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_{2A} 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.

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Introduction

About 45 million people worldwide are living with Alzheimer's disease,[1] and between 25% and 50% of these individuals will develop psychotic symptoms at some point in the course of their illness.[2,3] 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.[4] 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.[5]

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

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.[1,6,7]

Although antipsychotics are commonly used to treat psychosis in patients with Alzheimer's disease,[8] 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.[9,10] 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.[11,12] 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.[8,13–15] 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_{2A} receptor inverse agonist and antagonist with a paucity of appreciable affinity to dopaminergic, muscarinic, histaminergic, or adrenergic receptors compared with other antipsychotics.[16] 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.[17,18] 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_{2A} receptor upregulation—is relevant as a treatment target.[19,20] 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.

We included participants of either sex who were aged 50 years or older with possible or probable Alzheimer's disease as defined by the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association[21] and who met the Jeste and Finkel[22] criteria for psychosis of Alzheimer's disease. We considered participants eligible if they had psychotic symptoms including visual or auditory hallucinations, delusions, or both, that developed after the diagnosis was established. Participants must also have been a nursing home resident for 4 weeks or more before randomisation, not bedridden, and expected to remain in the facility throughout the study. Additionally, they must have actively experienced and verbally communicated psychotic symptoms during the month before screening, at least once per week during the previous 2 weeks before baseline, and required treatment for symptoms of psychosis in Alzheimer's disease.[22] We required participants to have symptoms at screening and baseline severe enough to warrant treatment with an antipsychotic agent, and to have a score of 4 or more on either the hallucinations (frequency×severity) or delusions (frequency×severity) domains of the Neuropsychiatric Inventory–Nursing Home version (NPI–NH)[23] psychosis scale, or a total combined score of 6 or more (hallucinations+delusions).

We excluded participants receiving treatment with antipsychotics, medications that prolong the QT interval, centrally acting anticholinergic medications, mianserin, nefazodone, cyproheptadine, and fluvoxamine. We also excluded those whose dose of antidepressant and anxiolytic drugs, if used, changed during the study. Those receiving an acetylcholinesterase inhibitor or memantine, or both, must have been on stable doses for 3 months before baseline and during the study. Additionally, participants were excluded if they were unable to communicate verbally and had a history of significant psychotic disorders before or concomitantly with the diagnosis of Alzheimer's disease, including but not limited to schizophrenia or bipolar disorder, as well as any medical condition or surgical procedure that could interfere with the conduct of the study. We obtained written informed consent from participants or their legally authorised representative before initiation of the study procedures.

Randomisation and masking

We randomly assigned participants (1:1) to receive either pimavanserin or placebo, stratified by baseline Mini-Mental State Examination (MMSE)[24] total score and NPI–NH psychosis score (four categories: MMSE <6 and NPI–NH psychosis score <12, MMSE ≥6 and NPI–NH psychosis score <12, MMSE <6 and NPI–NH psychosis score ≥12, and MMSE ≥6 and NPI–NH psychosis score ≥12). An independent statistician without any other involvement in the study generated the randomisation sequence with use of permuted block sizes of four, which was implemented using Trident software (version 1.2).

We masked participants, caregivers, the study sponsor, and study personnel at the clinic site to treatment assignment. We achieved masking of active treatment and placebo by using identical-appearing tablets. The study was unmasked after all participants had completed the study and following database lock.

Procedures

All study personnel had extensive training on study procedures and assessments. MedAvante provided training for the NPI–NH raters using their accredited and widely recognised programme, which achieves very high rates of inter-rater reliability. NPI–NH raters did not do any other assessments associated with the trial, and the pool of these individuals was limited to a dedicated group of trained and experienced raters. Brief psychosocial therapy (BPST)[8] therapists were trained by the senior investigators who developed the intervention, and certification was required on the basis of a written work plan and video recording of a BPST session. The senior investigator team provided training for other assessments over a 2-day training course. The aim of extensive training was to contain investigator duties to a core principal investigator or coinvestigator team of three experienced clinical trial physicians, and to streamline the number of raters completing each of the assessments to maintain high levels of quality and consistency.

During screening, participants entered a 3-week period in which BPST was used to ensure that only individuals who required a pharmacological treatment progressed to randomisation in the study, to minimise subsequent placebo response. BPST is a simple and practical non-pharmacological intervention, which enables a shared activity with social interaction between a person with dementia and a caregiver on a daily basis. Provision of BPST was planned between the BPST therapist and the caregiver to design and provide weekly oversight of the intervention and interactions. The therapy was then delivered between the caregiver and the study participant for 10–30 min per day up to five times per week. This period also allowed for washout in participants taking antipsychotic medication.

