Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial

Jeffrey Cummings, Stuart Isaacson, Roger Mills, Hilde Williams, Kathy Chi-Burris, Anne Corbett, Rohit Dhall, Clive Ballard

Summary

Background Parkinson's disease psychosis, which includes hallucinations and delusions, is frequent and debilitating in people with Parkinson's disease. We aimed to assess safety and efficacy of pimavanserin, a selective serotonin 5-HT2A inverse agonist, in this population.

Methods In our 6 week, randomised, double-blind, placebo-controlled study, we enrolled adults (aged ≥40 years) with Parkinson's disease psychosis. Antipsychotic treatments were not permitted during the study, but controlled antiparkinsonian medication or deep brain stimulation was allowed. Eligible participants entered a 2 week non-pharmacological lead-in phase to limit the placebo response, after which they were randomly allocated (1:1) to receive pimavanserin 40 mg per day or matched placebo. The primary outcome was antipsychotic benefit as assessed by central, independent raters with the Parkinson's disease-adapted scale for assessment of positive symptoms (SAPS-PD) in all patients who received at least one dose of study drug and had a SAPS assessment at baseline and at least one follow-up. We assessed safety and tolerability in all patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT01174004.

Findings Between Aug 11, 2010, and Aug 29, 2012, we randomly allocated 199 patients to treatment groups. For 90 recipients of placebo and 95 recipients of pimavanserin included in the primary analysis, pimavanserin was associated with a −5·79 decrease in SAPS-PD scores compared with −2·73 for placebo (difference −3·06, 95% CI −4·91 to −1·20; p=0·001; Cohen's *d* 0·50). Ten patients in the pimavanserin group discontinued because of an adverse event (four due to psychotic disorder or hallucination within 10 days of start of the study drug) compared with two in the placebo group. Overall, pimavanserin was well tolerated with no significant safety concerns or worsening of motor function.

Interpretation Pimavanserin may benefit patients with Parkinson's disease psychosis for whom few other treatment options exist. The trial design used in this study to manage placebo response could have applicability to other studies in neuropsychiatric disease.

Funding ACADIA Pharmaceuticals.

Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV, USA (J Cummings MD); Parkinson's Disease and Movement Disorders Center of Boca Raton, *Boca Raton*, FL, USA (S Isaacson MD); ACADIA Pharmaceuticals, San Diego, CA, USA (R Mills MD, H Williams, K Chi-Burris); Wolfson Centre for Age-Related Diseases, King's College, London, UK (A Corbett PhD, C Ballard MD); and Barrow Neurology Institute, Phoenix, AZ, USA (R Dhall MD)

Correspondence to:
Prof Clive Ballard, Wolfson Centre for Age-Related Diseases, King's College London, Guy's Campus, London SE1 1UL, UK
clive.ballard@kcl.ac.uk

Introduction

7–10 million people worldwide have Parkinson's disease.[1] The combined global cost of the disorder is estimated to be nearly £41 billion per year. Parkinson's disease is a synucleinopathy resulting in progressive neurodegeneration marked by motor dysfunction and non-motor symptoms including psychosis. More than 50% of patients with Parkinson's disease have psychosis at some time.[2] Psychosis affects up to 75% of patients with Parkinson's disease dementia, and symptoms are more intractable in this group.[3] Such psychosis is expressed primarily as hallucinations and delusions, which can cause great distress for patients and their caregivers. These episodes present a major challenge for treatment and care, increase the likelihood of placement in nursing homes, and are associated with increased mortality.[2]

Best-practice treatment guidelines promote initial consideration of comorbidities and reduction of dopaminergic therapy. However, these approaches are often insufficient and few other therapeutic options exist. Typical antipsychotics can cause profound dopamine D2 antagonism and worsen parkinsonism. Therefore, atypical antipsychotics are commonly used. Among these drugs, risperidone and olanzapine are poorly tolerated. Quetiapine seems better tolerated, with a small trial of 16 patients showing some clinical benefit.[4] However, the four largest randomised controlled trials of quetiapine (including 153 patients) showed no evidence of efficacy,[5–8] suggesting that quetiapine is not efficacious for control of Parkinson's disease psychosis.

Clozapine has shown antipsychotic benefit without worsening motor symptoms in several randomised controlled trials, including two 4 week trials that had large effect sizes (Cohen's *d* >0·8) in the treatment groups and in one longer trial.[9–11] However, clozapine is associated with increased risk of agranulocytosis, mortality, seizures, myocarditis and other cardiovascular and respiratory effects. These risks have particular relevance for frail elderly people with neurodegenerative disease and require strict monitoring protocols. The UK's National Institute for Health and Care Excellence (NICE) Parkinson's disease guideline indicates that clozapine is rarely used. Thus, safe and efficacious

treatment options for Parkinson's disease psychosis are a clinical priority.

Pimavanserin (ACADIA Pharmaceuticals, San Diego, CA, USA) is a selective serotonin 5-HT2A inverse agonist without dopaminergic, adrenergic, histaminergic, or muscarinic affinity, and is in development as a treatment for Parkinson's disease psychosis.[12] In Parkinson's disease, the binding of 5-HT2A receptors is increased in the neocortex, and visual hallucinations are associated with increased numbers of 5-HT2A receptors in visual processing areas.[13] Post-mortem and genetic studies also suggest that in Parkinson's disease dementia, dementia with Lewy bodies, and Alzheimer's disease, delusions and hallucinations are linked to alterations in the 5-HT system.[14,15] Polymorphisms of 5-HT2A, 5-HT2C, and the 5-HT transporter are linked to psychosis, and possibly with treatment response to atypical antipsychotics in Alzheimer's disease.[16–18] Atypical antipsychotics target the 5-HT2A pathway but at varying levels and also affect other receptor families. With its receptor selectivity, pimavanserin has been developed to provide anti-psychotic benefit without the adverse effects of current antipsychotics. Previous randomised controlled trials and ongoing open-label safety extension studies in

Parkinson's disease psychosis provide preliminary evidence of pimavanserin's antipsychotic benefits and good tolerability.[19,20] We aimed to assess efficacy and safety of pimavanserin for treatment of Parkinson's disease psychosis in a phase 3 trial, incorporating design features on the basis of results of a previous trial[20] intended to minimise placebo response and optimise trial quality.

