PIMIDES I – Clinical Investigation Plan

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PIMIDES I - A pilot study to assess the feasibility of patient-controlled neurostimulation with the EASEE® System to treat medically refractory focal epilepsy

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SPONSOR SIGNATURE PAGE

PIMIDES I - A pilot study to assess the feasibility of patient-controlled neurostimulation with the EASEE® System to treat medically refractory focal epilepsy

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INVESTIGATOR SIGNATURE PAGE

PIMIDES I - A pilot study to assess the feasibility of patient-controlled neurostimulation with the EASEE® System to treat medically refractory focal epilepsy

I have read the PIMIDES I Clinical Investigation Plan (CIP) and agree to adhere to the requirements outlined within. I will provide all pertinent information regarding the CIP to the study personnel under my supervision. I will review and discuss this material with them and ensure they are fully informed of the requirements of this CIP. I will also ensure that this study is conducted in compliance with this CIP, Good Clinical Practice (GCP), EN ISO 14155 and any applicable local and/or national regulatory agencies and their requirements.

Investigator/Sub-investigator Name (*print*): _____

Date (*dd.mm.yyyy*): _____

Trial site: _____

Signature: _____

Contents

1 Revision History

Lists details of all protocol amendments whenever a new version of the protocol is produced.

Protocol Version No.	Date	Author(s) of changes	Modification Description
1.0	07-Aug-2019	Erdmann Zippel	Initial Protocol Version
2.0	11-Nov-2019	Anja Resler	Implemented changes during initial approval process according to CA and EC requirements dd 30-Sep-2019 and 10-Oct-2019 respectively
3.0	21-Jan-2020	Dr. Carolin Jenkner, Anja Resler	- specification of statistical analysis based on feedback of the Ethics Committee Freiburg (chapter 10.5.1.1, page 36 and synopsis, page 14) - further specification of neuropsychological tests (table 1, page16) - increasing the number of clinical sites from 5 to 7 - minor editorial changes
4.0	29-Apr-2020	Anja Resler	- increasing the number of clinical sites from 7 to 8 (page 10, page 20)
5.0	12-Aug-2020	Anja Resler	- Synopsis page 12; 5.4 page 21; 5.5 page 22: Inclusion criterion #9 (specification), Exclusion criterion #10 - 6.4 page 25: Risk-Benefit Assessment during Covid-19 pandemic - Table I, page 16; 9.2.1 page 30: Clarification for timing of Baseline testing (SSQ, QOLIE 31-P, NDDI-E, Neurocognition) - 11.5.1, page 41: differentiation between SAE definition of DIN EN ISO 14155 and MPSV §2 (5) for Germany
6.0	01-Dec-2020	Anja Resler	- 7.1.1. Implantable Components and 7.1.2. Surgical Accessories: - Added reference for tunnelling system - Addition of an EASEE Lead model variant for an additional screw supplier
7.0	30-Apr-2021	Anja Resler	- Synopsis to reflect LTFU **(updated)** - Data Collection Table to include LTFU visits **(updated)**

			- 5.3 Study duration to include LTFU **(updated)** - 5.6 Eligibility criteria LTFU **(added new section)** - Supplementary info for: 5.7, 5.7.2 **(updated)** - 8.2 Secondary endpoints supplemented with LTFU timepoints **(updated)** - 9.1 Study overview to include LTFU period **(updated)** - 9.4.2. "i.e. 16 months" **(deleted)** - 9.8 Follow-up period – decision regarding continuation of stimulation at 8 months post-implant **(updated)** and information regarding decision to enter LTFU **(added)** - 9.9 Long-term follow-up Period **(added)** - Previous "9.9.1. Device Deactivation" section worked into 5.7.2 **(deleted),** replaced by "Rationale" - 9.10 Battery Depletion **(moved)** - 9.11 Device Explantation **(added)** to replace "Removal of EASEE® Power" and "Removal of EASEE® Lead" - 9.12 Plan for Further Treatment **(updated complete section)** - 10.5.2 Secondary Outcomes to include LTFU **(updated**) - 11.5. Adverse Events **(updated)** - 11.5.6 Early Termination of Clinical Trial **(updated)** - 17. Glossary **(updated)**

2 Synopsis

Full Title

PIMIDES I – A pilot study to assess the feasibility of patient-controlled neurostimulation with the EASEE® System to treat medically refractory focal epilepsy

Running Title

PIMIDES I

Study Design

This is a prospective, interventional, unblinded, multicenter study designed to collect data on 18 subjects implanted with the EASEE® System with patient controlled neurostimulation capability in up to 8 European Centers.

Study Objectives

Primary study objective:

The primary study objective is to demonstrate the safety and performance of patient-controlled-neurostimulation with the EASEE® System in subjects with medically refractory focal epilepsy.

Secondary study objectives:

1. Assess changes from baseline seizure frequency
2. Assess changes from baseline seizure severity
3. Assess changes from baseline seizure symptoms
4. Assess changes from baseline seizure duration
5. Assess changes from baseline EEG
6. Assess changes from baseline quality of life
7. Assess changes from baseline mood
8. Assess changes from baseline neurocognition

Device Description

The EASEE® (Epicranial Application of Stimulation Electrodes for Epilepsy) System is an implantable stimulation device, which is intended for the treatment of medically refractory focal epilepsy. The EASEE® System consists of the implantable components EASEE® Power (IPG) and EASEE® Lead (electrode array and connecting link), none of which have the CE Mark. The surgical tools include EASEE® Template (tool for determining implant location) and a torque wrench which do not have the CE Mark, a screw/screwdriver set used to fix the array onto the skull and a tunneler, which have the CE Mark. The external control elements include EASEE® Set (physician programmer), EASEE® Connect (telemetry wand) and EASEE® Access, none of which have the CE Mark and an activation Magnet which has CE Mark. All study personnel must complete training on study procedures before implanting and programming the EASEE® System.

Intended Use

The EASEE® System is intended for use as an adjunctive therapy in reducing the burden of epilepsy in adults with focal onset seizures that are refractory to two or more antiepileptic medications.

Rationale

This is a pilot study to explore the feasibility of patient-controlled neurostimulation with a modified stimulation protocol using the EASEE® System in a small patient collective as part of a research project supported by the BMBF. Safety and performance aspects of treatment with the EASEE® System with patient controlled neurostimulation capability will be evaluated. In order to treat refractory focal epilepsy a patient-triggered stimulation of the epileptic focus during a seizure will be carried out using the EASEE® Access handheld external control device.

The extra-cranial, subgaleal patient-individualized stimulation of the epileptic focus proposed here is a less invasive procedure, but with similar focus on the epileptogenic brain area as the invasive RNS approved in the US. For EASEE®, safety and performance data are to be generated in this clinical trial to test the feasibility of responsive neurostimulation.

Patient Population

Patients with a clinical diagnosis of medically refractory focal epilepsy. Potential patients include those eligible based on the inclusion/exclusion criteria and willing to undergo implantation with the EASEE® System.

Study Duration

Total study duration from FPI to study analysis is anticipated to be approx. 49 months. The enrolment period for the study is anticipated to be approx. 12 months. The total duration of the study per subject is:

a) 17 months for subjects who do not consent to the long-term follow-up, including 1 month of baseline monitoring, 1 month of post-implant recovery, 3 months of evaluation period and 12 months of follow-up.

b) 37 months for subjects who consent to long-term follow-up (as listed above + additional 20 months of long-term follow-up).

Key Inclusion Criteria:

Patients enrolled in the study must meet the following criteria:

1. Patients with a clinical diagnosis of focal seizures or focal to bilateral tonic clonic seizures.
2. Patients with a diagnosis of lateral temporal lobe epilepsy or extra-temporal lobe epilepsy.
3. Patients with a predominant epileptic focus, which can be clearly identified as the site of implantation for the electrode based on EEG and clinical presentation.
4. Patients who are able to initiate a stimulation bolus during their seizure (intact consciousness at least during part of a habitual seizure type, as well as motor ability to operate the device to trigger stimulation in this phase).
5. Patients, if they have had prior resective surgery to treat epilepsy, need to have a clearly identifiable epileptic focus and a preserved neocortex in the region of implantation.
6. Patients who have failed treatment with a minimum of two anti-seizure medications (used in appropriate doses).
7. Patients having seizures which are distinct, stereotypical events and can be reliably counted, in the opinion of the Investigator, by the patient or caregiver and recorded in a seizure diary.

8. Patients having an anticipated average of 3-200 partial-onset seizures (focal to bilateral tonic clonic seizures) during the baseline period.
9. Patients taking a constant dose of antiepileptic medication(s) over the most recent 28-day period prior to the baseline period or over most recent 58-day period prior to implantation (use of medication for acute treatment of seizures is allowed).
10. Patients between the ages of 18 and 75 years.
11. Patients able and willing to provide appropriate consent prior to study procedures.
12. Patients able to complete regular office appointments per the protocol requirements, including behavioral (mood) surveys and neuropsychological testing.
13. Patients willing to be implanted with the EASEE® System as a treatment for his/her seizures.

Key Exclusion Criteria:

Patients who meet any of the following criteria are not eligible to be enrolled in the study:

1. Patients with a diagnosis of mesial temporal lobe epilepsy.
2. Patients with a previous diagnosis of psychogenic or non-epileptic seizures, which are semiologically non-distinguishable from epileptic seizures.
3. Patients with a diagnosis of primarily generalized seizures.
4. Patients, if after resective surgery, with non-preserved neocortex in the region of implantation
5. Patients with unprovoked status epilepticus in the preceding 6 months prior to enrolment.
6. Patients with a clinically significant or unstable medical condition (including cardiac conditions, alcohol and/or drug abuse) or a progressive central nervous system disease.
7. Patients with a diagnosis of active psychosis, major depression or suicidal ideation in the preceding year (excluding postictal psychosis).
8. Females who are pregnant or have a pregnancy wish in the next 2 years.
9. Patients enrolled in a therapeutic investigational drug or device trial.
10. Patients who are anatomically not eligible for EASEE® System implant in the opinion of the Investigator, as for example but not limited to: Patients having a metal implant intra- or extracranial in the region of targeted electrode implantation that cannot be safely removed during the neurosurgical intervention (e.g. CranioFix® 2 Titanium Clamp, cranial plates, screws, etc.)
11. Patients with an implanted electronic medical device that delivers electrical energy to the body (e.g. DBS, cardiac pacemaker or defibrillator) except for an existing VNS device that can be reliably switched off for the duration of the trial.
12. Patients requiring scheduled MRIs during the study phase.
13. Patients who are unable to properly operate the EASEE® Access handheld device (no intact consciousness during part of habitual seizure type or no motor ability to operate device for bolus stimulation).

Eligibility Criteria Long-term Follow-Up

LTFU Inclusion Criteria

1. Patients with an implanted and active EASEE® System who are willing to continue stimulation or patients with an **inactive** system who are willing to reactivate stimulation or undergo EASEE® Power (IPG) exchange if the battery is depleted.
2. Patients able and willing to provide appropriate consent prior to additional study procedures.

LTFU Exclusion Criteria

1. Patient's overall condition or life perspective is not compatible with participation in the long-term follow-up (e.g. planned pregnancy during the duration of the study, planned participation in another drug- or device study, other planned treatment which does not allow continuation of stimulation with EASEE® System).

Endpoints

Primary Endpoint

The primary endpoint is the safety of the EASEE® System with patient-controlled neurostimulation capability evaluated at 4 months post-implant measured in SAE rates. Safety is defined as follows:

1. Short-term chronic safety: Incidence of device/procedure related SAEs for the surgical implant procedure and the following 4 months.

