Date: April 3, 2018

ATTN: Jonathan C. Javitt, MD, MPH
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Wilmington, DE 19801

Subject: Biomarker Letter of Support

Dear Dr. Javitt:

We are issuing this Letter of Support to the Glx Consortium to encourage further development of an imaging biomarker representative of the combined levels of glutamine and glutamate (Glx) in the brain as measured by magnetic resonance spectroscopy(MRS). Glx is a proposed as a pharmacodynamic biomarker[1] to provide an objective measure of depression to be used in combination with current measures of depression (i.e., validated psychometric rating scales) in depression clinical trials.

The FDA encourages the development of biomarkers for the assessment of depression. Major depressive disorder is a debilitating and chronic illness, a leading cause of disability worldwide, and a major contributor to the global burden of disease. In its most severe form, patients with depression may also experience suicidal ideation and behavior, or may commit suicide. Suicide is the 10th leading cause of death in the United States and, in service members and veterans, it ranked #1 and #2, respectively, in 2016.[2] The successful development of a reliable pharmacodynamic biomarker could be useful, including to help alleviate patient and rater subjectivity and variability characteristic of psychometric scales.

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[1] A pharmacodynamic biomarker, as defined by the BEST Resource, "is used to show that a biological response has occurred in an individual who has been exposed to a medical product or an environmental agent." BEST is located at https://www.ncbi.nlm.nih.gov/books/NBK326791/

[2] https://www.usatoday.com/story/news/nation/2016/12/29/suicide-kills-more-us-troops-than-isil-middle-east/95961038/ and https://afsp.org/wp-content/uploads/2016/06/2016-National-Facts-Figures.pdf and https://www.va.gov/opa/pressrel/pressrelease.cfm?id=2951

To date, published and non-published information submitted by NeuroRx to FDA suggests that measurement of Glx in the anterior cingulate cortex (ACC) has the potential to be developed as a pharmacodynamic biomarker. Glx has been observed to be reduced in patients with severe depression. Glx levels have been shown to increase in correlation with a temporally-related reduction in depression scores on psychometric rating scales in patients treated with electroconvulsive therapy. Peer-reviewed studies have shown that Glx is immediately increased following ketamine infusion and oral administration of D-cycloserine. The Glx increase observed with ketamine has been shown to be associated with a decrease in depression scores, as measured on standard psychometric rating scales, and appears to be sustained beyond systemic clearance of the drug. Thus, there is evidence that NMDA-blocking drugs may result in increased Glx, but this effect has not been observed in drugs targeting the serotonin pathway.

Current data suggest the potential of Glx measurement as a marker of the pharmodynamic/ pathiophysiologic effect of NDMA receptor blockers (potentially useful in dose-finding). Greater experience with the use of Glx biomarker in clinical trials is needed to determine its clinical utility as a drug development tool. We encourage further investigation of Glx as a pharmacodynamic biomarker in patients with depressive illness to determine if there is a biological response to NMDA-receptor blocking investigational drugs. In addition, we encourage further investigation into the utility of this biomarker in clinical trials and clinical practice when compared to current evaluation methods such as psychometric scales. We note it would not be expected to correlate with the depression response in selective serotonin reuptake inhibitors (SSRI). Whether Glx is a pharmodynamic marker for NDMA receptor blockers (because of their mechanism), or is in fact a general marker of depression severity should be assessed.

Strong emphasis on applying good scientific, laboratory, and software development practices for quality control and validation of the Glx biomarker is imperative. If, after further research, Glx as measured by MRS is formally proposed as a biomarker for qualification, the analytical validation should include imaging acquisition protocols and data analysis algorithms.

If the Glx biomarker is included in early clinical studies of a specific drug development program, sponsors should prospectively discuss any proposed use of the biomarker with the appropriate CDER review division.

Any groups (academia, industry, government) that would like to join in this effort or have information or data that may be useful can contact Daniel Javitt, PhD, MD (djavitt@neurorxpharma.com) or view the Glx Consortium webpage (www.glxconsortium.org).

Sincerely,

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