Methods

Study design and participants

In our randomised, double-blind, parallel group, placebo-controlled trial, we enrolled participants at 52 centres (academic hospitals or other experienced neurology research centres) in the USA and two centres in Canada. Eligibility criteria were unchanged throughout. Eligible participants had to be aged 40 years or older, meet established diagnostic criteria for Parkinson's disease psychosis,[21] including idiopathic Parkinson's disease consistent with UK Brain Bank criteria[22] lasting at least 1 year, and have psychotic symptoms that developed after Parkinson's disease diagnosis that were present for at least 1 month, occurred at least weekly in the month before screening, and were severe enough to warrant
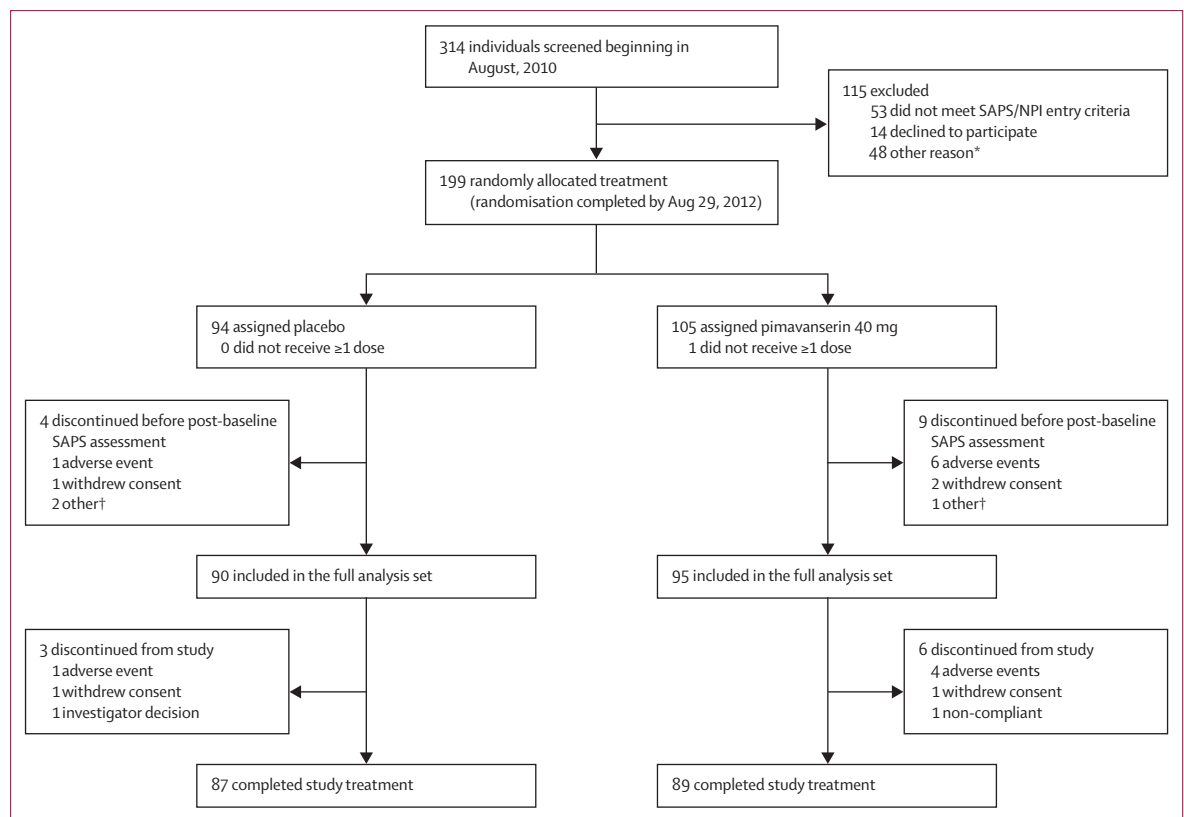
Figure 1: Trial profile
SAPS=scale for assessment of positive symptoms. NPI=neuropsychiatric inventory. *Did not meet mini-mental status examination criteria, was using prohibited medications, had unstable medical conditions, caregiver was unwilling, discretion of sponsor, QTc or laboratory test results did not meet study inclusion criteria. †Discontinued at the discretion of the sponsor (participants did not meet the SAPS-PD entry criterion and were randomly allocated in error).

treatment with antipsychotics. Patients had to have a mini-mental status examination (MMSE) score of at least 21 points out of 30 and no delirium. A caregiver (usually a spouse or family member) was required at all visits.

We excluded potential participants if their psychosis was secondary to other toxic or metabolic disorders, if dementia was diagnosed concurrent with or before Parkinson's disease, or if the psychosis occurred after ablative stereotaxic surgery. For participants receiving antiparkinsonian drugs or having deep brain stimulation, stable dosage and settings were required throughout the trial and for 1 month before enrolment. No reductions in dopaminergic drugs were required at study entry. Other exclusion criteria included stroke or other uncontrolled serious medical illness, myocardial infarction within 6 months of baseline, congestive heart failure, history of long QT syndrome, a long QTcB (>460 ms for men or >470 ms for women), or clinically significant laboratory abnormalities. Antipsychotics drugs were prohibited (with discontinuation ≥5 half-lives), as were centrally acting anticholinergics and drugs prolonging QT interval.

In compliance with the Declaration of Helsinki, patients provided written informed consent. Caregivers also provided consent. Participating centres received institutional review board approval.

