Relationship Between Pimavanserin Exposure and Negative Symptoms in Patients with Schizophrenia: Data Analysis from the Phase 2 ADVANCE Study

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INTRODUCTION

- Negative symptoms in schizophrenia are associated with poor psychosocial function and long-term outcomes,[1,2] yet no pharmacological treatments are currently approved in the United States to treat negative symptoms.
- Pimavanserin is a selective serotonin receptor-modulating agent with inverse agonist/antagonist activity at 5-HT_{2A} receptors and to a lesser extent at 5-HT_{2C} receptors.[3]
- Pimavanserin is being investigated in negative symptoms of schizophrenia.
- Exposure–response (E–R) analyses can be useful to help determine an optimal dose and to support clinical evidence of efficacy.[4]

OBJECTIVE

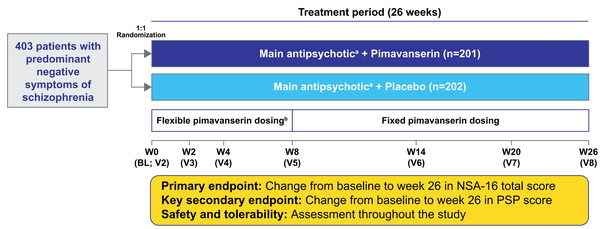
- To evaluate the relationships between efficacy and relevant safety endpoints and pimavanserin exposure in patients with negative symptoms of schizophrenia.

METHODS

Study Design and Analysis Population

- Data were from ADVANCE, a phase 2, double-blind, placebo-controlled study conducted in outpatients with predominant negative symptoms of schizophrenia from centers in Europe and North America (NCT02970305). ADVANCE methodology and primary results have been previously presented.[5]
- Patients were diagnosed with schizophrenia ≥1 year before randomization, were 18–55 years of age, and had a score ≥20 on the 7 Marder negative symptom items from the Positive and Negative Syndrome Scale, including a score ≥4 on at least 3 items or ≥5 on at least 2 items. Patients were treated with an antipsychotic for at least 8 weeks, on a stable dose at least 4 weeks prior to screening, and medically stable at least 12 weeks prior to screening.
- Patients received either oral pimavanserin or matching placebo once daily added to background antipsychotic 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 during weeks 2–8 (**Figure 1**).

Figure 1. ADVANCE Study Design[5]



[a]One of aripiprazole (oral or long-acting injection), asenapine, brexpiprazole, cariprazine, lurasidone, olanzapine, or risperidone (oral or long-acting injection).
[b]Pimavanserin 20 mg daily initially and adjusted to 34 mg or 10 mg daily after 2 weeks at investigator discretion.
BL, baseline; NSA-16, Negative Symptom Assessement-16; PSP, Personal and Social Performance; V, visit; W, week.

Outcome Measures

- Primary outcome: Negative Symptom Assessment-16 (NSA-16), a 16-item evaluation of negative symptoms of schizophrenia.
- Key secondary outcome: Personal and Social Performance (PSP) scale, a validated 100-point rating scale to assess psychosocial function of patients with schizophrenia.
- Other secondary outcome: Clinical Global Impression of Schizophrenia–Severity (CGI-SCH-S) scale, a clinician-rated, 7-point scale designed to evaluate severity of schizophrenia.
- Safety: Adverse events were recorded from the time informed consent was obtained through the duration of the study.

Exposure Measures

- Blood samples for pharmacokinetic analyses were collected at baseline and weeks 2, 8, 14, and 26.
- Individual measures of pimavanserin exposure parameters included: maximum drug concentration (C_{max}), area under the plasma concentration-time curve from time 0 to 24 hours ($AUC_{0\text{-}24}$), and average drug concentration during a dosing interval (C_{av}), and were generated via integration of predicted concentration-time profiles for each patient based on the final population model and individual empiric Bayesian parameter estimates.

