December 2, 2021

Tilmann Kluge, Ph.D.
Official Correspondent
Austrian Institute of Technology GmbH
Giefinggasse 4
1210 Vienna, Austria

Re: K211452
Trade/Device Name: Encevis
Regulation Number: 21 CFR 882.1400
Regulation Name: Electroencephalograph
Regulatory Class: Class II
Product Code: OMB, OLT, OMA
Dated: November 2, 2021
Received: November 4, 2021

Dear Tilmann Kluge:

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,

for
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)*
K211452

Device Name
encevis

Indications for Use *(Describe)*
1. encevis is intended for the review, monitoring and analysis of EEG recordings made by electroencephalogram (EEG) devices using scalp electrodes and to aid neurologists in the assessment of EEG. This device is intended to be used by qualified medical practitioners who will exercise professional judgment in using the information.
2. The seizure detection component of encevis is intended to mark previously acquired sections of adult (greater than or equal to 18 years) EEG recordings that may correspond to electrographic seizures, in order to assist qualified clinical practitioners in the assessment of EEG traces. EEG recordings should be obtained with a full scalp montage according to the standard 10/20-system.
3. The spike detection component of encevis is intended to mark previously acquired sections of the patient's EEG recordings that may correspond to spikes, in order to assist qualified clinical practitioners in the assessment of EEG traces. The Spike Detection component is intended to be used in adult patients greater than or equal to 18 years. encevis Spike Detection performance has not been assessed for intracranial recordings.
4. encevis includes the calculation and display of a set of quantitative measures intended to monitor and analyze the EEG waveform. These include frequency bands, rhythmic and periodic patterns and burst suppression. These quantitative EEG measures should always be interpreted in conjunction with review of the original EEG waveforms.
5. The aEEG functionality included in encevis is intended to monitor the state of the brain.
6. encevis provides notifications on an on-screen display for seizure detection, spike detection, quantitative EEG and aEEG that can be used when processing a record during acquisition. Delays of up to several minutes can occur between the beginning of a seizure, the occurrence of a spike or detection of quantitative EEG features and when the encevis notifications will be shown to a user. encevis notifications cannot be used as a substitute for real time monitoring of the underlying EEG by a trained expert.
7. encevis PureEEG (Artifact Reduction) is intended to reduce EMG and electrode artifacts in a standard 10-20 EEG recording. PureEEG does not remove the entire artifact signal, and is not effective for other types of artifacts. PureEEG may modify portions of waveforms representing cerebral activity. Waveforms must still be read by a qualified medical practitioner trained in recognizing artifact, and any interpretation or diagnosis must be made with reference to the original waveforms.
8. This device does not provide any diagnostic conclusion about the patient's condition to the user.

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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Traditional 510(k)	**510(k) Premarket Notification encevis**	AUSTRIAN INSTITUTE OF TECHNOLOGY

510k Summary encevis

510k Summary encevis

1. Submission Sponsor and Application Correspondent

A. Submission Sponsor

AIT Austrian Institute of Technology GmbH
Giefinggasse 4
1210 Vienna – Austria
Phone: +43 50550-4203
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eMail: tilmann.kluge@ait.ac.at

2. Date Prepared

May 5th, 2021

3. Device Identification

Trade/Proprietary Name:	encevis
Common Name:	Electroencephalograph
Classification Regulation:	21CFR882.1400
Product Code:	OMB, OLT, OMA
Class:	II
Panel:	Neurology

4. Legally Marketed Predicate Devices

Primary Predicate:	K132306	Persyst 12 EEG Review and Analysis Software
Additional Predicate:	K171720	encevis 1.6

5. Device Description

encevis combines several modalities for viewing and analyzing EEG data in one integrated software package. Encevis consists of the following modalities:

encevis EEG-Viewer

The encevis EEG-viewer is intended for the review and the analysis of EEG-recordings that were recorded with an electroencephalography device using scalp electrodes. It shall aid the user in the examination of EEG-recordings. This includes frequency filtering of data, scaling of data in x and y direction and visualization in different montages. In addition, the encevis EEG-viewer can start several modules that automatically analyze the EEG and present the results in form of markers or in the form of modified EEG-curves. All included modules are intended for the support of the user in the examination and monitoring of EEG-recordings.

encevis artifact reduction (PureEEG)

The artefact reduction encevis PureEEG is an analysis module that automatically recognizes and reduces artefacts in the EEG-data that come from EMG or electrode artefacts.

encevis seizure detection

The encevis seizure detection is a module for the automatic marking of areas in the EEG that could correspond to epileptic seizures with electrographic correlate. encevis seizure detection makes the results available to the user in form of marker in a marker list. The marker list is shown in the encevis EEG-viewer and in the EEG-trending user interface. This analysis can take place in parallel to the recording (ad-hoc) or after the recording finished (post-hoc).

encevis spike detection (EpiSpike)

The spike detection encevis EpiSpike is a module for the automatic marking of areas in the EEG that could correspond to pikes or spike-waves. A graphical user interface presents the results to the user. The user interface contains a time line per channel, a list of spike clusters that contain spikes and a list of spikes contained in a selected cluster. In addition, either the EEG or the averaged EEG 0.5 seconds before the spike maximum to 0,5 seconds after spike maximum for all spikes in a selected cluster is shown. This post-hoc analysis can take place in parallel to the recording or after the recording finished.

encevis rhythmic and periodic patterns

encevis rhythmic and periodic patterns is a feature for the analysis of EEG-recordings. It automatically detects EEG-patterns defined in the Standardized Critical Care EEG Terminology of the American Clinical Neurophysiology Society (Hirsch, L.J., et al., 2013. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version. J. Clin. Neurophysiol. 30, 1–27) and graphically presents the results to the user. Additionally, it detects and visualizes rhythmic patterns with frequencies of up to 12Hz. It serves as a support during the examination of EEG-recordings in the ICU. This post-hoc analysis can take place in parallel to the recording or after the recording finished.

encevis aEEG

Encevis aEEG calculate and visualize a continuous measure that describes the EEG by showing the aEEG as defined in "Zhang, D., Ding, H., 2013. Calculation of compact amplitude-integrated EEG

tracing and upper and lower margins using raw EEG data. Health (N. Y.) 05, 885–891. doi:10.4236/health.2013.55116".

encevis frequency bands

Encevis frequency bands calculate and visualize a continuous measure that describe the EEG by showing the frequency distribution of the EEG. The relative proportions of the four frequency bands Delta, Theta, Alpha, and Beta are shown. The intensity of the colors corresponds to the amplitudes in these four frequency bands.

encevis Burst Suppression

Encevis burst suppression feature calculates and visualizes suppression rate and suppression time in percent. It calculates periods of burst suppression in the EEG and marks them by vertical bars with red color. The definition of burst suppression patterns follows the guidelines of the American Clinical Neurophysiology Society ICU EEG Terminology (Hirsch, L.J., LaRoche, S.M., Gaspard, N., Gerard, E., Svoronos, A., Herman, S.T., Mani, R., Arif, H., Jette, N., Minazad, Y., Kerrigan, J.F., Vespa, P., Hantus, S., Claassen, J., Young, G.B., So, E., Kaplan, P.W., Nuwer, M.R., Fountain, N.B., Drislane, F.W., 2013. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version. J. Clin. Neurophysiol. 30, 1–27. doi:10.1097/WNP.0b013e3182784729).

6. Indication for Use Statement

1. encevis is intended for the review, monitoring and analysis of EEG recordings made by electroencephalogram (EEG) devices using scalp electrodes and to aid neurologists in the assessment of EEG. This device is intended to be used by qualified medical practitioners who will exercise professional judgment in using the information.

2. The seizure detection component of encevis is intended to mark previously acquired sections of adult (greater than or equal to 18 years) EEG recordings that may correspond to electrographic seizures, in order to assist qualified clinical practitioners in the assessment of EEG traces. EEG recordings should be obtained with a full scalp montage according to the standard 10/20-system.