Randomisation and masking

Within each centre, randomisation was done in a double blind manner by use of a preprogrammed kit randomisation schedule generated by PharmaNet (Princeton, NJ, USA) in which pimavanserin or matched placebo were randomly assigned in a 1:1 ratio with a block size of four. We did not use any other stratification factors. Participants who met eligibility criteria were randomly allocated to once-daily pimavanserin 40 mg (two 20 mg tablets) or matched placebo. Tablets (and placebo in concealed kits) were manufactured by ACADIA Pharmaceuticals and packaged in compliance with good manufacturing practice.

Procedures

At screening, participants had to have a combined score of at least 6 or an individual score of at least 4 on the neuropsychiatric inventory (NPI)[23] items A (delusions) and/or B (hallucinations). After screening, participants entered a 2 week lead-in period during which non-pharmacological brief psychosocial therapy[24] adapted for Parkinson's disease (BPST-PD) was used to help elicit a placebo response ahead of baseline. BPST-PD consisted of daily social interactions between participant and caregiver based on a plan tailored to their interests and capabilities. Follow-up was done after 3 days and 7 days. Eligibility was confirmed at baseline and required a score of at least 3 on the scale for assessment of positive symptoms (SAPS) hallucinations or delusions global item[25] and at least 3 on at least one other non-global item on the Parkinson's disease-adapted SAPS (SAPS-PD).[26]

	Placebo (n=90)	Pimavanserin (n=95)
Age, years	72·4 (7·92)	72·4 (6·55)
Sex, female	38 (42%)	31 (33%)
Ethnic group, white	85 (94%)	90 (95%)
Body-mass index, kg/m²	26·4 (5·65)	26·2 (4·57)
Stereotactic surgery	3 (3%)	10 (11%)
Mini-mental status examination score	26·6 (2·40)	26·0 (2·61)
UPDRS-II score	19·3 (6·77)	18·7 (6·62)
UPDRS-III score	33·3 (12·23)	32·8 (12·86)
Time since first PDP symptoms, months	36·4 (39·57)	30·9 (30·01)
Antipsychotic exposure within 21 days before baseline	15 (17%)	18 (19%)
Clozapine	0	2 (2%)
Quetiapine	13 (14%)	16 (17%)
Risperidone	1 (1%)	0
Ziprasidone	1 (1%)	0
Use of dopaminergic drugs at baseline and throughout trial	89 (99%)	94 (99%)
Use of cholinesterase inhibitors at baseline and throughout trial	32 (36%)	31 (33%)
NPI total (H+D) score	12·2 (5·33)	11·8 (5·85)
SAPS-PD	14·7 (5·55)	15·9 (6·12)
SAPS-H+D	15·8 (6·52)	17·5 (7·57)
CGI-S	4·32 (0·91)	4·27 (0·92)
SCOPA-sleep (night-time score)	5·48 (3·82)	5·84 (3·84)
Caregiver burden scale score	30·66 (15·92)	28·71 (14·23)

Data are mean (SD) or n (%). The full analysis set consisted of all patients who received ≥1 dose and had SAPS assessments at baseline and ≥1 post-baseline. UPDRS=unified Parkinson's disease rating scale. PDP=Parkinson's disease psychosis. NPI=neuropsychiatric inventory. H+D=hallucinations and delusions. SAPS=scale for the assessment of positive symptoms. SAPS-PD=sum of nine item Parkinson's disease-adapted SAPS. CGI-S=clinical global impression severity. SCOPA=scale for outcomes of Parkinson's disease.

Table 1: **Baseline characteristics (full analysis set)**

Assessments were done at baseline and days 15, 29, and 43. The primary outcome was change in total SAPS-PD[26] score from baseline to day 43. The SAPS-PD includes nine items, seven assessing individual symptoms, a global hallucinations item, and a global delusions item. This measure was derived from the SAPS, which was previously used in Parkinson's disease psychosis trials of pimavanserin and clozapine. It specifically shows symptoms that occur frequently and are sensitive to change in Parkinson's disease psychosis.[26] SAPS-PD assessments were done by live video conference between the participant and a centralised, independent rater who was masked to treatment assignment.

Secondary outcomes included change by day 43 in clinical global impression-severity (CGI-S) and improvement (CGI-I) scale scores,[27] completed by a site investigator who was masked to SAPS-PD scores. Exploratory measures included the Zarit 22-item caregiver burden scale (CBS), which was completed by the caregiver and scales for outcomes in Parkinson's disease-sleep (parts B and C) assessing night-time sleep quality (SCOPA-NS) and daytime wakefulness (SCOPA-DS).[28] A key secondary endpoint assessed parkinsonism with the unified Parkinson's disease rating scale parts II and III (UPDRS II and III).[29] We routinely monitored safety throughout the

