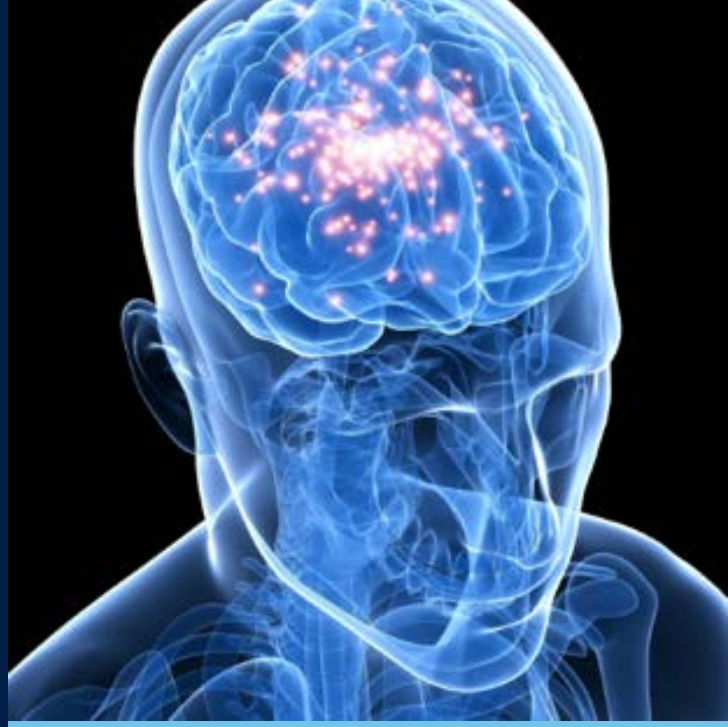
ANT DBS THERAPY FOR EPILEPSY



SANTE CLINICAL STUDY FINAL RESULTS: LONG TERM SAFETY & EFFECTIVENESS OUTCOMES

MORE REGISTRY: STUDY OVERVIEW & STATUS UPDATES

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Off Label Disclosure Slide

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SANTÉ STUDY: FINAL STUDY RESULTS

Long-term safety and effectiveness outcomes

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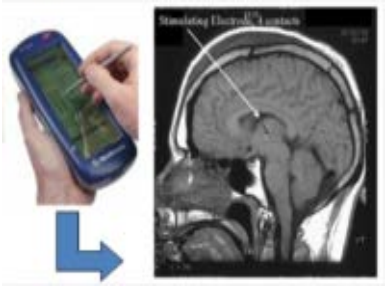
OUTLINE

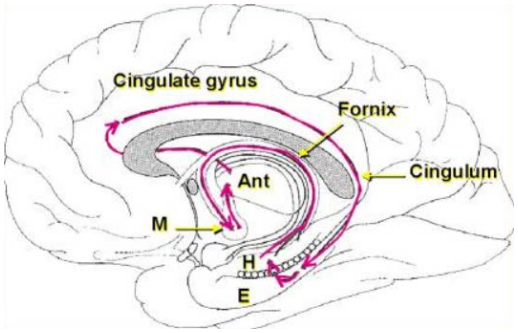
- SANTE Clinical Trial
  - Study Design
  - Results
    - Effectiveness
    - Safety
- Conclusions

ANTERIOR THALAMIC DBS
ROBERT FISHER, MD, PH.D



ANT DBS

Remote Stimulation Concept →



Circuit of Papez

Table 1. Clinical outcomes following deep brain stimulation of the anterior nucleus of the thalamus.

	Study [Ref]	Patients (n)	Average length of postoperative follow-up (months)	Type of stimulation	Reduction in seizure frequency per month (%)
*	Osorio et al. [34]	4	36	Cycling	76**
	Lee et al. [32]	3	13	Cycling	75
	Lim et al. [33]	4	44	Continuous†	51
*	Hodaie et al. [29]	5	15	Cycling	54††
*	Kerrigan et al. [30]	5	12	Cycling	14††
*	Andrade et al. [31]*	6	48	Cycling†	51***
	Fisher et al. [35]	110	25	Cycling	56

*Andrade et al. include results from patients included in the study of Hodaie et al. †Intermittent stimulation was later used to prolong battery life, although the timescale was not reported. ‡Multiple changes in stimulation parameters, including continuous versus cycling, were performed in this study. **$p<0.01$. ††$p<0.05$. ‡‡This study noted a >50% reduction in the number of serious seizures (generalized tonic-clonic seizures and complex partial seizures) frequency. ***Four of the six patients had a significant reduction in the frequency of seizures/month ($p<0.05$), but the significance for the overall mean reduction was not reported. Adapted from [42].

Image courtesy of Remedica Journals
http://www.remedicajournals.com/CML-Neurology/BrowseIssues/Volume-27-Issue-2/Article-Deep-Brain-Stimulation-for-the-Treatment-of-Epilepsy

* ANT DBS PILOTS

SANTE

ClinicalTrials.gov Identifier:

NCT00101933

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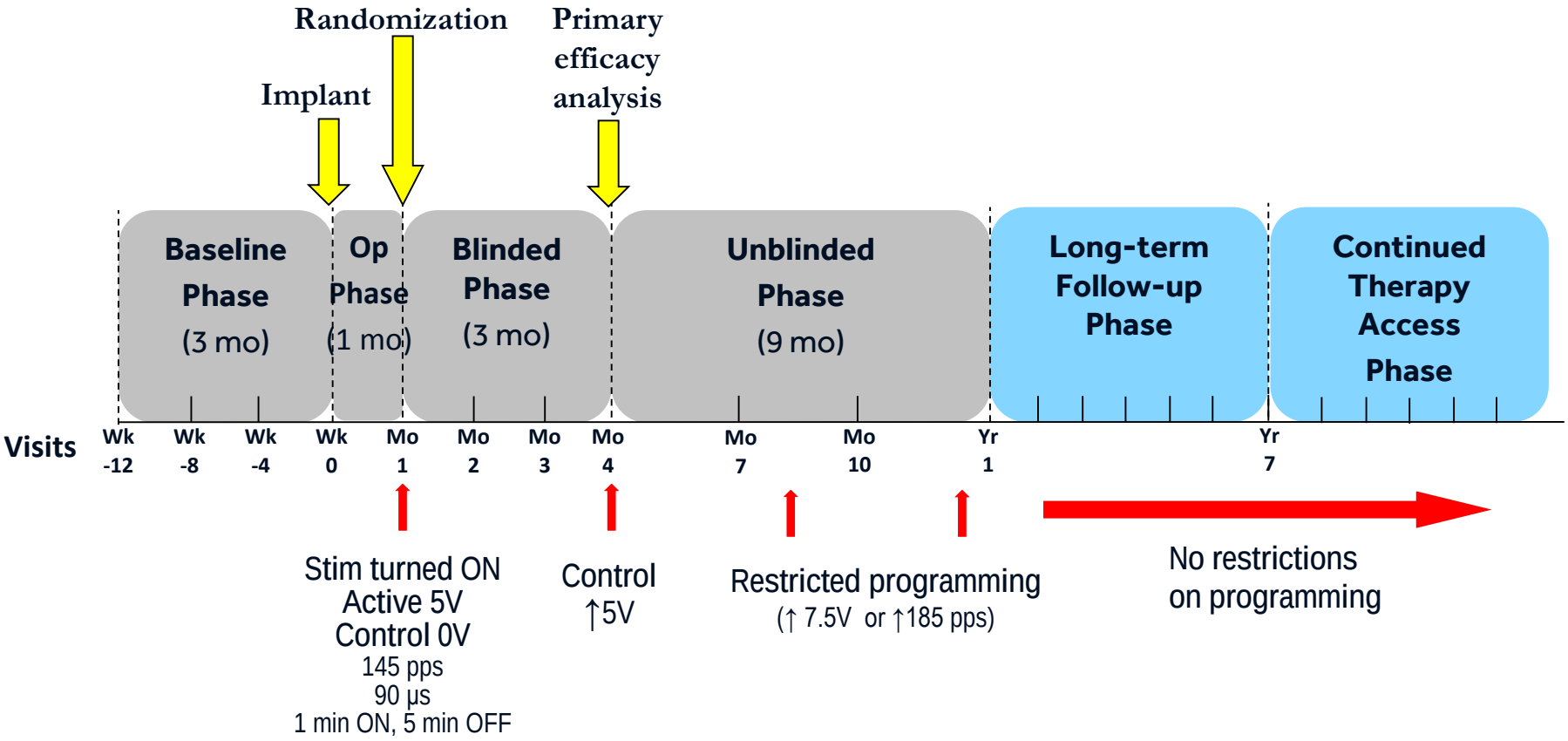
SANTÉ CLINICAL TRIAL

SANTÉ: Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy

Medtronic-sponsored, multicenter, prospective randomized controlled pivotal clinical trial conducted at 17 centers in the United States with initial implant in 2004.



