LivaNova

Health innovation that matters

October 25, 2017

Tamara Syrek Jensen, Esq.
Director, Coverage and Analysis Group
Office of Clinical Standards and Quality
The Centers for Medicare and Medicaid Services
7500 Security Blvd.
Baltimore, MD 21244

Re: Formal Request for Reconsideration of National Coverage Determination 160.18 for Vagus Nerve Stimulation for Treatment of Resistant Depression

Dear Ms. Syrek-Jensen,

As a result of evolving standards of care and the level of evidence accumulated over the past ten years supporting improved health outcomes associated with Vagus Nerve Stimulation (VNS) Therapy®, LivaNova PLC (formerly Cyberonics, Inc.) respectfully requests a formal reconsideration of the current National Coverage Determination (NCD) for VNS Therapy in treatment-resistant depression (TRD). This formal request for reconsideration is submitted on behalf of a small, but underserved, subpopulation of Medicare beneficiaries who already benefit from VNS Therapy and Medicare-eligible patients currently suffering from TRD who could benefit by having access to this FDA-approved treatment option for TRD. Treatment with many other antidepressant therapies has failed to provide relief for the latter group of patients, resulting in prolonged suffering, negative health outcomes and increased risk of pre-mature mortality.

In the intervening years since the NCD was considered in 2007, a significant body of new evidence has emerged about TRD and the role of VNS Therapy in its treatment. This compelling new evidence addresses the concerns expressed by the Centers for Medicare and Medicaid Services (CMS) in its non-coverage decision memo that demonstrates:

- TRD can be defined and characterized;
- Appropriate methods to study the effectiveness of TRD treatments are defined; and
- New evidence supports that VNS Therapy has a treatment benefit for Medicare beneficiaries with TRD.

We believe this new evidence supports reconsideration of VNS Therapy for TRD as reasonable and necessary for a defined patient subpopulation of Medicare beneficiaries. We outline our rationale for reconsideration and initiate a formal request with this letter and the supplemental evidence contained herein.

Vagus Nerve Stimulation for TRD

The vagus nerve (cranial nerve X) is a mixed nerve composed primarily of sensory afferents carrying information from the thorax, abdomen, head and neck to the brain. It connects the lower part of the brain to the heart, lungs and intestines.

The VNS Therapy system consists of two implantable components: a programmable electronic pulse generator that is connected to a bipolar electrical lead. The surgery to implant the VNS Therapy system involves a subcutaneous implantation of the pulse generator in the intraclavicular region and wrapping 2 spiral electrodes around the left vagus nerve within the carotid sheath.

Following implant and recovery, the physician programs the pulse generator to intermittently stimulate the vagus nerve at a level that balances efficacy and patient tolerability. The pulse generator delivers stimulation via the bipolar electrical lead to the cervical portion of the left vagus nerve near the carotid sheath. The stimulation relays information to the brain stem, thereby modulating structures relevant to depression (see the section of this letter entitled "**New evidence on the VNS Therapy mechanism of action in TRD**"). Stimulation typically consists of a 30 second period of "on time," during which the device stimulates at a fixed level of output current, followed by a 5 minute "off time" period of no stimulation.

LivaNova has regulatory approval in both the United States and Europe for the use of VNS Therapy to treat patients with TRD. In Europe, the VNS Therapy system is indicated for the treatment of chronic or recurrent depression in patients that are in a treatment-resistant or treatment-intolerant major depressive episode.

VNS Depression Indication (US)

The US Food and Drug Administration (FDA) approved this treatment in July 2005 for the *adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to 4 or more adequate antidepressant treatments.*

TRD can be defined and characterized

Since 2007, TRD has been defined and characterized in two systematic reviews performed by the Agency for Healthcare Research and Quality (AHRQ) in 2011[1] and 2017[2] (Key Question 1) and a April 2016 Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) expert panel.

The 2011 AHRQ review found that *"…the most common TRD definition for MDD [major depressive disorder] required a minimum of two prior treatment failures and confirmation of prior adequate dose and duration."*[3] The 2017 AHRQ review elaborated and provided the following operational definition:

> *"TRD can be understood as two or more prior treatment failures of an adequate treatment dose (at least minimally effective) and an adequate treatment duration (approximately 4 or more weeks of treatment)."*[4]

This operational definition is consistent with the consensus of the 2016 MEDCAC Panel that the definition of TRD should incorporate the "…number, duration, dosage, and/or classes of antidepressants attempted." This MEDCAC further affirmed that:

1. A standard definition of TRD could be applied to Medicare beneficiaries in clinical research; and
2. General and specialty psychiatrists could apply this definition to Medicare beneficiaries.

These reviews and expert panels support that psychiatry has agreed upon a commonly understood definition of TRD which can be applied in clinical research and practice. Further, this definition is consistent with the current FDA-approved indication for VNS Therapy which specifies that it is an adjunctive therapy intended for patients with major depressive disorder (MDD) who "…have not had an adequate response to *4 or more adequate* antidepressant treatments." This indication statement captures both the number of failed treatments as well as adequacy of duration and dosage and far exceeds the accepted TRD definition of two or more prior treatment failures.