	Rater	Population	Analysis*	Day 43 outcome†		Treatment change†‡	95% CI	p value	Effect size§
				Placebo (n=90)	Pimavanserin 40 mg (n=95)				
Anti-psychotic efficacy									
Primary analysis									
SAPS-PD	Independent (central)	FAS	MMRM	−2·73 (0·67)	−5·79 (0·66)	−3·06 (0·94)	−4·91 to −1·20	0·0014	0·50
Sensitivity analysis									
SAPS-PD	Independent (central)	PP	MMRM	−2·73 (0·68)	−5·91 (0·67)	−3·18	−5·07 to −1·28	0·0011	..
SAPS-PD	Independent (central)	FAS	LOCF	−2·65 (0·67)	−5·56 (0·65)	−2·91	−4·75 to −1·07	0·0021	..
SAPS-PD	Independent (central)	FAS	WOCF	−2·65 (0·67)	−5·43 (0·65)	−2·78	−4·63 to −0·93	0·0034	..
SAPS-PD	Independent (central)	All randomised	WOCF/BOCF	−2·56 (0·65)	−4·92 (0·61)	−2·36	−4·12 to −0·61	0·0084	..
Supportive analyses									
SAPS-PD percentage change	Independent (central)	FAS	MMRM	−14% (4·7%)	−37% (4·6%)	−23% (6·6%)	−36 to −10	0·0006	..
SAPS-H+D	Independent (central)	FAS	MMRM	−3·14 (0·73)	−6·51 (0·72)	−3·37 (1·03)	−5·40 to −1·35	0·0012	0·50
SAPS-H+D percentage change	Independent (central)	FAS	MMRM	−15% (4·7%)	−38% (4·7%)	−24% (6·7%)	−37 to −10	0·0005	..
SAPS-H	Independent (central)	FAS	MMRM	−2·10 (0·49)	−4·18 (0·49)	−2·08 (0·70)	−3·46 to −0·71	0·0032	0·45
SAPS-D	Independent (central)	FAS	MMRM	−1·12 (0·38)	−2·28 (0·38)	−1·16 (0·54)	−2·22 to −0·10	0·0325	0·33
SAPS-PD ≥20% reduction¶	Independent (central)	FAS	χ² test	47%	63%	17%	2 to 31	0·0242	..
Secondary analyses									
CGI-I	Site investigator	FAS	MMRM	3·45 (0·14)	2·78 (0·14)	−0·67 (0·20)	−1·06 to −0·27	0·0011	0·51
CGI-I responder	Site investigator	FAS	χ² test	26%	49%	23%	9 to 37	0·0015	..
CGI-S	Site investigator	FAS	MMRM	−0·44 (0·12)	−1·02 (0·12)	−0·58 (0·17)	−0·92 to −0·25	0·0007	0·52
Other exploratory efficacy endpoints									
SCOPA-night	Site investigator	FAS	MMRM	−0·49 (0·33)	−1·42 (0·32)	−0·93 (0·46)	−1·84 to −0·02	0·0446	0·31
SCOPA-day wake	Site investigator	FAS	MMRM	−0·99 (0·34)	−2·21 (0·34)	−1·22 (0·48)	−2·17 to −0·27	0·0120	0·39
Caregiver burden	Caregiver	FAS	MMRM	0·40 (0·96)	−3·94 (0·95)	−4·34 (1·35)	−7·00 to −1·67	0·0016	0·50
Caregiver burden (categorical)‖	Caregiver	FAS	CMH	35%	43%	..	..	0·0036	..

SAPS=Scale for assessment of positive symptoms. SAPS-PD=sum of nine item Parkinson's disease-adapted SAPS. FAS=full analysis set (all patients who received ≥1 dose and had SAPS assessment at baseline and ≥1 post-baseline). MMRM=mixed model repeated measures analysis. PP=per protocol. LOCF=last observation carried forward. WOCF=worst observation carried forward. BOCF=baseline observation carried forward. SAPS-H+D=sum of 20 items for hallucinations plus delusions domains. SAPS-H=sum of seven items for hallucinations domain. SAPS-D=sum of 13 items for delusions domain. CGI-I=clinical global impression improvement. CGI-S=clinical global impression severity. SCOPA=scale for outcomes of Parkinson's disease. CMH=Cochran-Mantel-Haenszel. *MMRM refers to MMRM (observed cases) analyses; ANCOVA was used for all LOCF, WOCF, and BOCF imputation methods. †For numerical outcomes, data are least squares means (standard error); for binary outcomes, data are the percentage of individuals who met criteria. ‡Least squares means treatment change is pimavanserin minus placebo. §For select numerical outcomes, effect sizes were estimated as the difference between least squares means multiplied by the square root of ([1/n1]+[1/n2]) and divided by the standard error. ¶This analysis was done post-hoc; individuals with missing SAPS-PD outcome at day 43 are considered as not achieving 20% reduction (missing counted as failures). ‖Four categories exist for caregiver burden; proportions of individuals with little or no burden at day 43 are shown in this table; the p value is based on a CMH row mean score test.

Table 2: Efficacy outcomes

study and included review of concomitant drug use, adverse events, physical examination findings, clinical laboratory measures, vital signs, and electrocardiogram results. Safety oversight included independent clinical and cardiology review of masked data every 3 months.

Statistical analyses

We calculated that a sample size of 200 participants (100 participants per group) would provide 90% power at 5% significance level to detect a 3 point difference in SAPS-PD between groups, assuming an SD of 6·5. We assessed efficacy in a full analysis set of randomly allocated participants who received at least one dose of study drug and had a SAPS assessments at baseline and at least one after baseline. For all efficacy measures, we analysed change from baseline for numerical end-points (observed cases) with the mixed model repeated measures (MMRM) method. The model included fixed categorical effects of treatment (pimavanserin or placebo), visit (days 15, 29, or 43), and treatment-by-visit interaction, and the continuous fixed covariate of baseline score. Missing values were not imputed. We used the χ² test to compare the proportion of CGI-I responders (very much improved or much improved) between groups and also the proportion of individuals with at least 20% improvement in SAPS-PD score. We did a categorical analysis of CBS with a Cochran-Mantel-Haenszel row mean score test, stratified by baseline category.

For change from baseline in UPDRS II and III score at day 43, we tested non-inferiority of pimavanserin versus placebo in the full analysis set with ANCOVA. The non-inferiority margin of 5 was discussed with and agreed by the US Food and Drug Administration (FDA) because it had been defined for Parkinson's disease trials as the

minimal clinically important change in part II and III of UPDRS score. We did descriptive safety analyses on randomised participants who received at least one dose of study drug. We calculated standardised effect sizes with Cohen's *d*. All statistical analysis was done by BDM Consulting (Somerset, NJ, USA) with SAS version 9.3.

This study is registered with ClinicalTrials.gov, number NCT01174004.

Role of the funding source

The study was sponsored and funded by ACADIA Pharmaceuticals. ACADIA designed the study with the input of the authors and other expert advisers, was responsible for study governance, led the statistical analysis, and the authors employed by ACADIA contributed to the writing of the manuscript. All authors had access to full data. JC and CB had final responsibility for the decision to submit for publication.

