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# Pimavanserin Exposure-Response Analyses in Patients With Schizophrenia

## Results From the Phase 2 ADVANCE Study

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### Abstract:

**Purpose/Background:** Pimavanserin is a selective serotonin 5-HT<sub>2A</sub> receptor inverse agonist/antagonist being investigated in patients with negative symptoms of schizophrenia. This analysis aimed to characterize exposure-response relationships of pimavanserin in this population.

**Methods/Procedures:** Exposure-response models were developed using data from ADVANCE. Patients with negative symptoms of schizophrenia receiving background antipsychotics were randomized to pimavanserin 20 mg (adjusted to 34 or 10 mg between weeks 2–8 based on efficacy or tolerability) or placebo for 26 weeks. Time-varying pimavanserin exposure measures were predicted for each patient using a population pharmacokinetic model and individual empiric Bayesian parameter estimates. Response measures were the Negative Symptom Assessment 16 (NSA-16, primary end point), Personal and Social Performance scale, negative symptoms component of the Clinical Global Impression of Schizophrenia–Severity Scale, and adverse events.

**Findings/Results:** A higher pimavanserin exposure was associated with greater improvement in NSA-16 score. For a median area under the pimavanserin plasma concentration-time curve from time 0 to 24 hours of 1465 ng × h/mL for the 34-mg dose, the model predicted a 10.5-point reduction in NSA-16 score. This exposure-response relationship with NSA-16 scores was not influenced by covariates. Similar results were observed with Personal and Social Performance and Clinical Global Impression of Schizophrenia–Severity, but not to the extent as NSA-16. There was no significant exposure-response relationship with anxiety, headache, insomnia, or somnolence.

**Implications/Conclusions:** Increasing pimavanserin plasma concentration was associated with improved NSA-16 scores (primary end point) in patients with negative symptoms of schizophrenia. No exposure-response relationship with select adverse events was observed.

**Key Words:** pimavanserin, schizophrenia, 5-HT<sub>2A</sub> serotonin receptor, pharmacology

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More than 50% of patients with schizophrenia have negative symptoms, including blunted affect, avolition, anhedonia.<sup>1,2</sup> Negative symptoms of schizophrenia are more strongly correlated with long-term morbidity and poor functional

outcomes than positive symptoms.<sup>3</sup> Second-generation antipsychotics provide only modest control of negative symptoms,<sup>4,5</sup> and there are no therapeutics currently approved in the United States for this indication specifically.

Pimavanserin is a selective serotonin receptor-modulating agent with inverse agonist/antagonist activity at 5-HT<sub>2A</sub> receptors and to a lesser extent at 5-HT<sub>2C</sub> receptors.<sup>6–8</sup> Experiments in rodents have shown that pimavanserin readily crosses the blood-brain barrier and acts as a central nervous system-active 5-HT<sub>2A</sub> inverse agonist.<sup>8</sup> A positron emission tomography study in healthy adult subjects on the relationship between oral dose, plasma level, and the uptake of pimavanserin demonstrated dose-dependent binding and near maximal saturation of 5-HT<sub>2A</sub> receptors after doses of 10 or 20 mg.<sup>6</sup> Pimavanserin had a very high binding affinity for the 5-HT<sub>2A</sub> receptor (pK<sub>i</sub> = 9.3) in membrane binding assays, which was higher still in whole cell studies (pK<sub>i</sub> = 9.70).<sup>7</sup> Positron emission tomography studies in pigs demonstrated that radiolabeled pimavanserin had high brain permeability dominated by nonspecific binding.<sup>9</sup> Only minimal displacement of <sup>11</sup>C-NMSP was observed in the striatum at pimavanserin doses as high as 100 mg, underscoring the pharmacological differences between pimavanserin and other antipsychotic drugs, which interact with dopamine receptors.<sup>8</sup>

After single oral doses of pimavanserin in healthy subjects, maximum drug concentration (C<sub>max</sub>) and area under the plasma concentration-time curve (AUC) values increase proportionally with dose.<sup>10</sup> Steady-state C<sub>max</sub> and AUC<sub>0–24</sub> values are approximately 3- to 5-fold greater after once-daily oral administration (50–150 mg) for 14 days, which is consistent with pimavanserin's long plasma half-life (57 hours).<sup>10</sup> Pimavanserin is slowly absorbed with a flat peak, and time to maximum concentration is achieved approximately 6 hours after dose, with a range of 4 to 12 hours.<sup>10,11</sup> Pimavanserin tablets are 99.7% bioavailable relative to oral solution,<sup>10–12</sup> and it is widely distributed, with an apparent V/F of 2730 L.<sup>13</sup> Disposition is primarily via metabolism, with less than 1% excreted unchanged in the urine. The metabolism of pimavanserin to its N-desmethylated metabolite occurs primarily via cytochrome P<sub>450</sub> enzyme (CYP) 3A4/5. Neither patient characteristics (ie, weight, age, sex, or ethnicity) nor food has significant effects on pimavanserin exposure, except for a minor increase in time to maximum concentration with food (fasted, 6 hours; fed, 10.5 hours).<sup>11,14</sup>

The ADVANCE study was a phase 2, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of adjunctive pimavanserin versus placebo in patients with predominant negative symptoms of schizophrenia on stable background antipsychotic therapy.<sup>15</sup> In ADVANCE, a statistically significant improvement in the primary end point of change from baseline to week 26 in the Negative Symptom Assessment 16 (NSA-16; primary end point) was observed in the pimavanserin group versus the placebo group.<sup>15</sup> No statistically significant difference was observed between the 2 treatment groups regarding the secondary