3. The spike detection component of encevis is intended to mark previously acquired sections of the patient's EEG recordings that may correspond to spikes, in order to assist qualified clinical practitioners in the assessment of EEG traces. The Spike Detection component is intended to be used in adult patients greater than or equal to 18 years. encevis Spike Detection performance has not been assessed for intracranial recordings.

4. encevis includes the calculation and display of a set of quantitative measures intended to monitor and analyze the EEG waveform. These include frequency bands, rhythmic and periodic patterns and burst suppression. These quantitative EEG measures should always be interpreted in conjunction with review of the original EEG waveforms.

5. The aEEG functionality included in encevis is intended to monitor the state of the brain.

6. encevis provides notifications on an on-screen display for seizure detection, spike detection, quantitative EEG and aEEG that can be used when processing a record during acquisition. Delays of up to several minutes can occur between the beginning of a seizure, the occurrence of a spike or detection of quantitative EEG features and when the encevis notifications will be shown to a user. encevis notifications cannot be used as a substitute for real time monitoring of the underlying EEG by a trained expert.

7. encevis PureEEG (Artifact Reduction) is intended to reduce EMG and electrode artifacts in a standard 10-20 EEG recording. PureEEG does not remove the entire artifact signal, and is not effective for other types of artifacts. PureEEG may modify portions of waveforms representing cerebral activity. Waveforms must still be read by a qualified medical practitioner trained in recognizing artifact, and any interpretation or diagnosis must be made with reference to the original waveforms.

8. This device does not provide any diagnostic conclusion about the patient's condition to the user.

7. Substantial Equivalence Discussion

The following table compares the encevis to the predicate device with respect to intended use, technological characteristics and principles of operation, providing more detailed information regarding the basis for the determination of substantial equivalence.

	encevis	**Persyst 12 (primary predicate)**	**Encevis 1.6 (additional predicate)**
510k Reference	(subject device)	K132306	K171720
Product Code	OMB	OMB	OMB
Additional Codes	OLT, OMA	OLT, OMA	OLT, OMA
Class	II	II	II
Regulation Number	21CFR882.1400	21CFR882.1400	21CFR882.1400
Regulation Name	Electroencephalograph	Electroencephalograph	Electroencephalograph
Manufacturer	AIT Austrian Institute of Technology GmbH	Persyst Development Corporation	AIT Austrian Institute of Technology GmbH
General Device Description	EEG Review and Analysis Software	EEG Review and Analysis Software	EEG Review and Analysis Software
Shows EEG	YES	YES	YES
Has Artefact reduction	YES	YES	YES
Identifies seizures	YES	YES	YES
Identifies spikes	YES	YES	YES
Calculates quantitative EEG measures	YES	YES	YES
Calculated EEG measures displayed	YES	YES	YES
Type of EEG-Analysis	Post-hoc analysis	Post-hoc analysis	Post-hoc analysis
Type of EEG	Scalp EEG	Scalp EEG	Scalp EEG
Population age	Adults (age > 18)	Adults (age >18); Spike detection for ages > 1 month.	Adults (age > 18)
User	This device is intended to be used by qualified medical practitioners who will exercise professional judgment in using the information.	This device is intended to be used by qualified medical practitioners who will exercise professional judgment in using the information.	This device is intended to be used by qualified medical practitioners who will exercise professional judgment in using the information.
Input Files	Display and calculation based on EEG data recorded by external EEG systems. They are either read from the EEG-file provided by the EEG system or can be send to encevis using the interface provided by AIT (AITInterfaceDLL)	Display and calculation is based on EEG data recorded by external EEG systems. They are read from the EEG-file provided by the EEG system	Display and calculation based on EEG data recorded by external EEG systems. They are either read from the EEG-file provided by the EEG system or can be send to encevis using the interface provided by AIT (AITInterfaceDLL)
Compliance	No standard data format available in the industry	No standard data format available in the industry	No standard data format available in the industry
Output Files	Results are stored in a database and/or is send over the interface AITInterfaceDLL to an external EEG system. User output is given by graphical user interfaces	Results are stored in additional files in the file system placed in the same folder as the EEG file. User output is given by graphical user interfaces	Results are stored in a database and/or is send over the interface AITInterfaceDLL to an external EEG system. User output is given by graphical user interfaces

Compatible Equipment and Software	Encevis can read and process EEG data from several EEG vendors. A list of compatible EEG systems can be found on http://www.encevis.com	Persys can read and process EEG data from several EEG vendors. A list of compatible EEG systems can be found on http://www.persyst.com/support/supported-formats/	Encevis can read and process EEG data from several EEG vendors. A list of compatible EEG systems can be found on http://www.encevis.com

Table 1: Comparison between encevis and the predicate device

8. Non-Clinical Performance Data

Software verification and validation testing was conducted and documentation provided as recommended by the FDA Guidance for Industry and FDA Staff, *Guidance for the Content of Software Contained in Medical Devices*. Traceability has been documented between all system specifications to validation test protocols. Verification and validation testing includes:

1. Code inspections
2. Unit level testing
3. Integration level testing
4. System level testing

In addition, tests according to “IEC 62366-1:2015, Medical Devices Part 1—Application of usability engineering to medical devices” have been performed.

The software for this device is determined as a “moderate” level of concern because a failure or latent flaw could lead to a minor injury to the patient through incorrect information or through the action of the care provider.

Verification and validation activities established the safety and performance characteristics of the subject device with respect to the predicate device. The following performance data have been provided in support of the substantial equivalence determination.

Test \ Feature	Viewer	Artifact reduction	Seizure detection	Spike detection	Rhythmic and periodic patterns	aEEG	Frequency bands	Burst Suppression
Direct comparison with predicate device		X	X	X		X		X
Bench test on large amount of EEG data		X	X	X	X	X	X	X
Software test (System, Integration, Unit)	X	X	X	X	X	X	X	X

Table 2: Type of performance test per feature

For bench tests, detection results of the modules were compared to annotations set by clinical EEG experts using large amount of EEG data from different centers. Where possible, the results of encevis

were directly compared with the results of the predicate device. Suitable statistical measures like sensitivity and specificity were calculated.

The encevis (stand-alone software) meets all the stated requirements for overall design, performance, biocompatibility and electrical safety and passed all the testing noted above.

9. Clinical Performance Data

Seizure detection performance testing:

For performance evaluation of the encevis seizure detection device we measured positive percentage agreement (detection sensitivity based on the reference standard) and negative disagreement rate (false detections per 24 hours based on reference standard) by comparing seizure detections to consensus annotations from three independent reviewers. Second, to define the acceptable performance level of the encevis seizure detection device we also measured positive percentage agreement and negative disagreement rate of the predicate device Persyst using the same study population and the same gold standard annotations. A statistical test is then used to show that the encevis seizure detection performance is non-inferior to the performance of the predicate device.

Study population

We included scalp-EEG recordings of 55 subjects that underwent video-EEG monitoring in an epilepsy monitoring unit for the purpose of differential diagnosis or pre-surgical evaluation. All patients where 18 years of age or older. 50 patients where included that showed seizure events during recording and were diagnosed of having epilepsy. Further, we included the five subjects that were diagnosed of not having epilepsy (Subject-ID 30-34). No further selection of subjects was made.

Reference Standard

To define the reference standard, a total of 1619 hours of EEG from these 55 subjects were presented to three independent neurologist for blinded review. The goal of the review sessions was to identify the start and end times of epileptic seizures to define “true seizure” epochs for later performance evaluation of the automatic seizure detection algorithm. The 1619 hours of EEG consisted of a maximum of 30 hours of continuous EEG data from each subject. For subjects without epilepsy the first available 30 hours of recording were included. The EEG experts were asked to mark the time positions of the seizure onset and end. An event was considered as “true seizure” only if the time interval of two out of three reviewers overlapped by at least 1 second. A *seizure epoch* was then defined as the overlapping time range of two reviewers.

