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

Moná Darwish, PhD; Dragana Bugarski-Klora, MD; Julie Passarell, MA; Mark Forman, MD, PhD; Daryll DeKranske, MPH; David Jakoiwicz, PhD; Joel Owen, PhD; Srdjan Stankovic, MD, MSHP

Acadia Pharmaceuticals Inc.; Pirbright, UK; Acadia Pharmacueticals_GmbH, Basel, Switzerland; Cognigen Corporation, a Simulations Plus company, Buffalo, New York, USA; All the line of these authors

INTRODUCTION

• Negative symptoms in schizophrenia are associated with poor psychosocial functioning and long-term outcomes. Many pharmacological treatments are currently approved in the United States to treat negative symptoms. [1]• Pimavanserin is a selective serotonin receptor-modulating agent with inverse agonist/antagonist activity at 5-HT₂C receptors and to a lesser extent at 5-HT₃ receptors. [2]• Pimavanserin is being investigated in negative symptoms of schizophrenia.

OBJECTIVE

• To evaluate the relationship 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, 26-week, placebo-controlled study conducted in outpatients with predominant negative symptoms of schizophrenia from centers in Europe, North America, and Australia (N=163). ADVANCE methodology and primary results have been previously presented. [3]• Patients were diagnosed with schizophrenia ≥1 year before randomization, were ≥18-50 years of age, and had a score ≥4 on at least 7 items from the Positive and Negative Syndrome Scale, including a score ≥4 on at least 4 or ≥5 on at least 2 items. Patients were treated with an antidepressant for ≥6 weeks prior to screening, at which time the investigator's discretion during weeks 2–8 (Figure 1). [4]

EXPOSURE MEASURES

• Blood samples for pharmacokinetic analyses were collected at baseline and weeks 2, 4, and 12.

• In ADVANCE, pimavanserin exposure parameters included: maximum drug concentration (Cmax), area under the plasma concentration-time curve from time 0 to 24 hours (AUC_{0-24}), 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 expected Bayesian parameter estimates.

EXPOSURE–RESPONSE EFFICACY AND SAFETY ANALYSES

• E–R models were developed to describe the relationship between 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.

RESULTS

Primary Analysis of NSA-16 from Baseline Change

• In ADVANCE, 403 patients were randomized and 346 (172 pimavanserin, 174 placebo) completed the 26-week study with negative symptoms of schizophrenia.

• 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. -6.5, P=0.043, effect size: 0.21). [5]• Post hoc analysis of NSA-16 showed that patients whose last dose was 34 mg (91/174) exhibited a statistically significantly improvement at the alpha level of 0.05 (Table 1).

Exposure–Response Model Predicted Change in PSP Scores from Baseline by Dose

• Statistically significant relationships were observed with increasing exposure in patients with negative symptoms of schizophrenia.

• The relationship between pimavanserin exposure and NSA-16 response was not statistically significant (data not shown). Here, CGI-SCH-S was analyzed with an E–R model.

Exposure–Response CGI-SCH-S Analysis

• A total of 262 CGI-SCH-S scores collected from 396 patients for up to 26 weeks were included 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_{0-24} best described the shallow E–R effect of pimavanserin.

Conclusions

• These results support further investigation using the 34-mg dose of pimavanserin in this patient population for the treatment of negative symptoms in schizophrenia.

Outcome Measures

• Primary outcome: Negative Symptom Assessment-16 (NSA-16), a 16-item evaluation of negative symptoms of schizophrenia.

• Secondary outcome: Personal and Social Performance (PSP) scale.

• Key safety parameter: Clinical Global Impression of Schizophrenia–Severity (CGI-SCH-S) scale, a clinician-rated, 7-point scale designed to evaluate severity of schizophrenia.

• Adverse events were recorded from the time informed consent was obtained through the duration of the study.

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

<table>
<thead>
<tr>
<th>Last Dose</th>
<th>Change from Baseline to Week 26</th>
<th>Difference from Baseline to Week 26</th>
<th>Pimavanserin 10 mg</th>
<th>Placebo</th>
<th>Coefficient (95% CI)</th>
<th>LSM (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=173)</td>
<td>-10.4 (9.4)</td>
<td>6.5 (5.8)</td>
<td>-10.4 (9.4)</td>
<td>6.5 (5.8)</td>
<td>-</td>
<td>-10.4 (9.4)</td>
</tr>
<tr>
<td>Pimavanserin 10 mg (n=73)</td>
<td>-5.2 (4.5)</td>
<td>1.3 (1.6)</td>
<td>-5.2 (4.5)</td>
<td>1.3 (1.6)</td>
<td>-</td>
<td>-5.2 (4.5)</td>
</tr>
<tr>
<td>Pimavanserin 20 mg (n=73)</td>
<td>-3.4 (2.7)</td>
<td>2.0 (2.3)</td>
<td>-3.4 (2.7)</td>
<td>2.0 (2.3)</td>
<td>-</td>
<td>-3.4 (2.7)</td>
</tr>
<tr>
<td>Pimavanserin 34 mg (n=73)</td>
<td>-1.6 (1.9)</td>
<td>3.7 (3.1)</td>
<td>-1.6 (1.9)</td>
<td>3.7 (3.1)</td>
<td>-</td>
<td>-1.6 (1.9)</td>
</tr>
</tbody>
</table>

References


Acknowledgments

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Disclosure

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