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end points, change from baseline to week 26 in Personal and Social Performance (PSP) Scale score (key secondary end point) or in negative symptoms using Clinical Global Impression of Schizophrenia–Severity (CGI-SCH-S) Scale.<sup>15</sup> However, there was a trend of greater improvement in CGI-SCH-S observed in the pimavanserin group compared with placebo group.<sup>15</sup> Importantly, as an adjunct to antipsychotic therapy, pimavanserin had similar tolerability to placebo, with the most common treatment-emergent adverse events (AEs) being headache and somnolence.<sup>15</sup>

The objective of these current analyses was to assess the relationships between pimavanserin exposure and response (efficacy and safety) in the ADVANCE study. Exposure-response (E-R) relationships have increasingly been examined to help optimize therapeutic dosage regimens and support clinical evidence of efficacy.<sup>16</sup> The E-R models were developed to characterize relationships between pimavanserin exposure and NSA-16, PSP, and CGI-SCH-S, as well as potentially relevant safety end points (anxiety, headache, insomnia, and somnolence).

## MATERIALS AND METHODS

### Study Design and Patient Population

The E-R models were developed using pharmacokinetic (PK), efficacy, and safety data from the ADVANCE study (ClinicalTrials.gov identifier: NCT02970305; EudraCT Number: 2016-003436-20), details of which have previously been described.<sup>15</sup> In brief, ADVANCE enrolled schizophrenia outpatients (aged 18–55 years) with predominant negative symptoms from centers in Europe and North America. Patients were diagnosed with schizophrenia 1 year or more before randomization and had a score of 20 or greater on the sum of 7 Marder negative symptom items from the Positive and Negative Syndrome Scale (including a score of  $\geq 4$  on 3 or more items or  $\geq 5$  on 2 or more items) at screening and baseline. The severity of positive symptoms, depression, and extrapyramidal symptoms was also limited per protocol.<sup>15</sup> Before screening, patients were treated with a background antipsychotic for at least 8 weeks, on a stable dose for at least 4 weeks, and medically stable for at least 12 weeks.

Patients received either oral pimavanserin or matching placebo once daily added to background antipsychotic therapy for 26 weeks. The pimavanserin starting dose of 20 mg once daily could be increased to 34 mg or decreased to 10 mg at the investigator's discretion based on efficacy or tolerability during weeks 2 to 8, after which no dose changes were allowed. Per the protocol, strong and moderate cytochrome P450 3A4 inhibitors and inducers were prohibited/restricted.

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines, and the protocol was approved by institutional review boards at participating centers. Written informed consent was provided by all patients before screening and enrollment.

### Exposure Measures

Blood samples for PK analyses were collected before dose at baseline and weeks 2, 8, 14, and 26. When possible, an additional PK sample was collected from patients who experienced a serious AE or an AE leading to discontinuation as soon as possible after the occurrence of that event. Bioanalytical analyses were performed to quantify pimavanserin in human plasma. Only pimavanserin was quantified for the reported population PK and E-R analysis. The assays were sensitive and specific, with an appropriate dynamic range; specifically, it demonstrated a range of percentage biases from 1.9 to 10.0 for the 5 quality control concentrations tested (range, 0.1 to 80.0 ng/mL).

### Population PK Model

A population PK model and empiric Bayesian parameter estimates were used to obtain individual exposure measures of pimavanserin for use in E-R modeling of the efficacy and safety outcomes (Fig. 1A). The population PK analysis from ADVANCE was conducted according to current best practice<sup>17</sup> using nonlinear mixed effects models. The first-order conditional estimation method with interaction was used during all stages of the model development process. The PK model structure was a 1 compartment model with first-order oral absorption (with relative bioavailability [F1] estimated for the highest [300-mg] dose) and first-order linear elimination. Interindividual variability was estimated for the first-order absorption rate constant, apparent clearance (CL/F), and apparent volume of distribution (V/F) using exponential error models.

Separate additive plus constant coefficient of variation models described the residual variability of the sparse and full profile concentration data. Daily and steady-state exposure measures calculated from the PK model were  $C_{max}$ , AUC from time 0 to 24 hours ( $AUC_{0-24}$ ), and average drug concentration during a dosing interval ( $C_{av}$ ). These measures were generated via integration of predicted concentration-time profiles for each patient based on the final population PK model, individual empiric Bayesian PK parameter estimates, and the dosing history of each patient. Average daily pimavanserin exposures between consecutive visits of PD measurements were calculated for use in E-R efficacy modeling. Pimavanserin exposure measures for placebo patients were set to 0.

