Journal Club - Trial of pimavanserin in dementia-related psychosis

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<table>
<tr><th colspan="3">BACKGROUND</th></tr>
<tr><td>Study/
Reference</td><td colspan="2">Tariot PN, Cummings JL, Soto-Martin ME, et al. Trial of pimavanserin in dementia-related psychosis. New England Journal of Medicine. 2021;385(4):309-319.</td></tr>
<tr><td>Background
&
Purpose</td><td colspan="2">● Pimavanserin is a second generation antagonist that primarily acts on the 5HT2A receptor as an inverse agonist and antagonist. This mechanism of action differs from that of other atypical antipsychotics which also binds to D2 dopamine, histaminergic, and/or muscarinic receptors
● Pimavanserin was FDA approved for the treatment of hallucinations and delusions associated with Parkinson’s disease psychosis based on a randomized, phase 3 trial conducted back in 2014
● Based on the preliminary findings in patients with psychosis due to Parkinson’s disease, this study was initiated to investigate the safety and efficacy of pimavanserin for the treatment of delusions and hallucinations associated with Alzheimer’s disease, Parkinson’s disease dementia, dementia with Lewy bodies, frontotemporal dementia, or vascular dementia</td></tr>
<tr><th colspan="3">GENERAL STUDY OVERVIEW</th></tr>
<tr><td>Funding</td><td colspan="2">● Acadia Pharmaceuticals (manufacturer of pimavanserin)</td></tr>
<tr><td>Trial design</td><td colspan="2">● Phase 3, double-blind, randomized, placebo-controlled discontinuation trial
● Conducted at 101 clinical sites in North America, eastern and western Europe, and Latin America</td></tr>
<tr><td>Objectives</td><td colspan="2">● Primary endpoint: Time from randomization to relapse of psychosis in the double-blind period
○ Relapse was defined as (1) $\geq$ 30% increase in SAPS H+D total score and CGI-I score $\geq$ 6, (2) treatment with antipsychotic for dementia-related delusions/hallucinations, (3) treatment/study discontinuation due to lack of efficacy, and/or (4) hospitalization for worsening dementia-related psychosis
● Secondary endpoint: Time from randomization to trial discontinuation from the double-blind period for any reason
● Safety endpoint: Adverse events</td></tr>
<tr><th colspan="3">METHODS (only pertinent trial information provided: refer to trial for further details)</th></tr>
<tr><td rowspan="2">Population</td><td>Inclusion criteria</td><td>Exclusion criteria</td></tr>
<tr><td>● Meets criteria for all-cause dementia per the NIA-AA guidelines
● Meets clinical criteria for: dementia associated with Parkinson’s disease, dementia with Lewy bodies, possible or probable Alzheimer’s disease, frontotemporal dementia, or vascular dementia
● MMSE score 6 to 24
● Psychotic symptoms for at least 2 months
● If patient is already on cholinesterase inhibitor or memantine, must be at stable dose
● Antipsychotic use prohibited 2 weeks before baseline assessment and during trial</td><td>● Psychotic symptoms that are primarily due to a condition other than dementia
● Has had a recent major depressive episode
● Experienced suicidal ideation or behavior within 3 months prior to study enrollment
● Evidence of non-neurologic medical comorbidity or medication use that could impair cognition
● History of ischemic stroke within the last 12 months or any evidence of hemorrhagic stroke
● History of cerebral amyloid angiopathy, epilepsy, CNS neoplasm, or unexplained syncope
● History of NYHA Class 2 congestive heart failure, grade 2 or greater angina pectoris, sustained ventricular tachycardia, ventricular fibrillation, torsade de pointes, syncope due to an arrhythmia, implantable cardiac defibrillator
● Myocardial infarction within the last 6 months
● Known personal or family history or symptoms of long QT syndrome</td></tr>
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<tr><td>Interventions</td><td colspan="2">Open-label period → Randomized, placebo-controlled, double-blind period
Patients received open-label pimavanserin (20 - 34mg daily) for initial 12 weeks
Patients who had a reduction from baseline of at least 30% in the score on the SAPS-H+D and a CGI-I score of 1 (very much improved) or 2 (much improved) at weeks 8 and 12 were randomized in a 1:1 ratio to continue receiving pimavanserin or placebo for up to 26 weeks</td></tr>
<tr><td>Enrollment</td><td colspan="2">Enrollment throughout August 2017 to October 2019
392 patients were included in the open-label phase
66.3% Alzheimer’s disease, 15.1% Parkinson’s disease dementia, 9.7% vascular dementia, 7.1% dementia with Lewy bodies, 1.8% frontotemporal dementia
217 patients underwent randomization
105 patients continued receiving pimavanserin
112 patients received placebo</td></tr>
<tr><td>Statistical analyses</td><td colspan="2">Goal enrollment of 356 subjects in the open-label period and 178 subjects in the randomization period to yield a power of 90%
Total number of post-randomization relapse events required at the final analysis was 75
If fewer than 75 post-randomization relapse events have been observed, the study may be terminated early if the interim analysis results establish the efficacy and safety of pimavanserin for the treatment of hallucinations and delusions associated with dementia-related psychosis
Primary efficacy analysis:
Intention-to-treat population (all patients who underwent randomization)
Cox regression model to compare time to relapse between trial groups
Secondary end point:
Tested at the same alpha level as primary efficacy analysis
Cox regression model to compare time to relapse between trial groups</td></tr>
<tr><td colspan="3">RESULTS</td></tr>
<tr><td rowspan="2">Efficacy/Safety</td><td>Efficacy</td><td>Safety</td></tr>
<tr><td>As total number of post-randomization relapse events was fewer than 75 (actual events = 40), the trial was terminated early for efficacy and interim analysis was conducted

