EUROPEAN COMMISSION

Expert decision and opinion in the context of the Clinical Evaluation Consultation Procedure (CECP)

Expert panels on medical devices and in vitro diagnostic devices (Expamed)

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Scope of this expert opinion

This scientific opinion reflects the views of independent experts (MDR Article 106) on the clinical evaluation assessment report (CEAR) of the NB. The advice is provided in the context of the clinical evaluation consultation procedure (CECP), which is an additional element of conformity assessment by notified bodies for specific high-risk devices (MDR Article 54 and Annex IX, Section 5.1).

The NB is obliged to give due consideration to views expressed in the scientific opinion of the expert panel and in particular in case experts find the level of clinical evidence not sufficient or have serious concerns about the benefit-risk determination, the consistency of the clinical evidence with the intended purpose including the medical indication(s) or with the post-market clinical follow-up (PMCF) plan.

Having considered the expert views, the NB must, if necessary, advise the manufacturer on possible actions, such as specific restrictions of the intended purpose, limitations on the duration of the certificate validity, specific post-market follow-up (PMCF) studies, adaption of instructions for use or the summary of safety and clinical performance (SSCP) or may impose other restrictions in its conformity assessment report.

In accordance with MDR Annex IX, 5.1.g., the notify body shall provide a full justification where it has not followed the advice of the expert panel in its conformity assessment report.

1 ADMINISTRATIVE INFORMATION

Date of reception of the dossier	30/05/2022
Notified Body number	0344
Internal CECP dossier #	2022-000222
Medical device type	Implantable stimulation device for neurological applications. This system has two implantable components: an implantable pulse generator and an electrode array and lead body.
Intended purpose	The device is intended for use as an adjunctive neurostimulation therapy in reducing the burden of epilepsy in adults over 18 years of age, with focal onset seizures that are refractory to two or more antiepileptic medications.
Risk class / type	☒ class III implantable ☐ class IIb active device intended to administer or remove medicinal products(s)
Screening step: medical field / competence area	Neurology

2 DECISION AND OPINION

PART 1 – DECISION OF SCREENING EXPERTS: NOTIFICATION OF NB AND COMMISSION REGARDING THE INTENTION TO PROVIDE AN OPINION

1.1 Decision of the screening experts

Table covers all three criteria, intended to support their consistent and conscientious application

Date of decision	08/06/2022
Screening panel decision	
Is there intention to provide a scientific opinion?	☒ **Yes** ☐ **No** ☐ **Insufficient information to reach a conclusion**
In case the information was found insufficient to reach a conclusion: summary of reasons (see MRD Annex IX Section 5.1 point c)	
N/A	
Summary as to why there is intention to provide an opinion	
This is a novel device, with no similar devices on the market. There is no published scientific data on similar devices (EU or elsewhere). Both the device as well as the clinical concept on its use are novel. According to the available data, the clinical impact is expected to be major but there is a large uncertainty around the outputs derived from this data.	
Summary as to why there is *no* intention to provide an opinion	
N/A	
Any other comments	
N/A	

1.2 Assessment of the three screening criteria

Criterion 1: Novelty of device under assessment and possible clinical / health impact
1.1 Novelty of device and/or of related clinical procedure
☐ No novelty: Neither device nor clinical procedure is novel ☒ Novelty: **Device** is novel ☒ Novelty: **Procedure** is novel
Short description of the novelty, including main dimension(s) of novelty
There is no similar device on the market. Subcutaneous electrode placement for electroencephalogram (EEG) registration has been done but the electrodes and device described in the dossier are used for

stimulation instead of registration (even if electrodes can be used for both functions) and for this reason the procedure should also be considered novel. Additionally, the whole clinical concept of combining low threshold alternating current (AC) stimulation with [redacted] and additional [redacted] AC bursts is also novel.

Overall degree of novelty

Level of novelty:

☐ Low level *or*
☐ Medium level *or*
☒ High level
☐ Not Applicable (neither the device nor the procedure is novel)

Uncertainties related to novelty

There is no similar device on the market.

1.2 Possible negative clinical / health impact resulting from novelty

Major clinical health impact

Estimated severity of clinical and/or health impact

Severity of clinical/health impact:

☐ No clinical or health impact
☐ Minor clinical or health impact
☐ Moderate clinical or health impact
☒ Major clinical or health impact

Uncertainties related to clinical/health impact

Based on the very limited available data, the clinical benefit is expected to be high. However, the patient series is very small (n=33) [redacted] The safety data analysis showed a low rate of serious adverse events. However, the same limitations already highlighted apply here as well, as the data comes from the same patient series.

