ORIGINAL ARTICLE

Trial of Pimavanserin in Dementia-Related Psychosis

Pierre N. Tariot, M.D., Jeffrey L. Cummings, M.D., Sc.D., Maria E. Soto-Martin, M.D., Ph.D., Clive Ballard, M.D., Deniz Erten-Lyons, M.D., David L. Sultzer, M.D., Davangere P. Devanand, M.D., Daniel Weintraub, M.D., Bradley McEvoy, Dr.P.H., James M. Youakim, M.D., Srdjan Stankovic, M.D., M.S.P.H., and Erin P. Foff, M.D., Ph.D.

ABSTRACT

BACKGROUND

Patients with dementia due to neurodegenerative disease can have dementia-related psychosis. The effects of the oral 5-HT_{2A} inverse agonist and antagonist pimavanserin on psychosis related to various causes of dementia are not clear.

METHODS

We conducted a phase 3, double-blind, randomized, placebo-controlled discontinuation trial involving patients with psychosis related to Alzheimer's disease, Parkinson's disease dementia, dementia with Lewy bodies, frontotemporal dementia, or vascular dementia. Patients received open-label pimavanserin for 12 weeks. Those who had a reduction from baseline of at least 30% in the score on the Scale for the Assessment of Positive Symptoms–Hallucinations and Delusions (SAPS–H+D, with higher scores indicating greater psychosis) and a Clinical Global Impression–Improvement (CGI-I) score of 1 (very much improved) or 2 (much improved) at weeks 8 and 12 were randomly assigned in a 1:1 ratio to continue receiving pimavanserin or to receive placebo for up to 26 weeks. The primary end point, assessed in a time-to-event analysis, was a relapse of psychosis as defined by any of the following: an increase of at least 30% in the SAPS–H+D score and a CGI-I score of 6 (much worse) or 7 (very much worse), hospitalization for dementia-related psychosis, stopping of the trial regimen or withdrawal from the trial for lack of efficacy, or use of antipsychotic agents for dementia-related psychosis.

RESULTS

Of the 392 patients in the open-label phase, 41 were withdrawn for administrative reasons because the trial was stopped for efficacy; of the remaining 351 patients, 217 (61.8%) had a sustained response, of whom 105 were assigned to receive pimavanserin and 112 to receive placebo. A relapse occurred in 12 of 95 patients (13%) in the pimavanserin group and in 28 of 99 (28%) in the placebo group (hazard ratio, 0.35; 95% confidence interval, 0.17 to 0.73; P=0.005). During the double-blind phase, adverse events occurred in 43 of 105 patients (41.0%) in the pimavanserin group and in 41 of 112 (36.6%) in the placebo group. Headache, constipation, urinary tract infection, and asymptomatic QT prolongation occurred with pimavanserin.

CONCLUSIONS

In a trial that was stopped early for efficacy, patients with dementia-related psychosis who had a response to pimavanserin had a lower risk of relapse with continuation of the drug than with discontinuation. Longer and larger trials are required to determine the effects of pimavanserin in dementia-related psychosis. (Funded by Acadia Pharmaceuticals; HARMONY ClinicalTrials.gov number, NCT03325556.)

From Banner Alzheimer's Institute and University of Arizona College of Medicine, Phoenix (P.N.T.); Chambers-Grundy Center for Transformative Neuroscience, Department of Brain Health, School of Integrated Health Sciences, University of Nevada, Las Vegas, Las Vegas (J.L.C.); Gérontopôle Alzheimer Clinical and Research Center, Centre Hospitalier Universitaire de Toulouse, Geriatric Department, Maintain Functions and Intrinsic Capacities with Aging Research Team, Center for Epidemiology and Population Health Research, INSERM, Université Paul Sabatier, Toulouse, France (M.E.S.-M.); University of Exeter School of Medicine, Exeter, United Kingdom (C.B.); the Department of Neurology, Oregon Health and Sciences University, Portland (D.E.-L.); the Department of Psychiatry and Human Behavior and the Institute for Memory Impairments and Neurological Disorders, University of California, Irvine, Irvine (D.L.S.), and Acadia Pharmaceuticals, San Diego (B.M., J.M.Y., S.S., E.P.F.) — both in California; the Department of Psychiatry, Columbia University Irving Medical Center, New York (D.P.D.); and Perelman School of Medicine at the University of Pennsylvania, Philadelphia (D.W.). Address reprint requests to Publications–Reprints, Clinical Development, Acadia Pharmaceuticals, 502 Carnegie Center, Suite 300, Princeton, NJ 08540, or to Dr. Foff at erin.foff@acadia-pharm.com.

A complete list of investigators and collaborators in the HARMONY trial is provided in the Supplementary Appendix, available at NEJM.org.

