**Extension Study of Neural Regulation Therapy on Myocardial Function in Heart Failure**

**(ENCORE 24 months follow up)**

**Statistical Analysis Report**

**(Version 1.0)**

**08th Feb 2018**

**Protocol No.:C-03**

**Prepared by:**

**Sponsor Signature:**

I hereby declare that I have reviewed the statistical analysis report and agree to its form and content. In addition, I confirm that the outlined statistical analysis report contains all relevant information of the data analysis, performed in the document **C-03** study by the Biostatistics Department.

Represented by:

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Date

**Sponsor:**

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## Table 14.1.2.1 Summary of Subject Demographics at Baseline ITT Population (N=49)

|  | | **VNS Therapy System** | |  |
| --- | --- | --- | --- | --- |
| **Parameters** | **Statistics / Category, n (%) [1]** | **Right Sided (n=26)** | **Left Sided (n=23)** | **Overall (N=49)** |
| **Gender** |  |  |  |  |
|  | Male | 22 (84.6 %) | 20 (87.0 %) | 42 (85.7 %) |
|  | Female | 4 (15.4 %) | 3 (13.0 %) | 7 (14.3 %) |
|  |  |  |  |  |
| **Age (years)** |  |  |  |  |
|  | n | 26 | 23 | 49 |
|  | Mean | 52.4 | 49.7 | 51.1 |
|  | SD | 12.7 | 13.0 | 12.8 |
|  | Q1 | 42.0 | 42.0 | 42.0 |
|  | Median | 51.5 | 49.0 | 50.0 |
|  | Q3 | 63.0 | 60.0 | 60.0 |
|  | Range (Min.: Max.) | (30.0: 79.0) | (25.0: 80.0) | (25.0: 80.0) |
|  |  |  |  |  |
| **Ethnicity** |  |  |  |  |
|  | Hispanic or Latino | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
|  | Non-Hispanic | 26 (100.0 %) | 23 (100.0 %) | 49 (100.0 %) |
|  |  |  |  |  |
| **Race** |  |  |  |  |
|  | American Indian or Alaska Native | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
|  | Asian | 26 (100.0 %) | 23 (100.0 %) | 49 (100.0 %) |
|  | Black or African American | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
|  | Native Hawaiian or other pacific islander | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
|  | White | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
|  |  |  |  |  |
| **Subject ever smoked** |  |  |  |  |
|  | Yes | 11 (42.3 %) | 10 (43.5 %) | 21 (42.9 %) |
|  | No | 15 (57.7 %) | 13 (56.5 %) | 28 (57.1 %) |
|  |  |  |  |  |
| **Smoking Status [2]** |  |  |  |  |
|  | Current Smoker | 0 (0.00 %) | 4 (40.0 %) | 4 (19.0 %) |
|  | Former Smoker | 11 (100.0 %) | 6 (60.0 %) | 17 (81.0 %) |
|  |  |  |  |  |
| **Note:** [1] Respective column header group counts was used as denominator for percentage calculation. [2] Percentage was calculated using the counts of ‘Yes’ Category of Subjects ever smoked. | | | | |

## Table 14.1.2.2 Summary of Medical and Surgical History ITT Population (N=49)

|  | | **VNS Therapy System** | |  |
| --- | --- | --- | --- | --- |
| **Body System** | **Category, n (%) [1]** | **Right Sided (n=26)** | **Left Sided (n=23)** | **Overall (N=49)** |
| **Respiratory** | **Surgical** | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) |
|  | **Medical** |  |  |  |
|  | Current Status |  |  |  |
|  | Past | 0 (0.0 %) | 2 (8.7 %) | 2 (4.1 %) |
|  | Ongoing | 0 (0.0 %) | 1 (4.3 %) | 1 (2.0 %) |
|  | On treatment Currently |  |  |  |
|  | Yes[2] | 0 (0.0 %) | 1 (100.0 %) | 1 (100.0 %) |
|  | No | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) |
|  |  |  |  |  |
| **Cardiovascular** |  |  |  |  |
|  | **Surgical** | 26 (100.0 %) | 23 (100.0 %) | 49 (100.0 %) |
|  | **Medical** |  |  |  |
|  | Current Status |  |  |  |
|  | Past | 1 (3.8 %) | 1 (4.3 %) | 2 (4.1 %) |
|  | Ongoing | 22 (84.6 %) | 23 (100.0 %) | 45 (91.8 %) |
|  | On treatment Currently |  |  |  |
|  | Yes[2] | 22 (100.0 %) | 23 (100.0 %) | 45 (100.0 %) |
|  | No | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) |
|  |  |  |  |  |
| **Genitourinary** | **Surgical** | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) |
|  | **Medical** |  |  |  |
|  | Current Status |  |  |  |
|  | Past | 0 (0.0 %) | 1 (4.3 %) | 1 (2.0 %) |
|  | Ongoing | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) |
|  | On treatment Currently |  |  |  |
|  | Yes[2] | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) |
|  | No | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) |
|  |  |  |  |  |
| **Endocrine/Metabolic** | **Surgical** | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) |
|  | **Medical** |  |  |  |
|  | Current Status |  |  |  |
|  | Past | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) |
|  | Ongoing | 2 (7.7 %) | 3 (13.0 %) | 5 (10.2 %) |
|  | On treatment Currently |  |  |  |
|  | Yes[2] | 2 (100.0 %) | 3 (100.0 %) | 5 (100.0 %) |
|  | No | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) |
|  |  |  |  |  |
| **Head, Eyes, Ear, Nose, Throat** | **Surgical** | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) |
|  | **Medical** |  |  |  |
|  | Current Status |  |  |  |
|  | Past | 0 (0.0 %) | 1 (4.3 %) | 1 (2.0 %) |
|  | Ongoing | 1 (3.8 %) | 0 (0.0 %) | 1 (2.0 %) |
|  | On treatment Currently |  |  |  |
|  | Yes[2] | 1 (100.0 %) | 0 (0.0 %) | 1 (100.0 %) |
|  | No | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) |
|  |  |  |  |  |
| **Musculoskeletal** | **Surgical** | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) |
|  | **Medical** |  |  |  |
|  | Current Status |  |  |  |
|  | Past | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) |
|  | Ongoing | 0 (0.0 %) | 1 (4.3 %) | 1 (2.0 %) |
|  | On treatment Currently |  |  |  |
|  | Yes[2] | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) |
|  | No | 0 (0.0 %) | 1 (100.0 %) | 1 (100.0 %) |
|  |  |  |  |  |
| **Note:** [1] Respective column header group counts were used as denominator for percentage calculation. [2] Percentages were calculated using ‘Ongoing’ Counts for the Yes Category for variable on VNS therapy     (Right/Left) currently. | | | | |

## Table 14.1.2.3 Summary of Heart Failure History at Visit 1 ITT Population (N=49)

|  | | **VNS Therapy System** | |  |
| --- | --- | --- | --- | --- |
| **Diagnosis** | **Statistics/Category, n (%) [1]** | **Right Sided (n=26)** | **Left Sided (n=23)** | **Overall (N=49)** |
| **Heart Failure Etiology** |  |  |  |  |
|  | Ischemic | 23 (88.5 %) | 18 (78.3 %) | 41 (83.7 %) |
|  | Non -Ischemic | 3 (11.5 %) | 5 (21.7 %) | 8 (16.3 %) |
|  |  |  |  |  |
| **NYHA Class** |  |  |  |  |
|  | Class I | 14 (53.8 %) | 11 (47.8 %) | 25 (51.0 %) |
|  | Class II | 12 (46.2 %) | 10 (43.5 %) | 22 (44.9 %) |
|  | Class III | 0 (0.00 %) | 2 (8.7 %) | 2 (4.1 %) |
|  | Class IV | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
|  |  |  |  |  |
| **Historical Echocardiogram Measurement** |  |  |  |  |
| **LVESD (cm)** |  |  |  |  |
|  | n | 26 | 23 | 49 |
|  | Mean | 4.93 | 5.05 | 4.99 |
|  | SD | 0.748 | 0.835 | 0.784 |
|  | Q1 | 4.50 | 4.40 | 4.40 |
|  | Median | 4.90 | 5.10 | 4.90 |
|  | Q3 | 5.40 | 5.60 | 5.50 |
|  | Range (Min.: Max.) | (3.31: 6.80) | (3.50: 7.10) | (3.31: 7.10) |
|  | Not reported | 0 | 0 | 0 |
|  |  |  |  |  |
| **LVESV (ml)** |  |  |  |  |
|  | n | 26 | 23 | 49 |
|  | Mean | 118 | 121 | 119 |
|  | SD | 40.1 | 49.5 | 44.3 |
|  | Q1 | 84.0 | 85.8 | 84.0 |
|  | Median | 113 | 111 | 113 |
|  | Q3 | 145 | 145 | 145 |
|  | Range (Min.: Max.) | (57.8: 221) | (51.6: 264) | (51.6: 264) |
|  | Not reported | 0 | 0 | 0 |
|  |  |  |  |  |
| **Ejection Fraction** |  |  |  |  |
|  | n | 26 | 23 | 49 |
|  | Mean | 28.8 | 29.7 | 29.2 |
|  | SD | 7.65 | 6.98 | 7.28 |
|  | Q1 | 25.0 | 25.0 | 25.0 |
|  | Median | 30.0 | 30.0 | 30.0 |
|  | Q3 | 35.0 | 35.0 | 35.0 |
|  | Range (Min.: Max.) | (10.0: 40.0) | (10.0: 40.0) | (10.0: 40.0) |
|  | Not reported | 0 | 0 | 0 |
|  |  |  |  |  |
| **Note:** [1] Respective column header group counts were used as denominator for percentage calculation. | | | | |

## Table 14.1.2.4 Summary of Duration of HF (Years) - ITT Population (N=49)

|  | | **VNS Therapy System** | |  |
| --- | --- | --- | --- | --- |
| **Visit** | **Statistics** | **Right Sided (n=26)** | **Left Sided (n=23)** | **Overall (N=49)** |
| Baseline | Total No. of Subjects | 26 | 23 | 49 |
|  | n | 26 | 23 | 49 |
|  | Mean | 4.32 | 4.14 | 4.23 |
|  | SD | 4.44 | 3.84 | 4.13 |
|  | Q1 | 1.53 | 1.39 | 1.48 |
|  | Median | 2.38 | 2.37 | 2.37 |
|  | Q3 | 4.69 | 5.21 | 4.69 |
|  | Range (Min.: Max.) | (0.90: 15.1) | (0.99: 13.9) | (0.90: 15.1) |

## Table 14.1.2.5 Summary of QRS with VNS off - ITT Population (N=49)

|  | | **VNS Therapy System** | |  |
| --- | --- | --- | --- | --- |
| **Visit** | **Statistics** | **Right Sided (n=26)** | **Left Sided (n=23)** | **Overall (N=49)** |
| **Baseline** | Total No. of Subjects | 26 | 23 | 49 |
|  | n | 26 | 23 | 49 |
|  | Mean | 95.9 | 97.2 | 96.5 |
|  | SD | 29.9 | 32.6 | 30.8 |
|  | Q1 | 80.0 | 83.0 | 80.0 |
|  | Median | 94.0 | 103 | 96.0 |
|  | Q3 | 104 | 120 | 119 |
|  | Range (Min.: Max.) | (40.0: 176) | (27.0: 149) | (27.0: 176) |
| **9 Months Follow-up Visit** | Total No. of Subjects | 22 | 18 | 40 |
|  | n | 22 | 18 | 40 |
|  | Mean | 111 | 94.3 | 103 |
|  | SD | 69.5 | 37.9 | 57.4 |
|  | Q1 | 86.0 | 74.0 | 84.0 |
|  | Median | 99.5 | 98.0 | 99.5 |
|  | Q3 | 104 | 110 | 110 |
|  | Range (Min.: Max.) | (42.0: 400) | (32.0: 154) | (32.0: 400) |
| **12 Months Follow-up Visit** | Total No. of Subjects | 25 | 21 | 46 |
|  | n | 25 | 21 | 46 |
|  | Mean | 96.1 | 104 | 99.7 |
|  | SD | 27.1 | 31.9 | 29.3 |
|  | Q1 | 86.0 | 88.0 | 86.0 |
|  | Median | 99.0 | 106 | 101 |
|  | Q3 | 107 | 115 | 114 |
|  | Range (Min.: Max.) | (40.0: 156) | (35.0: 152) | (35.0: 156) |
| **18 Months Follow-up Visit** | Total No. of Subjects | 23 | 20 | 43 |
|  | n | 23 | 20 | 43 |
|  | Mean | 97.2 | 103 | 100 |
|  | SD | 25.0 | 39.0 | 32.0 |
|  | Q1 | 84.0 | 82.0 | 84.0 |
|  | Median | 100 | 106 | 101 |
|  | Q3 | 113 | 134 | 114 |
|  | Range (Min.: Max.) | (27.0: 151) | (35.0: 164) | (27.0: 164) |
| **24 Months Follow-up Visit** | Total No. of Subjects | 21 | 19 | 40 |
|  | n | 21 | 19 | 40 |
|  | Mean | 96.3 | 106 | 101 |
|  | SD | 24.2 | 37.2 | 31.0 |
|  | Q1 | 92.0 | 88.0 | 90.0 |
|  | Median | 103 | 106 | 104 |
|  | Q3 | 111 | 144 | 115 |
|  | Range (Min.: Max.) | (42.0: 134) | (40.0: 160) | (40.0: 160) |

## 

## Table 14.1.2.6 Summary of Output Current for all the Visits at Entry(N=49)

|  | | **VNS Therapy System** | | |
| --- | --- | --- | --- | --- |
| **Parameters/Visit** | **Statistics** | **Right Sided (n=26)** | **Left Sided (n=23)** | **Overall (N=49)** |
| **Enrollment Visit** | Total No. of Subjects | 26 | 23 | 49 |
|  | n | 26 | 23 | 49 |
|  | Mean | 1.64 | 2.00 | 1.81 |
|  | SD | 0.5 | 0.5 | 0.5 |
|  | Q1 | 1.25 | 1.75 | 1.50 |
|  | Median | 1.50 | 2.00 | 1.75 |
|  | Q3 | 2.00 | 2.25 | 2.25 |
|  | Range (Min.:Max.) | (0.75:2.75) | (1.00:3.00) | (0.75:3.00) |
| **9 Month Follow-up Visit** | Total No. of Subjects | 22 | 18 | 40 |
|  | n | 22 | 18 | 40 |
|  | Mean | 1.63 | 2.29 | 1.93 |
|  | SD | 0.5 | 0.57 | 0.6 |
|  | Q1 | 1.25 | 2.00 | 1.50 |
|  | Median | 1.63 | 2.50 | 2.00 |
|  | Q3 | 2.00 | 2.75 | 2.50 |
|  | Range (Min.:Max.) | (1.00:2.50) | (1.00:3.00) | (1.00:3.00) |
| **12 Month Follow-up Visit** | Total No. of Subjects | 25 | 21 | 46 |
|  | n | 25 | 21 | 46 |
|  | Mean | 1.71 | 2.30 | 1.98 |
|  | SD | 0.5 | 0.6 | 0.6 |
|  | Q1 | 1.25 | 2.00 | 1.50 |
|  | Median | 1.75 | 2.50 | 2.00 |
|  | Q3 | 2.00 | 2.75 | 2.50 |
|  | Range (Min.:Max.) | (1.00:3.00) | (1.00:3.00) | (1.00:3.00) |
| **18 Month Follow-up Visit** | Total No. of Subjects | 23 | 20 | 43 |
|  | n | 23 | 20 | 43 |
|  | Mean | 1.71 | 2.25 | 1.96 |
|  | SD | 0.6 | 0.6 | 0.6 |
|  | Q1 | 1.25 | 2.00 | 1.50 |
|  | Median | 1.75 | 2.50 | 2.00 |
|  | Q3 | 2.00 | 2.50 | 2.50 |
|  | Range (Min.:Max.) | (1.00:3.00) | (1.00:3.00) | (1.00:3.00) |
| **24 Month Follow-up Visit** | Total No. of Subjects | 21 | 19 | 40 |
|  | n | 21 | 19 | 40 |
|  | Mean | 1.71 | 2.16 | 1.93 |
|  | SD | 0.6 | 0.7 | 0.67 |
|  | Q1 | 1.25 | 2.00 | 1.38 |
|  | Median | 1.75 | 2.50 | 2.00 |
|  | Q3 | 2.00 | 2.50 | 2.50 |
|  | Range (Min.:Max.) | (1.00:3.00) | (0.50:3.00) | (0.50:3.00) |

## Table 14.2.1.1 Summary of LVESV and EF at each Visit (core lab data)-ITT Population (N=49)

|  | | **VNS Therapy System** | | |
| --- | --- | --- | --- | --- |
| **Parameters/Visit** | **Statistics** | **Right Sided (N=26)** | **Left Sided (N=23)** | **Overall (N=49)** |
| LVESV |  |  |  |  |
| Baseline | Total No. of Subjects | 26 | 23 | 49 |
|  | n | 26 | 23 | 49 |
|  | Mean | 101 | 103 | 102 |
|  | SD | 33.7 | 41.0 | 36.9 |
|  | Q1 | 80.0 | 65.0 | 76.0 |
|  | Median | 95.5 | 106 | 98.0 |
|  | Q3 | 113 | 125 | 119 |
|  | Range (Min.:Max.) | (59.0:200) | (48.0:191) | (48.0:200) |
|  |  |  |  |  |
| 9 months Follow-up Visit | Total No. of Subjects | 22 | 18 | 40 |
|  | n | 21 | 18 | 39 |
|  | Mean | 96.9 | 89.9 | 93.7 |
|  | SD | 44.9 | 44.7 | 44.4 |
|  | Q1 | 70.0 | 54.0 | 63.0 |
|  | Median | 96.0 | 85.5 | 90.0 |
|  | Q3 | 118 | 119 | 119 |
|  | Range (Min.:Max.) | (18.0:200) | (29.0:186) | (18.0:200) |
|  |  |  |  |  |
| 12 months Follow-up Visit | Total No. of Subjects | 25 | 21 | 46 |
|  | n | 25 | 21 | 46 |
|  | Mean | 95.3 | 87.2 | 91.6 |
|  | SD | 43.0 | 44.8 | 43.5 |
|  | Q1 | 70.0 | 60.0 | 63.0 |
|  | Median | 91.0 | 73.0 | 82.0 |
|  | Q3 | 135 | 99.0 | 122 |
|  | Range (Min.:Max.) | (18.0:191) | (37.0:217) | (18.0:217) |
|  |  |  |  |  |
| 24 months Follow-up Visit | Total No. of Subjects | 21 | 19 | 40 |
|  | n | 20 | 19 | 39 |
|  | Mean | 102 | 77.4 | 90.1 |
|  | SD | 46.0 | 36.0 | 42.8 |
|  | Q1 | 77.0 | 50.0 | 54.0 |
|  | Median | 97.2 | 67.0 | 82.0 |
|  | Q3 | 126 | 95.0 | 116 |
|  | Range (Min.:Max.) | (18.0:210) | (32.0:178) | (18.0:210) |
|  |  |  |  |  |
| Ejection Fraction |  |  |  |  |
| Baseline | Total No. of Subjects | 26 | 23 | 49 |
|  | n | 26 | 23 | 49 |
|  | Mean | 32.2 | 33.9 | 33.0 |
|  | SD | 6.43 | 8.32 | 7.34 |
|  | Q1 | 28.0 | 29.0 | 28.0 |
|  | Median | 34.0 | 35.0 | 35.0 |
|  | Q3 | 37.0 | 38.0 | 37.0 |
|  | Range (Min.:Max.) | (20.0:40.0) | (20.0:56.0) | (20.0:56.0) |
|  |  |  |  |  |
| 9 months Follow-up Visit | Total No. of Subjects | 22 | 18 | 40 |
|  | n | 21 | 18 | 39 |
|  | Mean | 38.6 | 42.1 | 40.2 |
|  | SD | 11.7 | 9.77 | 10.8 |
|  | Q1 | 31.0 | 36.0 | 33.0 |
|  | Median | 37.0 | 40.5 | 39.0 |
|  | Q3 | 43.0 | 47.0 | 43.0 |
|  | Range (Min.:Max.) | (24.0:70.0) | (28.0:63.0) | (24.0:70.0) |
|  |  |  |  |  |
| 12 months Follow-up Visit | Total No. of Subjects | 25 | 21 | 46 |
|  | n | 25 | 21 | 46 |
|  | Mean | 38.7 | 40.4 | 39.5 |
|  | SD | 11.0 | 9.79 | 10.4 |
|  | Q1 | 34.0 | 34.0 | 34.0 |
|  | Median | 37.0 | 41.0 | 38.0 |
|  | Q3 | 42.0 | 45.0 | 44.0 |
|  | Range (Min.:Max.) | (20.0:72.0) | (24.0:63.0) | (20.0:72.0) |
|  |  |  |  |  |
| 24 months Follow-up Visit | Total No. of Subjects | 21 | 19 | 40 |
|  | n | 21 | 19 | 40 |
|  | Mean | 38.3 | 42.2 | 40.2 |
|  | SD | 11.0 | 9.93 | 10.5 |
|  | Q1 | 33.0 | 37.0 | 35.0 |
|  | Median | 38.0 | 40.0 | 39.0 |
|  | Q3 | 43.0 | 50.0 | 47.5 |
|  | Range (Min.:Max.) | (23.0:70.0) | (18.0:59.0) | (18.0:70.0) |
|  |  |  |  |  |
|  | | | | |