For participants who progressed through screening and met all study eligibility criteria at baseline (day 1), nursing home staff administered within 24 h a single oral dose of either pimavanserin (two 17 mg tablets) or placebo (two tablets), and subsequent doses were administered once daily up to 12 weeks. During the double-blind treatment period, study visits were done at baseline and days 15, 29, 43, 64, and 85 (or early termination). A follow-up for safety was done by telephone 4 weeks after the last dose of study medication.

Outcomes

Historically, in the assessment of antipsychotic efficacy, including in neurodegenerative diseases,[25,26] 6-week treatment duration is considered sufficient to show

clinically and statistically superior drug effects. Additionally, the NPI is well validated, is widely used in clinical practice and clinical trials, and has been the measure used to calculate the effect of antipsychotics on psychosis in Alzheimer's disease in several previous studies.[23,27–29] Therefore, the primary outcome was the efficacy of pimavanserin versus placebo, defined as change from baseline to week 6 in the NPI–NH psychosis score (hallucinations + delusions). Prespecified sensitivity analyses for the primary outcome were responder analyses and different imputation models (pattern mixture model and last observation carried forward). Correlation analysis at week 6 (NPI–NH psychosis score, NPI–NH total score, NPI–NH agitation/aggression, Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change [ADCS–CGIC],[30] Alzheimer's Disease Cooperative Study–Activities of Daily Living [ADCS–ADL][31] total score, and the Cohen–Mansfield Agitation Inventory–Short Form [CMAI-SF][32] total score) was also done.

Secondary outcomes were the assessment of behavioural symptoms at 6 and 12 weeks with use of ADCS-CGIC (measured as the effect on all clinical domains including cognition and function to evaluate any global deterioration associated with treatment), NPI–NH agitation/aggression and sleep and nighttime behaviour disorders domains, and CMAI-SF total and subdomain scores as a measure of agitation.

Prespecified exploratory outcomes included the NPI–NH total score as an overall measure of neuropsychiatric symptoms and each of its remaining individual domains, NPI–NH psychosis score by subgroups, durability of response from weeks 6 to 12, NPI–NH occupational distress total score, ADCS–ADL (total, basic, and instrumental subdomain scores), and use of rescue medications for behavioural disturbances and sleep. Subgroup analyses were also prespecified, focusing on baseline NPI–NH psychosis score (<12 or ≥12), baseline MMSE (<6 or ≥6), sex (men or women), age (≤85 years or >85 years), concomitant use of selective serotonin reuptake inhibitor, concomitant use of anti-dementia medication, and previous antipsychotic use. Additionally, cognitive impairment was assessed by the MMSE and extrapyramidal symptoms were measured with the Unified Parkinson's Disease Rating Scale (UPDRS) part III from baseline to week 12.[33] We used the 1987 UPDRS part III, as this version has been validated in people with dementia.

All participants who were randomly assigned and received the study intervention were included in the safety analysis. Safety outcomes, measured over 12 weeks, included reported adverse events, adverse events leading to study discontinuations, serious adverse events, and mortality, and included assessment by physical examinations, vital signs (ECGs were obtained at baseline, day 15, and day 85 or early termination to calculate corrected QT interval using Fridericia's method [QTcF]), and clinical laboratory tests (haematology, clinical chemistry, and urinalysis).