### Response Measures

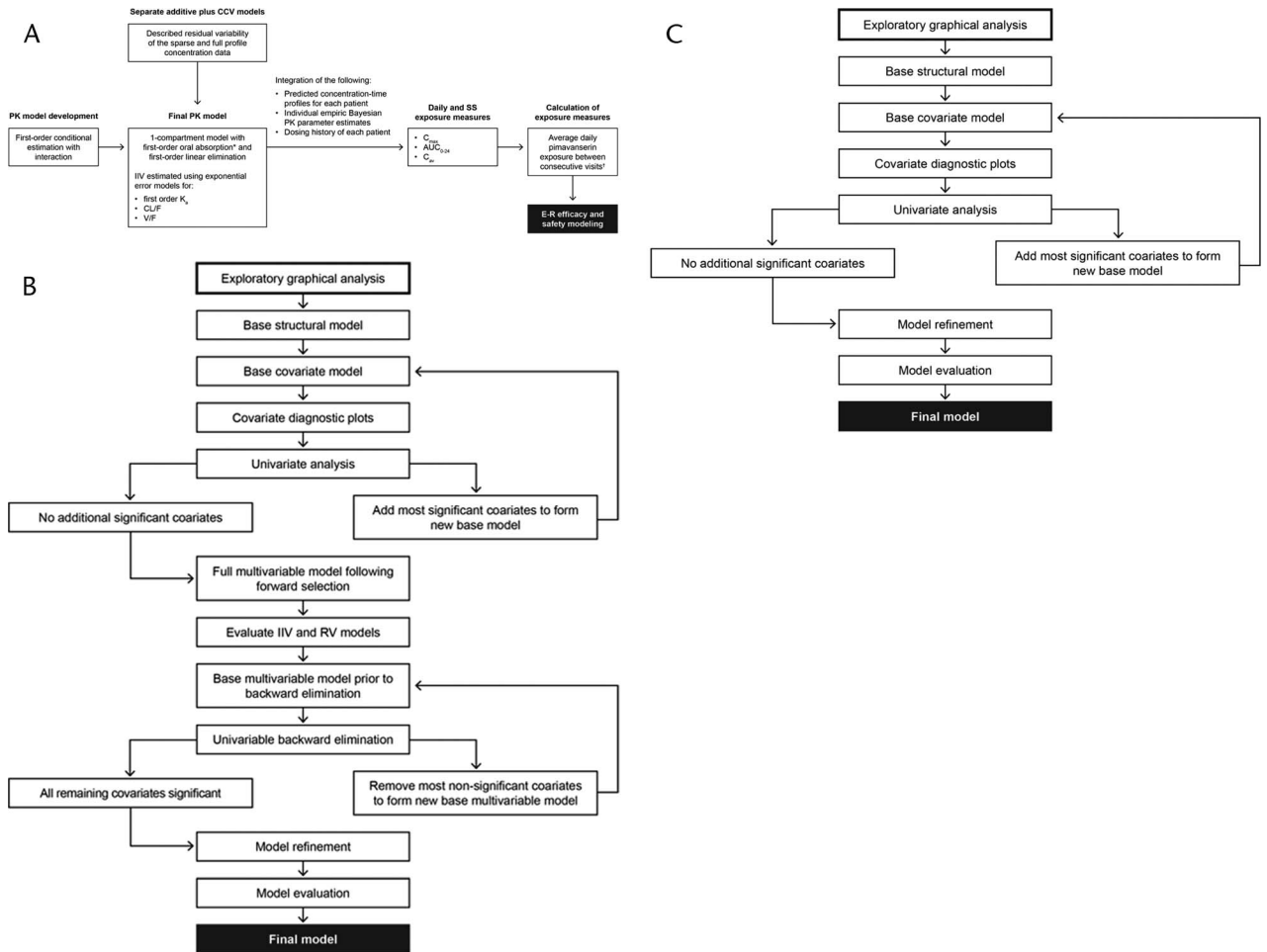
The efficacy measures investigated in these analyses were the NSA-16 (primary outcome of ADVANCE), PSP (key secondary outcome), and CGI-SCH-S, all of which are psychometrically validated and reliable.<sup>18–20</sup> The NSA-16 is a 16-item evaluation of negative symptoms of schizophrenia<sup>18</sup> that was completed at baseline, and weeks 2, 4, 8, 14, 20, and 26/end of treatment (ET) visits. The 100-point PSP scale score, used to rate psychosocial functioning of patients with schizophrenia,<sup>19</sup> was assessed at baseline, week 8, and week 26/ET visits. The CGI-SCH-S is a clinician-rated, 7-point scale designed to evaluate severity of schizophrenia.<sup>20</sup> In ADVANCE, the CGI-SCH-S focused on negative symptoms and was completed at screening, baseline, weeks 2, 4, 8, 14, 20, and 26/ET visits.

Safety in ADVANCE was measured by assessing treatment-emergent AEs, vital signs, electrocardiograms, and clinical biochemistry. An AE was defined as any untoward medical occurrence within the treatment window associated with the use of a drug in humans, whether or not considered drug related. The AEs investigated in the E-R safety analyses were anxiety, headache, insomnia, and somnolence, because these were the most commonly reported AEs in ADVANCE.<sup>15</sup>

### Exposure-Response Analyses

Exposure-response analyses of data from the ADVANCE study were conducted in accordance with current best practice.<sup>21</sup> Four separate E-R analyses were conducted, 3 efficacy E-R analyses (NSA-16, PSP, and CGI-SCH-S scores), and safety E-R analyses of anxiety, headache, insomnia, and somnolence.

To be considered in the E-R efficacy analyses, patients must have received more than or equal to 1 dose of study drug and had both a baseline value and greater than or equal to 1 postbaseline value for the NSA-16 scores (full analysis set). The safety analysis set (ie, all randomized patients who received at least 1 dose of study drug) was used for the E-R safety modeling. If a patient did not report a specific AE, it was assumed that the event did



**FIGURE 1.** Methodology used to conduct the (A) population PK analysis, (B) efficacy E-R analyses, and (C) safety E-R analysis. CCV, coefficient of variation; IIV, intraindividual variability;  $K_{ar}$ ,  $K_a$  absorption rate constant; PK, pharmacokinetic; RV, residual variability; SS, steady state; V/F, apparent volume of distribution.

not occur. Patients randomized to receive pimavanserin with end point data must have been evaluable for the PK analysis to avoid exclusion from the E-R analysis for that end point.

