Reanalysis of a Phase 3 Trial of a Monthly Extended-Release Risperidone Injection for the Treatment of Acute Schizophrenia

To the Editors:

PERSERIS, a once-monthly, subcutaneous, extended-release risperidone formulation, was approved by the Food and Drug Administration (FDA) in 2018 for treating schizophrenia in adults based on the positive results of a pivotal 8-week, phase 3, double-blind, placebo-controlled inpatient study (NCT02109562). In this study, both doses of the extended-release risperidone formulation were found to be statistically superior to placebo on the primary and secondary end points. In addition, a 52-week open-label safety study (N = 500, NCT02203838) was conducted with participants receiving 120 mg of extended-release risperidone for up to 13 months noting a favorable safety profile with both studies' leading to FDA approval (see PERSERIS US package insert [USPI]).

The original analyses of the double-blind study, published before the FDA review of the New Drug Application, evaluated changes from baseline scores across all visits (day 15, 29, 43, and 57) on the Positive and Negative Syndrome Scale (PANSS) total score (primary end point), subscores (exploratory end points), and the Clinical Global Impression–Severity of Illness (CGI-S) scale (secondary end point) using a mixed-effects model for repeated measures for extended-release risperidone 90 and 120 mg compared with placebo.6 Final assessment scores for those who terminated the study early were carried forward to the end of the study (day 57) before the mixed-effects model for repeated measure analysis was performed. The FDA requested a revised analysis of the efficacy end points where the results of the last assessment were not carried forward to day 57 and early termination assessments that were collected during an unscheduled visit were excluded. In addition, the statistical inferences for the primary and secondary end point analyses were conducted on the change from baseline to day 57 to better reflect the objectives stated in the protocol. Lastly, the FDA requested unadjusted 95% confidence intervals (CIs) for the USPI. This Letter to the Editors discusses the revised analysis because it is thought to provide a more reliable evaluation of treatment effects2 and explains the differences between the results presented in the original publication and those in the USPI.

Men and women aged 18 to 55 years with a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision diagnosis of schizophrenia and acute exacerbation of schizophrenia within 8 weeks of screening who were likely to benefit from psychiatric hospitalization or continued hospitalization were enrolled and randomized to receive 2 monthly subcutaneous injections of extended-release risperidone (90 or 120 mg) or placebo. Additional entry criteria included PANSS total score of 80 to 120 at screening and a score greater than 4 on at least 2 of the following PANSS Positive Symptoms subscale items: hallucinatory behavior, delusions, conceptual disorganization, or suspiciousness/persecution.

Revised analyses were performed with the original analysis population, which comprised all randomized subjects who received at least 1 dose of extended-release risperidone or placebo and had data recorded for at least 1 postbaseline PANSS total score, and used the original adjustments for multiplicity (the significance level for the PANSS total score and subscores was determined by Dunnett procedure controlling for PANSS total score and subscores for a 2-sided 0.05 type I error). A total of 111 and 114 subjects were in the extended-release risperidone 90- and 120-mg groups, respectively, and 112 subjects were in the placebo group; early termination assessments from unscheduled visits in 26 (23.2%), 19 (17.1%), and 27 (23.1%) patients in the placebo, 90-mg, and 120-mg groups, respectively, were removed from the analyses. Two assessments at planned scheduled visits in each group were not carried forward at day 57.

In the revised analyses, the improvements in PANSS total score and in CGI-S score at day 57 (primary and secondary end points) were significantly greater for both extended-release risperidone doses than placebo. The least-squares (LS) mean change (SE) from baseline to day 57 in the PANSS total score for placebo was −13.4 (1.6), whereas the LS mean change for extended-release risperidone 90 and 120 mg was −19.9 (1.6) and −23.6 (1.6), respectively. The LS mean change from baseline differences between each active treatment and placebo (95% adjusted and unadjusted CIs) were −6.5 (adjusted = −11.4 to −1.6, unadjusted = −10.9 to −2.1) and −10.2 (adjusted = −15.2 to −5.3, unadjusted = −14.6 to −5.9) with P values of 0.007 and less than 0.0001 for 90 and 120 mg, respectively. These significant improvements were observed as early as day 15 (first assessment) and at each subsequent time point (Fig. 1). The LS mean (SE) change from baseline to day 57 in the CGI-S score for extended-release risperidone 90 and 120 mg was −1.12 (0.09) and −1.35 (0.09), respectively, whereas the LS mean change for placebo was −0.81 (0.09). The LS mean change from baseline differences between each active dose and placebo were −0.35 (adjusted = −0.64 to −0.07, unadjusted = −0.61 to −0.10) and −0.58 (adjusted = −0.87 to −0.29, unadjusted = −0.83 to −0.32) with an adjusted P values of 0.0115 and less than 0.0001 for 90 and 120 mg, respectively.

