# Supplementary Online Content

Shulze-Bonhage A, Hirsch M, Knake S, et al; EASEE Study Group. Focal cortex stimulation with a novel implantable device and antiseizure outcomes in 2 prospective multicenter single-arm trials. *JAMA Neurol*. Published online April 3, 2023. doi:10.1001/jamaneurol.2023.0066



This supplementary material has been provided by the authors to give readers additional information about their work.

**eMethods.** Eligibility Criteria

*EASEE II*

Inclusion 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, if they have had prior resective surgery to treat epilepsy, who have a clearly identifiable epileptic focus and a preserved neocortex in the region of implantation.
5. Patients who have failed treatment with a minimum of two anti-seizure medications (used in appropriate doses).
6. 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.
7. Patients having an anticipated average of 3-300 partial-onset seizures (focal to bilateral tonic clonic seizures) during the baseline period.
8. Patients taking a constant dose of antiepileptic medication(s) over the most recent 28-day period prior to the baseline period (use of medication for acute treatment of seizures is allowed).
9. Patients between the ages of 18 and 75 years.
10. Patients able and willing to provide appropriate consent prior to study procedures.
11. Patients able to complete regular office appointments per the protocol requirements, including behavioral (mood) surveys and neuropsychological testing.
12. Patients willing to be implanted with the EASEE® System as a treatment for his/her seizures.

Exclusion criteria:

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.
11. Patients with an implanted electronic medical device that delivers electrical energy to the body (e.g. DBS, cardiac pacemaker or defibrillator) with the exception of 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, or do not have the necessary assistance, to properly operate the EASEE® Access handheld device.

*PIMIDES I*

Idem, except for below changes.

Inclusion criteria:

7. Patients having an anticipated average of 3-200 partial-onset seizures (focal to bilateral tonic clonic seizures) during the baseline period.
13. 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).

Exclusion criteria:

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.)

**eTable 1.** Demographic and Clinical Data

| Characteristics | EASEE II (n = 15) | PIMIDES I (n = 18) | EASEE Pooled-analysis (n = 33) |
|---|---|---|---|
| Female / male sex, n (%) | 4 (26.7%) / 11 (73.3%) | 11 (61.1%) / 7 (38.9%) | 15 (45.5 %) / 18 (54.5%) |
| Age in years, mean ± SD (range) | 33.3± 13.1 (18 – 68) | 35.7 ± 14.2 (22 – 75) | 34.6 ± 13.5 (18 - 75) |
| Duration of epilepsy in years, mean ± SD (range) | 22.3 ±14.8 (3 - 66) | 18.9 ± 10.1 (3 - 38) | 20.4 ± 12.4 (3 – 66) |
| Baseline seizure count per 30 days (median / IQR) | 16 / 30 | 12 / 49 | 12 / 29 |
| Baseline seizure count per 30 days (mean / SD) | 32.7 / 45.4 | 34.6 / 43.8 | 33.7 / 43.9 |
| Number of antiseizure medication tested prior to enrollment, mean ± SD | 8.2 ± 4.8 | 7.5 ± 3.8 | 7.8 ± 4.3 |
| Number of antiseizure medications at baseline, mean ± SD | 3.1 ± 1.4 | 3.3 ± 1.0 | 3.2 ± 1.2 |
| 2 ASM, n (%) | 7 (46.7%) | 5 (27.8%) | 12 (36.4%) |
| 3 ASM, n (%) | 2 (13.3%) | 5 (27.8%) | 7 (21.2%) |
| 4 ASM, n (%) | 5 (33.3%) | 6 (33.3%) | 11 (33.3%) |
| 5 ASM, n (%) | 0 (0.0%) | 2 (11.1%) | 2 (6.1%) |
| 6 ASM, n (%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| 7 ASM, n (%) | 1 (3.0%) | 0 (0.0%) | 1 (3.0%) |
| Prior Vagal Nerve Stimulation, n (%) | 1 (3.0%) | 3 (16.7%) | 4 (12.1%) |
| Location of seizure onset, n (%) | .. | .. | .. |
| temporal | 6 (40.0%) | 9 (50.0%) | 15 (45.4%) |
| frontal | 5 (33.3%) | 4 (22.2%) | 9 (27.3%) |
| other | 4 (26.7%) | 5 (27.8%) | 9 (27.3%) |
| Hemisphere of seizure onset, n (%) | .. | .. | .. |
| Left | 10 (66.7%) | 10 (55.6%) | 20 (60.6%) |
| Right | 5 (33.3%) | 8 (44.4%) | 13 (39.4%) |

EEG: electroencephalogram, IQR: interquartile range, MRI: magnetic resonance imaging, SD: standard deviation

Populations from the phase 1 and 2 trials are very similar, except for a gender bias (men seem over-represented in EASEE II and women over-represented in PIMIDES I). The data was deemed acceptable to pool in the meta-analysis.