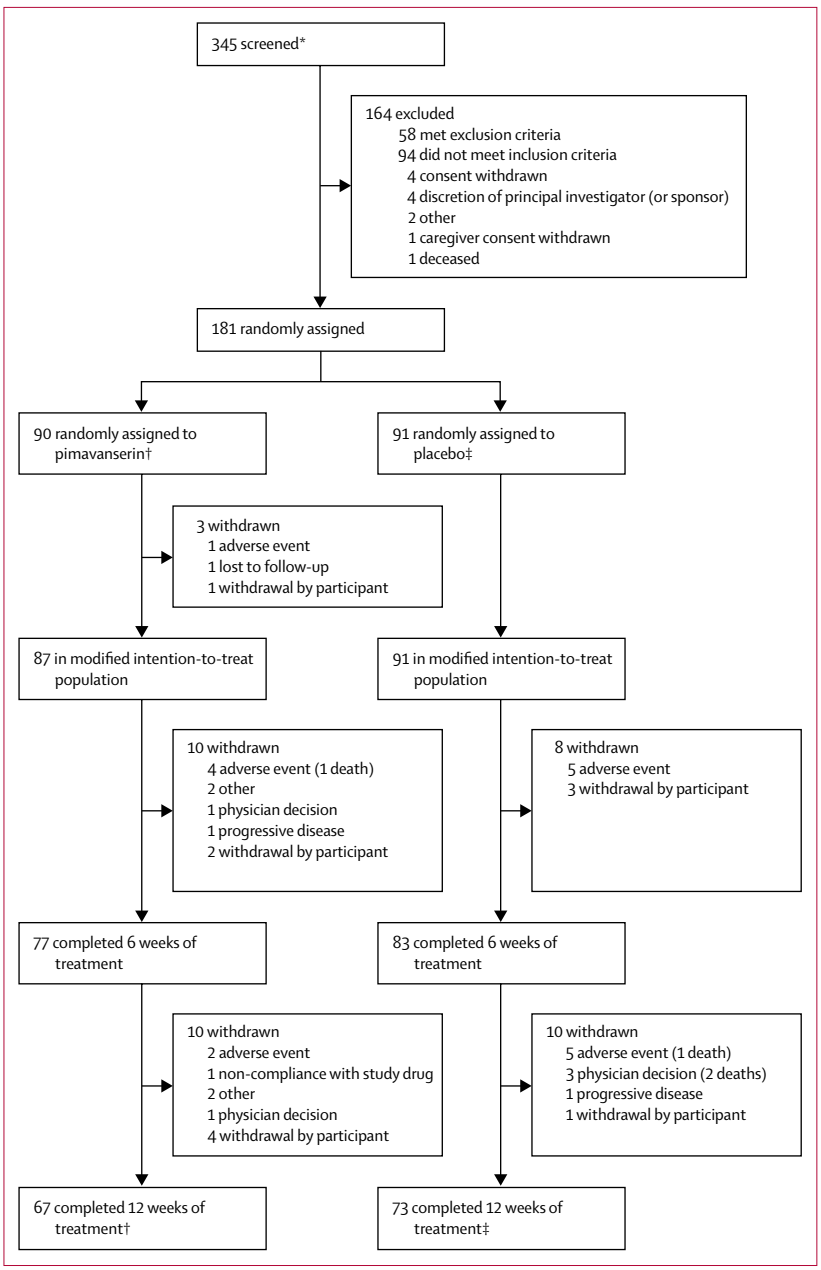

Figure 1: **Trial profile**
Brief psychosocial therapy was administered to all screened participants for 10–30 min per day up to five times per week during the 3-week screening period. †Four participants receiving pimavanserin died during the study, one during the 12-week treatment period and three during the post-treatment 4-week telephone follow-up. ‡Four participants receiving placebo died during the study, three during the 12-week treatment period and one during the post-treatment 4-week telephone follow-up.

Statistical analysis

For the purpose of sample size calculation, we assumed that an effect size of 0·4–0·5 SD between active treatment and placebo would be clinically meaningful.[34] Assuming the true difference in the mean change of the NPI–NH

psychosis score from baseline to week 6 was 3 points between pimavanserin and placebo, and the common SD was 6 points, 170 participants provided 90% power to detect a difference between treatment groups at the significance level of 0·05 using a two-sided *t* test. Adjusting for a potential dropout of 20%, enrolment of 212 participants was initially planned.

Analysis of the primary outcome was done using the mixed model repeated measures method. The model included fixed effects of baseline MMSE category (<6 or ≥6), baseline NPI–NH psychosis score (as a continuous covariate), treatment (pimavanserin or placebo), study visits (days 15, 29, 43, 64, and 85), and treatment-by-visit interaction. An unstructured covariance matrix was used to model the within-participant errors (random effect). The Kenward–Roger approximation[35] was used to estimate denominator degrees of freedom. For the responder analyses, we imputed missing responses as non-responders using a conservative approach. The reported responder rates were the observed proportions at week 6, after imputing any missing values. The treatment groups were compared using a Cochran–Mantel–Haenszel test, stratified by baseline NPI–NH psychosis score category (<12 or ≥12) and baseline MMSE category (<6 or ≥6).

For the prespecified secondary and exploratory efficacy outcomes as well as the safety outcomes, the analysis model included fixed effects of baseline MMSE category, baseline NPI–NH psychosis score, treatment, study visit days, treatment-by-visit interaction, and continuous and fixed covariate of baseline score (except for ADCS–CGIC for which there is no baseline score). Primary, secondary, and exploratory efficacy analyses used the modified intention-to-treat population, which included all randomly assigned participants who received at least one dose of study drug and had both a baseline and at least one post-baseline NPI–NH psychosis score assessment. All efficacy analyses were done using two-sided tests at the 5% level of significance. No adjustment for multiplicity of testing was used. Additional sensitivity analyses included placebo-based multiple imputation, last observation carried forward, and the non-parametric van Elteren test. Additional details of the statistical analyses are provided in the appendix.

All statistical analyses were done with use of SAS (version 9.3). The study was overseen by an Independent Data Monitoring Ethics Committee.

This trial is registered with ClinicalTrials.gov, number NCT02035553.

Role of the funding source

The funder of the study had a role in study design, data analysis, data interpretation, and writing of the report. All authors had full access to all the data in the study and had full responsibility for the content of the manuscript for publication. The corresponding author was responsible for the final review and had final responsibility for the decision to submit for publication.

