

A Phase 3 Study to Evaluate Pimavanserin for the Treatment of Hallucinations and Delusions Associated With Dementia-related Psychosis: Study Population and Design

Foff, E¹; Youakim, JM¹, Owen R¹, Knowles, M¹, Ballard, C²; Cummings, J³; Tariot, P⁴; Stankovic, S¹

¹ ACADIA Pharmaceuticals Inc.

² The University of Exeter Medical School

³ Cleveland Clinic Lou Ruvo Center, Center for Neurodegeneration and Translational Neuroscience, Cleveland Clinic Lerner College of Medicine

⁴ Banner Alzheimer's Institute, University of Arizona College of Medicine

The Methodological Question Being Addressed: Methodological and clinical advantages of the randomized-withdrawal study design for assessment of antipsychotic treatment benefit in patients with psychosis across multiple major dementias.

Introduction: There are no FDA-approved treatments for psychosis in any of the major dementias. Pimavanserin is an atypical antipsychotic which acts as an inverse agonist/antagonist at the 5-HT_{2A} receptor. The antipsychotic efficacy and safety of pimavanserin for treatment of hallucinations and delusions has been shown in patients with Parkinson's disease psychosis, with or without cognitive impairment. There is also evidence of efficacy and favorable tolerability of pimavanserin in a short-term study in Alzheimer's disease psychosis. Like most antipsychotic trials in dementia, previous trials of pimavanserin have used an acute treatment paradigm and evaluated, as the primary endpoint, a change from baseline in a hallucinations and delusions score on a psychometric scale (e.g., SAPS-H+D, NPI-NH Psychosis Score). Such psychometric scales are used principally in clinical trials but seldom in clinical practice. The aim of this study (HARMONY) is to employ a randomized-withdrawal study design and the clinically relevant endpoint (relapse of psychosis) to evaluate the efficacy and safety of pimavanserin for dementia-related psychosis in a long-term (chronic) treatment paradigm. Additionally, because the clinical approach to psychosis is shared across neurodegenerative dementias, the study population includes multiple major dementias: dementia associated with Parkinson's disease, dementia with Lewy bodies, Alzheimer's disease, frontotemporal degeneration spectrum disorders, and vascular dementia.

Methods: HARMONY is a Phase 3, multi-national, placebo-controlled relapse prevention trial. Approximately 360 participants with dementia experiencing moderate to severe psychosis (based on SAPS-H+D and clinical global impression scores) will be enrolled. All patients will receive pimavanserin once daily for 12 weeks during the open-label period. After 12 weeks, participants who experienced a clinically meaningful improvement in their hallucinations and/or delusions (defined as a predetermined level of improvement based on rating scales and clinical impression) will be randomized 1:1 to either continue pimavanserin or initiate placebo for up to 26 weeks (double-blind period). The primary outcome measure is the time from randomization to relapse of a participant's dementia-related psychosis during the double-blind period.

Results: Methodological and clinical advantages of this approach will be discussed. These include patient-friendly active treatment initiation, efficiency and power of the enriched design, management of natural symptom variability and placebo response, as well as clinically meaningful end-points. These and other design features contribute to increased probability of operational success and to results that are clinically meaningful and translate readily to clinical practice.

Conclusions: There are no approved therapies for the treatment of dementia-related psychosis. Variable and only modest efficacy along with significant safety concerns complicate the off-label use of

other available antipsychotics. The goal of HARMONY is to evaluate the efficacy and safety of pimavanserin in patients with dementia-related psychosis. Use of a randomized-withdrawal study design and a relapse prevention paradigm allows for assessment of long-term efficacy in a clinically relevant manner.

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