The following tables show the number of EEG hours and seizures per subject.

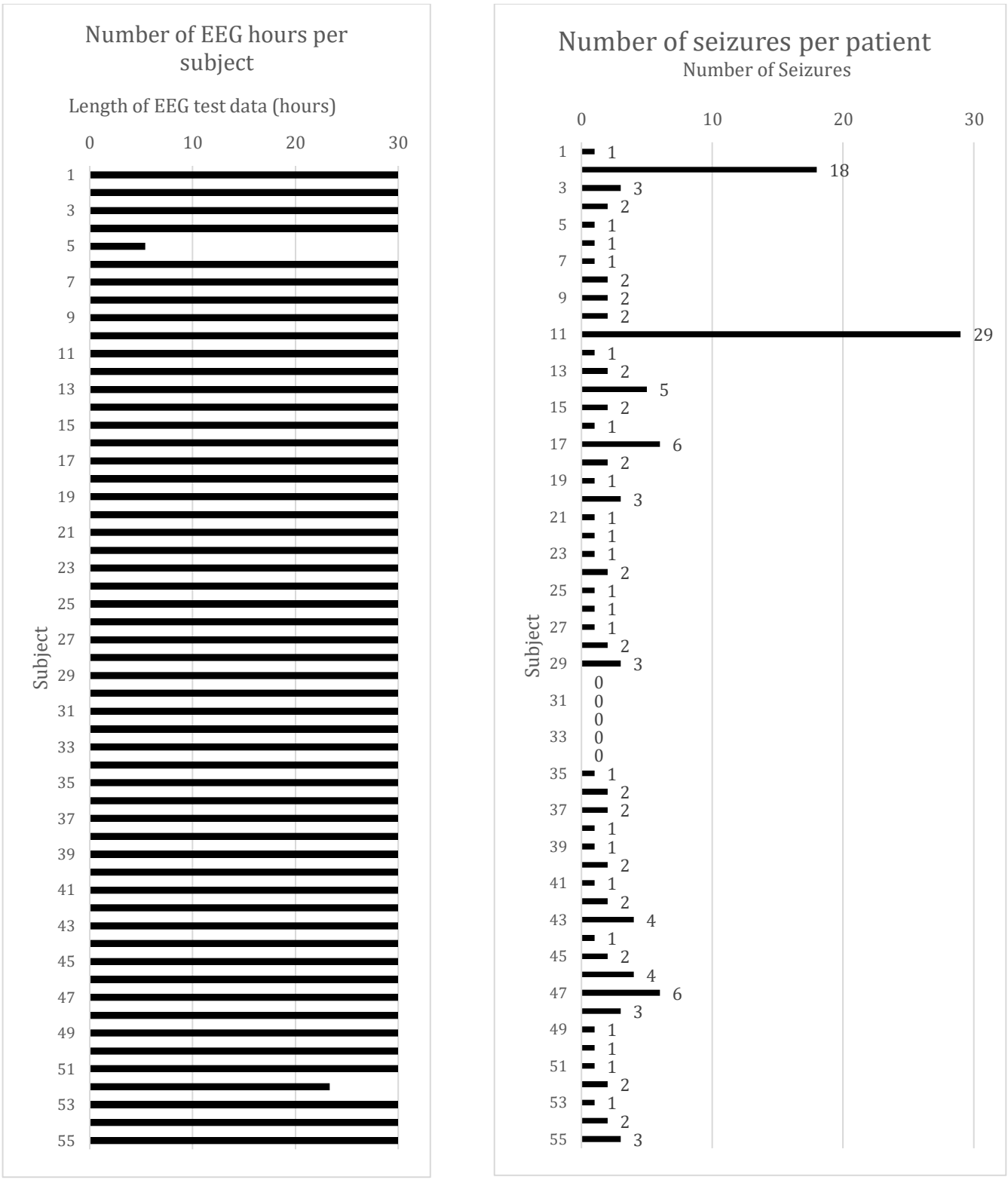

Figure 1: Number of EEG hours and seizures per subject

Inter-rater agreement

Inter-rater agreement was measured between any pair of reviewers using Cohen's kappa (κ). The agreement values were κ=0.69 (95% CI=[0.62, 0.77]) between reviewer 1 to reviewer 2, κ=0.76 (95% CI=[0.69, 0.83]) between reviewer 1 and reviewer 3, and κ=0.79 (95% CI=[0.72, 0.85]) between reviewer 2 and reviewer 3. The average agreement resulted in κ=0.74. According to the qualitative classification of Landis and Koch (Landis JR, Koch GG, Biometrics. 1977 Mar;33(1):159-74) the average κ value of 0.74 can be interpreted as substantial agreement.

Detection Performance

To define positive percentage agreement (PPA) and negative disagreement rate (NDR, given as false detections in 24 hours) for each patient the *seizure epochs* defined by consensus annotations of two out of three reviewers were compared to automatically calculated seizure time points of the encevis seizure detection device and the predicate device Persyst. The encevis seizure detection device results in a single time point for each detection that is used in this validation. The predicate device Persyst was used with default settings (perception score = 0.5) and the given start time point was used in this validation. The logical variables true positive (TP), false positive (FP), and false negative (FN) are defined as follows: seizure epochs are counted as TP if at least one detection occurred within the epoch time range. Detections outside of seizure epochs were defined as false positives (FP). Seizure epochs without a matching detection were defined as false negative (FN).

Results

The average positive percentage agreement of the subjects with at least one "true seizure" event resulted in 86.52% (95% CI=[78.54, 94.49]) for encevis seizure detection and in 75.94% (95% CI=[65.5, 86.4]) for the predicate device Persyst.

The average negative disagreement rate (NDR) was 11.2 false detections in 24 hours (95% CI=[7.04,15.3]) for the encevis seizure detection and 10.61 false detections in 24 hours (95% CI=[6.8, 14.5]) for predicate device Persyst. The following two figures show the average results including confidence intervals.

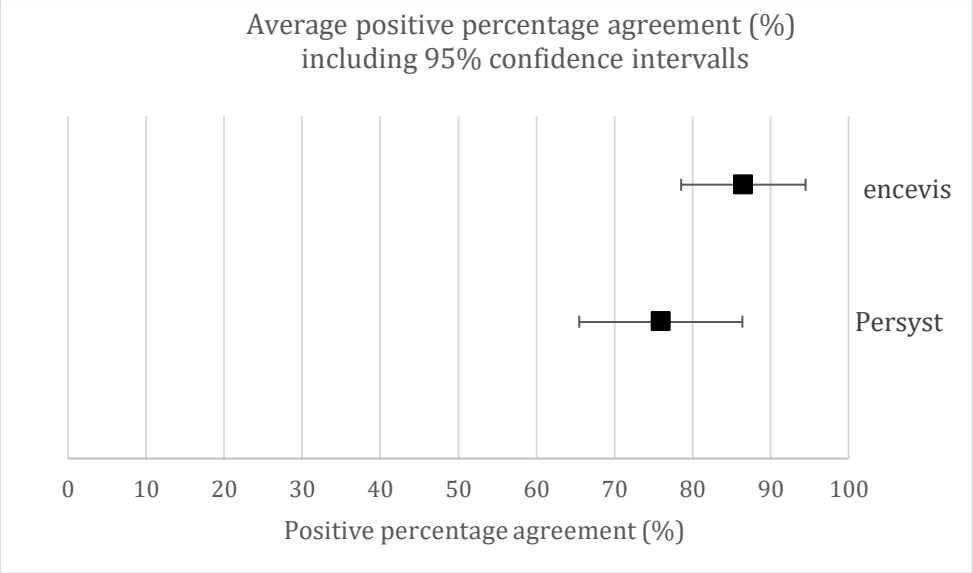

Figure 2: Average and the confidence interval of the positive agreement performance between encevis and Persyst.