Results

Between Jan 16, 2014, and Oct 27, 2016, 345 participants across 133 nursing homes were screened, of which 164 participants were excluded upon screening and 181 were randomly assigned to receive pimavanserin (n=90) or placebo (n=91; figure 1). 70 (43%) of 164 participants were excluded for not meeting entry criteria for severity of NPI–NH hallucinations and delusions, of which 25 (36%) were excluded at screening visit three, indicating that they had improved and were no longer eligible for the study. In these participants, BPST during screening might have contributed to the improvement. 23 (26%) of 90 participants in the pimavanserin group and 18 (20%) of 91 in the placebo group withdrew and discontinued intervention over the 12-week study period. Three participants in the pimavanserin group were excluded from the modified intention-to-treat population because they did not have a post-baseline NPI–NH psychosis score. Therefore, 178 participants were included in the efficacy analysis, of whom 160 completed 6 weeks of treatment and 140 completed 12 weeks of treatment (figure 1). Rescue medications for behavioural or sleep disturbances were used by seven (8%) of 87 participants in the pimavanserin group and eight (9%) of 91 participants in the placebo group.

Baseline demographic and clinical characteristics of participants were generally well balanced between treatment groups (table 1). 27 (31%) of 87 participants in

	Pimavanserin (n=87)	Placebo (n=91)
Sex		
Women	71 (82%)	73 (80%)
Men	16 (18%)	18 (20%)
Mean age (years)	85·6 (7·0)	86·1 (6·0)
Ethnicity		
White	81 (93%)	89 (98%)
Other	6 (7%)	2 (2%)
Mean BMI (kg/m^2)	24·1 (5·1)	23·1 (4·6)
Previous antipsychotic usage	10 (12%)	6 (7%)
Concomitant SSRI	21 (24%)	20 (22%)
Concomitant anti-dementia medication	33 (38%)	40 (44%)
Mean NPI–NH psychosis score	9·5 (4·8)	10·0 (5·6)
NPI–NH psychosis score <12	60 (69%)	61 (67%)
Mean NPI–NH psychosis score <12	6·9 (2·0)	6·7 (2·0)
NPI–NH psychosis score ≥12	27 (31%)	30 (33%)
Mean NPI–NH psychosis score ≥12	15·3 (4·2)	16·7 (4·5)
Mean NPI–NH agitation/aggression	4·9 (4·0)	4·5 (3·8)
Mean MMSE	10·3 (5·4)	9·8 (5·0)
MMSE <6*	18 (21%)	15 (18%)

Data are n (%) or mean (SD). BMI=body-mass index. SSRI=selective serotonin reuptake inhibitor. NPI–NH=Neuropsychiatric Inventory–Nursing Home version. MMSE=Mini-Mental State Examination. *Denominators are based on participants with no missing MMSE score (n=84 for pimavanserin and n=85 for placebo).

Table 1: **Baseline demographic and clinical characteristics**

See Online for appendix

the pimavanserin group and 30 (33%) of 91 in the placebo group had more severe psychotic symptoms as documented by NPI–NH psychosis score of 12 or more, and 18 (21%) of 84 participants in the pimavanserin group and 15 (18%) of 85 participants in the placebo group had an MMSE score of less than 6.

For the primary outcome, the adjusted mean change of the NPI–NH psychosis score from baseline to week 6 was –3·76 (SE 0·65) for pimavanserin and –1·93 (0·63) points for placebo (mean difference –1·84 [95% CI –3·64 to –0·04], Cohen's *d*=–0·32; p=0·045; figure 2). On average, participants in the pimavanserin group had a 39·5% reduction in their NPI–NH psychosis score at week 6 compared with 19·3% reduction in the placebo group. Response, defined as ≥30% improvement, was observed in 48 (55%) for pimavanserin versus 34 (37%) for placebo (p=0·016; figure 3). The results of the other sensitivity analyses were consistent with the primary analysis and are shown in the appendix. Responder analysis for the baseline NPI–NH psychosis score ≥12 subgroup is also included in the appendix.

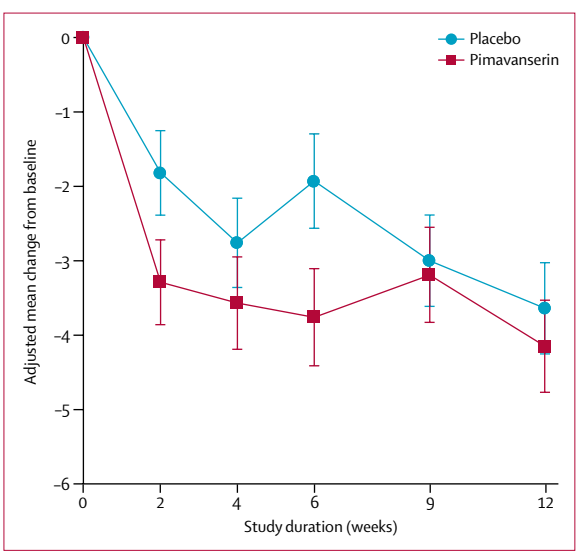

Figure 2: **Adjusted mean change from baseline to week 12 in the NPI–NH psychosis score**
Error bars are SE. NPI–NH=Neuropsychiatric Inventory-Nursing Home version.