[1] Gaynes BN, Lux L, Lloyd S, Hansen RA, Gartlehner G, Thieda P, Brode S, Swinson Evans T, Jonas D, Crotty K, Viswanathan M, Lohr KN. Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults. Comparative Effectiveness Review No. 33. (Prepared by RTI International-University of North Carolina (RTI-UNC) Evidence-based Practice Center under Contract No. 290-02-0016I.) AHRQ Publication No. 11-EHC056-EF. Rockville, MD: Agency for Healthcare Research and Quality. September 2011. www.effectivehealthcare.ahrq.gov/reports/final.cfm. (Attachment 1)

[2] Definition of Treatment-Resistant Depression in the Medicare Population. Draft Technology Assessment Project ID: PSYT0816 Date: August 23, 2017 (Attachment 2)

[3] p. 2, AHRQ Publication No. 11-EHC056-EF. (Attachment 1)

[4] p. 100-101, Definition of Treatment-Resistant Depression in the Medicare Population. (Attachment 2)

Appropriate methods to study the effectiveness of TRD treatments are defined

In the 2007 non-coverage decision memo (Section VII.A), CMS expressed concerns regarding methodology used to develop evidence.

The 2017 AHRQ review addressed 10 additional questions relating to appropriate study design methodology to develop evidence that establishes the safety and effectiveness of treatments for TRD. Attachment 1 summarizes the research questions in this review along with the recommendations that clearly define appropriate methods to develop evidence. This table also describes how the new evidence on the effectiveness of VNS Therapy presented in this letter meets these recommendations.

New evidence supports that VNS Therapy has a treatment benefit for Medicare beneficiaries with TRD

1. New data on the epidemiology of TRD shows the relevance to Medicare beneficiaries

In its non-coverage decision memo from 2007, CMS questioned the relevance of TRD to the Medicare population and the generalizability of evidence. The eligible Medicare population includes, but is not limited to, individuals who are age 65 or older **and** individuals who are under age 65, but are eligible on the basis of disability. Sec. 1811. [42 U.S.C. 1395c]

Recent epidemiological studies of major depressive disorder (MDD) indicate that, unlike other diseases, patients are younger at disease onset, 22 years old on average[5]. Patients who are eventually diagnosed with TRD have been documented as having an even earlier age of onset, up to 50% experience onset before the age of 18[6]. These figures are consistent with the National Institute of Mental Health (NIMH)-sponsored STAR*D study in which patients at Step 3 (having failed two adequate doses and duration of antidepressant medications, thus meeting the 2017 AHRQ definition of TRD) were, on average, 43.6 years old[7]. These same studies showed that women were at higher risk of TRD.

A 2013 study estimated that MDD has an age-standardized prevalence rate in excess of 3,500 patients per 100,000 and is the second leading cause of years lived with disability (YLD), both globally and in the United States[8]. Further, a 2014 case series review in a Canadian general practice setting demonstrated that patients with TRD had greater work impairment compared to those with non-resistant MDD; with 17.6% of patients with TRD were on long-term disability vs. 10.1% in the non-resistant MDD group[9].

Thus, based on the disability prevalence and earlier age of onset in the TRD population, patients with TRD will be younger than the typical Medicare beneficiary and will likely become eligible for Medicare as a result of disability, not age. Further, because of this, while most clinical trials do not exclude patients over 65 years of age, patients over 65 tend to be under-represented in studies based on the epidemiology of MDD.

2. Evidence-based Guidelines

Two American Psychiatric Association (APA) documents have been published since 2007 that support the use of VNS Therapy in treating patients with TRD.

In June 2009, APA published a "Vagal Nerve Stimulation (VNS) White Paper" (Attachment 19) that addressed the use of VNS Therapy to treat patients with TRD. The report concluded that, after considering electroconvulsive therapy (ECT) as an option, VNS can be considered as:

> *"VNS has been shown to be effective for some patients with significant treatment resistant depression and is approved by the FDA in this patient population."*

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[5] RC Kessler and EJ Bromet, Annu Rev Public Health. 2013;34:119–138. doi:10.1146/annurev-publhealth-031912-114409. (Attachment 3)

[6] Conway CR, Gebara MA, Walker MC. Clinical characteristics and management of treatment-resistant depression. *J Clin Psychiatry*; 2015 Nov;76(11):1569-70. (Attachment 4)

[7] AJ Rush, et. al. Am J Psychiatry 2006;163:1905–1917 (Attachment 5)

[8] Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet, 2015;386(9995);743 – 800. (Attachment 6)

[9] Rizvi SJ, Grima E, Tan M, Rotzinger S, Lin P, McIntyre RS, Kennedy SH. Treatment-resistant depression in primary care across Canada. Can J Psychiatry. 2014;59(7):349–357. (Attachment 7)

APA updated its *Practice Guideline for the Treatment of Patients with Major Depressive Disorder* in October 2010 in which TRD is acknowledged (Attachment 8). The updated treatment guideline represents the first revision in ten years and recommends several potential strategies for depression that is non-responsive to treatment, ***including VNS Therapy when symptoms persist after at least four adequate trials of antidepressant treatment, including electroconvulsive therapy (ECT).***[10]

3. Updated regulatory status of VNS Therapy in TRD

As the result of positive outcomes in the long-term clinical studies with two-year follow up that compared VNS Therapy to ongoing treatment-as-usual, the US Food and Drug Administration (FDA) approved this treatment in July 2005 (under PMA Supplement P970003 S050) for the ***adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to 4 or more adequate antidepressant treatments.***

Two post-approval studies (PAS) were required as conditions of approval of this supplement:

- D-21 Dosing Study (P970003 S050/ PAS002); and
- D-23 TRD Registry (P970003 S050/ PAS001).