Moreover, some aspects are not clear:

1) The criteria for patient selection in terms of minimum or maximum number of seizures per month.

2) The reporting of the adverse events (AEs) in the studies mentioned in the Clinical Evaluation Report (CER): in the study [redacted] it is written (p. 24/82 CER) that "while [redacted] were classified as possible, probable or highly probable relationship. The latter group included events such as tingling, pain at implant site, and worsening of seizure situation". Similarly in the report of AEs in the [redacted] study it reads (p. 26/82) "while [redacted] were classified as possible, probable or causal relationship. The latter group included events such as headache, increase in seizure frequency, pain at implant site, morning tiredness". In both cases neither the exact number of patients experiencing the increase in seizure situation or frequency is reported nor is it mentioned the duration of the increase (transitory? permanent?). Because the detailed distribution of the AE "increase in seizure frequency" in both studies is not presented, it is difficult to confirm the total number of patients that actually benefited from the procedure.

Criterion 2: Scientifically valid health concerns leading to significantly adverse changes in the benefit-risk profile of a specific group / category of devices and relating to a) Component(s) b) Source material(s) c) Impact on health in case of failure of the device	
2.1 Information received from Secretariat:	☐ Yes ☒ No
2.2 Other information available to experts:	☐ Yes ☒ No

Criterion 3: Significant increase of serious incidents of a specific group / category of devices relevant for the device under assessment *(if information is available, it will always be provided by the expert panel secretariat)*	
3.1 Information received from secretariat?	☐ Yes ☒ No

1.3 Indication of appropriate thematic panel in case opinion is required

Indication of appropriate thematic panel and competence area		
	Expert panels	Medical and scientific/technical competence areas (these may correspond to sub-groups)
☐	**Orthopaedics, traumatology, rehabilitation, rheumatology**	☐ 1. Joint replacements (hip, knee, shoulder) ☐ 2. Spinal devices ☐ 3. Non-articulating devices, rehabilitation
☐	**Circulatory system**	☐ 1. Prosthetic heart valves and devices for heart valve repair ☐ 2. Cardiovascular stents (metallic and bio-resorbable) and vascular prostheses ☐ 3. Active implantable cardiac devices and electrophysiological devices ☐ 4. Structural interventions and new devices (e.g. LAA/PFO occluders, heart failure devices) ☐ 5. Cardiac surgery including extracorporeal membrane oxygenation, cardiopulmonary bypass devices, artificial hearts and left ventricular assist devices
☒	**Neurology**	☒ 1. Central and peripheral nervous system devices ☐ 2. Implants for hearing and vision (sensory recovery) ☐ 3. Neurosurgical devices
☐	**Respiratory, anaesthesiology, intensive care**	☐ Respiratory and anaesthetic devices
☐	**Endocrinology and diabetes**	☐ Endocrinology and diabetes devices

☐	**General and plastic surgery Dentistry**	☐ 1. Surgical implants and general surgery ☐ 2. Plastic surgery and wound care ☐ 3. Maxillofacial surgery & Devices for dentistry e.g. oral surgery, implantology, dental materials etc.
☐	**Obstetrics and gynaecology including reproductive medicine**	☐ Devices for obstetrics and gynaecology
☐	**Gastroenterology and hepatology**	☐ Devices for gastroenterology and hepatology
☐	**Nephrology and urology**	☐ Devices for nephrology and urology
☐	**Ophthalmology**	☐ Devices for ophthalmology

PART 2 – SCIENTIFIC OPINION OF THE THEMATIC EXPERT PANEL/SUB-GROUP

2.1 Information on panel and sub-group

Date of opinion	01/08/2022
Expert panel name	Neurology
Sub-group of expert panel (where relevant)	Central and peripheral nervous system devices

2.2 Summary of expert panel opinion

- **Device description**

The device is designed to apply weak, pulsed electrical stimuli from beneath the scalp to specific areas of the brain for the treatment of focal epilepsy. It consists of leads implanted in the epicranial area (i.e., under the scalp and outside the skull) and a connected battery-powered pulse generator implanted near the clavicle.

The system is intended for use as an adjunctive neurostimulation therapy for reducing the burden of epilepsy in adults over 18 years of age, with focal onset seizures that are refractory to two or more antiepileptic medications, identified not to be current candidates for epilepsy surgery.

The device lead is placed on the skull surface to transmit electrical stimulation through the skull bone to the brain in the area of a seizure onset zone. The pulse generator, containing a battery pack and other elements including the stimulation/charge balancing control electronics, could be externally monitored by telemetry.