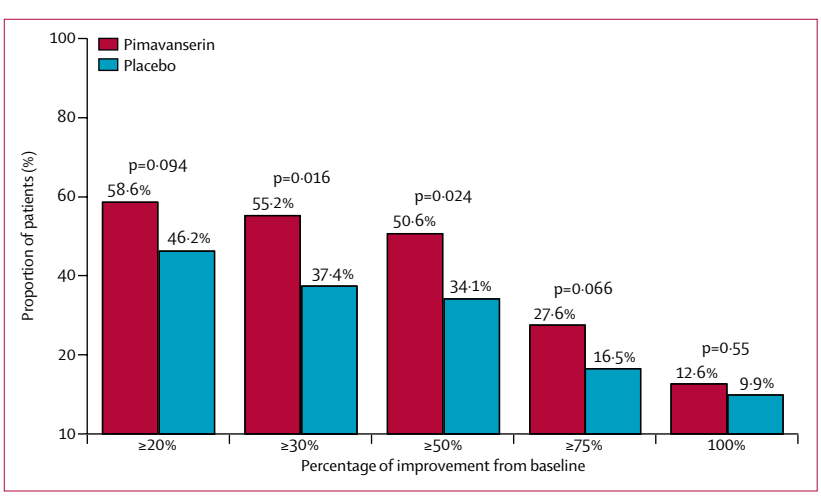

Figure 3: **Response rate at week 6 for NPI–NH psychosis score**
NPI–NH=Neuropsychiatric Inventory-Nursing Home version.

No significant differences were observed between pimavanserin and placebo for ADCS–CGIC, NPI–NH agitation/aggression, NPI–NH sleep and nighttime behaviour disorders, and CMAI–SF at week 6 (figure 4) or week 12 (appendix).

NPI–NH total score at either 6 weeks or 12 weeks was not different between groups, although at 6 weeks there was a 5 point non-significant difference for pimavanserin compared with placebo (95% CI –10·53 to 0·28; p=0·063). There was no treatment effect seen in each of the remaining NPI–NH individual domains other than irritability/lability at week 6 (figure 4).

In participants with more severe psychotic symptoms (NPI–NH psychosis score ≥12), a prespecified subgroup analysis, the adjusted mean change of the score from baseline to week 6 was –10·15 (95% CI –12·50 to –7·80) for pimavanserin and –5·72 (–8·14 to –3·30) for placebo (mean difference –4·43 [95% CI –7·81 to –1·04], Cohen's *d*=–0·73; p=0·011). In participants with mild psychotic symptoms (NPI–NH psychosis score <12), the adjusted mean change of the score from baseline to week 6 was –0·58 (95% CI –2·10 to 0·95) for pimavanserin and –0·16 (–1·60 to 1·28) for placebo (mean difference –0·42 [95% CI –2·52 to 1·68], Cohen's *d*=–0·077; p=0·694. 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) or for the severe subgroup with an NPI–NH psychosis score of 12 or more (–1·31 [–5·15 to 2·54]; p=0·497]; appendix).

Among subgroups stratified by previous antipsychotic use, the treatment difference at week 6 was –6·53 (95% CI –15·61 to 2·56; p=0·145) in 16 participants with previous use (n=10 for pimavanserin and n=6 for placebo), whereas the treatment difference was –1·9 (–3·69 to –0·11; p=0·037) in 162 with no prior use (n=77 for pimavanserin and n=85 for placebo). No significant differences were observed between treatment groups when stratified by concomitant use of selective serotonin reuptake inhibitor (appendix). Additionally, there were no significant differences observed between pimavanserin and placebo for ADCS–ADL at week 6 (figure 4). Figure 4 summarises the other prespecified secondary and exploratory outcomes.

Minimal change from baseline was observed for the mean MMSE score in either treatment group over 12 weeks (appendix). Similarly, mean UPDRS part III scores over 12 weeks were comparable in both treatment groups (appendix).