In the intervening time since 2007, both studies have been completed.

The D-21 Dosing Study 4-year final report was filed on August 27, 2010 and approved by FDA on April 26, 2012 (Attachment 20). Device labeling was updated with D-21 Dosing Study results and approved under PMA Supplement P970003/S146 on November 26, 2013 (Attachment 21).

The D-23 TRD Registry 10-year final report was filed on July 31, 2015 and approved by FDA on August 1, 2016 (Attachment 22). Device labeling was updated with D-23 TRD Registry study results and approved under PMA Supplement P970003/S198 on April 28, 2017 (Attachment 23).

The current labeling, which includes the results of both studies, is provided as Attachment 24 and is publically available at https://us.livanova.cyberonics.com/healthcare-professionals/resources/product-training.

All FDA-mandated post-approval obligations associated with P970003 S050 have been completed and are closed.

4. New evidence on VNS Therapy effectiveness in treating patients with TRD

Despite the lack of Medicare coverage after 2007, researchers have continued to generate new evidence regarding the effectiveness of VNS Therapy in patients with TRD. We provide a systematic literature review through September 2015 (Attachment 25) and literature reviews for 2016 and 2017 provided to FDA as fulfillment of LivaNova's obligations under 21 CFR 814.82(a)(7) and 814.84(b) (Attachment 26 and 27).

Included in these reviews were two of the largest and longest duration studies that assess the safety and effectiveness of a treatment for TRD, the D-21 Dosing Study and D-23 TRD Registry referred to above. Both included VNS Therapy treatment arms, and both study designs conform to the recommendations outlined in the 2017 AHRQ review as described by Attachment 2 (See Appendix 1). The publications are provided in Attachments 9 and 10 and are briefly summarized here.

- **D-21 Dosing Study** outcomes published in *Brain Stimulation*[11] (Attachment 9) showed significant and sustained improvement with adjunctive VNS Therapy in a patient population experiencing severe, chronic TRD in all dosing groups. Further details on psychiatric and other medical comorbidities are provided in Appendix 2; these were not provided in the paper due to editorial constraints, but were part of the final study report that was reviewed and approved by FDA.
    - **Study design**: Multicenter, double-blind study in which 331 patients with TRD were randomized to one of three VNS Therapy dose groups.

[10] p. 18-19 Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Third Edition, Am J Psychiatry. 2010:167. (Attachment 8)

[11] Aaronson ST, Carpenter LL, Conway CR, et al: Vagus nerve stimulation therapy randomized to different amounts of electrical charge for treatment-resistant depression: acute and chronic effects. *Brain Stimulation* 2013;6:631–640 (Attachment 9)

- **Study duration**: Safety and effectiveness were assessed for patients in each dose group at various points over a 22-week period (acute phase), after which output current could be adjusted if clinically warranted. Assessments then continued another 28 weeks (long-term phase) for a total period of 50 weeks.
- **Patient Population**: A highly treatment-resistant population (*>97% had failed to respond to ≥6 previous treatments*) was enrolled. Consistent with previously cited epidemiology studies, patients were on average *48* years old and *68%* were female. Of the enrolled patient population *46% had attempted suicide, 57% had prior ECT therapy* and the average patient had been hospitalized over 3 times for mood disorders.
- **Results**: During the acute phase, all dose groups showed statistically significant improvement on the primary assessment endpoint (change in Inventory of Depressive Symptomatology Clinician Administered Version [IDS-C]) compared to baseline. There were no significant differences between any of the dose groups; importantly, the low dose did not function as a sham arm, but as an active treatment arm. In the long-term phase, mean change in IDS-C scores showed continued improvement. The likelihood of a durable, sustained response was much greater for patients in the high (88.2%) and medium (81.8%) dose groups than for patients in the low dose group (43.8%), as measured by the IDS-C.
- **Conclusions:** Patients with TRD who received adjunctive VNS Therapy showed significant improvement at study endpoint compared with baseline, and the effect was durable over one year. Higher electrical dose parameters were associated with response durability. VNS Therapy was well tolerated.

- **D-23 TRD Registry Study** outcomes were published in *The American Journal of Psychiatry*[12] (Attachment 10) and demonstrated significant and sustained benefit with adjunctive VNS Therapy relative to patients treated with treatment-as-usual over a 5 year follow-up. Further details on psychiatric and other medical comorbidities are provided in Appendix 2; these were not provided in the paper due to editorial constraints, but were part of the final study report that was reviewed and approved by FDA. Additionally, Appendix 2 provides supplemental re-analysis of key endpoints in terms of hazard ratios.
  - **Study design**: Multicenter, prospective, open-label, nonrandomized, observational registry study in which 795 patients with TRD were treated: 494 with adjunctive VNS therapy and 301 with treatment-as-usual.
  - **Study duration**: Patients were followed for 5 years.
  - **Patient Population**: The patient population was highly treatment-resistant (patients failed to respond to an average of *≥7 previous treatments*), over *50% had prior ECT therapy,* averaged between *1 and 2 prior suicide attempts* and *2-3 psychiatric hospitalizations over the past 5 years*. Consistent with epidemiology studies, patients were on average *49* years old and *70%* were female.
  - **Results**: The registry results indicate that the adjunctive VNS group had better clinical outcomes than the treatment-as-usual group, including a significantly higher 5-year cumulative response rate (67.6% compared with 40.9%) and a significantly higher remission rate (cumulative first-time remitters, 43.3% compared with 25.7%). A sub-analysis demonstrated that among patients with a history of response to ECT, those in the adjunctive VNS group had a significantly higher 5-year cumulative response rate than those in the treatment-as-usual group (71.3% compared with 56.9%). A similar significant response differential was observed among ECT non-responders (59.6% compared with 34.1%).
  - **Conclusions:** This registry represents the longest and largest naturalistic study of efficacy outcomes in treatment-resistant depression, and it provides additional evidence that adjunctive VNS has enhanced antidepressant effects compared with treatment as usual in this severely ill patient population.