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The most common causes of dementia — Alzheimer's disease, dementia with Lewy bodies, Parkinson's disease dementia, vascular dementia, and frontotemporal dementia[1] — may be associated with hallucinations and delusions.[2,3] This syndrome of dementia-related psychosis causes behavioral disturbances, increased caregiver burden, decreased quality of life, nursing home placement, and more rapid cognitive decline.[4-7] Typical and atypical antipsychotic agents are used off-label to manage psychotic symptoms,[8] regardless of underlying dementia subtype, and are used cautiously in patients with dementia with Lewy bodies owing to the risk of worsening parkinsonism and other side effects. Antipsychotics may have modest short-term efficacy for dementia-related psychosis[9-13] but may be associated with worsening cognition, extrapyramidal effects, sedation, falls, and metabolic abnormalities. Labels for these drugs include a warning for increased risk of death among elderly patients. This situation has contributed to clinical guidelines that focus on minimizing the use of antipsychotics, discontinuing treatment when improvement is not observed, and reassessing continued use after initial improvement.[3]

Pimavanserin is a serotonin-receptor modulator that acts primarily as a selective 5-hydroxytryptamine receptor subtype 2A (5-HT_{2A}) inverse agonist and antagonist, with lesser activity at 5-HT_{2C} and no appreciable activity at other receptors in vitro. This profile is different from those of conventional antipsychotics, which bind to D2 dopamine receptors and have varying activity at other receptors, including at histaminergic and muscarinic receptors.[14]

In a 6-week trial of pimavanserin for the treatment of hallucinations and delusions associated with Parkinson's disease–related psychosis,[15] a subgroup of patients with cognitive impairment had a change from baseline in the psychosis score with pimavanserin that was better than the change observed in cognitively unimpaired patients.[16] In a brief, double-blind, placebo-controlled trial involving patients with possible or probable Alzheimer's disease–related psychosis, more than half of whom also had cerebrovascular disease, pimavanserin resulted in a larger effect in patients with more severe psychosis.[17]

On the basis of these preliminary findings in patients with psychosis due to Parkinson's disease or Alzheimer's disease, the current HARMONY trial was initiated as a phase 3, randomized discontinuation trial of the safety and efficacy of pimavanserin for the treatment of delusions and hallucinations associated with several common forms of dementia. The randomized discontinuation design has been used in a trial of risperidone involving patients with Alzheimer's disease and behavioral complications.[18] This design addresses the question of whether treatment with pimavanserin would confer sustained benefits with respect to psychosis in patients with an initial response to the drug; the design also translates to decisions about medication discontinuation and minimizes exposure to ineffective therapy.

Methods

Trial Design and Oversight

The trial was conducted at 101 clinical sites in North America, eastern and western Europe, and Latin America from August 2017 through October 2019. The trial included a 5-week screening period, a 12-week open-label period, a double-blind treatment period of up to 26 weeks, and a 4-week safety follow-up period (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). During screening, patients received brief psychosocial therapy,[19] a simple psychological therapy tailored to each patient and partner to encourage frequent social interaction and engagement in activities of interest. This technique was used to follow best practices that encourage initiation of nonpharmacologic intervention for dementia and psychosis and to ensure that only patients with persistent psychosis that warranted pharmacologic treatment were enrolled.

Open-label treatment was initiated with pimavanserin at a dose of 34 mg once daily; dose reduction to 20 mg daily on the basis of side effects was permitted from weeks 1 to 4, after which the dose remained fixed for the remainder of the open-label phase. Patients who met prespecified criteria for treatment response were randomly assigned to continue receiving pimavanserin at their final open-label dose or to receive placebo and were regularly evaluated for relapse of psychosis. Identical tablets and packaging were provided for pimavanserin and placebo.

A pregenerated permuted-block schedule was used to randomly assign patients in a 1:1 ratio

to receive pimavanserin or placebo, with stratification according to dementia subtype (Alzheimer's disease or frontotemporal dementia vs. vascular dementia vs. Parkinson's disease dementia or dementia with Lewy bodies) and geographic region. The investigators and site staff, who assessed clinical responses; the members of the adjudication committee, who determined whether the criteria for protocol-defined relapse were met; and sponsor personnel were unaware of the trial-group assignments.

The trial protocol (available at NEJM.org) was approved by an independent ethics committee or institutional review board at each trial site and implemented following the principles of Good Clinical Practice derived from the Declaration of Helsinki and in accordance with local regulations and International Council for Harmonisation guidelines. All the patients or their authorized representatives provided written informed consent before any trial procedures.

The sponsor, Acadia Pharmaceuticals, designed and conducted the trial, provided the active drug and placebo, and performed the statistical analysis. All the authors vouch for the completeness and accuracy of the data, for the complete reporting of adverse events, and for the fidelity of the trial to the protocol. The first draft of the manuscript was written primarily by the last author, with assistance from a medical writer who was paid by the sponsor. There were confidentiality agreements in place between the authors and the sponsor, but there were no restrictions on the academic authors in submitting the trial results for publication.

PATIENTS

Adults 50 to 90 years of age were eligible if they met criteria for dementia (National Institute on Aging–Alzheimer's Association[20]) and met clinical criteria for one or more of the following: Parkinson's disease dementia,[21] dementia with Lewy bodies,[22] possible or probable Alzheimer's disease,[20] frontotemporal dementia,[23] or vascular dementia.[24] Patients were required to have a score of 6 to 24 on the Mini–Mental State Examination (MMSE; range, 0 to 30; with higher scores indicating better performance),[25] psychotic symptoms for at least 2 months, and a care partner who was able to reliably report patient symptoms. At screening and baseline, patients were required to have a total score on the Scale for the Assessment of Positive Symptoms (SAPS)–Hallucinations and Delusions (SAPS–H+D) of 10 or more,[26] a SAPS–H+D global rating subscore of 4 or more, and a Clinical Global Impression–Severity (CGI-S)[27] score of 4 or more (range, 1 to 7, with higher scores indicating greater impairment). The SAPS–H+D is a subset of the SAPS, which was devised for the assessment of schizophrenia symptoms; the range is 0 to 100, and the scale contains 7 hallucination items (6 individual items and 1 global item) and 13 delusion items (12 individual items and 1 global item), each with a range of 0 to 5 and with higher scores indicating more severe symptoms.[26] Patients who were receiving an acetylcholinesterase inhibitor or memantine had to be receiving a stable dose for 12 weeks before screening, and the use of antipsychotics was prohibited for 2 weeks or five half-lives before baseline and during the trial. Full eligibility criteria are provided in the protocol.