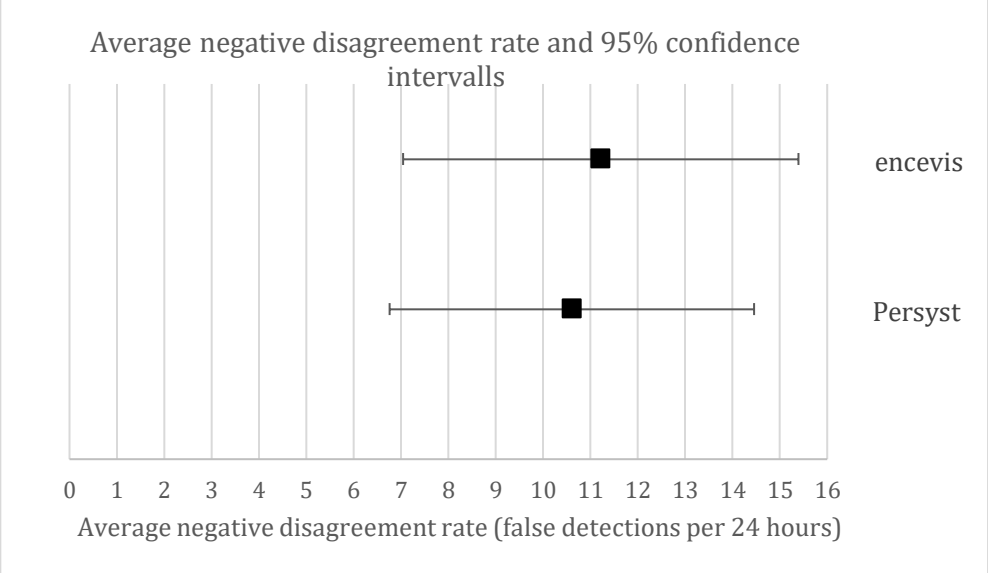

Figure 3: Average and the confidence interval of the negative disagreement performance between encevis and Persyst. Low numbers are better.

A Two One-Sided Test (TOST) procedure for paired samples (Walker E, Nowacki AS, J Gen Intern Med. 2011 Feb;26(2):192-6) was used to test the non-inferiority of the encevis seizure detection device to the predicate device. For statistical comparison, a type I error of 0.05 and non-inferiority margins of 10% for positive percentage agreement (PPA) and 4 for negative disagreement rate (NDR) were used.

The two performance parameters PPA and NDR were tested independently to measure the non-inferiority of both device parameters.

Both device parameters PPA and NDR of the encevis seizure detection are found to be non-inferior to the parameters of predicate device Persyst.

encevis spike detection performance testing

The clinical truth was determined based on the results of blinded review sessions from three neurologists. The “true spike” events (clinical truth) were then compared to automatically calculated spike time points of the encevis spike detection device to define true positives (TP), false positives (FP), false negatives (FN), and true negatives (TN) for each patient. With these values the positive percentage agreement (PPA) and negative percentage agreement (NPA) for each patient are calculated. In addition, “true spike” events were compared to the automatic detections of Persyst resulting in PPA and NPA values for the predicate device. Furthermore, the localization performance of both systems encevis spike detection and Persyst was evaluated based on the localization information given by the detection systems and the spatial information provided by the reviewer (clinical truth). We define a positive localization percentage agreement (PLPA) which is calculated for each patient.

Study population

To prove the validity of the spike detection system, encevis spike detection was tested with the EEG of 23 patients. For clinical validation, we included scalp-EEG recordings of 23 subjects that underwent video-EEG monitoring in an epilepsy monitoring unit for differential diagnosis or pre-surgical evaluation. 18 subjects of 18 years of age or older that showed spike events during recording based on initial clinical information where included. In addition, five subjects of 18 years of age or older that were diagnosed of not having epilepsy were included (Subject-ID 9-13). No further selection of subjects were made.

The statistical parameters PPA, NPA and PLPA were used in a two one-sided test (TOST, (Walker E et. al.) using paired samples in order to show the non-inferiority of encevis spike detection device compared to the predicate of Persyst.

Reference standard

To define the clinical truth the EEG from all subjects were presented to three independent Neurologists for blinded review. The goal of the review sessions was to identify all “true focal spikes” for later performance evaluation of the automatic spike detection algorithm. The EEG experts were asked to mark the time positions at the beginning and the end of the spike. Furthermore, the reviewers were asked to specify the electrode which is next to the spike maximum (phase reversal).

An event was considered as “true spike” only if the time interval of two out of three reviewers overlapped. For the determination of the localization performance, the 3D-coordinates of the electrode which is next to the spike maximum averaged over reviewers was used. The determined average position is considered as the clinical truth with respect to the localization and is used to evaluate the localization performance of encevis spike detection and the predicate Persyst.

Performance evaluation

Data of all 23 subjects was processed with encevis spike detection. In order to compare the obtained results of encevis spike detection with the predicate Persyst, the same data was processed with the spike detector of *Persyst 12*. The detection systems were evaluated by means of suitable performance measures like positive percentage agreement (PPA) and negative percentage agreement (NPA). For measuring the localization performance, we defined a positive localization percentage agreement

(PLPA). The basis for the performance evaluation are the annotations of the EEG experts which were placed at the onset and the end of the spike. Comparison between the time instances of the annotations and the time instances of automatic detections allows assessing the performance. The detection resolution of both systems, encevis spike detection and the *Persyst* spike detection was one microsecond.

Results of the performance measures

The average positive percentage agreement of the 15 subjects with at least one “true spike” event resulted in 79.15% (95% CI=[67.7-90.6]) for encevis spike detection and in 8.7% (95% CI=[4.4-13.0]) for the predicate device Persyst.

The average negative percentage agreement of all 23 subjects was 97.64 (95% CI=[96.6.-98.6]) for the encevis spike detection and 99.69 (95% CI=[99.4-99.9]) for predicate device Persyst.

The average positive localization percentage agreement of the 12 subjects with at least one “true positive” event was 93,39 (95% CI=[84.8.-102.0]) for the encevis spike detection and 93.97 (95% CI=[83.6-104.3]) for predicate device Persyst.

In the following figures the averages and the confidence intervals for the PPA, NPA and PLPA are visualized.

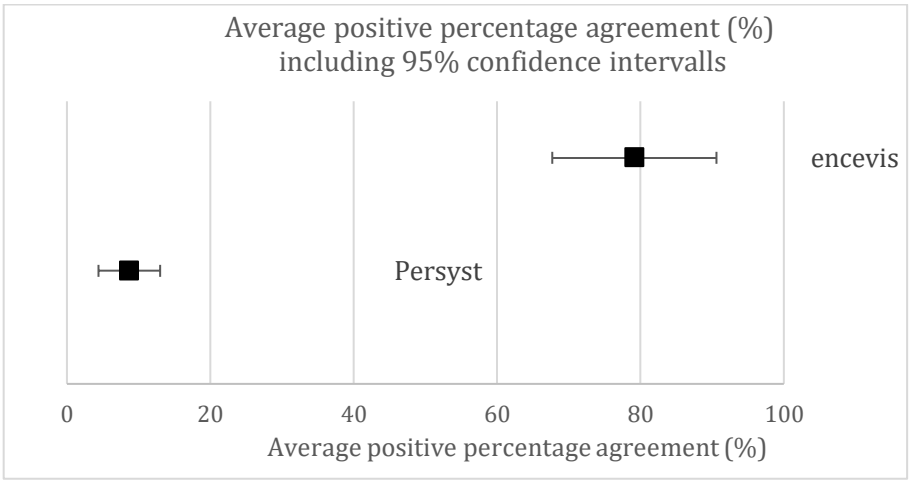

Figure 4: This figure compares the average and the confidence interval of the positive percentage agreement performance between encevis and Persyst.