Both extended-release risperidone 90 and 120 mg had a statistically significantly larger mean decrease (improvement) from baseline in PANSS Positive Symptoms subscale score (adjusted P = 0.0019 and P < 0.0001, unadjusted 95% CI = −3.8 to −1.0 and −4.8 to −2.0 for 90 and 120 mg, respectively) and PANSS General Psychopathology subscale score (adjusted P = 0.0015 and P < 0.0001, unadjusted 95% CI = −6.1 to −1.6 and −7.7 to −3.2 for 90 and 120 mg, respectively) compared with placebo at day 57.

The revised analysis detected a significant improvement in the PANSS Negative Symptoms subscale score with 120 mg compared with placebo (adjusted P = 0.0058, LS mean = −1.4, unadjusted 95% CI = −2.6 to −0.2). A numerical nonsignificant improvement was observed with 90 mg.

This revised analysis, in which only data collected at planned scheduled assessment points were included and missing data were not imputed, confirms the original conclusion that extended-release risperidone 90 and 120 mg are effective for the treatment of acute schizophrenia in adults.7 The results from this more sensitive analysis were similar to the original analysis for both the PANSS total score and CGI-S score as well as the Positive Symptoms and General Psychopathology subscale scores. However, in the revised analysis, extended-release risperidone 120 mg (P < 0.05), but not 90 mg, was statistically superior to placebo for the PANSS Negative Symptoms subscale; no such difference was observed in the original analysis.

The revised statistical approach gives an accurate evaluation of the effects of this extended-release risperidone formulation in patients who remain in care because those who withdrew from the study were no longer considered as completers. The main advantages of this long-acting injectable
Another limitation was the fact that this was a 9-month study; thus, adherence may become more relevant during longer-term treatment courses where treatment adherence may become more relevant.

It is difficult to extrapolate these results to other conditions, possibly caused by genetically predisposed direct and/or immune-mediated toxicity mechanisms. The risk of occurrence is approximately 2%, with a higher incidence rate in the first 18 months of treatment, where up to 90% of cases occur within 1 year. The incidence is even rarer when it comes to severe neutropenia (varying definition in the literature, with neutrophil count <500 or <1000). We discuss the heterogeneous definition in the literature, with neutropenia (absolute neutrophil count <1500), which is an idiosyncratic condition, possibly caused by genetically predisposed direct and/or immune-mediated toxicity mechanisms. The risk of occurrence is approximately 2%, with a higher incidence rate in the first 18 months of treatment, where up to 90% of cases occur within 1 year.

A limitation of this study is that it was conducted in an inpatient setting and only 2 injections of the study drug were administered over the course of the study. Therefore, it is difficult to extrapolate these results to longer-term treatment courses where treatment adherence may become more relevant. Another limitation was the fact that this was not the prespecified analytical approach, even though the analyses were requested post hoc by the FDA and are more aligned with current methodological approaches.

FIGURE 1. The PANSS total score change from baseline by visit in the intent-to-treat population for the revised analysis. Note: Baseline is the last measurement on or before the date of randomization. The P values have been adjusted for multiple comparisons using Dunnett procedure. Estimates, SEs, and P values are based on a repeated measures linear regression model of the change from baseline score, with fixed effects for visit as a categorical variable, baseline score, treatment, and treatment by visit interaction, assuming an unstructured covariance matrix. *P < 0.05, risperidone 90 mg vs placebo. †P < 0.05, risperidone 120 mg vs placebo.

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Delayed-Onset Severe Neutropenia Associated With Clozapine With Successful Rechallenge at Lower Dose

To the Editors:

Clozapine has historically been associated with neutropenia (absolute neutrophil count <1500), which is an idiosyncratic condition, possibly caused by genetically predisposed direct and/or immune-mediated toxicity mechanisms. The risk of occurrence is approximately 2%, with a higher incidence rate in the first 18 months of treatment, where up to 90% of cases occur within 1 year. The incidence is even rarer when it comes to severe neutropenia (varying definition in the literature, with neutrophil count <500 or <1000). We discuss an unusual case of severe neutropenia after 9 years of clozapine use. The patient has given verbal informed consent for publication of his case.

CASE REPORT

A male patient, 47 years old, single, experienced his first psychotic episode when he was 26 years old, shortly after his undergraduate education. He presented with paranoid ideas encompassing mystical and religious content. Over the course of 21 years, he was admitted a few times. He underwent outpatient follow-up and received therapeutic doses in sequence of haloperidol, risperidone, and olanzapine in monotherapy, lasting for 8 weeks or more, with no response. He was...