Secondary Endpoints

2. Acute safety: Incidence of device/procedure related SAEs for the surgical implant procedure and the following month.
3. Seizure frequency: baseline seizure frequency and responder rate (defined as at least 50 % reduction in seizure rate from baseline) compared to respective values at 4 months, 8 months, 16 months, 24 months, and 36 months post-implant.
4. Seizure severity: baseline seizure severity compared to seizure severity at 4 months, 8 months, 16 months, 24 months, and 36 months post-implant.
5. Seizure duration: baseline average seizure duration compared to seizure duration at 4 months, 8 months, 16 months, 24 months, and 36 months post-implant.
6. Seizure symptoms: most debilitating baseline epilepsy symptom compared to epilepsy symptom(s) at 4 months, 8 months, 16 months, 24 months, and 36 months post implant.
7. Epileptiform activity: baseline measurements of scalp EEG compared to data collected at 1 month, 8 months, 16 months, 24 months, and 36 months post-implant.
8. Quality of life: baseline subject rated quality of life compared to 8 months, 16 months, 24 months, and 36 months post-implant.
9. Mood: baseline subject rated mood compared to 8 months, 16 months, 24 months, and 36 months post-implant.
10. Neurocognition: baseline neurocognition compared to 8 months, 16 months, 24 months, and 36 months post-implant.

Study Procedures and Measurements

The main study phases and respective procedures are as follows:

Screening

Subjects will be screened according to the pre-defined inclusion and exclusion criteria. If all criteria are met and the informed consent form has been signed, then the subject is considered as enrolled in the PIMIDES I study

Baseline Period

During the 1-month baseline period, subjects are requested to record seizure data on a daily basis in the PIMIDES seizure diary. At the conclusion of this period, the implant eligibility criteria will be reviewed.

Implantation

The EASEE® System will be implanted after the baseline period has been completed and the implant eligibility criteria have been met. EASEE® Lead will be implanted over the predominant focus, as identified by the physician. Following implantation of EASEE® Lead and EASEE® Power, technical testing of the device will be performed to confirm that the implantation has been successful.

Recovery

There will be a post-operative recovery period of 1 month to ensure that healing processes can take place. The device will remain off during this period. Subjects will continue to record seizure data on a daily based in the seizure diary.

Configuration

After the 1-month recovery period, a one-hour scalp EEG recording will be completed prior to configuration of the device. The device incl. the patient-controlled stimulation parameters will be configured individually for each subject by the treating physician according to current EASEE® System Instructions for Use (IFU) and the stimulation will be turned on.

Evaluation Period

The evaluation period begins after configuration of the device at 1-month post-implant and lasts for a duration of 3 months. Stimulation will remain on during this time. At 4 months post-implant the primary safety endpoint will be analyzed.

Follow-up Period

At 8 months post-implant the Investigator will evaluate and document the benefit for the subject in a qualified subject interview:

- If it is deemed that the subject has benefited from the stimulation i.e. there is a reduction in the burden of epilepsy in terms of reduction in seizure frequency, seizure severity, seizure duration, and/or improvement in QoL, neurocognition and the subject wishes to receive further stimulation, then the device may remain active up to the end of the follow-up period.
- If there has been no documented positive effect of stimulation, but the subject wishes to receive further stimulation, then the stimulation parameters may be changed at the discretion of the treating physician.

- If the subject does not wish further stimulation, then the device will be inactivated and explanted at the latest at the end of the follow-up period (unless subject agrees to reactivation and entry into the LTFU – see section below).

There will be a follow-up visit at 12 months post-implantation and a (final) visit will take place at 16 months post-implantation regardless of whether the device is active or has been inactivated or explanted.

Long-Term Follow-Up Period:
Patients eligible and willing to consent to the long-term follow-up period will be asked to complete further study visits at 24 months and 36 months post-implantation.

Other than the above visits, the subjects will not be required to visit the clinic more often than for their routine treatment.

The data to be collected during each phase is outlined in table 1. PIMIDES I Data Collection Table

Statistical Considerations

This is a prospective, interventional, unblinded, multicentre study. All included patients for whom the surgery was performed will be analysed. The primary endpoint is chosen to be safety defined as the probability of device/procedure related SAEs for the surgical implant procedure and the following 4 months. The incidence of all adverse events, of those being related, of those being severe, and of serious adverse events will be summarized with corresponding one-sided 95 % confidence intervals based on a binominal distribution.

Secondary endpoints are safety and efficacy related and will assess probability of benefit to the patient. Efficacy endpoints of the long-term follow-up (24- and 36 months) will only be evaluated descriptively due to the potential selection bias.

Sample Size

The primary goal of the study is to generate data regarding the feasibility and performance of neurostimulation with the EASEE® System with patient controlled neurostimulation capability. The results of this feasibility study will aid in the planning of a larger, sufficiently powered CE-Mark trial. When no device/procedure related SAEs for the surgical implant procedure and the following 4 months are observed, to obtain an upper bound of 0.153 on the 0.95 confidence interval for the probability of a rare event, would require a sample size of 18 patients (nQuery 8.3) (Machin, D., Campbell, M.J. , 1987).

Table 1 – PIMIDES I Visit schedule and Data collection table	**Visit 1** Screening/ Inclusion	**Visit 2:** Eligibility/ Implantation	**Visit 3:** Configuration/ Stimulation ON	**Visit 4:** End of Evaluation Period	**Visit 5:** Treatment Evaluation Visit	**Visit 6** Follow-up	**Visit 7:** Final Visit	**Visit 8:** LTFU 24 months	**Visit 9:** LTFU 36 months
Timing (in months relative to implantation)	**-1**	**0**	**+1**	**+4**	**+8**	**+12**	**+16**	**+24**	**+36**
Visit Window		+2 weeks	±1 week	±2 weeks	±2 weeks	±1 month	±1 month	±1 month	±1 month
Informed Consent	X								
Inclusion/Exclusion	X	X							
Demographics	X								
Medical History	X								
Pregnancy Test		A							
Drug Log (AED/ concomitant med.)	X	X	X	X	X	X	X	X	X
Scalp EEG (1-hour recording)		X	X,**		X,***		X,***	X,***	X,***
Intra-op EEG recording via EASEE Lead		X							
Seizure Diary, incl. Seizure duration*	X	X	X	X	X	X	X	X	X
Seizure Severity / Symptoms (SSQ)	(X)	(X)		X	X		X	X	X
Quality of Life (QOLIE-31-P)	(X)	(X)			X		X	X	X
Depression Inventory (NDDI-E)	(X)	(X)			X		X	X	X
Neurocognitive Testing [1]	(X)	(X)			X		X	X	X
Device Parameters		X	X	X	X	X	X	X	X
Device Interrogation		X	X	X	X	X	X	X	X
Adverse Events/Device Deficiency		X	X	X	X	X	X	X	X
Study Completion							X		X

X	required activity
(X)	test can be completed alternatively at screening **OR** prior to implantation. If AED are not stable for ≥28 days at visit 1, tests has to be done prior to implantation (visit 2).
*	Diary to be completed by subject throughout the study and brought to the site for evaluation at every FU visit
**	1-hour EEG recording to be completed prior to configuration of the device
***	EASEE® System must **be switched off** for all EEG recordings occurring post-implant to prevent interference
A	activity to be completed as needed (*** see above)
[1]	Intelligence (MWT-B/A), Attention and executive functions (EpiTrack®, incl. TMT A and B), Executive functions (RWT semantic, 5-points test), Memory (VLMT, DCS-R, Subtest Digit spans and Block spans), Language (BNT, AAT subtest speech comprehension), Visuospatial function (block design, VSWin), Motor functions (Perdue Pegboard), CES-D ***NOTE:*** *Sites which are not able to perform the full test battery are asked to perform EpiTrack® as a minimum requirement*

3 Introduction

3.1 Background

Epilepsy is a recurrent tendency to spontaneous, intermittent, abnormal electrical activity in the brain, manifesting as seizures. It is a common neurological disorder affecting approximately 1 % of the population (Longmore M et al., 2014). Epileptiform discharges involve either a localized area of the brain resulting in a focal seizure or the entire brain resulting in a generalized seizure. In adults, the most common type is focal epilepsy (Panebianco M et al., 2015). The majority of patients has a good prognosis to achieve satisfactory seizure control by treatment with anti-epileptic drugs (AEDs).

The goal of antiepileptic drugs is seizure control, which means reduction of seizure frequency and/or severity to the point that the patient is able to live a normal lifestyle without epilepsy-related limitations and with minimal or no drug toxicity (Greenberg MS, 2016). Drug choice depends on seizure type and epilepsy syndrome, other medication, co-morbidities and patient preference (Longmore M et al., 2014). The majority of epileptic patients has a good prognosis to achieve satisfactory seizure control by treatment with a single AED (Panebianco M et al., 2015). However, in 20 – 30 % of patients, seizures are not effectively controlled by monotherapy and often require treatment with a combination of different AEDs (Panebianco M et al., 2015). A failure of monotherapy indicates an 80 % chance that seizures will not be controllable pharmacologically. Indeed, only 10 % of patients benefit significantly from the addition of a second drug (Greenberg MS, 2016) and the chance to achieve complete seizure control with subsequent trials of antiepileptic drug is less than 5 % (Brodie et al., 2012). In contrast, increased drug load, due to polytherapy in patients non-responsive to antiepileptic treatment in monotherapy, often leads to an increased rate of medication-related adverse effects, such as cognitive impairment or mood disturbance (Eddy et al., 2011).

People with epilepsy are more likely to have psychological problems, especially depression, anxiety and suicidal thoughts and behaviors. Problems may be a result of difficulties dealing with the condition itself as well as medication side effects. Employment, social interactions, family relationships, and experiential activities, are at considerable risk in patients with epilepsies. Epilepsy patients have an increased risk of having impaired social cognitive skills and suffering from communication problems and interpersonal difficulties (Steiger et al. 2016).

Therefore, despite aggressive medical management with AEDs, seizures are not effectively controlled in 20 – 30 % of patients (Panebianco M et al., 2015). Non-pharmacological treatments are becoming increasingly attractive as a way to improve seizure control and to improve quality of life of patients with pharmacoresistant epilepsy. Epilepsy surgery is one option with high success rates; however, the procedure can be performed only in a limited number of patients and carries risks for cognitive decline specific to the regions of the brain which have been resected or

disconnected (Loring DW et al., 2015). For those who are not surgical candidates or those who continue to have seizures after surgery, neurostimulation may offer an alternative treatment option (Sprengers M et al., 2014, Salanova V et al., 2015; Stefan H et al., 2012).

Over the last 20 years, the clinical efficacy of electrical stimulation of the vagus nerve and deep brain structures for the treatment of several neurologic and psychiatric conditions, including epilepsy, depression, and Parkinson disease, has been extensively investigated (Varga ET et al., 2011; Sohal VS and Sun FT, 2011). Both extracranial, including vagus nerve and transcranial direct current stimulation, as well as intracranial stimulation, comprising deep brain and cortical stimulation, have been applied as adjunctive treatment options for medically refractory epilepsy. Despite their potential clinical benefit, the mechanisms by which deep brain stimulation and other forms of neurostimulation modulate neuronal activity remain unknown (Sohal VS et al., 2011).

Depending on the invasiveness of the procedure, as well as on the location of the electrodes (extracranial or intracranial), different neurostimulation techniques are associated with specific adverse events. Vagus nerve implantation and stimulation is primarily associated with hoarseness (4.9 to 66.3 %, Ghani S et al., 2015), cough (7.3 to 45.3 %, Klinkenberg S et al., 2012 and Ghani S et al., 2015), dyspnea (1.7 to 25.3 %, Ghani S et al., 2015), pain (1.6 to 30.1 %, Klinkenberg S et al., 2012; Ghani S et al., 2015; Ryvlin P et al., 2014), paresthesia (4.9 to 25.2 %, Klinkenberg S et al., 2012 and Ghani S et al., 2015), nausea (14.7 to 20.4 %, Ghani S et al., 2015) and headache (2.4 to 24.2 %, Klinkenberg S et al., 2012; Ghani S et al., 2015; Ryvlin P et al., 2014). The majority of adverse events associated with implantation of deep brain or subdural electrodes and intracranial stimulation occur in the first months following device implantation. Adverse events include implant site infection (3.7 to 12.7 %, Heck CN et al., 2014; Bergey GK et al., 2015; Salanova V et al., 2015), implant site pain (23.6 %, Salanova V et al., 2015), paresthesia including tingling, vibration or shocking sensations at the stimulator implant site (9.3 to 22.7 %, Fisher R et al., 2010 and Salanova V et al., 2015), neurostimulator migration (5.5 %, Salanova V et al., 2015), lead migration or damage (2.6 to 8.2 %, Heck CN et al., 2014; Bergey GK et al., 2015; Salanova V et al., 2015), memory impairment (7.3 to 13.0 %, Salanova V et al., 2015 and Fisher R et al., 2010), dizziness (5.6 to 6.4 %, Fisher R et al., 2010 and Salanova V et al., 2015). Furthermore, intracranial stimulation is associated worsening of depression symptoms (3.1 to 14.8 %, Bergey GK et al., 2015 and Fisher R et al., 2010).