At least one adverse event was reported in 173 (96%) of 181 participants. Eight (9%) of 90 participants in the pimavanserin group and 11 (12%) of 91 in the placebo

group discontinued treatment because of adverse events. Serious adverse events occurred in 15 (17%) participants with pimavanserin and ten (11%) with placebo. Agitation (19 [21%] *vs* 13 [14%]), aggression (nine [10%] *vs* four [4%]), and peripheral oedema (seven [8%] *vs* two [2%]) were more common with pimavanserin than with placebo,

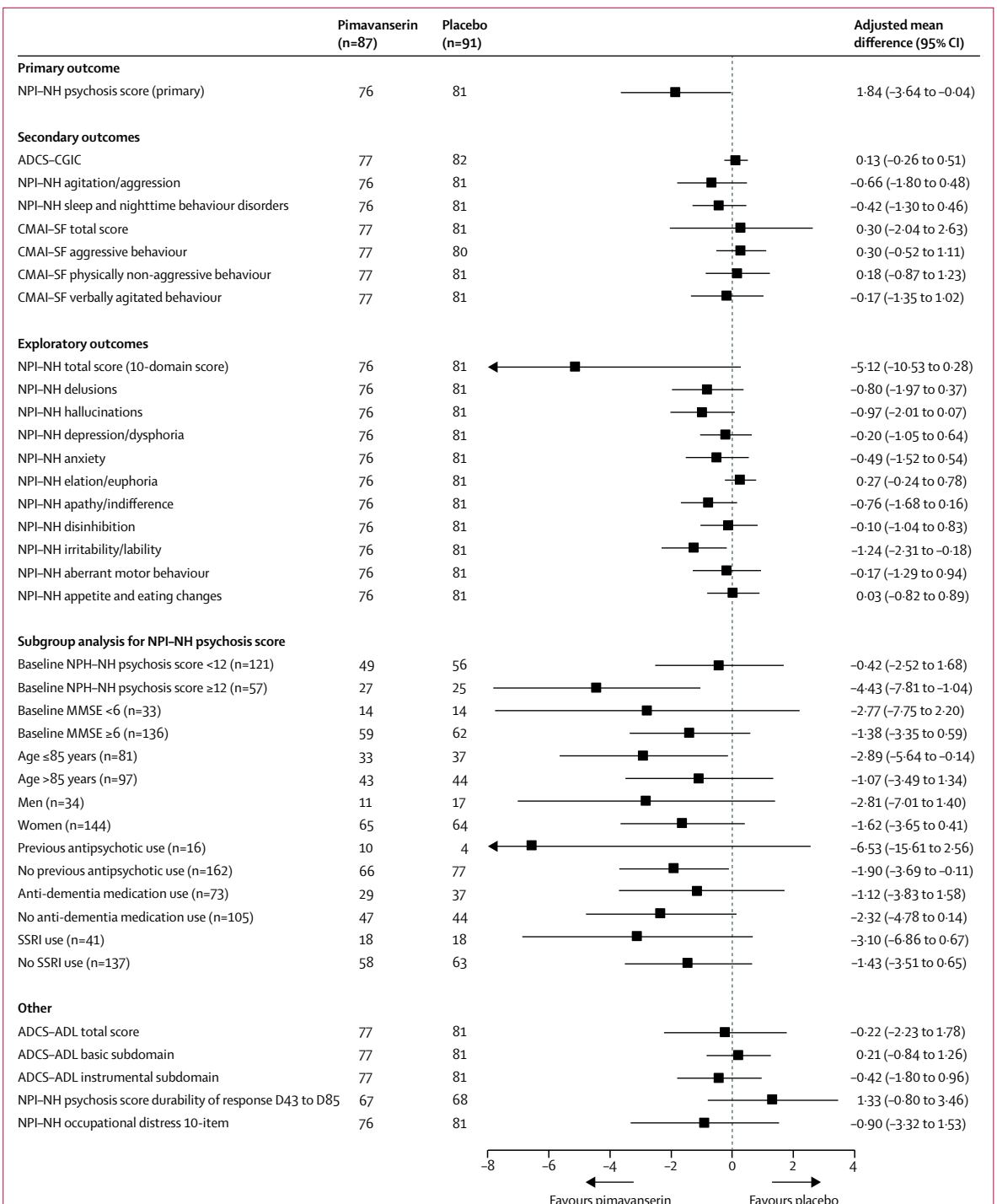

Figure 4: **Adjusted mean differences from baseline to week 6 for prespecified endpoints**
Error bars are 95% CIs. NPI–NH=Neuropsychiatric Inventory–Nursing Home version. ADCS–CGIC=Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change. CMAI–SF=Cohen–Mansfield Agitation Inventory–Short Form. MMSE=Mini-Mental State Examination. SSRI=selective serotonin reuptake inhibitor. ADCS–ADL=Alzheimer's Disease Cooperative Study–Activities of Daily Living.

	Pimavanserin (n=90)	Placebo (n=91)
Summary of adverse events		
Any adverse event	88 (98%)	85 (93%)
Any serious adverse event	15 (17%)	10 (11%)
Any adverse event causing discontinuation	8 (9%)	11 (12%)
Adverse events*		
Fall	21 (23%)	21 (23%)
Urinary tract infection	20 (22%)	25 (28%)
Agitation	19 (21%)	13 (14%)
Lower respiratory tract infection	13 (14%)	12 (13%)
Contusion	11 (12%)	14 (15%)
Aggression	9 (10%)	4 (4%)
Anaemia	9 (10%)	8 (8%)
Blood urea increased	7 (8%)	8 (8%)
Peripheral oedema	7 (8%)	2 (2%)
Cellulitis	6 (7%)	3 (3%)
Anxiety	5 (6%)	2 (2%)
Behavioural and psychiatric symptoms of dementia	5 (6%)	2 (2%)
Blood potassium increased	5 (6%)	3 (3%)

Data are n (%). No significant differences between groups were noted. *Number of adverse events occurring in any patient in the placebo group and in at least 5% of patients in the pimavanserin group. A full list of adverse events is reported in the appendix.