Different external control elements allow:

– medical personnel to set the stimulation parameters, to test the functionality of the power supply unit, and provide access to data recorded;
– the patient to check the battery level, trigger the treatment with pre-set stimulation pulses, and turn the system off in case of an emergency.

The system delivers different stimulation patterns, alternating current (AC) and [redacted] with programmable current amplitude. Patients can directly request additional [redacted] bursts via the Access remote control when they feel an upcoming seizure or during a seizure.

Technical points resulted from a preclinical report ("hypothesis on clinical performance") with simulations of the current density and the electrical field in the human brain, intracortical in situ measurements and comparisons with literature and clinically confirmed therapies for patients suffering from focal epilepsy like transcranial direct current stimulation (tDCS) and responsive neurostimulation (RNS). The simulation demonstrated that the device stimulation lies well between the tDCS and the RNS stimulation paradigms with regard to current densities and focality of the stimulation, indicating the potential for an effective treatment with a voltage gradient between [redacted] necessary to affect neuronal spiking and subthreshold currents and therefore to influence brain activity.

The notified body (NB) should require additional information about the replacement of the device or the battery. It appears that the lifetime of the device is 5 years (Post-Market Clinical Follow-up - PMCF Plan version 2.0, p 13: expected lifetime: [redacted] Lead: 5 years; [redacted] Power: 5 years (lifetime of implantable pulse generator housing); actual implantation time depends on battery lifetime (expected ~12 months), but the patient has to undergo surgical replacement to be planned with reasonable timing with respect to the battery duration, which is indicated in the Clinical Evaluation Plan (version 3.0, p 42: Battery life: minimum approximately 40 weeks). If only the battery is going to be replaced every 40 weeks, but not the device which is expected to last 5 years, then the clinical follow-up (see below) should be planned with a duration of at least 5 years for each patient (instead of the proposed 3 years), in order to cover the whole life cycle of the implanted device in each patient. With this respect, also a description of procedures and frequency of technical tests needed to operate the system would be useful. Likewise, additional information should be requested regarding the 5 years lifetime of the implantable components which have been tested prior to the clinical phase. In particular, the NB should request the reason for the 5-year lead lifetime, including more details on what is the critical lead component (e.g. the point of epicranial insertion, or the wires, or other).

- **Novelty**

The device is an implantable focal neurostimulation therapy which differs from existing therapies on:

- the subgaleal area implantation
- an original lead design (pseudo-Laplacian subcutaneous electrode)
- various stimulation patterns available for the users (AC, [redacted] and on [redacted]

The system presents benefits compared to other modalities of brain stimulation. It is less invasive compared with deep brain stimulation (DBS) and RNS.

Being implantable, it potentially requires less compliance by the patient or caregiver compared with less invasive methods such as tDCS, that cannot be used to deliver constant stimulation. Moreover, the original electrode design (US10737091B2), adapted to epicranial positioning, presents performant electrophysiological properties.

Comparison with other indirect brain stimulation such as vagus nerve stimulation would require additional evidence being the latter a procedure with a relatively low invasiveness as well.

The surgical procedure and accessories or wearable devices are presently used in a variety of procedures like epidural cord stimulation or DBS.

The novel use of epicranial lead electrodes in a laplacian montage presents a weakness as in the PMCF Plan (version 2.0, p 13) it is stated that the expected lifetime of [redacted] Lead is 5 years. Therefore, replacements of the battery (every 12 months approximately) or of the leads (every 5 years approximately) or the stimulus generator (every 5 years approximately will involve iterative surgical procedures. The NB should further inquiry on the reasons for the 5 years lifetime (according to the PMCF) which is quite shorter than other intracranial brain stimulation electrodes.

The possible negative clinical impact is the occurrence of stimulation induced epileptic seizures (see below).

- **Adequacy of clinical evidence assessment by the notified body**

The NB should request additional data on inclusion criteria in terms of minimum or maximum number of seizures per month and criteria for determining continuing or removing the device based upon response in terms of seizure reduction.

The NB should request additional information concerning the adverse effects (AE) reported in the Clinical Evaluation Report (CER) (pp 22-25). In the CER, for [redacted] study (pp 23, 24), [redacted] AEs were reported in 15 patients included, but the number of patients is not stated. [redacted] of these (i.e. [redacted] were considered as related to the device: e.g. "...tingling, pain at implant site, and worsening of seizure situation". However, the number and details on seizure worsening should be provided. In fact, it is not clear whether worsening refers to the frequency and severity of seizures, how many patients experienced it, whether the worsening was transient or permanent, whether it was associated with some stimulation parameters.