## Table 14.2.1.2 Summary of Change in LVESV from Baseline (Core lab data)-ITT Population (N=49)

|  | | **VNS Therapy System** | | | |
| --- | --- | --- | --- | --- | --- |
| **Parameters/Visit** | **Statistics** | **Right Sided (N=26)** |  | **Left Sided (N=23)** | **Overall (N=49)** |
| **Change from Baseline to 9 months follow up Visit** |  |  |  |  |  |
|  | n | 21 |  | 18 | 39 |
|  | Mean | -1.26 |  | -15.4 | -7.80 |
|  | SD | 26.0 |  | 26.5 | 26.8 |
|  | Q1 | -12.0 |  | -24.0 | -18.0 |
|  | Median | -5.00 |  | -11.0 | -7.00 |
|  | Q3 | 6.00 |  | -3.00 | 4.00 |
|  | Range (Min.: Max.) | (-46.0:56.0) |  | (-72.0:30.0) | (-72.0:56.0) |
|  | Missing | 5 |  | 5 | 10 |
|  |  |  |  |  |  |
| **ANOVA Analysis Result** |  |  |  |  |  |
|  | LS Mean Estimate | -1.39 |  | -13.9 |  |
|  | Difference Estimate [1] |  | 12.5 |  |  |
|  | SE |  | 7.94 |  |  |
|  | 95% CI (L.:U.) |  | (-3.48: 28.6) |  |  |
|  | p-value [3] |  | 0.12 |  |  |
|  |  |  |  |  |  |
| **Paired t-test** |  |  |  |  |  |
|  | p-value [4] | 0.8268 |  | 0.0243 |  |
|  |  |  |  |  |  |
| **Change from Baseline to 12 months follow up Visit** |  |  |  |  |  |
|  | n | 25 |  | 21 | 46 |
|  | Mean | -7.23 |  | -14.2 | -10.4 |
|  | SD | 24.4 |  | 24.3 | 24.3 |
|  | Q1 | -20.0 |  | -19.0 | -20.0 |
|  | Median | -3.00 |  | -12.0 | -9.00 |
|  | Q3 | 4.00 |  | -4.00 | 2.00 |
|  | Range (Min.: Max.) | (-49.0:64.0) |  | (-80.0:33.0) | (-80.0:64.0) |
|  | Missing | 1 |  | 2 | 3 |
|  |  |  |  |  |  |
| **ANOVA Analysis Result** |  |  |  |  |  |
|  | LS Mean Estimate | -7.23 |  | -14.2 |  |
|  | Difference Estimate [1] |  | 7.02 |  |  |
|  | SE |  | 7.21 |  |  |
|  | 95% CI (L.:U.) |  | (-7.52: 21.6) |  |  |
|  | p-value [3] |  | 0.34 |  |  |
|  |  |  |  |  |  |
| **Paired t-test** |  |  |  |  |  |
|  | p-value [4] | 0.1511 |  | 0.0143 |  |
|  |  |  |  |  |  |
| **Change from Baseline to 24 months follow up Visit** |  |  |  |  |  |
|  | n | 20 |  | 19 | 39 |
|  | Mean | -2.27 |  | -18.7 | -10.3 |
|  | SD | 20.2 |  | 25.9 | 24.3 |
|  | Q1 | -12.5 |  | -30.8 | -19.0 |
|  | Median | -5.50 |  | -15.0 | -9.70 |
|  | Q3 | 9.61 |  | -2.00 | 4.00 |
|  | Range (Min.: Max.) | (-46.0:51.0) |  | (-81.0:31.0) | (-81.0:51.0) |
|  | Missing | 6 |  | 4 | 10 |
|  |  |  |  |  |  |
| **ANOVA Analysis Result** |  |  |  |  |  |
|  | LS Mean Estimate | -5.44 |  | -15.3 |  |
|  | Difference Estimate [1] |  | 9.85 |  |  |
|  | SE |  | 7.41 |  |  |
|  | 95% CI (L.:U.) |  | (-5.18: 24.9) |  |  |
|  | p-value [3] |  | 0.19 |  |  |
|  |  |  |  |  |  |
| **Paired t-test** |  |  |  |  |  |
|  | p-value [4] | 0.6199 |  | 0.0056 |  |
|  |  |  |  |  |  |
| [1] Difference estimate indicate Difference [(Right Sided) – (Left Sided)]. [2] SE indicates Standard Error of Differences [[(Right Sided) – (Left Sided)]. [3] Mean change in LVESD was compared between the two VNS Therapy System using Mixed Model for Repeated Measures (MMRM)     , with VNS Therapy System (Right/Left Sided),Visit, VNS Therapy System\*Visit as factors. [4] P-value for comparing baseline assessment to consecutive visits i.e.9 month vs. baseline, 12 month vs. baseline, 24 month vs.     baseline) computed from paired t-test. | | | | | |

## Table 14.2.1.2c\_a Summary of Change in LVESV from Baseline (Core lab data) (Pooled Analysis)-ITT Population -(N=49)

| **Parameters/Visit** | **Statistics** | **VNS Therapy System (N=49)** |
| --- | --- | --- |
|  |  |  |
| **Change from Baseline to 9 months follow up Visit** |  |  |
|  | n | 39 |
|  | Mean | -7.80 |
|  | SD | 26.8 |
|  | Q1 | -18.0 |
|  | Median | -7.00 |
|  | Q3 | 4.00 |
|  | Range (Min.: Max.) | (-72.0:56.0) |
|  | Missing | 10 |
|  |  |  |
| **ANOVA Analysis Result** |  |  |
|  | LS Mean Estimate | -7.79 |
|  | SE | 4.04 |
|  | 95% CI (L.:U.) | (-15.9: 0.339) |
|  | p-value [1] | 0.06 |
|  |  |  |
| **Paired t-test** |  |  |
|  | p-value [2] | 0.0774 |
|  |  |  |
| **Change from Baseline to 12 months follow up Visit** |  |  |
|  | n | 46 |
|  | Mean | -10.4 |
|  | SD | 24.3 |
|  | Q1 | -20.0 |
|  | Median | -9.00 |
|  | Q3 | 2.00 |
|  | Range (Min.: Max.) | (-80.0:64.0) |
|  | Missing | 3 |
|  |  |  |
| **ANOVA Analysis Result** |  |  |
|  | LS Mean Estimate | -10.4 |
|  | SE | 3.59 |
|  | 95% CI (L.:U.) | (-17.7: -3.20) |
|  | p-value [1] | <.01 |
|  |  |  |
| **Paired t-test** |  |  |
|  | p-value [2] | 0.0056 |
|  |  |  |
| **Change from Baseline to 24 months follow up Visit** |  |  |
|  | n | 39 |
|  | Mean | -10.3 |
|  | SD | 24.3 |
|  | Q1 | -19.0 |
|  | Median | -9.70 |
|  | Q3 | 4.00 |
|  | Range (Min.: Max.) | (-81.0:51.0) |
|  | Missing | 10 |
|  |  |  |
| **ANOVA Analysis Result** |  |  |
|  | LS Mean Estimate | -10.5 |
|  | SE | 3.69 |
|  | 95% CI (L.:U.) | (-17.9: -3.08) |
|  | p-value [1] | <.01 |
|  |  |  |
| **Paired t-test** |  |  |
|  | p-value [2] | 0.0119 |
| **Note:** [1] LS Mean Estimate, SE and p-value for Mean change was compared for visit using Mixed Model for Repeated Measures (MMRM)     ANOVA with visit as only factor. [2] P-value for comparing baseline assessment to consecutive visits i.e.9 month vs. baseline, 12 month vs. baseline, 24 month vs.     baseline) computed from paired t-test.  **General Note:** > As interaction has not been significant, Right sided and Left sided implant groups has been pooled for this analysis by    omitting all factors involving side of the implant from ANOVA. | | |

## Table 14.2.1.3c Summary of Change in in Ejection Fraction (EF) from Baseline (Core Lab data)-ITT Population(N=49)

|  | | **VNS Therapy System** | | | |
| --- | --- | --- | --- | --- | --- |
| **Parameters/Visit** | **Statistics** | **Right Sided (N=26)** |  | **Left Sided (N=23)** | **Overall (N=49)** |
|  |  |  |  |  |  |
| **Change from Baseline to 9 months follow up Visit** |  |  |  |  |  |
|  | n | 21 |  | 18 | 39 |
|  | Mean | 5.67 |  | 7.94 | 6.72 |
|  | SD | 9.00 |  | 8.90 | 8.91 |
|  | Q1 | -1.00 |  | 3.00 | 1.00 |
|  | Median | 5.00 |  | 6.50 | 5.00 |
|  | Q3 | 8.00 |  | 13.0 | 9.00 |
|  | Range(Min.:Max.) | (-4.00:32.0) |  | (-5.00:31.0) | (-5.00:32.0) |
|  | Missing | 5 |  | 5 | 10 |
|  |  |  |  |  |  |
| **ANOVA Analysis Result** |  |  |  |  |  |
|  | LS Mean Estimate | 5.76 |  | 7.42 |  |
|  | Difference Estimate [1] |  | -1.66 |  |  |
|  | SE [2] |  | 2.61 |  |  |
|  | 95% CI (L.:U.) |  | (-6.93: 3.61) |  |  |
|  | p-value [3] |  | 0.53 |  |  |
|  |  |  |  |  |  |
| **Paired t-test** |  |  |  |  |  |
|  | p-value [4] | 0.0091 |  | 0.0015 |  |
|  |  |  |  |  |  |
| **Change from Baseline to 12 months follow up Visit** |  |  |  |  |  |
|  | n | 25 |  | 21 | 46 |
|  | Mean | 6.64 |  | 5.76 | 6.24 |
|  | SD | 8.60 |  | 5.60 | 7.32 |
|  | Q1 | 2.00 |  | 2.00 | 2.00 |
|  | Median | 4.00 |  | 5.00 | 5.00 |
|  | Q3 | 9.00 |  | 8.00 | 9.00 |
|  | Range(Min.:Max.) | (-6.00:34.0) |  | (-4.00:17.0) | (-6.00:34.0) |
|  | Missing | 1 |  | 2 | 3 |
|  |  |  |  |  |  |
| **ANOVA Analysis Result** |  |  |  |  |  |
|  | LS Mean Estimate | 6.64 |  | 5.76 |  |
|  | Difference Estimate [1] |  | 0.878 |  |  |
|  | SE [2] |  | 2.11 |  |  |
|  | 95% CI (L.:U.) |  | (-3.38: 5.14) |  |  |
|  | p-value [3] |  | 0.68 |  |  |
|  |  |  |  |  |  |
| **Paired t-test** |  |  |  |  |  |
|  | p-value [4] | 0.0007 |  | 0.0001 |  |
|  |  |  |  |  |  |
| **Change from Baseline to 24 months follow up Visit** |  |  |  |  |  |
|  | n | 21 |  | 19 | 40 |
|  | Mean | 6.05 |  | 6.84 | 6.43 |
|  | SD | 8.51 |  | 7.76 | 8.06 |
|  | Q1 | 1.00 |  | 1.00 | 1.00 |
|  | Median | 4.00 |  | 5.00 | 4.50 |
|  | Q3 | 10.0 |  | 15.0 | 11.5 |
|  | Range(Min.:Max.) | (-8.00:30.0) |  | (-5.00:19.0) | (-8.00:30.0) |
|  | Missing | 5 |  | 4 | 9 |
|  |  |  |  |  |  |
| **ANOVA Analysis Result** |  |  |  |  |  |
|  | LS Mean Estimate | 5.66 |  | 6.54 |  |
|  | Difference Estimate [1] |  | -0.879 |  |  |
|  | SE [2] |  | 2.4 |  |  |
|  | 95% CI (L.:U.) |  | (-5.72: 3.96) |  |  |
|  | p-value [3] |  | 0.72 |  |  |
|  |  |  |  |  |  |
| **Paired t-test** |  |  |  |  |  |
|  | p-value [4] | 0.0039 |  | 0.0012 |  |
| [1] Difference estimate indicate Difference [(Right Sided) – (Left Sided)]. [2] SE indicates Standard Error of Differences [[(Right Sided) – (Left Sided)]. [3] Mean change in LVESD was compared between the two VNS Therapy System using Mixed Model for Repeated Measures (MMRM)     , with VNS Therapy System (Right/Left Sided),Visit, VNS Therapy System\*Visit as factors. [4] P-value for comparing baseline assessment to consecutive visits i.e.9 month vs. baseline, 12 month vs. baseline, 24 month vs.     baseline) computed from paired t-test. | | | | | |

## Table 14.2.1.3c\_a Summary of Change in Ejection Fraction (EF) from Baseline (Core Lab data) (Pooled Analysis) -IIT Population -(N=49)

| **Parameters/Visit** | **Statistics** | **VNS Therapy System (N=49)** |
| --- | --- | --- |
|  |  |  |
| **Change from Baseline to 9 months follow up Visit** |  |  |
|  | n | 39 |
|  | Mean | 6.72 |
|  | SD | 8.91 |
|  | Q1 | 1.00 |
|  | Median | 5.00 |
|  | Q3 | 9.00 |
|  | Range (Min.: Max.) | (-5.00:32.0) |
|  | Missing | 10 |
|  |  |  |
| **ANOVA Analysis Result** |  |  |
|  | LS Mean Estimate | 6.51 |
|  | SE | 1.29 |
|  | 95% CI (L.:U.) | (3.91: 9.12) |
|  | p-value [1] | <.01 |
|  |  |  |
| **Paired t-test** |  |  |
|  | p-value [2] | <.0001 |
|  |  |  |
| **Change from Baseline to 12 months follow up Visit** |  |  |
|  | n | 46 |
|  | Mean | 6.24 |
|  | SD | 7.32 |
|  | Q1 | 2.00 |
|  | Median | 5.00 |
|  | Q3 | 9.00 |
|  | Range (Min.: Max.) | (-6.00:34.0) |
|  | Missing | 3 |
|  |  |  |
| **ANOVA Analysis Result** |  |  |
|  | LS Mean Estimate | 6.24 |
|  | SE | 1.08 |
|  | 95% CI (L.:U.) | (4.07: 8.41) |
|  | p-value [1] | <.01 |
|  |  |  |
| **Paired t-test** |  |  |
|  | p-value [2] | <.0001 |
|  |  |  |
| **Change from Baseline to 24 months follow up Visit** |  |  |
|  | n | 40 |
|  | Mean | 6.43 |
|  | SD | 8.06 |
|  | Q1 | 1.00 |
|  | Median | 4.50 |
|  | Q3 | 11.5 |
|  | Range (Min.: Max.) | (-8.00:30.0) |
|  | Missing | 9 |
|  |  |  |
| **ANOVA Analysis Result** |  |  |
|  | LS Mean Estimate | 6.10 |
|  | SE | 1.19 |
|  | 95% CI (L.:U.) | (3.71: 8.48) |
|  | p-value [1] | <.01 |
|  |  |  |
| **Paired t-test** |  |  |
|  | p-value [2] | <.0001 |
| **Note:** [1] LS Mean Estimate, SE and p-value for Mean change was compared for visit using Mixed Model for Repeated Measures (MMRM)     ANOVA with visit as only factor. [2] P-value for comparing baseline assessment to consecutive visits i.e.9 month vs. baseline, 12 month vs. baseline, 24 month vs.     baseline) computed from paired t-test. | | |

## Table 14.2.2.1c Summary of Left Ventricular End Systolic Dimensions (cm) (LVESD) (Core lab data)-ITT Population(N=49)

|  | | **VNS Therapy System** | | |
| --- | --- | --- | --- | --- |
| **Parameters/Visit** | **Statistics** | **Right Sided (N=26)** | **Left Sided (N=23)** | **Overall (N=49)** |
|  |  |  |  |  |
| Baseline | Total No. of Subjects | 26 | 23 | 49 |
|  | n | 26 | 23 | 49 |
|  | Mean | 5.03 | 5.02 | 5.02 |
|  | SD | 0.8 | 0.7 | 0.8 |
|  | Q1 | 4.70 | 4.40 | 4.70 |
|  | Median | 4.90 | 5.00 | 4.90 |
|  | Q3 | 5.50 | 5.50 | 5.50 |
|  | Range (Min.:Max.) | (3.31:7.20) | (3.80:6.30) | (3.31:7.20) |
|  |  |  |  |  |
| 9 months Follow-up Visit | Total No. of Subjects | 22 | 18 | 40 |
|  | n | 21 | 18 | 39 |
|  | Mean | 4.91 | 4.71 | 4.82 |
|  | SD | 0.8 | 0.8 | 0.8 |
|  | Q1 | 4.50 | 4.20 | 4.50 |
|  | Median | 4.90 | 4.65 | 4.80 |
|  | Q3 | 5.40 | 5.00 | 5.40 |
|  | Range (Min.:Max.) | (3.10:6.20) | (3.40:6.50) | (3.10:6.50) |
|  |  |  |  |  |
| 12 months Follow-up Visit | Total No. of Subjects | 25 | 21 | 46 |
|  | n | 25 | 21 | 46 |
|  | Mean | 4.85 | 4.78 | 4.82 |
|  | SD | 0.8 | 0.9 | 0.8 |
|  | Q1 | 4.50 | 4.30 | 4.35 |
|  | Median | 4.90 | 4.50 | 4.70 |
|  | Q3 | 5.40 | 5.00 | 5.30 |
|  | Range (Min.:Max.) | (2.80:6.20) | (3.20:7.10) | (2.80:7.10) |
|  |  |  |  |  |
| 24 months Follow-up Visit | Total No. of Subjects | 21 | 19 | 40 |
|  | n | 20 | 19 | 39 |
|  | Mean | 5.08 | 4.72 | 4.90 |
|  | SD | 0.8 | 0.7 | 0.8 |
|  | Q1 | 4.50 | 4.10 | 4.20 |
|  | Median | 5.10 | 4.60 | 4.80 |
|  | Q3 | 5.55 | 5.20 | 5.40 |
|  | Range (Min.:Max.) | (3.80:6.70) | (3.50:6.20) | (3.50:6.70) |
|  |  |  |  |  |
|  | | | | |