Table 2: **Summary of adverse events**

although no significant differences were noted between treatments (table 2). There was no difference in the frequency of discontinuations due to adverse events of agitation (one [1%] of 90 *vs* one [1%] of 91) or aggression (one [1%] *vs* two [2%]) with pimavanserin versus placebo. Four deaths occurred in each treatment group, from pneumonia (pimavanserin n=1 and placebo n=2), bronchopneumonia (pimavanserin n=1), dementia (pimavanserin n=1), malignant neoplasm of the thorax (pimavanserin n=1), cardiopulmonary failure (placebo n=1), and general physical health deterioration (placebo n=1; figure 1).

No notable differences between treatment groups were observed for physical examination, vital signs, or clinical laboratory tests. At week 12, mean change in body-weight was –0·7 kg (SE 0·66) with pimavanserin and –0·1 kg (0·28) with placebo. Categorical analysis showed that more participants in the pimavanserin group experienced weight loss of 7% or more (seven [15%] of 48 for pimavanserin and one [2%] of 57 for placebo). Similar numbers of participants reported clinically significant weight gain of 7% or more (four [8%] for pimavanserin and five [9%] for placebo)

At baseline, mean QTcF was 417 ms (range 362–485) for pimavanserin and 419 ms (372–479) for placebo. After 12 weeks of treatment the mean change from baseline in the QTcF interval in patients receiving pimavanserin was 9·4 ms (SE 2·1) versus –2·0 ms (2·0) in patients receiving placebo. Three patients in each group had an adverse event of prolonged QTcF: all were mild, no doses were changed, and no patient discontinued because of QTcF prolongation. The QTcF outlier analysis showed no clinically meaningful difference in outliers with a QTcF of 500 ms or more or change from baseline of 60 ms or more (one patient in each group had a change from baseline of ≥60 msec at day 15). Cardiac adverse events considered related to the study treatment occurred in two (2%) of 90 participants in the pimavanserin group versus six (7%) of 91 in the placebo group.

Discussion

In an elderly frail population of participants with Alzheimer's disease and psychosis, pimavanserin showed a significant reduction in psychosis over 6 weeks of treatment compared with placebo. With respect to the secondary outcomes, there is no evidence from the current study that pimavanserin conferred benefit in the treatment of agitation, although it should be noted that this finding was a secondary outcome measure and that the symptoms were generally mild and below the usually recognised threshold of clinical significance. With respect to other neuropsychiatric symptoms (ie, NPI domains), the study showed benefit of pimavanserin treatment on irritability/lability but not on other NPI domains. No significant benefit was reported on the occupational distress associated with NPI symptoms. There was no difference in change in activities of daily living or the use of rescue medications between treatment groups. Prespecified subgroup analyses provided evidence of increased benefit in the group of participants with more severe psychotic symptoms (NPI–NH psychosis score ≥12), but not in those with mild symptoms (NPI–NH psychosis score <12), who were given pimavanserin compared with those given placebo. The treatment benefit of pimavanserin compared with placebo was not however maintained at the secondary timepoint of week 12.

Although it should be noted that measures of cognition and function have limited sensitivity over 12 weeks and need to be interpreted cautiously, pimavanserin showed no evidence of worsening in cognition, function, global outcome, or motor symptoms over 12 weeks of treatment. The adverse event and safety profile of pimavanserin was generally consistent with a previous study in participants with Parkinson's disease and psychosis.[17] The most common adverse events reported in both treatment groups were falls, urinary tract infections, and agitation. The numbers of falls and urinary tract infections were similar in both groups, but the incidence was higher for participants with agitation receiving pimavanserin than for those receiving placebo, which will need further evaluation in future trials. As reported in previous studies, an excess of peripheral oedema was also identified for participants receiving pimavanserin.[17] A higher proportion of participants receiving pimavanserin

than those receiving placebo had weight loss of 7% or more over the course of 12 weeks. This effect was reported in a few patients and has been observed in previous studies[36] with pimavanserin but at a lower rate (3% for pimavanserin *vs* 1% for placebo). This observation requires evaluation in future studies. Consistent with previous reports,[17] QTcF prolongation was observed for participants receiving pimavanserin. Importantly, this effect was not associated with related adverse events, but nevertheless does require some clinical caution as outlined in the current US Food and Drug Administration approval for pimavanserin for the treatment of hallucinations and delusions associated with psychosis in Parkinson's disease. No difference in mortality rates was observed between both groups in this study.