In the CER, for [redacted] (p 25), including 18 patients with 8 months follow-up, [redacted] AEs were reported, but the number of patients is not indicated. [redacted] events [redacted] were classified as having a "possible, probable or causal relationship to the medical device, such as headache, increase in seizure frequency, pain at implant site, morning tiredness" (p 26). However, the information on the amount of this increase in seizure is not available.

Overall, [redacted] serious adverse events (SAE) were reported (in [redacted] patients) but considered as not related to the procedure. However, it is not clear whether the increase in frequency was considered a SAE or not and whether it was considered related to the procedure or not.

The NB should request to receive further information about both SAE and the number of patients presenting with "worsening of seizure situation": whether it was transient or permanent, whether it was associated to particular stimulation parameters or periods, including the [redacted] applied by the patient.

Most importantly, the NB should request further data about pre-existing clinical features - or implant location – for those patients experiencing "worsening of seizure situation". This could be relevant in order to assess the opportunity to impose some limitations to the use of the device as per the intended purpose, thus introducing further restrictions to its prescription.

Finally, the NB needs to consider that the number of patients included in the two studies is low to allow a reliable determination of the frequency of patient responders, claimed being over [redacted]. This frequency of responders should be compared with the frequency of patients worsened to allow an adequate benefit-risk assessment. In the absence of this information, this expert panel has serious concerns on the adequacy of the benefit-risk assessment performed.

In the opinion of this expert panel, it is paramount that the NB obtains this missing information to be used for the assessment and requires it to be collected in a higher number of patients. In fact, based upon this missing information, the NB may advise the manufacturer on possible actions, such as specific restrictions of the intended purpose (if applicable owing to data from pre-existing clinical features or electrode locations for patients experiencing worsening) or adaption of instructions for use (if applicable owing to the possible identification of specific stimulation parameters associated with "worsening of seizure situation", or the summary of safety and clinical performance (SSCP).

- **Sufficiency of clinical evidence**

The opinion of this expert panel is that the clinical evidence presented by the manufacturer and assessed by the NB is not sufficient in view of the device's intended purpose and possible risks and uncertainties. In detail, the inclusion criteria in terms of number of seizures per month should be described. More importantly, and as stated above, more information is needed about pre-existing conditions associated with adverse events described as "worsening of seizure situation": clinical data, namely the type and frequency of seizures, including the identified focus, and technical data, namely stimulation parameters (e.g. intensity and periods of stimulation, including information about the patient delivered [redacted]. About the description of the adverse event itself, the type of worsening (seizure frequency, duration, severity - e.g. more frequent generalization into tonic-clonic seizures), number of patients, whether it was long lasting

or transient and whether changes in stimulation parameters did reverse these events. The NB should consider that "worsening of seizure situation", including increased seizure frequency, not only represents a relevant adverse event, with a significant impact on the benefit-risk determination and, most importantly, represents an evident contradiction with the intended purpose as claimed by the manufacturer.

There is no post-market surveillance information available: being the device novel, no information about similar systems is available.

The major limitation is the low number of patients from which the overall clinical evidence has been collected (one clinical study with 15 and the other with 18 patients, respectively). This limits the reliability of the estimate of the proportion of responders. The "worsening of seizure situation" is described with insufficient detail and in contrast with the indications for use of the device. There is lack of information on the clinical and electrophysiological pictures described in the clinical evidence provided by the manufacturer. In fact, no information is provided about the key elements to adapt the stimulation parameters. With this respect, some pending issues persist, namely an explanation on why brain stimulation succeeded in only half of the patients (is it the brain stimulation method which is inefficient for some epileptic foci or is it a "technical" issue about electrode localisation and settings?). The NB should point to this limitation in the information available and request that it is addressed in the PMCF in a larger sample and for a longer time period than in the two clinical studies (i.e. at least five years for each patient), in order to refine the clinical indications with the aim of increasing the proportion of responder patients.

The medical indications for the device have to be further developed, even because epileptic focus definition is a complex issue, clinical pictures and traditional electroencephalogram (EEG) are insufficient to localize it.

Finally, manufacturer's parameters settings are based on a theoretical preclinical study. A [redacted] at the time of a seizure was subsequently added. Indeed, the mechanism by which brain stimulation is effective on seizure control is not fully understood. Different stimulation patterns have been associated within the same device and different mechanisms were probably involved with a potential rapid effect at the time of the seizure and a long-term effect (on plasticity?) to prevent seizure occurrence.