Results

Between Aug 11, 2010, and Aug 29, 2012, we screened 314 participants, of whom 199 were randomly allocated to treatment and 185 were included in the full analysis set (figure 1). Demographics and clinical characteristics did not differ at baseline (table 1). Mean duration of symptoms of Parkinson's disease psychosis was 30·9 months (SD 30·01) in the pimavanserin group and 36·4 months (39·57) in the placebo group.

In the primary analysis, SAPS-PD scores at day 43 showed a significant improvement in psychosis for pimavanserin compared with placebo (table 2, figure 2). Patients who received pimavanserin had a mean change equating to a 37% improvement from baseline compared with 14% for placebo (table 2; p=0·0006). Pimavanserin also conferred benefit compared with placebo in terms of the full 20 item SAPS-hallucinations plus delusions (H+D) scale and on the separate hallucinations and delusions domains (table 2). Additionally, more patients in the pimavanserin group had a greater than 20% reduction in SAPS-PD scores (table 2). A sensitivity analysis including all randomly allocated patients was consistent with the full analysis set, as were ANCOVA analyses with the last, baseline, or worst observation carried forward (table 2). Additionally, subgroup analyses suggested that treatment with pimavanserin was effective irrespective of age (65–75 years *vs* >75 years), sex, and screening MMSE score (<25 *vs* ≥25; appendix).

Compared with placebo, patients in the pimavanserin group had greater improvements in investigator-assessed measures of antipsychotic benefit, including CGI-S and CGI-I (table 2, figure 2).

In exploratory analyses, caregivers of patients in the pimavanserin group also reported reduction in burden compared with caregivers of patients who received placebo, and participants reported improvements on night-time sleep and daytime wakefulness for pimavanserin compared with placebo (table 2, figure 3)
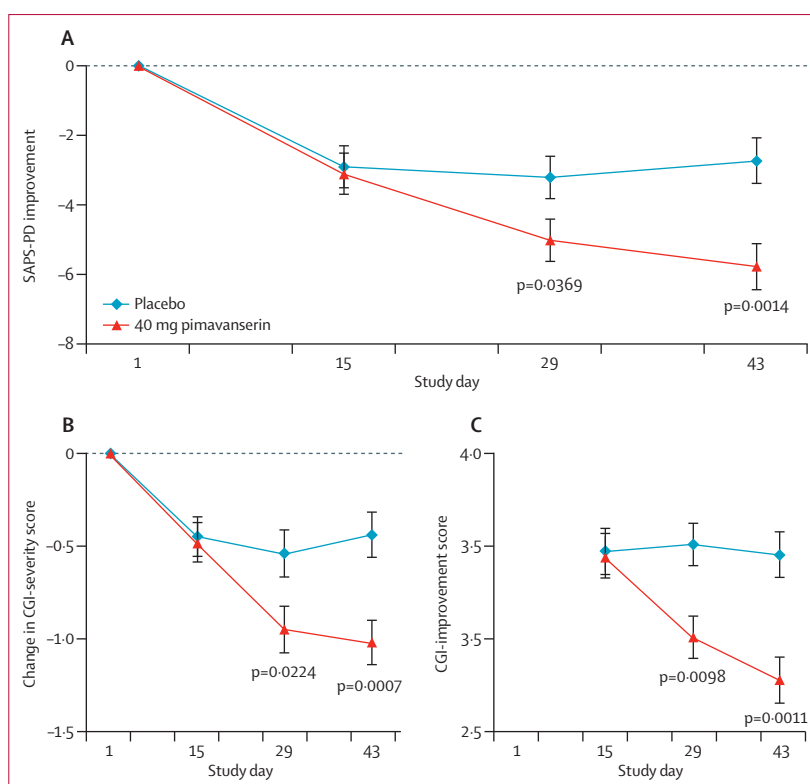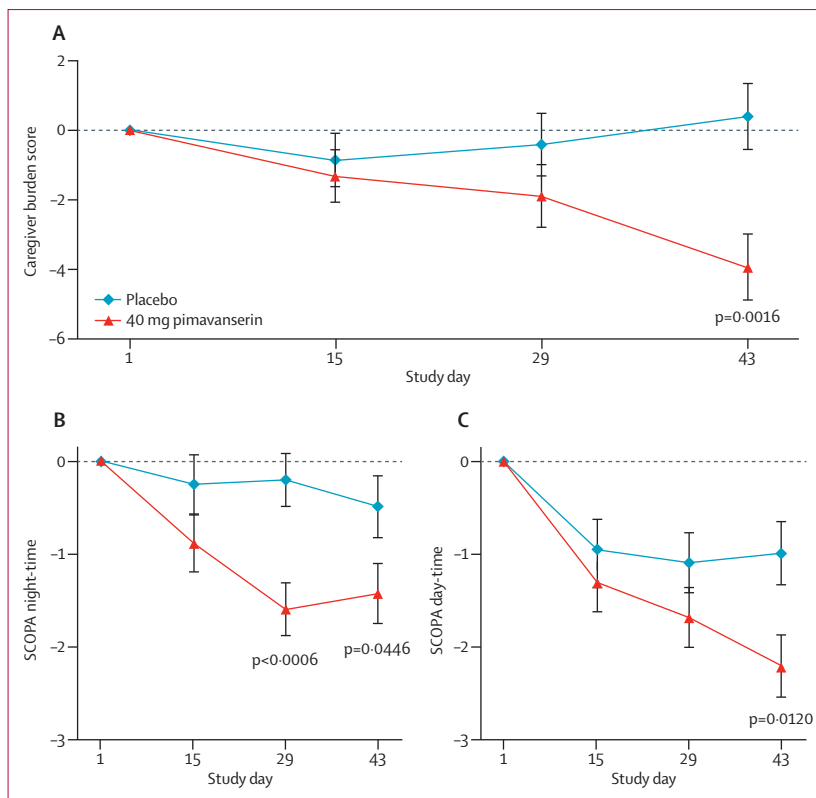

Figure 2: Treatment effects on psychosis severity reduction in the 6 week study period in the full analysis set
The full analysis set includes all patients who received ≥1 dose and had a SAPS assessment at baseline and at least one afterwards. Datapoints show least squares means (standard error). (A) SAPS-PD improvement. (B) Change in CGI-severity score. (C) CGI-improvement scores. SAPS=scale for assessment of positive symptoms. CGI=clinical global impression.