[12] Aaronson ST, Sears P, Ruvuna F, Bunker M, Conway CR, Dougherty DD, Reimherr FW, Schwartz TL, and Zajecka JM. A 5-Year Observational Study of Patients With Treatment-Resistant Depression Treated With Vagus Nerve Stimulation or Treatment as Usual: Comparison of Response, Remission, and Suicidality. *American Journal of Psychiatry* 2017;174(7):640-648 (Attachment 10)

- A Medicare claims database analysis conducted by the Moran Company published in *Journal of Medical Economics*[13] showed positive health outcomes for Medicare beneficiaries with TRD who are treated with adjunctive VNS Therapy, including an all-cause mortality rate that is approximately 50% lower than the Medicare patient population with TRD not receiving VNS Therapy.
    - **Study design**: A retrospective analysis of 100% standard analytic file (SAF) Medicare claims from 2006–2009 to identify Medicare beneficiaries treated with VNS Therapy (VNSB) and an extract of the 5% sample SAF from 2001-2009 to identify two comparators, managed depression (Mdeps) and TRD. These groups were compared for mortality and negative healthcare utilization events (i.e., psychiatric hospitalization, emergency room (ER) use, hospitalization, ECT, or diagnoses for poisoning, risk for suicide or self-injury).
    - **Study duration**: Results were tabulated for 2 years post-implant (VNS Therapy) and 2 years post-identification (comparators).
    - **Patient Population**: Consistent with epidemiology studies, the average age of patients ranged from *51-59* years old and *67-73%* were female. Notably, *50-80%* of the Medicare beneficiaries across the three subgroups were disabled without end-stage renal disease. Among the frequent comorbidities, 16-59% of the patients had anxiety disorders, less than 10% were at risk for suicide, 11-20% experienced chronic pain, and 68% had hypertension.
    - **Results**: Among patients meeting study criteria for VNSBs (n=690), TRDBs (n=4639), Mdeps (n=7524), and GMBs (n>36 million), VNSBs were on average: younger, more likely to be female, and white, with Medicare eligibility due to disability. Of the VNSBs in the 2-year post-implantation period: 5% died; 22% experienced no negative events (defined as hospitalizations for psychoses or poisoning, emergency room use, electroconvulsive therapy, or poisoning, suicidal ideation, or self-harm diagnoses); 29% experienced multiple negative events and 41% had either a single hospitalization or only all-cause ER visits. VNSBs experiencing negative events had more complex co-occurring psychiatric diagnoses. The annual mortality rate for VNSBs post-implant was 19.9 deaths per 1000 patient years, compared with 46.2 (CI: 41.9–51.6) and 46.8 (CI: 43.4–50.4) deaths for TRDBs and Mdeps, respectively. The medical costs per patient-year post-VNS implantation for VNSBs ($8749) was similar to the Mdeps ($8960; CI $8555–$9381) and was substantially lower than TRDBs ($13,618; CI $12,937–$14,342).
    - **Conclusions:** VNSBs achieving positive health outcomes (measured by lack of negative events post-implantation) tend to have fewer psychiatric co-occurring conditions. Lowered costs post-implantation with evidence of response to VNS suggest the therapy represents an option for carefully screened TRDBs who have failed other therapies.

5. New evidence on the VNS Therapy mechanism of action in TRD

In addition to the clinical evidence base described above, considerable progress has been made on further characterizing the mechanism of action of VNS in TRD. Brain imaging studies have demonstrated that sustained treatment with VNS Therapy acts powerfully upon several regions of the brain known to be critical in mood regulation.

In a National Institute of Mental Health (NIMH)-sponsored brain imaging trial, using ^{18}Fluorodeoxyglucose positron emission tomography (FDG-PET) and resting state cerebral metabolic regional glucose update (CMRGlu), Conway et al. (2013)[14] serially imaged 13 patients with TRD at baseline (post-implantation, pre-stimulation) and after 3 and 12 months of VNS stimulation. The patient population was highly treatment-resistant (patients failed to respond to an average of ≥7 antidepressants), 69% had prior ECT therapy, and experienced an average of over 2 psychiatric hospitalizations. Consistent with epidemiology studies, patients were, on average, 46 years old, 77% were female and had an average early age of onset of 19 years old.