Non-implantable stimulation therapy, such as cathodal transcranial direct current stimulation (tDCS) is a non-invasive and safe brain stimulation method to suppress regional cortical excitability. Although currently tDCS is not FDA-approved for clinical use, clinical data indicates that tDCS may offer a practical therapeutic option for the treatment of epilepsy, with the benefit of an easy, rapid and focal application (Larkin M et al., 2016; Auvichayapat N et al., 2013; Varga ET et al., 2011). Indeed, tDCS is associated with few and relatively mild side effects compared to the implanted stimulation systems. These include mild itching sensation during the stimulation, mild headache (San-Juan D et al., 2017; Karvigh SA et al., 2017; Assenza G et al., 2016) and transient erythematous rash under the reference electrode (3.7 %, Auvichayapat N et al., 2013).

In epilepsy drug trials, a ≥50 % reduction in seizure frequency is often used as the outcome measure to assess treatment efficacy (Chambers A and Bowen JM, 2013). Similarly, this measure is the most commonly reported seizure frequency outcome in clinical trials investigating the performance of neurostimulation devices as adjunctive therapy in medically refractory epilepsy. All neurostimulation techniques are associated with a positive benefit/risk profile in patients with medically refractory epilepsy, and a significant decrease in seizure frequency with a reduction of ≥50 % has been demonstrated for VNS (Panebianco M et al., 2015; Chambers A and Bowen JM, 2013; Ghani S et al., 2015), ATN DBS (Salanova V et al., 2015; Lee KJ et al., 2012) and responsive neurostimulation (Bergey GK et al., 2015; Heck CN et al., 2014). Furthermore, several studies showed that tDCS compared to sham stimulation significantly reduces the number of epileptiform discharges and/or seizure frequency in patients with medically refractory epilepsy with a single epileptogenic focus (San-Juan D et al., 2017; Assenza G et al., 2016; Auvichayapat N et al., 2013; Fregni F et al., 2006).

The intended patient population has limited treatment options as patients have medically refractory epilepsy and are not candidates for epilepsy surgery. Therefore, any reduction in seizure frequency can be considered as clinically meaningful (Chambers A and Bowen JM, 2013).

3.2 Rationale

This is a pilot study to explore the feasibility of patient-controlled neurostimulation with a modified stimulation protocol using the EASEE® System with patient controlled neurostimulation capability in a small patient collective as part of a research project supported by the BMBF. Safety and performance aspects of treatment with the EASEE® System will be evaluated. In order to treat refractory focal epilepsy a patient-triggered stimulation of the epileptic focus during an incipient seizure will be carried out using the EASEE® Access handheld external control device.

The extra-cranial, subgaleal patient-controlled stimulation of the epileptic focus proposed here is a less invasive procedure, but with similar focus on the epileptogenic brain area as the invasive RNS approved in the US. For EASEE®, safety and performance data are to be generated in this clinical trial to test the feasibility of responsive neurostimulation.

4 Objectives

Primary study objective:

The primary study objective is to demonstrate the safety and performance of patient-controlled-neurostimulation with the EASEE® System in subjects with medically refractory focal epilepsy.

Secondary study objectives:

1. Assess changes from baseline seizure frequency

2. Assess changes from baseline seizure severity
3. Asses changes from baseline seizure symptoms
4. Assess changes from baseline seizure duration
5. Assess changes of seizure patterns (epileptiform discharges) from baseline EEG
6. Assess changes from baseline quality of life
7. Assess changes from baseline mood
8. Assess changes from baseline neurocognition

5 Protocol

5.1 Study Design

This is a prospective, interventional, unblinded, multicenter study designed to collect data on subjects implanted with the EASEE® System.

Good Clinical Practices shall be followed during the study, including Declaration of Helsinki, EN ISO 14155, WMO and MEDDEV 2.7.1.

5.2 Number of Subjects/Sites

Up to 8 clinical sites will be asked to enroll a collective total of 18 subjects. Each site will be asked to enroll a minimum of 2 subjects, however inability to meet the minimum will not constitute a protocol deviation. There will be no upper limit per site for enrolment, as long as the overall study sample size is not exceeded.

5.3 Study Duration

Total study duration from FPI to study analysis is anticipated to be approx. 49 months. The enrolment period for the study is anticipated to be approx. 12 months. The total duration of the study per subject is

a) 17 months for subjects who do not consent to the long-term follow-up, including 1 month of baseline monitoring, 1 month of post-implant recovery, 3 months of evaluation period and 12 months of follow-up.

b) 37 months for subjects who consent to long-term follow-up (as listed above + additional 20 months of long-term follow-up).

5.4 Inclusion Criteria

Patients enrolled in the study must meet all of the following criteria:

1. Patients with a clinical diagnosis of focal seizures or focal to bilateral tonic clonic seizures.
2. Patients with a diagnosis of lateral temporal lobe epilepsy or extra-temporal lobe epilepsy.

3. Patients with a predominant epileptic focus, which can be clearly identified as the site of implantation for the electrode based on EEG and clinical presentation.
4. Patients who are able to initiate a stimulation bolus during their seizure (intact consciousness at least during part of a habitual seizure type, as well as motor ability to operate the device to trigger stimulation in this phase).
5. Patients, if they have had prior resective surgery to treat epilepsy, need to have a clearly identifiable epileptic focus and a preserved neocortex in the region of implantation.
6. Patients who have failed treatment with a minimum of two anti-seizure medications (used in appropriate doses).
7. Patients having seizures which are distinct, stereotypical events and can be reliably counted, in the opinion of the Investigator, by the patient or caregiver and recorded in a seizure diary.
8. Patients having an anticipated average of 3-200 partial-onset seizures (focal to bilateral tonic clonic seizures) during the baseline period.
9. Patients taking a constant dose of antiepileptic medication(s) over the most recent 28-day period prior to the baseline period or over most recent 58-day period prior to implantation (use of medication for acute treatment of seizures is allowed).
10. Patients between the ages of 18 and 75 years.
11. Patients able and willing to provide appropriate consent prior to study procedures.
12. Patients able to complete regular office appointments per the protocol requirements, including behavioral (mood) surveys and neuropsychological testing.
13. Patients willing to be implanted with the EASEE® System as a treatment for his/her seizures.

5.5 Exclusion Criteria

Patients who meet any of the following criteria are not eligible to be enrolled in the study:

1. Patients with a diagnosis of mesial temporal lobe epilepsy.
2. Patients with a previous diagnosis of psychogenic or non-epileptic seizures, which are semiologically non-distinguishable from epileptic seizures.
3. Patients with a diagnosis of primarily generalized seizures.
4. Patients, if after resective surgery, with non-preserved neocortex in the region of implantation
5. Patients with unprovoked status epilepticus in the preceding 6 months prior to enrolment.
6. Patients with a clinically significant or unstable medical condition (including cardiac conditions, alcohol and/or drug abuse) or a progressive central nervous system disease
7. Patients with a diagnosis of active psychosis, major depression or suicidal ideation in the preceding year (excluding postictal psychosis).
8. Females who are pregnant or have a pregnancy wish in the next 2 years.
9. Patients enrolled in a therapeutic investigational drug or device trial.
10. Patients who are anatomically not eligible for EASEE® System implant in the opinion of the Investigator, as for example but not limited to: Patients having a metal implant intra- or extracranial in the region of targeted electrode implantation that cannot be safely removed

during the neurosurgical intervention (e.g. CranioFix ® 2 Titanium Clamp, cranial plates, screws, etc.)

11. Patients with an implanted electronic medical device that delivers electrical energy to the body (e.g. DBS, cardiac pacemaker or defibrillator) except for an existing VNS device that can be reliably switched off for the duration of the trial.
12. Patients requiring scheduled MRIs during the study phase.
13. Patients who are unable to properly operate the EASEE® Access handheld device (no intact consciousness during part of habitual seizure type or no motor ability to operate device for bolus stimulation).

The following criteria must be met for the subject to be considered as enrolled:

1. All inclusion and exclusion criteria are satisfied at the screening visit
2. Informed Consent has been correctly obtained and properly documented on the Informed Consent Form.

The following criteria must be met for the subject to be implanted:

1. The subject continues to meet the inclusion and exclusion criteria directly prior to implantation (i.e. between successful screening/consent and implantation). If any criteria are not met, then the subject will be considered as a screening failure. All screening failures will be documented on a screening log.

All subjects who are considered as enrolled and have undergone the implantation procedure will be analysed for safety and efficacy parameters. Subjects with unsuccessful implant attempt (no EASEE Device implanted) will undergo a 1-month safety follow-up post-implant and can be terminated from the study once any reported adverse event (if applicable) has resolved or stabilized.

5.6 Eligibility Criteria Long-Term Follow-Up

5.6.1 LTFU Inclusion Criteria

Patients who meet all of the following criteria are eligible to enter the long-term follow-up:

1. Patients with an implanted and active EASEE® System who are willing to continue stimulation or patients with an inactive system who are willing to reactivate stimulation or undergo EASEE® Power (IPG) exchange if the battery is depleted.
2. Patients able and willing to provide appropriate consent prior to additional study procedures.

5.6.2 LTFU Exclusion Criteria

Patients who meet the following criteria are not eligible to enter the long-term follow-up:

1. Patient's overall condition or life perspective is not compatible with participation in the long-term follow-up (e.g. planned pregnancy during the duration of the study, planned

participation in another drug- or device study, other planned treatment which does not allow continuation of stimulation with EASEE® System).

5.7 Discontinuation of Subjects

Each subject who is enrolled and treated should remain in the clinical trial until completion of the required follow-up period. However, a subject's participation in any clinical trial is voluntary and the subject has the right to withdraw at any time without prejudice. Should this occur, the reason for withdrawal must be documented in the subject medical record. A subject may be discontinued from study treatment at any time if the subject or the Investigator feels that it is not in the subject's best interest to continue.

Conceivable reasons for discontinuation may include, but are not limited to the following:

Subject Withdrawal:	Subject participation in a clinical trial is voluntary and the subject may discontinue participation (refuse all subsequent testing/ follow-up) at any time without loss of benefits they would be otherwise entitled to.
Investigator Termination:	Investigator may terminate the subject´s participation without the subject´s consent if the Investigator believes it´s medically necessary.
Lost to Follow-up:	Subject does not complete the scheduled follow-up visits but has not "officially withdrawn" from the trial (this does not apply to missed visits).

If a subject is withdrawn from treatment, due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

Please also refer to section 5.7.2 Study Discontinuation.

5.7.1 Lost-to-Follow-up

Site personnel should make all reasonable efforts to locate and communicate with subjects at each contact time point. If there is difficulty contacting the subject, a minimum of two telephone calls to contact the subject should be recorded in the source documents, including date, time, and initials of site personnel trying to make contact. If these attempts are unsuccessful, a letter should be sent to the subject. If the subject misses two consecutive scheduled contact time points and the above-mentioned attempts at communicating with the subject are unsuccessful, the subject will be considered lost-to-follow-up.

5.7.2 Study Discontinuation

The Study Completion/Discontinuation Form must be completed when:

- the subject is considered lost to follow-up (per the above definition) before the 16 months or (if applicable) before the 36 months follow-up time point has been reached *or*
- the subject withdraws from the study *or*
- the Investigator withdraws the subject from the study *or*
- the subject has completed the study (either at 16 months or at 36 months post-implant).