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STUDY POPULATION

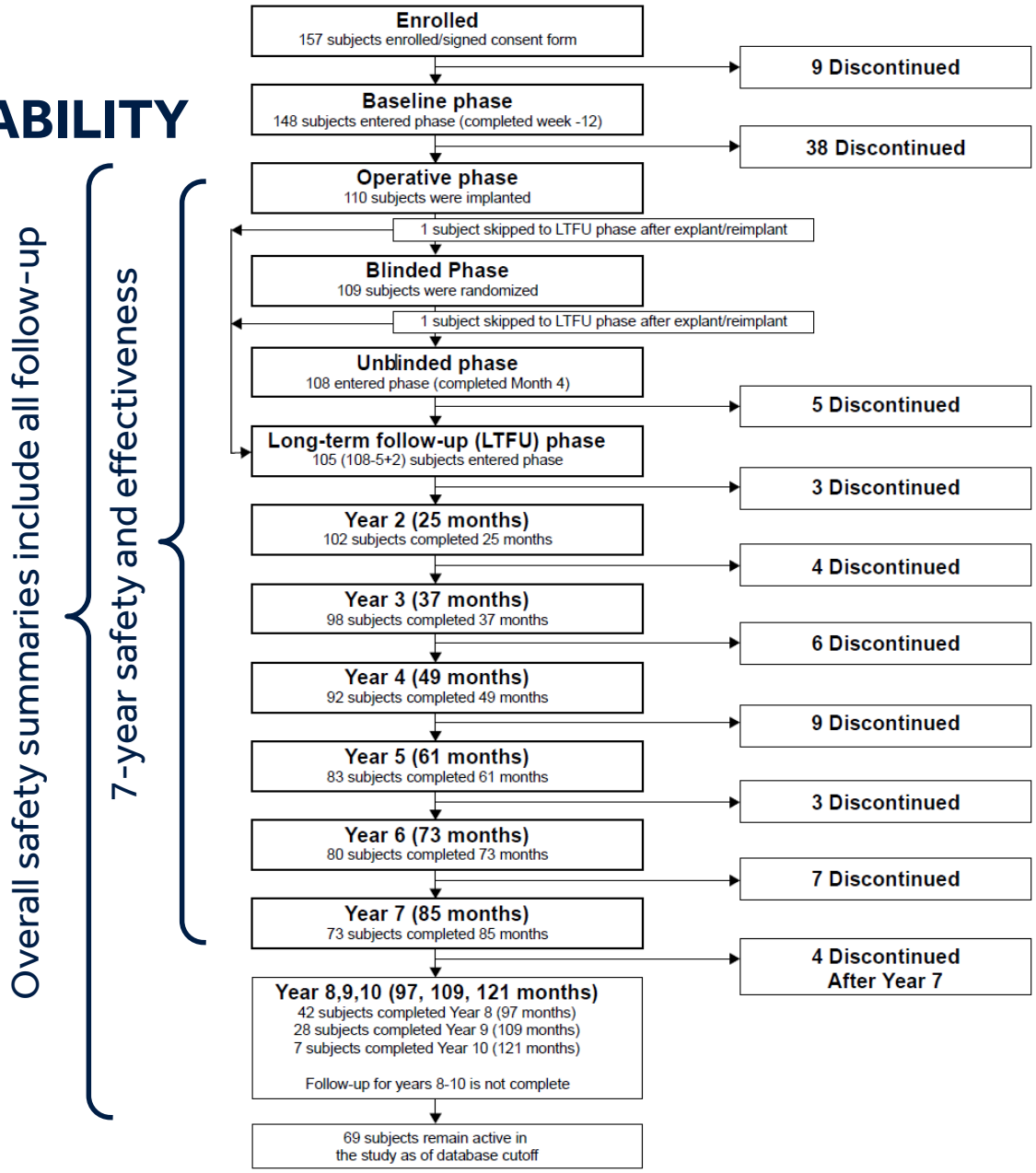
Eligibility Criteria (abbreviated)

- Age 18-65, inclusive
- 6 or more partial seizures with or without secondary generalization per month
- Refractory to at least 3 antiepileptic drugs (AEDs), currently taking 1-4 AEDs

Demographics (n=110 implanted)

Age (mean)	36.1 years
Female (%)	50%
Years with epilepsy (mean)	22.3 years
Baseline seizure counts per month (median)	19.5
Number of epilepsy meds (%):	
1	11%
2	49%
3	37%
4	3%
Previous VNS (%)	45%
Previous epilepsy surgery (%)	25%

SUBJECT ACCOUNTABILITY



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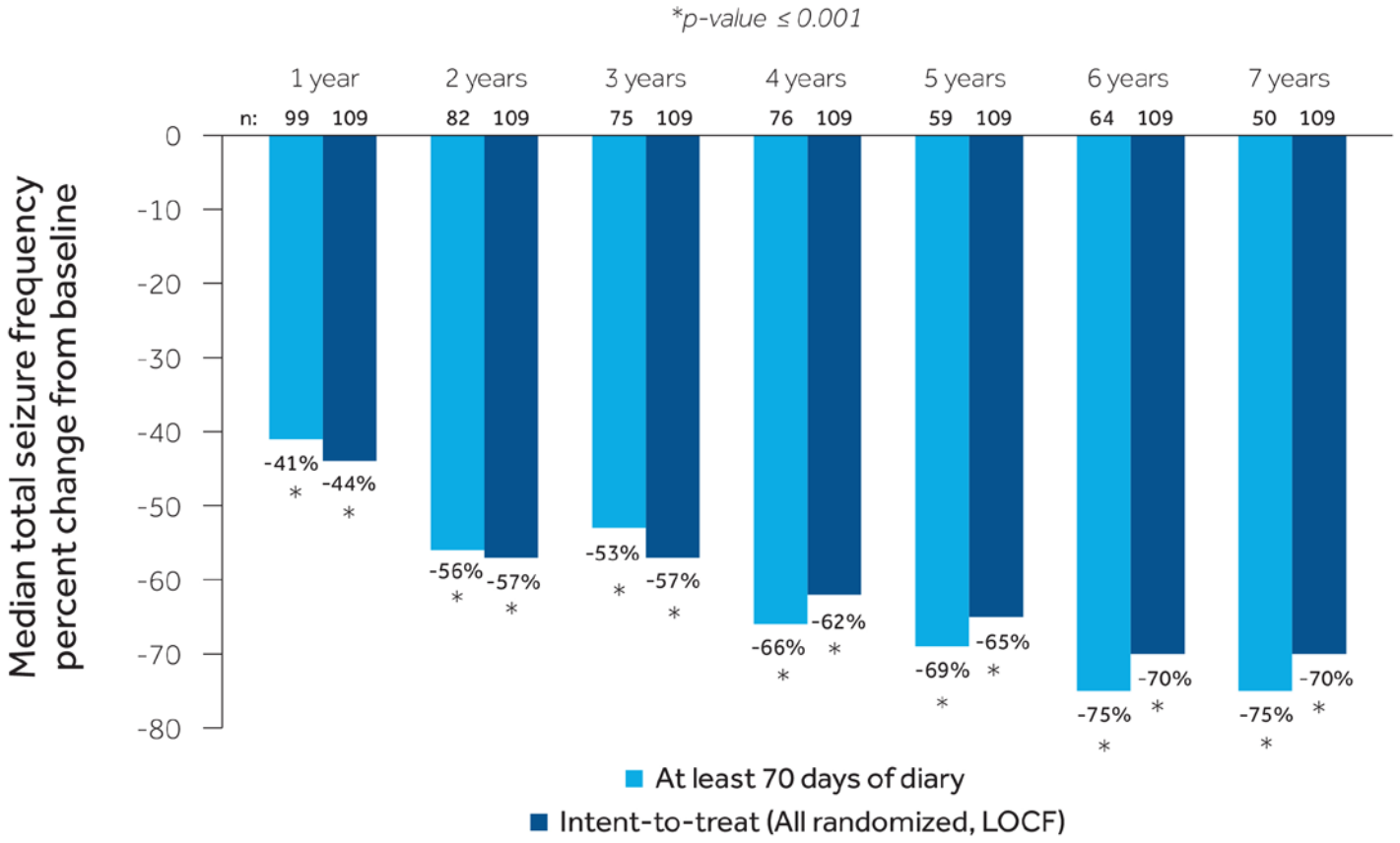
LONG TERM EFFECTIVENESS RESULTS

EFFECTIVENESS OUTCOME MEASURES

- Seizure reduction
- Responder rate
- Seizure severity
- Quality of life

TOTAL SEIZURE FREQUENCY

WITH AND WITHOUT IMPUTATION



Median seizure frequency percent change from baseline at years 1-7. Analyses include subjects with at least 70 days of diary in the 3 months prior to the annual visit, and intent-to-treat analyses at each time point.

