

## Figure S1.

Study flow chart of the registered patients. The safety analysis population, intent to treat population, and efficacy analysis population included 385, 370, and 362 patients, respectively. \*a case in which VNS was removed.

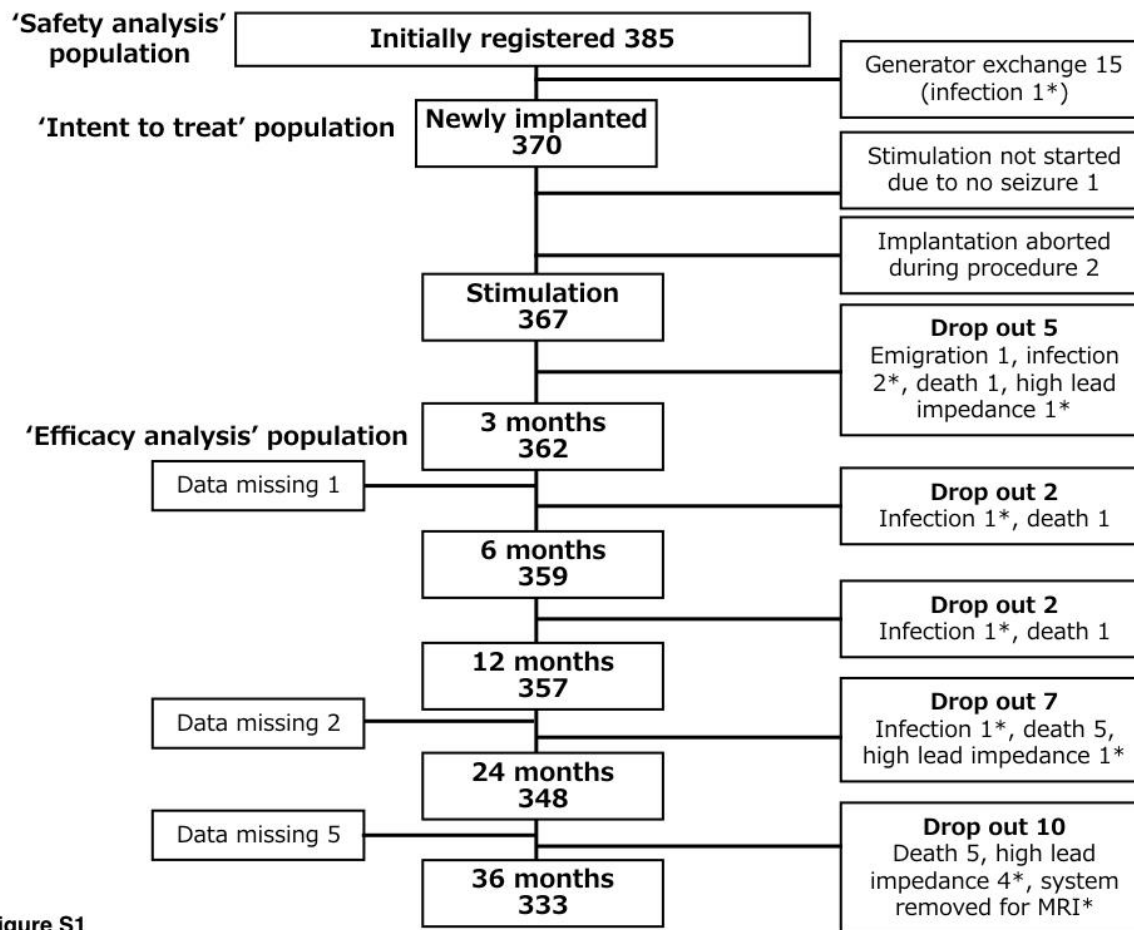


Figure S1

**Table S1.** Changes in seizure frequency.

|            |                    | Overall                  | <12 years old           | ≥ 12 years old           | Focal seizure            | Generalized seizure       |
|------------|--------------------|--------------------------|-------------------------|--------------------------|--------------------------|---------------------------|
| 3 months   | N                  | 356                      | 76                      | 280                      | 220                      | 265                       |
|            | SC mean (SD)       | -3.19% (163.47%)         | -12.38% (89.44%)        | -0.70% (178.38%)         | -8.97% (159.82%)         | -8.15% (208.86%)          |
|            | SC median (95% CI) | -25.00% (-100.0~1400.0%) | -8.97% (-100.0~500.0%)  | -27.92% (-100.0~1400.0%) | -30.00% (-100.0~1400.0%) | -36.67% (-100.0~2507.1%)  |
|            | P                  | p<0.0001                 | p=0.0015                | p<0.0001                 | p<0.0001                 | p<0.0001                  |
| 6 months   | N                  | 354                      | 75                      | 279                      | 221                      | 262                       |
|            | SC mean (SD)       | -17.35% (128.59%)        | -21.29% (87.81%)        | -16.29% (137.62%)        | -25.29% (116.45%)        | 11.75% (653.77%)          |
|            | SC median (95% CI) | -40.95% (-100.0~1400.0%) | -40.23% (-100.0~450.0%) | -41.18% (-100.0~1400.0%) | -46.67% (-100.0~1116.7%) | -50.68% (-100.0~10328.6%) |
|            | P                  | p<0.0001                 | p=0.0002                | p<0.0001                 | p<0.0001                 | p<0.0001                  |
| 12 months  | N                  | 351                      | 75                      | 276                      | 218                      | 260                       |
|            | SC mean (SD)       | -25.22% (127.44%)        | -35.71% (69.31%)        | -22.37% (139.07%)        | -22.13% (136.90%)        | -40.14% (131.13%)         |
