



# Evaluation of the safety, tolerability, and efficacy of pimavanserin versus placebo in patients with Alzheimer's disease psychosis: a phase 2, randomised, placebo-controlled, double-blind study

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## Summary

**Background** Pimavanserin is a selective 5-HT<sub>2A</sub> receptor inverse agonist and antagonist approved in the USA for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis. No safe or effective pharmacological treatment is approved for psychosis in patients with Alzheimer's disease. Therefore, we aimed to evaluate the safety, tolerability, and efficacy of pimavanserin versus placebo in patients with Alzheimer's disease psychosis.

**Methods** We did a phase 2, randomised, double-blind, placebo-controlled, single-centre (with multiple affiliated nursing home sites across the UK) study. We included participants of either sex who were aged 50 years or older with possible or probable Alzheimer's disease and psychotic symptoms including visual or auditory hallucinations, delusions, or both. Participants were randomly assigned (1:1) to 12 weeks of oral treatment with either pimavanserin (two 17 mg tablets daily) or placebo, with use of permuted block sizes of four and stratified by baseline Mini-Mental State Examination (MMSE) total score (<6 or ≥6) and Neuropsychiatric Inventory–Nursing Home version (NPI–NH) psychosis score (<12 or ≥12). Participants, caregivers, the study sponsor, and study personnel at the clinic site were masked to treatment assignment. The primary endpoint was mean change from baseline to week 6 in the NPI–NH psychosis score for pimavanserin versus placebo in the modified intention-to-treat population. Sustained benefit and safety of pimavanserin were assessed through week 12. This study is registered at ClinicalTrials.gov, number NCT02035553.

**Findings** Between Jan 16, 2014, and Oct 27, 2016, 345 participants across 133 nursing homes were screened, of whom 181 were randomly assigned treatment (n=90 pimavanserin and n=91 placebo). 178 participants were included in the modified intention-to-treat population. Mean total baseline NPI–NH psychosis scores were 9.5 (SD 4.8) for the pimavanserin group and 10.0 (5.6) for the placebo group. Mean change in the NPI–NH psychosis score at week 6 was –3.76 points (SE 0.65) for pimavanserin and –1.93 points (0.63) for placebo (mean difference –1.84 [95% CI –3.64 to –0.04], Cohen's *d* = –0.32; *p* = 0.045). By week 12, no significant advantage for pimavanserin versus placebo was observed for the overall study population (treatment difference –0.51 [95% CI –2.23 to 1.21]; *p* = 0.561). Common adverse events were falls (21 [23%] of 90 participants in the pimavanserin group vs 21 [23%] of 91 in the placebo group), urinary tract infections (20 [22%] vs 25 [28%]), and agitation (19 [21%] vs 13 [14%]). Eight (9%) participants on pimavanserin and 11 (12%) on placebo discontinued treatment because of adverse events. No detrimental effect was observed on cognition or motor function in either group.

**Interpretation** Pimavanserin showed efficacy in patients with Alzheimer's disease psychosis at the primary endpoint (week 6) with an acceptable tolerability profile and without negative effect on cognition. Further follow-up to week 12 did not show significant advantage for pimavanserin versus placebo.

**Funding** ACADIA Pharmaceuticals.

## Introduction

About 45 million people worldwide are living with Alzheimer's disease,<sup>1</sup> and between 25% and 50% of these individuals will develop psychotic symptoms at some point in the course of their illness.<sup>2,3</sup> The most common symptoms are delusions and visual hallucinations. If untreated, psychotic symptoms tend to have an intermittent and variable course with a pattern of recovery and relapse, in which symptom severity can increase and

decrease.<sup>4</sup> For example, in a monthly follow-up study, 30 (54%) of 56 patients had resolution of symptoms over 3 months without specific treatment, with eight (27%) having a subsequent relapse of symptoms over 12 months.<sup>5</sup>

Despite the periods of remission, psychotic symptoms have a substantial effect on people with Alzheimer's disease and their caregivers. The occurrence and presence of psychosis in Alzheimer's disease is associated with more rapid cognitive and functional decline, greater

*Lancet Neurology* 2018; 17: 213–22

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### Research in context

#### Evidence before this study

We searched PubMed for randomised controlled trials using the search terms “Alzheimer’s disease” and “psychosis” and “meta-analysis” or “systematic review” with no date restrictions. No drugs are currently approved for treating psychosis in Alzheimer’s disease, although antipsychotics are commonly used. Several meta-analyses have been published that examined the effects of antipsychotics in patients with dementia. Overall, in comparison with placebo, antipsychotics produced significant, albeit modest, effects on psychotic symptoms (including agitation and aggression) in patients with dementia. However, use of antipsychotics was associated with substantial side-effects, including decreased cognition, as well as an increased risk for mortality.