## Table 14.2.2.2c Summary of Change in LVESD from Baseline-(Core lab data) -ITT Population(N=49)

|  | | **VNS Therapy System** | | | |
| --- | --- | --- | --- | --- | --- |
| **Parameters/Visit** | **Statistics** | **Right Sided (N=26)** |  | **Left Sided (N=23)** | **Overall (N=49)** |
|  |  |  |  |  |  |
| **Change from Baseline to 9 months follow up Visit** |  |  |  |  |  |
|  | n | 21 |  | 18 | 39 |
|  | Mean | -0.0243 |  | -0.303 | -0.153 |
|  | SD | 0.434 |  | 0.461 | 0.463 |
|  | Q1 | -0.20 |  | -0.60 | -0.50 |
|  | Median | 0.00 |  | -0.30 | -0.10 |
|  | Q3 | 0.13 |  | 0.00 | 0.10 |
|  | Range (Min.: Max.) | (-1.03:0.70) |  | (-1.10:0.70) | (-1.10:0.70) |
|  | Missing | 5 |  | 5 | 10 |
|  |  |  |  |  |  |
| **ANOVA Analysis Result** |  |  |  |  |  |
|  | LS Mean Estimate | -0.0625 |  | -0.236 |  |
|  | Difference Estimate [1] |  | 0.174 |  |  |
|  | SE |  | 0.141 |  |  |
|  | 95% CI (L.:U.) |  | (-0.111: 0.459) |  |  |
|  | p-value [3] |  | 0.23 |  |  |
|  |  |  |  |  |  |
| **Paired t-test** |  |  |  |  |  |
|  | p-value [4] | 0.8004 |  | 0.0127 |  |
|  |  |  |  |  |  |
| **Change from Baseline to 12 months follow up Visit** |  |  |  |  |  |
|  | n | 20 |  | 19 | 39 |
|  | Mean | -0.032 |  | -0.155 | -0.0921 |
|  | SD | 0.446 |  | 0.66 | 0.556 |
|  | Q1 | -0.335 |  | -0.60 | -0.50 |
|  | Median | 0.00 |  | -0.10 | -0.10 |
|  | Q3 | 0.30 |  | 0.20 | 0.30 |
|  | Range (Min.: Max.) | (-1.10:0.70) |  | (-1.60:1.50) | (-1.60:1.50) |
|  | Missing | 6 |  | 4 | 10 |
|  |  |  |  |  |  |
| **ANOVA Analysis Result** |  |  |  |  |  |
|  | LS Mean Estimate | -0.188 |  | -0.183 |  |
|  | Difference Estimate [1] |  | -0.00467 |  |  |
|  | SE |  | 0.15 |  |  |
|  | 95% CI (L.:U.) |  | (-0.308: 0.299) |  |  |
|  | p-value [3] |  | 0.98 |  |  |
|  |  |  |  |  |  |
| **Paired t-test** |  |  |  |  |  |
|  | p-value [4] | 0.0552 |  | 0.1353 |  |
|  |  |  |  |  |  |
| **Change from Baseline to 24 months follow up Visit** |  |  |  |  |  |
|  | n | 20 |  | 19 | 39 |
|  | Mean | -0.032 |  | -0.155 | -0.0921 |
|  | SD | 0.446 |  | 0.66 | 0.556 |
|  | Q1 | -0.335 |  | -0.60 | -0.50 |
|  | Median | 0.00 |  | -0.10 | -0.10 |
|  | Q3 | 0.30 |  | 0.20 | 0.30 |
|  | Range (Min.: Max.) | (-1.10:0.70) |  | (-1.60:1.50) | (-1.60:1.50) |
|  | Missing | 6 |  | 4 | 10 |
|  |  |  |  |  |  |
| **ANOVA Analysis Result** |  |  |  |  |  |
|  | LS Mean Estimate | -0.0504 |  | -0.0558 |  |
|  | Difference Estimate [1] |  | 0.0054 |  |  |
|  | SE |  | 0.189 |  |  |
|  | 95% CI (L.:U.) |  | (-0.383: 0.394) |  |  |
|  | p-value [3] |  | 0.98 |  |  |
|  |  |  |  |  |  |
| **Paired t-test** |  |  |  |  |  |
|  | p-value [4] | 0.7517 |  | 0.3186 |  |
| **Note:** [1] Difference estimate indicate Difference [(Right Sided) – (Left Sided)]. [2] SE indicates Standard Error of Differences [[(Right Sided) – (Left Sided)]. [3] Mean change in LVESD was compared between the two VNS Therapy System using Mixed Model for Repeated Measures (MMRM)     , with VNS Therapy System (Right/Left Sided),Visit, VNS Therapy System\*Visit as factors. [4] P-value for comparing baseline assessment to consecutive visits i.e.9 month vs. baseline, 12 month vs. baseline, 24 month vs.     baseline) computed from paired t-test. | | | | | |

## Table 14.2.2.2c\_a Summary of LVESD (Pooled Analysis (Core Lab data)) -IIT Population -(N=49)

| **Parameters/Visit** | **Statistics** | **VNS Therapy System (N=49)** |
| --- | --- | --- |
|  |  |  |
| **Change from Baseline to 9 months follow up Visit** |  |  |
|  | n | 39 |
|  | Mean | -0.2 |
|  | SD | 0.5 |
|  | Q1 | -0.50 |
|  | Median | -0.10 |
|  | Q3 | 0.10 |
|  | Range (Min.: Max.) | (-1.10:0.70) |
|  | Missing | 10 |
|  |  |  |
| **ANOVA Analysis Result** |  |  |
|  | LS Mean Estimate | -0.13 |
|  | SE | 0.07 |
|  | 95% CI (L.:U.) | (-0.28: 0.01) |
|  | p-value [1] | 0.07 |
|  |  |  |
| **Paired t-test** |  |  |
|  | p-value [2] | 0.0461 |
|  |  |  |
| **Change from Baseline to 12 months follow up Visit** |  |  |
|  | n | 46 |
|  | Mean | -0.2 |
|  | SD | 0.5 |
|  | Q1 | -0.50 |
|  | Median | -0.20 |
|  | Q3 | 0.20 |
|  | Range (Min.: Max.) | (-1.33:0.90) |
|  | Missing | 3 |
|  |  |  |
| **ANOVA Analysis Result** |  |  |
|  | LS Mean Estimate | -0.19 |
|  | SE | 0.07 |
|  | 95% CI (L.:U.) | (-0.33: -0.04) |
|  | p-value [1] | 0.01 |
|  |  |  |
| **Paired t-test** |  |  |
|  | p-value [2] | 0.0145 |
|  |  |  |
| **Change from Baseline to 24 months follow up Visit** |  |  |
|  | n | 39 |
|  | Mean | -0.1 |
|  | SD | 0.6 |
|  | Q1 | -0.50 |
|  | Median | -0.10 |
|  | Q3 | 0.30 |
|  | Range (Min.: Max.) | (-1.60:1.50) |
|  | Missing | 10 |
|  |  |  |
| **ANOVA Analysis Result** |  |  |
|  | LS Mean Estimate | -0.07 |
|  | SE | 0.09 |
|  | 95% CI (L.:U.) | (-0.25: 0.11) |
|  | p-value [1] | 0.46 |
|  |  |  |
| **Paired t-test** |  |  |
|  | p-value [2] | 0.3080 |
| **Note:** [1] LS Mean Estimate, SE and p-value for Mean change was compared for visit using Mixed Model for Repeated Measures (MMRM)     ANOVA with visit as only factor. [2] P-value for comparing baseline assessment to consecutive visits i.e.9 month vs. baseline, 12 month vs. baseline, 24 month vs.     baseline) computed from paired t-test. | | |

## Table 14.2.2.3.4 Summary of 6 Minute Walk for the Distance Covered -ITT Population (N=49)

|  | | **VNS Therapy System** | | |
| --- | --- | --- | --- | --- |
| **Visit/Category** | **Statistics, n (%)** | **Right Sided (n=26)** | **Left Sided (n=23)** | **Overall (N=49)** |
| **Baseline** |  |  |  |  |
| **Distance Covered (meters)** |  |  |  |  |
|  | No. of Patients | 26 | 23 | 49 |
|  | n | 26 | 23 | 49 |
|  | Mean | 275 | 296 | 285 |
|  | SD | 73.6 | 58.7 | 67.2 |
|  | Q1 | 214 | 285 | 255 |
|  | Median | 307 | 309 | 309 |
|  | Q3 | 323 | 329 | 323 |
|  | Range (Min.: Max.) | (140: 440) | (80.0: 361) | (80.0: 440) |
|  | 95% CI | (245: 305) | (270: 321) | (265: 304) |
| **Subject stop or pause before 6 minutes[1]** |  |  |  |  |
|  | Yes | 2 (7.69 %) | 2 (8.70 %) | 4 (8.16 %) |
|  | No | 24 (92.3 %) | 21 (91.3 %) | 45 (91.8 %) |
| **9 Month follow up** |  |  |  |  |
| **Distance Covered (meters)** |  |  |  |  |
|  | No. of Patients | 22 | 18 | 40 |
|  | n | 21 | 18 | 39 |
|  | Mean | 353 | 323 | 339 |
|  | SD | 48.7 | 50.0 | 50.9 |
|  | Q1 | 330 | 300 | 315 |
|  | Median | 347 | 323 | 343 |
|  | Q3 | 366 | 363 | 365 |
|  | Range (Min.: Max.) | (245: 480) | (175: 393) | (175: 480) |
|  | 95% CI | (331: 375) | (299: 348) | (323: 356) |
| **Subject stop or pause before 6 minutes[1]** |  |  |  |  |
|  | Yes | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
|  | No | 20 (90.9 %) | 18 (100 %) | 38 (95.0 %) |
| **12 Month follow up** |  |  |  |  |
| **Distance Covered (meters)** |  |  |  |  |
|  | No. of Patients | 25 | 21 | 46 |
|  | n | 25 | 21 | 46 |
|  | Mean | 366 | 335 | 352 |
|  | SD | 68.4 | 50.4 | 62.2 |
|  | Q1 | 325 | 300 | 310 |
|  | Median | 366 | 328 | 353 |
|  | Q3 | 389 | 360 | 373 |
|  | Range (Min.: Max.) | (194: 500) | (234: 480) | (194: 500) |
|  | 95% CI | (338: 394) | (312: 358) | (333: 370) |
| **Subject stop or pause before 6 minutes[1]** |  |  |  |  |
|  | Yes | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
|  | No | 24 (96.0 %) | 21 (100 %) | 45 (97.8 %) |
| **24 Month follow up** |  |  |  |  |
| **Distance Covered (meters)** |  |  |  |  |
|  | No. of Patients | 21 | 19 | 40 |
|  | n | 20 | 19 | 39 |
|  | Mean | 377 | 331 | 355 |
|  | SD | 58.9 | 91.1 | 78.7 |
|  | Q1 | 333 | 310 | 318 |
|  | Median | 374 | 351 | 371 |
|  | Q3 | 415 | 375 | 390 |
|  | Range (Min.: Max.) | (270: 481) | (0.00: 425) | (0.00: 481) |
|  | 95% CI | (349: 404) | (287: 375) | (329: 380) |
| **Subject stop or pause before 6 minutes[1]** |  |  |  |  |
|  | Yes | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
|  | No | 20 (95.2 %) | 18 (94.7 %) | 38 (95.0 %) |
| **Note:** [1] Respective visit counts is used as denominator for percentage calculation.  **General Note:** > Baseline value was defined as average of the all baseline 6-minute walk tests. If those values are within 10% of each other, otherwise   the last available 6-minute walk test was used. | | | | |

## Table14.2.2.3.4-a Summary of Change in 6 Minute Walk for the Distance Covered - ITT Population (N=49)

|  | | **VNS Therapy System** | | | |
| --- | --- | --- | --- | --- | --- |
| **Visit/Category** | **Statistics, n (%)** | **Right Sided (n=26)** |  | **Left Sided (n=23)** | **Overall (N=49)** |
| **Change from Baseline to 9 Month follow up** |  |  |  |  |  |
|  | n | 21 |  | 18 | 39 |
|  | Mean | 76.9 |  | 31.3 | 55.8 |
|  | SD | 58.8 |  | 49.4 | 58.7 |
|  | Q1 | 39.0 |  | -23.0 | 13.0 |
|  | Median | 66.5 |  | 37.5 | 45.5 |
|  | Q3 | 109 |  | 77.5 | 95.0 |
|  | Range (Min.: Max.) | (-24.0: 202) |  | (-44.0: 102) | (-44.0: 202) |
|  | Missing | 5 |  | 5 | 10 |
| **ANOVA Analysis Result** |  |  |  |  |  |
|  | LS Mean Estimate | 68.6 |  | 30.5 |  |
|  | Difference Estimate [1] |  | 38.1 |  |  |
|  | SE [2] |  | 18.0 |  |  |
|  | 95% CI (L.:U.) |  | (1.42: 74.7) |  |  |
|  | p-value [3] |  | 0.0422 |  |  |
| **Paired t-test** |  |  |  |  |  |
|  | p-value [4] | <.0001 |  | 0.0156 |  |
| **Change from Baseline to 12 Month follow up** |  |  |  |  |  |
|  | n | 25 |  | 21 | 46 |
|  | Mean | 90.7 |  | 38.1 | 66.7 |
|  | SD | 77.2 |  | 52.7 | 71.5 |
|  | Q1 | 42.5 |  | 5.00 | 25.0 |
|  | Median | 60.0 |  | 36.5 | 52.3 |
|  | Q3 | 155 |  | 52.5 | 115 |
|  | Range (Min.: Max.) | (-19.0: 314) |  | (-46.0: 154) | (-46.0: 314) |
|  | Missing | 1 |  | 2 | 3 |
| **ANOVA Analysis Result** |  |  |  |  |  |
|  | LS Mean Estimate | 89.9 |  | 38.1 |  |
|  | Difference Estimate [1] |  | 51.7 |  |  |
|  | SE [2] |  | 19.1 |  |  |
|  | 95% CI (L.:U.) |  | (13.3: 90.1) |  |  |
|  | p-value [3] |  | 0.00942 |  |  |
| **Paired t-test** |  |  |  |  |  |
|  | p-value [4] | <.0001 |  | 0.0035 |  |
| **Change from Baseline to 24 Month follow up** |  |  |  |  |  |
|  | n | 20 |  | 19 | 39 |
|  | Mean | 95.3 |  | 37.6 | 67.2 |
|  | SD | 77.5 |  | 49.6 | 70.9 |
|  | Q1 | 38.0 |  | 3.00 | 22.5 |
|  | Median | 86.5 |  | 28.0 | 52.5 |
|  | Q3 | 138 |  | 67.5 | 101 |
|  | Range (Min.: Max.) | (-10.0: 314) |  | (-80.0: 134) | (-80.0: 314) |
|  | Missing | 6 |  | 4 | 10 |
| **ANOVA Analysis Result** |  |  |  |  |  |
|  | LS Mean Estimate | 91.2 |  | 36.3 |  |
|  | Difference Estimate [1] |  | 54.9 |  |  |
|  | SE [2] |  | 20.0 |  |  |
|  | 95% CI (L.:U.) |  | (14.3: 95.5) |  |  |
|  | p-value [3] |  | 0.00938 |  |  |
| **Paired t-test** |  |  |  |  |  |
|  | p-value [4] | <.0001 |  | 0.0039 |  |
| **Note:** [1] Difference estimate indicate Difference [(Right Sided) – (Left Sided)]. [2] SE indicates Standard Error of Differences [[(Right Sided) – (Left Sided)]. [3] Mean change in Distance Covered was compared between the two VNS Therapy System using Mixed Model for Repeated Measures (MMRM), with VNS     Therapy System (Right/Left Sided), Visit, VNS Therapy System\*Visit as factors. [4] P-value for comparing baseline assessment to consecutive visits i.e.9 month vs. baseline, 12 month vs. baseline, 24 month vs.     baseline) computed from paired t-test.  **General Note:** > If the interaction is not significant, Right-sided and Left sided implant groups was pooled for further analysis by omitting all   factors involving side of the implant from ANOVA. > Baseline value was defined as average of the all baseline 6-minute walk tests. If those values are within 10% of each other,   otherwise the last available 6-minute walk test will be used. | | | | | |

## Table 14.2.2.3.4-b Summary of Change in 6 Minute Walk for the Distance Covered (Pooled Analysis) - ITT Population (N=49)

| **Visit/Category** | **Statistics, n (%)** | **VNS Therapy System (n=49)** |
| --- | --- | --- |
| **Change from Baseline to 9 Month follow up** |  |  |
|  | n | 39 |
|  | Mean | 55.8 |
|  | SD | 58.7 |
|  | Q1 | 13.0 |
|  | Median | 45.5 |
|  | Q3 | 95.0 |
|  | Range (Min.: Max.) | (-44.0: 202) |
|  | Missing | 10 |
| **ANOVA Analysis Result** |  |  |
|  | LS Mean Estimate | 51.6 |
|  | SE [1] | 9.36 |
|  | 95% CI (L.:U.) | (32.6: 70.5) |
|  | p-value [1] | <.0001 |
| **Paired t-test** |  |  |
|  | p-value [2] | <.0001 |
| **Change from Baseline to 12 Month follow up** |  |  |
|  | n | 46 |
|  | Mean | 66.7 |
|  | SD | 71.5 |
|  | Q1 | 25.0 |
|  | Median | 52.3 |
|  | Q3 | 115 |
|  | Range (Min.: Max.) | (-46.0: 314) |
|  | Missing | 3 |
| **ANOVA Analysis Result** |  |  |
|  | LS Mean Estimate | 66.6 |
|  | SE [1] | 10.5 |
|  | 95% CI (L.:U.) | (45.5: 87.6) |
|  | p-value [1] | <.0001 |
| **Paired t-test** |  |  |
|  | p-value [2] | <.0001 |
| **Change from Baseline to 24 Month follow up** |  |  |
|  | n | 39 |
|  | Mean | 67.2 |
|  | SD | 70.9 |
|  | Q1 | 22.5 |
|  | Median | 52.5 |
|  | Q3 | 101 |
|  | Range (Min.: Max.) | (-80.0: 314) |
|  | Missing | 10 |
| **ANOVA Analysis Result** |  |  |
|  | LS Mean Estimate | 63.9 |
|  | SE [1] | 11.2 |
|  | 95% CI (L.:U.) | (41.3: 86.5) |
|  | p-value [1] | <.0001 |
| **Paired t-test** |  |  |
|  | p-value [2] | <.0001 |
| **Note:** [1] LS Mean Estimate, SE and p-value for Mean change in Distance Covered was compared for visit using Mixed Model     for Repeated Measures (MMRM) ANOVA with visit as only factor [2] P-value for comparing baseline assessment to consecutive visits i.e.9 month vs. baseline, 12 month vs. baseline, 24 month vs.     baseline) computed from paired t-test.  **General Note:** > As interaction has not been significant, Right-sided and Left sided implant groups has been pooled for this analysis   by omitting all factors involving side of the implant from ANOVA. > Baseline value was defined as average of the all baseline 6-minute walk tests. If those values are within 10% of each other,   otherwise the last available 6-minute walk test have been used. | | |

## Table 14.2.2.4 Summary of Minnesota Living with Heart Failure (QOL) Questionnaire (Overall) -ITT Population (N=49)

|  | | **VNS Therapy System** | | |
| --- | --- | --- | --- | --- |
| **Visit/Category** | **Statistics, n (%)** | **Right Sided (n=26)** | **Left Sided (n=23)** | **Overall (N=49)** |
| **Baseline** |  |  |  |  |
|  | No. of Patients | 26 | 23 | 49 |
|  | n | 26 | 23 | 49 |
|  | Mean | 41.2 | 37.0 | 39.2 |
|  | SD | 10.8 | 13.0 | 12.0 |
|  | Q1 | 34.0 | 27.0 | 32.0 |
|  | Median | 38.0 | 36.0 | 37.0 |
|  | Q3 | 48.0 | 48.0 | 48.0 |
|  | Range (Min.: Max.) | (22.0: 70.0) | (10.0: 60.0) | (10.0: 70.0) |
|  |  |  |  |  |
| **9 Month follow up** |  |  |  |  |
|  | No. of Patients | 22 | 18 | 40 |
|  | n | 22 | 18 | 40 |
|  | Mean | 17.8 | 19.2 | 18.5 |
|  | SD | 6.79 | 10.6 | 8.63 |
|  | Q1 | 12.0 | 12.0 | 12.0 |
|  | Median | 19.5 | 15.0 | 17.5 |
|  | Q3 | 23.0 | 25.0 | 23.0 |
|  | Range (Min.: Max.) | (6.00: 32.0) | (7.00: 47.0) | (6.00: 47.0) |
|  |  |  |  |  |
| **12 Month follow up** |  |  |  |  |
|  | No. of Patients | 25 | 21 | 46 |
|  | n | 25 | 21 | 46 |
|  | Mean | 18.0 | 18.8 | 18.4 |
|  | SD | 8.46 | 9.46 | 8.84 |
|  | Q1 | 13.0 | 12.0 | 12.0 |
|  | Median | 16.0 | 16.0 | 16.0 |
|  | Q3 | 23.0 | 24.0 | 24.0 |
|  | Range (Min.: Max.) | (7.00: 47.0) | (6.00: 39.0) | (6.00: 47.0) |
|  |  |  |  |  |
| **24 Month follow up** |  |  |  |  |
|  | No. of Patients | 21 | 19 | 40 |
|  | n | 19 | 19 | 38 |
|  | Mean | 20.4 | 22.6 | 21.5 |
|  | SD | 13.2 | 12.2 | 12.5 |
|  | Q1 | 11.0 | 12.0 | 12.0 |
|  | Median | 16.0 | 18.0 | 16.5 |
|  | Q3 | 28.0 | 30.0 | 28.0 |
|  | Range (Min.: Max.) | (7.00: 61.0) | (7.00: 52.0) | (7.00: 61.0) |
|  |  |  |  |  |
|  | | | | |