The Sponsor shall be notified of the reason for subject discontinuation. The site will provide this information on the Study Completion/Discontinuation Form (e-CRF) and on source documents. Investigators must also report this to their EC if defined by their institution's procedure.

If a subject decides to discontinue the study, or a subject is excluded by investigator, or the study is prematurely terminated by Sponsor, Ethics Committee or Competent Authority it should be discussed between Sponsor and Investigator on individual basis, if and how further treatment shall occur or whether the device is disabled (turned off) or explanted. For subjects who exit the study prematurely, but still have a device implanted (i.e. EASEE® Power and/or EASEE® Lead), any device-related issues detected or reported should be notified to the Sponsor immediately by phone and/or email and followed up until the device is explanted and surgical AEs (if applicable) are resolved or stabilized.

Please also refer to section 9.12 Plan for Further Treatment.

6 Risk Analysis

6.1 Potential Risks

The potential hazards and harms have been identified by conducting the Questionnaire of EN ISO 14971, Annex C, D and E. Detailed results can be found in the EASEE® System Investigator's Brochure and/ or Instructions for Use for this section. The risks associated with the implantation of the EASEE® System can be classified into the following main categories:

- Risks related to the surgical procedure
- Risks related to electrical stimulation
- Risks related to device failure/ deficiency

6.2 Potential Benefits

The Sponsor and the Investigators have determined that this study is justified, based on the potential benefit to subject's quality of life by a possible reduction in the frequency and/or severity of the epileptic seizures or other relevant parameters.

Additional potential benefits of participating in the PIMIDES I study include:

- Information from this study may provide data that can lead to further improvement of the EASEE® System or even other potential treatments for epilepsy, thus benefitting patients in the future.
- Patients participating in the PIMIDES I study may in some cases receive treatment with the EASEE® System sooner than patients who do not participate in the study, as they will not have to wait for approval and reimbursement of the device.

6.3 Risk-Benefit Analysis

Based on the available clinical data on currently applied neurostimulation techniques, a positive risk-benefit profile for the EASEE® System, as an adjunctive therapy for medically refractory focal epilepsy can be expected. Since the electrode array of the EASEE® System will be implanted extracranially in the subgaleal area, the implantation procedure is less invasive, and is therefore assumed to be associated with a considerably lower risk of implantation-related adverse events compared to intracranial implantation. The efficacy of the EASEE® System is expected to be like other neurostimulation techniques. Safety and preliminary efficacy of the EASEE® System will be investigated in the course of the PIMIDES I trial, which will be conducted by Precisis according to Council Directive 90/385/EEC for active implantable medical devices.

Despite the risks of all epilepsy treatments, the risks of doing nothing are often greater. Patients with a higher frequency of seizures have poorer cognitive function, a significant increase in anxiety, depression and suicidality and a poorer employment status, lower quality of life and worse overall health compared to patients with fewer seizures. A reduction in seizure frequency and/or severity, even without seizure freedom, can improve mood, employment, perceived health and quality of life. These observations reinforce the need for alternative therapies, which can reduce the burden of seizures (Heck CN et al., 2014).

6.4 Risk-Benefit Assessment during Covid-19 pandemic

A separate risk assessment was prepared to identify potential risks to the study as well as risk mitigation measures during the COVD-19 pandemic. This will be reviewed and updated during the ongoing pandemic and for the duration of the clinical trial. Updates will be notified to ECs and Competent Authorities as required.

Protocol required follow-up visits shall be performed at the study centre if possible. If this is not feasible due to pandemic related travel restrictions, lock-down and/or hospital restrictions, a phone follow-up* must be performed within the protocol defined time window. A site visit shall be made up as soon as possible, incl. retrieval of required data that could not be collected by phone (e.g. device interrogation, questionnaires, EpiTrack®)**.

The evaluation of the primary safety endpoint and most important secondary efficacy endpoint (seizure frequency) will not be affected by performing phone follow-up versus site visits. If required, subjects can switch-off the stimulation via remote control EASEE® Access.

**For this specific case, phone follow-up´s during COVID-19 pandemic will not be considered as Protocol Deviation if performed within time window. Delayed device activation (stimulation "ON" at 1M) will not constitute a Protocol Deviation. In this case, subsequent time windows will be calculated based on activation of stimulation rather than implantation date.*

***For this specific case, time window for questionnaires and EpiTrack® test at 8- ,16-, 24- and 36 months follow-up can be extended to +/- 1 month outside the defined time window and will not constitute a Protocol Deviation.*

7 Device Description

7.1 EASEE® System Description

The EASEE® (Epicranial Application of Stimulation Electrodes for Epilepsy) System is an implantable stimulation device, which is intended for the treatment of patients with medically refractory focal epilepsy.

7.1.1 Implantable Components

The sterile components developed for the EASEE® System and intended for implantation are EASEE® Lead and EASEE® Power. These are shown below in Figure 1.

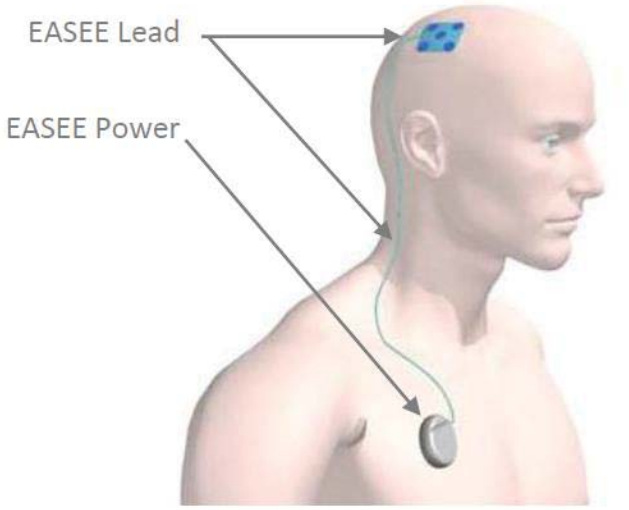

Figure 1 Implantable components of the EASEE® System

EASEE® Lead, Models EALE00 and EALE01

EASEE® Lead consists of a specialized electrode array on the distal side and a connector on the proximal side. Both are linked by a non-detachable lead body. The array consists of five electrodes arranged in a pseudo-Laplacian form, with a central electrode surrounded by four peripheral electrodes allowing precise targeting of defined brain areas. The array of EASEE® Lead is implanted between the subject's scalp and skull, in the so-called subgaleal area, while the lead body is tunneled subcutaneously from the head to the chest and connected to EASEE® Power. EASEE® Lead is manufactured by Precisis AG and is not CE-Marked. The Model variants are equal in design and manufacturing, except for the seven screw inlays required for fixation of the five electrodes and the strain relief. Please also refer to section 7.1.2 below (fixation screws and screwdriver) and to Investigator Brochure section 3.1.1.

EASEE® Power, Model EAPW00

EASEE® Power is a generator of electrical pulses which is implanted in the thorax, caudal to the clavicle. It is equipped with batteries and stimulation control electronics. The header of EASEE® Power contains the connector block for connecting EASEE® Lead, as well as a radio frequency (RF) antenna to communicate with the external control components. EASEE® Power is manufactured by Precisis AG and is not CE-Marked.

7.1.2 Surgical Accessories

The surgical accessories are used during the implantation and are all supplied in a sterile form:

Tunnelling tool

The tunnelling tool is used by the neurosurgeon to aid the subcutaneous routing of the link of EASEE® Lead between the skull and the chest. The tunnelling tool has not been developed by Precisis AG. A suitable, commercially available CE marked tunnelling tool as listed in Investigator Brochure, section 4.1.2., Table 1 will be used at the discretion of the local Neurosurgeon. Information about validation of devices related to this usage can be requested by Precisis AG.

Fixation screws and screwdriver

Screws are needed to fix the array of EASEE® Lead onto the skull. Several types of screws have been defined, according to the need related to the anatomical situation. The corresponding instrumentation such as the appropriate screwdriver is also provided. These components have not been developed by Precisis AG and are already CE-Marked.

The following product combinations need to be respected:

- For EASEE® Lead, **REF EALE00**
  Stryker self-drilling Screws REF 56-15903S4, REF 56-15904S4 and REF 56-17304S1
  Stryker Handle Medium REF 65-15002 with Stryker Blade Long REF 65-15003
- For EASEE® Lead, **REF EALE01**
  VigoMed self-drilling Screws REF LP-7024-S, REF LP-5024-S and REF LP-5064-S

VigoMed ideFixx screwdriver handle, titanium REF P-6000 with ideFixx CR screwdriver blade REF P-5100

Torque wrench, 8C-65-209X-X-00
A torque wrench is needed in order to enable the mechanical fixation between EASEE® Lead and EASEE® Power. This is manufactured by Precisis AG, with the reference number 8C-65-209X-X-00.

EASEE® Template, 8C-61-015X-X-00
EASEE® Template is provided to the surgeon to check the prepared implantation site for the array of EASEE® Lead prior to implantation. Thus, dimension and accessibility of the electrode areas can be tested without risks of mechanical damage to the implant. EASEE® Template is manufactured by Precisis AG, with the reference number 8C-61-015X-X-00.

7.1.3 External Control Components for the Physician

These external control components allow trained medical personnel to set the stimulation parameters according to the individual needs of the subject, as well as to test the functionality of EASEE® Power (battery life, impedance). There are three components:

EASEE® Connect, Model EACT00
EASEE® Connect is a compact device which enables RF communication between EASEE® Set and EASEE® Power. It is manufactured by Precisis AG and is not CE-Marked.

EASEE® Set, Model EASE00
The software used to program EASEE® Power will be pre – installed on a tablet PC. Both, the software application and the tablet are referred to as EASEE® Set. The software has been developed by Precisis AG and is not CE-Marked.The tablet PC has not been developed by Precisis AG and is already CE-Marked. Model Mio Care L130 from Mitac International Corp, with reference number 5420027523972 will be used.

Activation Magnet (Medtronic REF 9466)
The activation magnet has two functions

1. Wake-up EASEE® Power at the first use
2. Re-activate EASEE® Power after stimulation has been deactivated using EASEE® Set

The Magnet is manufactured by Medtronic and is CE-Marked.

7.1.4 External Control Component for the Patient

EASEE® Access, Model EAAC00
This external control component is known as EASEE® Access and allows the subject to communicate with the implanted device and trigger additional stimulation. The following functionalities are available within the PIMIDES I study:

1. Turn stimulation off
2. Check battery life of EASEE® Power

3. Check battery life of EASEE® Access
4. Trigger additional patient-controlled stimulation

EASEE® Access is manufactured by Precisis AG and is not CE-Marked.

7.2 Intended Use

The PIMIDES I Clinical Study will assess the safety and performance of the EASEE® System, which is intended for the treatment of medically refractory focal epilepsy.

7.3 Manufacturers

The legal manufacturer of the EASEE® System is Precisis AG:

Precisis AG
Hauptstr. 73
69117 Heidelberg
Germany
Tel.: +49 6221 6559300
Fax: +49 6221 6559310
Email: info@precisis.de

7.4 Device Training

The training of the Investigators and appropriate clinical site and CRO personnel will be the responsibility of Sponsor and/or designee and may be conducted during a site initiation visit, or other appropriate training sessions.

8 Endpoints

8.1 Primary Endpoint

The primary endpoint is the safety of the EASEE® System with patient-controlled neurostimulation capability evaluated at 4 months post-implant measured in SAE rates.
Safety is defined as follows:

1. Short-term chronic safety: Incidence of device/procedure related SAEs for the surgical implant procedure and the following 4 months.