But the key question is to assess the evidence of the system efficacy. The clinical investigation involved only two single-arm prospective studies with a small number of participants (33). A double blind randomized controlled trial (RCT) could be designed as the stimulations are not perceived by the patient. Such a study was performed with the RNS system (a direct brain stimulation method with the same indication) and a significant reduction in seizure frequency by RNS was confirmed.

Reference:

Heck CN, King-Stephens D, Massey AD, et al. Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: final results of the RNS System Pivotal trial. Epilepsia. 2014 Mar; 55(3):432-41.

- **Adequacy of benefit-risk determination**

The adequacy of the benefit-risk determination is limited on one hand by the limited number of patients included in the two clinical studies (15 and 18 patients, respectively), limiting the reliability of the estimate of the proportion of responders (about [redacted] On the other hand, the adequacy of the benefit-risk determination is limited by insufficient information about adverse events, in particular "worsening of seizure situation" (see above for detailed information that should be obtained and assessed in the opinion of the expert panel). In addition, the availability of more information on patient selection (in terms of seizure type and frequency) and clinical (patients characteristics) and technical (stimulation parameter and

electrode location) features associated with seizure worsening may result in additional restrictions to the indication for the use of the device, or establish restrictions to the stimulation parameters allowed during setting of the device, or add further procedures to prevent such events (e.g. monitoring electrode heating and optimising stimulation parameters / electrode locations) with the aim of improving the benefit-risk ratio for the selected patient population.

- **Consistency of clinical evidence with purpose / medical indication(s)**

The described clinical evidence is consistent with the purpose and medical indication only concerning the efficacy data (from the CEAR: "responder rate (defined as at least 50% reduction in seizure frequency from baseline to month 7 post-implant) of [redacted] and a median seizure frequency reduction of [redacted]).

However, the adverse event of "worsening of seizure situation" is in principle in clear contrast with the purpose of use of the device. Therefore, the NB should require additional information on this adverse event, including longer follow-up data from patients who have participated into the two clinical trials.

- **Consistency of clinical evidence with PMCF plan**

According to the manufacturer, no post-market surveillance data is available at this stage considering the recent development of the system. Patients included in the two clinical trials studies will be followed up to 36 months post-implant and a post-market observational study will be initiated to confirm the safety and performance of the system in a larger patient population. Finally, more studies are in progress and results would be available in 2023.

This expert panel suggests that the NB should consider that as the lifetime of the instrument is described as 5 years, a long-term follow-up monitoring patients – and their devices with technical tests - for at least 5 years would be adequate to provide more information about safety.

This expert panel also suggests that the information on patients who have experienced a "worsening of seizure situation" should be monitored for at least 5 years for a better assessment the duration of this adverse event.

Moreover, the patients' perspective (specifically, patient-reported outcomes) is missing, including the burden of treatment and the perceived benefit on quality of life, which is not only determined by seizure frequency. Such burden should also include surgery required for battery exhaustion, so a follow-up of 3 years may be insufficient with this respect. This duration may also be insufficient in case the battery is replaced every 40 weeks, as the lifetime of the device is expected to be around 5 years, making it important to collect data on effective device lifetime and potential safety hazard related to malfunctioning once the end of life of the device is approaching.

- **Overall conclusions and recommendations on clinical evaluation**

Overall, the clinical evaluation informs on the frequency of seizure reduction and the proportion of patients experiencing it. However, details with similar accuracy should be provided on AE, particularly the one referring to "worsening of seizure situation". It is not obvious whether this means increase in seizure severity, frequency or in how many patients this has occurred and for how long.

Details on the stimulation procedures should be considered as for direct stimulation, it is not clear whether the pseudo-Laplacian montage is delivering anodal or cathodal stimulation in the central electrode, when the device delivers direct current. This aspect should be clarified as the cathodal stimulation has been reported to reduce cortical excitability while anodal stimulation leads to its increase and should be detrimental in the case of epilepsy. This is relevant for the [redacted] that has two different stimulation patterns: [redacted]

[redacted]. From the technical description it is not clear whether the longer pulse will deliver cathodal current or anodal current to the epileptic focus.