The relationship between pimavanserin exposure (based on the average of daily exposure measures [ $AUC_{0-24}$ ,  $C_{av}$ , and  $C_{max}$ ] between consecutive visits) and each efficacy outcome (NSA-16, PSP, and CGI-SCH-S scores) was evaluated using nonlinear mixed-effects models (Fig. 1B). Exploratory data analysis and data visualizations were used to understand the informational content of the data set with respect to the anticipated model, search for extreme values and potential outliers, assess possible trends in the data, and identify potential errors in the analysis data set. The most appropriate functional forms for the base structural models were selected and developed based on results from the exploratory analyses.

The base models were the sum of a placebo effect (time course) plus a drug effect described by either a direct-effect linear or nonlinear function of exposure (maximum pharmacologic effect [ $E_{max}$ ] function). Proportional odds models were used to describe the ordered categorical CGI-SCH-S end point data. Evaluation of the impact of covariates on the base E-R efficacy models focused on the influence of age, sex, baseline weight, baseline body mass index, geographical region, race, duration of schizophrenia illness, smoking status, antipsychotic medications (aripiprazole, aripiprazole long-acting, olanzapine, risperidone, risperidone

long-acting, asenapine, brexpiprazole, cariprazine, and lurasidone), antipsychotic medication doses equivalent to risperidone, and concomitant use of benzodiazepines, anticholinergics, or antidepressants. A stepwise covariate search was used consisting of forward addition ( $\alpha = 0.01$ ), followed by backward elimination ( $\alpha = 0.001$ ). The adequacy of the final models was evaluated using a simulation-based, visual predictive check (VPC) method to assess concordance between the model-based simulated data and the observed data.<sup>22</sup> The final models were used to simulate a large number of replicates of the analysis data set sufficient to achieve at least 10,000 patients overall or 10,000 patients per stratum if the VPC was stratified.

A procedure similar to those described previously for the efficacy E-R analyses was used to develop the E-R safety models (Fig. 1C). Steady-state pimavanserin exposures, based on the last administered dose for a patient, were used for the analysis of safety end points. Stationary covariates evaluated in the analysis of safety end points were age, sex, baseline weight, race, and antipsychotic medication use. Safety end points were treated as binary variables. The relationship between pimavanserin exposure and the probability of an AE was evaluated using logistic regression analysis. The effect of steady-state pimavanserin exposures ( $AUC_{0-24}$ ,  $C_{av}$ , and  $C_{max}$ ) on the frequency of anxiety or somnolence was evaluated using linear models based on exploratory graphical displays, while the effect of steady-state pimavanserin



exposures on the frequency of headache or insomnia was evaluated using linear,  $E_{\max}$ , and exponential models based on exploratory graphical displays. The final E-R safety models were validated using 2 methods of model evaluation, including the Hosmer-Lemeshow goodness-of-fit test and the area under the receiver operating characteristic curve.

Model building for PK, efficacy, and safety end points was conducted using nonlinear mixed effects models in NONMEM Version 7.3 (ICON, Hanover, Md). All exploratory data analyses and data presentations were performed using SAS Version 9.4 (SAS Analytics Solutions, Cary, NC) and KIWI Version 4.2 (Cognigen, Buffalo, NY).

## RESULTS

### Patient Disposition and Baseline Patient-Related Characteristics

Of the 403 patients who were randomized and received at least 1 dose of study drug in ADVANCE (safety analysis set), 346 (85.6%) completed the study (172 in the pimavanserin group and 174 in the placebo group). Patient demographics and clinical characteristics (including schizophrenia history) were well balanced between the pimavanserin group and the placebo group.<sup>15</sup> There were comparable rates of completion for the NSA-16, PSP, and CGI-SCH-S (negative symptoms) efficacy measurements between the pimavanserin and placebo groups throughout the study (Table S1, Supplemental Digital Content, <http://links.lww.com/JCP/A828>).

### Final Population PK Model

The analysis data set used for population PK model development included 731 quantifiable plasma pimavanserin concentrations from 196 patients from ADVANCE. The complete pooled population PK model development data set included 9493 concentration values from 1159 patients enrolled in a total of 19 clinical studies. A total of 3 covariate-parameter relationships were described in the model, including age as a significant predictor of CL/F (with CL/F predicted to remain constant for subjects younger than 50 years, then to decline linearly with increasing age in subjects aged 50 years), and both age and body weight as significant predictors of V/F (with V/F predicted to increase less than proportionally with increasing age and to increase linearly with increasing body weight). The final population PK model parameters are given in Table S2, <http://links.lww.com/JCP/A828>.

### Exposure-Response NSA-16 Analysis

The E-R NSA-16 analysis revealed that higher pimavanserin exposure in patients with negative symptoms of schizophrenia was associated with a greater reduction in NSA-16 score, the primary efficacy end point in ADVANCE.

A total of 2628 NSA-16 scores from 396 patients (pimavanserin group,  $n = 195$ ; placebo group,  $n = 201$ ) were collected up to week 26 and included in this E-R efficacy data set. Among the 396 patients, one third were women ( $n = 133$ , 33.6%), and most were white ( $n = 367$ , 92.7%; Table S3, <http://links.lww.com/JCP/A828>). The median age was 37 years (range, 18–55 years), and the median body weight at baseline was 81.3 kg (range, 49.9–122.7 kg). The median NSA-16 score at baseline was 61 (range, 37–87). The proportions of NSA-16 measurements associated with concomitant administration of antipsychotics were as follows: risperidone (30.9%), olanzapine (27.7%), aripiprazole (25.7%), risperidone long-acting injectable (8.8%), aripiprazole long-acting injectable (5.8%), and other (1.1%).