8.2 Secondary Endpoints

2. Acute safety: Incidence of device/procedure related SAEs for the surgical implant procedure and the following month.

3. Seizure frequency: baseline seizure frequency and responder rate (defined as at least 50 % reduction in seizure rate from baseline) compared to values at 4 months, 8 months, 16 months, 24 months, and 36 months post-implant.
4. Seizure severity: baseline seizure severity compared to seizure severity at 4 months, 8 months, 16 months, 24 months, and 36 months post-implant.
5. Seizure duration: baseline average seizure duration compared to seizure duration at 4 months, 8 months, 16 months, 24 months, and 36 months post implant.
6. Seizure symptoms: most debilitating baseline epilepsy symptom compared to seizure symptom(s) at 4 months, 8 months, 16 months, 24 months, and 36 months post implant.
7. Epileptiform activity: baseline measurements of scalp EEG will be collected and compared to data collected at 1 month, 8 months, 16 months, 24 months, and 36 months post-implant.
8. Quality of life: baseline subject rated quality of life compared to 8 months, 16 months, 24 months, and 36 months post-implant.
9. Mood: baseline subject rated mood compared to 8 months, 16 months, 24 months, and 36 months post-implant.
10. Neurocognition: baseline neurocognition compared to 8 months, 16 months, 24 months, and 36 months post-implant.

9 Study Procedures

9.1 Overview

The different phases of the study are shown in Figure 2 below:

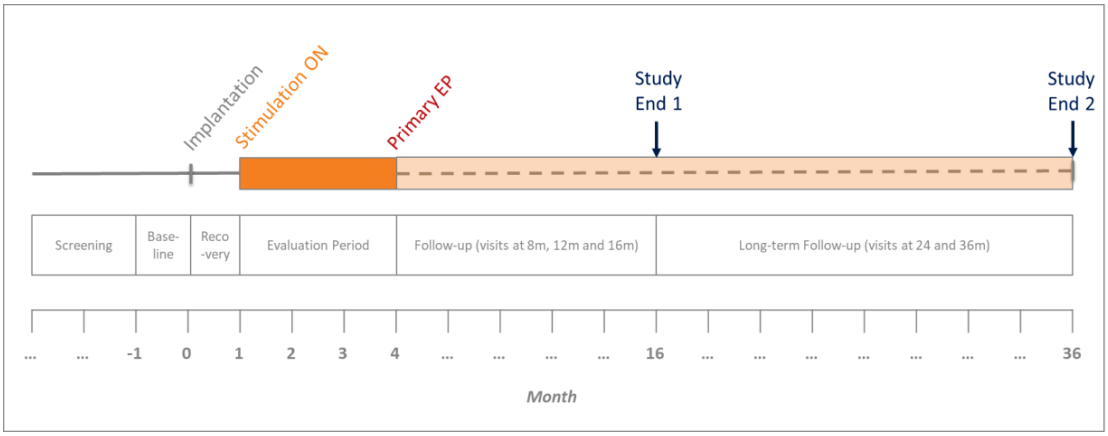

Figure 2 **Study Phases and Timelines**

For clarification: Study End 1 is relevant for subjects who do not enter the long-term follow-up, Study End 2 is relevant for all subjects who do enter the long-term follow-up.

9.2 Screening and Informed Consent

9.2.1 Screening

Subjects planned to be included in the PIMIDES I study should be screened for eligibility by study staff members as delegated to this task after having been trained on the Clinical Investigation Plan. Subjects who do not meet the inclusion and exclusion criteria will not be enrolled in this clinical investigation. Screening failures will be captured on a screening log. Subjects meeting the inclusion and exclusion criteria will be asked to sign an informed consent form. “Non-routine” assessments, which are specific to the clinical investigation cannot be done before an informed consent form has been signed.

The investigator will then record the details of these trial patients on the following trial-specific lists:

- Subject Screening log: for the documentation of trial patients who were checked for eligibility. The following will be entered: consecutive screening number (e.g. 1, 2, 3 etc.), date of written consent (if obtained), as well as details on whether the patient was enrolled in the trial and, if not, the reason for screening failure. For all enrolled patients, the individual patient identification code will be recorded on the subject screening log.

NOTE: If implant eligibility criteria are not met (i.e. after successful screening/consent and prior to implantation), then the subject will be considered as a screening failure and will be documented on a screening log.

- Subject identification log: A confidential log of the names of all trial patients with the identification code[1] assigned to each patient at the time of enrolment in the clinical trial. With this list, the identity of each patient can be revealed. The list must be kept confidential and remain at the trial site. Access to the subject identification log is restricted to the principal investigator, sub-Investigators and involved study nurse(s) only. It must not be copied or otherwise be passed on. However, Sponsor representatives, clinical research associates (CRAs), auditors and representatives of competent authorities (CA) must be allowed to inspect the list on request.

The following data will be collected at screening:

- Demographic data
- Medical history

[1] Patient identification code: A unique trial-specific identification number which identifies the patient and consists of three parts: The first part corresponds to the study acronym, for example <PI>, the next <2> digits correspond to the site number, the next <3> digits stand for a consecutive number of the patient enrolled at a particular site, for example: <PI-01-001 (Site No. 1, Patient No. 1)>, <PI-01-002 (Site No. 1, Patient No. 2)> so that each patient is numbered uniquely across the entire database.

- Epilepsy history
- Seizure related data (incl. frequency, -type, -duration)
- Seizure symptoms
- Antiepileptic and concomitant medication

The patient will be asked if he/she is able and willing to provide a seizure diary with daily recording of seizures for at least one month prior to this timepoint to confirm whether in/exclusion criteria related to seizure frequency are met. After successful screening the subject will be requested to give informed consent to participate in the study. Subjects will undergo additional testing either at screening or baseline visit but prior to implantation according to table 1: PIMIDES I Data Collection Table. If the antiepileptic medication is not stable for ≥28 days at time of visit 1 (Screening), the tests have to be performed prior to implantation at visit 2.

9.2.2 Informed Consent

Clinical investigation-specific procedures cannot be started until a signed informed consent has been obtained. The Investigator or a Sub-Investigator appointed by the Investigator who has been trained on the Clinical Investigation Plan, will explain the nature and scope of the clinical investigation, potential risks and benefits of participation, and answer any questions that the subject may have. All subjects and Investigators must sign, date and time the Ethics Committee (EC)-approved informed consent prior to any clinical trial/investigation-specific procedure. This clinical study will not be performed on persons who are legally incapacitated or whose capacity is limited by contract. No minors (<18 years), pregnant women, subjects belonging to a vulnerable population, or dependent on the Investigator or Sponsor (e.g., subordinate hospital staff or Sponsor staff) or subjects unable to read or write will be enrolled. The obtaining of the informed consent, provision of a copy to the subject, along with the date and time must be documented in the subject's medical records. In addition, the original signed informed consent must be kept in the study site file, a copy in the subject's medical records and another copy must be given to the subject.

9.2.3 Point of Enrollment

The subject is considered as enrolled in the trial at the time he/she has signed and dated the patient informed consent.

9.2.4 Patient Registration

Patients eligible for implantation will be registered by in the e-CRF and receive a unique trial-specific identification code, so that each patient is numbered uniquely across the entire PIMIDES I database.

9.3 Baseline Period:

During the 1-month baseline period, subjects will be provided with study specific seizure diaries and will be requested to record daily seizure data. At the conclusion of this period, the implant eligibility criteria will be reviewed. Subjects who fail to meet implant eligibility criteria, will be captured on a screening log and are considered as screening failure subjects. Only the data of

subjects who have undergone the implantation procedure will be included in the analysis report for safety and efficacy.

9.4 Implantation

9.4.1 Implant Eligibility

The EASEE® System will be implanted after the 1-month baseline period has been completed and the implant eligibility has been reviewed and met. Only when the following implant eligibility criteria are met, may the subject proceed to implantation:

1. Seizure frequency as specified in the inclusion criteria
2. Constant AEDs as specified in the inclusion criteria
3. No pregnancy

9.4.2 Baseline Testing

After implant eligibility has been established subjects will undergo baseline testing (see table 1: PIMIDES I Data Collection Table). The following data will be collected:

1. Patient surveys: in addition to the seizure frequency data collected in the baseline period, the subject will be asked to conduct a seizure diary for the complete duration of the study. Furthermore, subjects will be requested to complete the Quality of Life in Epilepsy-Patient-Weighted (QOLIE-31-P) survey, the Seizure Severity Questionnaire (SSQ), the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) questionnaire and to undergo neurocognitive testing. (All neurocognitive tests listed in table 1: PIMIDES I Data Collection Table will be applied on individual basis according to the epileptic focus location. Sites which are not able to perform the full test battery are asked to perform EpiTrack® as a minimum requirement)
2. Scalp EEG: a one-hour EEG-recording during wakefulness will be completed for each subject to establish baseline values.
3. Determination of implantation site for EASEE® Lead: the implantation site for EASEE® Lead will be determined based on existing diagnostic data such as EEG, clinical presentation etc. EASEE® Lead will be implanted over the predominant focus, as identified by the physician. This should also be documented in the patient chart.

A blood assessment will be completed prior to the implantation procedure as per standard of care. No study-specific blood assessment is required.

9.4.3 Surgery

Once the implantation site has been determined (see above) the neurosurgeon will mark the implantation site to ensure that the central electrode of the EASEE® Lead will be fixed in place over the pre-determined epileptic focus. Routine surgical planning or navigation systems may be used at the discretion of the Investigator.

First, a skin incision is made, and the mobilized skin flap is folded away to reveal the periosteum. This layer is removed using standard surgical equipment, so that the surface of the skull becomes visible. Care has to be taken when implanting EASEE® Lead under the temporal muscle so as not to damage the temporal branches of the fascial nerve (Rami temorales nervi facialis) and to ensure functionality of the temporal muscle after the intervention. At this point EASEE® Template is used to test the correct orientation and position of the electrode array. After this is established, the array itself is placed in the determined location. The cable part of the EASEE® Lead is then tunneled subcutaneously using the tunneling tool to the EASEE® Power implantation pocket via a retro-auricular site. Once the tunneling has been completed, EASEE® Lead is screwed into place, starting with the central electrode. The peripheral electrodes are then attached one by one to the skull. The fixation of the EASEE® Lead Array using the bone screws need direct and perpendicular access to the fixation holes, meaning that the skin has to be retracted completely from the fixation hole. Finally, the strain relief is screwed onto the skull. If the 1.5 mm diameter screws shipped with the EASEE® System do not securely anchor the electrodes or the strain relief on the skull, 1.7 mm diameter screws ("rescue screws", also provided) should be used. For research purposes, intra-operative EEG measurements will be done in max. 15 subjects for max. 15 minutes before connecting the lead to EASEE® Power.

EASEE® Power is implanted in a procedure similar to other implantable pulse generators and may be implanted and secured in the implantation site before or after EASEE® Lead is implanted. After the cable has been connected to EASEE® Power, the surgical/neurological team will perform standard system diagnostic testing using the hand-held programmer EASEE® Set and EASEE® Connect, to ensure that the system is functional. A representative of the Sponsor may be present during the operation to offer any technical support. Once the system diagnostic test is complete, EASEE® Power is sutured to the adjacent fascia and all the open wounds are closed.

Caution: Please refer to the Instructions for Use for a complete account of the implantation procedure.

9.5 Recovery

There will be a post-operative recovery period of 1 month to ensure that the healing processes can take place. The device will remain off during this period. Subjects are asked to continue completing the seizure diary.

9.6 Configuration

After the 1-month recovery period, a one-hour scalp EEG recording will be completed prior to configuration of the device. The device incl. the patient-controlled stimulation parameters will be configured individually for each subject by the neurologist according to the current EASEE® System Instructions for Use (IFU) and the stimulation will be turned on. The current amplitude should be configured individually for each subject and should be set at maximum 0.1mA below the perception level. If the subject does not perceive the stimulation, then the current amplitude can be set to the

maximum level i.e. 4mA. The ULFA starting time is recommended to be adjusted to 10 am. This timepoint may be changed at the discretion of the treating physician. Subjects should be observed for at least 30 minutes after the last stimulation adjustment to make certain that they are comfortable with the programmed stimulation pattern. Subjects will receive the EASEE® Access device and be trained on the use of EASEE® Access. All testing and parameters will be completed according to table 1: PIMIDES I Data Collection Table.