TRIAL ASSESSMENTS

The SAPS–H+D and CGI-S scores were assessed at each clinic visit in the open-label and double-blind phases. In the double-blind phase, clinic visits were at weeks 13, 14, 16, 18, 22, 26, 30, 34, and 38. Physical and neurologic examination with vital signs, clinical laboratory testing, and 12-lead electrocardiography were performed at screening and during the open-label and double-blind phases (Fig. S1). The MMSE and Global Clinician Assessment of Suicidality were conducted at each clinic visit, and the score on the Extrapyramidal Symptom Rating Scale–Abbreviated (ESRS-A; range, 0 to 120, with higher scores indicating greater motor dysfunction)[28] was assessed at baseline, week 12 of the open-label phase, and at each visit during the double-blind phase.

Response criteria were assessed at weeks 8 and 12 of the open-label phase, and response was required at both visits in order for the patient to proceed in the trial; thus, the week 12 population was enriched with patients who had a response to pimavanserin. Response was defined as both a reduction (improvement) from baseline of at least 30% in the SAPS–H+D total score and a CGI–Improvement (CGI-I) score[27] of 1 (very much improved) or 2 (much improved) relative to baseline at both weeks 8 and 12. Patients who met these criteria entered the double-blind phase. Assessment for relapse occurred throughout the double-blind phase. Discontinuations in the

double-blind phase were adjudicated by an independent committee to determine whether the criteria for protocol-defined relapse were met.

END POINTS

The primary end point was the time from randomization to relapse of psychosis, as defined as one or more of the following: an increase from baseline (double-blind phase) of at least 30% in the SAPS–H+D total score and a CGI-I score of 6 (much worse) or 7 (very much worse), hospitalization due to dementia-related psychosis, stopping the trial regimen or withdrawal from the trial owing to lack of efficacy, or the use of other antipsychotics for the treatment of dementia-related psychosis. The data and safety monitoring board interrogated the data at the interim analysis to determine whether prespecified efficacy stopping criteria had been met.

The secondary end point was the time from randomization to trial discontinuation for any reason. Exploratory end points included the CGI-I score and the change from baseline in the double-blind phase in scores on the following scales: SAPS–H+D, SAPS–Hallucinations (SAPS-H), SAPS–Delusions (SAPS-D), CGI-S, Zarit Burden Interview, Karolinska Sleepiness Scale, and EuroQol Group 5-Dimension 5-Level questionnaire. (Details on these scales are provided in Section 6.2 in the protocol.)

STATISTICAL ANALYSIS

The sample-size calculation assumed 75 post-randomization relapse events on the basis of an assumed hazard ratio of 0.47, an overall two-sided alpha level of 0.05, a power of 90%, and use of the O'Brien–Fleming stopping boundary for a single interim analysis. A two-sided P value of 0.0066 for the hazard ratio for the between-group difference in time to relapse was established as the value that justified stopping the trial at the interim analysis.

The primary efficacy analysis was based on the intention-to-treat population, defined as all the patients who underwent randomization. The time from randomization to relapse in the double-blind phase was compared between trial groups with the use of a Cox regression model with covariates for trial-group assignment, dementia strata, and geographic region and with a robust sandwich variance–type estimator.[29] We tested the assumptions of the primary analysis with the use of a global goodness-of-fit test based on Schoenfeld residuals. There was no evidence that the assumptions were violated for the primary and key secondary end points. Data for patients who did not have a relapse event were censored at the time of their last assessment before the date of data cutoff for the interim analysis. The secondary end point, time to trial discontinuation for any reason, was tested at the same alpha level and analyzed with the use of the Cox regression model as described for the primary end point. A hierarchical testing procedure was used to control the overall type I error rate for the primary and secondary end points at a significance level of $P<0.0066$ for each step. There was no plan for imputation of missing data; however, a sensitivity analysis was planned to investigate the assumption of noninformative censoring for the primary efficacy end point that imputed possible outcomes for the patients who had discontinued participation in the trial without having had a relapse, as well as additional sensitivity analyses that included events up to trial discontinuation and the end of the trial. The statistical analysis plan is available with the protocol at NEJM.org.