Modelling of the depth of the electric field reaching the brain target tissue, obtained with the device connected to electrodes with the pseudo-Laplacian montage, should be available as "lateral temporal lobe epilepsy or extra-temporal lobe epilepsy" is in the inclusion criteria. As the maximal amplitude of stimulation available is 4 mA (p 5 of the CEAR), it is not clear whether this would be sufficient to reach deeper structures such as the supplementary motor area, as no detailed specification is provided about which "extra-temporal lobe" areas may be targeted. Moreover, the orientation of the stimulation current relative to the orientation of the neural population producing the focal epileptic activity might be of importance. In tDCS, optimization approaches for electrode configurations typically take the orientation and location of the targeted region into account. The electrode positioning is consequently a compromise between target location and orientation fit. Therefore, the electrode positioning might be crucial for the success of the approach and thus for the risk/benefit analysis.

It is not clear whether a system or procedure is in place to define the stimulation setting, in particular how to set the stimulus intensity to the best compromise between safety and efficacy.

According to the manufacturer, no post-market surveillance data is available at this stage considering the recent development of the system. Patients included in the two clinical trials studies will be followed up to 36 months post-implant and a post-market observational study will be initiated to confirm the safety and performance of the System in a larger patient population. Finally, more studies are in progress and results would be available in 2023.

The NB may have overlooked the fact that the medical indications need to be further developed. Firstly, by providing data on patients' selection for the clinical trials. Secondly, by analysing pre-existing clinical features and stimulus parameters that led to "worsening of seizure situation" within the clinical trials, or specific procedures associated with side effects (for example, specific electrode lead locations in relation to temporal muscle and the related side effects in case of temporal epileptic focus below the temporal line). Thirdly, by extending the planned follow-up to 5 years for each patient. Fourthly, we should consider that:

- epileptic focus definition is a complex issue: clinical pictures and traditional EEG are insufficient to characterize the target population.
- manufacturer parameters settings are based on a theoretical preclinical study. A [redacted] at the time of a seizure was subsequently added. Indeed, the mechanism by which brain stimulation is effective on seizure control is not fully understood. Different mechanisms were probably involved with a potential rapid effect at the time of the seizure and a long-term effect (on plasticity?) to prevent seizure occurrence. Different parameters settings had to be explored.

Clinical follow-up should take into consideration the need for surgical replacement of the stimulator because of battery exhaustion ("Battery life: minimum approximately 40 weeks"). The patients' perspective having to undergo surgery every 40 weeks for replacement should be collected as well.

References:

- Manzouri F, Zöllin M, Schillinger S, Dümpelmann M, Mikut R, Woias P, Comella LM, Schulze-Bonhage A. A Comparison of Energy-Efficient Seizure Detectors for Implantable Neurostimulation Devices. Front Neurol. 2022 Mar 4; 12:703797.
- Manzouri F, Meisel C, Kunz L, Dümpelmann M, Stieglitz T, Schulze-Bonhage A. Low-frequency electrical stimulation reduces cortical excitability in the human brain. Neuroimage Clin. 2021; 31:102778.
- Schulze-Bonhage A. A realistic and patient-specific perspective on EEG-based seizure detection. Clin Neurophysiol. 2022 Jun; 138:191-192.

– Schulze-Bonhage A. Seizure prediction: Time for new, multimodal and ultra-long-term approaches. Clin Neurophysiol. 2022 Jan; 133:152-153.

2.3 Detailed aspects of the opinion as required by MDR Annex IX Section 5.1

Opinion of the expert panel on the specific aspects of the clinical evaluation assessment report of the notified body (CEAR)[1]

1. Overall opinion on the NB's assessment of the adequacy of the manufacturer's clinical evaluation report

Overall, this expert panel recommends the NB to collect and assess more technical data on the system itself, namely:

1. What is to be replaced with each surgery required for battery exhaustion, for a better assessment of the expected patient burden and for a better estimate of the duration of follow-up for the post-market study and for the participants in the two clinical trials described for the clinical evaluation assessment.
2. What is the depth of the expected effective stimulation to assess whether additional restrictions to the indications are needed (e.g. distance between the brain regions identified as originating the focal seizures and the electrodes placed on the skull).
3. What were the stimulation parameters and electrode locations associated with "worsening of seizure situation". With this respect, the NB should request a description of the pre-existing clinical features of patients experiencing worsening of seizure situation (including the duration, if transient, of this adverse event), request access to the most recent follow-up data about these patients, and to extend at 5 years the clinical follow-up of these patients. This implies that future studies should comprise a post-surgical verification of the relationship between electrode location and epileptogenic zone, to be taken into account in the PMCF plan.

The NB did not take into account that patient's selection criteria should be better described and perhaps refined on the basis of the analysis of clinical and technical pre-existing conditions that led to lack of response on one side (about [redacted] of participants) and to "worsening of seizure situation" on the other side.