9.7 Evaluation Period

The evaluation period begins after configuration of the device at 1-month post-implant and lasts for a duration of 3 months. Stimulation will remain on during this time. At 4 months post-implant the primary safety endpoint will be analyzed. All testing and parameters will be completed according to table 1: PIMIDES I Data Collection Table.

9.8 Follow-up Period

Once the evaluation period has been completed, the 12-month follow-up period will begin. AEDs should be kept constant during this time. All testing and parameters will be completed according to table 1: PIMIDES I Data Collection Table. Note: the EASEE® System may be switched off for all protocol required EEG recordings occurring post-implant to prevent interference.

The stimulation parameters as defined in current EASEE® System Instructions for Use (IFU) should be used until 8 months post-implant. At 8 months post-implant the Investigator will evaluate the benefit for the subject in agreement with the Sponsor:

- If it is deemed that the subject has benefited from the stimulation i.e. there is a reduction in the burden of epilepsy in terms of reduction in seizure frequency and/or severity, and/or improvement in QoL, neurocognition and the subject wishes to receive further stimulation, then the device may remain active up to the end of the follow-up period.
- If there has been no documented positive effect of stimulation, but the subject wishes to receive further stimulation, then the stimulation parameters may be changed at the discretion of the treating physician and in agreement with the Sponsor.
- If the subject does not wish further stimulation, then the device will be inactivated and explanted at the latest at the end of the follow-up period (unless subject agrees to reactivation and entry into the LTFU – see section below).

There will be a follow-up visit at 12 months post-implant and a (final) visit will take place at 16 months post-implant regardless of whether the device is active or has been inactivated and/or explanted. All testing and parameters will be completed according to table 1: PIMIDES I Data Collection Table.

At the latest at the 16 months follow-up visit, the Investigator will evaluate together with the subject if he/she will continue to the long-term follow-up:

A. If the subject meets the eligibility criteria for the long-term follow-up (see section 5.6) and wishes to continue stimulation, then the subject will be consented for long-term follow-up.
B. If the subject does not wish to continue stimulation or does not meet the eligibility criteria, then the subject will not enter the long-term follow-up period. In this case the EASEE® System should be explanted in a timely manner. Subjects will be followed up until all surgical AEs haven been resolved or stabilized.

9.9 Long-Term Follow-Up (LTFU) Period

9.9.1 Rationale

The goal of the long-term follow-up (LTFU) is to enable subjects to continue receiving stimulation in a controlled environment within the framework of the PIMIDES I study for up to three years post-implant. In addition, long-term safety and performance data are generated for the EASEE® System, which may be important for the future treatment of patients.

9.9.2 Overview

Once the 16 months follow-up period has been completed, the long-term follow-up period will begin. Only those subjects who meet the eligibility criteria (see section 5.6) and provide written informed consent will enter the long-term follow-up (LTFU).
The LTFU will include two additional visits, one at 24- and one at 36 months post-implant. All testing and parameters are to be completed according to Table 1: PIMIDES I Data Collection Table.

Other than the above visits, the subjects will not be required to visit the clinic more often than for their routine treatment.

9.10 Battery Depletion (IPG exchange)

In case of battery depletion, EASEE® Power might require exchange during the course of the study.

9.11 Device Explantation

At any point during the study or after study completion any implanted component (EASEE® Power, EASEE® Lead) may be removed at the discretion of the physician and the patient.

9.12 Plan for Further Treatment

9.12.1 Premature Termination or Suspension of Study

The Sponsor may suspend or prematurely terminate either a clinical investigation in an individual investigation site or the entire clinical investigation for significant and documented reasons.

A principal investigator, EC, or competent authority may suspend or prematurely terminate participation in a clinical investigation at the investigation sites for which they are responsible.

If suspension or premature termination occurs, the terminating party shall justify its decision in writing and promptly inform the other parties with whom they are in direct communication. The principal investigator and Sponsor shall keep each other informed of any communication received from either the EC or the regulatory authority.

Should the study be prematurely terminated or suspended by one of aforementioned parties, the ECs and regulatory authorities (as applicable) will be notified in writing. Ongoing care of participants will be discussed with the Principal Investigators at study centers and their implanted device will be disabled (turned off) or explanted as indicated in section 5.7.2.

If suspension or premature termination occurs,

a) the Sponsor shall remain responsible for providing resources to fulfil the obligations of the CIP and existing agreements for following up the subjects enrolled in the clinical investigation, and
b) the principal investigator or authorized designee shall promptly inform the enrolled subjects at his/her investigation site, if appropriate.

NOTE: The method and the timing of this communication will depend on the circumstances and the perceived risks.

9.12.2 Further treatment after Study Completion (16M)

If the patient has benefited from the stimulation with the EASEE® System and/or wishes to continue treatment, then the patient should enter the long-term follow-up at 16 months post-implant.

If the patient has not benefited from treatment with the EASEE® System and/or does not wish to continue treatment, then the patient will not enter the LTFU. In this case it is recommended that the device is fully explanted in a timely manner. Subjects will be followed up until all surgical AEs have been resolved or stabilized.

Furthermore, the Principal Investigator will continue to follow up all patients on a regular basis and as per routine hospital practice.

9.12.3 Further treatment after Study Completion (36M)

If the EASEE® System has not received CE-mark at 36M and the patient has benefited from treatment and/or wishes to continue treatment, the study physician, and the Sponsor, in agreement with ECs and the competent authorities who have approved this study, may consider all options allowing the patient continued treatment with the EASEE® System after completion of the study.

If after study end at 36 months the device is CE-marked the patient's treatment will be continued as per standard of care.

If the patient has not benefited from treatment with the EASEE® System and/or does not wish to continue treatment, then it is recommended that the device is fully explanted at the end of the study (at 36 months post-implant). Subjects will be followed up until all surgical AEs haven been resolved or stabilized.

After the end of the study, the Principal Investigator will continue to follow up all subjects on a regular basis and as per routine hospital practice.

10 Statistical Considerations

10.1 General Statistical Considerations

This is a prospective, interventional, unblinded, multicentre study. All included patients for whom the surgery was performed will be analysed. As a first in human study, the primary endpoint is chosen to be safety related and will assess the probability of device/procedure related SAEs for the surgical implant procedure and the following 4 months. The incidence of all adverse events, of those being related, of those being severe, and of serious adverse events will be summarized with corresponding two-sided 95 % confidence intervals. Secondary endpoints are efficacy related and will assess probability of benefit to the patient.

10.2 Sample Size Calculation

The primary goal of the study is to generate data regarding the feasibility and performance of neurostimulation with the EASEE® System with patient controlled neurostimulation capability. The results of this feasibility study will aid in the planning of a larger, sufficiently powered CE-Mark trial. When no device/procedure related SAEs for the surgical implant procedure and the following 4 months are observed, to obtain an upper bound of 0.153 on the 0.95 confidence interval for the probability of a rare event, would require a sample size of 18 patients (nQuery 8.3) (Machin, D., Campbell, M.J. , 1987).

10.3 Study Population

The study population will consist of adult subjects with medically refractory focal epilepsy, both males and females.

10.4 Demographic and Baseline Disease Characteristics

Demographic and disease baseline characteristics data collected will be summarized using descriptive statistics. Continuous assessments will be collated and summarized. In case of normal distribution of the data, mean and standard deviation will be shown, otherwise standard boxplots will be used to present the data.

10.4.1 Statistical Methods

Continuous baseline variables will be summarized using the number of observations, mean, standard deviation, median, minimum, and maximum values. Categorical baseline variables will be summarized using frequencies and percentages.

10.5 Outcome Analysis

10.5.1 Primary Outcome

The following measures will be evaluated as part of the primary endpoint analysis:

- Incidence of short-term chronic SAEs, related to device or procedure.

10.5.1.1 Statistical Methods

Safety analyses will be performed in the safety set including all patients for whom the surgery was performed. Adverse events will be coded with MedDRA and summarized by body system. The incidence of device/procedure related serious adverse event (SAE) for the surgical implant procedure and the following 4 months will be summarized with corresponding exact one-sided 95 % confidence intervals based on a binominal distribution.

10.5.2 Secondary Outcomes

1. Incidence of acute SAEs.
2. Seizure frequency: mean and median changes in seizure frequency compared to baseline and responder rate (defined as at least 50 % reduction in seizure rate from baseline) at 4 months, 8 months, 16 months, 24 months, and 36 months post-implant.
3. Seizure severity: baseline measurements of seizure severity compared to seizure severity data collected at 4 months, 8 months, 16 months, 24 months, and 36 months post-implant. Seizure severity will be evaluated using the SSQ scale (to be completed by the subject).
4. Seizure duration: baseline average seizure duration compared to seizure duration at 4 months, 8 months, 16 months, 24 months, and 36 months post-implant.
5. Seizure symptoms: most debilitating baseline seizure symptom compared to epilepsy symptom(s) at 4 months, 8 months, 16 months, 24 months, and 36 months post implant.
6. Epileptiform activity[2]: scalp EEG data will be collected at baseline and at 1 month, 8 months, 16 months, 24 months, and 36 months post-implant. This data will be evaluated for typical surrogate markers of epileptic seizures e.g. spike and wave frequency.

[2] EEG Analysis: Ground Rhythm; Electrode location of highest spike frequency, Spike frequency /hour, Electrode location of highest spike amplitude
Ictal patterns: Electrodes involved in the ictal onset, description of pattern shown, spreading pattern
Other: Polymorphic deceleration with maximum, extension, frequency and characteristics (% of time), Rhythmic deceleration, other forms of irritative activity (e.g. beta-activity, poly-spikes, rhythmic spikes)

7. Quality of life: subjects will complete the Quality of Life in Epilepsy-Patient-Weighted (QOLIE-31-P) survey at baseline, 8 months, 16 months, 24 months, and 36 months post-implant. The post-implant scores will be compared to baseline for each patient.
8. Mood: subjects will complete the Neurological Disorder Depression Inventory for Epilepsy (NDDI-E) survey at baseline, 8 months, 16 months, 24 months, and 36 months post-implant. The post-implant scores will be compared to baseline for each patient.
9. Neurocognition: subjects will complete a battery of cognitive tests* at baseline, 8 months, 16 months, 24 months, and 36 months post-implant. The post-implant scores will be compared to baseline for each patient.

Patients with no treatment effect after the initial 16 months might potentially not be willing to continue the stimulation and therefore not be part of the long-term follow-up data collection. Due to the potential selection bias, the secondary efficacy endpoints of the long-term follow-up (24- and 36 months) will be only evaluated descriptively and interpreted with special care.

**All neurocognitive tests listed in Table 1: PIMIDES I Data Collection Table will be applied on individual basis according to the epileptic focus location. Sites which are not able to perform the full test battery are asked to perform EpiTrack® as a minimum requirement.*

10.5.2.1 Statistical Methods

For investigation of the obtained dataset, descriptive statistics will be performed by presenting frequency tables. In case of normal distribution of the data, mean and standard deviation may be shown, otherwise standard boxplots will be used to present the data. As this is a pilot study with a very small sample size, only descriptive analyses will be performed.

Seizure frequency will be analyzed via the monthly count of seizures for each subject, calculated from the seizure diary. A mixed-effects Poisson regression model will be used to analyze the monthly count data. Responder rate will be analyzed as a repeated binary variable via generalised estimating equations. Details of these analyses will be provided in the statistical analysis plan.

For normally distributed variables, classical analysis of longitudinal data from one group of subjects at different time points is done using uni- or multivariate analysis of variance ((M)ANOVA) for parameter-based analysis and i.e. Friedmann-test for non-parametrical testing, respectively. However, the test power of the latter is usually low, and ANOVA is very specific regarding prerequisites of the data. Modern statistical analysis uses for example linear mixed effects models (LME, Galecki 2013). These regression- based statistical models are very robust with respect to missing data or a lack in precision of the control variables and therefore often preferred over the classical approaches. The general model equation:

$$y = \mathbf{X}\beta + \mathbf{Zb} + \epsilon$$

thereby contains the response vector y with the measured parameter values, the known design matrix $\mathbf{X}$ describing the relationship between parameters and variables, the unknown fixed effects vector β, the known design matrix $\mathbf{Z}$ and the unknown vector of random effects $\mathbf{b}$. The results for β of the maximum likelihood estimation may be tested for statistical significance using students t-test.