RESULTS

OPEN-LABEL PHASE

A total of 794 patients were screened during approximately 24 months of trial enrollment (Fig. 1), and 392 patients were enrolled in the open-label phase. The distribution of dementia diagnoses was as follows: 66.3% of the patients had Alzheimer's disease, 15.1% had Parkinson's disease dementia, 9.7% had vascular dementia, 7.1% had dementia with Lewy bodies, and 1.8% had frontotemporal dementia. The mean (±SD) age of the enrolled patients was 74.5±8.3 years, the mean duration of cognitive impairment was 4.3±2.8 years, 95.2% of the patients were living at home (Table 1), and 81.6% had both delusions and hallucinations at baseline. The mean MMSE score was 16.7±4.7. The mean baseline SAPS–H+D score was 24.4±9.2, and the mean CGI-S score for psychosis was 4.7±0.7, consistent with moderate psychosis. A total of 46.4% of the pa-

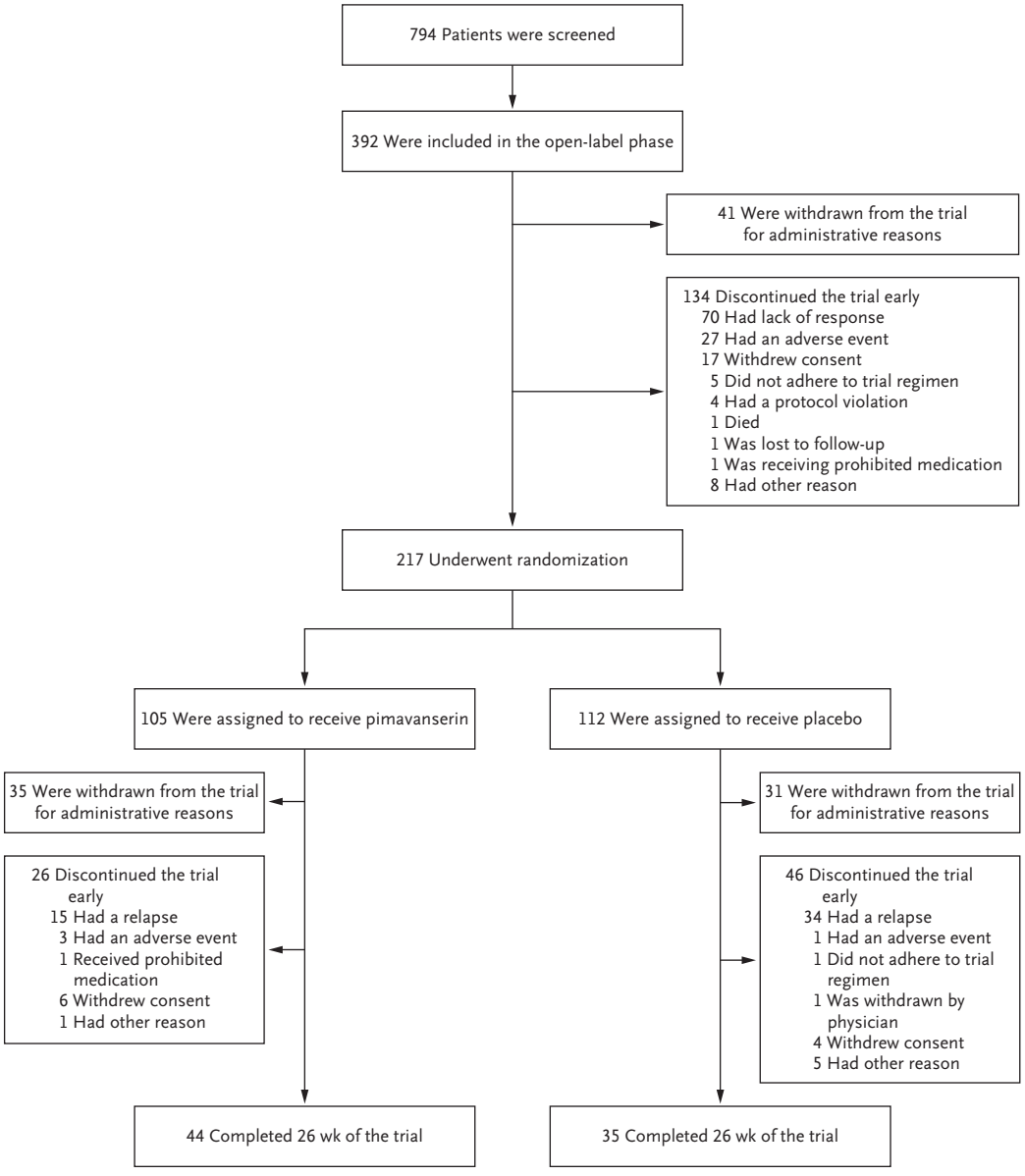

Figure 1. Screening, Randomization, and Follow-up.