Exposure–Response Efficacy and Safety Analyses

- E–R models were developed to describe the effect of pimavanserin exposure on the primary efficacy endpoint, NSA-16 score, and on the secondary endpoints PSP and CGI-SCH-S scales using the average of daily exposure measures between consecutive visits.
- For efficacy, covariate analysis was performed to assess the influence of age, sex, baseline weight, baseline body mass index, region, race, duration of schizophrenia illness, smoking status, antipsychotic medication equivalent to risperidone, benzodiazepine use, anticholinergic use, antidepressant use, or concomitant use of antipsychotic medications.
- The final E–R efficacy model was validated by visual predictive check.
- E–R models were also used to investigate safety, including adverse events of anxiety, headache, insomnia, and somnolence. Steady-state pimavanserin exposure measures, based on the last dose, were used in E–R analyses of safety.
- Covariates evaluated in the analysis of safety endpoints were age, sex, baseline weight, race, and antipsychotic medication use.

RESULTS

Primary Analysis of NSA-16 Change from Baseline

- In ADVANCE, 403 patients were randomized and 346 (172 pimavanserin, 174 placebo) completed the study.
- On the primary endpoint, statistically significant improvement was observed for the NSA-16 total score at week 26 with pimavanserin versus placebo (least squares mean: −10.4 vs. −8.5, P=0.043, effect size: 0.21).[5]
- 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 at the alpha level of 0.05 (**Table 1**).

Table 1. NSA-16 Score Change from Baseline to Week 26 by Last Pimavanserin Dose

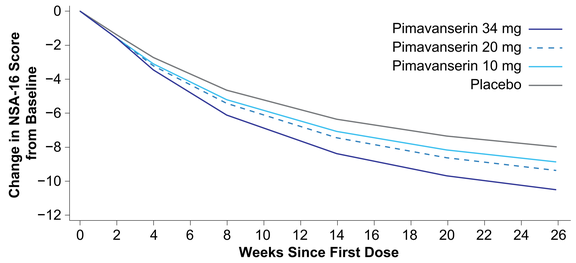
Last Dose	Change from Baseline to Week 26, LSM (SE)	Difference from Placebo, MMRM LSM (SE)	*P* value	Cohen's d
Pimavanserin 34 mg (n=99)	−11.6 (0.90)	−3.1 (1.12)	0.0065	0.339
Pimavanserin 20 mg (n=73)	−9.0 (1.02)	−0.5 (1.22)	0.6847	0.055
Pimavanserin 10 mg (n=2)	−8.3 (6.01)	0.2 (6.05)	0.9783	-0.018
Placebo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

LSM, least squares mean; MMRM, mixed-effect model repeated measures; NSA-16, Negative Symptom Assessment-16; SE, standard error.

Exposure–Response NSA-16 Analysis

- A total of 2628 NSA-16 scores from 396 patients for up to 26 weeks were included in the E–R efficacy dataset after removing patients not in the full analysis set or missing pharmacokinetic exposure measures.
- The E–R relationship was described by a sigmoid maximum pharmacologic effect time-course model. The relationship between $AUC_{0\text{-}24}$ 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 $AUC_{0\text{-}24}$.
- Assuming the median pimavanserin $AUC_{0\text{-}24}$ of 1465 ng x h/mL and 805 ng x h/mL for the 34-mg and 20-mg doses, the model-predicted reductions in NSA-16 score from baseline are 10.5 and 9.4 at week 26 at the respective dose levels as compared with 8.0 for placebo.
- A statistically significant E–R relationship was observed between NSA-16 scores and pimavanserin drug exposure (**Figure 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.

Figure 2. Exposure–Response Model-Predicted Change in NSA-16 Scores from Baseline by Dose[a]

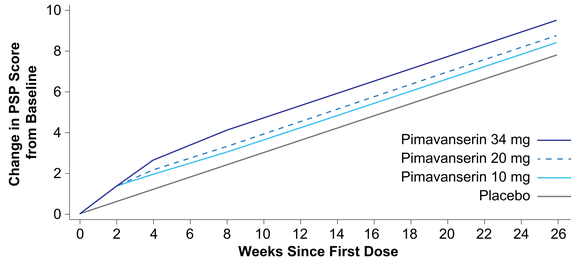


[a]The model-predicted lines represent the response at the median average daily pimavanserin $AUC_{0\text{-}24}$ at each week for each dose level.
$AUC_{0\text{-}24}$, area under the plasma concentration-time curve from time 0 to 24 hours; NSA-16, Negative Symptom Assessment-16.