## Table 14.2.2.4.1 Summary of Minnesota Living with Heart Failure (QOL) Questionnaire (Physical Factors) -ITT Population (N=49)

|  | | **VNS Therapy System** | | |
| --- | --- | --- | --- | --- |
| **Visit/Category** | **Statistics, n (%)** | **Right Sided (n=26)** | **Left Sided (n=23)** | **Overall (N=49)** |
| **Baseline** |  |  |  |  |
|  | No. of Patients | 26 | 23 | 49 |
|  | n | 26 | 23 | 49 |
|  | Mean | 17.7 | 16.7 | 17.2 |
|  | SD | 6.19 | 5.48 | 5.83 |
|  | Q1 | 12.0 | 13.0 | 13.0 |
|  | Median | 17.0 | 17.0 | 17.0 |
|  | Q3 | 22.0 | 20.0 | 22.0 |
|  | Range (Min.: Max.) | (9.00: 31.0) | (4.00: 27.0) | (4.00: 31.0) |
|  |  |  |  |  |
| **9 Month follow up** |  |  |  |  |
|  | No. of Patients | 22 | 18 | 40 |
|  | n | 22 | 18 | 40 |
|  | Mean | 7.95 | 8.78 | 8.33 |
|  | SD | 3.36 | 5.61 | 4.47 |
|  | Q1 | 5.00 | 5.00 | 5.00 |
|  | Median | 8.00 | 7.50 | 8.00 |
|  | Q3 | 10.0 | 11.0 | 10.5 |
|  | Range (Min.: Max.) | (1.00: 15.0) | (3.00: 26.0) | (1.00: 26.0) |
|  |  |  |  |  |
| **12 Month follow up** |  |  |  |  |
|  | No. of Patients | 25 | 21 | 46 |
|  | n | 25 | 21 | 46 |
|  | Mean | 8.68 | 8.71 | 8.70 |
|  | SD | 4.06 | 4.58 | 4.26 |
|  | Q1 | 7.00 | 6.00 | 6.00 |
|  | Median | 8.00 | 8.00 | 8.00 |
|  | Q3 | 10.0 | 11.0 | 11.0 |
|  | Range (Min.: Max.) | (2.00: 23.0) | (2.00: 19.0) | (2.00: 23.0) |
|  |  |  |  |  |
| **24 Month follow up** |  |  |  |  |
|  | No. of Patients | 21 | 19 | 40 |
|  | n | 19 | 19 | 38 |
|  | Mean | 8.37 | 10.3 | 9.32 |
|  | SD | 5.12 | 5.92 | 5.55 |
|  | Q1 | 5.00 | 6.00 | 5.00 |
|  | Median | 7.00 | 9.00 | 8.00 |
|  | Q3 | 11.0 | 13.0 | 11.0 |
|  | Range (Min.: Max.) | (2.00: 24.0) | (3.00: 26.0) | (2.00: 26.0) |
|  |  |  |  |  |
| **General Note:** > Physical factors: Sum of Questions 2,3,4,5,6,7,12 and 13 was taken for analysis. | | | | |

## Table 14.2.2.4.2 Summary of Minnesota Living with Heart Failure (QOL) Questionnaire (Emotional Factors) -ITT Population (N=49)

|  | | **VNS Therapy System** | | |
| --- | --- | --- | --- | --- |
| **Visit/Category** | **Statistics, n (%)** | **Right Sided (n=26)** | **Left Sided (n=23)** | **Overall (N=49)** |
| **Baseline** |  |  |  |  |
|  | No. of Patients | 26 | 23 | 49 |
|  | n | 26 | 23 | 49 |
|  | Mean | 9.73 | 6.70 | 8.31 |
|  | SD | 4.11 | 3.89 | 4.25 |
|  | Q1 | 7.00 | 5.00 | 5.00 |
|  | Median | 9.00 | 6.00 | 8.00 |
|  | Q3 | 13.0 | 8.00 | 11.0 |
|  | Range (Min.: Max.) | (3.00: 17.0) | (0.00: 17.0) | (0.00: 17.0) |
|  |  |  |  |  |
| **9 Month follow up** |  |  |  |  |
|  | No. of Patients | 22 | 18 | 40 |
|  | n | 22 | 18 | 40 |
|  | Mean | 3.95 | 4.50 | 4.20 |
|  | SD | 1.91 | 3.40 | 2.66 |
|  | Q1 | 3.00 | 2.00 | 3.00 |
|  | Median | 5.00 | 4.00 | 4.00 |
|  | Q3 | 5.00 | 6.00 | 6.00 |
|  | Range (Min.: Max.) | (0.00: 6.00) | (1.00: 15.0) | (0.00: 15.0) |
|  |  |  |  |  |
| **12 Month follow up** |  |  |  |  |
|  | No. of Patients | 25 | 21 | 46 |
|  | n | 25 | 21 | 46 |
|  | Mean | 3.72 | 4.24 | 3.96 |
|  | SD | 2.64 | 2.74 | 2.67 |
|  | Q1 | 2.00 | 2.00 | 2.00 |
|  | Median | 4.00 | 3.00 | 3.50 |
|  | Q3 | 5.00 | 6.00 | 6.00 |
|  | Range (Min.: Max.) | (0.00: 10.0) | (0.00: 11.0) | (0.00: 11.0) |
|  |  |  |  |  |
| **24 Month follow up** |  |  |  |  |
|  | No. of Patients | 21 | 19 | 40 |
|  | n | 19 | 19 | 38 |
|  | Mean | 5.11 | 5.11 | 5.11 |
|  | SD | 3.16 | 3.84 | 3.47 |
|  | Q1 | 3.00 | 3.00 | 3.00 |
|  | Median | 5.00 | 5.00 | 5.00 |
|  | Q3 | 6.00 | 7.00 | 6.00 |
|  | Range (Min.: Max.) | (1.00: 15.0) | (0.00: 18.0) | (0.00: 18.0) |
|  |  |  |  |  |
| **General Note:** > Emotional factors: Sum of Questions 17,18,19,20 and 21 was taken for analysis. | | | | |

## Table 14.2.2.5 Summary of Change in Minnesota Living with Heart Failure (QOL) Questionnaire from Baseline (Overall) -ITT Population (N=49)

|  | | **VNS Therapy System** | | | |
| --- | --- | --- | --- | --- | --- |
| **Visit/Category** | **Statistics, n (%)** | **Right Sided (n=26)** |  | **Left Sided (n=23)** | **Overall (N=49)** |
| **Change from Baseline to 9 Month follow up** |  |  |  |  |  |
|  | n | 22 |  | 18 | 40 |
|  | Mean | -24.5 |  | -17.9 | -21.6 |
|  | SD | 12.8 |  | 10.5 | 12.2 |
|  | Q1 | -31.0 |  | -25.0 | -29.5 |
|  | Median | -22.0 |  | -19.0 | -21.5 |
|  | Q3 | -17.0 |  | -11.0 | -15.0 |
|  | Range (Min.: Max.) | (-62.0: 2.00) |  | (-36.0: -2.00) | (-62.0: 2.00) |
|  | Missing | 4 |  | 5 | 9 |
| **ANOVA Analysis Result** |  |  |  |  |  |
|  | LS Mean Estimate | -22.7 |  | -17.7 |  |
|  | Difference Estimate [1] |  | -4.99 |  |  |
|  | SE [2] |  | 3.56 |  |  |
|  | 95% CI (L.:U.) |  | (-12.2: 2.20) |  |  |
|  | p-value [3] |  | 0.168 |  |  |
| **Paired t-test** |  |  |  |  |  |
|  | p-value [4] | <.0001 |  | <.0001 |  |
| **Change from Baseline to 12 Month follow up** |  |  |  |  |  |
|  | n | 25 |  | 21 | 46 |
|  | Mean | -23.5 |  | -18.1 | -21.0 |
|  | SD | 14.2 |  | 10.9 | 12.9 |
|  | Q1 | -29.0 |  | -26.0 | -27.0 |
|  | Median | -21.0 |  | -16.0 | -20.5 |
|  | Q3 | -18.0 |  | -12.0 | -14.0 |
|  | Range (Min.: Max.) | (-63.0: 10.0) |  | (-38.0: 5.00) | (-63.0: 10.0) |
|  | Missing | 1 |  | 2 | 3 |
| **ANOVA Analysis Result** |  |  |  |  |  |
|  | LS Mean Estimate | -23.3 |  | -18.1 |  |
|  | Difference Estimate [1] |  | -5.20 |  |  |
|  | SE [2] |  | 3.64 |  |  |
|  | 95% CI (L.:U.) |  | (-12.5: 2.12) |  |  |
|  | p-value [3] |  | 0.16 |  |  |
| **Paired t-test** |  |  |  |  |  |
|  | p-value [4] | <.0001 |  | <.0001 |  |
| **Change from Baseline to 24 Month follow up** |  |  |  |  |  |
|  | n | 19 |  | 19 | 38 |
|  | Mean | -19.8 |  | -14.8 | -17.3 |
|  | SD | 13.7 |  | 16.0 | 14.9 |
|  | Q1 | -29.0 |  | -27.0 | -28.0 |
|  | Median | -19.0 |  | -17.0 | -17.5 |
|  | Q3 | -15.0 |  | -3.00 | -11.0 |
|  | Range (Min.: Max.) | (-44.0: 19.0) |  | (-44.0: 13.0) | (-44.0: 19.0) |
|  | Missing | 7 |  | 4 | 11 |
| **ANOVA Analysis Result** |  |  |  |  |  |
|  | LS Mean Estimate | -20.5 |  | -14.4 |  |
|  | Difference Estimate [1] |  | -6.14 |  |  |
|  | SE [2] |  | 4.77 |  |  |
|  | 95% CI (L.:U.) |  | (-15.8: 3.51) |  |  |
|  | p-value [3] |  | 0.206 |  |  |
| **Paired t-test** |  |  |  |  |  |
|  | p-value [4] | <.0001 |  | 0.0008 |  |
| **Note:** [1] Difference estimate indicate Difference [(Right Sided) – (Left Sided)]. [2] SE indicates Standard Error of Differences [[(Right Sided) – (Left Sided)]. [3] Mean change in score was compared between the two VNS Therapy System using Mixed Model for Repeated Measures (MMRM), with VNS     Therapy System (Right/Left Sided), Visit, VNS Therapy System\*Visit as factors. [4] P-value for comparing baseline assessment to consecutive visits i.e.9 month vs. baseline, 12 month vs. baseline, 24 month vs.     baseline) computed from paired t-test.  **General Note:** > If the interaction is not significant, Right-sided and Left sided implant groups was pooled for further analysis by omitting all   factors involving side of the implant from ANOVA. | | | | | |

## Table 14.2.2.5-a Summary of Change in Minnesota Living with Heart Failure (QOL) Questionnaire from Baseline (Overall) (Pooled Analysis) - ITT Population (N=49)

| **Visit/Category** | **Statistics, n (%)** | **VNS Therapy System (n=49)** |
| --- | --- | --- |
| **Change from Baseline to 9 Month follow up** |  |  |
|  | n | 40 |
|  | Mean | -21.6 |
|  | SD | 12.2 |
|  | Q1 | -29.5 |
|  | Median | -21.5 |
|  | Q3 | -15.0 |
|  | Range (Min.: Max.) | (-62.0: 2.00) |
|  | Missing | 9 |
| **ANOVA Analysis Result** |  |  |
|  | LS Mean Estimate | -20.6 |
|  | SE [1] | 1.81 |
|  | 95% CI (L.:U.) | (-24.2: -16.9) |
|  | p-value [1] | <.0001 |
| **Paired t-test** |  |  |
|  | p-value [2] | <.0001 |
| **Change from Baseline to 12 Month follow up** |  |  |
|  | n | 46 |
|  | Mean | -21.0 |
|  | SD | 12.9 |
|  | Q1 | -27.0 |
|  | Median | -20.5 |
|  | Q3 | -14.0 |
|  | Range (Min.: Max.) | (-63.0: 10.0) |
|  | Missing | 3 |
| **ANOVA Analysis Result** |  |  |
|  | LS Mean Estimate | -21.0 |
|  | SE [1] | 1.88 |
|  | 95% CI (L.:U.) | (-24.8: -17.2) |
|  | p-value [1] | <.0001 |
| **Paired t-test** |  |  |
|  | p-value [2] | <.0001 |
| **Change from Baseline to 24 Month follow up** |  |  |
|  | n | 38 |
|  | Mean | -17.3 |
|  | SD | 14.9 |
|  | Q1 | -28.0 |
|  | Median | -17.5 |
|  | Q3 | -11.0 |
|  | Range (Min.: Max.) | (-44.0: 19.0) |
|  | Missing | 11 |
| **ANOVA Analysis Result** |  |  |
|  | LS Mean Estimate | -18.3 |
|  | SE [1] | 2.47 |
|  | 95% CI (L.:U.) | (-23.3: -13.3) |
|  | p-value [1] | <.0001 |
| **Paired t-test** |  |  |
|  | p-value [2] | <.0001 |
| **Note:** [1] LS Mean Estimate, SE and p-value for Mean change in score was compared for visit using Mixed Model     for Repeated Measures (MMRM) ANOVA with visit as only factor [2] P-value for comparing baseline assessment to consecutive visits i.e.9 month vs. baseline, 12 month vs. baseline,     24 month vs. baseline) computed from paired t-test.  **General Note:** > As interaction has not been significant, Right-sided and Left sided implant groups has been pooled for this analysis   by omitting all factors involving side of the implant from ANOVA. | | |

## Table 14.2.2.5-b Summary of Change in Minnesota Living with Heart Failure (QOL) Questionnaire from Baseline (Physical Factors) (Pooled Analysis) - ITT Population (N=49)

| **Visit/Category** | **Statistics, n (%)** | **VNS Therapy System (n=49)** |
| --- | --- | --- |
| **Change from Baseline to 9 Month follow up** |  |  |
|  | n | 40 |
|  | Mean | -9.03 |
|  | SD | 5.02 |
|  | Q1 | -13.0 |
|  | Median | -9.00 |
|  | Q3 | -6.00 |
|  | Range (Min.: Max.) | (-19.0: 1.00) |
|  | Missing | 9 |
| **ANOVA Analysis Result** |  |  |
|  | LS Mean Estimate | -8.77 |
|  | SE [1] | 0.806 |
|  | 95% CI (L.:U.) | (-10.4: -7.14) |
|  | p-value [1] | <.0001 |
| **Paired t-test** |  |  |
|  | p-value [2] | <.0001 |
| **Change from Baseline to 12 Month follow up** |  |  |
|  | n | 46 |
|  | Mean | -8.61 |
|  | SD | 5.90 |
|  | Q1 | -13.0 |
|  | Median | -8.00 |
|  | Q3 | -5.00 |
|  | Range (Min.: Max.) | (-19.0: 11.0) |
|  | Missing | 3 |
| **ANOVA Analysis Result** |  |  |
|  | LS Mean Estimate | -8.48 |
|  | SE [1] | 0.869 |
|  | 95% CI (L.:U.) | (-10.2: -6.73) |
|  | p-value [1] | <.0001 |
| **Paired t-test** |  |  |
|  | p-value [2] | <.0001 |
| **Change from Baseline to 24 Month follow up** |  |  |
|  | n | 38 |
|  | Mean | -7.45 |
|  | SD | 6.16 |
|  | Q1 | -11.0 |
|  | Median | -8.00 |
|  | Q3 | -3.00 |
|  | Range (Min.: Max.) | (-19.0: 5.00) |
|  | Missing | 11 |
| **ANOVA Analysis Result** |  |  |
|  | LS Mean Estimate | -7.88 |
|  | SE [1] | 0.977 |
|  | 95% CI (L.:U.) | (-9.85: -5.90) |
|  | p-value [1] | <.0001 |
| **Paired t-test** |  |  |
|  | p-value [2] | <.0001 |
| **Note:** [1] LS Mean Estimate, SE and p-value for Mean change in score was compared for visit using Mixed Model     for Repeated Measures (MMRM) ANOVA with visit as only factor [2] P-value for comparing baseline assessment to consecutive visits i.e.9 month vs. baseline, 12 month vs. baseline,     24 month vs. baseline) computed from paired t-test.  **General Note:** > As interaction has not been significant, Right-sided and Left sided implant groups has been pooled for this analysis   by omitting all factors involving side of the implant from ANOVA. > Physical factors: Sum of Questions 2,3,4,5,6,7,12 and 13 was taken for analysis. | | |

## Table 14.2.2.5-c Summary of Change in Minnesota Living with Heart Failure (QOL) Questionnaire from Baseline (Emotional Factors) (Pooled Analysis) - ITT Population (N=49)

| **Visit/Category** | **Statistics, n (%)** | **VNS Therapy System (n=49)** |
| --- | --- | --- |
| **Change from Baseline to 9 Month follow up** |  |  |
|  | n | 40 |
|  | Mean | -4.35 |
|  | SD | 4.25 |
|  | Q1 | -6.00 |
|  | Median | -4.50 |
|  | Q3 | -2.00 |
|  | Range (Min.: Max.) | (-16.0: 5.00) |
|  | Missing | 9 |
| **ANOVA Analysis Result** |  |  |
|  | LS Mean Estimate | -4.19 |
|  | SE [1] | 0.607 |
|  | 95% CI (L.:U.) | (-5.41: -2.97) |
|  | p-value [1] | <.0001 |
| **Paired t-test** |  |  |
|  | p-value [2] | <.0001 |
| **Change from Baseline to 12 Month follow up** |  |  |
|  | n | 46 |
|  | Mean | -4.48 |
|  | SD | 4.28 |
|  | Q1 | -7.00 |
|  | Median | -4.50 |
|  | Q3 | -1.00 |
|  | Range (Min.: Max.) | (-16.0: 2.00) |
|  | Missing | 3 |
| **ANOVA Analysis Result** |  |  |
|  | LS Mean Estimate | -4.51 |
|  | SE [1] | 0.622 |
|  | 95% CI (L.:U.) | (-5.76: -3.26) |
|  | p-value [1] | <.0001 |
| **Paired t-test** |  |  |
|  | p-value [2] | <.0001 |
| **Change from Baseline to 24 Month follow up** |  |  |
|  | n | 38 |
|  | Mean | -3.11 |
|  | SD | 5.08 |
|  | Q1 | -7.00 |
|  | Median | -3.00 |
|  | Q3 | 2.00 |
|  | Range (Min.: Max.) | (-12.0: 6.00) |
|  | Missing | 11 |
| **ANOVA Analysis Result** |  |  |
|  | LS Mean Estimate | -3.52 |
|  | SE [1] | 0.791 |
|  | 95% CI (L.:U.) | (-5.12: -1.93) |
|  | p-value [1] | <.0001 |
| **Paired t-test** |  |  |
|  | p-value [2] | 0.0006 |
| **Note:** [1] LS Mean Estimate, SE and p-value for Mean change in score was compared for visit using Mixed Model     for Repeated Measures (MMRM) ANOVA with visit as only factor [2] P-value for comparing baseline assessment to consecutive visits i.e.9 month vs. baseline, 12 month vs. baseline,     24 month vs. baseline) computed from paired t-test.  **General Note:** > As interaction has not been significant, Right-sided and Left sided implant groups has been pooled for this analysis   by omitting all factors involving side of the implant from ANOVA. > Physical factors: Sum of Questions 2,3,4,5,6,7,12 and 13 was taken for analysis. > Emotional factors: Sum of Questions 17,18,19,20 and 21 was taken for analysis. | | |