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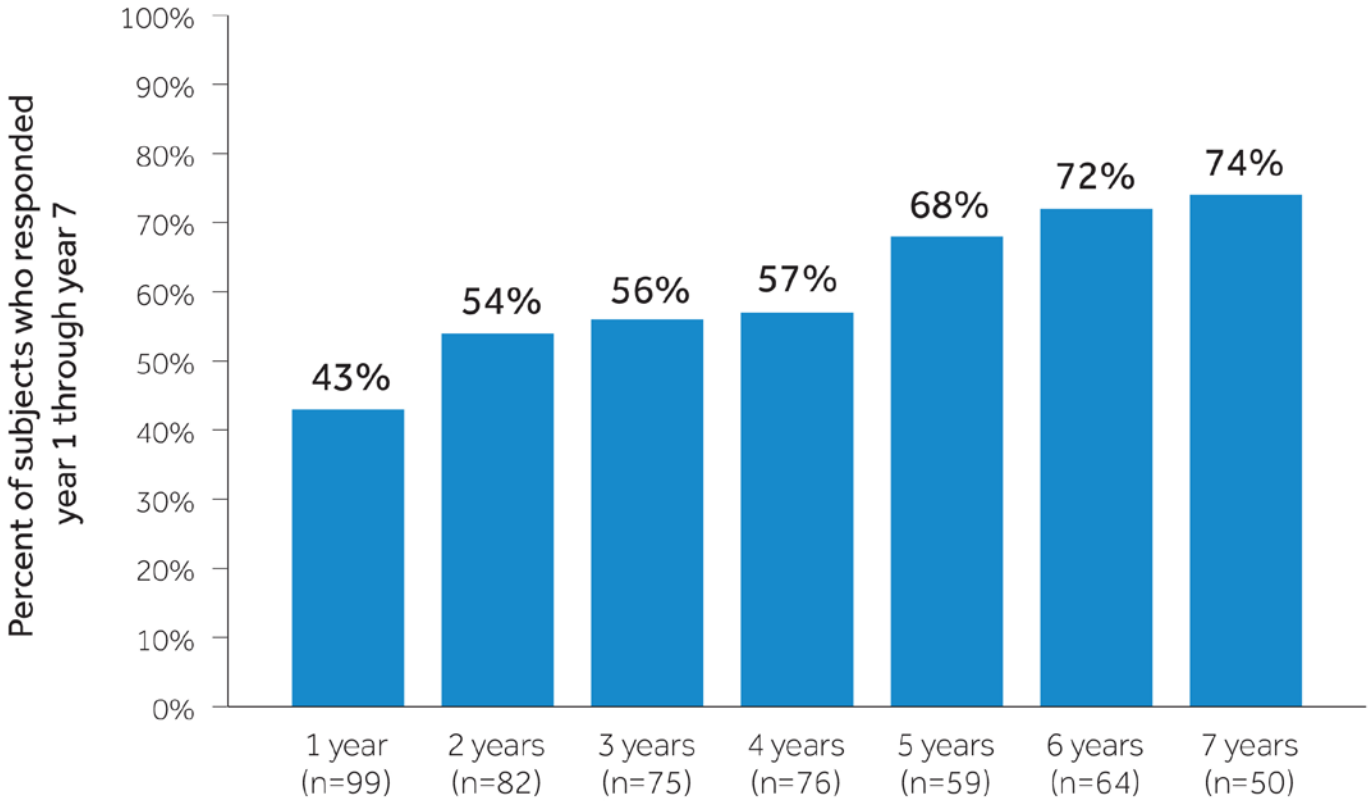
TOTAL SEIZURE FREQUENCY

RESPONDER RATE



Responder rate. The percentage of subjects with at least 50% seizure reduction was 43% at Year 1 and 74% at Year 7.

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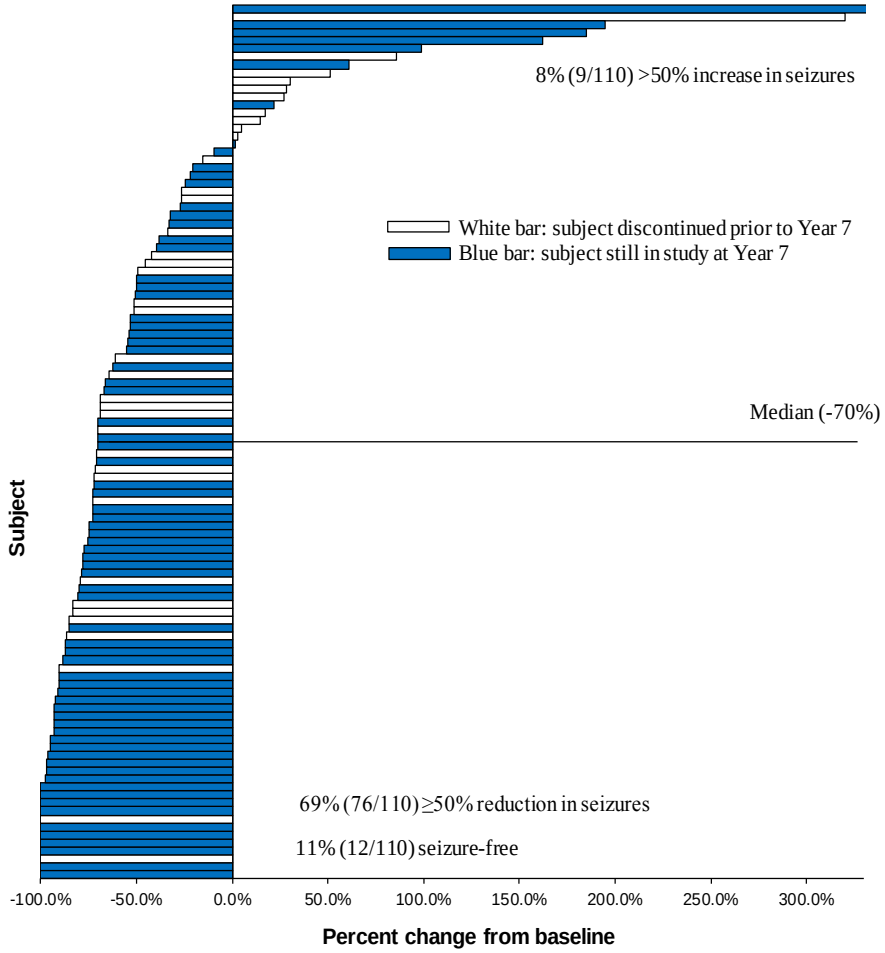
TOTAL SEIZURE FREQUENCY

SUBJECT DATA AT 7 YEARS



Negative values indicate a seizure frequency reduction compared with baseline.

Subject total seizure frequency percent change from baseline to most recent 3 months of follow-up.

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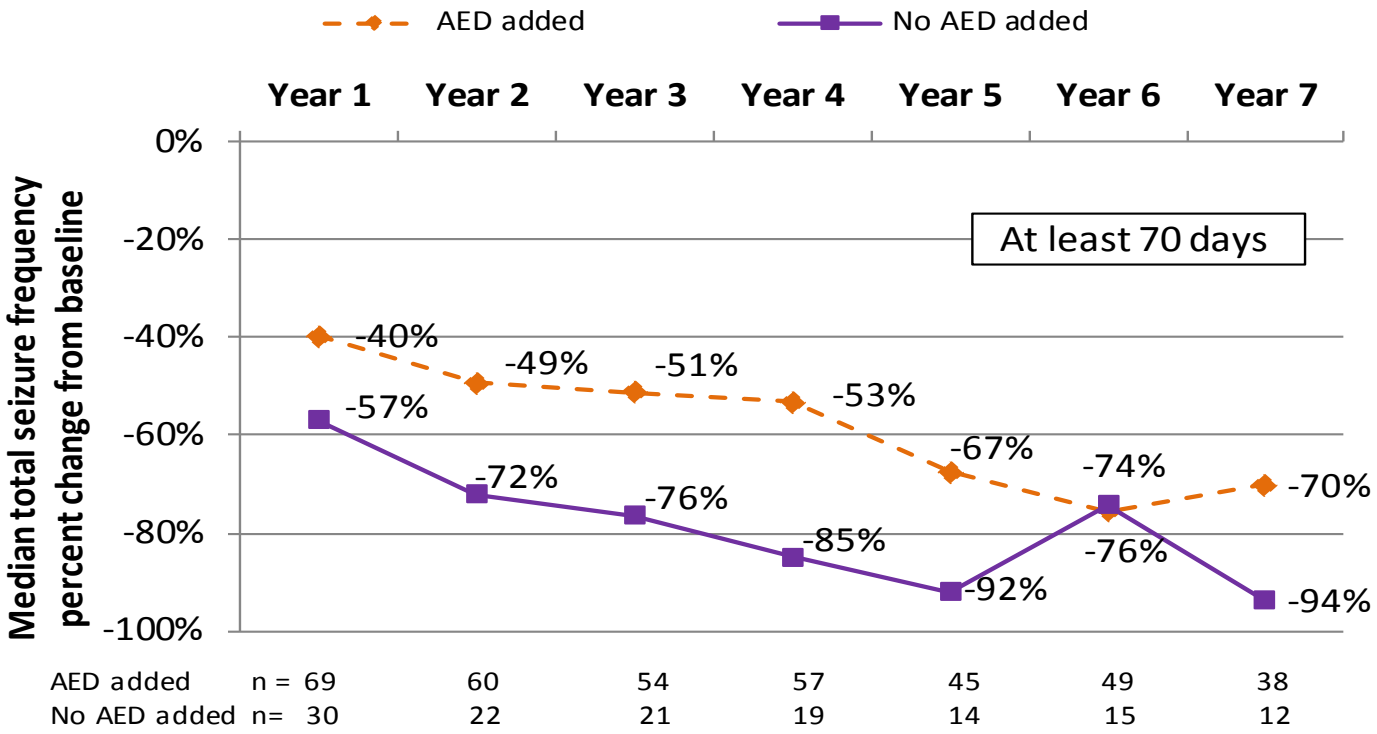
TOTAL SEIZURE FREQUENCY
BY MEDICATION ADDITION



AED added: at least one AED recorded at any point between implant and Year 7 that was not used during baseline prior to implant.