|            | SC median (95% CI) | -53.33% (-100.0~1400.0%) | -50.00% (-100.0~300.0%) | -53.85% (-100.0~1400.0%) | -51.67% (-100.0~1116.7%) | -69.85% (-100.0~1700.0%)  |
|            | P                  | p<0.0001                 | p<0.0001                | p<0.0001                 | p<0.0001                 | p<0.0001                  |
| 24 months  | N                  | 339                      | 71                      | 268                      | 213                      | 250                       |
|            | SC mean (SD)       | -28.37% (145.96%)        | -24.52% (93.23%)        | -29.38% (157.12%)        | -28.76% (147.87%)        | -42.56% (143.59%)         |
|            | SC median (95% CI) | -60.00% (-100.0~1475.0%) | -50.00% (-100.0~449.5%) | -61.91% (-100.0~1475.0%) | -65.00% (-100.0~1400.0%) | -75.17% (-100.0~1700.0%)  |
|            | P                  | p<0.0001                 | p=0.0003                | p<0.0001                 | p<0.0001                 | p<0.0001                  |
| 36 months  | N                  | 330                      | 72                      | 258                      | 207                      | 245                       |
|            | SC mean (SD)       | -27.16% (141.75%)        | -34.31% (93.91%)        | -25.17% (152.53%)        | -18.75% (185.75%)        | -43.39% (140.59%)         |
|            | SC median (95% CI) | -66.24% (-100.0~1400.0%) | -60.00% (-100.0~493.0%) | -66.67% (-100.0~1400.0%) | -66.67% (-100.0~1400.0%) | -83.33% (-100.0~1700.0%)  |
|            | P                  | p<0.0001                 | p<0.0001                | p<0.0001                 | p<0.0001                 | p<0.0001                  |
| Last visit | N                  | 360                      | 77                      | 283                      | 223                      | 268                       |
|            | SC mean (SD)       | -29.33% (136.78%)        | -35.59% (91.12%)        | -27.63% (146.86%)        | -21.26% (180.17%)        | -45.13% (134.94%)         |
|            | SC median (95% CI) | -66.67% (-100.0~1400.0%) | -60.00% (-100.0~493.0%) | -66.67% (-100.0~1400.0%) | -66.67% (-100.0~1400.0%) | -81.43% (-100.0~1700.0%)  |
|            | P                  | p<0.0001                 | p<0.0001                | p<0.0001                 | p<0.0001                 | p<0.0001                  |

SC: seizure change; P: Wilcoxon signed rank test.