## Table 14.2.2.6 Summary of NYHA Class-ITT Population (N=49)

|  | **VNS Therapy System** | | | | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Right Sided** | | | | **Left Sided** | | | | **Overall** | | | |
| **Parameters/Visit** | **Class I** | **Class II** | **Class III** | **Class IV** | **Class I** | **Class II** | **Class III** | **Class IV** | **Class I** | **Class II** | **Class III** | **Class IV** |
| **Baseline Visit** |  |  |  |  |  |  |  |  |  |  |  |  |
| **Total no. of subjects** | 26 | 26 | 26 | 26 | 23 | 23 | 23 | 23 | 49 | 49 | 49 | 49 |
|  | 0(0.0%) | 13(50.0%) | 13(50.0%) | 0(0.0%) | 0(0.0%) | 15(65.2%) | 8(34.8%) | 0(0.0%) | 0(0.0%) | 28(57.1%) | 21(42.9%) | 0(0.0%) |
| **12 Months Follow-up Visit** |  |  |  |  |  |  |  |  |  |  |  |  |
| **Total no. of subjects** | 25 | 25 | 25 | 25 | 21 | 21 | 21 | 21 | 46 | 46 | 46 | 46 |
|  | 20(80.0%) | 5(20.0%) | 0(0.0%) | 0(0.0%) | 13(61.9%) | 8(38.1%) | 0(0.0%) | 0(0.0%) | 33(71.7%) | 13(28.3%) | 0(0.0%) | 0(0.0%) |
| **24 Months Follow-up Visit** |  |  |  |  |  |  |  |  |  |  |  |  |
| **Total no. of subject** | 21 | 21 | 21 | 21 | 18 | 18 | 18 | 18 | 39 | 39 | 39 | 39 |
|  | 15(71.4%) | 6(28.6%) | 0(0.0%) | 0(0.0%) | 12(66.7%) | 5(27.8%) | 1(5.6%) | 0(0.0%) | 27(69.2%) | 11(28.2%) | 1(2.6%) | 0(0.0%) |
| **Note:s** [1] Respective Subject count was used as denominator for percentage calculation. | | | | | | | | | | | | |

## Table 14.2.2.7 Summary of NYHA Class-ITT Population (N=49)

|  | | **VNS Therapy System** | |  |
| --- | --- | --- | --- | --- |
| **Visit** | **Category** | **Right Sided (N=26)** | **Left Sided (N=23)** | **Overall (N=49)** |
| **Change from Baseline to 12 Months Follow-up Visit** |  |  |  |  |
|  | **Total No. of Subjects** | 25 | 21 | 46 |
|  | **Improved** | 25(100.0%) | 18(85.7%) | 43(93.5%) |
|  | **No change** | 0(0.0%) | 3(14.3%) | 3(6.5%) |
|  | **Worsened** | 0(0.0%) | 0(0.0%) | 0(0.0%) |
| **Change from Baseline to 24 Months Follow-up Visit** |  |  |  |  |
|  | **Total No. of Subjects** | 21 | 19 | 40 |
|  | **Improved** | 20(95.2%) | 16(84.2%) | 36(90.0%) |
|  | **No change** | 1(4.8%) | 1(5.3%) | 2(5.0%) |
|  | **Worsened** | 0(0.0%) | 1(5.3%) | 1(2.5%) |
|  | **p-value [2]** |  | 0.0490 |  |
| **Note:** [1] Respective Subject count was used as denominator for percentage calculation. [2] p-value was calculated using CMH test with time (Baseline,12 Months Follow-up Visit and 30 Months Follow-up Visit) as a repeated measure.  **General Note:** Improved -Decrease in NYHA class No Change-Same NYHA class in both the visits Worsened -Increase NYHA class | | | | |

## Table 14.2.2.8d Summary of Heart Rate by Holter ECG (Average HR-24 Hour (bpm))- ITT Population(N=49)

|  | | **VNS Therapy System** | | |
| --- | --- | --- | --- | --- |
| **Parameters/Visit** | **Statistics** | **Right Sided (n=26)** | **Left Sided (n=23)** | **Overall (N=49)** |
| **Average HR-24 Hour (bpm)** |  |  |  |  |
| **Baseline** |  |  |  |  |
|  | Total No. of Subjects | 26 | 23 | 49 |
|  | n | 26 | 23 | 49 |
|  | Mean | 76.7 | 75.3 | 76.0 |
|  | SD | 10.4 | 9.16 | 9.76 |
|  | Median | 76.0 | 77.0 | 77.0 |
|  | Range (Min.: Max.) | (56.0: 99.0) | (59.0: 94.0) | (56.0: 99.0) |
|  | 95% CI | (72.5: 80.9) | (71.3: 79.3) | (73.2: 78.8) |
|  | Status |  |  |  |
|  | Normal | 25 (96.2 %) | 23 (100 %) | 48 (98.0 %) |
|  | Abnormal | 1 (3.85 %) | 0 (0.00%) | 1 (2.04 %) |
|  | Clinically Significant |  |  |  |
|  | Yes | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
|  | No | 1 (100 %) | 0 (0.00%) | 1 (100 %) |
| **9 months Follow-up Visit** |  |  |  |  |
|  | Total No. of Subjects | 22 | 18 | 40 |
|  | n | 22 | 18 | 40 |
|  | Mean | 68.4 | 72.5 | 70.3 |
|  | SD | 10.3 | 11.1 | 10.7 |
|  | Median | 69.0 | 69.0 | 69.0 |
|  | Range (Min.: Max.) | (53.0: 95.0) | (54.0: 94.0) | (53.0: 95.0) |
|  | 95% CI | (63.8: 73) | (67: 78) | (66.8: 73.7) |
|  | Status |  |  |  |
|  | Normal | 22 (100 %) | 18 (100 %) | 40 (100 %) |
|  | Abnormal | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
|  | Clinically Significant |  |  |  |
|  | Yes | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
|  | No | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| **12 months Follow-up Visit** |  |  |  |  |
|  | Total No. of Subjects | 25 | 21 | 46 |
|  | n | 25 | 21 | 46 |
|  | Mean | 69.3 | 70.2 | 69.7 |
|  | SD | 8.65 | 11.1 | 9.77 |
|  | Median | 69.0 | 70.0 | 69.0 |
|  | Range (Min.: Max.) | (55.0: 87.0) | (52.0: 90.0) | (52.0: 90.0) |
|  | 95% CI | (65.7: 72.9) | (65.2: 75.3) | (66.8: 72.6) |
|  | Status |  |  |  |
|  | Normal | 25 (100 %) | 21 (100 %) | 46 (100 %) |
|  | Abnormal | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
|  | Clinically Significant |  |  |  |
|  | Yes | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
|  | No | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| **24 months Follow-up Visit** |  |  |  |  |
|  | Total No. of Subjects | 21 | 19 | 40 |
|  | n | 18 | 18 | 36 |
|  | Mean | 68.4 | 70.9 | 69.7 |
|  | SD | 9.57 | 9.00 | 9.25 |
|  | Median | 67.0 | 70.0 | 67.5 |
|  | Range (Min.: Max.) | (50.0: 87.0) | (57.0: 85.0) | (50.0: 87.0) |
|  | 95% CI | (63.7: 73.2) | (66.5: 75.4) | (66.6: 72.8) |
|  | Status |  |  |  |
|  | Normal | 18 (85.7 %) | 18 (94.7 %) | 36 (90.0 %) |
|  | Abnormal | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
|  | Clinically Significant |  |  |  |
|  | Yes | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
|  | No | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
|  | | | | |

## Table 14.2.2.9d Summary of Change in Heart Rate Variability Average HR-24 Hour (bpm) -ITT Population(N=49)

|  | | **VNS Therapy System** | | | |
| --- | --- | --- | --- | --- | --- |
| **Parameters/Visit** | **Statistics** | **Right Sided (n=26)** |  | **Left Sided (n=23)** | **Overall (N=49)** |
| **Change from Baseline to 9 months Follow-up Visit** |  |  |  |  |  |
|  | n | 22 |  | 18 | 40 |
|  | Mean | -7.09 |  | -2.83 | -5.18 |
|  | SD | 9.69 |  | 9.04 | 9.53 |
|  | Q1 | -13.0 |  | -9.00 | -11.0 |
|  | Median | -3.50 |  | -4.00 | -3.50 |
|  | Q3 | -3.00 |  | 2.00 | 0.50 |
|  | Range(Min.:Max.) | (-29.0: 14.0) |  | (-18.0: 15.0) | (-29.0: 15.0) |
|  | Missing | 4 |  | 5 | 9 |
| **Change from Baseline to 12 months Follow-up Visit** |  |  |  |  |  |
|  | n | 25 |  | 21 | 46 |
|  | Mean | -6.52 |  | -4.76 | -5.72 |
|  | SD | 8.95 |  | 9.13 | 8.98 |
|  | Q1 | -12.0 |  | -11.0 | -12.0 |
|  | Median | -5.00 |  | -6.00 | -6.00 |
|  | Q3 | 0.00 |  | 2.00 | 0.00 |
|  | Range(Min.:Max.) | (-26.0: 9.00) |  | (-19.0: 11.0) | (-26.0: 11.0) |
|  | Missing | 1 |  | 2 | 3 |
| **Change from Baseline to 24 months Follow-up Visit** |  |  |  |  |  |
|  | n | 18 |  | 18 | 36 |
|  | Mean | -7.56 |  | -4.50 | -6.03 |
|  | SD | 11.0 |  | 11.4 | 11.1 |
|  | Q1 | -20.0 |  | -12.0 | -14.0 |
|  | Median | -6.00 |  | -2.50 | -4.50 |
|  | Q3 | -1.00 |  | 2.00 | 1.50 |
|  | Range(Min.:Max.) | (-24.0: 10.0) |  | (-33.0: 14.0) | (-33.0: 14.0) |
|  | Missing | 8 |  | 5 | 13 |
| **ANOVA Analysis Result** |  |  |  |  |  |
|  | LS Mean Estimate | -6.53 |  | -4.25 |  |
|  | Difference Estimate [1] |  | -2.28 |  |  |
|  | SE [2] |  | 2.89 |  |  |
|  | 95% CI (L.:U.) |  | (-8.11: 3.55) |  |  |
|  | p-value [3] |  | 0.434 |  |  |
| **Paired t-test** |  |  |  |  |  |
|  | p-value [4] | 0.0025 |  | 0.2014 |  |
| **ANOVA Analysis Result** |  |  |  |  |  |
|  | LS Mean Estimate | -6.42 |  | -4.76 |  |
|  | Difference Estimate [1] |  | -1.66 |  |  |
|  | SE [2] |  | 2.65 |  |  |
|  | 95% CI (L.:U.) |  | (-7.00: 3.69) |  |  |
|  | p-value [3] |  | 0.536 |  |  |
| **Paired t-test** |  |  |  |  |  |
|  | p-value [4] | 0.0013 |  | 0.0268 |  |
| **ANOVA Analysis Result** |  |  |  |  |  |
|  | LS Mean Estimate | -7.46 |  | -5.01 |  |
|  | Difference Estimate [1] |  | -2.46 |  |  |
|  | SE [2] |  | 3.49 |  |  |
|  | 95% CI (L.:U.) |  | (-9.53: 4.62) |  |  |
|  | p-value [3] |  | 0.486 |  |  |
| **Paired t-test** |  |  |  |  |  |
|  | p-value [4] | 0.0095 |  | 0.1125 |  |
| **Note:** [1] Difference estimate indicate Difference [(Right Sided) – (Left Sided)]. [2] SE indicates Standard Error of Differences [[(Right Sided) – (Left Sided)]. [3] Mean change in Heart Rate by Holter ECG was compared between the two VNS Therapy System using Mixed Model for Repeated     Measures (MMRM), with VNS Therapy System (Right/Left Sided), Visit, VNS Therapy System\*Visit as factors. [2] P-value for comparing baseline assessment to consecutive visits i.e.9 month vs. baseline, 12 month vs. baseline, 24 month vs  baseline) computed from paired t-test. **General Note:**  If the interaction is not significant, Right-sided and Left sided implant groups was pooled for further analysis by omitting al factors involving side of the implant from ANOVA. | | | | | |

## Table 14.2.2.9d\_a Summary of Change in Heart Rate by Holter ECG - Average HR-24 Hour (bpm)(Pooled Analysis) (N=49)

| **Parameters/Visit** | **Statistics** | **VNS Therapy System (N=49)** |
| --- | --- | --- |
|  |  |  |
| **Change from Baseline to 9 months Follow-up Visit** |  |  |
|  | n | 40 |
|  | Mean | -5.18 |
|  | SD | 9.53 |
|  | Q1 | -11.0 |
|  | Median | -3.50 |
|  | Q3 | 0.50 |
|  | Range(Min.:Max.) | (-29.0: 15.0) |
|  | Missing | 9 |
|  |  |  |
| **ANOVA Analysis Result** |  |  |
|  | LS Mean Estimate | -4.98 |
|  | SE [2] | 1.44 |
|  | 95% CI (L.:U.) | (-7.88: -2.09) |
|  | p-value [3] | 0.0012 |
|  |  |  |
| **Paired t-test** |  |  |
|  | p-value [4] | 0.0014 |
|  |  |  |
| **Change from Baseline to 6 months Follow-up Visit** |  |  |
|  | n | 46 |
|  | Mean | -5.72 |
|  | SD | 8.98 |
|  | Q1 | -12.0 |
|  | Median | -6.00 |
|  | Q3 | 0.00 |
|  | Range(Min.:Max.) | (-26.0: 11.0) |
|  | Missing | 3 |
|  |  |  |
| **ANOVA Analysis Result** |  |  |
|  | LS Mean Estimate | -5.69 |
|  | SE [2] | 1.31 |
|  | 95% CI (L.:U.) | (-8.32: -3.05) |
|  | p-value [3] | <.0001 |
|  |  |  |
| **Paired t-test** |  |  |
|  | p-value [4] | <.0001 |
|  |  |  |
| **Change from Baseline to 18 months Follow-up Visit** |  |  |
|  | n | 36 |
|  | Mean | -6.03 |
|  | SD | 11.1 |
|  | Q1 | -14.0 |
|  | Median | -4.50 |
|  | Q3 | 1.50 |
|  | Range(Min.:Max.) | (-33.0: 14.0) |
|  | Missing | 13 |
|  |  |  |
| **ANOVA Analysis Result** |  |  |
|  | LS Mean Estimate | -6.13 |
|  | SE [2] | 1.75 |
|  | 95% CI (L.:U.) | (-9.65: -2.60 ) |
|  | p-value [3] | 0.0011 |
|  |  |  |
| **Paired t-test** |  |  |
|  | p-value [4] | 0.0026 |
| **Note:** [1] Difference estimate indicate Difference [baseline vs 3 months, baseline vs 6 months]. [2] SE indicates Standard Error of Differences [baseline vs 3 months ,baseline vs 6 months]. [3] Mean change in Heart Rate by Holter ECG was compared the Pooled VNS Therapy System using Mixed Model for Repeated    Measures (MMRM) . | | |

## Table 14.2.2.10 Summary of Heart Rate Variability by Holter ECG (SDNN (ms)) at Each Visit(N=49)

|  | | **VNS Therapy System** | | |
| --- | --- | --- | --- | --- |
| **Parameters/Visit** | **Statistics** | **Right Sided (N=26)** | **Left Sided (N=23)** | **Overall (N=49)** |
| SDNN (ms) |  |  |  |  |
| Baseline | Total No. of Subjects | 26 | 23 | 49 |
|  | n | 25 | 22 | 47 |
|  | Mean | 95.7 | 102 | 98.8 |
|  | SD | 28.6 | 51.0 | 40.3 |
|  | Q1 | 69.5 | 81.5 | 69.5 |
|  | Median | 100 | 91.5 | 98.1 |
|  | Q3 | 110 | 117 | 113 |
|  | Range (Min.:Max.) | (47.0:161) | (46.3:286) | (46.3:286) |
|  |  |  |  |  |
| 9 months Follow-up Visit | Total No. of Subjects | 22 | 18 | 40 |
|  | n | 20 | 18 | 38 |
|  | Mean | 101 | 96.6 | 98.9 |
|  | SD | 30.6 | 40.6 | 35.3 |
|  | Q1 | 82.1 | 81.0 | 81.2 |
|  | Median | 89.1 | 87.6 | 87.6 |
|  | Q3 | 122 | 111 | 111 |
|  | Range (Min.:Max.) | (54.0:182) | (53.6:242) | (53.6:242) |
|  |  |  |  |  |
| 12 months Follow-up Visit | Total No. of Subjects | 25 | 21 | 46 |
|  | n | 25 | 21 | 46 |
|  | Mean | 106 | 113 | 109 |
|  | SD | 29.8 | 49.9 | 39.9 |
|  | Q1 | 82.9 | 77.0 | 82.0 |
|  | Median | 103 | 105 | 104 |
|  | Q3 | 126 | 115 | 126 |
|  | Range (Min.:Max.) | (68.0:181) | (63.4:280) | (63.4:280) |
|  |  |  |  |  |
| 24 months Follow-up Visit | Total No. of Subjects | 21 | 19 | 40 |
|  | n | 19 | 19 | 38 |
|  | Mean | 114 | 101 | 107 |
|  | SD | 44.4 | 42.3 | 43.3 |
|  | Q1 | 84.0 | 70.5 | 82.0 |
|  | Median | 104 | 95.0 | 98.4 |
|  | Q3 | 123 | 127 | 123 |
|  | Range (Min.:Max.) | (62.7:243) | (29.0:209) | (29.0:243) |
|  |  |  |  |  |
|  | | | | |

## Table 14.2.2.11 Summary of Change in Heart Rate variability SDNN (ms) -ITT Population (N=49)

|  | | **VNS Therapy System** | | | |
| --- | --- | --- | --- | --- | --- |
| **Parameters/Visit** | **Statistics** | **Right Sided (N=26)** |  | **Left Sided (N=23)** | **Overall (N=49)** |
|  |  |  |  |  |  |
| **Change from Baseline to 9 months follow up Visit** |  |  |  |  |  |
|  | n | 19 |  | 17 | 36 |
|  | Mean | 2.91 |  | -8.31 | -2.39 |
|  | SD | 26.7 |  | 69.6 | 51.1 |
|  | Q1 | -24.0 |  | -12.0 | -19.4 |
|  | Median | 11.7 |  | -1.50 | 1.25 |
|  | Q3 | 26.0 |  | 23.1 | 23.6 |
|  | Range(Min.:Max.) | (-37.9:54.0) |  | (-232:117) | (-232:117) |
|  | Missing | 7 |  | 6 | 13 |
|  |  |  |  |  |  |
| **ANOVA Analysis Result** |  |  |  |  |  |
|  | LS Mean Estimate | 2.30 |  | -12.9 |  |
|  | Difference Estimate [1] |  | 15.2 |  |  |
|  | SE [2] |  | 16.2 |  |  |
|  | 95% CI (L.:U.) |  | (-18.1: 48.6) |  |  |
|  | p-value [3] |  | 0.36 |  |  |
|  |  |  |  |  |  |
| **Paired t-test** |  |  |  |  |  |
|  | p-value [4] | 0.6408 |  | 0.6292 |  |
|  |  |  |  |  |  |
| **Change from Baseline to 12 months follow up Visit** |  |  |  |  |  |
|  | n | 24 |  | 20 | 44 |
|  | Mean | 8.90 |  | 8.83 | 8.87 |
|  | SD | 39.7 |  | 57.6 | 48.0 |
|  | Q1 | -20.3 |  | -8.55 | -14.3 |
|  | Median | 7.65 |  | 9.05 | 7.65 |
|  | Q3 | 32.2 |  | 39.7 | 34.6 |
|  | Range(Min.:Max.) | (-64.0:101) |  | (-187:104) | (-187:104) |
|  | Missing | 2 |  | 3 | 5 |
|  |  |  |  |  |  |
| **ANOVA Analysis Result** |  |  |  |  |  |
|  | LS Mean Estimate | 8.90 |  | 8.83 |  |
|  | Difference Estimate [1] |  | 0.0742 |  |  |
|  | SE [2] |  | 15.2 |  |  |
|  | 95% CI (L.:U.) |  | (-30.9: 31.0) |  |  |
|  | p-value [3] |  | 1.00 |  |  |
|  |  |  |  |  |  |
| **Paired t-test** |  |  |  |  |  |
|  | p-value [4] | 0.2830 |  | 0.5011 |  |
|  |  |  |  |  |  |
| **Change from Baseline to 24 months follow up Visit** |  |  |  |  |  |
|  | n | 18 |  | 18 | 36 |
|  | Mean | 16.6 |  | -1.81 | 7.37 |
|  | SD | 35.4 |  | 76.9 | 59.7 |
|  | Q1 | -7.50 |  | -18.0 | -16.5 |
|  | Median | 18.6 |  | 3.40 | 14.1 |
|  | Q3 | 37.2 |  | 32.1 | 33.6 |
|  | Range(Min.:Max.) | (-47.0:82.5) |  | (-257:121) | (-257:121) |
|  | Missing | 8 |  | 5 | 13 |
|  |  |  |  |  |  |
| **ANOVA Analysis Result** |  |  |  |  |  |
|  | LS Mean Estimate | 13.7 |  | 4.47 |  |
|  | Difference Estimate [1] |  | 9.24 |  |  |
|  | SE [2] |  | 19.9 |  |  |
|  | 95% CI (L.:U.) |  | (-32.1: 50.6) |  |  |
|  | p-value [3] |  | 0.65 |  |  |
|  |  |  |  |  |  |
| **Paired t-test** |  |  |  |  |  |
|  | p-value [4] | 0.0640 |  | 0.9215 |  |
| **Note:** [1] Difference estimate indicate Difference [(Right Sided) – (Left Sided)]. [2] SE indicates Standard Error of Differences [[(Right Sided) – (Left Sided)]. [3] Mean change in SDNN (ms) was compared between the two VNS Therapy System using Mixed Model for     , with VNS Therapy System (Right/Left Sided),Visit, VNS Therapy System\*Visit as factors. [4] P-value for comparing baseline assessment to consecutive visits i.e.9 month vs. baseline, 12 month vs. baseline, 24 month vs. baseline) computed from paired t-test. | | | | | |