[13] Feldman RL, Dunner DL, Muller JS and Stone DA. Medicare patient experience with vagus nerve stimulation for treatment-resistant depression. *Journal of Medical Economics* 2013;16(1). (Attachment 11)

[14] Conway CR, Chibnall JT, Gebara MA, Price JL, Snyder AZ, Mintun MA, Craig AD, Cornell ME, Perantie DC, Giuffra LA, Bucholz RD, Sheline YI. Association of cerebral metabolic activity changes with vagus nerve stimulation antidepressant response in treatment-resistant depression. *Brain Stimulation*, 2013;6(5):788-97. PMCID: PMC3954813.(Attachment 12)

The majority of TRD patients (9/13) in this study responded (decreased baseline depression score by ≥ 50%) to 12 months of stimulation. A within-subjects (responders-only), regions-of-interest design was used to assess changes in CMRGlu. Key findings of this study were as follows:

- Statistically significant decreases in mean regional CMRGlu in the right dorsolateral prefrontal cortex (DLPFC; Brodmann's area 46) after three months of stimulation in patients whose depressive symptoms eventually (12 months) responded to VNS Therapy.
- In contrast, no DLPFC changes were seen in those 4 patients with TRD who failed to respond to 12 months of VNS Therapy.
- CMRGlu decreases (not statistically significant) were noted at 3 months in the right anterior insular and cingulate cortices, also regions known to be critical in depression[15].
- Increased regional CMRGlu was noted in the left substantia nigra/ventral tegmental area (VTA) brainstem region at 12 months in all 9 responders, while the opposite pattern (VTA decrease in regional CMRGlu) was noted in non-responders.

These results are important in confirming the antidepressant role of VNS Therapy given that:

- Brodmann's area 46 is a region well-known to be critical in depression[16]; and
- The VTA is the primary brainstem region modulating dopamine, a neurotransmitter thought to be potentially critical in major depressive disorder and TRD[17]. The 12 month findings may suggest VNS Therapy acts in TRD by activation of dysfunctional brainstem dopaminergic loci. This is further substantiated by research[18] which demonstrated active VNS Therapy (but not sham VNS) in TRD brought about increased cerebrospinal fluid concentrations of homovanillic acid, the primary metabolite of dopamine.

A second NIMH-sponsored study[19] assessed whether baseline regional cerebral metabolic activity correlated with eventual antidepressant outcome using FDG-PET and a regions-of-interest regression analysis. Key findings of this study included:

- The lower anterior insular cortex CMRGlu ($p = 0.004$) and higher orbitofrontal cortex CMRGlu ($p = 0.047$), both regions known to be critical in depression[20] jointly predicted change in the 24 item Hamilton Depression Rating Scale (HDRS) ($R^2 = 0.58$, $p = 0.005$).
- In a whole brain, voxel-wise analysis, baseline CMRGlu in the right anterior insular cortex correlated with HDRS change ($r = 0.78$, $p = 0.001$).

These findings suggest that baseline anterior insular and orbitofrontal cortex metabolic activity may influence antidepressant outcomes at 12 months.

In summary, there has been significant progress in understanding the mechanism of action of VNS Therapy in TRD. This work continues to demonstrate that VNS Therapy acts by changing activity in brain regions known to be critical in depression (prefrontral and insular cortex, dorsolateral prefrontal regions, anterior cingulate cortex, as well as brainstem mesolimbic regions).

[15] Price JL, Drevets WC. Neurocircuitry of Mood Disorders. Neuropsychopharmacology. 2010;35(1):192–216. (Attachment 13)
[16] Price, et al. op. cit. (Attachment 13)
[17] Nestler EJ, Carlezon Jr. WA. The Mesolimbic Dopamine Reward Circuit in Depression. Biol Psychiatry, 2006; 59(12):1151-1159. (Attachment 14)
[18] Carpenter LL, Moreno FA, Kling MA. Effect of vagus nerve stimulation on cerebrospinal fluid monoamine metabolites, norepinephrine, and gamma-aminobutyric acid concentrations in depressed patients. Biol Psychiatry, 2006;56(6):418-426. (Attachment 15)
[19] Conway CR, Chibnall JT, Gangwani S, Mintun MA, Price JL, Hershey T, Giuffra LA, Bucholz RD, Christensen JJ, Sheline YI. Pretreatment cerebral metabolic activity correlates with antidepressant efficacy of vagus nerve stimulation in treatment-resistant major depression: A potential marker for response? J Aff Disorders, 2012;139(3):283-290 PMCID: PMC3598572. (Attachment 16)
[20] Price, et al. op. cit. (Attachment 13)

Formal reconsideration request

Based on the scientific evidence provided, LivaNova formally requests that the CMS Coverage and Analysis Group (CAG) reconsider coverage of VNS Therapy for TRD as reasonable and necessary for Medicare-eligible patients meeting the following criteria:

1. Benefit Category

For an item or service to be covered by the Medicare program, it must meet one of the statutorily defined benefit categories outlined in the Social Security Act. Vagus Nerve Stimulation, at a minimum, falls under the benefit categories set forth in sections §1861(s) (6) (durable medical equipment), 1861(s) (q) (physicians' services), and 1861(s) (2) (B), (hospital services "incident to" physicians' services rendered to outpatients). This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

2. Defined Patient Populations for Coverage

Patients are eligible for coverage if they are over the age of 18 and are diagnosed with depression that has persisted after four or more adequate antidepressant treatments. Qualifying ICD-10 codes for depression diagnoses include:

- F32.x: Major depressive disorder, single episode, unspecified (exclude F32.0 – mild)
- F33.x: Recurrent depressive disorder
- F31.81: Bipolar II disorder
- F31.32, F31.4 and F31.9: Bipolar I disorder, current or most recent episode depressed, Unspecified, Moderate and Severe

Patients with TRD are currently eligible for coverage if they are already receiving VNS Therapy and require a replacement battery/device. We wish that this positive coverage determination remain intact to ensure continuity of care for patients.