New AED use and median total seizure frequency percent change from baseline at years 1-7. Subjects in the "AED added" category had at least one new medication added after implant, while those in the "no AED added" category had no medications added through Year 7.

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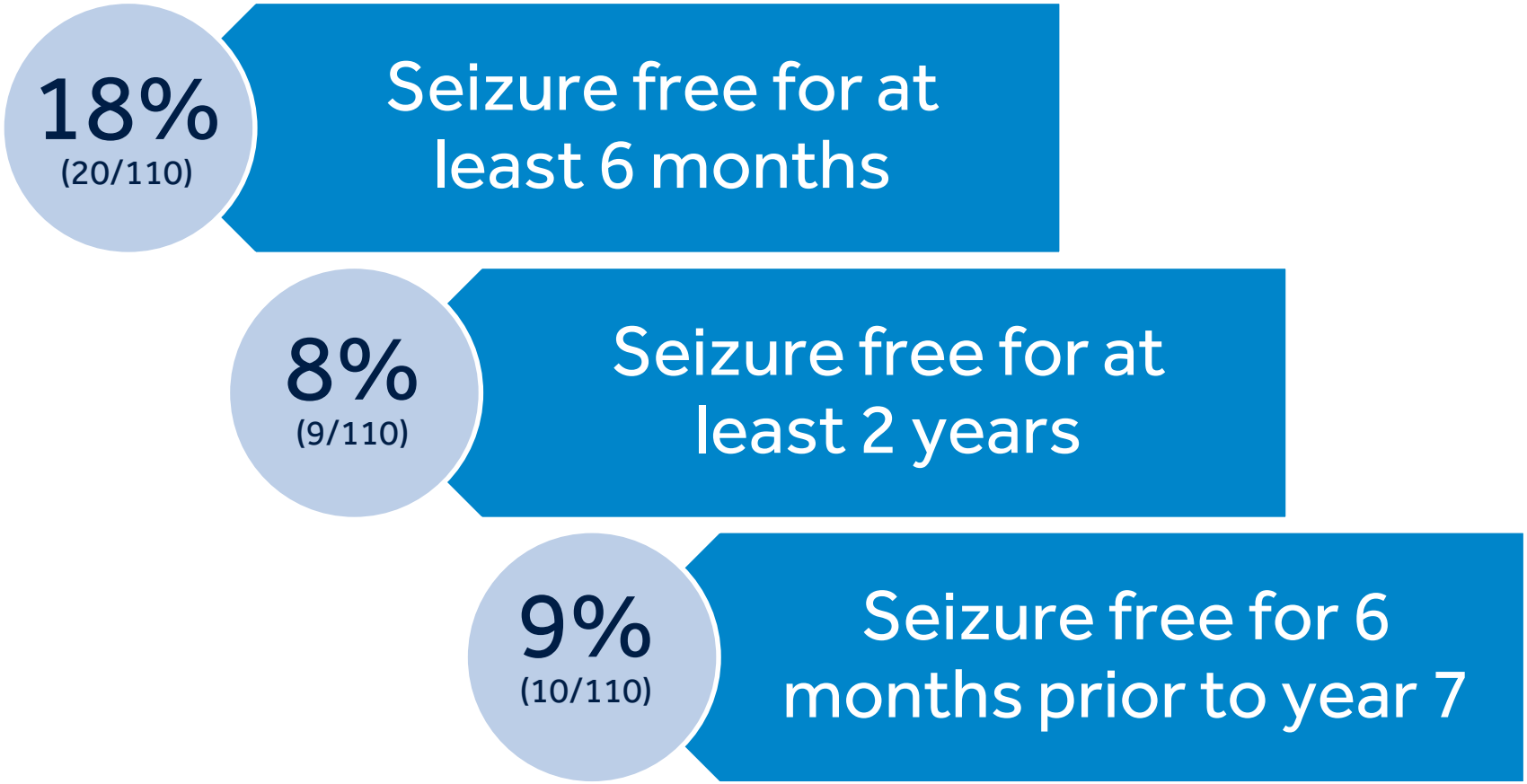
SEIZURE FREEDOM



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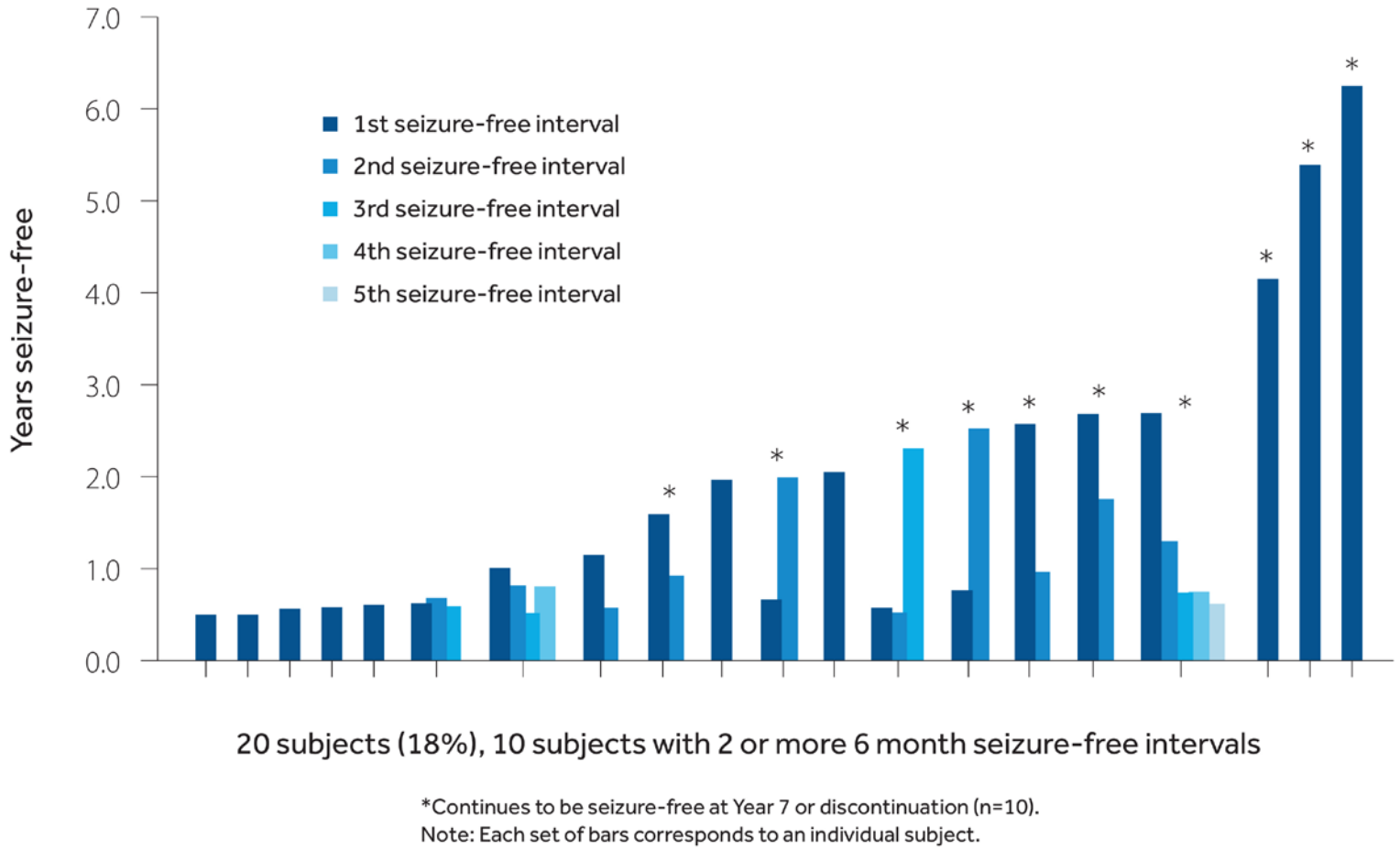
SEIZURE FREEDOM



Subjects who were seizure-free for at least 6 months. 18% (20/110) of subjects were seizure-free for at least 6 months at any time in the 7 years after device implant.