Reasons for screening failure included (in order of frequency) criteria for severity of psychosis not being met, electrocardiographic criteria not being met, laboratory exclusions, criteria for Mini–Mental State Examination score not being met, other reasons, withdrawal of consent during screening period, investigator or medical monitor judgment, use of prohibited medication, and other inclusion criteria not being met or exclusion criteria being met. Formal response criteria were assessed at weeks 8 and 12 of the open-label phase. Patients who did not meet the full response criteria at either of those visits were withdrawn from the trial, according to the protocol, and entered the safety follow-up period. Administrative withdrawal of patients occurred when patients were ongoing in the open-label or double-blind phase at the time of the interim analysis and trial termination for positive efficacy. Because 41 patients were withdrawn for administrative reasons before being permitted to reach week 8, week 12, or both in the trial, only 351 patients were eligible to undergo randomization.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Open-Label Phase†	Double-Blind Phase	
	Pimavanserin (N=392)	Pimavanserin (N=105)	Placebo (N=112)
Age — yr			
Mean	74.5±8.3	73.8±8.4	74.9±8.6
Range	52–90	53–89	52–90
Female sex — no. (%)	229 (58.4)	62 (59.0)	69 (61.6)
White race — no./total no. (%)‡	371/384 (96.6)	103/105 (98.1)	107/109 (98.2)
Hispanic or Latino ethnic group — no./total no. (%)‡	86/384 (22.4)	25/105 (23.8)	26/109 (23.9)
Living at home — no. (%)	373 (95.2)	94 (89.5)	109 (97.3)
Age at onset of cognitive impairment — yr	70.6±8.9	70.1±9.1	71.2±9.2
Duration of cognitive impairment — yr	4.3±2.8	4.2±2.2	4.2±3.1
History of psychotic symptoms — no./total no. (%)			
Auditory hallucinations	287/382 (75.1)	81/101 (80.2)	92/111 (82.9)
Visual hallucinations	302/382 (79.1)	77/101 (76.2)	92/111 (82.9)
Delusions	319/382 (83.5)	77/101 (76.2)	96/111 (86.5)
Primary dementia subtype — no. (%)			
Alzheimer's disease	260 (66.3)	67 (63.8)	70 (62.5)
Dementia with Lewy bodies	28 (7.1)	6 (5.7)	4 (3.6)
Frontotemporal dementia	7 (1.8)	1 (1.0)	2 (1.8)
Parkinson's disease dementia	59 (15.1)	19 (18.1)	23 (20.5)
Vascular dementia	38 (9.7)	12 (11.4)	13 (11.6)
Geographic region — no. (%)			
North America	118 (30.1)	28 (26.7)	29 (25.9)
Latin America	27 (6.9)	7 (6.7)	9 (8.0)
Eastern Europe	209 (53.3)	65 (61.9)	67 (59.8)
Western Europe	38 (9.7)	5 (4.8)	7 (6.2)
Antidementia drug use — no. (%)§			
Any	273 (69.6)	81 (77.1)	72 (64.3)
Acetylcholinesterase inhibitor	172 (43.9)	49 (46.7)	42 (37.5)
Antidepressant use — no. (%)	81 (20.7)	14 (13.3)	23 (20.5)
MMSE total score¶	16.7±4.7	18.3±5.4	17.9±5.9
SAPS–H+D score‖	24.4±9.2	5.0±5.3	5.2±5.4
CGI-S score**	4.7±0.7	2.3±1.0	2.3±1.0

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.

† The patients who did not undergo randomization had several reasons for not doing so, including 41 patients who were withdrawn for administrative reasons at the time of trial discontinuation and who were therefore not given the opportunity to complete the open-label phase. The 175 patients who did not undergo randomization, in aggregate, had the following characteristics: female sex, 56.0%; mean (±SD) age, 74.6±8.0; White race, 94.7%; mean (±SE) score on the Mini–Mental State Examination (MMSE) (described below), 16.5±5.1; and mean (±SE) score on the Scale for the Assessment of Positive Symptoms–Hallucinations and Delusions (SAPS–H+D) (described below), 23.1±8.7.

‡ Race and ethnic group were determined by site staff or by the patient or care partner.

§ Antidementia drugs included acetylcholinesterase inhibitors, memantine, or both. The use of an acetylcholinesterase inhibitor alone or in a combination pill is noted as a subcategory.

¶ The MMSE is a brief 30-point questionnaire that is used to quantitatively assess cognition.[25] Scores range from 0 to 30, with higher scores indicating higher performance.

‖ The SAPS–H+D consists of 20 items, including 7 hallucination items (6 individual items and 1 global item) and 13 delusion items (12 individual items and 1 global item). Scores on each item range from 0 to 5 (total scores range from 0 to 100, with higher scores indicating a greater degree of psychosis).

** The Clinical Global Impression–Severity (CGI-S) scale is a clinician-rated, 7-point scale that is designed to rate the severity of the patient's hallucinations and delusions at the time of assessment using the investigator's judgment and past experience with patients who have the same disorder (i.e., dementia-related psychosis).[27] Scores range from 1 to 7, with higher scores indicating greater impairment.

tients were taking at least five concomitant medications, and 46.9% had at least five coexisting medical conditions.

Pimavanserin at a dose of 20 mg was administered to 31 of 392 patients (7.9%) in the open-label phase, and the 34-mg dose was administered to the other patients. A total of 41 patients remained in the open-label portion of the trial at the time of trial discontinuation and were withdrawn for administrative reasons. Of 351 remaining eligible patients, 217 (61.8%) had a sustained response and were randomly assigned to continue receiving pimavanserin or to receive placebo. A total of 70 patients (19.9%) did not meet the criteria for a response at week 8, week 12, or both and were not carried over to the randomized portion of the trial; 27 (7.7%) discontinued owing to an adverse event; 1 (0.3%) died; and 36 had other reasons for discontinuing (Fig. 1).