Of the 195 evaluable patients in the pimavanserin group, 80 (41.0%) remained on the starting 20 mg once daily throughout the study, 110 (56.4%) had their starting daily dose increased to 34 mg, and 5 (2.6%) had their starting daily dose decreased to 10 mg during weeks 2 to 8. A 2.4-fold increase in dose (from 10 to 34 mg) was associated with a 1.7-fold increase in pimavanserin exposure (Table S4, <http://links.lww.com/JCP/A828>). As expected with a linear 1-compartment model, matrix plots of pimavanserin exposure measures showed that all pairs of calculated pimavanserin exposure measures were highly correlated.

Post hoc analysis of NSA-16 by last dose level showed that patients whose last dose was 34 mg (99/174) exhibited a nominally statistically significant improvement ( $P = 0.0065$ ; Table 1).

The effects of average daily  $AUC_{0-24}$ ,  $C_{\text{av}}$ , and  $C_{\text{max}}$ , as linear functions of  $E_{\max}$  were statistically significant and produced nearly identical magnitudes of change in the objective function. As all exposure measures were significant and highly correlated,  $AUC_{0-24}$  was chosen for inclusion in the base E-R model because it was clinically relevant.

The E-R relationship was described by a sigmoid maximum pharmacologic effect time-course model. The relationship between  $AUC_{0-24}$  and the maximum response in NSA-16 ( $E_{\max}$ ) was best described by a linear function where lower model-predicted NSA-16 scores were observed with increasing pimavanserin  $AUC_{0-24}$  as follows:

$$NSA_{ij} = 61.2 + \left( \frac{E_{\max i} \times \text{Week}_{ij}^{1.19}}{T_{50i}^{1.19} + \text{Week}_{ij}^{1.19}} \right) \quad (1)$$

$$E_{\max i} = -10.4 - 0.00226 \times AUC_{ij} \quad (2)$$

where  $NSA_{ij}$  is the model-predicted NSA-16 score in the  $i$ th patient at the  $j$ th week;  $E_{\max i}$  is the model-estimated maximum effect for the  $i$ th patient;  $\text{Week}_{ij}$  is the week corresponding to the NSA-16 score in the  $i$ th patient at the  $j$ th week;  $T_{50i}$  is the time at half maximal response for placebo (weeks); and  $AUC_{ij}$  is the

**TABLE 1.** Change in NSA-16 Scores From Baseline to Week 26 by Last Pimavanserin Dose

Last Dose	Change From Baseline to Week 26, LSM (SE)	Difference From Placebo, MMRM LSM (SE)	<i>P</i>	Cohen <i>d</i> *
Pimavanserin 34 mg (n = 99)	-11.6 (0.90)	-3.1 (1.12)	0.0065	0.339
Pimavanserin 20 mg (n = 73)	-9.0 (1.02)	-0.5 (1.22)	0.6847	0.055
Pimavanserin 10 mg (n = 2)	-8.3 (6.01)	0.2 (6.05)	0.9783	-0.018
Placebo (n = 173)	-8.5 (0.67)	—	—	—

\*Cohen *d* effect size for the change from baseline between the treatment groups was calculated using the following formula: Effect size =  $\frac{\text{LSM difference}}{\sqrt{\text{variance}}}$ .  
LSM, least squares mean; MMRM, mixed-effect model repeated measures; SD, standard deviation; SE, standard error.

average daily pimavanserin  $AUC_{0-24}$  between visits at the time of NSA-16 score in the  $i$ th patient at the  $j$ th week.  $T_{50i}$  was estimated as 9.58 weeks. The value of 1.19 in Equation 1 represents the estimate of the Hill coefficient used to describe the steepness of the E-R relationship.

The final model parameter estimates and their associated precisions (relative standard error expressed as a percent) for the final E-R model of NSA-16 scores are presented in Table S5, <http://links.lww.com/JCP/A828>. Visual predictive check 90% prediction intervals (PIs) corresponded well between the observed and simulated data, indicating that the magnitude of variability in NSA-16 response was well characterized by the model.

Assuming the median pimavanserin average daily  $AUC_{0-24}$  of 1465 ng  $\times$  h/mL for the 34-mg dose, the corresponding model-predicted reductions in NSA-16 score from baseline is 10.5 at week 26 compared with 8.0 for placebo. A statistically significant E-R relationship was observed between NSA-16 scores and pimavanserin drug exposure (Fig. 2). All exposure measures were significant predictors of the variability in NSA-16 scores. The relationship between pimavanserin exposure and NSA-16 response was not influenced by any of the examined covariates.

### Exposure-Response PSP Analysis

The E-R PSP analysis revealed that higher pimavanserin exposure was associated with improvements in the PSP scale, but these improvements did not achieve the same levels as those described previously for the NSA-16 score. In ADVANCE, improvement on the PSP scale from baseline to week 26 was observed in the pimavanserin group, but statistical separation from placebo was not detected.<sup>15</sup> A total of 1125 PSP scores were collected from 386 patients up to 26 weeks, which were used to develop a linear time-course model, including parameters estimating the baseline PSP score and slope for time.