## Table 14.2.2.11-a Summary of Change in Heart Rate variability (SDNN (ms)) (Pooled Analysis) -ITT Population (N=49)

| **Parameters/Visit** | **Statistics** | **VNS Therapy System (N=49)** |
| --- | --- | --- |
| **Change from Baseline to 9 months follow up Visit** |  |  |
|  | n | 36 |
|  | Mean | -2.39 |
|  | SD | 51.1 |
|  | Q1 | -19.4 |
|  | Median | 1.25 |
|  | Q3 | 23.6 |
|  | Range (Min.:Max.) | (-232:117) |
|  | Missing | 13 |
|  |  |  |
| **ANOVA Analysis Result** |  |  |
|  | LS Mean Estimate | -4.25 |
|  | SE | 7.61 |
|  | 95% CI (L.:U.) | (-19.6: 11.1) |
|  | p-value [1] | 0.58 |
|  |  |  |
| **Paired t-test** |  |  |
|  | p-value [2] | 0.7811 |
|  |  |  |
| **Change from Baseline to 12 months follow up Visit** |  |  |
|  | n | 44 |
|  | Mean | 8.87 |
|  | SD | 48.0 |
|  | Q1 | -14.3 |
|  | Median | 7.65 |
|  | Q3 | 34.6 |
|  | Range(Min.:Max.) | (-187:104) |
|  | Missing | 5 |
|  |  |  |
| **ANOVA Analysis Result** |  |  |
|  | LS Mean Estimate | 8.87 |
|  | SE | 7.24 |
|  | 95% CI (L.:U.) | (-5.73: 23.5) |
|  | p-value [1] | 0.23 |
|  |  |  |
| **Paired t-test** |  |  |
|  | p-value [2] | 0.2272 |
|  |  |  |
| **Change from Baseline to 24 months follow up Visit** |  |  |
|  | n | 36 |
|  | Mean | 7.37 |
|  | SD | 59.7 |
|  | Q1 | -16.5 |
|  | Median | 14.1 |
|  | Q3 | 33.6 |
|  | Range (Min.:Max.) | (-257:121) |
|  | Missing | 13 |
|  |  |  |
| **ANOVA Analysis Result** |  |  |
|  | LS Mean Estimate | 5.68 |
|  | SE | 9.29 |
|  | 95% CI (L.:U.) | (-13.1: 24.4) |
|  | p-value [1] | 0.54 |
|  |  |  |
| **Paired t-test** |  |  |
|  | p-value [2] | 0.4639 |
|  |  |  |
| **Note:** **Note:** [1] LS Mean Estimate, SE and p-value for Mean change was compared for visit using Mixed Model for Repeated Measures (MMRM) ANOVA with visit as only factor. [2] P-value for comparing baseline assessment to consecutive visits i.e.9 month vs. baseline, 12 month vs. baseline, 24 month vs.     baseline) computed from paired t-test.  **General Note:** > As interaction has not been significant, Right sided and Left sided implant groups has been pooled for this analysis by    omitting all factors involving side of the implant from ANOVA. | | |

## Table 14.3.2.1 Summary of Adverse Events– Overall Summary (N=49)

|  | **VNS Therapy System** | |  |
| --- | --- | --- | --- |
|  | **Right Sided (n=26)** | **Left Sided (n=23)** | **Overall (n=49)** |
|  |  |  |  |
| AEs Reported | 66 | 30 | 96 |
|  |  |  |  |
| Subjects Reporting 1 AE | 6(23.1%) | 7(30.4%) | 13(26.5%) |
|  |  |  |  |
| Subjects Reporting >1 AE | 14(53.8%) | 7(30.4%) | 21(42.9%) |
|  |  |  |  |
| Subjects Reporting AEs Leading to Withdraw | 1(3.8%) | 0(0.0%) | 1(2.0%) |
|  |  |  |  |
| Subjects Reporting Any AEs, n (%) [1] | 20(76.9%) | 14(60.9%) | 34(69.4%) |
|  |  |  |  |
| Subjects Reporting Death | 5(19.2%) | 3(13.0%) | 8(16.3%) |
|  |  |  |  |
| Subjects Reporting No AEs | 6(23.1%) | 9(39.1%) | 15(30.6%) |
|  |  |  |  |
| Subjects Reporting Serious AEs | 9(34.6%) | 5(21.7%) | 14(28.6%) |
| **Note:** [1] Respective column header group counts were used as denominator for percentage calculation. **General Note:** > Zero frequencies are presented by “0(0.0) “. | | | |

## Table 14.3.2.2 Summary of Adverse Events by SOC and Preferred Term - Safety Population (N=49)

|  | **VNS Therapy System** | |  |
| --- | --- | --- | --- |
| **System Organ Class (SOC) / Preferred Term (PT)** | **Right Sided (N=26)** | **Left Sided (N=23)** | **Overall (N=49)** |
| Total Number of Subjects with at least One Adverse Event, n (%) [1] | 20 (76.9%) | 14 (60.9%) | 34 (69.4%) |
|  |  |  |  |
| Total Number of Adverse Events | 66 | 30 | 96 |
|  |  |  |  |
| Blood and lymphatic system disorders | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Anaemia megaloblastic, Malaria | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |
| Cardiac disorders | 8 (30.8%) | 4 (17.4%) | 12 (24.5%) |
| Angina pectoris | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Arrhythmia | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cardiac failure | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cardiac failure congestive | 2 (7.7%) | 0 (0.0 %) | 2 (4.1%) |
| Dyspnoea | 3 (11.5%) | 3 (13.0%) | 6 (12.2%) |
| Dyspnoea exertional | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Ventricular tachycardia | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |
| Ear and labyrinth disorders | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Ear pain | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Otorrhoea | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |
| Eye disorders | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cataract | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |
| Gastrointestinal disorders | 4 (15.4%) | 2 (8.7%) | 6 (12.2%) |
| Abdominal pain | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Diarrhoea | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Dysphagia | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Mouth haemorrhage | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Vomiting | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |
| General disorders and administration site conditions | 9 (34.6%) | 5 (21.7%) | 14 (28.6%) |
| Implant site pain | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Non-cardiac chest pain | 4 (15.4%) | 2 (8.7%) | 6 (12.2%) |
| Pain | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Pyrexia | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Sudden cardiac death | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Sudden death | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
| Swelling | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |
| Infections and infestations | 3 (11.5%) | 1 (4.3%) | 4 (8.2%) |
| Bacterial infection | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Diarrhoea infectious | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Nasopharyngitis | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Viral infection | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |
| Injury, poisoning and procedural complications | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Fall | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Joint injury | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |
| Investigations | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Weight increased | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |
| Metabolism and nutrition disorders | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Hypoglycaemia | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Hypoproteinemia | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |
| Musculoskeletal and connective tissue disorders | 4 (15.4%) | 3 (13.0%) | 7 (14.3%) |
| Arthritis | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Muscle spasms | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Musculoskeletal pain | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Neck pain | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Pain in extremity | 2 (7.7%) | 2 (8.7%) | 4 (8.2%) |
|  |  |  |  |
| Nervous system disorders | 8 (30.8%) | 4 (17.4%) | 12 (24.5%) |
| Amnesia | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Burning sensation | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
| Cerebrovascular accident, Aphasia, Hemiplegia | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Dizziness | 4 (15.4%) | 0 (0.0 %) | 4 (8.2%) |
| Facial paralysis | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Haemorrhagic transformation stroke, Cerebrovascular accident, Hemiparesis | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Headache | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Ischaemic stroke, Cerebrovascular accident | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Loss of consciousness | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Tremor | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |
| Psychiatric disorders | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Insomnia | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |
| Respiratory, thoracic and mediastinal disorders | 9 (34.6%) | 5 (21.7%) | 14 (28.6%) |
| Cough | 3 (11.5%) | 2 (8.7%) | 5 (10.2%) |
| Dysphonia | 3 (11.5%) | 1 (4.3%) | 4 (8.2%) |
| Productive cough | 2 (7.7%) | 2 (8.7%) | 4 (8.2%) |
| Throat tightness | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |
| Skin and subcutaneous tissue disorders | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Skin lesion | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |
| Vascular disorders | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Peripheral embolism,Cardiac failure congestive | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |
| **Note:** [1] Respective column header group counts were used as denominator for percentage calculation. **General Note:** > Adverse events were coded using MedDRA version 21.1. Patients were reported more than one event per system organ class or preferred term. Patients were counted once for each system organ class or preferred term. > An AE is defined as any event that existed before study drug administration and increased in severity, or any event that only occurred after study drug administration. > Zero frequencies are presented by “0(0.0) “. | | | |

## Table 14.3.2.3 Summary of Adverse Events by Maximum Intensity - Safety Population (N=49)

|  | | **VNS Therapy System** | |  |
| --- | --- | --- | --- | --- |
| **System Organ Class (SOC) / Preferred Term (PT)** | **Intensity** | **Right Sided (N=26)** | **Left Sided (N=23)** | **Overall (N=49)** |
| Total Number of Subjects with at least One Adverse Event, n (%) [1] |  | 20 (76.9%) | 14 (60.9%) | 34 (69.4%) |
|  |  |  |  |  |
| Total Number of Adverse Events |  | 66 | 30 | 96 |
|  |  |  |  |  |
| Blood and lymphatic system disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Anaemia megaloblastic, Malaria |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Severe | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Cardiac disorders |  | 8 (30.8%) | 4 (17.4%) | 12 (24.5%) |
| Angina pectoris |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Mild | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Arrhythmia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Severe | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cardiac failure |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Mild | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cardiac failure congestive |  | 2 (7.7%) | 0 (0.0 %) | 2 (4.1%) |
|  | Severe | 2 (7.7%) | 0 (0.0 %) | 2 (4.1%) |
| Dyspnoea |  | 3 (11.5%) | 3 (13.0%) | 6 (12.2%) |
|  | Mild | 2 (7.7%) | 2 (8.7%) | 4 (8.2%) |
|  | Severe | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Dyspnoea exertional |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Mild | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Ventricular tachycardia |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Severe | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Ear and labyrinth disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Ear pain |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Mild | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Otorrhoea |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Mild | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Eye disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cataract |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Moderate | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Gastrointestinal disorders |  | 4 (15.4%) | 2 (8.7%) | 6 (12.2%) |
| Abdominal pain |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Mild | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Diarrhoea |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | Mild | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Dysphagia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Mild | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Mouth haemorrhage |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Mild | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Vomiting |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Mild | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| General disorders and administration site conditions |  | 9 (34.6%) | 5 (21.7%) | 14 (28.6%) |
| Implant site pain |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Mild | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Non-cardiac chest pain |  | 4 (15.4%) | 2 (8.7%) | 6 (12.2%) |
|  | Mild | 4 (15.4%) | 2 (8.7%) | 6 (12.2%) |
| Pain |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Mild | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Pyrexia |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | Mild | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Moderate | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Sudden cardiac death |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Severe | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Sudden death |  | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
|  | Severe | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
| Swelling |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Moderate | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Infections and infestations |  | 3 (11.5%) | 1 (4.3%) | 4 (8.2%) |
| Bacterial infection |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Mild | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Diarrhoea infectious |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Mild | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Nasopharyngitis |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Mild | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Viral infection |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Mild | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Injury, poisoning and procedural complications |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Fall |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Mild | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Joint injury |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Mild | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Investigations |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Weight increased |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Mild | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Metabolism and nutrition disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Hypoglycaemia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Mild | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Hypoproteinemia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Mild | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Musculoskeletal and connective tissue disorders |  | 4 (15.4%) | 3 (13.0%) | 7 (14.3%) |
| Arthritis |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Moderate | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Muscle spasms |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Mild | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Musculoskeletal pain |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | Mild | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Neck pain |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Mild | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Pain in extremity |  | 2 (7.7%) | 2 (8.7%) | 4 (8.2%) |
|  | Mild | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Moderate | 1 (3.8%) | 2 (8.7%) | 3 (6.1%) |
|  |  |  |  |  |
| Nervous system disorders |  | 8 (30.8%) | 4 (17.4%) | 12 (24.5%) |
| Amnesia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Mild | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Burning sensation |  | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
|  | Mild | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
| Cerebrovascular accident, Aphasia, Hemiplegia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Severe | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Dizziness |  | 4 (15.4%) | 0 (0.0 %) | 4 (8.2%) |
|  | Mild | 4 (15.4%) | 0 (0.0 %) | 4 (8.2%) |
| Facial paralysis |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Mild | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Haemorrhagic transformation stroke, Cerebrovascular accident, Hemiparesis |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Severe | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Headache |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | Mild | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Ischaemic stroke, Cerebrovascular accident |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Severe | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Loss of consciousness |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Mild | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Tremor |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Moderate | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Psychiatric disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Insomnia |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Mild | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Respiratory, thoracic and mediastinal disorders |  | 9 (34.6%) | 5 (21.7%) | 14 (28.6%) |
| Cough |  | 3 (11.5%) | 2 (8.7%) | 5 (10.2%) |
|  | Mild | 3 (11.5%) | 1 (4.3%) | 4 (8.2%) |
|  | Moderate | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Dysphonia |  | 3 (11.5%) | 1 (4.3%) | 4 (8.2%) |
|  | Mild | 3 (11.5%) | 1 (4.3%) | 4 (8.2%) |
| Productive cough |  | 2 (7.7%) | 2 (8.7%) | 4 (8.2%) |
|  | Mild | 2 (7.7%) | 2 (8.7%) | 4 (8.2%) |
| Throat tightness |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Mild | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Skin and subcutaneous tissue disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Skin lesion |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Mild | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Vascular disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Peripheral embolism,Cardiac failure congestive |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Severe | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| **Note:** [1] Respective column header group counts were used as denominator for percentage calculation. **General Note:** > Adverse events were coded using MedDRA version 21.1. Patients were reported more than one event per system organ class or preferred term. Patients were counted once for each system organ class or preferred term. > An AE is defined as any event that existed before study drug administration and increased in severity, or any event that only occurred after study drug administration. > Zero frequencies are presented by “0(0.0) “. | | | | |

## Table 14.3.2.4 Summary of Adverse Events by Causality Relationship to Implant - Safety Population (N=49)

|  | | **VNS Therapy System** | |  |
| --- | --- | --- | --- | --- |
| **System Organ Class (SOC) / Preferred Term (PT)** | **Causality Relationship to Implant** | **Right Sided (N=26)** | **Left Sided (N=23)** | **Overall (N=49)** |
| Total Number of Subjects with at least One Adverse Event, n (%) [1] |  | 20 (76.9%) | 14 (60.9%) | 34 (69.4%) |
|  |  |  |  |  |
| Total Number of Adverse Events |  | 66 | 30 | 96 |
|  |  |  |  |  |
| Blood and lymphatic system disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Anaemia megaloblastic, Malaria |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Cardiac disorders |  | 8 (30.8%) | 4 (17.4%) | 12 (24.5%) |
| Angina pectoris |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Arrhythmia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cardiac failure |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cardiac failure congestive |  | 2 (7.7%) | 0 (0.0 %) | 2 (4.1%) |
|  | Not Related | 2 (7.7%) | 0 (0.0 %) | 2 (4.1%) |
| Dyspnoea |  | 3 (11.5%) | 3 (13.0%) | 6 (12.2%) |
|  | Not Related | 3 (11.5%) | 3 (13.0%) | 6 (12.2%) |
| Dyspnoea exertional |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Ventricular tachycardia |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Ear and labyrinth disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Ear pain |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Otorrhoea |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Eye disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cataract |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Gastrointestinal disorders |  | 4 (15.4%) | 2 (8.7%) | 6 (12.2%) |
| Abdominal pain |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Diarrhoea |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | Not Related | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Dysphagia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Mouth haemorrhage |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Vomiting |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| General disorders and administration site conditions |  | 9 (34.6%) | 5 (21.7%) | 14 (28.6%) |
| Implant site pain |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Non-cardiac chest pain |  | 4 (15.4%) | 2 (8.7%) | 6 (12.2%) |
|  | Not Related | 4 (15.4%) | 2 (8.7%) | 6 (12.2%) |
| Pain |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Pyrexia |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | Not Related | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Sudden cardiac death |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Sudden death |  | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
|  | Not Related | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
| Swelling |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Infections and infestations |  | 3 (11.5%) | 1 (4.3%) | 4 (8.2%) |
| Bacterial infection |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Diarrhoea infectious |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Nasopharyngitis |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Viral infection |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Injury, poisoning and procedural complications |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Fall |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Joint injury |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Investigations |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Weight increased |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Metabolism and nutrition disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Hypoglycaemia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Hypoproteinemia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Musculoskeletal and connective tissue disorders |  | 4 (15.4%) | 3 (13.0%) | 7 (14.3%) |
| Arthritis |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Muscle spasms |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Musculoskeletal pain |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Neck pain |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Pain in extremity |  | 2 (7.7%) | 2 (8.7%) | 4 (8.2%) |
|  | Not Related | 2 (7.7%) | 2 (8.7%) | 4 (8.2%) |
|  |  |  |  |  |
| Nervous system disorders |  | 8 (30.8%) | 4 (17.4%) | 12 (24.5%) |
| Amnesia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Burning sensation |  | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
|  | Not Related | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
| Cerebrovascular accident, Aphasia, Hemiplegia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Dizziness |  | 4 (15.4%) | 0 (0.0 %) | 4 (8.2%) |
|  | Not Related | 4 (15.4%) | 0 (0.0 %) | 4 (8.2%) |
| Facial paralysis |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Haemorrhagic transformation stroke, Cerebrovascular accident, Hemiparesis |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Headache |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Ischaemic stroke, Cerebrovascular accident |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Loss of consciousness |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Tremor |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Psychiatric disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Insomnia |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Respiratory, thoracic and mediastinal disorders |  | 9 (34.6%) | 5 (21.7%) | 14 (28.6%) |
| Cough |  | 3 (11.5%) | 2 (8.7%) | 5 (10.2%) |
|  | Not Related | 3 (11.5%) | 2 (8.7%) | 5 (10.2%) |
| Dysphonia |  | 3 (11.5%) | 1 (4.3%) | 4 (8.2%) |
|  | Not Related | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
|  | Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Productive cough |  | 2 (7.7%) | 2 (8.7%) | 4 (8.2%) |
|  | Not Related | 2 (7.7%) | 2 (8.7%) | 4 (8.2%) |
| Throat tightness |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Skin and subcutaneous tissue disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Skin lesion |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Vascular disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Peripheral embolism,Cardiac failure congestive |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| **Note:** [1] Respective column header group counts were used as denominator for percentage calculation. **General Note:** > Adverse events were coded using MedDRA version 21.1. Patients were reported more than one event per system organ class or preferred term. Patients were counted once for each system organ class or preferred term. > An AE is defined as any event that existed before study drug administration and increased in severity, or any event that only occurred after study drug administration. > Zero frequencies are presented by “0(0.0) “. | | | | |

