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Reply to letter

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Dear Editor:

I appreciate the reader's[1] insights and opinions on the topic of pimavanserin and Parkinson disease psychosis (PDP) and welcome this opportunity for added scholarly discussion concerning "Treatment of psychotic symptoms in patients with Parkinson disease." The reader highlights additional clinical trial data, some of which are unpublished, extracted from the Food and Drug Administration briefing document prepared for the Psychopharmacologic Drugs Advisory Committee (PDAC).[2] After review of the cumulative clinical trials data, the Food and Drug Administration PDAC voted 12 to 2 that the benefits of pimavanserin for the treatment of PDP outweigh the risk of treatment.[3] According to the PDAC minutes, "given that [pimavanserin] is the only effective agent for a very serious condition that did not worsen motor symptoms, the benefits outweighed the risks."[3]

The reader expresses concerns regarding the validity and use of the Parkinson's disease-adapted scale for assessment of positive symptoms (SAPS-PD) as a primary outcome measurement in the pivotal phase III study by Cummings and colleagues (ACP-103-020).[4] The 9-item SAPS-PD is a shortened version of the 35-item SAPS (which was originally designed for use in schizophrenia).[5] To construct the SAPS-PD, Voss and colleagues[5] extracted PDP symptom data from 1 clozapine and 3 pimavanserin double-blind, placebo-controlled trials.[6-9] The SAPS-PD was found to retain the reliability, sensitivity to change, and effect size of the larger SAPS scale while reducing administration time and score variability.[5] The SAPS-PD has been deemed an effective outcome measure for use in clinical trials.[5]

I appreciate the reader's[1] opinion about the assignment of clinical meaningfulness with pimavanserin treatment. As previously demonstrated by myself and others, the assignment of a clinically meaningful change differs based on the perspective of the individual assessing the change and may result in a lack of concordance between patient and clinician perceived benefit.[10] For example, a clinician-rendered assessment may indicate a mildly meaningful change while the patient may self-assess a larger (or smaller) degree of meaningfulness. Regarding the SAPS-PD, Voss and colleagues[5] report that a 2.33-point change is associated with clinically meaningful 1-unit change in the clinical global impression of improvement (CGI-I) scale. In the ACP-103-020 study,[4] treatment with pimavanserin 34 mg daily was associated with a 5.79 decrease (improvement) in the SAPS-PD compared with 2.73 for placebo for a difference of 3.06 (95% confidence interval −4.91 to −1.20; $P = .001$). The CGI-I is a clinician-rated scale, and thus, from a clinician's perspective, the primary outcome difference of 3.06 in SAPS-PD meets the threshold for clinical meaningfulness. Descriptors (eg, minimal, moderate, robust) assigned to the magnitude of changes in which quantitative thresholds are surpassed are inherently subjective. Nevertheless, one may characterize the difference in SAPS-PD of 3.06 (95% confidence interval −4.91 to −1.20; $P = .001$) as an improvement that is modestly clinically meaningful yet strongly statistically significant. To gain greater insight on clinically meaningful differences associated with atypical antipsychotics for the treatment PDP, a CGI-anchored quantitative analysis, such as a network analysis that provides indirect comparative analysis, is warranted.

The reader[1] suggests that a 3-point change on the SAPS-PD is not a good indicator of clinical improvement. Further examination of the distribution of change in SAPS-PD is available on the pimavanserin product label.[11] For example, the proportion of pimavanserin-treated subjects with $\geq$5, 7, or 10 points improvement in SAPS-PD were 53.7%, 41.1%, and 33.7%, respectively. At all levels, rates of response were numerically greater than placebo.[11] Additionally, 13.7% of pimavanserin-treated subjects had complete response (ie, no hallucinations or delusions at end point) compared to 1.1% of those taking placebo.[11] Another important consideration is the meaningfulness of the therapeutic outcome on caregivers. It is noteworthy that caregivers of pimavanserin-treated subjects reported a statistically significant reduction in burden compared with caregivers of those taking placebo (based on the 22-item Zarit Burden interview).[4]

The reader[1] raises concerns regarding the safety and tolerability of pimavanserin. Citrome and colleagues[12] have calculated number needed to treat (NNT) and number needed to harm in order to better provide clinical

perspective. Utilizing multiple definitions of clinical response, the NNT values for pimavanserin 34 mg/d versus placebo were <10.[12] The number needed to harm values for tolerability outcomes were >10. These values are consistent with other psychotropic medications that have NNT values between 3 and 9 (eg, bipolar disorder, major depression, schizophrenia).[13]

The reader[1] provides information extracted from the Institute of Safe Medication Practices QuarterWatch™ report. It is important to be aware that pimavanserin is distributed through a specialty pharmaceuticals network, and by design, this distribution model provides frequent interaction with patients, caregivers, and providers. In my experience, these interactions result in greater rates of solicited adverse event reporting, which generally has a higher reporting rate than that of spontaneous reporting. It is important for patients, caregivers, and providers to be aware that it may take up to 6 weeks to achieve full therapeutic benefit.[4] Reporting a lack of efficacy during the first few weeks of therapy will result in over-reporting of inefficacy.

At this time, no single atypical antipsychotic has been formally endorsed as a first-line agent for PDP.[14] I anticipate that updates to various evidence-based statements on the treatment of PDP will include pimavanserin data and provide additional guidance for providers in making informed decisions to optimize patient care.

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