The main limitation of this study is that it was powered as a phase 2 study for the primary outcome at week 6, and there was insufficient power to control for multiple secondary and exploratory endpoints. Additionally, many of the participants had moderate rather than severe psychosis and there were only a small proportion of participants who had been prescribed previous atypical antipsychotics. However, the rigorous diagnosis of psychosis and high completion rates for a study with a frail population of people with moderate-to-severe Alzheimer's disease strengthens our findings.

The significant benefit in the primary outcome measure at week 6 in the overall study population is encouraging. The absence of significant benefit of pimavanserin over placebo at 12 weeks might indicate the absence of sustained benefit, but might also not be surprising in the context of the remitting and relapsing course of psychosis in people with Alzheimer's disease.

Atypical antipsychotics are commonly used to treat psychosis in Alzheimer's disease,[8] but they have little efficacy (effect size ≤0·2)[9,10,12] and are associated with major side-effects and risks, including stroke, parkinsonism, accelerated cognitive decline, and death,[8,13–15] highlighting the urgent need for a safe and effective pharmacological therapy for psychosis in Alzheimer's disease. In controlled studies, citalopram was effective for reducing agitation and aggression as well as irritability, anxiety, and delusions in patients with Alzheimer's disease and agitation. However, its use was associated with a greater risk for adverse events, accelerated cognitive decline, and an increased risk for QT interval prolongation compared with placebo and risperidone.[37,38] Pimavanserin has a different mechanism of action and distinct safety profile compared with other antipsychotics, including no detrimental effects on cognitive and motor symptoms that offer potentially unique advantages in this population.

Few previous randomised controlled trials have shown significant benefit in the treatment of psychosis in Alzheimer's disease; therefore, this study is potentially an important step forward in identifying treatment for this condition. The effect size of benefit, although modest, was also favourable compared with previous studies of atypical antipsychotics, with a suggestion of substantial benefit in people with severe psychosis, and therefore the population potentially most in need of pharmacological treatment.

It should be noted that biomarker confirmation of diagnosis is not possible in a trial population of nursing home patients with generally moderate-to-severe Alzheimer's disease, and patients with non-Alzheimer's dementia and mixed dementia were possibly present in the trial population.

Participants were assessed at care homes because some of them would not have been able to travel to the clinic for study visits, which gave them access to a clinical study that would not otherwise be possible. This assessment method also allowed for study of frail elderly participants in a natural setting and facilitated recruitment. This study also used BPST during screening to help participants and caregivers manage psychiatric and behavioural symptoms and to identify those participants who did not require pharmacological therapy. All patients progressing to the pharmacological phase of the trial met study criteria for psychosis following BPST, but it should be noted that 50% of these individuals had only a moderate level of symptom severity. Few study participants were taking acetylcholinesterase inhibitors or memantine during the study, which is consistent with other studies in a similar population.[39]

The findings from this study suggest potential efficacy and acceptable tolerability of pimavanserin for psychosis in Alzheimer's disease, encouraging the development of a phase 3 clinical trial programme. Further studies will be helpful to clarify the response to pimavanserin in subgroups of participants by baseline psychosis score and to refine the ideal target group for treatment. Finally, further studies should help to characterise the long-term efficacy, safety, and tolerability of pimavanserin in participants with Alzheimer's disease and psychosis.

Contributors

GD, JC, and CBal contributed to the study design. RO, JMY, and BC contributed to the statistical analysis plan. CBal, CBan, and the ADP Investigators contributed to the conduct of the study and data collection. ZK contributed to the development and set up of the study. SS, RO, JMY, GD, BC, and the study sponsor contributed to the data analysis. GD, JMY, and RO provided oversight of the safety monitoring. All authors contributed to the interpretation of the data, drafted and edited the manuscript, and approved the final manuscript.

Declaration of interests

CBal has received grants and personal fees from ACADIA and Lundbeck, personal fees from Heptares, Roche, Lilly, Otsuka, Orion, GlaxoSmithKline, and Pfizer. SS, RO, JMY, GD, and BC are employees of ACADIA Pharmaceuticals. CBan has received personal fees from ACADIA, during the conduct of the study. JC has received personal fees from AbbVie, ACADIA, Actinogen, Alzheon, Anavex, Avanir, Axovant, Biogen, Boehringer Ingelheim, Bracket, Dart, Eisai, Genentech, Kyowa, Lilly, Lundbeck, Medavante, Merck, Orion, Otsuka, Pfizer, QR Pharma, Roche, Suven, Takeda Pharmaceutical, and assessment companies, outside the submitted work; and has a patent copyright ownership of Neuropsychiatric Inventory with royalties paid. ZK declares no competing interests.

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