan Output

	DeltaScan Output: NEGATIVE (green)	**DeltaScan Output: POSITIVE (red)**
Clinician positive for delirium signs	Negative result for acute encephalopathy, but with clinical signs of delirium Further evaluate other causes of the observed clinical behavior to determine the correct diagnosis	DeltaScan confirms clinician's evaluation
Clinician negative for delirium signs	DeltaScan confirms clinician's evaluation	Positive result for acute encephalopathy without clinical signs of delirium Further evaluate causes for the presence of PMD in the EEG to determine the correct diagnosis

Table 5-4 indicates that, especially when there is a difference in the clinician's evaluation and the DeltaScan Output, the combination aids the clinician in finding the correct diagnosis. Either by considering an alternative for the positive delirium signs (e.g., psychosis or hallucinations without delirium), or by providing evaluation that explains the presence of PMD waves in the EEG (e.g., a bladder infection, or acute kidney failure).

Repeatability of DeltaScan results

The repeatability (test-retest reliability) of the DeltaScan Score was estimated from a set of DeltaScan EEG recordings in which each patient or volunteer was recorded 3 times within 30 minutes. There were 9 patients (same inclusion and exclusion criteria as the main DeltaStudy as presented above) and 30 volunteers included in this analysis. The intraclass correlation coefficient (ICC) of repeated DeltaScan Scores includes the 1-5 scale. The calculated ICC is 0.799 and $p = 0.0000$, which satisfies the pre-specified criteria of ICC > 0.75 and $p < 0.05$. The calculated ICC for the binary DeltaScan Output: ICC is 0.829, $p = 0.0000$.

Conclusions on clinical study results

- Acute encephalopathy
    - Diagnostic performance in acute encephalopathy assessment is good, almost meeting the pre-specified criterium for NPV. the NPV end-point is just missed due to a higher than anticipated prevalence, both on the ICU and on wards. Under the condition where the prevalence is adjusted to the expected values, the pre-specified criteria are met. The results for NPV+PPV for both the ICU and the ward exceed the

pre-specified criterium.
    - On the 67% subgroup of patients who had congruent results using the reference EEG and Clinical assessments, the found NPV was especially high at 0.94.

- Repeatability
    - Repeatability testing for the 5 point DeltaScan Scale satisfied the pre-specified criteria (ICC ≥ 0.75) and resulted in an ICC of 0.799.
      The ICC for the binary DeltaScan Output is higher at 0.829.

- Generalizability
    - The patients in this study are a good representation of the intended use population. From site to site, department to department, and between US and OUS, the prevalence of the condition can vary. Our sensitivity analysis on prevalence shows that performance remains strong regardless.

- Safety
    - Safety of the DeltaScan Monitor has been established. Physical use of the device has been shown to be safe. EEG collection is a safe, non-invasive procedure. No adverse device events and no unanticipated adverse device events were reported in the clinical investigation.

- Suggested clinical interpretation
    - It is suggested that differences in a clinician's evaluation and a DeltaScan Output can lead to further evaluation to determine the correct diagnosis.

These results present convincing evidence to justify the Indications for Use of the DeltaScan Monitor.

The clinical data demonstrate that the DeltaScan Monitor performs as intended, is safe and effective for its intended use, and provides similar safety and effectiveness results to the predicate device.

VIII. CONCLUSION

The DeltaScan Monitor has the same Intended Use and similar Indication for Use and substantially equivalent technological characteristics as the identified predicate device.

Both the DeltaScan Monitor and predicate devices are EEG based applications as support for the clinician's decision.

Based on the Intended Use, technological characteristics, and performance data provided in this premarket notification, the subject device has been shown to be substantially equivalent to the currently marketed predicate device.