PANEL QUESTIONS

1. A chief limitation of the long-term D02, D04 comparative analysis is that the data are not derived from a randomized subject data set, but rather a comparison of outcomes from an investigational device study and observational control study. A propensity adjustment strategy was used to reduce potential bias (i.e., patient characteristics, disease characteristics) in the comparative analysis. This type of strategy is not able to address the problems of potential bias due to other unmeasured patient variables (e.g., past thyroid dysfunction, neurotic pre-morbid personality, familial predisposition for affective disorder, multiple loss events, or socio-cultural level). Please discuss the impact of a comparative analysis of non-randomized subject data, comparison of outcomes from an investigational study and observational study, and unmeasured patient variables upon efficacy outcomes in the PMA.

2. The Sponsor believes D02 long-term outcomes are not due to a placebo effect. Data provided in the PMA includes a 20% (21/106) placebo effect rate in sham-treatment control subjects at acute phase exit (12 weeks) as defined by a HAM-D score less than 18. Patient expectation of participating in an investigational study for a new therapy (D02 study) may have also been greater than the expectation of participating in an observational, control study. Please discuss the placebo effect and impact upon clinical outcomes presented in the PMA.

3. Concomitant medications and ECT use were not standardized in either the D02 long-term study or the D04 observational, control study. Please discuss the impact of concomitant medications and ECT use on interpretation of the efficacy of VNS therapy for treatment resistant depression.

4. 21 CFR 860.7(d)(1) states that there is a reasonable assurance that the device is safe when it can be determined that the probable benefits to health from use of the device for its intended uses, when accompanied by adequate instructions for use and warnings against unsafe use, outweigh any probable risks. Do the clinical data in P970003/S050 provide reasonable assurance that the device is safe?

5. 21 CFR 860.7(e)(1) states that there is a reasonable assurance that a device is effective when it can be determined, based on valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will produce clinically significant results. Considering your responses to questions 1, 2, and 3, do the clinical data in P970003/S050 provide reasonable assurance that the device is effective?