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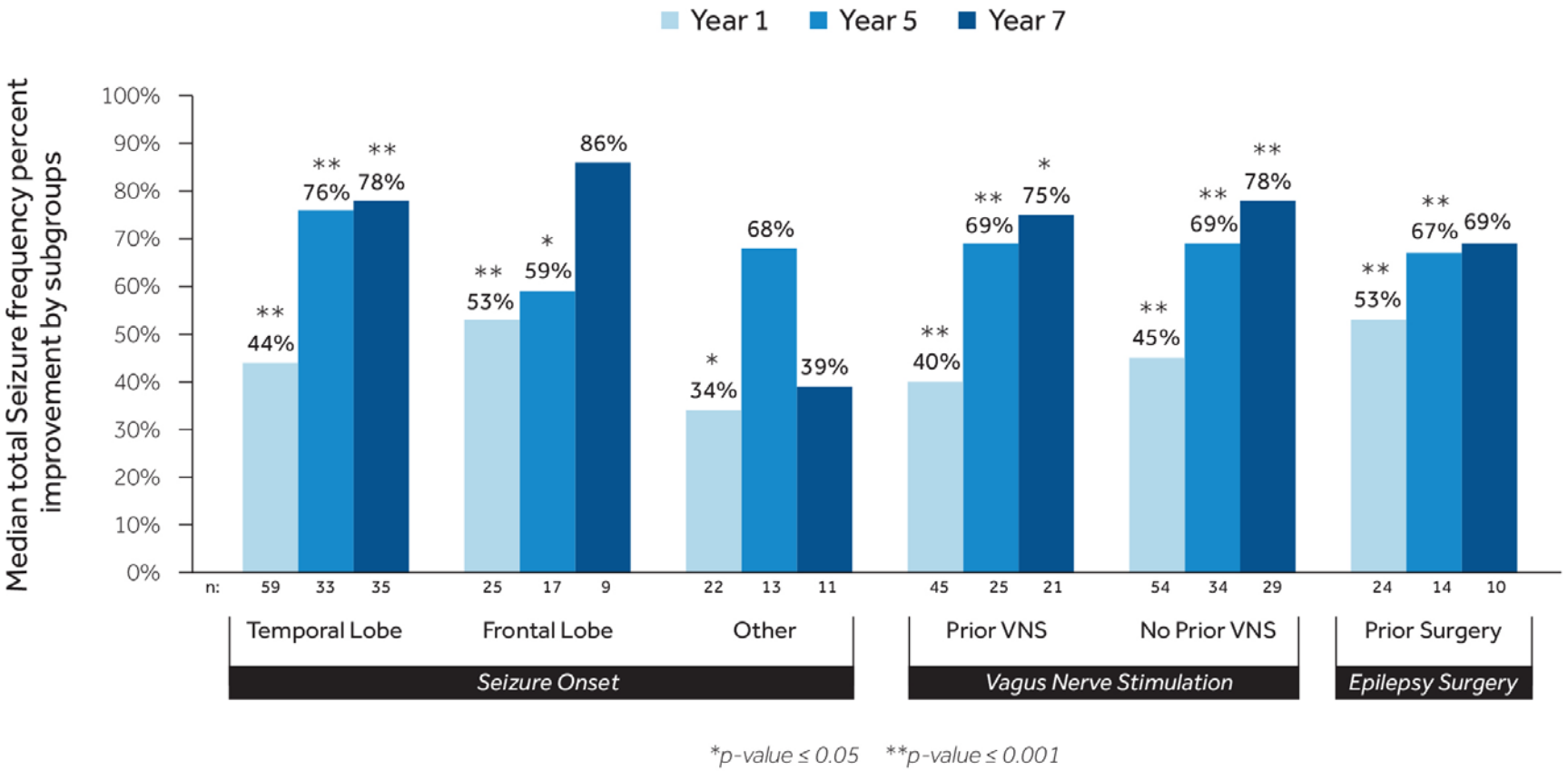
SEIZURE FREQUENCY

SUBGROUPS: SEIZURE ONSET, PRIOR VNS/SURGERY



*p-value ≤ 0.05 **p-value ≤ 0.001

Median seizure frequency percent improvement by subgroups at Years 1, 5, and 7. Analyses were performed by seizure onset location, previous VNS device implant, and previous epilepsy surgery.

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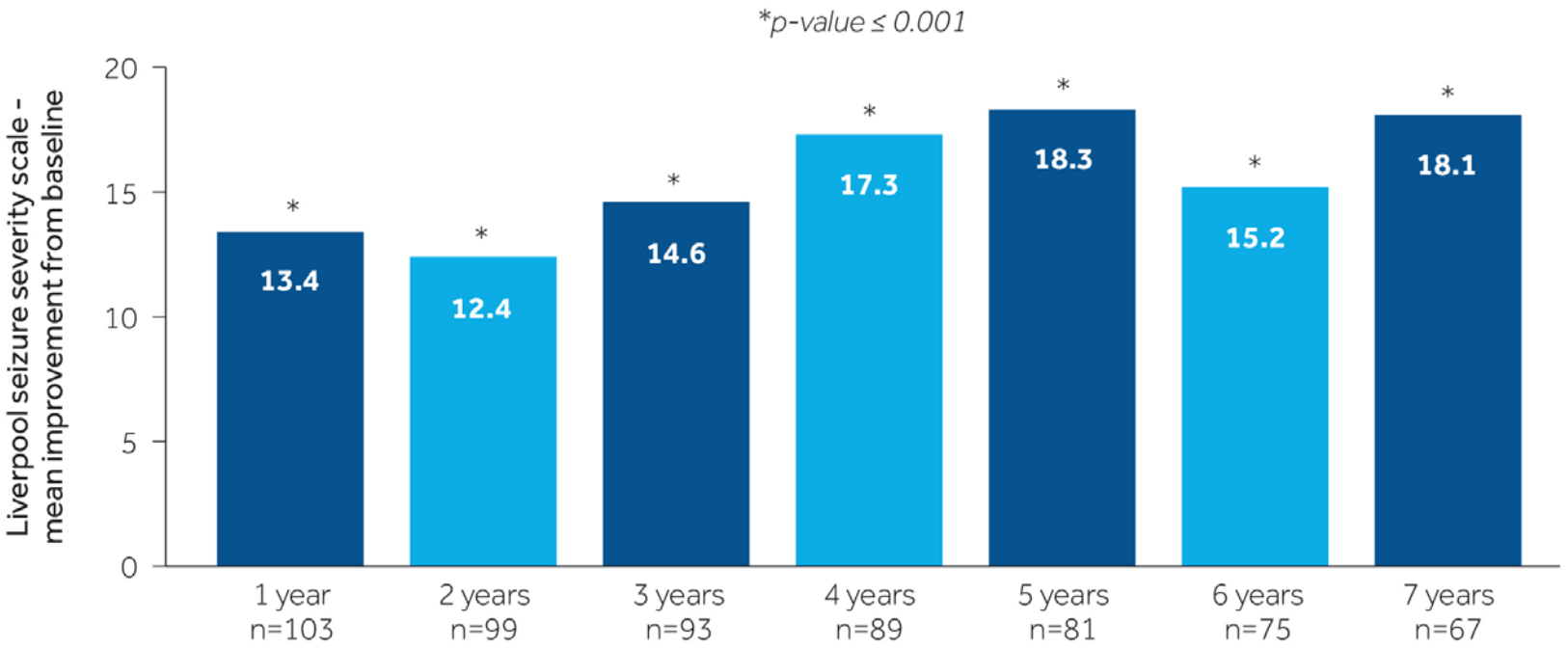
LIVERPOOL SEIZURE SEVERITY SCALE



Liverpool Seizure Severity Scale at Years 1-7. Analysis includes all randomized subjects with LSSS scores at baseline and follow up. Statistically significant improvements from baseline were found for years 1-7 ($p<0.001$).