In the safety analyses, we noted no evidence of treatment-related impairment of motor function in either group. We noted small non-significant improvements in motor performance in participants in both groups in terms of UPDRS II and III composite score (–1·69 in the pimavanserin group *vs* –1·40 in the placebo group; 95% CI –2·14 to 2·72) and individual UPDRS II scores (–0·88 *vs* –0·52; –0·66 to 1·24) and UPDRS III scores (–0·86 *vs* –0·80; –2·22 to 0·60).

Table 3 summarises treatment-emergent adverse events occurring in at least 5% of patients in either treatment group. 11 (11%) participants in the pimavanserin group and four (4%) patients in the placebo group had a serious adverse event. Ten patients in the pimavanserin group discontinued because of an adverse event compared with two in the placebo group. Six discontinuations in the pimavanserin group were for psychosis, but we noted no other patterns, and discontinuations did not influence the primary outcome in a sensitivity analysis. Three deaths occurred (one in the placebo group from sudden cardiac death and two in the pimavanserin group from sepsis and septic shock); all were regarded as unrelated to study drug. Laboratory assessments were unremarkable and no safety signals were reported. With pimavanserin, a mean increase of 7·3 ms in QTcB interval from baseline to

See **Online** for appendix

Figure 3: Treatment effects on SCOPA-sleep (night-time sleep and daytime wakefulness measures) and caregiver burden in the full analysis set

The full analysis set includes all patients who received ≥1 dose and had a SAPS assessment at baseline and at least one afterwards. Data are least squares means (standard error), from mixed model repeated measures analysis (observed cases). SCOPA=scale for outcomes of Parkinson's disease. SAPS=scale for assessment of positive symptoms.

	Placebo (n=94)	Pimavanserin 40 mg (n=104)
Nausea	6 (6%)	6 (6%)
Peripheral oedema	3 (3%)	7 (7%)
Urinary tract infection	11 (12%)	14 (13%)
Fall	8 (9%)	11 (11%)
Confusional state	3 (3%)	6 (6%)
Headache	5 (5%)	1 (1%)
Hallucination (including visual)	4 (4%)	7 (7%)

Data are n (%).

Table 3: Treatment-emergent adverse events group in all participants who received ≥1 dose of study drug (occurring in ≥5% in either treatment)

day 43 was reported compared with no change for placebo. No clinical events were associated with this increase.

Discussion

In our study, pimavanserin was able to significantly reduce psychotic symptoms in patients with moderate to severe Parkinson's disease (panel). The 6 week duration is consistent with the accepted precedent for psychosis studies according to the FDA and is longer than most trials of other antipsychotics in Parkinson's disease

psychosis. Notably, efficacy was achieved without worsening parkinsonism and without other tolerability or safety concerns.

Although hallucinations are more common than delusions in Parkinson's disease psychosis, delusions are often a hallmark of more advanced disease and comorbid dementia. Benefits in terms of both symptom types might translate into therapeutic advantages relevant to long-term disease progression. The effect sizes we noted suggest that the magnitude of benefit of pimavanserin is clinically meaningful,[30] which is further supported by the consistency of results across datasets, subgroups, and sensitivity analyses. This suggestion is reinforced by the improvements noted in global measures of psychosis and reduction of caregiver burden. Our three main outcome measures provide independent support for the clinical benefits of pimavanserin treatment as each was assessed by a different person, who was masked to other findings: centralised independent raters assessed SAPS-PD, experienced site-based raters assessed CGI, and caregivers assessed CBS. Improvement on night-time sleep without increasing daytime sedation is consistent with the 5-HT2A mechanism and previous trial data[31] and suggests additional benefit for people with Parkinson's disease who commonly have sleep disturbances and excessive daytime somnolence. SAPS-PD scores were strongly correlated with CGI-I scores (Spearman's r 0·6, 95% CI 0·5–0·7) and CGI-S scores (0·5, 0·4–0·6), whereas improvements in sleep and psychosis were not ($r<0·2$), suggesting improvement in sleep was an independent effect of treatment. Caregiver burden score did not strongly correlate with psychosis ($r<0·3$), or sleep ($r<0·1$) suggesting that a broader range of effects might have contributed to the benefit noted. In view of the established link between Parkinson's disease psychosis and nursing-home placement, improving caregiver burden could have important benefits for patients.

The antipsychotic benefits reported with pimavanserin are smaller in magnitude than were those reported with clozapine. However, the clozapine trials were small and undertaken in patients with more advanced Parkinson's disease psychosis. Therefore, comparisons with pimavanserin should be interpreted cautiously. Furthermore, safety concerns and monitoring requirements have meant that in practice few patients receive clozapine treatment.

Consistent with previous studies, pimavanserin was well tolerated in our study. Although we noted an increase in discontinuation because of adverse events in the pimavanserin group compared with placebo, the number of patients who dropped out was low compared with other reported studies in Parkinson's disease psychosis and similar neuropsychiatric conditions. More patients dropped out of the pimavanserin group than the placebo group because of a psychotic disorder or hallucination. Four of six discontinuations occurred within 10 days of start of the study drug (and before

steady state). Four occurred in participants in both groups who had been washed out of a previous antipsychotic before baseline. No similar pattern of discontinuations has occurred in previous studies of pimavanserin. Three deaths occurred, none of which was ascribed to study medication. The only sudden death occurred in a patient who received placebo. The most common adverse events were urinary tract infections and falls, which are common in the population, and incidence did not differ between groups. A small but clear increase in QT interval without association to cardiac adverse events was noted in the pimavanserin group. Motor control improved slightly and to the same extent in both groups. We noted no evidence of increased sedation or drowsiness in either group.