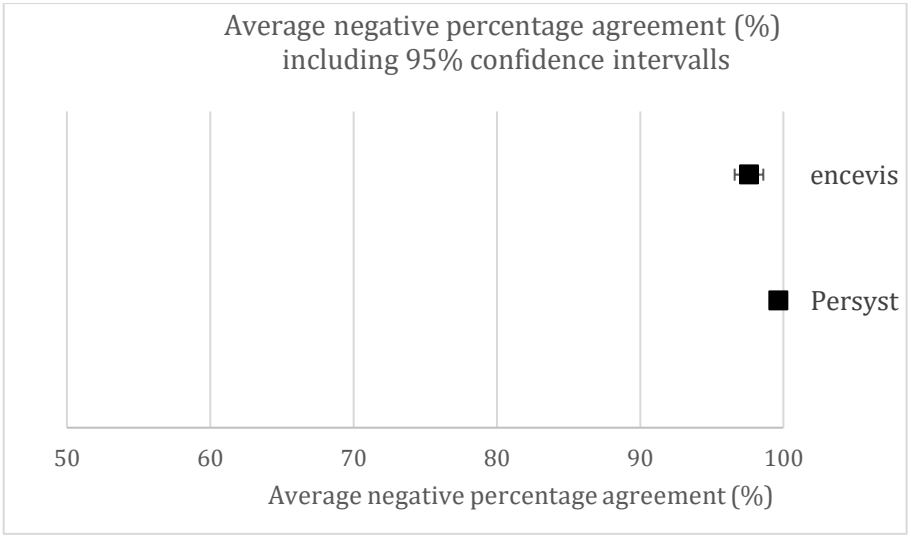

Figure 5: This figure compares the average and the confidence interval of the negative percentage agreement performance between encevis and Persyst.

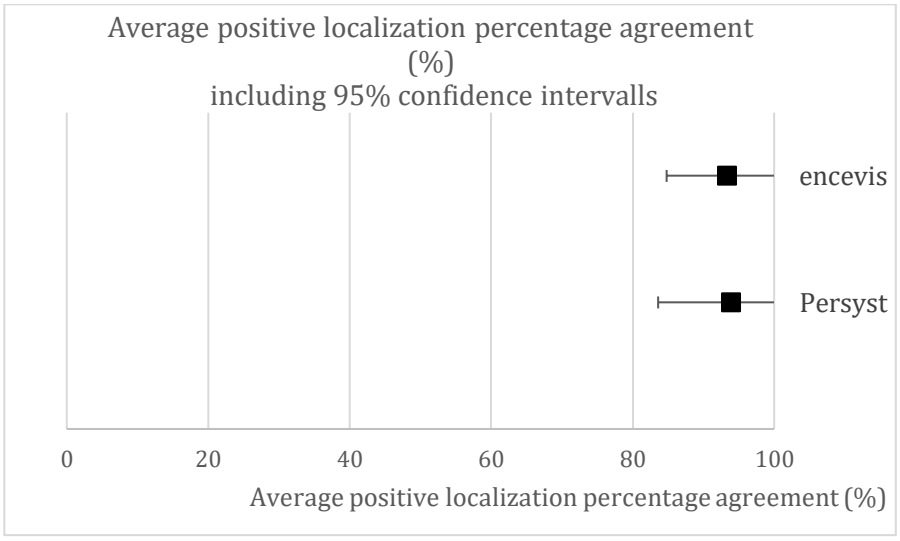

Figure 6: This figure compares the average and the confidence interval of the positive localization percentage agreement performance between encevis and Persyst.

A Two One-Sided Test (TOST) for paired samples (Walker et al) was used to test the non-inferiority of the encevis spike detection device to the predicate device. For statistical comparison, a type I error of 0.05 and non-inferiority margins of 3% for positive percentage agreement (PPA), the negative percentage agreement (NPA) and the positive localization percentage agreement (PLPA) are used. The three performance measures PPA, NPA and PLPA were tested independently to measure the non-inferiority of all device parameters separately.

encevis artifact reduction performance testing:

The quality of an artifact removal algorithm is determined by two aspects.

1. The method should not significantly modify true, clean EEG pattern that are not disturbed by artifacts. To quantify the performance of the algorithms with regard to this aspect, changes in clean EEG patterns due to the algorithms are evaluated.
2. The method should suppress artifacts that are superimposed on the true EEG as far as possible, revealing the underlying, pure EEG patterns. To quantify the ability of the algorithms to remove artifacts, signal-to-noise ratios will be measured before and after artifact removal.

For these measurements we need clean, pure EEG patterns and artifacts of different types. In order to identify these patterns, three EEG experts Neurologists are engaged as independent reviewers.

Validation data

For the validation study, 128 EEG data records from different patient groups are used, covering all intended use populations of encevis, i.e., adult patients in epilepsy monitoring and in critical care. Each record consisted of 10 seconds of data to be evaluated. The datasets include 60 patients from epilepsy monitoring units and 65 from ICU patients. These data were selected as follows:

Epilepsy monitoring – seizure EEGs: We include 31 EEG segments from 31 subjects of 18 years of age or older that underwent video-EEG monitoring in an epilepsy monitoring unit for the purpose of differential diagnosis or pre-surgical evaluation and that showed seizure events during recording and were diagnosed of having epilepsy.

Epilepsy monitoring – spikes: We include 33 EEG segments from 6 subjects of 18 years of age or older that underwent video-EEG monitoring in an epilepsy monitoring unit for the purpose of differential diagnosis or pre-surgical evaluation that showed spikes during recording.

Intensive care unit: We include 65 EEG segments from 65 subjects of 18 years of age or older that have been admitted to an intensive care unit due to severe neurological disorders (cerebral hypoxia, cerebral ischemia, cerebral hemorrhage of different genesis, cerebral tumors, status epilepticus, infections, toxidromes, encephalopathies of different genesis, cerebral malformations and craniocerebral traumas) on a systemic or localized basis. The random selection includes 9 segments with seizures, 10 segments with rhythmic activity, 11 segments with periodic discharges, 17 segments with burst-suppression and 18 segments without any pattern.

Expert review

For this validation study we need annotations of clean EEG recordings without any artifacts, and moreover annotations of artifacts that can be superimposed to the clean recordings. We engage three independent epileptologists or neurologists for blinded review of the EEG data from EMU and ICU.

Statistical testing

A Two One-Sided Test (TOST) procedure for paired samples (Walker E, Nowacki AS, J Gen Intern Med. 2011 Feb;26(2):192-6) is used to test the non-inferiority of the encevis artifact reduction compared to the predicate device. For statistical comparison, a type I error of 0.05 and non-inferiority margins of 1dB.

The hypothesis to test non-inferiority of the relative suppression of true EEG in dB is defined as:

- H0: The relative suppression of true EEG in dB of the encevis artifact removal is higher than the suppression of true EEG in dB of the predicate device.

- H1: The relative suppression of true EEG in dB of the encevis artifact removal is lower than or equal to the suppression of true EEG in dB of the predicate device.

The hypothesis to test the signal-to-noise ratio after artifact removal is defined as:

- H0: The signal-to-noise ratio after artifact removal by encevis is lower than the signal-to-noise ratio after artifact removal by of the predicate device.
- H1: The signal-to-noise ratio after artifact removal by encevis is higher than or equal to the signal-to-noise ratio after artifact removal by of the predicate device.

The results of the evaluation of relative suppression of clean EEG are summarized in the following table in %. This number means, that the variance of the clean EEG activity has been suppressed by this relative value, i.e., low values are desired. Due to technical reasons, only 127 out of 131 test cases could be evaluated: in the remaining 4 cases, Persyst produced zero lines in all channels.

