Supplemental Methods and Results

Supplemental Methods

Sensitivity Analyses

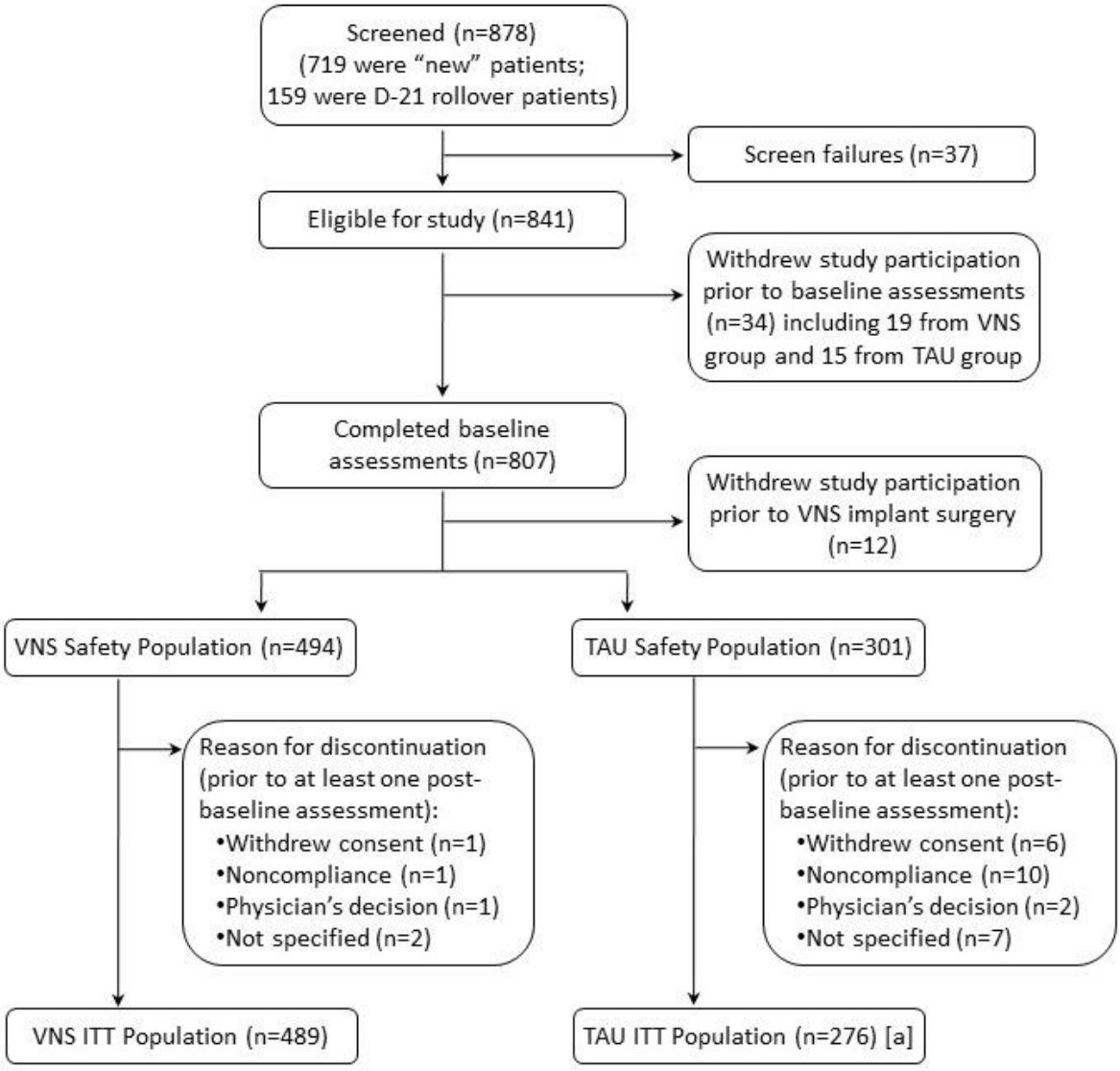
Sensitivity analyses were performed comparing treatment effectiveness outcomes of the TAU arm versus 2 different groups of patients in the VNS+TAU arm: one group included the pooled "new patients" plus "D-21 rollover patients" and the second group included the "new patients" only. No differences were observed between the outcomes of the VNS+TAU groups (with or without D-21 rollover patients) versus the TAU arm for any of the efficacy assessments. Therefore, the results of the analyses based on the VNS+TAU pooled data which includes a larger sample size than the "new patients" alone is reported in the main body of the article. Note that the reporting of the pooled VNS+TAU data is in agreement with the US FDA.