Major concerns associated with use of antipsychotics in Parkinson's disease include exacerbation of motor symptoms and severe neuroleptic sensitivity reactions. Antipsychotics also raise safety concerns even with short-term use because they are associated with severe adverse outcomes, including a 1·5–1·8 times increased risk of mortality, stroke, and pulmonary embolism, and accelerated cognitive decline. However, we did not note these outcomes in this short study of pimavanserin.

Our sample size provided a well powered study with robust outcomes. Although the study did not reach the planned sample size, the strongly significant outcomes mitigates this issue and removes any concern about type II error (failure to reject null hypothesis). Furthermore, although the power calculation was based on a *t* test, the final analysis was done with a MMRM method that uses repeated correlated measurements, and would therefore provide higher power. The use of BPST-PD and other methodological techniques might have been effective in moderating the placebo response, which has been a confounding issue in previous studies. The consistency of multiple sensitivity analyses reinforces the robustness of the primary outcome. Internal validity was supported across different measures and done by independent raters, each masked to the other study data. The 6 week duration was adequate to show efficacy and is longer than most previous randomised controlled trials in Parkinson's disease psychosis. In view of the distressing nature of symptoms of Parkinson's disease psychosis, treatment benefit needs to be conferred within this timeframe and maintenance of patients in a placebo-controlled trial for longer would be complex. However, a limitation of our study is that it does not provide safety data or evidence regarding durability of response beyond 6 weeks. The modest duration of our trial also restricts our ability to capture longer-term benefits such as reduced nursing home admission that might arise from symptom improvement and reduced caregiver burden. The usefulness of pimavanserin for chronic use in Parkinson's disease psychosis is supported by ongoing open-label safety studies, in which the longest duration of treatment is more than 8 years and total exposure exceeds 700 patient-years.

Panel: Research in context

Systematic review

Parkinson's disease psychosis, which includes hallucinations and delusions, is frequent and debilitating in people with Parkinson's disease. We searched PubMed and Medline electronic databases for articles published in English after Jan 1, 1990, with the search terms "Parkinson's", "psychosis", "antipsychotic" AND "clinical trial". This search identified several key publications including five randomised controlled trials of quetiapine, of which the four largest reported no efficacy, and three of clozapine, which reported the most significant benefit (Cohen's *d* >0·8). Importantly, all previous trials of existing typical and atypical antipsychotics report high levels of adverse events, which are well established throughout the published work.

Interpretation

In our trial, the first in a new class of selective 5-HT2A inverse agonists, pimavanserin, was efficacious for treatment of Parkinson's disease psychosis. We showed benefit to symptoms of psychosis through three independently measured outcomes, in addition to secondary outcomes including sleep and caregiver burden. These data support the notion that this drug confers clinically significant benefit within a timescale that is relevant and meaningful to the context of the disorder. It shows that pimavanserin is a viable alternative for the treatment of psychosis in Parkinson's disease, in which previously the only available option was the use of unlicensed atypical antipsychotics with an unknown efficacy and safety profile. By comparison with other antipsychotics, pimavanserin's treatment effects were not associated with exacerbation of motor disability, sedation, or other safety challenges. In view of the success of this drug in this group of patients, assessment of its effectiveness in other groups where psychosis will be important, especially in Alzheimer's disease and other dementias. This study also emphasises the importance and urgency of development of better treatment options for behavioural and psychological symptoms to remove the dependency on antipsychotic drugs. Additionally, this study supports the use of a non-pharmacological lead-in stage to reduce placebo response, and this approach should be considered for future trials of this type.

These data suggest continued tolerability and long-term safety and suggest potential durability of response.

Psychotic symptoms are frequent, burdensome, and distressing in people with Parkinson's disease, posing a major challenge to clinical management because no safe and effective therapies exist. Our 6 week randomised-controlled trial suggests that pimavanserin is efficacious compared with placebo in Parkinson's disease psychosis, showing clinically meaningful improvements within a practical timescale for clinical utility. Benefits on sleep and caregiver burden suggest a broader effect on well-being of patients. Across measures, benefits were reported by masked central raters, experienced site raters masked to centrally assessed SAPS-PD scores, family caregivers, and the study participants themselves. This robust approach confirms the integrity and relevance of the findings. By comparison with other antipsychotics, pimavanserin's treatment effects were not associated with exacerbation of motor disability, sedation, or other safety challenges. As a selective 5-HT2A inverse agonist, pimavanserin is to our knowledge the first in a new class of therapeutic agents able to confer antipsychotic benefit in Parkinson's disease psychosis without unnecessary receptor activity that compromises safety and tolerability.

References

1 Parkinson's Disease Foundation. Statistics on Parkinson's. http://www.pdf.org/en/parkinson_statistics (accessed April 16, 2013).

2 Starkstein SE, Brockman S, Hayhow BD. Psychiatric syndromes in Parkinson's disease. *Curr Opin Psychiatry* 2012; **25:** 468–72.

3 Aarsland D, Ballard C, Larsen JP, McKeith I. A comparative study of psychiatric symptoms in dementia with Lewy bodies and Parkinson's disease with and without dementia. *Int J Geriatr Psychiatry* 2001; **16:** 528–36.

4 Fernandez HH, Okun MS, Rodriguez RL, et al. Quetiapine improves visual hallucinations in Parkinson disease but not through normalization of sleep architecture: results from a double-blind clinical-polysomnography study. *Int J Neurosci* 2009; **119:** 2196–205.