Moreover, the NB should request data on patients' perspective, namely on the burden of treatment and the perceived benefit on quality of life, which is not only determined by seizure frequency. Such burden should also include the surgery required because of battery exhaustion, so a follow-up of eight months cannot be informative with this respect. These data should be collected within the post-market plan as well, including data on effective device lifetime and potential safety hazard related to malfunctioning once the end of life of the device is approaching. With this respect, details on whether surgery will require battery replacement or replacement of the whole stimulator should be assessed by the NB, making sure that the duration of follow-up, of participants in both the presented clinical trials and in the post-market setting, will be coherent with the expected lifetime of the device. All these data may help refining the indications for device substitution or definite removal.

The NB should further inquiry on the reasons for the 5 years lifetime of both the leads and the pulse generator. About the leads, the NB should also request more details on what is the critical lead component (e.g. the point of epicranial insertion, or the wires, or other).

[1] According to Annex IX Section 5.1 of Regulation (EU) 2017/745 - Assessment procedure for certain class III and class IIb devices.

2. Opinion on the NB's assessment of the sufficiency of the clinical evidence provided by the manufacturer

This expert panel suggests that the NB should consider that, as the lifetime of the instrument is of 5 years, a long-term follow-up monitoring patients – and their devices with technical tests - for at least 5 years would be the adequate minimal follow-up period.

This expert panel also suggests that the information on patients who have experienced a "worsening of seizure situation" should be clinically determined and monitored for at least 5 years for a better assessment the duration of this adverse event.

Moreover, the NB should request data on the patients' perspective, namely on the burden of treatment and their perceived benefit on quality of life, which is not only determined by seizure frequency. Such burden should also include surgery required for battery exhaustion, so a follow-up of 3 years may be too short with this respect. This duration may also be insufficient in case the battery is replaced every 40 weeks, as the lifetime of the device is expected to be around 5 years, making it important to collect data on effective device lifetime and potential safety hazard related to malfunctioning once the end of life of the device is approaching.

The question remains whether brain stimulation can improve outcomes in optimally treated patients with refractory focal epilepsy. The two clinical trials presented showed that about [redacted] of patients had significant improvements in number of seizures. However, it is well documented that surgical interventions can have a significant placebo effect. In this setting, a sham-controlled clinical trial could provide more evidence supporting the efficacy of brain stimulation for patients with intractable epilepsy. A sham-controlled clinical trial is possible when stimulations are not perceived by the patient. A multicenter, double-blinded, randomized controlled trial of responsive neurostimulation with RNS as adjunctive therapy for medically refractory partial epilepsy was carried out (Heck *et al*, 2014) and a significant reduction in seizure frequency after RNS treatment was confirmed.

Reference:

Heck CN, King-Stephens D, Massey AD, et al. Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: final results of the RNS System Pivotal trial. Epilepsia. 2014 Mar; 55(3):432-41.

3. Opinion on the NB's assessment of the adequacy of the manufacturer's benefit-risk determination

The NB should request more clinical assessment data allowing a better estimate of the benefit-risk determination. In particular, the NB should have requested more information about the type of worsening (more severe seizures? More frequent? How many patients presented with this unwanted event?). Moreover, the NB should have requested more data on the pre-existing condition of patients presenting with seizure worsening (including epileptic focus) and technical features of the treatment (stimulation parameters, current polarity when applicable, electrode location). Finally, the NB should request additional data on extended individual follow-up in patients participating in the two clinical studies described, particularly in those patients presenting worsening condition after the implant.

4. Opinion on the NB's assessment of the consistency of the manufacturer's clinical evidence with the intended purpose, including medical indication(s)

The NB 's assessment of the consistency of the manufacturer's clinical evidence with the intended purpose,

including medical indications, has margins for improvement in two aspects. The first concerns the need for a refinement of the medical indications claimed by the manufacturer, as details on patients' selection (e.g. number of seizures per month) in the clinical trials were not provided. With this respect, also modelling on the biologically active electric field is lacking. The latter may provide further restrictions based on a limit distance between the stimulating electrodes and the brain regions identified as generating the focal seizures in the individual patient (e.g. patients with deep foci may be excluded from treatment in reason of technical limitations and not of clinical features). Another important clinical aspect that may impact the medical indication is the type of epilepsy. The clinical data were provided without distinction between temporal and other types of epilepsy, while a subgroup analysis concerning the baseline clinical features of patients undergoing treatment, including the type of epilepsy, will allow to confirm the current medical indication or to introduce further restriction to the use of the device. The NB should recommend a subgroup analysis of the available data in patients who participated in the two studies – including extended follow-up data on these patients - and the collection of new prospective post-market data.