We note that NCD 160.18 also includes a positive coverage determination for VNS Therapy for patients with medically refractory partial onset seizures for whom surgery is not recommended or for whom surgery has failed, effective for services performed on or after July 1, 1999. Our formal request for reconsideration of NCD 160.18 only applies to VNS Therapy for TRD, and we ask that the current positive coverage determination for patients with medically refractory partial onset seizures remain intact.

Summary

TRD is a deadly illness (an estimated 15% die by suicide) and recent evidence from the Centers for Disease Control and Prevention (CDC)[21] shows rates of suicide have increased by 24% over the past decade. Similarly, recent studies demonstrate that, on average, a U.S. Veteran dies by suicide every hour[22].

Carefully designed, prospective studies, such as the large, multicenter VNS Therapy studies described in this request (D-21 Dosing Study and D-23 TRD Registry) that studied patients with TRD having well-documented treatment failure (with adequate dose and duration) histories should be sufficient to reconsider coverage of VNS Therapy for TRD.

These patients are in desperate need of treatment options and we believe that the weight of scientific evidence provided in this formal request for reconsideration supports coverage of VNS Therapy as a treatment option.

On behalf of this underserved and vulnerable patient population, the physicians who provide care for them and LivaNova, we want to thank you and your staff at CMS for the collaborative discussions regarding reconsideration of coverage. We are confident that a re-evaluation of the new evidence accumulated over the past decade, combined with the body of evidence that began appearing in the scientific literature in 1998, presents a compelling rationale for positive coverage of this treatment option

[21] Curtin SC, Warner M, Hedegaard H. Increase in suicide in the United States, 1999–2014. NCHS data brief, no 241. Hyattsville, MD: National Center for Health Statistics. 2016. (Attachment 17)
[22] Kemp J, Bossarte R. Suicide Data Report, 2012. Department of Veterans Affairs Mental Health Services Suicide Prevention Program. https://www.va.gov/opa/docs/suicide-data-report-2012-final.pdf. (Attachment 18)

in a subpopulation of Medicare beneficiaries who face this debilitating, deadly illness and disability as a result of TRD.

Thank you for your consideration of this formal request for reconsideration of coverage for these specific patient populations.

Sincerely,

Carla Monacelli
Vice President, Government Affairs and Market Access

Bryan D. Olin, Ph.D.
Senior Vice President, Clinical, Quality and Regulatory

APPENDIX 1: AHRQ Recommendations for Study Design
APPENDIX 2; Additional Information on D-21 Dosing Study and D-23 TRD Registry
APPENDIX 3: History of Medicare Coverage
Attachments 1-31

APPENDIX 1: AHRQ Recommendations for Study Design

Key Question	AHRQ Review Recommendations[23]	D-21 Dosing Study[24]	D-23 TRD Registry[25]
2. What methods do investigators use to diagnose this condition in clinical research, and does a consensus exist about the best ways to reach a clear diagnosis?	Recommends using a structured interview tool (p. 41), a careful history or structured staging tool (p. 41 and 42) and clinical confirmation that the patient was still depressed in their current episode. (p.42) Further, the review recommends that the tools be user-friendly to accommodate clinical practice.	Study used the Mini-International Neuropsychiatric Interview to diagnose patients with MDD. A medical history and record review documented a history of failure to respond to ≥4 adequate dose/duration of antidepressant treatment trials from at least 2 different antidepressant treatment categories.	Study used the Mini-International Neuropsychiatric Interview to diagnose patients with MDD. A medical history and record review documented a history of failure to respond to ≥4 adequate dose/duration of antidepressant treatment trials from at least 2 different antidepressant treatment categories.
3. What measures (i.e., endpoints or outcomes) exist to determine the success or failure of treatment in TRD studies; what clinical focus do they represent (e.g., severity); what psychometric and other properties do they have?	Agreement on a core package of outcomes "…including one measure of depressive severity, one measure of general psychiatric status, one measure of functional impairment or quality of life, and one measure of adherence to medications or other interventions." (p. 102)	Several patient and clinician-rated measures of depressive severity were measured (MADRS, IDS-C, IDS-SR) along with a general measure of psychiatric status (CGI). The study focused on anti-depressant effectiveness and did not include a measure of functional impairment. Medication changes were assessed as was safety and suicidality.	Study included clinician (MADRS) and patient (QIDS-SR) measures of depressive severity, a general measure of psychiatric status (CGI), a measure of quality of life (Q-LES-Q SF) and gathered information regarding mood disorder treatment (including non-pharmacological) throughout the 5 year study duration.
4. What research designs do investigators use in TRD studies and does any consensus exist about best approaches to minimize bias and placebo effects and other elements of study design (e.g., length)?	Report indicates preference for randomized controlled design of a duration of at least 2 months. (p. ES-7, 102) However, the report also states that "…other robust types of observational studies to test the effectiveness of all such interventions in real-world settings are necessary. Targeting only efficacy (via RCTs) may produce information for clinicians, patients, or policymakers that cannot easily be applied in "ordinary," every-day circumstances." (p. 102) Additionally, recommends the use of structured clinical interviews to confirm diagnoses and psychiatric comorbidities seen as potential confounders. (p. 52)	The study was a double blind, randomized comparison of VNS using 3 target ranges of electrical charge. The blinded period lasted a total of 22 weeks (6 months), including up to a 8 week (2 month) period of titration followed by a 14 week (≥ 3 month) period where the charge and anti-depressant medications were held constant to the degree possible. Study extended to 50 weeks post-implant. As noted above, the Mini-International Neuropsychiatric Interview was used to confirm diagnoses and gather information about psychiatric comorbidities.	This study was a non-randomized registry that included patients treated with VNS Therapy and patients treated with treatment-as-usual. Propensity adjustments were made to address any potential biases due to differences between baseline characteristics of the two treatment groups. The study lasted for a total of 5 years, significantly in excess of the AHRQ recommendations. As noted above, the Mini-International Neuropsychiatric Interview was used to confirm diagnoses and gather information about psychiatric comorbidities.
5. What are the risk factors for TRD?	The most important risk factors appear to be number of prior failed antidepressant treatments, disease severity and duration of current episode and number of previous hospitalizations. (p. 60)	These risk factors were all present in this study and described in Table 1 of Aaronson et. al. (2012).	These risk factors were all present in this study and described in Table 1 of Aaronson et. al. (2017).