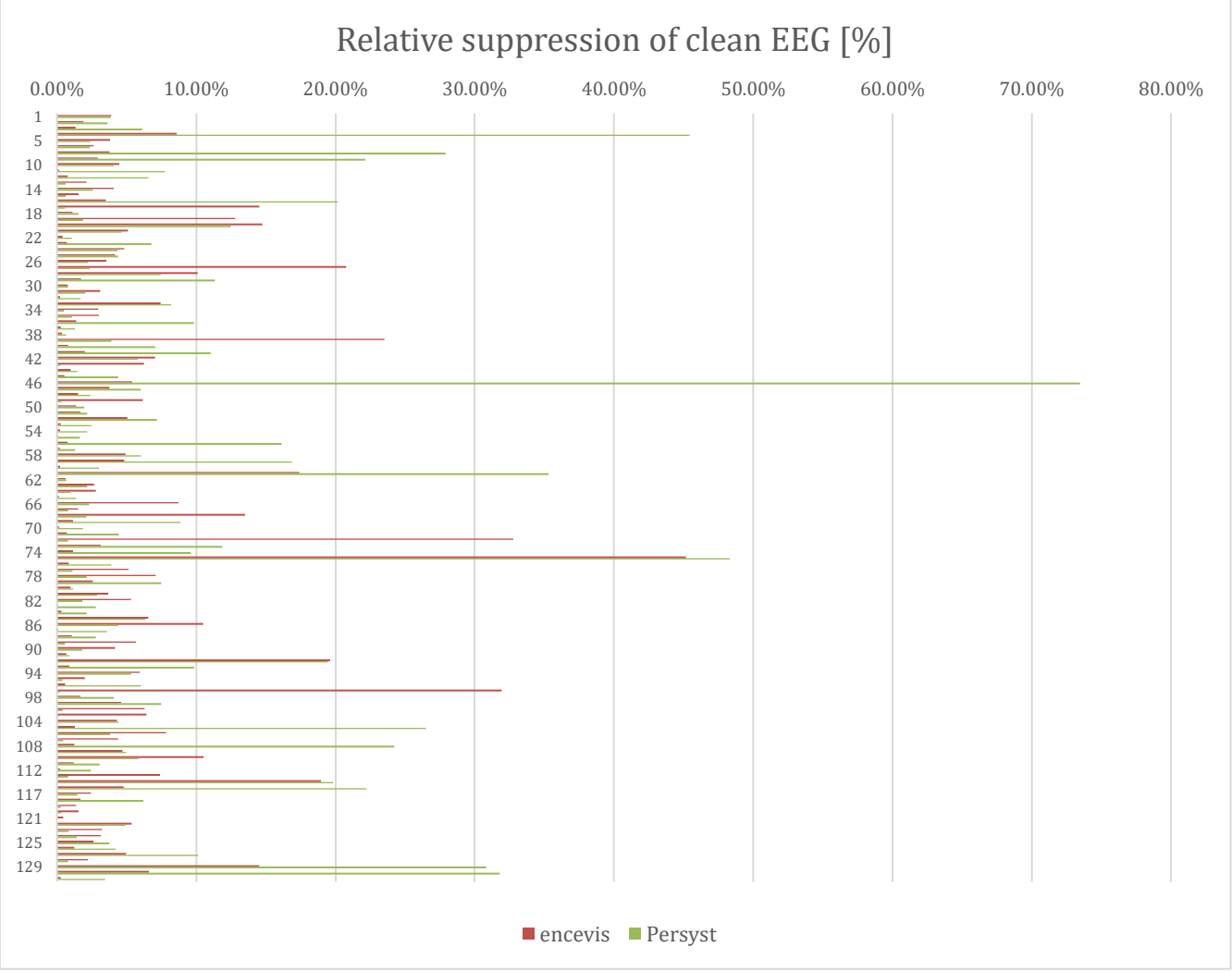

Figure 7: Relative suppression of clean EEG by encevis and Persyst

The results of the evaluation SNR prior and post artifact removal are summarized in the following table in dB. This numbers show the signal-to-noise ratio (noise=artifacts) that has been achieved after artifact removal, i.e., high values are desired. Eleven out of 104 test cases could not be evaluated, since the artifacts in these cases were on channels, where the initial EEG was not undistorted according to reviewers.

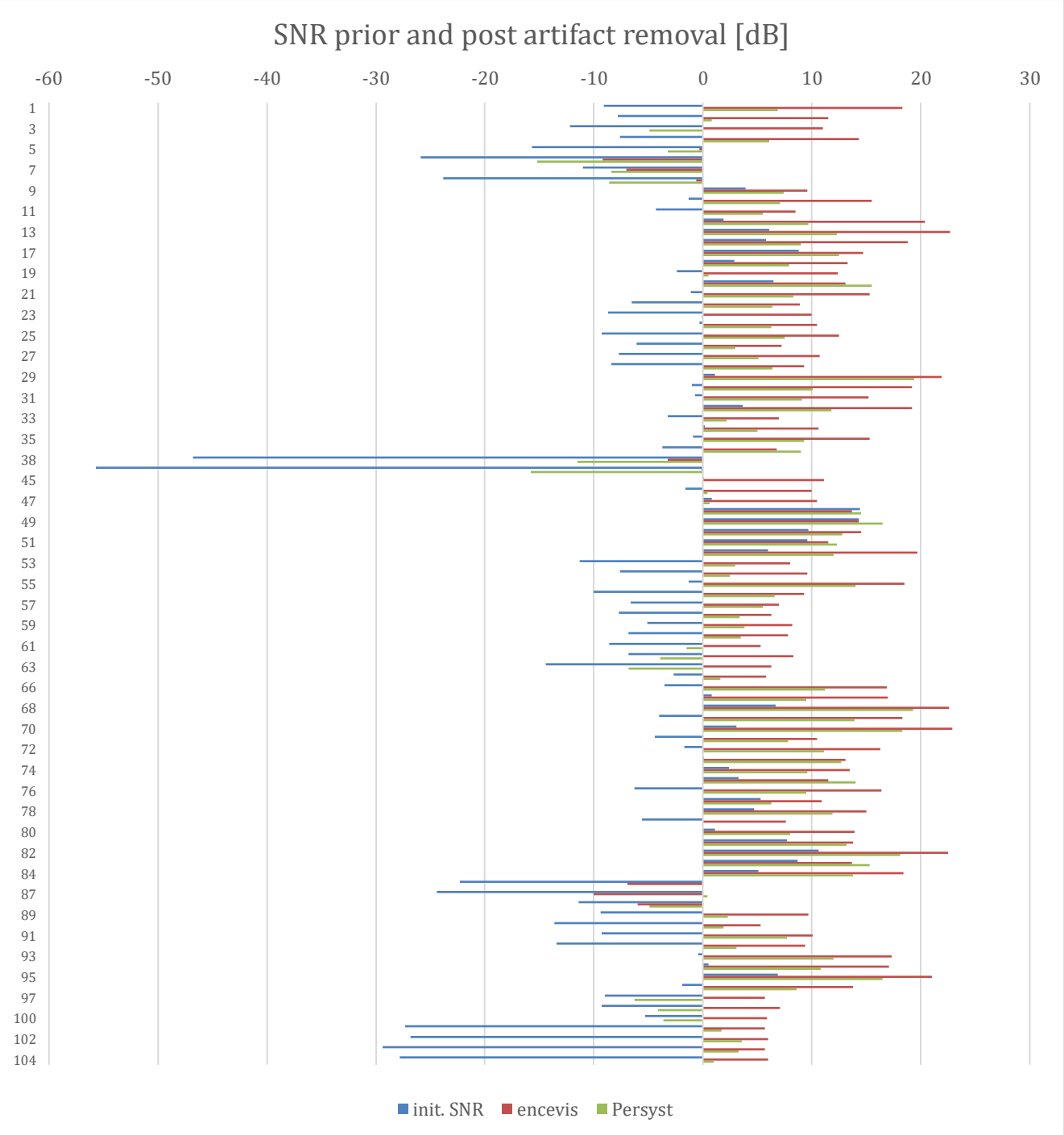

Figure 8: SNR prior and post artifact removal by encevis and Persyst

Results of Statistical testing

The results of the Two One-Sided Test for relative Suppression of clean EEG (Test-Control) are (95% delta CI=[-0.07, -0.02], margin = 0.01):

-0.02 < 0.01 -> H1

The results of the Two One-Sided Test for signal-to-noise ratios after artifact removal are (95% delta CI=[4.37,5.88], margin = 0.01):

4.37 > -0.01 -> H1

Both device parameters, “relative Suppression of clean EEG” and “signal-to-noise ratios after artifact removal” of the encevis artifact reduction are therefore non-inferior to the parameters of predicate device Persyst.