Primary endpoint: relapse of psychosis
13% pimavanserin vs. 28% placebo
HR 0.35 (95% CI 0.17 - 0.73); p=0.005
Secondary endpoint: trial discontinuation
22% pimavanserin vs. 38% placebo
HR 0.45 (95% CI 0.26 - 0.79); p=0.005</td><td>Open-label phase:
36.2% treatment-emergent adverse event
Mean prolongation of the corrected QT interval was 5.4±0.9 msec
Adverse event that occurred in more than 2% of the patients: urinary tract infection (5.1%), constipation (2.6%), and hypertension (2.3%)
Double-blind phase:
Treatment-emergent adverse event
41% pimavanserin vs 36.6% placebo
Serious adverse event
4.8% pimavanserin vs. 3.6% placebo
Adverse event leading to trial discontinuation
2.9% pimavanserin vs. 3.6% placebo</td></tr>
<tr><td rowspan="2">Comments</td><td>Strengths</td><td>Weaknesses</td></tr>
<tr><td>Randomized, multicenter study
Heterogeneity in dementia type and dementia severity amongst subjects
Intention-to-treat analysis of primary efficacy</td><td>No true evidence for the indication for drug initiation as there was no comparison placebo group during open-label phase
Diminished ability to assess clinical predictors of relapse due to early termination of trial
Pimavanserin has shown efficacy in patients with hallucinations and delusions associated with Parkinson’s disease psychosis. Potential skew of results in favor of pimavanserin as 15% of the patients had Parkinson’s disease psychosis.
Almost all of the patients in the trial were White (> 95%)
Multiple exclusion criteria, difficult to extrapolate to real clinical scenario</td></tr>
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	Author's Conclusion	Reviewer's Conclusion
Conclusions	In a trial stopped early for efficacy, patients with dementia-related psychosis who had a response to pimavanserin had a lower risk of relapse with continuation of the drug than with discontinuation.	Pimavanserin should only be used as indicated for hallucinations and delusions associated with Parkinson's disease psychosis based on current evidence. The deprescribing design of this trial does not address the question of who is indicated to initiate pimavanserin therapy (other than in Parkinson's disease) as there is no comparison with a placebo group. In addition, the subjects were a highly selected population based on inclusion/exclusion criteria. There is a need for larger, longer trial to address the potential role of pimavanserin for psychosis in other types of dementia.

SAPS-H+D: Scale for the Assessment of Positive Symptoms-Hallucinations and Delusions; CGI-I: Clinical Global Impression-Improvement; NIA-AA: National Institute on Aging and the Alzheimer's Association; MMSE: Mini-Mental State Exam; NYHA: New York Heart Association

References

1. Tariot PN, Cummings JL, Soto-Martin ME, et al. Trial of pimavanserin in dementia-related psychosis. *New England Journal of Medicine*. 2021;385(4):309-319.
2. Cummings J, Isaacson S, Mills R, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. *Lancet*. 2014;383(9916):533-540.