The second, more important aspect that the NB needs to improve, is the information regarding the "worsening of seizure situation", that clearly speaks against the main medical indication of the device. The characterization of such worsening situations should be requested as well as details on the proportion of patients with this adverse event, together with their pre-existing clinical features (including epileptic focus) and stimulation parameters (including stimulation intensity, polarity where applicable and the use of [redacted] applied by the patient) and follow-up data. In the opinion of this expert panel, a deeper analysis of these issues requires a longer follow-up period than the proposed 3 years in the PMCF plan (see point 5 below), particularly in the patients participating in one of the two reported clinical studies, which should be monitored for at least 5 years.

5. Opinion on the NB's assessment of the consistency of the manufacturer's clinical evidence with the PMCF plan

The NB should have considered that the clinical evidence of [redacted]esponders is in contrast with the report of patients experiencing "worsening of seizure situation".

The NB should request additional data on the reported cases of "worsening of seizure situation" and ask for these patients be monitored for at least 5 years for a better assessment on the duration of this adverse event.

The NB should have considered that, as the lifetime of the instrument is described as 5 years, a long-term follow-up monitoring patients – and their devices with technical tests - for at least 5 years would provide more information about safety.

The NB should request data on the patients' perspective on quality of life and burden of treatment, including that related to the surgery required because of battery exhaustion.

The NB should further explore the details on the medical indications, after considering the data on patients' selection in the two clinical studies and on those cases with seizure worsening.

The NB should require a subgroup analysis of data collected within the prospective ongoing and post-market studies, based upon the type of epilepsy. This analysis will allow to confirm the current medical indication or to introduce further restrictions to the use of the device.

The NB should request additional data allowing to determine the most appropriate timing to assess treatment response, which will be important to allow patients and their clinicians addressing the issue of deciding to continue treatment or to remove the device.

The NB should consider that the epileptic focus definition is a complex issue: clinical pictures and traditional EEG are insufficient to fully characterize the target population.

The NB may consider asking for the collection of data from a sham-controlled clinical trial, where the starting of active stimulation is delayed in a randomly assigned subgroup, in order to grant active stimulation to all patients for ethical reasons.

The NB should require that future studies include a post-surgical measurement of the spatial relationship between the electrode subgaleal locations and the epileptogenic zone.

In the PMCF plan, the NB should require comparison with other indirect brain stimulation such as vagus nerve stimulation, being the latter a procedure with a relatively low invasiveness as well.

2.4 Overall conclusions and recommendations

This is a newly developed device proposed as an adjunctive therapy for medically refractory focal epilepsy. In principle, it could be considered as a breakthrough considering its novelties and its low invasiveness with the potential for providing a strong clinical impact. However, the number of patients studied is small, which limits the estimate on the proportion of responders (50% of patients undergoing [redacted] seizure frequency reduction). More data are needed to provide a high level of evidence and to compare different stimulation parameters. This expert panel recommends further analysis on the data available on patients showing "worsening of seizure situation" with reference to obtaining more detailed information on how "worsening" was defined, how many patients presented with this event, which pre-existing clinical features (including epileptic focus) and stimulation parameters (including electrode location, stimulation intensity and delivery of [redacted] by the patient). A more detailed post-market plan is needed, with collection of patient-reported outcomes on quality of life, taking into account not only the burden of treatment implant and management, but also that of battery (or device?) replacement. Within the latter issue, what is being replaced at each surgery should be clearly described, to provide the NB additional information to be used when defining the minimum requirement for the long-term follow-up in the post-market study, that should extend from 3 to 5 years for each patient not only to better define clinical safety, duration of effect, possible indication for treatment stopping, but also potential additional safety hazards related to approaching the end of life of the device.

Details are also required concerning the definition of the electrode localization and the stimulation settings according to the clinical, anatomical and neurophysiological pictures, although more precise information could result from long-term experience in a larger number of patients.

2.5 Stakeholder information, where available

Relevant information provided by stakeholders, if applicable[2]
Has the Secretariat provided information from stakeholders?
☐ Yes ☒ No
Summary of the information that was taken into account and how it was taken into account.
Not applicable

2.6 Divergent positions in case no consensus was reached

Summary of divergent positions
No divergent opinions emerged among the expert panel members

Please indicate how many of the experts of the panel or sub-group had divergent views
None.

[2] According to Article 106.4 of Regulation (EU) 2017/745, expert panels shall take into account relevant information provided by stakeholders including patients' organisations and healthcare professionals when preparing their scientific opinions.