In the statistical evaluation of both device parameters, “relative Suppression of clean EEG” and “signal-to-noise ratios after artifact removal” of the encevis artifact reduction are shown to be non-inferior to the parameters of predicate device Persyst. Moreover in 73 out of 127 test cases, the suppression of clean EEG by encevis was lower compared to Persyst. And in 83 out of 93 test cases, the SNR after artifact removal by encevis was higher compared to Persyst. It can be concluded that the encevis artifact reduction “PureEEG” does not perform worse that the artifact reduction by the predicate device.

encevis rhythmic and periodic patterns performance testing:

The detection of rhythmic and periodic patterns in NeuroTrend is used to visually mark EEG segments with rhythmic or periodic signal content. The definition of rhythmic and periodic patterns follow the guidelines of the ACNS (American Clinical Neurophysiology Society) ICU EEG Terminology (Hirsch et al., 2013). NeuroTrend displays all detected rhythmic and periodic patterns in plots called “Pattern Localization” and “Pattern Frequency”.

For the validation we compared and statistically analyze annotations of two human EEG-readers with the detections of NeuroTrend. We showed that the detected patterns have a high sensitivity and specificity compared to manual annotated EEG segments. We prospectively recorded 83 long term EEGs from ICU-patients at two different centers using the international 10-20 electrode system with a sampling rate of 256Hz.

EEGs were annotated by two clinical neurophysiologists that were naive to these EEGs. The annotation procedure included the first minute of each hour, were each minute was split into three independent segments of 20 seconds resulting in 11935 common annotation segments. Several non-overlapping annotations were allowed in each annotation segment. Each annotation may have an arbitrary start and end position but has to be fully included in the annotation segment. For each annotation, the reviewer was allowed to choose between one of the following pattern types:

1) PD: periodic pattern
2) RDA: rhythmic delta activity
3) RTA: rhythmic theta activity
4) RAA: rhythmic alpha activity
5) RDA+S: rhythmic delta activity with superimposed sharp waves or spikes (RDA+S). (equivalent to SW in Version 1.6)
6) BS: burst suppression pattern
7) No annotation (short NOPA).

In addition to the type of the pattern the localization property had to be set by the human reviewers. This property was defined in (Hirsch et al., 2013) as main term 1:

1) G: generalized pattern
2) L: lateralized pattern

The annotations from the two reviewers were then used as gold standard condition to test sensitivity and specificity of the rhythmic and periodic pattern detection of NeuroTrend. Annotations had to be consistent between both reviewers to be used in the sensitivity and specificity measurement.

The detection performance was defined by assigning one of four possible test conditions to each of the 1 minute annotation segments: true positive (TP), false positive (FP), true negative (TN), and false negative (FN). An annotation segment was counted as TP if a detection and an annotation was present. An annotation segment with a gold standard annotation but without any detection will be counted as FN. An annotation segment with detections but without annotations will be counted as FP. An annotation segment without gold standard annotation and without detections will be counted as TN.

The sensitivity is defined as:

$$SE\ [\%] = \#TP/(\#TP+\#FN) * 100$$

The specificity is defined as:

$$SP\ [\%] = \#TN/(\#TN+\#FP) * 100$$

The # symbol stands for “number of”. The symbol “#TP” represents therefore the number of true positive annotation segments.

The localization information will be validated by comparing the concise annotations of the two human reviewers for all correctly detected markers (the TP detections).

The result of the manual annotation procedure was evaluated using the Cohens’ kappa statistic. This statistic measures the level of agreement between two reviewers. A kappa value of 0.66 was measured between reviewer 1 and reviewer 2.

		REVIEWER 2					
		NOPAT	PD	RAA	RDA	RTA	RDA+S
REVIEWER 1	NOPAT	10757	311	14	78	23	4
	PD	588	1290	0	63	14	0
	RAA	1	1	6	1	10	0
	RDA	135	5	0	119	1	4
	RTA	50	25	1	23	107	0
	RDA+S	10	0	3	0	0	20
Cohens Kappa:		**0.66 (CI=0.64-0.67)**			**Substantial agreement**		

Table 3: Cohens’ kappa statistic for the evaluation of the pattern detection

The overall detection performance measures the sensitivity and specificity of the NeuroTrend detections without evaluating the pattern type. The result is marked with the label “ANY” in the result file. This result proofs the ability of NeuroTrend to detect any relevant pattern and ignores pattern type mismatches. The result of the periodic pattern group is labeled as “PD”. This result shows the sensitivity and specificity of the periodic pattern detections. The result of the rhythmic delta activity

pattern detections is labeled as “RDA”. The result of the ARA group shows the result of aggressive rhythmic activity, including the pattern types RTA, RAA, and RDA+S.

Pattern Type	Sensitivity[%]	Specificity[%]
ANY	81.86 (79.9 - 83.8)	83.80 (83.1 - 84.5)
PD	69.73 (67.2 - 72.3)	95.89 (95.5 - 96.3)
ARA (RTA, RAA, RDA+S)	89.40 (84.2 - 94.6)	94.85 (94.5 - 95.3)
RDA	91.73 (86.4 - 97.1)	86.05 (85.4 - 86.7)

Table 4: Sensitivity and specify for encevis pattern detection

The inter reader agreement table of the localization information (ACNS Main Term 1) compares the consistent annotations of two EEG experts to the localization shown in NeuroTrend. The result is shown in the following table:

REVEWER 1+2		NeuroTrend	
		G	L
	G	891	86
	L	130	175
Cohens Kappa:		**0.51, CI=0.45-0.57 (Moderate agreement)**	

Table 5: Inter-reader agreement between reviewers and NeuroTrend for encevis pattern localization

encevis aEEG performance testing:

Amplitude-integrated EEG (aEEG) is a popular method for monitoring cerebral function by displaying the amplitude trend of brain activity. It is the boundary of the EEG waveform (i.e. the envelope) and not the EEG itself (i.e. the carrier) that characterizes the tendency of amplitude changes (Zhang and Ding, 2013).

The Background-AEEG module of NeuroTrend estimates and visualizes the temporal evolution (trend) of the EEG amplitude. The implementation is oriented on the proposed method of (Zhang and Ding, 2013)

In the first step the frequency response of the module is checked for equality with the proposed method of (Zhang and Ding, 2013). This test only considers the correct slope (dB loss per decade) not the correct filter gain factor. In this test, sinusoidal one-channel test data with increasing frequencies from 0.5Hz to 32Hz and amplitude of 40µV are generated, one test case for each hemisphere. With the results of the module the frequency response is determined and checked if the dB loss per decade within the band pass (cut-off frequencies of 2 and 15Hz) is -12db/dec and the maximum gain factor in the stop band is not greater than -30dB. This step validates the correct implementation of the filters and its characteristics (expect the gain factor) within the module.