**Table S2.** Changes in seizure frequency after VNS (excluding simple partial seizures).

|            |                    | Overall                  | <12 years old           | ≥12 years old            | Focal seizure            | Generalized seizure       |
|------------|--------------------|--------------------------|-------------------------|--------------------------|--------------------------|---------------------------|
| 3 months   | N                  | 340                      | 73                      | 267                      | 181                      | 265                       |
|            | SC mean (SD)       | -9.55% (167.91%)         | -26.98% (58.88%)        | -4.79% (186.78%)         | -14.87% (161.28%)        | -8.15% (208.86%)          |
|            | SC median (95% CI) | -29.29% (-100.0~1700.0%) | -20.00% (-100.0~200.0%) | -30.46% (-100.0~1700.0%) | -33.33% (-100.0~1400.0%) | -36.67% (-100.0~2507.1%)  |
|            | P                  | p<0.0001                 | p<0.0001                | p<0.0001                 | p<0.0001                 | p<0.0001                  |
| 6 months   | N                  | 338                      | 72                      | 266                      | 181                      | 262                       |
|            | SC mean (SD)       | -20.90% (139.73%)        | -35.18% (66.12%)        | -17.04% (153.59%)        | -24.37% (125.13%)        | 11.75% (653.77%)          |
|            | SC median (95% CI) | -49.35% (-100.0~1700.0%) | -51.67% (-100.0~250.0%) | -45.01% (-100.0~1700.0%) | -50.00% (-100.0~1116.7%) | -50.68% (-100.0~10328.6%) |
|            | P                  | p<0.0001                 | p<0.0001                | p<0.0001                 | p<0.0001                 | p<0.0001                  |
| 12 months  | N                  | 335                      | 72                      | 263                      | 177                      | 260                       |
|            | SC mean (SD)       | -28.97% (136.88%)        | -47.55% (54.22%)        | -23.89% (151.55%)        | -30.01% (123.53%)        | -40.14% (131.13%)         |
|            | SC median (95% CI) | -54.58% (-100.0~1700.0%) | -60.00% (-100.0~250.0%) | -53.33% (-100.0~1700.0%) | -57.14% (-100.0~1116.7%) | -69.85% (-100.0~1700.0%)  |
|            | P                  | p<0.0001                 | p<0.0001                | p<0.0001                 | p<0.0001                 | p<0.0001                  |
| 24 months  | N                  | 323                      | 68                      | 255                      | 173                      | 250                       |
|            | SC mean (SD)       | -30.57% (163.13%)        | -30.50% (131.34%)       | -30.58% (170.83%)        | -36.59% (144.32%)        | -42.56% (143.59%)         |
|            | SC median (95% CI) | -62.50% (-100.0~1700.0%) | -65.83% (-100.0~903.8%) | -60.27% (-100.0~1700.0%) | -65.00% (-100.0~1400.0%) | -75.17% (-100.0~1700.0%)  |
|            | P                  | p<0.0001                 | p<0.0001                | p<0.0001                 | p<0.0001                 | p<0.0001                  |
| 36 months  | N                  | 314                      | 69                      | 245                      | 166                      | 245                       |
|            | SC mean (SD)       | -31.89% (149.86%)        | -53.32% (52.22%)        | -25.85% (166.99%)        | -35.87% (128.42%)        | -43.39% (140.59%)         |
|            | SC median (95% CI) | -66.67% (-100.0~1700.0%) | -66.67% (-100.0~183.3%) | -66.67% (-100.0~1700.0%) | -68.11% (-100.0~1025.0%) | -83.33% (-100.0~1700.0%)  |
|            | P                  | p<0.0001                 | p<0.0001                | p<0.0001                 | p<0.0001                 | p<0.0001                  |
| Last visit | N                  | 344                      | 74                      | 270                      | 182                      | 268                       |
|            | SC mean (SD)       | -34.51% (143.83%)        | -53.36% (50.80%)        | -29.35% (159.85%)        | -38.92% (123.66%)        | -45.13% (134.94%)         |
|            | SC median (95% CI) | -67.06% (-100.0~1700.0%) | -65.00% (-100.0~183.3%) | -67.45% (-100.0~1700.0%) | -73.21% (-100.0~1025.0%) | -81.43% (-100.0~1700.0%)  |
|            | P                  | p<0.0001                 | p<0.0001                | p<0.0001                 | p<0.0001                 | p<0.0001                  |

SC: Seizure change (excluding simple partial seizures); P: Wilcoxon signed rank test.