#### Added value of this study

This is the first study to examine the effects of pimavanserin on psychotic symptoms in patients with Alzheimer’s disease.

Pimavanserin significantly improved Neuropsychiatric Inventory–Nursing Home version psychosis score at 6 weeks without negative effects on cognition or motor function in the overall trial population and in the patients with severe psychosis. In our view, the results of this study provide initial evidence of a treatment benefit of pimavanserin compared with placebo at 6 weeks, and offer some important insights regarding the potential relationship between effect size and severity and the long-term remitting and relapsing course of psychosis.

#### Implications of all the available evidence

The findings from this study support further evaluation of pimavanserin as treatment for patients with Alzheimer’s disease and psychosis. However, the results should not be overinterpreted and a large randomised controlled phase 3 trial study is required to examine this key question on the basis of magnitude, breadth, and sustainability of benefit.

caregiver burden and depression, earlier institutionalisation, and greater treatment-related mortality than having no psychotic symptoms.<sup>1,6,7</sup>

Although antipsychotics are commonly used to treat psychosis in patients with Alzheimer’s disease,<sup>8</sup> no drug is approved for treating psychosis in Alzheimer’s disease. Compared with placebo, most randomised controlled trials of atypical or typical antipsychotics (mainly over treatment periods of 10–12 weeks) have shown no efficacy benefits in the treatment of psychosis.<sup>9,10</sup> Robust improvement in the placebo group is commonly observed. Results from meta-analyses suggest a small but significant effect size (Cohen’s *d*) of less than 0·2 in the treatment of psychosis in patients with Alzheimer’s disease across trials.<sup>11,12</sup> Importantly, the very modest benefits have to be balanced against side-effects. Antipsychotic use in people with Alzheimer’s disease is associated with side-effects that include accelerated decline in cognition; increased serious medical adverse events, such as stroke, bronchopneumonia, and pulmonary embolism; and increased short-term mortality.<sup>8,13–15</sup> Therefore, although psychosis has a major impact in people with Alzheimer’s disease, no safe or effective pharmacological treatment is approved, leaving a key unmet treatment need.

Pimavanserin is a selective 5-HT<sub>2A</sub> receptor inverse agonist and antagonist with a paucity of appreciable affinity to dopaminergic, muscarinic, histaminergic, or adrenergic receptors compared with other antipsychotics.<sup>16</sup> Pimavanserin was approved in 2016 in the USA for the treatment of hallucinations and delusions associated with psychosis in patients with Parkinson’s disease, on the basis of results from a clinical trial programme showing benefits for the treatment of psychosis compared with the use of placebo over 6 weeks.<sup>17,18</sup> This mechanism might also be relevant for treating psychosis in people with

Alzheimer’s disease, on the basis of data from post-mortem, PET imaging, and genetic polymorphism studies, suggesting that the same mechanism—ie, 5-HT<sub>2A</sub> receptor upregulation—is relevant as a treatment target.<sup>19,20</sup> Therefore, we hypothesised that pimavanserin would be an effective therapy and aimed to evaluate the safety, tolerability, and efficacy of pimavanserin versus placebo for the treatment of psychosis in patients with Alzheimer’s disease.

## Methods

### Study design and participants

We did a phase 2, randomised, double-blind, placebo-controlled, single centre (with multiple affiliated nursing home sites) study. We did this study through the Biomedical Research Centre for Mental Health at King’s College London in a network of 133 nursing homes across Greater London, Essex, the south of England, and areas of the Midlands in the UK. The nursing homes were granted site-specific exemption by the research ethics committee; hence, all study procedures (dispensed medication, assessed compliance, recorded clinical response, and adverse events) were done at the nursing home sites by the central investigator team from King’s College London. Nursing home staff were not part of the study team.

This study was done in accordance to guidance from the Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice guidelines, and the US Code of Federal Regulations. Ethics committee approval was obtained from the National Health Service Health Research Authority and the Research Ethics Committee for Wales for the study protocol and informed consent form.

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