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MOST SEVERE SEIZURES

Time period	n	Median	25th percentile	75th percentile	Wilcoxon p-value[a]
Year 1	74	-39.2%	-90.3%	-8.3%	<0.001
Year 2	62	-58.4%	-87.6%	-10.8%	<0.001
Year 3	55	-61.9%	-92.1%	-18.5%	<0.001
Year 4	55	-47.5%	-86.1%	-13.5%	<0.001
Year 5	42	-75.4%	-100.0%	-42.4%	<0.001
Year 6	44	-63.7%	-91.5%	-14.7%	0.005
Year 7	30	-71.1%	-100.0%	-25.5%	<0.001

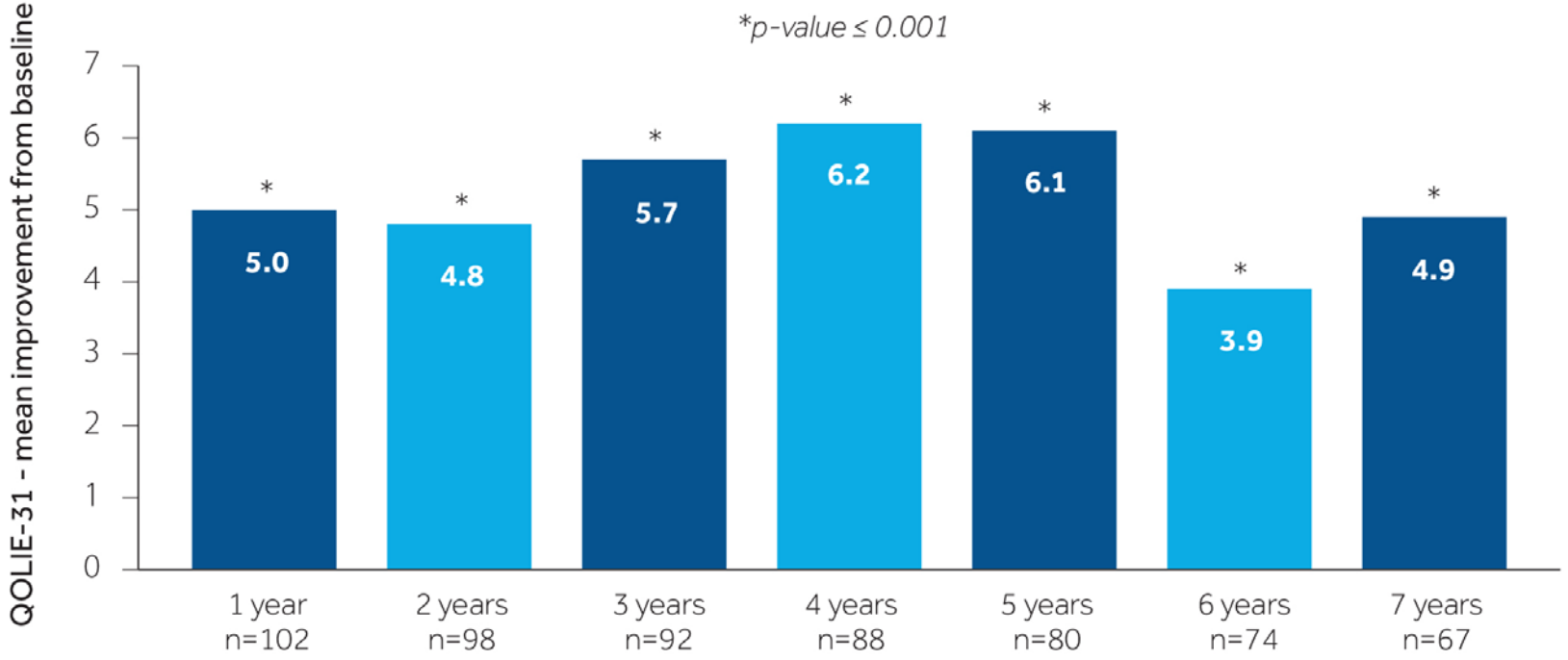
* Subjects were asked at baseline to identify which of their seizure types they considered to be the most severe.

Median seizure frequency percent change for self-reported most severe seizures at Years 1-7.
Analyses includes all seizure types prospectively identified by patients to be most severe.

QUALITY OF LIFE

QOLIE-31 SCORES

84% PATIENT SATISFACTION RATE AFTER 7 YEARS
(54 out of 64 patients)



Quality of Life in Epilepsy-31 at Years 1-7. Analysis includes all randomized subjects with QOLIE-31 scores at baseline and follow up. Statistically significant improvements from baseline were found for years 1-7 ($p<0.001$).

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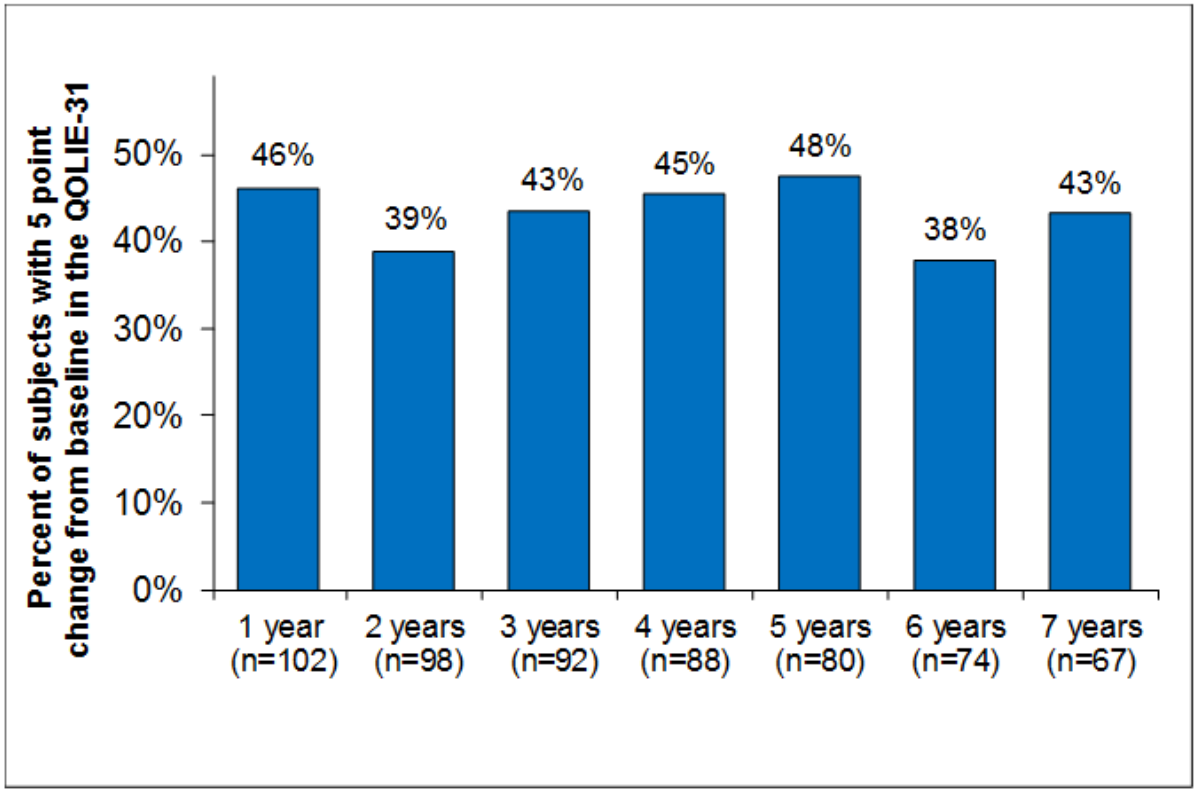
QUALITY OF LIFE

QOLIE-31 – RESPONDER RATE[1]



Responder rate. The percentage of subjects with at least a 5-point change in QOLIE-31 score was 46% at Year 1 and 43% at Year 7.

[1] A 5-point change in QOLIE-31 score has been estimated to be clinically meaningful.
Borghs S, de la Loge C, Cramer JA. Defining minimally important change in QOLIE-31 scores: estimates from three placebo-controlled lacosamide trials in patients with partial-onset seizures. Epilepsy Behav 2012;23:230-234.

SAFETY RESULTS

SAFETY OUTCOME MEASURES

- Adverse events
- Neuropsychological testing
- Sudden unexpected death in epilepsy (SUDEP)

DEVICE-RELATED SERIOUS ADVERSE EVENTS

- Device-related SAE rate was 34.5% (32.7% at 7 years)
- Most occurred during the first few months after implant
  - Rate in the first year after implant was 25.5%
- Most frequent SAEs
  - Implant site infection (10.9%)
  - Leads not in target (8.2%)
  - All others occurred in 1.8% or fewer subjects

INTRACRANIAL HEMORRHAGE

- Eight intracranial hemorrhage events were reported in 8 of the 110 implanted subjects (7.3%). Six of the 8 events were device-related (5.5%).
- Of the 8 intracranial hemorrhage events, there was one SAE resulting in clinical manifestations reported in 1 subject (0.9%). This event occurred after 2 "seizure related" falls during the Long Term Follow-up. Surgical intervention was not needed.
- Seven non-serious adverse events related to intracranial hemorrhage were reported in 7 subjects. None of these events resulted in clinical manifestations.
- No intracranial hemorrhage SAEs observed after implantation or revision of the DBS system.

SERIOUS DEVICE-RELATED INFECTION

- 12 subjects (10.9%) reported 13 serious adverse events of implant site infection
  - SAEs of implant site infection occurred at the neurostimulator pocket (6), lead-extension tract (5), and burr hole site (2). None of the infections were in the brain parenchyma.

- Nine subjects (8.2%) required partial or complete system explant. The device components were subsequently replaced in 3 of the 9 explanted subjects.