The mean SAPS–H+D scores at weeks 2, 4, and 8 of the open-label phase are shown in Figure S2A. Among patients who were assessed at week 12, there was a 75.2% mean reduction from baseline in the SAPS–H+D score (Table S1). Changes from baseline in the open-label phase through week 12 in the SAPS-H, SAPS-D, and CGI-S scores are also shown in Table S1. The proportion of patients who met full response criteria increased over time (Fig. S2B).

DOUBLE-BLIND PHASE

At the time of the interim analysis, 194 patients had undergone randomization (95 to pimavanserin and 99 to placebo); at the time of trial discontinuation, 23 additional patients had entered the double-blind phase (total, 105 in the pimavanserin group and 112 in the placebo group). Disease characteristics were similar in the two trial groups (Table 1). The median duration of exposure in the double-blind phase was 17.7 weeks with pimavanserin and 10.9 weeks with placebo. By the end of the trial, 72 patients (26 in the pimavanserin group and 46 in the placebo group) had discontinued the trial early during the double-blind phase; the most common reasons were relapse of psychosis (15 patients in the pimavanserin group and 34 in the placebo group) and withdrawal of consent (6 patients in the pimavanserin group and 4 in the placebo group). A total of 79 patients completed the 26-week double-blind phase (44 in the pimavanserin group and 35 in the placebo group), and 66 patients (35 in the pimavanserin group and 31 in the placebo group) who remained in the double-blind portion were withdrawn for administrative reasons because the trial was stopped early at the interim analysis (Fig. 1).

At the time of the interim analysis, the frequency of relapse was 13% in the pimavanserin group and 28% in the placebo group (hazard ratio for time to relapse, 0.35; 95% confidence interval [CI], 0.17 to 0.73; P=0.005). The significance level for the Cox regression analysis was below the prespecified stopping boundary of 0.0066, and the trial was stopped (Table 2). The risk of relapse over time is shown in Figure 2. Prespecified sensitivity analyses, including in the full enrolled population and per-protocol population, are shown in Table S2. Trial discontinuation for any reason occurred in 21 patients (22%) in the pimavanserin group and in 38 patients (38%) in the placebo group (hazard ratio for time to trial discontinuation for any reason, 0.45; 95% CI, 0.26 to 0.79; P=0.005) (Table 2). There were no missing data for the primary or secondary end points.

To assess the effect on specific measures known to be affected by antipsychotics in this trial, patients were regularly assessed for cognitive function (with the use of the MMSE) and motor function (with the use of the ESRS-A). During the open-label phase, the mean (±SE) change in the total MMSE score was 1.0±0.2 points, and the mean change from baseline in the ESRS-A score was −0.7±0.2 points, with both changes indicating improvement (Figs. S4 and S5). During the double-blind phase, the mean change in the MMSE score did not differ substantially between patients who received pimavanserin and those who received placebo, and the mean change from baseline was 1.2±0.5 in patients treated with pimavanserin for the 38-week duration of the trial (Fig. S4). During the double-blind phase, the mean change in the ESRS-A score at 26 weeks was −0.9±0.6 with pimavanserin and −0.4±0.3 with placebo, favoring pimavanserin (Fig. S5).

ADVERSE EVENTS AND SAFETY

During the open-label phase, 142 patients (36.2%) had a treatment-emergent adverse event, defined

Table 2. Cox Proportional-Hazards Regression Analysis of the Primary and Secondary End Points.*

End Point	Pimavanserin (N=95)	Placebo (N=99)	Hazard Ratio (95% CI)	P Value
Primary end point: relapse of psychosis				
Patients who had a relapse event — no. (%)	12 (13)	28 (28)	0.35 (0.17–0.73)	0.005
Patients with censored data — no. (%)	83 (87)	71 (72)		
Completed wk 26 without a relapse	37 (39)	28 (28)		
Prematurely discontinued before wk 26	9 (9)	10 (10)		
Were continuing in trial at time of data cutoff	37 (39)	33 (33)		
Secondary end point: trial discontinuation				
Patients who discontinued for any reason — no. (%)	21 (22)	38 (38)	0.45 (0.26–0.79)	0.005
Patients with censored data — no. (%)	74 (78)	61 (62)		
Completed wk 26 without a relapse	37 (39)	28 (28)		
Were continuing in trial at time of data cutoff	37 (39)	33 (33)		

* Shown are the results at the interim analysis among the 95 patients who were randomly assigned to continue receiving pimavanserin and the 99 patients who were assigned to receive placebo during the double-blind phase. The primary and secondary end points, which were assessed in time-to-event analyses, were tested hierarchically at the two-sided 0.0066 level to control trial-wise type I error, with relapse of psychosis being tested first.

as an adverse event with an onset on or after the date of the first trial dose and no later than the date of the last trial dose plus 30 days. Such events that occurred in more than 2% of the patients in the open-label phase were urinary tract infection (in 5.1% of patients), constipation (in 2.6%), and hypertension (in 2.3%) (Table 3). Serious adverse events occurred in 20 patients (5.1%) in the open-label phase (Table S3). One patient (0.3%) died from suspected myocardial infarction that was considered by the investigator to be unrelated to pimavanserin. In addition to the investigator's opinion, the case was internally reviewed by the sponsor's pharmacovigilance group and was also reviewed by the independent data and safety monitoring board; neither group proposed modification to the investigator's determination of causality. No clinically significant mean changes in clinical laboratory values or vital signs were observed. The mean (±SE) prolongation of the corrected QT interval, calculated with the use of Fridericia's formula (QTcF), during the open-label phase was 5.4±0.9 msec; 1 patient (0.3%) had an asymptomatic increase in the QTcF of more than 60 msec with pimavanserin. In total, five adverse events involving an asymptomatic prolongation of the QT interval were reported with pimavanserin (two in the open-label phase and three in the double-blind phase), affecting 1.3% of the patients.

