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

**INTRODUCTION**

- There are no approved treatments for Dementia-related Psychosis.
- Neuropsychiatric symptoms are associated with a worse prognosis in dementia.
- Off-label use of older atypical antipsychotics demonstrates modest or equivocal efficacy, and significant safety concerns.
- Meta-analysis of antipsychotic studies in Alzheimer’s disease suggests a small, though statistically significant, effect size (Cohen’s d) of approximately 0.23.
- Older antipsychotics are associated with compromised cognition and adverse events.

**RATIONALE FOR THE NOVEL DESIGN OF ACP-103-045 (HARMONY)**

**BACKGROUND**

Pimavanserin mechanism of action:
- Selective serotonin antagonist/inverse agonist with activity at 5-HT2A and to a lesser extent 5-HT2C receptors.
- No appreciable binding affinity for dopaminergic, histaminergic, muscarinic, or adrenergic receptors per in vitro studies.

Pimavanserin efficacy in Alzheimer’s disease psychosis (ADP):
- Phase 2, double-blind, placebo-controlled trial designed to evaluate the safety and efficacy of pimavanserin (n=90) vs placebo (n=91) as a treatment for subjects with ADP.
- Significant improvement in psychotic symptoms at the primary endpoint (Week 6).
- Improvements maintained through Week 12; however, difference from placebo not sustained from Week 6.
- Pimavanserin well tolerated with no new safety observations.
- No negative impact on cognition over 12 weeks of treatment as assessed by MMSE.

**HARMONY STUDY DESIGN**

- Randomized, double-blind, placebo-controlled, multi-center relapse prevention outpatient study.
- Subjects who are non-responders to pimavanserin are eligible to leave the study and receive open-label pimavanserin for additional 12 weeks.
- Fewer discontinuations due to adverse events in the pimavanserin group (17%) than the placebo group (12%).

**REFERENCES**


**INCLUSION/EXCLUSION CRITERIA**

**Key Inclusion Criteria**
- Adults age 50 – 90 meeting clinical criteria for one of the following disorders: Dementia associated with Parkinson’s disease, Dementia with Lewy bodies, Possible or probable Alzheimer’s disease, Possible or probable frontotemporal degeneration spectrum disorders, Vascular dementia, MMSE score ≥26 and ≤24.

**Key Exclusion Criteria**
- Psychotic symptoms for at least 2 months.

**Key Exclusion Criteria**
- Psychotic symptoms that are primarily attributable to a condition other than dementia.
- Personal or family history or symptoms of long QT syndrome.
- Evidence of a non-neurologic medical comorbidity or medication use that could substantially impair cognition.