**Table S3.** Mean and median changes in seizure frequency and responder rate with vs without prior epilepsy surgery.

| Duration of VNS | Prior craniotomy | Number of patients | Change in seizure change (%) |             |        | Seizure change +/- prior craniotomy p value** | Responders rate (≥50% seizure reduction) | Responder rate +/- prior craniotomy p value*** |
|-----------------|------------------|--------------------|------------------------------|-------------|--------|-----------------------------------------------|------------------------------------------|------------------------------------------------|
|                 |                  |                    | Mean                         | 95% CI      | Median |                                               |                                          |                                                |
| 3 months        | +                | 180                | 0.0                          | -21.4-21.3  | -20.0  | 0.116                                         | 35.6%                                    | 0.385                                          |
|                 | -                | 182                | -6.2                         | -32.8-20.4  | -30.0  |                                               | 41.2%                                    |                                                |
| 6 months        | +                | 178                | -9.6                         | -31.2-12.0  | -40.0  | 0.202                                         | 44.9%                                    | 0.671                                          |
|                 | -                | 181                | -24.9                        | -41.2--8.7  | -42.9  |                                               | 47.5%                                    |                                                |
| 12 months       | +                | 177                | -13.8                        | -35.4--7.8  | -50.0  | 0.033                                         | 52.5%                                    | 0.283                                          |
|                 | -                | 180                | -36.4                        | -52.3--20.5 | -65.3  |                                               | 58.3%                                    |                                                |
| 24 months       | +                | 172                | -13.4                        | -41.5--14.7 | -53.3  | 0.035                                         | 53.5%                                    | 0.124                                          |
|                 | -                | 176                | -42.9                        | -57.0--28.8 | -66.7  |                                               | 61.9%                                    |                                                |
| 36 months       | +                | 165                | -11.1                        | -37.9--15.6 | -53.2  | 0.010                                         | 52.7%                                    | 0.033                                          |
|                 | -                | 168                | -43.0                        | -58.2--27.7 | -71.0  |                                               | 64.3%                                    |                                                |
| Last visit      | +                | 179                | -13.6                        | -38.3--11.0 | -53.3  | 0.005                                         | 53.6%                                    | 0.018                                          |
|                 | -                | 181                | -44.9                        | -59.0--30.8 | -71.4  |                                               | 66.3%                                    |                                                |

\*Significant changes from baseline. Wilcoxon signed rank test <0.001.

\*\*Wilcoxon rank sum test.

\*\*\*Fisher's exact test.

**Table S4.** Changes in number and burden of antiepileptic drugs.

|                       |                  | VNS therapy (months) |      |      |      |      |
|-----------------------|------------------|----------------------|------|------|------|------|
|                       | Pre-implantation | 3                    | 6    | 12   | 24   | 36   |
| Median number of AEDs | 3                | 3                    | 3    | 3    | 3    | 3    |
| Median AED burden     | 2.82             | 2.91                 | 2.76 | 2.78 | 2.87 | 2.90 |

AED: antiepileptic drug.