Common adverse events (occurring in ≥3% of the patients in either group) were headache (in 9.5% of patients in the pimavanserin group and in 4.5% in the placebo group), urinary tract infection (in 6.7% and 3.6%, respectively), and nasopharyngitis (in 1.0% and 3.6%) (Table 3). Among all the patients receiving pimavanserin during the trial, the most common adverse events were constipation (in 3.1%), headache (in 4.1%), and urinary tract infection (in 6.4%). In the double-blind phase, the incidence of serious adverse events (Table S4) and adverse events leading to trial discontinuation (Table 3) was similar in the two trial groups. One patient in the pimavanserin group died during the double-blind phase from septic and metabolic encephalopathy caused by a dental abscess. No clinically significant differences were observed between the pimavanserin group and the placebo group in mean laboratory values or vital signs during this phase of the trial. Two patients (one in each group) had asymptomatic QTcF values greater than 500 msec.

DISCUSSION

This randomized discontinuation trial examined sustained response to pimavanserin treatment followed by the effect of treatment discontinuation on recurrence of psychosis in patients with several types of neurodegenerative disease. After randomization, the percentage of patients who had a relapse of psychosis was 13% among those who continued to receive pimavanserin and 28%

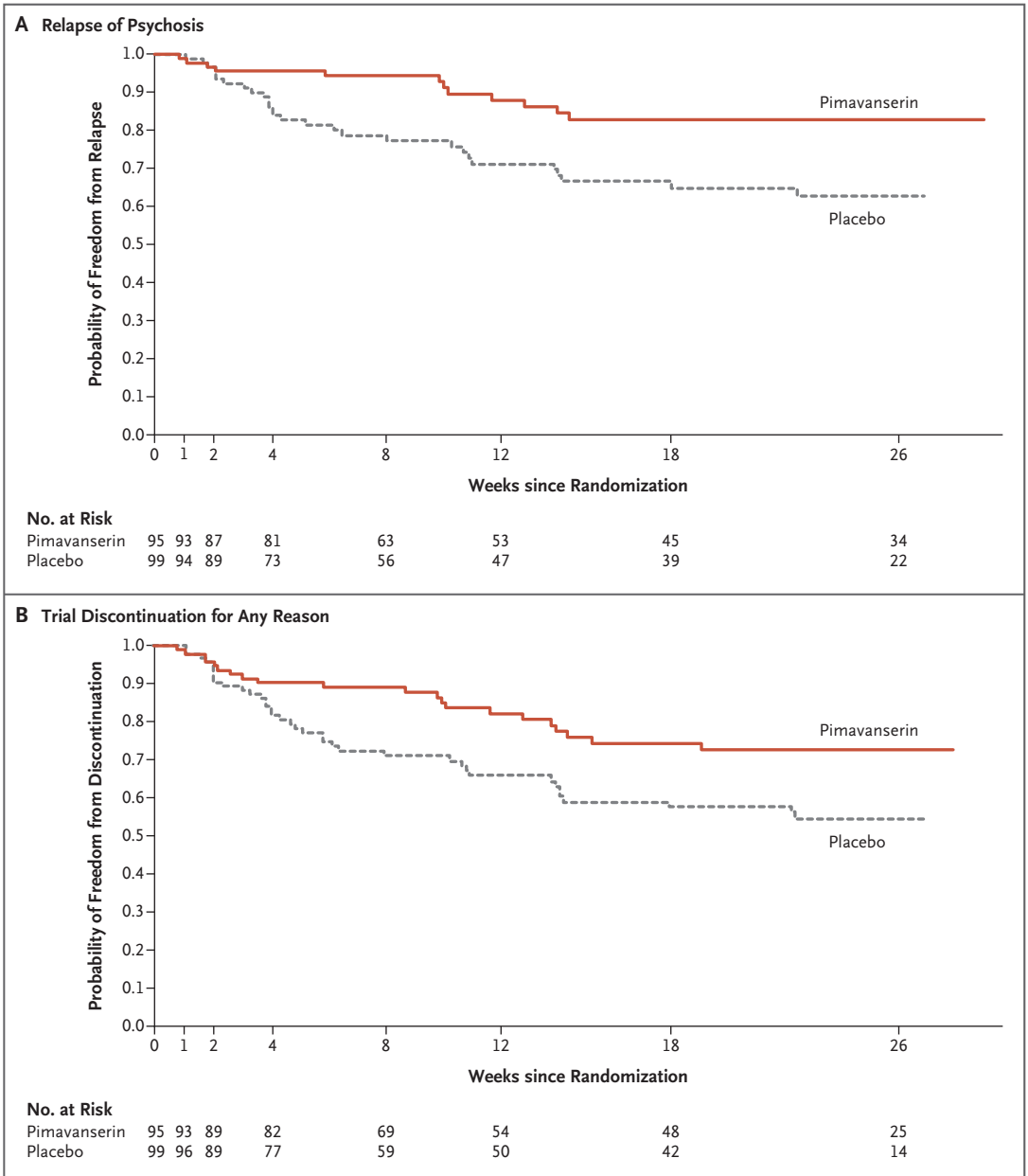

Figure 2. Relapse of Psychosis and Trial Discontinuation.