[23] The page references of AHRQ Review recommendations or key conclusions in parentheses.
[24] Aaronson, ST 2013 op. cit. ClinicalTrials.gov identifier: NCT00305565. Provided as Attachment 9.
[25] Aaronson ST 2017 op. cit., ClinicalTrials.gov identifier: NCT00320372. Provided as Attachment 10.

Key Question	AHRQ Review Recommendations[23]	D-21 Dosing Study[24]	D-23 TRD Registry[25]
6. What are the inclusion criteria for patients in these studies, specifically concerning patient characteristics, prior treatments, and diagnostic characteristics?	The review implies the following as key factors for eligibility criteria: age, confirmation of diagnosis, severity, history and duration of prior treatments. (p. 65-66) The review indicated also that study sites were poorly defined.	Enrollment criteria for the study included each of the recommended elements as described in the Methods section of Aaronson et. al. (2012) and clinicaltrials.gov identifier NCT00305565. Sites are listed in the publication and NCT00305565.	Enrollment criteria for the study included each of the recommended elements as described in the Method section of Aaronson et. al. (2017) and clinicaltrials.gov identifier NCT00320372. Sites are listed in NCT00320372, referenced in the publication.
7. How do these criteria compare or contrast with definitions encountered in the narrative review?	The review assessed study quality by the degree to which studies assessed the following factors for: minimum number of treatment failures, prior adequate treatment dose, prior adequate treatment duration, and formal staging of TRD.	A medical history and record review documented a history of failure to respond to ≥4 adequate dose/duration of antidepressant treatment trials from at least 2 different antidepressant treatment categories. Documented in Table 1 of Aaronson et. al. (2012).	A medical history and record review documented a history of failure to respond to ≥4 adequate dose/duration of antidepressant treatment trials from at least 2 different antidepressant treatment categories. Documented in Table 1 of Aaronson et. al. (2017).
8. What were primary characteristics of included studies, such as design, run-in or wash-out periods, and length?	The review identified that most studies were RCTs (p. 79) and 81% had durations of 6 months or less. (p. 81)	Total study duration was 50 weeks, exceeding AHRQ recommendation.	Total study duration was 5 years, well in excess of AHRQ recommendations.
9. How were included studies designed to account for TRD risk factors identified in the narrative review?	Most studies used some combination of exclusion criteria to limit entry of patients with confounders and / or randomization balance the impact. (p. 82)	Study excluded patients with confounders such as a history of any psychotic disorder, a history of rapid cycling BP, clinically significant suicidal intent at the time of screening, a history of drug or alcohol dependence in the last 12 months, a current diagnosis of BP mixed phase or a history of borderline personality disorder.	Study excluded patients who were currently psychotic, had a history of schizophrenia, schizoaffective disorder, any other psychotic disorder, a current MDE that included psychotic features, or a history of rapid cycling bipolar disorder.
10. What are relationships between risk factors and results of included TRD studies?	The review identifies numerous factors that could influence placebo response. (p. 86)	Many identified risk factors were reported in the publication.	The study used propensity adjustments to account for any potential bias associated with baseline risk factors.
11. What variables or information did included studies report (e.g., patient outcomes, time to relapse, treatment adherence, attrition, and use of health care resources)?	The review identifies the MADRS and CGI as commonly reported outcomes along with several other outcomes that perhaps should, but rarely are, reported. (p. 90)	Study reports response and remission for MADRS, IDS-C, IDS-SR and CGI. It also includes a discussion of mortality, suicidality and adverse events.	Study reports response and remission, time to first response, time to first remission and duration of response using MADRS. Additionally, safety (measured by the Frequency, Intensity, and Burden of Side Effects Rating, used in STAR*D), suicidality and mortality are reported. Finally, NCT00320372 and the publically available VNS Therapy Physician Manual, referenced in the publication, describes the outcome of the Q-LES-Q SF quality of life endpoint, along with other endpoints that could not be fit into the initial publication due to lack of editorial space.