**Table S5.** Adverse events (number of patients).

|                                        | At implan-<br>tation | At the<br>start of<br>simulati-<br>on | 3<br>mo-<br>nth<br>s | 6<br>mo-<br>nth<br>s | 12<br>mo-<br>nth<br>s | 24<br>mo-<br>nth<br>s | 36<br>mo-<br>nth<br>s | Anyti-<br>me<br>during<br>follow-<br>up |
|----------------------------------------|----------------------|---------------------------------------|----------------------|----------------------|-----------------------|-----------------------|-----------------------|-----------------------------------------|
| Voice change/hoarseness                | 17                   | 15                                    | 19                   | 11                   | 2                     | 7                     | 9                     | 58                                      |
| Coughing                               | 13                   | 21                                    | 5                    | 7                    | 5                     | 4                     | 3                     | 50                                      |
| High lead impedance                    | 0                    | 1                                     | 1                    | 2                    | 3                     | 3                     | 10                    | 19                                      |
| Dysphagia                              | 6                    | 4                                     | 3                    | 1                    | 0                     | 1                     | 1                     | 16                                      |
| Death                                  | 0                    | 0                                     | 1                    | 0                    | 3                     | 5                     | 5                     | 14                                      |
| Local pain                             | 4                    | 2                                     | 0                    | 2                    | 1                     | 1                     | 1                     | 11                                      |
| Local paresis                          | 0                    | 3                                     | 0                    | 2                    | 1                     | 0                     | 0                     | 6                                       |
| Local infection                        | 0                    | 1                                     | 2                    | 0                    | 2                     | 0                     | 1                     | 6                                       |
| Dyspnoea                               | 0                    | 1                                     | 0                    | 0                    | 1                     | 1                     | 1                     | 4                                       |
| Cardiac dysrhythmia                    | 3                    | 0                                     | 0                    | 0                    | 1                     | 0                     | 0                     | 4                                       |
| Seizure                                | 0                    | 3                                     | 1                    | 0                    | 0                     | 0                     | 0                     | 4                                       |
| Hiccupping                             | 0                    | 0                                     | 0                    | 1                    | 1                     | 0                     | 1                     | 3                                       |
| Bradycardia                            | 3                    | 0                                     | 0                    | 0                    | 0                     | 0                     | 0                     | 3                                       |
| Aspiration pneumonia                   | 0                    | 1                                     | 0                    | 0                    | 0                     | 0                     | 1                     | 2                                       |
| Vertigo                                | 0                    | 0                                     | 1                    | 0                    | 0                     | 1                     | 0                     | 2                                       |
| Bronchitis/lower respiratory infection | 0                    | 0                                     | 0                    | 0                    | 1                     | 0                     | 1                     | 2                                       |
| Salivation                             | 0                    | 0                                     | 1                    | 0                    | 0                     | 1                     | 0                     | 2                                       |
| Asystole                               | 1                    | 0                                     | 0                    | 0                    | 0                     | 0                     | 0                     | 1                                       |
| Discomfort                             | 1                    | 0                                     | 0                    | 0                    | 0                     | 0                     | 0                     | 1                                       |
| Right femoral head fracture            | 0                    | 0                                     | 0                    | 0                    | 0                     | 0                     | 1                     | 1                                       |
| Agitation                              | 0                    | 0                                     | 0                    | 0                    | 0                     | 1                     | 0                     | 1                                       |
| Myoclony                               | 0                    | 0                                     | 0                    | 0                    | 1                     | 0                     | 0                     | 1                                       |
| Weight loss                            | 0                    | 0                                     | 0                    | 1                    | 0                     | 0                     | 0                     | 1                                       |
| Nausea                                 | 0                    | 0                                     | 0                    | 0                    | 0                     | 1                     | 0                     | 1                                       |
| Local irritation                       | 0                    | 1                                     | 0                    | 0                    | 0                     | 0                     | 0                     | 1                                       |
| Restlessness                           | 0                    | 0                                     | 1                    | 0                    | 0                     | 0                     | 0                     | 1                                       |
| Fever                                  | 1                    | 0                                     | 0                    | 0                    | 0                     | 0                     | 0                     | 1                                       |
| Chest pain                             | 0                    | 0                                     | 0                    | 1                    | 0                     | 0                     | 0                     | 1                                       |
| Belching                               | 0                    | 0                                     | 1                    | 0                    | 0                     | 0                     | 0                     | 1                                       |
| Muscle spasm                           | 0                    | 0                                     | 0                    | 0                    | 1                     | 0                     | 0                     | 1                                       |
| Incontinence                           | 0                    | 0                                     | 0                    | 0                    | 0                     | 0                     | 1                     | 1                                       |
| Violent behaviour                      | 0                    | 0                                     | 0                    | 0                    | 0                     | 1                     | 0                     | 1                                       |
| Early battery depletion                | 0                    | 0                                     | 0                    | 0                    | 1                     | 0                     | 0                     | 1                                       |
| Shortness of breath                    | 0                    | 0                                     | 0                    | 0                    | 0                     | 1                     | 0                     | 1                                       |
| Facial pallor                          | 0                    | 0                                     | 0                    | 0                    | 1                     | 0                     | 0                     | 1                                       |
| Decreased oxygen desaturation          | 0                    | 0                                     | 0                    | 1                    | 0                     | 0                     | 0                     | 1                                       |
| Dry vomiting                           | 0                    | 0                                     | 0                    | 0                    | 0                     | 1                     | 0                     | 1                                       |
| Nausea                                 | 0                    | 0                                     | 1                    | 0                    | 0                     | 0                     | 0                     | 1                                       |
| Wheezing                               | 0                    | 0                                     | 0                    | 0                    | 0                     | 1                     | 0                     | 1                                       |
| Acute pancreatitis                     | 0                    | 0                                     | 0                    | 0                    | 0                     | 1                     | 0                     | 1                                       |
| Vocal cord cordopexy (paralysis)       | 0                    | 0                                     | 0                    | 0                    | 0                     | 1                     | 0                     | 1                                       |