In the second step the results of the module are compared with the aEEG results of *Persyst* (CE certified and FDA approved software; http://www.persyst.com/) using real EEG data. The configuration of *Persyst* is set in a way to allow an adequate comparison.

After successful validation according to the description above we will have shown that the Background-AEEG module correctly determines the averaged EEG amplitude of the left and right hemisphere according to the proposes method of (Zhang and Ding, 2013)

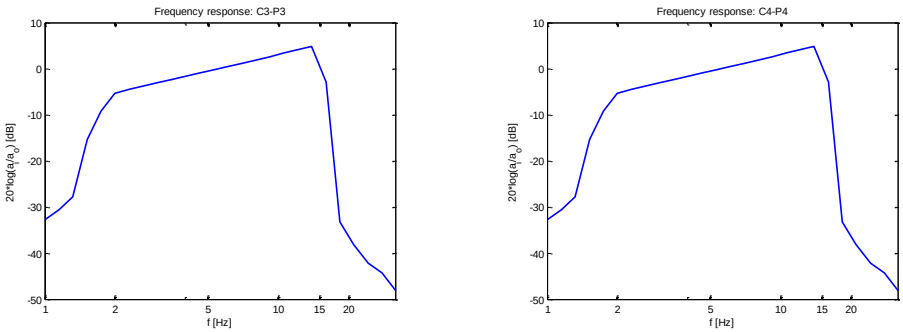

Figure 9: Frequency response of the left (left side) and the right hemisphere (right side).

In the first validation step the frequency response of the aEEG module is checked for equality with the pro-posed method of (Zhang and Ding, 2013). The resulting frequency response of the Background-AEEG module is shown in Figure 9 .The following conclusions were drawn from the results:

- The determined characteristic is very similar to the published version in (Zhang and Ding, 2013). Only the absolute shift of the complete frequency response is different but because only changes in aEEG values are of clinical relevance this detail is irrelevant.
- Both hemispheres show the same characteristic
- In the stop band there is a suppression of -30dB and higher
- The slope in the pass band is approximately -12dB/decade

In the second step the results of the aEEG module are compared with the aEEG results of Persyst. For this test, real EEG data were used. The aEEG of the same EEG segment using either *Persyst* or the Background-AEEG module of encevis NeuroTrend were compared. The test cases showed that the aEEG values of the Background-AEEG module of encevis NeuroTrend and *Persyst* are in good accordance. Furthermore, the aEEG values are in good accordance with the corresponding raw EEG.

encevis frequency bands performance testing:

The background-frequency module of NeuroTrend estimates and visualizes the temporal evolution (trend) of relative proportions of dominant EEG-waveform-frequencies. The result is graphically presented using a plot (cf. Figure 10), where the x-axis represents the time-axis, and four stacked areas in different colors and widths represent the relative proportions of the four frequency bands Delta, Theta, Alpha, and Beta for subsequent time windows with lengths of 15 seconds. The intensity of the colors furthermore corresponds to the amplitudes in these four frequency bands. This representation allows the user to identify time epochs that are dominated by a specific frequency band. E.g., EEG-slowing or, in other words, an epoch with dominant delta- or theta-wave can be recognized in the graphical representation by broad stretches of the corresponding areas.

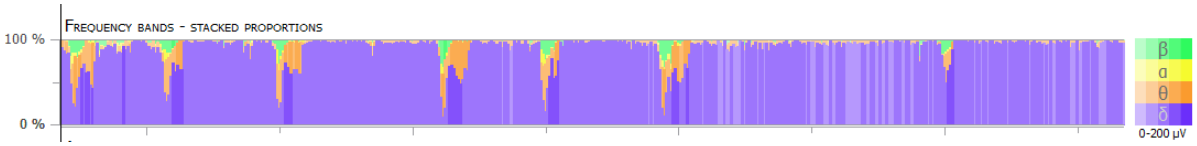

Figure 10: Graphical representation of the Background-EEG-Frequency evaluation results.

In order to proof the validity of the result of the Background-EEG-frequency module we followed a two-step approach. In the first step it was shown that the assignment of sinusoidal test data to frequency bands (Delta, Theta, Alpha, or Beta) is correct according to the above definitions of frequency borders. In this test, sinusoidal test data with frequencies across all four bands and amplitudes ranging from 2 µV to 200 µV were generated. Then it was verified, that the algorithm correctly assigns each test signal to the corresponding frequency band, and that the measurement error for amplitudes are below 5 %. This validates the correct assignments of single, 3-second EEG epochs to a frequency band and amplitude.

In a seconds step it is shown that the globally dominant background frequency within a 15-seconds window is correctly identified. This is done using manually selected EEG recordings from epilepsy- or ICU patients. Each of these EEG samples is representative for a specific background-EEG-frequency band, i.e., it is mainly dominated by delta-, theta-, alpha-, or beta-waves. For these samples the background-EEG-frequency module calculates the proportional composition of frequency bands. The one frequency band with the largest proportion can be seen as the globally dominant background frequency, if this proportion is particularly high. Thus it is verified for each of these representative examples that the relative proportion corresponding to the true frequency band is greater than 50 %.

encevis Burst Suppression performance testing:

The detection of burst suppression patterns and quantitative measure for the discontinuity of the EEG shown in NeuroTrend was validated using the following approach:

1. The time point of the detected burst suppression patterns will be compared to annotations defined by two clinical EEG experts using EEG data from a multicenter study. Sensitivity and specificity will be calculated.
2. The quantitative measure of the amplitude loss of the suppression and the suppression time in percent will be validated using an artificial EEG. The EEG file includes a set burst suppression patterns with different values for suppression time and suppression amplitude loss. The calculation results of the quantitative burst suppression plots shown in NeuroTrend will be compared to pre-calculated values.

We recorded 83 long term EEGs from intensive care patients from two different centers using the international 10-20 electrode system with a sampling rate of 256Hz. EEGs were annotated by two clinical neurophysiologists that were naive to these EEGs. The annotation procedure included the first minute of each hour resulting in 3978 valid annotation segments. The reviewers were allowed to assign two categories for each annotation segment:

8) EEG with burst suppression patterns (BS)
9) EEG without burst suppression patterns ($\overline{BS}$)

Statistical analysis of the detection performance was done by defining the annotations of the reviewers as gold standard and by comparing these annotations to the detection results of the computational method. Each one minute EEG segments annotated as “EEG with burst suppression” with an overlapping burst suppression detection segment of 15 seconds was defined as true positive (TP) event. One minute EEG segments annotated as “EEG with burst suppression patterns” without any overlapping burst suppression detection result were defined as false negatives (FN). One minute segments annotated as “EEG without burst suppression patterns” and with an overlapping burst suppression detection result are defined as false positives (FP), all other segments are defined as true negatives (TN).

The following table shows the evaluation results of the automatic burst suppression detection method in NeuroTrend using 3978 segments annotated by two reviewers. The results of the automatic burst suppression detection method were compared to the manual annotations of the reviewers. The detection performance was analyzed for consensus annotations of the two reviewers. The consensus annotations only include annotation segments where both reviewers showed the same decision about Burst Suppression pattern. The measured values for sensitivity (SE), specificity (SP), positive predictive value (PPV), and negative predictive value (NPV) prove the validly of the detection algorithm. The very large sample size does imply a statistically high confidence.

Rev. (n)	SE (%)	SP (%)	PPV (%)	NPV (%)
2	87 (84.7-89.9)	92 (91.4-92.9)	61 (57.9-64.3)	98 (97.7-98.5)

Table 6: Performance of the automatic burst suppression detection method

10. Statement of Substantial Equivalence

encevis is substantially equivalent in design and intended use to the predicate device. Any differences between the subject and predicate device have no significant influence on safety or effectiveness as established through performance testing. Therefore, the encevis raises no new issues of safety or effectiveness when compared to the predicate device.