DEVICE-RELATED ADVERSE EVENTS

Adverse Event	Rate, 7-Year (% Subjects with Event) *(n=110 years=611)*	Rate, Total Post-implant (% Subjects with Event) *(n=110 years=713)*
Implant site pain	30.9%	31.8%
Paraesthesia	23.6%	23.6%
Therapeutic product ineffective	12.7%	14.5%
Implant site infection	12.7%	13.6%
Sensory disturbance	9.1%	9.1%
Lead(s) not within target	8.2%	8.2%
Implant site inflammation	7.3%	8.2%
Memory impairment	7.3%	7.3%
Post procedural pain	6.4%	6.4%
Dizziness	6.4%	6.4%
Neurostimulator migration	5.5%	5.5%
Postoperative fever	4.5%	5.5%
Extension fracture	4.5%	5.5%

- All other device-related events had a total rate of <5%.

NEUROPSYCHOLOGICAL OUTCOMES

- Mild impairment at baseline
  - Including verbal and visual memory, and verbal fluency
  - Aspects of executive functioning, such as cognitive flexibility
- No statistically significant differences between Active and Control
- Improvements in neuropsychological testing observed Year 1 through 7
  - Most improvement seen in visual attention, executive function, and subjective cognitive function.
- None of the domains on the neuropsychological tests showed a consistent worsening during follow-up.

DEPRESSION EVENTS

- Depression*: 39.1% (37.3% in 7 years)
  - Depression events were reported by 43 subjects (1 subject with SAE)
  - 3 events in 3 subjects were device-related (none considered serious).
  - All 3 of the device-related events resolved, in an average of 61 days.
  - 1 SAE was reported (blinded phase) in one subject with a history of depression.
  - Of the 43 subjects, 65% had a history of depression.

	Change at year 7		
Test	N	mean ± std	p-value
POMS Depression (T)	66	0.1 ± 11.6	0.964

* During the Blinded phase, depression was reported in a significantly higher percentage of subjects in the active group as compared to the control group.

SUICIDALITY

- Suicidality: 10.9% (total post implant)
  - Suicidality events were reported by 12 subjects (7 subjects with SAEs)
  - 1 completed suicide, not device-related
  - 6 of 7 subjects with SAE had a medical history of depression or suicide attempt
  - None considered device-related by the investigator

MEMORY IMPAIRMENT

- Memory impairment*: 30.9% (30.0% in 7 years)
  - Memory impairment events were reported by 34 subjects (none were serious)
  - Of the 34 subjects, 38% had a history of memory impairment
  - Neuropsychological test results remained stable through 7 years, including tests for cognition and mood.

	Change at year 7		
Test	N	mean ± std	p-value
Verbal memory			
CVLT Trials 1-5 Total (T)	66	0.2 ± 10.9	0.758
CVLT Long Delay Free Recall (z)	66	0.2 ± 1.2	0.347
Visuospatial memory			
BVMT-R Total Recall (T)	66	2.9 ± 10.1	0.012
BVMT-R Delayed Recall (T)	66	0.4 ± 12.3	0.624

* During the Blinded phase, memory impairment was reported in a significantly higher percentage of subjects in the active group as compared to the control group.

STATUS EPILEPTICUS

- Status epilepticus: 7 events experienced in 7 subjects (6.4%)
  - 4 events were nonconvulsive
  - 3 events occurred in subjects who were not receiving stimulation
  - 6 subjects required hospitalization (SAEs).

- 1 additional death reported after the database cutoff was attributed to status epilepticus.

DEATHS/SUDEP

- There were 8 deaths in the study, with no death directly attributed by the investigator to the implant or therapy (none device related).
- Four deaths were attributed to definite (2 subjects), probable (1), or possible (1: drowning) SUDEP.
- Non-SUDEP deaths were attributed to completed suicide (1), cardiorespiratory arrest (1), liver cancer (1), and status epilepticus (1).

DEATHS/SUDEP

Table 21. Sudden unexplained death in epilepsy rate

Source of Data	# of SUDEP[a]	# of device years	SUDEP rate/ 1000 years	95% Poisson Confidence Interval
SANTÉ	2	713 years	2.8 /1000 years	[0.34, 10.13]
Pilot Follow-up[b]	0	76 years	0 /1000 years	[0, 48.54]
Total	2	789 years	2.5 /1000 years	[0.31, 9.16]

[a] One probable SUDEP occurred during the Baseline phase prior to device implant and is not included.

[b] Combined data from 3 pilot centers participating in the Brain Stimulation for Epilepsy Long Term Follow-up study and 2 pilot centers not participating in the follow-up study.

- SUDEP rates inclusive of definite or probable SUDEP determinations for the SANTÉ study and for the subjects who participated in the pilot studies.
- Benchmark - published SUDEP rate for epilepsy surgery candidates: 9.3/1000 patient years [1]

[1] Dasheiff RM. Sudden unexpected death in epilepsy: a series from an epilepsy surgery program and speculation on the relationship to sudden cardiac death. J Clin Neurophysiol 1991;8(2):216-222.

STIMULATION PARAMETERS AND NEUROSTIMULATOR BATTERY LIFE

Parameter	Year	n	25th percentile	Median	75th percentile
Amplitude (V)	2	97	5.0	7.2	7.5
	3	93	5.0	7.5	7.5
	4	87	5.5	7.5	7.5
	5	79	5.0	7.5	7.5
	6	74	5.6	7.5	7.5
	7	62	6.0	7.5	7.5
Pulse width (µs)	2-4, 6	--	90	90	90
	5,7	--	90	90	120
Rate (Hz)	2	99	145	145	185
	3	93	145	145	185
	4	87	145	145	185
	5	79	145	145	185
	6	74	145	147.5	185
	7	62	145	145	185
Cycling on interval (min)	All	--	1	1	1
Cycling off interval (min)	All	--	2	3	5

- SANTE study patients were implanted with Kinetra
- Half of the subjects needed their first battery replacement after an average of 35.4 months (3.0 years)

CONCLUSIONS

- At 7 years, DBS of the ANT is well-tolerated, is associated with significant and sustained seizure reduction, and improves quality of life in a refractory patient population.

MORE REGISTRY

Study overview and status updates

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MORE REGISTRY – DBS FOR EPILEPSY
INTRODUCTION

The Medtronic Registry for Epilepsy (MORE; Medtronic Inc.) is a post-market, open label, observational study evaluating the long-term effectiveness, safety, and performance of deep brain stimulation (DBS) of the anterior nucleus of thalamus (ANT) for the treatment of refractory epilepsy.

MORE REGISTRY – DBS FOR EPILEPSY
DESIGN

Study Phase : Follow-up (recruitment closed)

Business Objective
Evaluate the long-term effectiveness, safety and performance of DBS for refractory epilepsy

Study Type
Post Market - 200 patients (prospective + retrospective) to ensure 150 evaluable patients

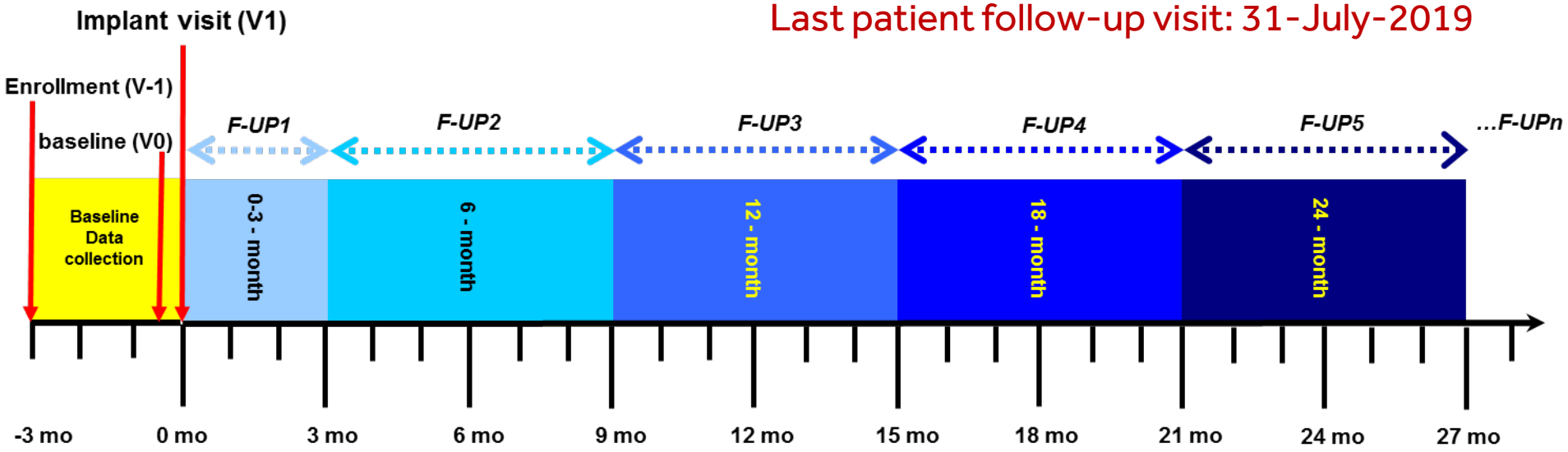
Study Endpoints

- Primary Endpoint
  - Evaluate the change in seizure rate from baseline over 2 years following DBS implant.