APPENDIX 2: Additional Information on D-21 Dosing Study and D-23 TRD Registry

D-21 Dosing Study

As a supplement to the efficacy results presented in the paper, to provide a better characterization of the population enrolled in this study, tabulations of the patients' medical (Table 3.1.1) and psychiatric comorbidities (Table 4.2.1, ascertained from the MINI International Neuropsychiatric Interview) from the D-21 Dosing Study report approved by FDA on April 26, 2012 are provided as Attachment 28.

Summary:

- Various anxiety disorders occurred in 10-20% of patients;
- ~35% of patients had a moderate to high suicide risk in their current episode;
- 30% of patients had current or past history of chronic pain or pain syndromes;
- 45% of patients had current or past history of gastrointestinal disorders; and
- 23% of patients had current or past history of hypertension.

D-23 TRD Registry

As a supplement to the efficacy results presented in the paper, to provide a better characterization of the population enrolled in this study, tabulations of the patients' medical (Table 2.6) and psychiatric comorbidities (Table 2.7, ascertained from the MINI International Neuropsychiatric Interview) from the D-23 TRD Registry Study report approved by FDA on August 1, 2016 are provided as Attachment 29.

Summary:

- Various anxiety disorders occurred in 10-40% of patients;
- 82% of patients were at risk for suicide in their current episode;
- 40% of patients had current or past history of chronic pain or pain syndromes;
- 35% of patients had current or past history of gastrointestinal disorders; and
- 30% of patients had current or past history of hypertension.

Table 1 provides hazard ratios and other statistical meaures for the key outcomes identified in the publication.

In general, patients treated with adjunctive VNS Therapy were more likely to respond and remit than patients treated with treatment-as-usual (TAU). Further, when they did respond and remit, patients treated with VNS Therapy were more likely to maintain response or remission than patients treated with TAU. The majority of patients treated with TAU did not attain remission. Consequently, due to the small sample size of TAU patients that did attain remission, the hazard ratio for duration of remission was not statistically significant.

Analyses of suicidality measures demonstrated that treatment with adjunctive VNS Therapy resulted in a greater reduction in the average suicidality profile through sixty months post baseline as compared to the TAU treatment group, after adjustment of the baseline risk. The odds of suicidality were greater for TAU patients (2.11; 95% CI: 1.28 to 3.48) as measured by Item 12 of the Quick Inventory of Depressive Symptomatology (Self-Report) scale (QIDS-SR)[26].

[26] See Section 1.3.2.1.2, Attachment 24; also available at https://us.livanova.cyberonics.com/healthcare-professionals/resources/product-training.

Patients treated with adjunctive VNS Therapy experienced greater average improvements in quality of life than did patients treated with TAU as measured by Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q), 16.4 vs. 10.3, p-value <0.001[27], well in excess of the minimally important difference (MID) of 11.89[28,29].

Table 1: Hazard Ratios and Other Statistical Meaures for Key Outcomes

Outcome	VNS Therapy[30]	TAU[30]	Hazard Ratio (95% confidence interval)	Interpretation
Time to first response (months)	12	48	2.1 (1.7, 2.7)	The likelihood of response for patients treated with adjunctive VNS Therapy is twice that of patients treated with TAU.
Duration of response (months)				
Relapse: Time at which the patient's MADRS reduction < 50%	12	7	0.7 (0.5, 0.9)	Patients who respond to adjunctive VNS Therapy are less likely to lose their response than patients treated with TAU.
Relapse: Time at which the patient's MADRS reduction < 40%	19	13	0.6 (0.4, 0.9)	
Time to first remission (months)	49	65	2.2 (1.6, 3)	The likelihood of remission for patients treated with adjunctive VNS Therapy is twice that of patients treated with TAU.
Duration of remission (months)	40	19	0.6 (0.4, 1.1)	Patients who remit when treated with adjunctive VNS Therapy are less likely to lose their remission than patients treated with TAU.

[27] See Section 1.3.2.2.2.5, Attachment 24; also available at https://us.livanova.cyberonics.com/healthcare-professionals/resources/product-training.
[28] Endicott J, Rajagopalan K et al. A randomized, double-blind, placebo-controlled study of quetiapine in the treatment of bipolar I and II depression: improvements in quality of life. *International Clinical Psychopharmacology* 2007;22:29–37 (Attachment 30)
[29] Stevanovic D. Quality of Life Enjoyment and Satisfaction Questionnaire – short form for quality of life assessments in clinical practice: a psychometric study *Journal of Psychiatric and Mental Health Nursing*, 2011;18:744–750 (Attachment 31)
[30] Aaronson, et al. op. cit. (Attachment 10)

APPENDIX 3: History of Medicare Coverage

CMS currently provides coverage for VNS for patients with medically refractory partial onset seizures, for whom surgery is not recommended or for whom surgery has failed. VNS is not covered for patients with other types of seizure disorders which are medically refractory and for whom surgery is not recommended or for whom surgery has failed (§160.18 of the Medicare National Coverage Determination Manual).

Between July 2005 and May 2007, VNS for TRD patients was covered by many payers, resulting in over 4000 patients being implanted with VNS. In May 2007, CMS issued the following NCD: *Vagus nerve stimulation is not covered for treatment resistant depression.* Shortly after the release of the NCD, all commercial payers stopped covering VNS for TRD.

Today, approximately 120 patients per year with TRD are receiveing a replacment generator when their battery depletes. This is covered by both Medicare and some private payers.