



March 28, 2016

Re: April 27, 2016 MedCAC meeting

Dear Committee Members,

We commend the Centers for Medicare & Medicaid Services (CMS) for soliciting a diverse range of stakeholder input in its April 27, 2016 Medicare Evidence Development & Advisory Committee (MedCAC) evaluating the definition of Treatment Resistant Depression (TRD). Adoption of new policies by CMS could have a tremendous impact on patients with TRD, their families and caregivers, as well as the clinicians who care for them.

We at Janssen recommend following the current Food and Drug Administration (FDA) regulatory standard definition for TRD which specifies non-response to two or more lines of pharmacologic antidepressant therapy of adequate dose and duration in patients with Major Depressive Disorder (MDD). This definition is applicable to all TRD patients, including Medicare beneficiaries and is, following U.S. FDA guidance, the most appropriate definition of the disease state for both research and clinical practice. This definition can be widely understood by clinicians in various treatment settings and in addition to being used by the FDA in new drug applications, is currently also used by other major U.S. healthcare organizations including the Agency for Healthcare Quality and Research (AHQR)¹ and the Patient-Centered Outcomes Research Institute (PCORI)² organizations.

With the overarching goal of improving health and quality of life, Janssen is committed to developing better treatments for individuals affected by Mood Disorders, including TRD. Our discovery and development program in Mood Disorders is led by scientific leaders drawn from the National Institute of Mental Health and supported by Janssen's deep expertise in epidemiology, trial design, and analytics. In the area of TRD specifically, we are currently studying intranasal esketamine, which is the first Central Nervous System compound to have received a "breakthrough" therapy designation by the FDA.

¹ *Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults*. Effective Health Care Program. AHRQ Pub. No. 11 (12)-EHC056-3. March 2012.

² <http://www.pcori.org/sites/default/files/PCORI-PFA-2015-Cycle-3-Treatment-Resistant-Depression.pdf>

Below are our comments to the specific questions being addressed in the April 27, 2016 MedCAC meeting.

1. How confident are you that there is a standard definition of TRD that can be applied to Medicare beneficiaries in clinical studies of therapies for this disease?

Research and development of new treatments for depression has benefited from an FDA definition of TRD which has become an important operating standard in clinical studies. The FDA definition includes previous non-response to two or more lines of pharmacologic antidepressant therapy of adequate dose and duration in MDD patients, without reference to class of agent, augmentation strategy, or non-pharmacologic treatments (i.e., electro-convulsive therapy, psychotherapy), or markers of severity like suicidality. This definition has been used in new drug applications and marketing approvals in the US (i.e., Symbyax), as well in a number of industry-sponsored clinical research programs. The standard FDA definition of TRD is also reflected in the definitions used by the AHQR¹ for U.S. quality recommendations and PCORI's recent request for proposals to study TRD². We believe that Medicare beneficiaries would benefit from consistency across major U.S. healthcare agencies including the CMS in following the FDA definition.

2. If intermediate confidence is noted above, please vote by "yes or no" as to whether the following are important defining characteristics of TRD that are to be considered in clinical research:

- **The number, duration, dosage, and/or classes of antidepressants attempted**
- **The use of augmentation/combination pharmacological therapies**
- **Type of depressive episode (unipolar, bipolar, psychotic, atypical, other)**
- **The use of nonpharmacological treatments such as electroconvulsive therapy**
- **The use of psychotherapy**
- **Score changes on standardized and validated depression rating instruments (e.g. Hamilton Depression Rating Scale)**
- **Suicidal ideation and suicide attempts**
- **Other**

Following FDA guidance, we believe that number, duration, and dosage of pharmacological therapies are important characteristics of TRD for consideration in clinical research. While the type of depressive episode, use of non-pharmacological treatment including psychotherapy, score changes on standardized and validated depression rating instruments, and suicidal ideation and suicide attempts are important factors in patient care, we do not support that these features should define TRD. In the absence of evidence that narrowing the definition of TRD will improve patient care, defining patient characteristics narrowly in clinical research can burden clinicians and limit patient access to treatments without improving outcomes.

3. If intermediate confidence is noted in Question #1, how confident are you that this definition can be applied to Medicare beneficiaries:

- **In primary care settings**
- **In general psychiatric settings**
- **In specialty psychiatric settings?**

The FDA definition can be implemented in primary and specialty care settings especially when adequate documentation of prior treatment exists. There is no evidence to suggest that a more complex definition will increase the accuracy of diagnosis or, more importantly, improve treatment outcomes. The more complex the definition, the less likely it will be manageable in either primary or specialty care setting and thus may create unnecessary barriers to care for patients with TRD.

4. How confident are you that each of the below is a reliable, valid and meaningful health outcome for Medicare beneficiaries in a clinical study on TRD?

- **Improvement or decline in function**
- **Improvement or decline in quality of life**
- **Decrease in suicide ideation**
- **Decrease in suicidal attempts**
- **Other**

Changes in functional status and quality of life (QoL) are important outcome measures for clinical studies of TRD, and there exist several validated scales to measure these outcomes. Not all MDD/TRD patients are suicidal so suicidal ideation and attempts should be used for subpopulations of MDD/TRD with suicidality in order to achieve adequate power to discern efficacy.

5. How confident are you that the strategies below, when applied to Medicare beneficiaries, represent meaningful and realistic study designs in research investigations performed to evaluate interventions for TRD?

- **Randomized sham-controlled double blinded trial**
- **Randomized sham-controlled single blinded trial**
- **Randomized controlled unblinded trial**
- **Randomized crossover study**
- **Nonrandomized crossover study**
- **Pre/post study design**
- **Other**

As professional researchers, we agree that clinical studies should be designed to offer the highest level of evidence (placebo-controlled, randomized clinical trials or PCRCT) and, in addition to core symptoms of depression, should include outcomes on function and QoL.

In closing, we wish to highlight that patients with TRD face unique challenges. By the nature of their illness these patients are not well-served by current therapies. TRD patients tend to experience longer

episodes of depression and use healthcare services (e.g., physician visits), and higher death rates, more frequently than other patients with MDD.^{3,4} They are twice as likely to be hospitalized as non-TRD patients and costs for hospitalized TRD patients are six times higher than for non-TRD patients.⁵

In light of the substantial burden and limited options for relief TRD patients live with, we encourage the committee to support the regulatory FDA definition of TRD, which is already in use for approved therapies and adopted by other major U.S. healthcare organizations.

We thank the Committee for the opportunity to provide written comments to these important questions.

Sincerely,

Allitia DiBernardo, MD
Global Medical Lead, Neuroscience
Janssen Pharmaceutical Companies of J&J

³ Gibson TB, Jing Y, Smith Carls G, Kim E, Bagalman JE, et al. (2010) Cost burden of treatment resistance in patients with depression. *Am J Manag Care* 16: 370–377

⁴ Corey-Lisle PK, Birnbaum HG, Greenberg PE, Marynchenko MB, Claxton AJ. (2002) Identification of a claims data “signature” and economic consequences for treatment-resistant depression. *J Clin Psychiatry*. 63:717–726

⁵ Crown WH, Finkelstein S, Berndt ER, Ling D, Poret AW, et al. (2002) The impact of treatment-resistant depression on health care utilization and costs. *J Clin Psychiatry* 63: 963–971