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

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INTRODUCTION

- There are no approved treatments for Dementia-related Psychosis
- Neuropsychiatric symptoms are associated with a worse prognosis in dementia[1]
- Off-label use of older atypical antipsychotics demonstrates modest or equivocal efficacy, and significant safety concerns[2]
  - Meta-analysis of antipsychotic studies in Alzheimer's disease suggests a small, though statistically significant, effect size (Cohen's d) of approximately 0.2[3]
- Older antipsychotics are associated with compromised cognition and adverse events[4]

BACKGROUND

Pimavanserin mechanism of action

- Selective serotonin antagonist/inverse agonist with activity at 5-HT2A and to a lesser extent at 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)[5]

- Phase 2, double-blind, placebo-controlled trial designed evaluated 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)
  - Multiple sensitivity and responder analyses supportive of primary results
- 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
- Adverse events
  - Serious adverse events more frequent in the pimavanserin group (17%) than the placebo group (11%)
    Fewer discontinuations due to adverse events in the pimavanserin group (9%) than the placebo group (12%)

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

Patient Population

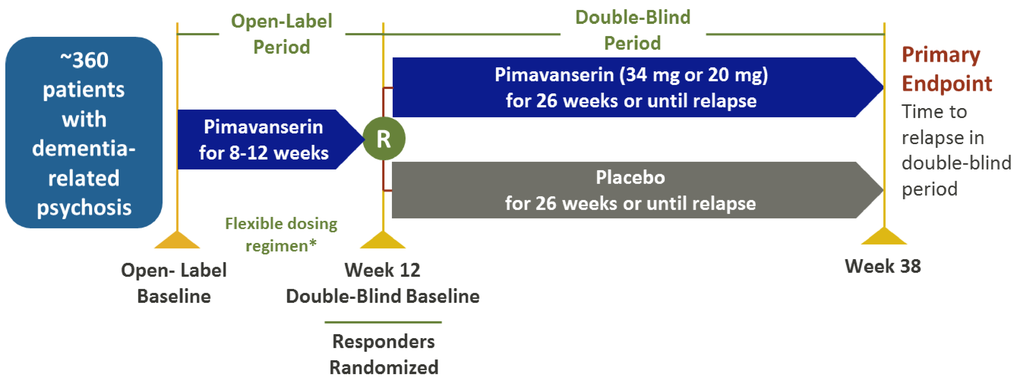
- Pimavanserin has demonstrated efficacy in treating psychosis in Parkinson's disease and Alzheimer's disease (AD)
  - AD accounts for ~70% of all dementias
- There is a significant overlap in clinical presentation and clinical pathology of the subtypes of dementias associated with psychosis
- Dementia-related psychosis is managed clinically the same way regardless of dementia subtype

Study Design

- Brief Psychosocial Therapy utilized in the screening period identifies subjects who respond without pharmacologic therapy[6]
- Active treatment initiation for all subjects should increase enrollment rates
- Subjects who do not respond to pimavanserin leave the study
  - Reduces exposure to drug for those for whom drug is not working
- Primary endpoint is based on protocol-defined relapse criteria applied by the investigator and confirmed by an Independent Adjudication Committee
- Time to relapse is inherently a clinically relevant outcome: mimics both clinical guidelines for approach to use of antipsychotics in dementia patients (American College of Physicians guidelines), and how clinicians practice
  - Minimizes treatment with placebo (or pimavanserin) in subjects who relapse

HARMONY STUDY DESIGN

Randomized, double-blind, placebo-controlled, multi-center relapse prevention outpatient study



*Starting daily dose of 34 mg of pimavanserin at open-label baseline may be adjusted between 20 mg and 34 mg, during weeks one and four, if clinically justified.

REFERENCES

1. Lyketsos CG, Colenda CC, Beck C, et al. Position statement of the American Association for Geriatric Psychiatry regarding principles of care for patients with dementia resulting from Alzheimer disease. *Am J Geriatr Psychiatry.* 2006;14(7):561-572.
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4. Maher AR, Maglione M, Bagley S, et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and meta-analysis. *JAMA.* 2011;306(12):1359-1369.
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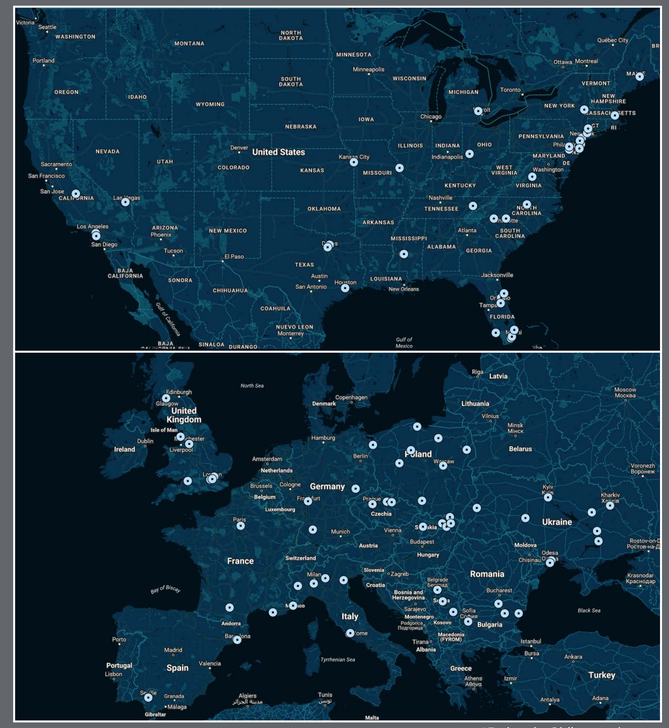
106 TRIAL SITES IN 13 COUNTRIES*



*5 sites in Chile not shown

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 ≥6 and ≤24
- 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

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