The characteristics of the PSP analysis population were similar to those of the E-R NSA-16 analysis population. The median PSP score at baseline was 46 within a range of 20 to 75. In the pimavanserin group, during weeks 2 to 8, 83 patients (43.4%) remained on the starting 20 mg once daily throughout the study, 105 patients (55.0%) had their starting daily dose increased to 34 mg, and 3 patients (1.6%) had their starting daily dose decreased to 10 mg. The patient-specific predicted exposure measures at the times of PSP efficacy assessments were similar to those in the E-R NSA-16 analysis.

All exposure measures and functional forms were statistically significant predictors of the variability in PSP scores. The effects of average daily  $AUC_{0-24}$ ,  $C_{av}$ , and  $C_{max}$ , as linear or exponential

functions, were each statistically significant, and the exponential forms produced similar magnitudes of change in the objective function. Because the exponential model of  $C_{max}$  resulted in the largest decrease in the value of the objective function, this exposure measure was chosen for inclusion in the base model. As no covariates were significant predictors of the variability in PSP scores and no model refinement was necessary, the base E-R model for PSP became the final model. An exponential function best described the E-R relationship as follows:

$$PSP_{ij} = 47.5 \times e^{0.000553 \times C_{maxij}} + 0.29961 \times Week_{ij} \quad (3)$$

where  $PSP_{ij}$  is the model-predicted PSP score in the  $i$ th patient at the  $j$ th week;  $C_{maxij}$  is the average daily pimavanserin  $C_{max}$  between visits at the time of PSP score in the  $i$ th patient at the  $j$ th week; and  $Week_{ij}$  is the week corresponding to the PSP score in the  $i$ th patient at the  $j$ th week.

The VPC plots showed that the majority of the observed data fell within the 90% PI, with an appropriate amount and similar distribution of observed data points falling below the 5th and above the 95th percentiles of simulated data. The PIs from both the observed and simulated data corresponded well, indicating that the magnitude of variability in PSP response was well characterized by the model.

Model-predicted PSP scores increased as pimavanserin  $C_{max}$  increased (Fig. 3). Assuming the median average daily pimavanserin  $C_{max}$  of 64 and 36 ng/mL for the 34- and 20-mg doses, respectively, the corresponding model-predicted increases in PSP score from baseline were 9.5 and 8.8 at week 26 compared with 7.8 for placebo.

### Exposure-Response CGI-SCH-S Analysis

The E-R CGI-SCH-S analysis revealed that higher pimavanserin exposure was associated with a greater probability of having a CGI-SCH-S score of 3 or less at week 26.

In ADVANCE, improvements from baseline to week 26 in the CGI-SCH-S of negative symptoms score were observed with pimavanserin and placebo, with no statistically significant between-group differences detected.<sup>15</sup> A total of 2629 CGI-SCH-S scores collected from 396 patients for up to 26 weeks were used in the E-R proportional odds model, which included the placebo time course and drug effect as components on the logit scale. The characteristics of the CGI-SCH-S analysis population were the same as those of the E-R NSA-16 analysis population. The median CGI-SCH-S score at baseline was 5 (range, 4–6).

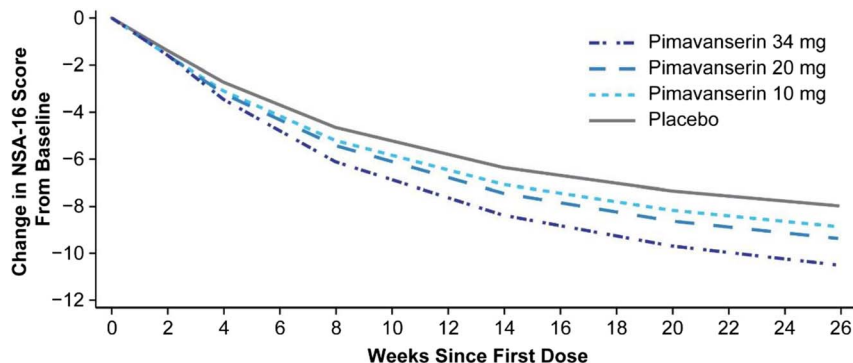
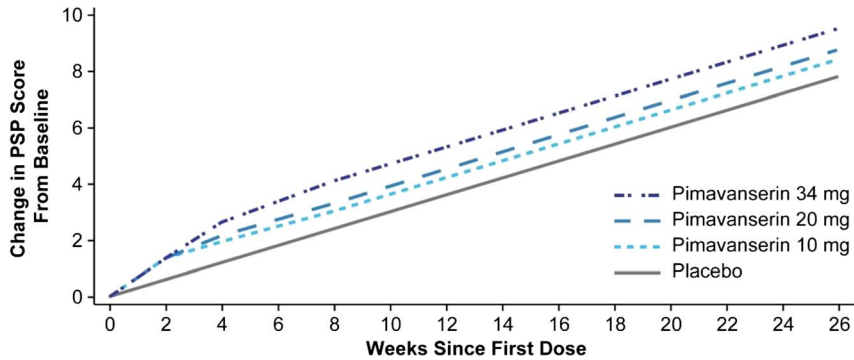


FIGURE 2. Exposure-response model-predicted change from baseline in NSA-16 score according to pimavanserin dose. The model-predicted lines represent the response at the median average daily pimavanserin  $AUC_{0-24}$  at each week for each dose level.



**FIGURE 3.** Exposure-response model–predicted change from baseline in PSP scores according to pimavanserin dose. The model-predicted lines represent the response at the median average daily pimavanserin  $C_{max}$  at each week for each dose level.