## Table 14.3.2.5 Summary of Adverse Events by Causality Relationship to Stimulation - Safety Population (N=49)

|  | | **VNS Therapy System** | |  |
| --- | --- | --- | --- | --- |
| **System Organ Class (SOC) / Preferred Term (PT)** | **Causality Relationship to Stimulation** | **Right Sided (N=26)** | **Left Sided (N=23)** | **Overall (N=49)** |
| Total Number of Subjects with at least One Adverse Event, n (%) [1] |  | 20 (76.9%) | 14 (60.9%) | 34 (69.4%) |
|  |  |  |  |  |
| Total Number of Adverse Events |  | 66 | 30 | 96 |
|  |  |  |  |  |
| Blood and lymphatic system disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Anaemia megaloblastic, Malaria |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Cardiac disorders |  | 8 (30.8%) | 4 (17.4%) | 12 (24.5%) |
| Angina pectoris |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Arrhythmia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cardiac failure |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cardiac failure congestive |  | 2 (7.7%) | 0 (0.0 %) | 2 (4.1%) |
|  | Not Related | 2 (7.7%) | 0 (0.0 %) | 2 (4.1%) |
| Dyspnoea |  | 3 (11.5%) | 3 (13.0%) | 6 (12.2%) |
|  | Not Related | 3 (11.5%) | 3 (13.0%) | 6 (12.2%) |
| Dyspnoea exertional |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Ventricular tachycardia |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Ear and labyrinth disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Ear pain |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Otorrhoea |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Eye disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cataract |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Gastrointestinal disorders |  | 4 (15.4%) | 2 (8.7%) | 6 (12.2%) |
| Abdominal pain |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Diarrhoea |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | Not Related | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Dysphagia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Mouth haemorrhage |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Vomiting |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| General disorders and administration site conditions |  | 9 (34.6%) | 5 (21.7%) | 14 (28.6%) |
| Implant site pain |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Non-cardiac chest pain |  | 4 (15.4%) | 2 (8.7%) | 6 (12.2%) |
|  | Not Related | 4 (15.4%) | 2 (8.7%) | 6 (12.2%) |
| Pain |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Pyrexia |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | Not Related | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Sudden cardiac death |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Sudden death |  | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
|  | Not Related | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
| Swelling |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Infections and infestations |  | 3 (11.5%) | 1 (4.3%) | 4 (8.2%) |
| Bacterial infection |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Diarrhoea infectious |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Nasopharyngitis |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Viral infection |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Injury, poisoning and procedural complications |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Fall |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Joint injury |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Investigations |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Weight increased |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Metabolism and nutrition disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Hypoglycaemia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Hypoproteinemia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Musculoskeletal and connective tissue disorders |  | 4 (15.4%) | 3 (13.0%) | 7 (14.3%) |
| Arthritis |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Muscle spasms |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Musculoskeletal pain |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | Not Related | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Neck pain |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Pain in extremity |  | 2 (7.7%) | 2 (8.7%) | 4 (8.2%) |
|  | Not Related | 2 (7.7%) | 2 (8.7%) | 4 (8.2%) |
|  |  |  |  |  |
| Nervous system disorders |  | 8 (30.8%) | 4 (17.4%) | 12 (24.5%) |
| Amnesia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Burning sensation |  | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
|  | Not Related | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
| Cerebrovascular accident, Aphasia, Hemiplegia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Dizziness |  | 4 (15.4%) | 0 (0.0 %) | 4 (8.2%) |
|  | Not Related | 4 (15.4%) | 0 (0.0 %) | 4 (8.2%) |
| Facial paralysis |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Haemorrhagic transformation stroke, Cerebrovascular accident, Hemiparesis |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Headache |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | Not Related | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Ischaemic stroke, Cerebrovascular accident |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Loss of consciousness |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Tremor |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Psychiatric disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Insomnia |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Respiratory, thoracic and mediastinal disorders |  | 9 (34.6%) | 5 (21.7%) | 14 (28.6%) |
| Cough |  | 3 (11.5%) | 2 (8.7%) | 5 (10.2%) |
|  | Not Related | 3 (11.5%) | 2 (8.7%) | 5 (10.2%) |
| Dysphonia |  | 3 (11.5%) | 1 (4.3%) | 4 (8.2%) |
|  | Not Related | 2 (7.7%) | 0 (0.0 %) | 2 (4.1%) |
|  | Related | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Productive cough |  | 2 (7.7%) | 2 (8.7%) | 4 (8.2%) |
|  | Not Related | 2 (7.7%) | 2 (8.7%) | 4 (8.2%) |
| Throat tightness |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Skin and subcutaneous tissue disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Skin lesion |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Vascular disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Peripheral embolism,Cardiac failure congestive |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| **Note:** [1] Respective column header group counts were used as denominator for percentage calculation. **General Note:** > Adverse events were coded using MedDRA version 21.1. Patients were reported more than one event per system organ class or preferred term. Patients were counted once for each system organ class or preferred term. > An AE is defined as any event that existed before study drug administration and increased in severity, or any event that only occurred after study drug administration. > Zero frequencies are presented by “0(0.0) “. | | | | |

## Table 14.3.2.6 Summary of Adverse Events by Action Taken-Safety Population (N=49)

|  | | **VNS Therapy System** | |  |
| --- | --- | --- | --- | --- |
| **System Organ Class (SOC) / Preferred Term (PT)** | **Action taken** | **Right Sided (N=26)** | **Left Sided (N=23)** | **Overall (N=49)** |
| Total Number of Subjects with at least One Adverse Event, n (%) [1] |  | 20 (76.9%) | 14 (60.9%) | 34 (69.4%) |
|  |  |  |  |  |
| Total Number of Adverse Events |  | 66 | 30 | 96 |
|  |  |  |  |  |
| Blood and lymphatic system disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Anaemia megaloblastic, Malaria |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | None Required | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Cardiac disorders |  | 8 (30.8%) | 4 (17.4%) | 12 (24.5%) |
| Angina pectoris |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Arrhythmia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cardiac failure |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Changed device parameters | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cardiac failure congestive |  | 2 (7.7%) | 0 (0.0 %) | 2 (4.1%) |
|  | Changed device parameters | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Dyspnoea |  | 3 (11.5%) | 3 (13.0%) | 6 (12.2%) |
|  | None Required | 3 (11.5%) | 3 (13.0%) | 6 (12.2%) |
| Dyspnoea exertional |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Ventricular tachycardia |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Changed device parameters | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Ear and labyrinth disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Ear pain |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Otorrhoea |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Eye disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cataract |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Gastrointestinal disorders |  | 4 (15.4%) | 2 (8.7%) | 6 (12.2%) |
| Abdominal pain |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | None Required | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Diarrhoea |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | None Required | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Dysphagia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Mouth haemorrhage |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Vomiting |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| General disorders and administration site conditions |  | 9 (34.6%) | 5 (21.7%) | 14 (28.6%) |
| Implant site pain |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Non-cardiac chest pain |  | 4 (15.4%) | 2 (8.7%) | 6 (12.2%) |
|  | None Required | 4 (15.4%) | 2 (8.7%) | 6 (12.2%) |
| Pain |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Pyrexia |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | None Required | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Sudden cardiac death |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Sudden death |  | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
|  | None Required | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
| Swelling |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | None Required | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Infections and infestations |  | 3 (11.5%) | 1 (4.3%) | 4 (8.2%) |
| Bacterial infection |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | None Required | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Diarrhoea infectious |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Nasopharyngitis |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Viral infection |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Injury, poisoning and procedural complications |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Fall |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Joint injury |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Investigations |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Weight increased |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Metabolism and nutrition disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Hypoglycaemia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Hypoproteinemia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Musculoskeletal and connective tissue disorders |  | 4 (15.4%) | 3 (13.0%) | 7 (14.3%) |
| Arthritis |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | None Required | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Muscle spasms |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Musculoskeletal pain |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | None Required | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Neck pain |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Changed device parameters | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Pain in extremity |  | 2 (7.7%) | 2 (8.7%) | 4 (8.2%) |
|  | None Required | 2 (7.7%) | 2 (8.7%) | 4 (8.2%) |
|  |  |  |  |  |
| Nervous system disorders |  | 8 (30.8%) | 4 (17.4%) | 12 (24.5%) |
| Amnesia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Burning sensation |  | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
|  | None Required | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
| Cerebrovascular accident, Aphasia, Hemiplegia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Dizziness |  | 4 (15.4%) | 0 (0.0 %) | 4 (8.2%) |
|  | None Required | 4 (15.4%) | 0 (0.0 %) | 4 (8.2%) |
| Facial paralysis |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Haemorrhagic transformation stroke, Cerebrovascular accident, Hemiparesis |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | None Required | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Headache |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | None Required | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Ischaemic stroke, Cerebrovascular accident |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | None Required | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Loss of consciousness |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Tremor |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Psychiatric disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Insomnia |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | None Required | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Respiratory, thoracic and mediastinal disorders |  | 9 (34.6%) | 5 (21.7%) | 14 (28.6%) |
| Cough |  | 3 (11.5%) | 2 (8.7%) | 5 (10.2%) |
|  | None Required | 3 (11.5%) | 2 (8.7%) | 5 (10.2%) |
| Dysphonia |  | 3 (11.5%) | 1 (4.3%) | 4 (8.2%) |
|  | None Required | 3 (11.5%) | 1 (4.3%) | 4 (8.2%) |
| Productive cough |  | 2 (7.7%) | 2 (8.7%) | 4 (8.2%) |
|  | None Required | 2 (7.7%) | 2 (8.7%) | 4 (8.2%) |
| Throat tightness |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Skin and subcutaneous tissue disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Skin lesion |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Vascular disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Peripheral embolism,Cardiac failure congestive |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | None Required | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| **Note:** [1] Respective column header group counts were used as denominator for percentage calculation. **General Note:** > Adverse events were coded using MedDRA version 21.1. Patients were reported more than one event per system organ class or preferred term. Patients were counted once for each system organ class or preferred term. > An AE is defined as any event that existed before study drug administration and increased in severity, or any event that only occurred after study drug administration. > Zero frequencies are presented by “0(0.0) “. | | | | |

## Table 14.3.2.7 Summary of Adverse Events by Frequency - Safety Population (N=49)

|  | | **VNS Therapy System** | |  |
| --- | --- | --- | --- | --- |
| **System Organ Class (SOC) / Preferred Term(PT)** | **Frequency** | **Right Sided (N=26)** | **Left Sided (N=23)** | **Overall (N=49)** |
| Total Number of Subjects with at least One Adverse Event, n (%) [1] |  | 20 (76.9%) | 14 (60.9%) | 34 (69.4%) |
|  |  |  |  |  |
| Total Number of Adverse Events |  | 66 | 30 | 96 |
|  |  |  |  |  |
| Blood and lymphatic system disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Anaemia megaloblastic, Malaria |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Intermittent | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Cardiac disorders |  | 8 (30.8%) | 4 (17.4%) | 12 (24.5%) |
| Angina pectoris |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Single Episode | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Arrhythmia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Continuous | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cardiac failure |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Continuous | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cardiac failure congestive |  | 2 (7.7%) | 0 (0.0 %) | 2 (4.1%) |
|  | Single Episode | 2 (7.7%) | 0 (0.0 %) | 2 (4.1%) |
| Dyspnoea |  | 3 (11.5%) | 3 (13.0%) | 6 (12.2%) |
|  | Continuous | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Intermittent | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | Single Episode | 1 (3.8%) | 2 (8.7%) | 3 (6.1%) |
| Dyspnoea exertional |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Single Episode | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Ventricular tachycardia |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Single Episode | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Ear and labyrinth disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Ear pain |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Single Episode | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Otorrhoea |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Single Episode | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Eye disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cataract |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Single Episode | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Gastrointestinal disorders |  | 4 (15.4%) | 2 (8.7%) | 6 (12.2%) |
| Abdominal pain |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Single Episode | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Diarrhoea |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | Single Episode | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Dysphagia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Intermittent | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Mouth haemorrhage |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Continuous | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Vomiting |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Intermittent | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| General disorders and administration site conditions |  | 9 (34.6%) | 5 (21.7%) | 14 (28.6%) |
| Implant site pain |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Continuous | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Non-cardiac chest pain |  | 4 (15.4%) | 2 (8.7%) | 6 (12.2%) |
|  | Continuous | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Intermittent | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Single Episode | 4 (15.4%) | 0 (0.0 %) | 4 (8.2%) |
| Pain |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Intermittent | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Pyrexia |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | Single Episode | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Sudden cardiac death |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Single Episode | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Sudden death |  | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
|  | Single Episode | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
| Swelling |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Single Episode | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Infections and infestations |  | 3 (11.5%) | 1 (4.3%) | 4 (8.2%) |
| Bacterial infection |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Intermittent | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Single Episode | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Diarrhoea infectious |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Single Episode | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Nasopharyngitis |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Single Episode | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Viral infection |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Single Episode | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Injury, poisoning and procedural complications |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Fall |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Single Episode | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Joint injury |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Single Episode | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Investigations |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Weight increased |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Intermittent | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Metabolism and nutrition disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Hypoglycaemia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Single Episode | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Hypoproteinemia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Single Episode | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Musculoskeletal and connective tissue disorders |  | 4 (15.4%) | 3 (13.0%) | 7 (14.3%) |
| Arthritis |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Continuous | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Muscle spasms |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Single Episode | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Musculoskeletal pain |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | Intermittent | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Single Episode | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Neck pain |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Single Episode | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Pain in extremity |  | 2 (7.7%) | 2 (8.7%) | 4 (8.2%) |
|  | Continuous | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Single Episode | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
|  |  |  |  |  |
| Nervous system disorders |  | 8 (30.8%) | 4 (17.4%) | 12 (24.5%) |
| Amnesia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Intermittent | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Burning sensation |  | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
|  | Intermittent | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
| Cerebrovascular accident, Aphasia, Hemiplegia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Single Episode | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Dizziness |  | 4 (15.4%) | 0 (0.0 %) | 4 (8.2%) |
|  | Intermittent | 4 (15.4%) | 0 (0.0 %) | 4 (8.2%) |
| Facial paralysis |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Continuous | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Haemorrhagic transformation stroke, Cerebrovascular accident, Hemiparesis |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Single Episode | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Headache |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | Intermittent | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Ischaemic stroke, Cerebrovascular accident |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Single Episode | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Loss of consciousness |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Single Episode | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Tremor |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Continuous | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Psychiatric disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Insomnia |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Intermittent | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Respiratory, thoracic and mediastinal disorders |  | 9 (34.6%) | 5 (21.7%) | 14 (28.6%) |
| Cough |  | 3 (11.5%) | 2 (8.7%) | 5 (10.2%) |
|  | Continuous | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Intermittent | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | Single Episode | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Dysphonia |  | 3 (11.5%) | 1 (4.3%) | 4 (8.2%) |
|  | Intermittent | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | Single Episode | 2 (7.7%) | 0 (0.0 %) | 2 (4.1%) |
| Productive cough |  | 2 (7.7%) | 2 (8.7%) | 4 (8.2%) |
|  | Intermittent | 1 (3.8%) | 2 (8.7%) | 3 (6.1%) |
|  | Single Episode | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Throat tightness |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Intermittent | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Skin and subcutaneous tissue disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Skin lesion |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Single Episode | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Vascular disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Peripheral embolism,Cardiac failure congestive |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Continuous | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| **Note:** [1] Respective column header group counts were used as denominator for percentage calculation. **General Note:** > Adverse events were coded using MedDRA version 21.1. Patients were reported more than one event per system organ class or preferred term. Patients were counted once for each system organ class or preferred term. > An AE is defined as any event that existed before study drug administration and increased in severity, or any event that only occurred after study drug administration. > Zero frequencies are presented by “0(0.0) “. | | | | |

## Table 14.3.2.8 Summary of Adverse Events by Outcome - Safety Population (N=49)

|  | | **VNS Therapy System** | |  |
| --- | --- | --- | --- | --- |
| **System Organ Class (SOC) / Preferred Term(PT)** | **Outcome** | **Right Sided (N=26)** | **Left Sided (N=23)** | **Overall (N=49)** |
| Total Number of Subjects with at least One Adverse Event, n (%) [1] |  | 20 (76.9%) | 14 (60.9%) | 34 (69.4%) |
|  |  |  |  |  |
| Total Number of Adverse Events |  | 66 | 30 | 96 |
|  |  |  |  |  |
| Blood and lymphatic system disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Anaemia megaloblastic, Malaria |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Recovered with sequelae | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Cardiac disorders |  | 8 (30.8%) | 4 (17.4%) | 12 (24.5%) |
| Angina pectoris |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Unknown | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Arrhythmia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Fatal | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cardiac failure |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Recovered without sequelae | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cardiac failure congestive |  | 2 (7.7%) | 0 (0.0 %) | 2 (4.1%) |
|  | Recovered without sequelae | 2 (7.7%) | 0 (0.0 %) | 2 (4.1%) |
| Dyspnoea |  | 3 (11.5%) | 3 (13.0%) | 6 (12.2%) |
|  | Fatal | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | Ongoing and Recovering | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Recovered without sequelae | 1 (3.8%) | 2 (8.7%) | 3 (6.1%) |
| Dyspnoea exertional |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Recovered without sequelae | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Ventricular tachycardia |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Recovered without sequelae | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Ear and labyrinth disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Ear pain |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Recovered without sequelae | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Otorrhoea |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Recovered without sequelae | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Eye disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cataract |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Recovered without sequelae | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Gastrointestinal disorders |  | 4 (15.4%) | 2 (8.7%) | 6 (12.2%) |
| Abdominal pain |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Recovered without sequelae | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Diarrhoea |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | Recovered without sequelae | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Dysphagia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Recovered without sequelae | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Mouth haemorrhage |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Recovered without sequelae | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Vomiting |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Recovered without sequelae | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| General disorders and administration site conditions |  | 9 (34.6%) | 5 (21.7%) | 14 (28.6%) |
| Implant site pain |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Recovered without sequelae | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Non-cardiac chest pain |  | 4 (15.4%) | 2 (8.7%) | 6 (12.2%) |
|  | Ongoing and Recovering | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Recovered without sequelae | 4 (15.4%) | 1 (4.3%) | 5 (10.2%) |
| Pain |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Ongoing and Recovering | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Pyrexia |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | Recovered without sequelae | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Sudden cardiac death |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Fatal | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Sudden death |  | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
|  | Fatal | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
| Swelling |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Recovered without sequelae | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Infections and infestations |  | 3 (11.5%) | 1 (4.3%) | 4 (8.2%) |
| Bacterial infection |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Recovered without sequelae | 0 (0.0 %) | 2 (8.7%) | 2 (4.1%) |
| Diarrhoea infectious |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Recovered without sequelae | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Nasopharyngitis |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Recovered without sequelae | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Viral infection |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Recovered without sequelae | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Injury, poisoning and procedural complications |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Fall |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Recovered without sequelae | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Joint injury |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Recovered without sequelae | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Investigations |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Weight increased |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Ongoing and Recovering | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Metabolism and nutrition disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Hypoglycaemia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Recovered without sequelae | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Hypoproteinemia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Recovered without sequelae | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Musculoskeletal and connective tissue disorders |  | 4 (15.4%) | 3 (13.0%) | 7 (14.3%) |
| Arthritis |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Recovered without sequelae | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Muscle spasms |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Recovered without sequelae | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Musculoskeletal pain |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | Recovered without sequelae | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Neck pain |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Recovered without sequelae | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Pain in extremity |  | 2 (7.7%) | 2 (8.7%) | 4 (8.2%) |
|  | Recovered without sequelae | 2 (7.7%) | 2 (8.7%) | 4 (8.2%) |
|  |  |  |  |  |
| Nervous system disorders |  | 8 (30.8%) | 4 (17.4%) | 12 (24.5%) |
| Amnesia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Ongoing and Recovering | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Burning sensation |  | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
|  | Recovered without sequelae | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
| Cerebrovascular accident, Aphasia, Hemiplegia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Recovered with sequelae | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Dizziness |  | 4 (15.4%) | 0 (0.0 %) | 4 (8.2%) |
|  | Ongoing and Recovering | 2 (7.7%) | 0 (0.0 %) | 2 (4.1%) |
|  | Recovered without sequelae | 2 (7.7%) | 0 (0.0 %) | 2 (4.1%) |
| Facial paralysis |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Recovered without sequelae | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Haemorrhagic transformation stroke, Cerebrovascular accident, Hemiparesis |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Fatal | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Headache |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | Recovered without sequelae | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Ischaemic stroke, Cerebrovascular accident |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Recovered with sequelae | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Loss of consciousness |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Recovered without sequelae | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Tremor |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Ongoing and Recovering | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Psychiatric disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Insomnia |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Recovered without sequelae | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Respiratory, thoracic and mediastinal disorders |  | 9 (34.6%) | 5 (21.7%) | 14 (28.6%) |
| Cough |  | 3 (11.5%) | 2 (8.7%) | 5 (10.2%) |
|  | Recovered without sequelae | 3 (11.5%) | 2 (8.7%) | 5 (10.2%) |
| Dysphonia |  | 3 (11.5%) | 1 (4.3%) | 4 (8.2%) |
|  | Ongoing and Not Recovering | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Recovered without sequelae | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
| Productive cough |  | 2 (7.7%) | 2 (8.7%) | 4 (8.2%) |
|  | Ongoing and Recovering | 0 (0.0 %) | 2 (8.7%) | 2 (4.1%) |
|  | Recovered without sequelae | 2 (7.7%) | 0 (0.0 %) | 2 (4.1%) |
| Throat tightness |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Recovered without sequelae | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Skin and subcutaneous tissue disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Skin lesion |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Recovered without sequelae | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| Vascular disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Peripheral embolism,Cardiac failure congestive |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Recovered with sequelae | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| **Note:** [1] Respective column header group counts were used as denominator for percentage calculation. **General Note:** > Adverse events were coded using MedDRA version 21.1. Patients were reported more than one event per system organ class or preferred term. Patients were counted once for each system organ class or preferred term. > An AE is defined as any event that existed before study drug administration and increased in severity, or any event that only occurred after study drug administration. > Zero frequencies are presented by “0(0.0) “. | | | | |

