External Responsive Neurostimulation (NeuroPace)

Cranially placed neurostimulator connected to one or two leads placed at seizure focus.

First closed loop responsive brain stimulator.
Typical patient receives 5 minutes of stimulation per day.
RNS Indication (2013)

“… as an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures who have undergone diagnostic testing that localized no more than 2 epileptogenic foci, are refractory to 2 or more antiepileptic medications, and currently have frequent and disabling seizures. The RNS System has demonstrated safety and effectiveness in patients who average 3 or more disabling seizures per month over the three most recent months (with no month with fewer than 2 seizures), and has not been evaluated in patients with less frequent seizures.”

FDA PMA Letter Nov. 14, 2013
The RNS System

- Retrieves data from neurostimulator
- Programs detection and stimulation settings specific to each patient
The RNS System

- Programmer transmits data to interactive web-based database for storage and physician remote access.
The RNS System

- Patient retrieves data from neurostimulator and sends to PDMS for physician review
RNS: Typical ECoG Patterns Detected

Figure 10: Typical electrographic patterns detected by the Neurostimulator

Spike Pattern

Frequency Specific Patterns

Theta

Beta

Gamma

Electrodecremental Pattern

FDA Hearing 2-22-2013
RNS System Pivotal Clinical Investigation: Study Design

Enrollment
Baseline Period (Min 12 weeks, Max 60 weeks)
Blinded Evaluation Period (12 weeks)
Open Label Evaluation Period (84 weeks)

Therapy ON
Week 4

Therapy OFF
Week 8

Post-operative Stabilization Period (4 weeks)
Stimulation Optimization Period (4 weeks)
Blinded Evaluation Period (12 weeks)
Open Label Evaluation Period (84 weeks)

Assessment Protocol
Treatment Protocol

Eligibility to Implant: 28 Days Maximum

18-70 years of age
POS 3/mo
Tried > 2 AEDs
No VNS

Typical stimulation parameters (100 ms burst): 160 microsec, 200 Hz, 1.5-3.0 mA
Morrell MJ et al. Neurology, 2011; 77; 1295-1304
Stimulation Parameters

• Initial Programming:
  - 200 Hz, 160 microsec pulse width,
    100 msec burst duration, start at 0.5 mA

• At 2 year Open-Label:
  - < 4.0 mA in 53.8%
  - 4.0 – 7.9 mA in 34.8%
  - 8 – 11.9 mA in 8.7%
  - 12 mA (max output) in 2.7%

• Total Duration of Stimulation:
  - 5.9 min/day (average) (median 4.7 min/d)
    (75% < 7.3 min/d)

Seizure Onset Location

Mesial Temporal (N=95)
- Right 9%, n=9
- Left 18%, n=17
- Bilateral 73%, n=69

Neocortical (N=96)
- Frontal 33%, n=32
- Temporal 55%, n=53
- Occipital 2%, n=2
- Parietal 9%, n=9

These subjects were not considered to be candidates for epilepsy surgery.
Responsive Neurostimulation: Efficacy

Morrell MJ. Neurology, 2011;77: 1295-1304
Responsive Neurostimulation: Efficacy

Morrell MJ. Neurology, 2011;77: 1295-1304

32.1% Difference (p=0.008)
RNS™ System (NeuroPace)

Combined Studies: Feasibility, Pivotal & Long-Term Treatment Studies

FDA Hearing 2-22-2013
RNS Long-Term Efficacy: Open-Label Extension (Most Recent 3 Months)

9% (20/183) seizure free
54% (99/183) ≥ 50% decrease in seizure frequency (Responder)

7% (13/183) > 50% increase in seizure frequency

Figure includes all patients with at least 3 months of data in the Open Label Period, N=183.

FDA Hearing 2-22-2013
Heck CH et al. Epilepsia, 2014; 55(3); 432-441.
Pre-specified Subset Analyses (Randomization Characteristics)

<table>
<thead>
<tr>
<th></th>
<th>Seizure Onset Zone</th>
<th>Number of Seizure Foci</th>
<th>Prior Epilepsy Surgery</th>
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</thead>
<tbody>
<tr>
<td>MTL N=95, Other N=96</td>
<td><img src="MTL.png" alt="Bar Chart" /></td>
<td><img src="Seizure.png" alt="Bar Chart" /></td>
<td><img src="Prior.png" alt="Bar Chart" /></td>
</tr>
<tr>
<td>One N=85, Two N=106</td>
<td></td>
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<tr>
<td>Yes N=62, No N=129</td>
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</tbody>
</table>

% Reduction in Seizure Frequency (GEE)

- MTL: Treatment (50%), Sham (25%)
- Other: Treatment (40%), Sham (15%)
- One: Treatment (35%), Sham (20%)
- Two: Treatment (40%), Sham (15%)
- Yes: Treatment (45%), Sham (20%)
- No: Treatment (30%), Sham (15%)
RNS™ System (NeuroPace)

RESPONDERS:

- Overall settings: 200 Hz, 3.5 mA, 160 microsec
- Neocortical epilepsy: 100 Hz, 5.0 mA
- Temporal epilepsy: 200 Hz, 3.0 mA

Morrell MJ et al. Neurology, 2011; 77; 1295-1304
RNS™ System (NeuroPace)

• Quality of Life

  - QOLIE-89 improved over 2 years (p-0.016)
  - Improved scores (P<0.005) for specific scales: language, memory, attention/concentration, work/driving/social function, health discouragement, seizure worry.
  - Neuropsychology showed improvement in verbal functioning, visuospatial ability and memory at 1 and 2 years (p<0.05).

Morrell MJ et al, Neurology, 2011; 77: 1295-1304
RNS™ System (NeuroPace)

Adverse Events

• Device-Related (Thru 1 year)
  - 2.6% paraesthesias
  - 15.7% implant site pain
  - 3.1% implant site infection
  - 2.6% (N=5) lead damage, 3.7% (N=7) lead revision

• Increased seizure frequency (2.6-3.1%)

• Depression (No difference treatment vs. sham group)

• Memory impairment (No difference treatment vs. sham group)

Morrell MJ et al, Neurology, 2011; 77: 1295-1304
Complications

- 9 (4.7%) clinical hemorrhages (6/9 post-operative, 3 evacuated epidural hematomas)
- N=10 (5.2%) infections (4 explanted)
- No implant related deaths
  (4 SUDEP, 1 suicide, 1 lymphoma)

Morrell MJ et al, Neurology, 2011; 77: 1295-1304
Contraindications

- MR Imaging
- Diathermy procedures anywhere on the body.
- Electroconvulsive Therapy (ECT)
- Transcranial Magnetic Stimulation (TMS)