5 Ondo WG, Tintner R, Voung KD, Lai D, Ringholz G. Double-blind, placebo-controlled, unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease. *Mov Disord* 2005; **20:** 958–63.

6 Rabey JM, Prokhorov T, Miniovitz A, Dobronevsky E, Klein C. Effect of quetiapine in psychotic Parkinson's disease patients: a double-blind labeled study of 3 months' duration. *Mov Disord* 2007; **22:** 313–18.

7 Shotbolt P, Samuel M, Fox C, David AS. A randomized controlled trial of quetiapine for psychosis in Parkinson's disease. *Neuropsychiatr Dis Treat* 2009; **5:** 327–32.

8 Kurlan R, Cummings J, Raman R, Thal L, and the Alzheimer's Disease Cooperative Study Group. Quetiapine for agitation or psychosis in patients with dementia and parkinsonism. *Neurology* 2007; **68:** 1356–63.

9 The Parkinson Study Group. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. *N Engl J Med* 1999; **340:** 757–63.

10 The French Clozapine Parkinson Study Group. Clozapine in drug-induced psychosis in Parkinson's disease. *Lancet* 1999; **353:** 2041–42.

11 Pollak P, Tison F, Rascol O, et al. Clozapine in drug induced psychosis in Parkinson's disease: a randomised, placebo controlled study with open follow up. *J Neurol Neurosurg Psychiatry* 2004; **75:** 689–95.

12 Vanover KE, Weiner DM, Makhay M, et al. Pharmacological and behavioral profile of N-(4-fluorophenylmethyl)-N-(1-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy)phenylmethyl) carbamide (2R,3R)-dihydroxybutanedioate (2:1) (ACP-103), a novel 5-hydroxytryptamine(2A) receptor inverse agonist. *J Pharmacol Exp Ther* 2006; **317:** 910–18.

13 Ballanger B, Strafella AP, van Eimeren T, et al. Serotonin 2A receptors and visual hallucinations in Parkinson disease. *Arch Neurol* 2010; **67:** 416–21.

14 Creese B, Ballard C, Aarsland D, Londos E, Sharp S, Jones E. Determining the association of the *5HTTLPR* polymorphism with delusions and hallucinations in Lewy body dementias. *Am J Geriatr Psychiatry* 2013; published online April 9. DOI:10.1016/j.jagp.2012.11.001.

15 Dombrovski AY, Mulsant BH, Ferrell RE, et al. Serotonin transporter triallelic genotype and response to citalopram and risperidone in dementia with behavioral symptoms. *Int Clin Psychopharmacol* 2010; **25:** 37–45.

16 Harvey L, Reid RE, Ma C, Knight PJ, Pfeifer TA, Grigliatti TA. Human genetic variations in the 5HT2A receptor: a single nucleotide polymorphism identified with altered response to clozapine. *Pharmacogenetics* 2003; **13:** 107–18.

17 Reynolds GP, Templeman LA, Zhang ZJ. The role of 5-HT2C receptor polymorphisms in the pharmacogenetics of antipsychotic drug treatment. *Prog Neuropsychopharmacol Biol Psychiatry* 2005; **29:** 1021–28.

18 Proitsi P, Lupton MK, Reeves SJ, et al. Association of serotonin and dopamine gene pathways with behavioral subphenotypes in dementia. *Neurobiol Aging* 2012; **33:** 791–803.

19 Meltzer HY, Mills R, Revell S, et al. Pimavanserin, a serotonin(2A) receptor inverse agonist, for the treatment of Parkinson's disease psychosis. *Neuropsychopharmacology* 2010; **35:** 881–92.

20 Friedman JH, Ravina B, Mills R, et al. A multicenter, placebo controlled, double blind trial to examine the safety and efficacy of pimavanserin in the treatment of psychosis in Parkinson's disease. *Neurology* 2010; **77:** abstr 1.

21 Ravina B, Marder K, Fernandez HH, et al. Diagnostic criteria for psychosis in Parkinson's disease: report of an NINDS, NIMH work group. *Mov Disord* 2007; **22:** 1061–68.

22 Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992; **55:** 181–84.

23 Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 1994; **44:** 2308–14.

24 Ballard C, Brown R, Fossey J, et al. Brief psychosocial therapy for the treatment of agitation in Alzheimer disease (the CALM-AD trial). *Am J Geriatr Psychiatry* 2009; **17:** 726–33.

25 Andreason N. Scale for the assessment of positive symptoms. Iowa City, IA: University of Iowa, 1984.

26 Voss T, Bahr D, Cummings J, Mills R, Ravina B, Williams H. Performance of a shortened Scale for Assessment of Positive Symptoms for Parkinson's disease psychosis. *Parkinsonism Relat Disord* 2013; **19:** 295–99.

27 Guy W. ECDEU assessment manual for psychopharmacology—revised (DHEW Publ No ADM 76-338). Rockville, MD: Department of Health, Education, and Welfare Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs, 1976: 218–22.

28 Marinus J, Visser M, van Hilten JJ, Lammers GJ, Stiggelbout AM. Assessment of sleep and sleepiness in Parkinson disease. *Sleep* 2003; **26:** 1049–54.

29 Fahn S, Elton RL, and the Members of the UPDRS Development Committee. Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Calne DB, Lieberman A, eds. Recent developments in Parkinson's disease. Florham Park, NJ: Macmillan Health Care Information, 1987: 153–63.

30 Howard R, Phillips P, Johnson T, et al. Determining the minimum clinically important differences for outcomes in the DOMINO trial. *Int J Geriatr Psychiatry* 2011; **26:** 812–17.

31 Ancoli-Israel S, Vanover KE, Weiner DM, Davis RE, van Kammen DP. Pimavanserin tartrate, a 5-HT(2A) receptor inverse agonist, increases slow wave sleep as measured by polysomnography in healthy adult volunteers. *Sleep Med* 2011; **12:** 134–41.