Title: Linking Adverse Events of Dissociation Reported With Esketamine Dosing by Clinician-Perceived Severity and CADSS Descriptors

Authors: David Williamson[1], Ibo Turkoz[2], Ewa Wajs[2], Leah Aluisio[2], J. Singh[2], H. Lynn Starr[1], Ella Daly[1]

[1]Janssen Scientific Affairs, LLC.
[2]Janssen Research & Development, LLC.

Methodological Question Being Addressed: Can structured assessment of dissociation with the Clinician-Administered Dissociative States Scale (CADSS) inform our understanding of specific phenomena identified as adverse events (AE) of "dissociation" following treatment with esketamine nasal spray (ESK)?

Introduction: Dissociation is a term used to describe widely varying phenomena within psychiatry. In past studies that evaluated glutamate receptor modulators (eg, esketamine) for treatment-resistant depression (TRD), dissociative symptoms have been reported. The CADSS is the primary measure used to quantify the severity and pattern of dissociative symptoms. In this analysis, we evaluate spontaneous (AE reported) and structured (CADSS) assessments of dissociation to better clarify symptoms reported, identify symptom clusters, and determine CADSS scores relationship to reported AEs of dissociation.

Methods: Using data from a global, open-label, long-term, multicenter, phase 3 study (NCT02497287) evaluating the safety and tolerability of ESK plus a newly initiated oral antidepressant for the treatment of TRD for up to 1 year, this post hoc analysis assessed AEs, symptom severity, and CADSS scores for patients on the first day of dosing (induction phase), when all patients received 28mg (patients >65 years) or 56mg of ESK. At this timepoint CADSS scores were at their highest magnitude, thus providing the greatest range and variability, and progressively diminished with repeated dosing. Patients were monitored for at least 90 minutes post-dose. At every dosing visit, the CADSS was administered at baseline, 40 minutes, and 90 minutes after dosing.

Equipercentile linking will demonstrate the range of CADSS scores associated with each level of dissociation AE severity. Receiver operator curve (ROC) analysis will identify the CADSS total score most associated with clinicians' decision to classify dissociation as "present" as an AE. Confirmatory factor analysis will be conducted to compare contrasting 1- and 3-factor models for goodness of fit of to our data compared to prior data (van Schalwyk et al., 2018; Niciu et al., 2018). Exploratory factor analysis results will be presented should either model fail to be replicated.

Results: 764 patients with TRD received ESK + an oral antidepressant on day 1, of whom 109 reported the adverse events of dissociation (mild=78, moderate=26, severe=5). By linking CADSS items endorsed at different levels of clinician-reported AE severity, ranging from "not

reported" to "severe", this analysis demonstrates that, while there is no unitary profile of dissociative symptoms associated with ESK treatment, some CADSS items are endorsed more frequently in subjects with dissociation (eg, "things seem to be unreal") than others (eg, "feel like you have more than one identity"). Additional results will be reported in the poster.

Conclusions: Dissociation is a term that can be described more precisely as it pertains to the AE reported with ESK. Novel combinations of analyses with large, relevant, clinical trial populations may assist in describing the likelihood of occurrence of specific events for patients and providers, and further develop our understanding of measurement tools.

References:

van Schalkwyka GI, et al. *J Affect Disord*. 2018 Feb;227:11-16.
Niciu MJ et al. *J Affect Disord*. 2018 May;232:310-315.

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