The placebo time-course was a linear model, including estimating the slope for time. A separate linear function of  $AUC_{0-24}$  best described the shallow E-R effect of pimavanserin as follows:

$$\text{logit}[P(\text{CGI-SCH-S}_{ij} \leq m)] = \sum_{k=0}^m B_k + f_{\text{placebo}_{ij}} + f_{\text{drug}_{ij}} + \eta_i \tag{4}$$

$$f_{\text{placebo}_{ij}} = 0.152 \times \text{Week}_{ij} \tag{5}$$

$$f_{\text{drug}_{ij}} = 0.000658 \times AUC_{ij} \tag{6}$$

where  $B_k$  is the population mean estimated intercept for the logit representing the baseline probability for the different CGI-SCH-S scores where  $k = 2, 3, 4,$  and  $5$ ;  $f_{\text{placebo}_{ij}}$  is the estimated placebo (time course) effect in the  $i$ th patient at the  $j$ th week;  $f_{\text{drug}_{ij}}$  is the estimated pimavanserin drug effect in the  $i$ th patient at the  $j$ th week;  $\eta_i$  is the interindividual random effect with zero mean and variance  $\omega^2$ ;  $\text{Week}_{ij}$  is the week corresponding to the CGI-SCH-S score in the  $i$ th patient at the  $j$ th week; and  $AUC_{ij}$  is the average daily pimavanserin  $AUC_{0-24}$  in the  $i$ th patient at the  $j$ th week. The CGI-SCH-S response was not significantly influenced by any examined covariates.

Visual predictive check evaluation demonstrated that the model fit was reasonable and essentially unbiased, with no significant trends or signs of substantial misfit. Exposure to pimavanserin increased the probability of lower CGI-SCH-S scores. Across the

range of pimavanserin  $AUC_{0-24}$ , the cumulative probabilities of lower scores increased with increasing exposure, indicating improvement in CGI-SCH-S scores (Fig. 4). The model-predicted cumulative probability of CGI-SCH-S score of 3 or less at week 26 was 0.30 for pimavanserin 34 mg, 0.27 for pimavanserin 20 mg, and 0.24 for placebo, compared with 0.07 at baseline.

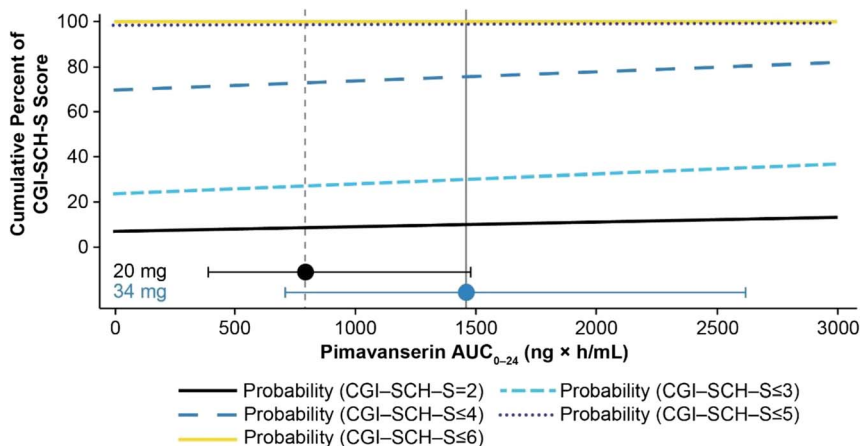
### Exposure-Response Safety Analysis

The E-R safety analyses did not demonstrate any apparent relationship between model-predicted steady-state pimavanserin exposures ( $AUC_{0-24}$ ,  $C_{av}$ , and  $C_{max}$ ) and the probability of experiencing key AEs, including anxiety, headache, insomnia, and somnolence.

The E-R safety analysis data set comprised 1592 records from 398 patients collected throughout the study, giving a maximum of 26 weeks follow-up. Anxiety, headache, insomnia, and somnolence were infrequently reported (Table 2). Pimavanserin exposures were not statistically significant predictors for the occurrence of anxiety, headache, insomnia, or somnolence. Because no E-R relationship was found for pimavanserin exposure and anxiety, headache, insomnia, or somnolence, no covariate analyses were performed.

### DISCUSSION

The E-R analyses indicate that pimavanserin 34 mg once daily is the dosage regimen that could provide improved efficacy without compromising tolerability in patients with negative symptoms



**FIGURE 4.** Exposure-response model–predicted cumulative percent of the negative symptom domain of the CGI-SCH-S.

**TABLE 2.** Occurrence of Select Adverse Events by Pimavanserin Dose

Adverse Event Occurrence, n (%)		Dose of Pimavanserin, mg				Overall
		0	10	20	34	
Anxiety	No	198 (97.1)	3 (100.0)	82 (97.6)	103 (96.3)	386 (97.0)
	Yes	6 (2.9)	0 (0)	2 (2.4)	4 (3.7)	12 (3.0)
Headache	No	194 (95.1)	3 (100)	79 (94.0)	99 (92.5)	375 (94.2)
	Yes	10 (4.9)	0 (0)	5 (6.0)	8 (7.5)	23 (5.8)
Insomnia	No	198 (97.1)	3 (100)	83 (98.8)	102 (95.3)	386 (97.0)
	Yes	6 (2.9)	0 (0)	1 (1.2)	5 (4.7)	12 (3.0)
Somnolence	No	194 (95.1)	2 (66.7)	78 (92.9)	104 (97.2)	378 (95.0)
	Yes	10 (4.9)	1 (33.3)	6 (7.1)	3 (2.8)	20 (5.0)

of schizophrenia. The ADVANCE study used a flexible dosing schedule that did not require all patients to receive pimavanserin 34 mg/d. In fact, only slightly more than half (53.8%) of the pimavanserin group received the 34-mg/d dosage, while 44.7% and 1.5% received pimavanserin 20 and 10 mg/d, respectively.<sup>15</sup> This approximately equal patient distribution based on the pimavanserin dose spread did not impair the detection of a statistically significant improvement on the NSA-16 versus placebo in the primary analysis of ADVANCE. On the PSP and CGI-SCH-S measures, absolute change from baseline improvements to week 26 was observed in the pimavanserin group, but the extent of the improvements was not statistically significant relative to those seen in the placebo group.