**eTable 2.** Effectiveness Outcomes

| | **EASEE II (n = 15)** | **PIMIDES I (n = 17)** | EASEE Pooled-analysis (n = 32) |
|---|---|---|---|
| Responder rate (n, % [CI]) | 7, 46.7% [21.3 - 73.4] | 10, 58.8% [32.9 - 81.6] | 17, 53.1% [34.7 - 70.9] * |
| Seizure reduction percentage (median) | 44% | 56% | 52% |
| Seizure frequency at month 6 (median / IQR) | 14 / 30 | 6 / 7 | 7 / 26 |
| Seizure frequency at month 6 (mean / SD) | 20.7 ± 22.7 | 14.3 ± 22.0 | 17.3 ± 22.2 |

CI: confidence interval; IQR: interquartile range; SD: standard deviation; Effectiveness outcomes in neurostimulation month 6 versus baseline. The responder rate is defined as at least 50% reduction in seizure frequency.

The independent data for the PIMIDES I trial looks slightly better than EASEE II (58.82% or 10/17 vs 46.67% or 7/15 responder rate). The meta-analysis, with a responder rate of 53.13% after 6 months of active stimulation, allows for a more reduced 95% confidence interval in the result (34.74%-70.91%).

[*] Primary endpoint

**eTable 3.** Safety Outcomes

| | EASEE II (n = 15) | PIMIDES I (n = 18) | EASEE Polled-analysis (n = 33) |
|---|---|---|---|
| Number of patients with device or procedure related[*] Serious Adverse Events at 4-month follow-up (n/ % [CI][**]) | 0 / 0.0% | 0 / 0.0% [0.0 - 18.5] [**] | 0 / 0.0% [0.0 – 10.6] |
| Number of patients with Serious Adverse Events at 1-month follow-up (n/ % [CI][**]) | 1 / 6.67% [0.31 – 31.9] [**] | 1 / 5.56% | 2 / 6.06% [0.7 – 20.2] |
| Number of patients with Serious Adverse Events at 4-month follow-up (n/ % [CI][**]) | 3 / 20.0% [4.3 – 48.1] [**] | 2 / 11.1% | 5 / 15.2% [5.1 – 31.9] |
| Number of patients with Serious Adverse Events at 8-month follow-up (n/ %) | 3 / 20.0% | 4 / 22.2% | 7 / 21.2% |
| Number of patients with Adverse Events at 8-month follow-up (n/ %) | 10 / 66.7% | 15 / 83.3% | 25 / 75.5% |

[*] Device or procedure related events correspond to serious adverse events deemed to have a possible, probable, or causal relationship to the device or to the procedure, according to the investigator.

[**] Primary endpoint, CI: confidence interval

The EASEE II study reported on the incidence of acute (up to 1-month follow-up) and short-term SAEs (up to 4-month follow-up) as the primary endpoint, as this is the necessary primary endpoint of a first-in-man trial for the use of a novel neurostimulator. The PIMIDES I study, also with the focus on the safety endpoint, reported on the device or procedure related SAEs at 4-month follow-up as the primary endpoint. All the above safety endpoints were reported on in the meta-analysis.

In EASEE II 6.67% (CI: [0.31 – 31.9]) of patients had a SAE up to one month and 20.0% (CI: [4.3 – 48.1]) of patients had a SAE up to four months. The upper limit of the confidence interval of the one-month SAE rate is 31.9% so that with 95% probability the true SAE-rate is below this value. For the four-month SAE rate the true SAE rate is below 48.1% with 95% probability.

In PIMIDES I, none of the patients experienced a procedure related SAE, which leads to an upper boundary of the confidence interval of 18.5 % so that it can be expected that with 95% probability the true procedure-related SAE rate is below this value.