Afterwards, Pearson residuals r may be calculated from the errors $\epsilon_i = y_i - \mu_i$, using

$$r = \frac{\epsilon_i}{\sqrt{V(\mu_i)}}$$

with the measurements y_i, the corresponding predicted value μ_i, and the variance function $V(\mu_i)$. They can be used to assess model validity by analysis of normality and correlation. This is done visually using a normalized histogram of the residuals, a normalized quantile-quantile plot, a symmetry plot, a plot of residuals vs. their case number, a plot of residuals vs. the fitted values, and a lagged residual plot. If the model describes the effects of the treatment well, the errors between data and model should be random, resulting in a normal distribution of residuals with mean zero and no self-correlation.

10.5.3 Other Exploratory Analyses

Additional exploratory analyses may be conducted as deemed necessary. These analyses will be determined and described parallel to performing the statistical analyses.

11 Administrative Requirements

11.1 Sponsor Responsibilities

Precisis AG holds the overall responsibility for the conduct of this study including ensuring:

- Compliance with the Declaration of Helsinki, and all applicable health authority regulations governing the conduct of clinical research studies.
- Protecting the rights, health, safety and welfare of study subjects.
- Informing the clinical Investigators of any new information about the study, which may affect the health, safety or welfare of the subjects, or may influence their decision to continue participation in the study.
- Providing the clinical Investigators with the study protocol and a full set of case report forms (CRF) on which to document the study evaluation variables for each subject entered into the study.
- Certifying that Ethics Committee (EC) approval of the study protocol and Investigator's Agreement will be completed prior to treatment at an investigational site.
- Compliance with EN ISO 14155.

11.1.1 Selection of Clinical Investigators and Sites

The Sponsor will select qualified Investigators according to the following criteria:

- Adequate study subject population to meet the requirements of the study
- Adequate time to be personally involved in the study
- Adequate research staff and resources to support the study
- Willingness to take the primary responsibility for the accuracy, legibility, and security of all study data
- Willingness to observe confidentiality at all times
- Willingness to follow protocol procedures and provide the Sponsor with accurate performance data in a timely fashion
- Associated with an Ethics Committee which satisfies all Competent Authority requirements and conducts meetings on a regular basis
- Access to appropriate medical facilities for pacing, defibrillation, and emergent cardiac surgery if needed
- Other requirements as previously noted in the study protocol

11.1.2 Training of Investigators and Site Personnel

The training of the Investigators and other clinical site personnel will be the responsibility of the Sponsor and/or designee and may be conducted during a site initiation visit, or other appropriate training sessions.

11.2 Investigator Responsibilities

The Investigator is responsible for the management of subjects involved in this clinical study as well as for the proper use of the investigational device at the study center. The Investigator will assume overall responsibility and accountability for the research team and for the clinical data obtained from subjects participating in the clinical study.

The responsibilities of the Investigator(s) comply with the requirements set forth in:

- The Declaration of Helsinki
- EN ISO 14155
- Local laws of the country – including the regulations of the European Union.

Additional responsibilities of the Investigator comprise:

- Ensuring that the clinical study is conducted according to the Clinical Investigational Plan (CIP).
- Obtaining informed consent on the approved Informed Consent Form prior to any study participation.

- Controlling any investigational device(s) stored at the site, if any. This includes supervising and disposal of devices and recording the receipt, disposition, and return of the investigational devices.
- Protecting the rights, safety, and welfare of the subjects.
- Maintaining records and reports as listed in this Clinical Investigational Plan (CIP).
- Ensure full access to source documents for the study Monitor and regulatory agencies.
- Reviewing and signing all e-CRFs for subjects enrolled in the clinical study under the Investigator's care.
- Retaining records after completion of the study for a period determined by applicable local and national regulatory requirements.

11.3 Ethics Committee and Competent Authority

Documentation that the study has been approved by the respective Ethics Committee (EC) and Competent Authority (CA) must be present prior to study initiation. No changes will be made to study related documents (e.g. study protocol, informed consent form, etc.) without appropriate approvals, including Sponsor, EC and/or CA. Any amendments to the study protocol as well as associated informed consent form changes will be submitted to the EC/ CA and written approval obtained prior to implementation, according to local EC/ CA requirements. No investigative procedures other than those defined in this study protocol will be undertaken on enrolled subjects without the agreement of EC/ CA and Sponsor.

11.4 Informed Consent Process

A signed and dated informed consent form, as approved by the EC, must be obtained from each subject prior before any trial-specific test are obtained and prior to enrollment in the study. Before recruitment and enrollment, each prospective subject will be given a full explanation of the study and be allowed to read the approved Informed Consent Form. Once the Investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing and dating the Informed Consent Form. The Investigator shall also sign and date the Informed Consent Form and provide a copy to the subject. The original form shall be maintained at the investigational study site file and a copy in the patient file. The informed consent process shall be documented in source document respectively. In the case of substantial amendments, the patient must be informed with an appropriate revised patient information/consent form. Changed trial procedures can only be carried out if they have been approved by the CA and the EC, and if the patient has been appropriately informed and has given his/her written consent.

11.5 Adverse Events

11.5.1 Definitions according to EU regulation 2017/745, MDCG 2020-10/1 and EN ISO 14155:

- **Adverse event (AE)**:
  Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device and whether anticipated or unanticipated.

  Note 1: This definition includes adverse events related to the investigational medical device or the comparator.
  Note 2: This definition includes events related to the procedures involved.
  Note 3: For user or other persons, this definition is restricted to events related to the use of the investigational medical devices or comparators.

- **Serious adverse event (SAE)**:
  Any adverse event that led to any of the following
  a) death,
  b) led to serious deterioration in the health of the subject, that resulted in any of the following:
     i. a life-threatening illness or injury
     ii. a permanent impairment of a body structure or a body function
     iii. hospitalization or prolongation of hospitalization, or
     iv. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
     v. chronic disease,
  c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

  Note: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

- **Adverse device effect (ADE)**:
  Any adverse event related to the use of an investigational medical device.
  Note 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
  Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
  Note 3: This includes 'comparator' if the comparator is a medical device.

- **Serious adverse device effect (SADE)**:
  Any adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

- **Unanticipated serious adverse device effect (USADE)**:
  Any serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.
  Note: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity, or outcome has been identified in the risk analysis report.

- **Device deficiency**:
  Any inadequacy in the identity, quality, durability, reliability, safety, or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

  (EN ISO 14155)
  Note 1: Device deficiencies include malfunctions, use errors, and inadequate labelling.
  Note 2: This definition includes device deficiencies related to the investigational medical device or the comparator.

For the purposes of this study, seizures are considered a pre-existing condition and need only to be reported as AEs/SAE (if applicable) if they worsen* (aggravation of epilepsy) during the study.

*NOTE: A worsening is defined as aggravation of pre-existing seizures or occurrence of new seizure types compared to prior to baseline or the development of status epilepticus.

11.5.2 Categorization of Adverse Events

Adverse events will be categorized according to , EN ISO 14155, Annex F and/or national regulatory requirements.

11.5.3 Device/Procedure Relationship

Whenever possible, the categorization and reporting of events will be performed using MDCG 2020-10/1, Annex 12 (MEDDEV 2.7/3) format:

Not Related
(*Unlikely*)
Possible
Probable
Causal Relationship

11.5.4 Safety Reporting to Sponsor, EC, Investigator and CA

The Investigator will monitor the occurrence of adverse events for each subject after enrollment (at the time the subject has signed and dated the Informed Consent Form) and during the entire course of the clinical investigation. Adverse events (AEs) reported by the subject, observed by the Investigator, or documented in medical records should be recorded on the adverse event e-CRF, whether believed by the Investigator to be related or unrelated to the investigational device. The Investigator will assess the nature, severity, and device/procedure relationship of each AE. The site should report any new AE/experience that was not present at baseline, and/or worsening of a pre-existing condition (severity, frequency) compared to baseline. In addition, subjects will be instructed to contact the Investigator and/or study coordinator if any significant AEs occur between study evaluation visits.

11.5.4.1 Investigator Reporting Requirements

If an event is serious, it has to be documented IMMEDIATELY** after knowledge by the investigator in the e-CRF according to applicable national legislation (§63 MPDG). The detailed procedure is described in the SAE reporting manual.
If only limited data are initially available, a follow-up report is required. If new information including outcome becomes available, the follow-up information has to be documented IMMEDIATELY** (details will be provided in the SAE reporting manual).

All device deficiencies have to be documented IMMEDIATELY** after knowledge by the investigator in the e-CRF.

*** Acceptable timeframe for SAE/Device Deficiency reporting:* ***as soon as possible, latest within 24 hours after knowledge***

11.5.4.2 Sponsor Reporting Requirements

The Sponsor and/or designee will report the SADEs and device deficiencies with SADE potential to the CAs in compliance with EU regulation 2017/745 and MDCG 2020-10/1 and local/ national regulations of the European countries participating in the study. In addition, the Sponsor and/or designee will submit, for the duration of the clinical trial, regular safety summary reports to the involved CAs if required per local/ national regulations. The Investigators and ECs will also be informed about all SAEs according to ISO 14155, 9.2.5,f). The detailed procedure is described in the vigilance manual.

Designee for Germany:

(Pharmaco-)Vigilance Clinical Trials Unit Medical Center – University of Freiburg Elsässer Str. 2, 79110 Freiburg Fax: +49 761 270-74390 Email: zks.pv@list.uniklinik-freiburg.de

11.5.5 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be in place for the duration of the study and will review study data, among others for participant safety, study conduct and progress on a regular basis. The independent Data Safety Monitoring Board (DSMB) will consist of at least three (3) members experienced in an associated discipline, one of them a biostatistician. The DSMB will advise the Sponsor regarding the continuing safety of trial subjects, including those to be recruited, as well as the continuing validity and scientific merit of the trial. If the DSMB finds an unfavorable risk-benefit ratio the study may be halted for further assessment and corrective actions. Ultimately the DSMB can recommend stopping the study. A decision on that will be subject of discussion between DSMB, PI and the sponsor. The proceedings of the DSMB will be governed by the DSMB Charter.

11.5.6 Early Termination of Clinical Trial

The Sponsor reserves the right to discontinue the clinical trial/investigation at any stage (e.g. for safety reasons) or reduce the follow-up period with suitable written notice to the Investigator.

Possible reason(s) include:

- Based on DSMB recommendation
- Further product development is cancelled.

Should the clinical trial be discontinued by the Sponsor, please refer to section 9.12 Plan for further treatment.

In this case, the Investigator shall return all clinical trial/investigation materials (including devices) to the Sponsor and provide a written statement as to why the premature termination has taken place to the EC (if applicable) and inform subjects still participating to the trial. All applicable Clinical Investigation documents shall be subject to the same retention policy as detailed in section 11.15 Archiving & Record Retention. Sponsor or designee will inform the CA about premature termination of Clinical Trial as per regulatory requirements.

11.6 Monitoring Procedures and Responsibilities

In order to comply with clinical study regulations, to ensure the accuracy of the final study database, to ensure the overall quality and consistency of the study and to help Investigators, an employee of Precisis AG or designated CRO (Monitor) will visit each study site during the course of the study in order to review the study records and source documentation at site in accordance with the Monitoring Plan.

The responsibilities of the Monitor will include, but are not limited to:

- Comparing study data with any relevant source documents, such as medical records, questionnaires etc.,
- Checking the Informed Consent Form for each subject,

- Monitoring the general study records, including Investigator Site File, device traceability,
- Checking the occurrence of possible adverse events.

11.7 Study Initiation

Sites will be selected based on the feasibility process. The study must not be initiated until the Investigator has received written confirmation from the Sponsor that all pre-study documentation has been completed and necessary approval received. This includes documentation that the study site has concluded training on the study devices and study procedures.