- Secondary Endpoint
  - Adverse events/safety, seizure type and severity, demographics, co-treatments, QOL, changes in depression score over time

- Exploratory Endpoints
  - Health care resources assessment
  - Implant technique characterization and device/feature utilization
  - Predictive factors of the response level of DBS therapy
  - Evaluate the change in seizure rate from baseline over 5 years following DBS implant

MORE REGISTRY – DBS FOR EPILEPSY
DESIGN



Last patient follow-up visit: 31-July-2019

Figure: The above scheme represents a typical visit window.

- **Baseline data collection: From enrollment visit (V-1) to baseline visit (V0)**
- **After implant, patient is followed every 6 months, according to the local standard of care.**
- **Up to 5 follow-up visits collected and compensated over a period of the first two years.**
- **Up to 10 follow-up visits in total collected and compensated over a period of four years (estimated total duration of the registry).**

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ESSENTIAL DATA FOR PRIMARY OBJECTIVES

- **Seizure diary**
  - 2 full consecutive calendar months at baseline
  - All seizure data following the implant

- **Date of implant and neurostimulator serial number**

- **Images (pre and post operative anonymized images)**
  - Reviewed by Medtronic (Frans Gielen)
  - Reviewed by External reviewer (Prof Mai, Düsseldorf/Germany)

- **All Programming data (to be uploaded online into Neuromodulation Programmer Upload - NPU)**

MORE REGISTRY – DBS FOR EPILEPSY

Study status (country and final enrollment)

City	Principal Investigator	Enrolled patients
Tampere	Dr. Peltola	13 / 15
Heeze	Prof. Boon	24 / 3
Budapest	Dr. Eross	10 / 8
Lisbon	Prof. Ferreira	10 / 5
Zwolle	Dr. Ardesch	10 / 1
Pécs	Prof. Janszky	7 / 3
Munich	Prof. Noachtar	7 / 2
Freiburg	Prof. Schulze-Bonhage	3 / 6
Vienna	Dr. Pataraia	7 / 1
Leuven	Prof. Theys	5 / 1
Tübingen	Dr. Rona	0 / 6
Gent	Prof. Boon	2 / 3
Tyumen	Prof. Sufianov	5 / 0
Porto	Prof. Vaz	4 / 1

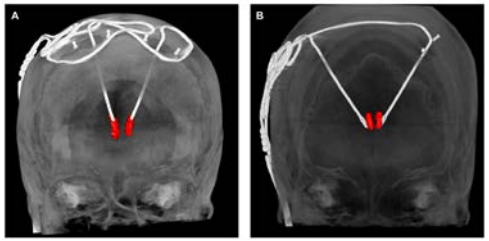
City	Principal Investigator	Enrolled patients
Bonn	Prof. Elger	5 / 0
London	Dr. Burneo	4 / 0
Heemstede	Dr. Zwemmer	4 / 0
Lublin	Dr. Gawlowicz	2 / 2
Ancona	Prof. Scerrati	2 / 1
Krakow	Dr. Bosak	1 / 2
Udine	Dr. Eleopra	0 / 1
Uppsala	Dr. Kumlien	1 / 1
Kiel	Dr. Laufs	0 / 1
Bristol	Dr. Faulkner	0 / 1
Umea	Prof. Blomstedt	1 / 0

Enrollment per site is indicating the number of prospective (in red) and retrospective patient **(in black)**

The final distribution (enrollment closed on 30 Apr 2017) is **127** / **64**

MORE REGISTRY – DBS FOR EPILEPSY

Overview on Study Status - Publication



- Neurosurgery manuscript published by « Neurosurgery » journal on 15 Mar 2018
- Public and free access on Pubmed

NEUROSURGERY
THE REGISTER OF THE NEUROSURGICAL MEME

CONGRESS OF NEUROLOGICAL SURGEONS
C N S

- **The Surgical Approach to the Anterior Nucleus of Thalamus in Patients With Refractory Epilepsy: Experience from the International Multicenter Registry (MORE).**
- Neurosurgery. 2018 Mar 15. doi: 10.1093/neuros/nyy023. [Epub ahead of print]

BRIEF STATEMENT: MEDTRONIC DBS THERAPY FOR EPILEPSY

- **Medtronic DBS Therapy for Epilepsy: Product labeling must be reviewed prior to use for detailed disclosure of risks**.

- **Indications:** Bilateral stimulation of the anterior nucleus of the thalamus (ANT) using the Medtronic DBS System for Epilepsy is indicated as an adjunctive therapy for reducing the frequency of seizures in individuals 18 years of age or older diagnosed with epilepsy characterized by partial-onset seizures, with or without secondary generalization, that are refractory to three or more antiepileptic medications.

- The Medtronic DBS System for Epilepsy has demonstrated safety and effectiveness for patients who average six or more seizures per month over the three most recent months prior to implant of the DBS system (with no more than 30 days between seizures). The Medtronic DBS System for Epilepsy has not been evaluated in patients with less frequent seizures.

- **Contraindications:** Medtronic DBS Therapy is contraindicated for patients who are unable to properly operate the neurostimulator. The following procedures are contraindicated for patients with DBS systems: diathermy (e.g., shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy), which can cause neurostimulation system or tissue damage and can result in severe injury or death; Transcranial Magnetic Stimulation (TMS); and certain MRI procedures using a full body transmit radio-frequency (RF) coil, a receive-only head coil, or a head transmit coil that extends over the chest area if the patient has an implanted Soletra™ Model 7426 Neurostimulator, Kinetra™ Model 7428 Neurostimulator, Activa™ SC Model 37602 Neurostimulator, or Model 64001 or 64002 pocket adaptor.

- **Warnings and Precautions:** There is a potential risk of brain tissue damage using stimulation parameter settings of high amplitudes and wide pulse widths. Extreme care should be used with lead implantation in patients with a heightened risk of intracranial hemorrhage. Sources of electromagnetic interference (EMI) may cause device damage or patient injury. Theft detectors and security screening devices may cause stimulation to switch ON or OFF and may cause some patients to experience a momentary increase in perceived stimulation. The DBS System may be affected by or adversely affect medical equipment such as cardiac pacemakers or therapies, cardioverter/defibrillators, external defibrillators, ultrasonic equipment, electrocautery, or radiation therapy. MRI conditions that may cause excessive heating at the lead electrodes which can result in serious injury, including coma, paralysis, or death, or that may cause device damage, include: neurostimulator implant location other than pectoral and abdominal regions; unapproved MRI parameters; partial system explants ("abandoned systems"); misidentification of neurostimulator model numbers; and broken conductor wires (in the lead, extension or pocket adaptor). The safety of electroconvulsive therapy (ECT) in patients receiving DBS Therapy has not been established. Tunneling the extension too superficially or too deeply may result in nerve or vascular injury, or tunneling through unintended anatomy. The lead-extension connector should not be placed in the soft tissues of the neck due to an increased incidence of lead fracture. Cessation, reduction, or initiation of stimulation may potentially lead to an increase in seizure frequency, severity, and new types of seizures. Symptoms may return with an intensity greater than was experienced prior to system implant, including the potential for status epilepticus. Loss of coordination in activities such as swimming may occur. Depression, suicidal ideations and suicide have been reported in patients receiving Medtronic DBS Therapy for Epilepsy, although no direct cause-and-effect relationship has been established. Preoperatively, assess patients for depression and carefully balance this risk with the potential clinical benefit. Postoperatively, monitor patients closely for new or changing symptoms of depression and manage these symptoms appropriately. Patients should be monitored for memory impairment. Memory impairment has been reported in patients receiving Medtronic DBS Therapy for Epilepsy, although no direct cause and effect relationship has been established. The consequences of failing to monitor patients are unknown. When stimulation is adjusted, monitor patients for new or increased seizures, tingling sensation, change in mood, or confusion.

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BRIEF STATEMENT: MEDTRONIC DBS THERAPY FOR EPILEPSY

- **Adverse Events**:

- Adverse events related to the therapy, device, or procedure can include intracranial hemorrhage, cerebral infarction, CSF leak, pneumocephalus, seizures, surgical site complications (including pain, infection, dehiscence, erosion, seroma, and hematoma), meningitis, encephalitis, brain abscess, cerebral edema, aseptic cyst formation, device complications (including lead fracture and device migration) that may require revision or explant, extension fibrosis (tightening or bowstringing), new or exacerbation of neurological symptoms (including vision disorders, speech and swallowing disorders, motor coordination and balance disorders, sensory disturbances, cognitive impairment, and sleep disorders), psychiatric and behavioral disorders (including psychosis and abnormal thinking), cough, shocking or jolting sensation, ineffective therapy and weight gain or loss.

- The safety and effectiveness of this therapy has not been established for patients without partial-onset seizures, patients who are pregnant or nursing, patients under the age of 18 years, patients with coagulopathies, and patients older than 65 years.

- USA Rx Only Rev 06/18