Sensitivity Analyses of the Primary Efficacy Evaluation of Response

A statistically significant difference in the primary efficacy evaluation of response rate was observed between the VNS+TAU arm (cumulative response rate of 67.6%) and the TAU arm (a cumulative response rate of 40.9%) through the 5-year follow-up period ($p < 0.001$). Similarly, a statistically significant difference in response was observed when comparing patients in the VNS+TAU "new patients" only group to patients in the TAU group (63.8% versus 40.9%, respectively, $p < 0.001$).

Supplemental Results

Chart of patient disposition in the Treatment-Resistant Depression Registry.



[a] Within the ITT population, 2 patients in the TAU arm did not have a baseline MADRS assessment and were not included in the primary efficacy analysis.

Assessment of Side Effects using the FIBSER Scale

The self-rated Frequency, Intensity, and Burden of Side Effects Rating (FIBSER) scale [Wisniewski et al 2006] was used to assess the overall impact of side-effects in the 2 treatment arms, and the data demonstrated that the percentage of patients experiencing a score of 5 or 6 (least favorable) on the "frequency," "intensity," and "burden" of side-effects subscales of the FIBSER, were comparable at baseline between VNS+TAU arm and TAU arm, and decreased over time in both treatment arms. Specifically, for the frequency of side effects, 23.9% in the VNS+TAU arm had a FIBSER score of 5 or 6 at baseline and the percentage decreased to 9.1% at 5 years; and in the TAU arm, a baseline rate of 17.8% decreased to 15.0% at 5 years. For the intensity of side-effects, a baseline rate of 10.3% in the VNS+TAU arm decreased to 3.1% at 5 years, and a baseline rate of 6.3% in the TAU arm decreased to 5.3% at 5 years. And for the burden of side-effects, a baseline rate of 5.8% in the VNS+TAU arm decreased to 2.1% at 5 years, and a baseline rate of 4.8% in the TAU arm decreased to 2.7% at 5 years.

Reference

Wisniewski SR, Rush AJ, Balasubramani GK, et al: Self-rated global measure of the frequency, intensity, and burden of side effects. J Psychiatr Pract 2006; 12:71–79 PubMed

Deaths (and Related Causes) During Participation in the Treatment-Resistant Depression Registry

Fifteen patients died during the study including 7 patients from the VNS+TAU arm and 8 patients from the TAU arm.

Of the 7 patients in the VNS+TAU arm who died: n=1 due to diabetes-related complications (death occurred 3 years after device implant), n=1 due to accidental acute opiate intoxication (4 years after implant), n=1 due to accidental overdose of methadone and paroxetine* (2.5 years after implant), n=1 due to homicide* (1.5 years after implant), n=1 from undetermined causes and autopsy results were not available (8 months after implant), and n=2 committed suicide (2 and 5 years after implant, respectively). None of the deaths in the VNS+TAU arm was attributed to the device implantation or stimulation. Asterisks denotes patients who were considered treatment responders at their last recorded visit.

Of the 8 patients in the TAU arm who died: n=3 due to natural causes, n=1 due to a heart attack related to atherosclerotic cardiovascular disease, n=1 due to hypertensive heart disease, n=1 due to cardiopulmonary arrest secondary to possible complications of liver cancer, and n=2 committed suicide. None of the TAU patients were considered treatment responders at their last recorded visit.