## Table 14.3.3 Summary of Serious Adverse Events – Overall Summary Safety Population (N=49)

|  | **VNS Therapy System** | |  |
| --- | --- | --- | --- |
|  | **Right Sided (n=26)** | **Left Sided (n=23)** | **Overall (n=49)** |
|  |  |  |  |
| SAEs Reported | 10 | 7 | 17 |
|  |  |  |  |
| Subjects Reporting Any SAEs, n (%) [1] | 9(34.6%) | 5(21.7%) | 14(28.6%) |
|  |  |  |  |
| Subjects Reporting 1 SAE | 8(30.8%) | 3(13.0%) | 11(22.4%) |
|  |  |  |  |
| Subjects Reporting >1 SAE | 1(3.8%) | 2(8.7%) | 3(6.1%) |
|  |  |  |  |
| Subjects Reporting SAEs Leading to Withdraw | 1(3.8%) | 0(0.0%) | 1(2.0%) |
| **Note:** [1] Respective column header group counts were used as denominator for percentage calculation. **General Note:** > Zero frequencies are presented by “0(0.0) “. | | | |

## Table 14.3.3.1 Summary of Serious Adverse Events - Safety Population (N=49)

|  | **VNS Therapy System** | |  |
| --- | --- | --- | --- |
| **System Organ Class (SOC) / Preferred Term (PT)** | **Right Sided (N=26)** | **Left Sided (N=23)** | **Overall (N=49)** |
| Total Number of Subjects with at least One Serious Adverse Event, n (%) [1] | 9 (34.6%) | 5 (21.7%) | 14 (28.6%) |
|  |  |  |  |
| Total Number of Serious Adverse Events | 10 | 7 | 17 |
|  |  |  |  |
| Blood and lymphatic system disorders | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Anaemia megaloblastic, Malaria | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |
| Cardiac disorders | 4 (15.4%) | 2 (8.7%) | 6 (12.2%) |
| Arrhythmia | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cardiac failure | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cardiac failure congestive | 2 (7.7%) | 0 (0.0 %) | 2 (4.1%) |
| Dyspnoea | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Ventricular tachycardia | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |
| Eye disorders | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cataract | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |
| General disorders and administration site conditions | 3 (11.5%) | 1 (4.3%) | 4 (8.2%) |
| Sudden cardiac death | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Sudden death | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
|  |  |  |  |
| Nervous system disorders | 1 (3.8%) | 2 (8.7%) | 3 (6.1%) |
| Cerebrovascular accident, Aphasia, Hemiplegia | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Haemorrhagic transformation stroke, Cerebrovascular accident, Hemiparesis | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Ischaemic stroke, Cerebrovascular accident | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |
| Vascular disorders | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Peripheral embolism,Cardiac failure congestive | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |
| **Note:** [1] Respective column header group counts were used as denominator for percentage calculation. **General Note:** > Adverse events were coded using MedDRA version 21.1. Patients were reported more than one event per system organ class or preferred term. Patients were counted once for each system organ class or preferred term. > An AE is defined as any event that existed before study drug administration and increased in severity, or any event that only occurred after study drug administration. > Zero frequencies are presented by “0(0.0) “. | | | |

## Table 14.3.3.2 Summary of Serious Adverse Events by Maximum Intensity - Safety Population (N=49)

|  | | **VNS Therapy System** | |  |
| --- | --- | --- | --- | --- |
| **System Organ Class (SOC) / Preferred Term(PT)** | **Intensity** | **Right Sided (N=26)** | **Left Sided (N=23)** | **Overall (N=49)** |
| Total Number of Subjects with at least One Serious Adverse Event, n (%) [1] |  | 9 (34.6%) | 5 (21.7%) | 14 (28.6%) |
|  |  |  |  |  |
| Total Number of Serious Adverse Events |  | 10 | 7 | 17 |
|  |  |  |  |  |
| Blood and lymphatic system disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Anaemia megaloblastic, Malaria |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Severe | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Cardiac disorders |  | 4 (15.4%) | 2 (8.7%) | 6 (12.2%) |
| Arrhythmia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Severe | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cardiac failure |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Mild | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cardiac failure congestive |  | 2 (7.7%) | 0 (0.0 %) | 2 (4.1%) |
|  | Severe | 2 (7.7%) | 0 (0.0 %) | 2 (4.1%) |
| Dyspnoea |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | Severe | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Ventricular tachycardia |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Severe | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Eye disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cataract |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Moderate | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| General disorders and administration site conditions |  | 3 (11.5%) | 1 (4.3%) | 4 (8.2%) |
| Sudden cardiac death |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Severe | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Sudden death |  | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
|  | Severe | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
|  |  |  |  |  |
| Nervous system disorders |  | 1 (3.8%) | 2 (8.7%) | 3 (6.1%) |
| Cerebrovascular accident, Aphasia, Hemiplegia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Severe | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Haemorrhagic transformation stroke, Cerebrovascular accident, Hemiparesis |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Severe | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Ischaemic stroke, Cerebrovascular accident |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Severe | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Vascular disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Peripheral embolism,Cardiac failure congestive |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Severe | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| **Note:** [1] Respective column header group counts were used as denominator for percentage calculation. **General Note:** > Adverse events were coded using MedDRA version 21.1. Patients were reported more than one event per system organ class or preferred term. Patients were counted once for each system organ class or preferred term. > An AE is defined as any event that existed before study drug administration and increased in severity, or any event that only occurred after study drug administration. > Zero frequencies are presented by “0(0.0) “. | | | | |

## Table 14.3.3.3 Summary of Serious Adverse Events by Causality Relationship to Implant - Safety Population (N=49)

|  | | **VNS Therapy System** | |  |
| --- | --- | --- | --- | --- |
| **System Organ Class (SOC) / Preferred Term (PT)** | **Causality Relationship to Implant** | **Right Sided (N=26)** | **Left Sided (N=23)** | **Overall (N=49)** |
| Total Number of Subjects with at least One Serious Adverse Event, n (%) [1] |  | 9 (34.6%) | 5 (21.7%) | 14 (28.6%) |
|  |  |  |  |  |
| Total Number of Serious Adverse Events |  | 10 | 7 | 17 |
|  |  |  |  |  |
| Blood and lymphatic system disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Anaemia megaloblastic, Malaria |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Cardiac disorders |  | 4 (15.4%) | 2 (8.7%) | 6 (12.2%) |
| Arrhythmia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cardiac failure |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cardiac failure congestive |  | 2 (7.7%) | 0 (0.0 %) | 2 (4.1%) |
|  | Not Related | 2 (7.7%) | 0 (0.0 %) | 2 (4.1%) |
| Dyspnoea |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | Not Related | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Ventricular tachycardia |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Eye disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cataract |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| General disorders and administration site conditions |  | 3 (11.5%) | 1 (4.3%) | 4 (8.2%) |
| Sudden cardiac death |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Sudden death |  | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
|  | Not Related | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
|  |  |  |  |  |
| Nervous system disorders |  | 1 (3.8%) | 2 (8.7%) | 3 (6.1%) |
| Cerebrovascular accident, Aphasia, Hemiplegia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Haemorrhagic transformation stroke, Cerebrovascular accident, Hemiparesis |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Ischaemic stroke, Cerebrovascular accident |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Vascular disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Peripheral embolism,Cardiac failure congestive |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| **Note:** [1] Respective column header group counts were used as denominator for percentage calculation. **General Note:** > Adverse events were coded using MedDRA version 21.1. Patients were reported more than one event per system organ class or preferred term. Patients were counted once for each system organ class or preferred term. > An AE is defined as any event that existed before study drug administration and increased in severity, or any event that only occurred after study drug administration. > Zero frequencies are presented by “0(0.0) “. | | | | |

## Table 14.3.3.4 Summary of Serious Adverse Events by Causality Relationship to Stimulation - Safety Population (N=49)

|  | | **VNS Therapy System** | |  |
| --- | --- | --- | --- | --- |
| **System Organ Class (SOC) / Preferred Term (PT)** | **Causality Relationship to Stimulation** | **Right Sided (N=26)** | **Left Sided (N=23)** | **Overall (N=49)** |
| Total Number of Subjects with at least One Serious Adverse Event, n (%) [1] |  | 9 (34.6%) | 5 (21.7%) | 14 (28.6%) |
|  |  |  |  |  |
| Total Number of Serious Adverse Events |  | 10 | 7 | 17 |
|  |  |  |  |  |
| Blood and lymphatic system disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Anaemia megaloblastic, Malaria |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Cardiac disorders |  | 4 (15.4%) | 2 (8.7%) | 6 (12.2%) |
| Arrhythmia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cardiac failure |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cardiac failure congestive |  | 2 (7.7%) | 0 (0.0 %) | 2 (4.1%) |
|  | Not Related | 2 (7.7%) | 0 (0.0 %) | 2 (4.1%) |
| Dyspnoea |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | Not Related | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Ventricular tachycardia |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Eye disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cataract |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| General disorders and administration site conditions |  | 3 (11.5%) | 1 (4.3%) | 4 (8.2%) |
| Sudden cardiac death |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Sudden death |  | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
|  | Not Related | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
|  |  |  |  |  |
| Nervous system disorders |  | 1 (3.8%) | 2 (8.7%) | 3 (6.1%) |
| Cerebrovascular accident, Aphasia, Hemiplegia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Not Related | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Haemorrhagic transformation stroke, Cerebrovascular accident, Hemiparesis |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Ischaemic stroke, Cerebrovascular accident |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Vascular disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Peripheral embolism,Cardiac failure congestive |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Not Related | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| **Note:** [1] Respective column header group counts were used as denominator for percentage calculation. **General Note:** > Adverse events were coded using MedDRA version 21.1. Patients were reported more than one event per system organ class or preferred term. Patients were counted once for each system organ class or preferred term. > An AE is defined as any event that existed before study drug administration and increased in severity, or any event that only occurred after study drug administration. > Zero frequencies are presented by “0(0.0) “. | | | | |

## Table 14.3.3.5 Summary of Serious Adverse Events by Action taken -Safety Population (N=49)

|  | | **VNS Therapy System** | |  |
| --- | --- | --- | --- | --- |
| **System Organ Class (SOC) / Preferred Term (PT)** | **Action taken** | **Right Sided (N=26)** | **Left Sided (N=23)** | **Overall (N=49)** |
| Total Number of Subjects with at least One Serious Adverse Event, n (%) [1] |  | 9 (34.6%) | 5 (21.7%) | 14 (28.6%) |
|  |  |  |  |  |
| Total Number of Serious Adverse Events |  | 10 | 7 | 17 |
|  |  |  |  |  |
| Blood and lymphatic system disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Anaemia megaloblastic, Malaria |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | None Required | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Cardiac disorders |  | 4 (15.4%) | 2 (8.7%) | 6 (12.2%) |
| Arrhythmia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cardiac failure |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Changed device parameters | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cardiac failure congestive |  | 2 (7.7%) | 0 (0.0 %) | 2 (4.1%) |
|  | Changed device parameters | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Dyspnoea |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | None Required | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Ventricular tachycardia |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Changed device parameters | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Eye disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cataract |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| General disorders and administration site conditions |  | 3 (11.5%) | 1 (4.3%) | 4 (8.2%) |
| Sudden cardiac death |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Sudden death |  | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
|  | None Required | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
|  |  |  |  |  |
| Nervous system disorders |  | 1 (3.8%) | 2 (8.7%) | 3 (6.1%) |
| Cerebrovascular accident, Aphasia, Hemiplegia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | None Required | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Haemorrhagic transformation stroke, Cerebrovascular accident, Hemiparesis |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | None Required | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Ischaemic stroke, Cerebrovascular accident |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | None Required | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Vascular disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Peripheral embolism,Cardiac failure congestive |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | None Required | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| **Note:** [1] Respective column header group counts were used as denominator for percentage calculation. **General Note:** > Adverse events were coded using MedDRA version 21.1. Patients were reported more than one event per system organ class or preferred term. Patients were counted once for each system organ class or preferred term. > An AE is defined as any event that existed before study drug administration and increased in severity, or any event that only occurred after study drug administration. > Zero frequencies are presented by “0(0.0) “. | | | | |

## Table 14.3.3.6 Summary of Serious Adverse Events by Frequency - Safety Population (N=49)

|  | | **VNS Therapy System** | |  |
| --- | --- | --- | --- | --- |
| **System Organ Class (SOC) / Preferred Term (PT)** | **Frequency** | **Right Sided (N=26)** | **Left Sided (N=23)** | **Overall (N=49)** |
| Total Number of Subjects with at least One Serious Adverse Event, n (%) [1] |  | 9 (34.6%) | 5 (21.7%) | 14 (28.6%) |
|  |  |  |  |  |
| Total Number of Serious Adverse Events |  | 10 | 7 | 17 |
|  |  |  |  |  |
| Blood and lymphatic system disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Anaemia megaloblastic, Malaria |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Intermittent | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Cardiac disorders |  | 4 (15.4%) | 2 (8.7%) | 6 (12.2%) |
| Arrhythmia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Continuous | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cardiac failure |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Continuous | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cardiac failure congestive |  | 2 (7.7%) | 0 (0.0 %) | 2 (4.1%) |
|  | Single Episode | 2 (7.7%) | 0 (0.0 %) | 2 (4.1%) |
| Dyspnoea |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | Continuous | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Single Episode | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Ventricular tachycardia |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Single Episode | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Eye disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cataract |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Single Episode | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| General disorders and administration site conditions |  | 3 (11.5%) | 1 (4.3%) | 4 (8.2%) |
| Sudden cardiac death |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Single Episode | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Sudden death |  | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
|  | Single Episode | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
|  |  |  |  |  |
| Nervous system disorders |  | 1 (3.8%) | 2 (8.7%) | 3 (6.1%) |
| Cerebrovascular accident, Aphasia, Hemiplegia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Single Episode | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Haemorrhagic transformation stroke, Cerebrovascular accident, Hemiparesis |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Single Episode | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Ischaemic stroke, Cerebrovascular accident |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Single Episode | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Vascular disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Peripheral embolism,Cardiac failure congestive |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Continuous | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| **Note:** [1] Respective column header group counts were used as denominator for percentage calculation. **General Note:** > Adverse events were coded using MedDRA version 21.1. Patients were reported more than one event per system organ class or preferred term. Patients were counted once for each system organ class or preferred term. > An AE is defined as any event that existed before study drug administration and increased in severity, or any event that only occurred after study drug administration. > Zero frequencies are presented by “0(0.0) “. | | | | |

## Table 14.3.3.7 Summary of Serious Adverse Events by Outcome - Safety Population (N=49)

|  | | **VNS Therapy System** | |  |
| --- | --- | --- | --- | --- |
| **System Organ Class (SOC) / Preferred Term (PT)** | **Outcome** | **Right Sided (N=26)** | **Left Sided (N=23)** | **Overall (N=49)** |
| Total Number of Subjects with at least One Serious Adverse Event, n (%) [1] |  | 9 (34.6%) | 5 (21.7%) | 14 (28.6%) |
|  |  |  |  |  |
| Total Number of Serious Adverse Events |  | 10 | 7 | 17 |
|  |  |  |  |  |
| Blood and lymphatic system disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Anaemia megaloblastic, Malaria |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Recovered with sequelae | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Cardiac disorders |  | 4 (15.4%) | 2 (8.7%) | 6 (12.2%) |
| Arrhythmia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Fatal | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cardiac failure |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Recovered without sequelae | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cardiac failure congestive |  | 2 (7.7%) | 0 (0.0 %) | 2 (4.1%) |
|  | Recovered without sequelae | 2 (7.7%) | 0 (0.0 %) | 2 (4.1%) |
| Dyspnoea |  | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
|  | Fatal | 1 (3.8%) | 1 (4.3%) | 2 (4.1%) |
| Ventricular tachycardia |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Recovered without sequelae | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Eye disorders |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Cataract |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Recovered without sequelae | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  |  |  |  |  |
| General disorders and administration site conditions |  | 3 (11.5%) | 1 (4.3%) | 4 (8.2%) |
| Sudden cardiac death |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Fatal | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Sudden death |  | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
|  | Fatal | 2 (7.7%) | 1 (4.3%) | 3 (6.1%) |
|  |  |  |  |  |
| Nervous system disorders |  | 1 (3.8%) | 2 (8.7%) | 3 (6.1%) |
| Cerebrovascular accident, Aphasia, Hemiplegia |  | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
|  | Recovered with sequelae | 1 (3.8%) | 0 (0.0 %) | 1 (2.0%) |
| Haemorrhagic transformation stroke, Cerebrovascular accident, Hemiparesis |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Fatal | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Ischaemic stroke, Cerebrovascular accident |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Recovered with sequelae | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| Vascular disorders |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
| Peripheral embolism,Cardiac failure congestive |  | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  | Recovered with sequelae | 0 (0.0 %) | 1 (4.3%) | 1 (2.0%) |
|  |  |  |  |  |
| **Note:** [1] Respective column header group counts were used as denominator for percentage calculation. **General Note:** > Adverse events were coded using MedDRA version 21.1. Patients were reported more than one event per system organ class or preferred term. Patients were counted once for each system organ class or preferred term. > An AE is defined as any event that existed before study drug administration and increased in severity, or any event that only occurred after study drug administration. > Zero frequencies are presented by “0(0.0) “. | | | | |

## Table 14.3.7.1 Summary of Concomitant Medication (24 Months Visit) (N=46)

|  | **VNS Therapy System** | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Right Sided** | | **Left Sided** | | **Overall** | |
| **Category** | **12 Months N= (25)** | **24 Months N= (21)** | **12 Months N= (21)** | **24 Months N= (19)** | **12 Months N= (46)** | **24 Months N= (40)** |
| ACE/ARB | 21 (80.8%) | 17 (81.0%) | 22 (95.7%) | 19 (100.0%) | 43 (87.8%) | 36 (90.0%) |
| Aldosterone | 20 (76.9%) | 8 (38.1%) | 19 (82.6%) | 6 (31.6%) | 39 (79.6%) | 14 (35.0%) |
| Beta blocking agents | 22 (84.6%) | 17 (81.0%) | 19 (82.6%) | 15 (78.9%) | 41 (83.7%) | 32 (80.0%) |
| Digoxin | 6 (23.1%) | 4 (19.0%) | 5 (21.7%) | 4 (21.1%) | 11 (22.4%) | 8 (20.0%) |
| Diuretics | 20 (76.9%) | 15 (71.4%) | 20 (87.0%) | 18 (94.7%) | 40 (81.6%) | 33 (82.5%) |
| **Note:** [1] Respective column header group counts were used as denominator for percentage calculation. | | | | | | |