The E-R analyses shed light on pimavanserin efficacy in ADVANCE as they infer an exposure-dependent pharmacologic effect on the NSA-16, PSP scale, and negative symptom severity as assessed by CGI-SCH-S scores. All pimavanserin exposure measures predicted statistically significant improvements in NSA-16 score. As pimavanserin exposure increased, the PSP response also improved, with a subsequent flattening of response at the highest exposures. Accounting for PK variability by using model-predicted individual measures of pimavanserin exposure helped enable characterization of the shallow E-R relationship present in the PSP data. Patients administered pimavanserin had slightly greater improvement in CGI-SCH-S scores over time compared with patients administered placebo.<sup>15</sup> Across the range of pimavanserin AUC<sub>0-24</sub>, the cumulative probabilities of lower CGI-SCH-S scores increased with increasing exposure. The E-R relationship on the CGI-SCH-S was shallow, as indicated by a small difference in the cumulative probabilities for the pimavanserin 20- and 34-mg doses.

Taken together, the E-R relationships for the clinically meaningful PSP ( $\geq 7$ -point improvement)<sup>23</sup> and CGI-SCH-S ( $\geq 1$ -point improvement)<sup>24</sup> measures indicate that pimavanserin could have a beneficial effect in this patient population despite no significant difference observed versus placebo in the primary statistical analysis. Achieving a more pronounced response in these measures may require exposures equivalent to those produced by the pimavanserin 34-mg/d dosage regimen. This strategy is under evaluation in the pivotal, quadruple-blinded, randomized, placebo-controlled ADVANCE-2 study (ClinicalTrials.gov identifier: NCT04531982) of more than 400 patients with negative symptoms of schizophrenia evaluating daily pimavanserin 34 mg.<sup>25</sup>

Although the primary and key secondary outcome measures showed positive results in the E-R modeling analysis, there are limitations to this study. The date and time of dose immediately before collection of each PK sample were captured, but specific dosing details were not captured in the patient diaries for the rest of at-home dosing. In addition, no explicit information was reported on dose adherence. Therefore, it was necessary to impute

the daily dosing history between clinic visits based on the protocol specified dosing plan and/or available data when adherence could be assumed. However, a model-based assessment of adherence was performed where the median and 90% PIs for the expected concentration-time profiles were simulated using the final PK model and assuming 100% dosing compliance. Overall, most observed concentration data fell within the 90% PIs for each dose level, with only a small subset of concentrations below the fifth percentile, suggesting possible nonadherence in a small proportion of instances.

There are several limitations to consider regarding these analyses. Only 5 patients received a dose reduction to the 10-mg dose of pimavanserin, and therefore, the results of this group should be interpreted with caution. In addition, the flexible-dose design, rather than a fixed-dose design, which was used in this study could be considered as a potential limitation. As the protocol did not require patients to be treated with the maximum dose of 34 mg, some patients might not have received an optimal dose of pimavanserin.<sup>15</sup> Changes in pimavanserin dosing were at the clinician's discretion, which would reflect real-world use of pimavanserin. Another potential limitation of this study was that 92.7% of the participants were White, which may limit the generalizability of these findings to other races/ethnicities. However, a prior study indicated a lack of effect of ethnicity on pimavanserin PKs.<sup>14</sup> Future studies should include greater ethnic diversity in their populations.

In conclusion, these E-R assessments support the clinical outcomes observed in ADVANCE. Exposure-response relationships were identified between pimavanserin exposure and scores for the NSA-16, PSP scale, and negative symptom domain of the CGI-SCH-S. As pimavanserin exposure increased, the extent of clinical improvement on the NSA-16 increased, while the corresponding improvements on the PSP scale and severity of negative symptoms assessed by the CGI-SCH-S score were not to the same magnitude by comparison. Given the lack of a relationship between pimavanserin exposure and AEs, these findings support investigation of the highest pimavanserin dose level evaluated in ADVANCE (34 mg/d) in patients with negative symptoms of schizophrenia.

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#### AUTHOR CONTRIBUTIONS

All authors contributed to the design, data analysis, interpretation of the research data, and writing and reviewing the final manuscript.



### AUTHOR DISCLOSURE INFORMATION

This analysis was designed and supported by Acadia Pharmaceuticals, Inc. and Cognigen Corporation. M.D., D.B.-K., D.D., and S.S. are employees of Acadia Pharmaceuticals, Inc. the sponsor of pimavanserin. J.P., J.O., and D.J., as employees of Cognigen Corporation, were paid consultants for their clinical pharmacology work by Acadia Pharmaceuticals, Inc. Medical writing and editing support for the development of this manuscript, under the direction of the authors, was provided by Malcolm Darkes, PhD, Meaghan Paganelli, PhD, and Dena McWain of Ashfield MedComms, an Ashfield Health company, and funded by Acadia Pharmaceuticals, Inc.

### DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are not available.

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