11.8 Protocol Adherence

The study must be conducted, as set out in the study protocol, unless an emergency arises, and immediate action is required that might deviate from the study protocol. Such deviations must be reported to the Sponsor and to the relevant EC. Protocol amendment is required for any non-emergency changes. This should be initiated by the Sponsor and must be approved by the involved ECs and CAs (as applicable). Depending on the impact of the change, supporting documents such as updated Informed Consent Forms must also be approved by the involved ECs. The approved and updated Informed consent forms must then be signed by each subject active in the study and by each new subject, prior to proceeding with the study. The Investigator shall conduct no further studies/research other than that specified in the study protocol, without written approval from the Sponsor.

11.9 Protocol Deviations

It is the responsibility of the Investigator to ensure there are no deviations from the study protocol and that all actions are in full compliance with the EC. All protocol deviations shall be documented and a justification for any missed assessments or other non-compliance shall be provided on the Protocol Deviation Form in the e-CRF. The Investigator is required to sign this form on the appropriate pages to verify that she/he has reviewed and agrees with the recorded data. In the event of repeated non-compliance with the signed agreement, the study protocol or any other conditions of the study, the Sponsor may terminate the Investigator´s participation in the study.

11.10 Electronic Case Report Forms (e-CRFs)

All data that is to be collected according to the study protocol shall be reported into a validated electronic database (e-CRF) that has been provided by Clinical Trials Unit Freiburg. Edit checks will be implemented to ensure data quality and accuracy. The Sponsor or designee will also provide e-CRF completion guidelines, to ensure that the data is recorded in a timely and accurate manner. The Investigator is responsible for ensuring that all sections of e-CRF are complete and correct and that those entries can be verified against source data. Completed e-CRFs will be verified by the appointed Monitor at the investigational site at regular intervals throughout the study, as defined in the Monitoring Plan. All e-CRFs will be reviewed for completeness and clarity upon receipt.

Missing or unclear data will be investigated by the Monitor and/ or Data Management and will be retrieved and clarified by study personnel as necessary throughout the study.

11.11 Source Documentation

Regulations and GCP require that the Investigator maintain information in the subject's medical records that corroborates the data collected in the e-CRF. In order to comply with these regulatory requirements/GCP, the following information should be included in the subject record at a minimum and if applicable to the study:

- Medical history of the subject before involvement in the trial sufficient to verify eligibility criteria
- Dated and signed notes on the day of entry into the trial referencing the Sponsor, protocol number, subject ID number and a statement that informed consent was obtained
- Dated and signed notes from each subject visit (for specific results of relevant procedures and examinations)
- Adverse events reported and their resolution, including supporting documents such as discharge summaries, EEGs, and lab results including documentation of site awareness of SAEs and of Investigator device relationship assessment of SAEs, death certificate or death confirmation (if applicable)
- Notes regarding prescription medication taken during the trial (including medication name, dose, frequency and duration as well as start and stop dates (day/month/year when possible)
- Subject's condition upon completion of or withdrawal from the trial
- Any other data required to substantiate data entered into the CRF

11.12 Source Document Review

The Investigator will allow the Monitor and/or the representative of the Sponsor, and any regulatory body to review and inspect the study files, subject e- CRF, subject medical records and other related study documents as required. The Sponsor and/or designee may request additional documentation from the Investigator such as physician procedure notes or physician written summaries when AEs are observed and reported.

11.13 Study Materials

11.13.1 Investigational Device Accountability

The Sponsor will provide investigational devices to each site, for which device accountability records must be maintained. All investigational devices, which have not been used must be returned to the Sponsor following completion of the study or as otherwise deemed necessary (e.g. expired devices).

Use of any investigational device supplied for use during this clinical trial outside of the study protocol (e.g. compassionate use) is strictly forbidden and may constitute grounds for removal of the Investigator/Institution from the clinical investigation. The Investigator will ensure no expired investigational devices are implanted.

All used investigational devices (explanted or external components), regardless if associated with a device failure or device deficiency, should be returned immediately to the Sponsor.

11.13.2 Other Study Materials

Unused subject binders may be destroyed at the end of the study; this should be documented. All other study materials should be returned to the Sponsor after the completion of the study.

11.14 Study Termination

The Sponsor reserves the right to terminate the entire study or a specific site's participation at any time for any of the following reasons: inadequate enrollment, protocol non-adherence, unethical practices, poor data quality or administrative decision.

11.15 Archiving & Record Retention

11.15.1 Record Retention

The Investigators and/or designee(s) will be instructed to retain all study records required by the Sponsor and regulatory authorities in a secure and safe facility, with limited access. All study material shall be stored for at least 15 years or as based on national regulations. The Investigator must request authorization from the Sponsor prior to destroying study records.

11.15.2 Archiving Requirements

Archiving of the clinical trial documents will be conducted according to MDR, Annex XV, chapter 3, No. 3 as well as national guidelines. Precisis AG will ensure that during the entire course of this clinical trial, all trial data will be protected against unauthorized access. In addition, the Sponsor and Investigators shall take all necessary measures for careful and confidential handling of all clinical trial information.

11.16 On-site Audits and inspections

According to the EN ISO 14155 guidelines, audits may be performed as a quality measure. Audits may be conducted by the sponsor or an independent external party, inspections may be conducted by CA(s).

If an Investigator is contacted by a regulatory agency in relation to this study, he/she shall notify the Sponsor and/or designee immediately. The Investigator and/or designee must be available to respond to reasonable requests and audit queries made by authorized regulatory representatives

during the audit process. The Investigator must provide the Sponsor and/or designee with copies of all correspondence that may affect the review of the current study or their qualification as an Investigator in studies conducted by the Sponsor and/or designee. The Sponsor and/or designee will provide any needed assistance to regulatory audits.

12 Labelling

All components will be labelled by the manufacturer (Precisis AG) according to Directive 90/385/EEC, Annex 1, clause 14 and 15 and related harmonized standards. In addition, all devices used in the clinical trial will be clearly marked as “for clinical trial use only”. Draft labelling for the EASEE® System is included within the study package.

13 Sponsor Contact Information

The primary Precisis AG contact for the study is:

Dr. med. Angela Liedler
Hauptstr. 73
69117 Heidelberg, Germany
Tel.: +49 6221 6559320
Fax: +49 6221 6559310
Email: a.liedler@precisis.de

14 Data Collection

14.1 Data Management Responsibilities

The handling of data, including data quality assurance, will comply with regulatory guidelines (for example GCP**,** EU- GDPR) and Clinical Trial Unit SOPs and work instructions. All steps and actions taken regarding data management and quality assurance will be documented in the Clinical Trials Unit SOPs and data handling guidelines. Completed e-CRFs will be verified against source data according to monitoring plan and visually checked by the study monitor for completeness, consistency, and legibility. Responses to requests for further clarification of data recorded in the e-CRF will be answered, dated and signed by the Investigator. Changes will be implemented in the Sponsors or designee’s database and the data review and validation procedures will be repeated as needed. At the end of the study, the e-CRF database will be locked and the data will be released for reporting and statistical evaluation.

14.2 Confidentiality

The Investigator and institution involved in this study will only provide direct access to source data and documents to the Sponsor and/or designee, and to appropriate authorities for the purposes of

monitoring, audit, EC review or regulatory inspection. Each subject taking part in the study will have agreed explicitly to such access in writing. All subject data will always be treated with strict adherence to professional standards of confidentiality and according to EU GDPR guidelines effective as of 25- May- 2018. All reports and communications relating to subjects in the study will identify the subjects by their subject ID number only.

14.3 Core Laboratory

In order to minimize inter-investigator/site bias, an independent core laboratory will be selected to analyze EEG data. The results of the analysis are provided to investigational sites in a report that contains all relevant information. EEG´s will be completed as per the core laboratory guidelines/ Instructions for Use. All investigational sites are required to upload pseudonymized EEG data electronically via the Core Laboratory´s secure web-based service platform as soon as possible. The Core Laboratory platform must be fully compliant with the GDPR regulations in Europe.

15 Liability

Study subject insurance will be provided according to the laws of the respective country where the study will be conducted.
Subject insurance (minimum: € 500.000, - per subject) according to applicable law has been taken out with:

(Policy No.: NEV19954416A)
Newline Europe Versicherung AG
Schanzenstr. 28a, 51063 Köln, Germany
Tel: +49 221 9669-4510
Fax: +49 221 9669-4511
Email: info@newlinegroup.de
www.newlinegroup.de

for all subjects participating in the clinical trial.
The investigator, or an individual who is designated by the investigator, will inform the subject of the existence of the insurance, including the obligations arising from it. The trial subjects must be afforded access to insurance documents and provided with a copy of the general conditions of insurance on request.

16 Publication Policy

The study will be registered in a Primary Registry of the WHO Registry Network. Registration will be the responsibility of the Sponsor and/or designee. The Sponsor shall have the right to access and use all data and results generated during the clinical investigation. Preparation of the publication will occur once the study has been concluded, but the Sponsor may at its discretion coordinate an

additional, interim publication. An abstract reporting the results will be prepared by the participating Principal Investigators at all sites and the Sponsor for presentation in an appropriate international forum. A manuscript will also be prepared for publication in a scientific journal. Results will be submitted for publication, regardless of the outcome. The publication of the results from any single center experience within the study shall only appear after publication of the multi-center study results and will be coordinated with the Sponsor.

The Sponsor maintains the right to be informed of any plans for publication by any investigator or anyone else using any data from the clinical study, and to review any resulting abstracts, presentations or manuscripts before they are submitted. The Sponsor will return comments to the authors so the investigators may submit the abstract or manuscript for publication in a timely fashion. The review by Sponsor will be for correctness and to protect intellectual property. An Investigator may only publish data generated by this clinical study in accordance with the terms of the Clinical Trial Agreement.

17 Glossary and Abbreviations

AC	Alternating Current
AE	Adverse Event
ADE	Adverse Device Effect
AED	Antiepileptic Drug
e-CRF	Electronical Case Report Form
DBS	Deep Brain Stimulation
DSMB	Data Safety Monitoring Board
DC	Direct Current
CA	Competent Authority
CRO	Clinical Research Organisation
EASEE®	Epicranial Application of Stimulating Electrodes for Epilepsy
EASEE® Access	A device that enables the subject to communicate with the implanted components
EASEE® Connect	A device that provides a wireless connection between EASEE® Set and EASEE® Power, enabling the input and extraction of data
EASEE® Lead	Part of the implant consisting of the electrode and the cable
EASEE® Power	Part of the implant which stores energy and generates electrical pulses for stimulation
EASEE® Set	A physician control device to set parameters and manage the EASEE® Power
EASEE® System	The complete stimulation system consisting of the implant, the tools for the surgery, and management and maintenance tools for the implant
EC	Ethics Committee
EEG	Electroencephalogram
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
Hz	Hertz
ICH	International Conference on Harmonization
IPG	Impulse Generator
LTFU	Long-term follow-up
mA	Milliampere
MDCG	Medical Device Coordination Group
MEDDEV	Guidance for the application of the classification rules for medical devices
min	Minutes
mm	Millimeter
MPDG	Medizinprodukterecht-Durchführungsgesetz
MPSV	Medizinproduktesicherheitsverordnung - Medical Products Safety Ordinance

MRI	Magnetic Resonance Imaging
NDDI-E	Neurological Disorder Depression Inventory – Epilepsy scale
NHS3	The National Hospital Seizure Severity Scale
PI	Principal Investigator
QOLIE-E	Quality of Life in Epilepsy Inventory
RNS	Responsive Neurostimulation
s / sec	second
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SANTE	Stimulation of the Anterior Nuclei of Thalamus for Epilepsy
SSQ	Seizure Severity Questionnaire
SUDEP	Sudden Unexpected Death in Epilepsy
tDCS	Transcranial Direct Current Stimulation
ULFA	Ultra Low Frequency Asymmetric (stimulation mode)
USADE	Unanticipated Serious Adverse Device Effect
V	Volt
VNS	Vagus Nerve Stimulation
WHO	World Health Organisation
WMO	The Medical Research Involving Human Subjects Act

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