Exposure–Response PSP Analysis

- In ADVANCE, improvement was observed; however, separation from placebo was not significant on the key secondary efficacy endpoint, change from baseline to week 26 in PSP score.[5] Here, PSP was analyzed with an E–R model.
- A total of 1125 PSP scores collected from 386 patients for up to 26 weeks were used to develop a linear time-course model, including parameters estimating the baseline PSP score and slope for time.
- An exponential function best described the E–R relationship and showed that model-predicted PSP scores increased as pimavanserin C_{max} increased (**Figure 3**).
- All exposure measures were statistically significant predictors of the variability in PSP scores.
- Assuming the median pimavanserin C_{max} of 64 ng/mL and 36 ng/mL for the 34-mg and 20-mg doses, the model-predicted increases in PSP score from baseline were 9.5 and 8.8 at week 26 at the respective dose levels, as compared with 7.8 for placebo.
- PSP response was not significantly influenced by any examined covariates.

Figure 3. Exposure–Response Model-Predicted Change in PSP Scores from Baseline by Dose[a]



[a]The model-predicted lines represent the response at the median average daily pimavanserin C_{max} at each week for each dose level.
C_{max}, maximum drug concentration; PSP, Personal and Social Performance.

Exposure–Response CGI-SCH-S Analysis

- In ADVANCE, CGI-SCH-S of negative symptoms score change from baseline to week 26 improved; however, separation between pimavanserin and placebo was not significant (data not shown). Here, CGI-SCH-S was analyzed with an E–R model.
- A total of 2629 CGI-SCH-S scores collected from 396 patients for up to 26 weeks were used in a proportional odds model with CGI-SCH-S score, placebo time course, and drug effect as components on the logit scale. A separate linear function of $AUC_{0\text{-}24}$ best described the shallow E–R effect of pimavanserin.
- Exposure to pimavanserin increased the probability of lower CGI-SCH-S scores. Across the range of pimavanserin $AUC_{0\text{-}24}$, the cumulative probabilities of lower scores increased with increasing exposure, indicating improvement in CGI-SCH-S scores.
- The model-predicted cumulative probability of CGI-SCH-S score ≤3 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.
- CGI-SCH-S response was not significantly influenced by any examined covariates.

Exposure–Response Models for Probability of Adverse Events

- The E–R safety analysis dataset consisted of 1592 records from 398 patients, collected through the study for a maximum of 26 weeks following randomization.
- Steady-state pimavanserin exposures ($AUC_{0\text{-}24}$, C_{av}, C_{max}) were not statistically significant predictors of first occurrence of anxiety, headache, insomnia, and somnolence.

CONCLUSIONS

- **Results of this modeling analysis predict higher pimavanserin exposure in patients with negative symptoms of schizophrenia is associated with a greater reduction in NSA-16 scores.**
- **Greater improvements in PSP scores and CGI-SCH-S scores were also associated with higher pimavanserin exposure, though not to the extent observed with the NSA-16.**
- **Pimavanserin exposure was not a predictor of relevant adverse events of anxiety, headache, insomnia, or somnolence.**
- **These results support further investigation using the 34-mg dose of pimavanserin in this patient population for the treatment of negative symptoms in schizophrenia.**

REFERENCES

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DISCLOSURES

This poster includes information from clinical trials investigating uses that have not been approved by the US Food and Drug Administration. This study was funded by Acadia Pharmaceuticals Inc. MD, DBK, and SS are employees of Acadia Pharmaceuticals. MF was an employee of Acadia Pharmaceuticals at the time of these analyses. JP, DJ, and JO are employees of Cognigen Corporation.

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