Shown are the results at the time of the interim analysis. Panel A shows Kaplan–Meier curves for the risk of relapse, assessed in a time-to-event analysis, during the double-blind phase among the 95 patients who had been randomly assigned to continue receiving pimavanserin and the 99 patients who had been assigned to receive placebo. Analysis of the differences in Kaplan–Meier probabilities at weeks 1, 2, 4, 8, 12, 18, and 26 showed statistical significance of the separation at the nominal 5% level at week 4 and for all time points thereafter. Panel B shows Kaplan–Meier curves for trial discontinuation for any reason, also assessed in a time-to-event analysis, during the double-blind phase.

among those who were switched to placebo, with an estimated difference of 16 percentage points. The risk of trial discontinuation for any reason was lower with pimavanserin than with placebo.

This trial has limitations. Requiring sustained response in the open-label phase limited the ability to assess future treatment response in patients who did not meet the full response criteria at week 8. Because the trial was stopped early for efficacy, the ability to assess clinical predictors of relapse is diminished, and it is possible that the active-treatment or placebo group would have

Table 3. Adverse Events.*

Adverse Event	Open-Label Phase	Double-Blind Phase	
	Pimavanserin (N=392)	Pimavanserin (N=105)	Placebo (N=112)
	number of patients (percent)		
Any adverse event	142 (36.2)	43 (41.0)	41 (36.6)
Serious adverse event†	20 (5.1)	5 (4.8)	4 (3.6)
Adverse event related to pimavanserin or placebo‡	45 (11.5)	9 (8.6)	10 (8.9)
Adverse event leading to trial discontinuation	30 (7.7)	3 (2.9)	4 (3.6)
Adverse event resulting in death§	1 (0.3)	1 (1.0)	0
Individual adverse events¶			
Anxiety	6 (1.5)	3 (2.9)	0
Asthenia	3 (0.8)	3 (2.9)	1 (0.9)
Confusional state	8 (2.0)	1 (1.0)	0
Constipation	10 (2.6)	2 (1.9)	1 (0.9)
Diarrhea	5 (1.3)	0	3 (2.7)
Dizziness	6 (1.5)	3 (2.9)	0
Headache	6 (1.5)	10 (9.5)	5 (4.5)
Hypertension	9 (2.3)	2 (1.9)	2 (1.8)
Nasopharyngitis	7 (1.8)	1 (1.0)	4 (3.6)
Nausea	8 (2.0)	0	2 (1.8)
Prolonged QT interval‖	2 (0.5)	3 (2.9)	0
Urinary tract infection	20 (5.1)	7 (6.7)	4 (3.6)
Weight decreased	5 (1.3)	1 (1.0)	3 (2.7)

* Shown are treatment-emergent adverse events that occurred in at least 2% of the patients in the open-label phase or in either trial group in the double-blind phase. A treatment-emergent adverse event is an adverse event with an onset on or after the date of the first trial dose and no later than the date of the last trial dose plus 30 days. For patients who underwent randomization in the double-blind phase, if the onset of the adverse event was on or after the date of first dose in the double-blind phase, the adverse event was assigned to the double-blind phase.

† A serious adverse event was an adverse event that met one or more of the following criteria: was fatal or life-threatening, resulted in disability or permanent damage, led to hospitalization, prolonged existing hospitalization, was a congenital anomaly or birth defect, or was medically significant. The classification of an adverse event as serious was made by the investigator.

‡ An adverse event was considered to be related to pimavanserin or placebo by the investigator if there was a reasonable possibility that the event may have been caused by the trial treatment under investigation. Events with a missing relationship were classified as being related.

§ A 75-year-old White man died during the open-label phase from suspected myocardial infarction, which was considered to be unrelated to the trial drug by the investigator. An 81-year-old White man who was assigned to receive pimavanserin in the double-blind phase died from septic and metabolic encephalopathy caused by a dental abscess, which was considered to be unrelated to drug therapy by the investigator.

¶ No significant between-group differences in adverse events were observed when tested at the 5% level.

‖ The adverse events involving prolongation of the corrected QT interval, calculated with the use of Fridericia's formula, involved maximum changes from baseline of 12 msec and 51 msec in two patients in the open-label phase (the former was in a patient who discontinued the trial owing to lack of response, and the latter resolved with dose reduction) and 6 msec, 22 msec, and 77 msec in three patients in the double-blind phase (the first two resolved without intervention, and the third remained stable until the patient discontinued the trial). All events were detected on electrocardiography and were asymptomatic.

had additional relapse events or adverse events if the trial had been longer. Pimavanserin has shown efficacy in patients with hallucinations and delusions associated with Parkinson's disease psychosis and is approved for that indication, and approximately 15% of the patients in the trial had Parkinson's disease, which may have skewed the results in favor of pimavanserin. Previous trials that involved patients with Parkinson's disease–related psychosis included only those with normal cognition or with MMSE scores of 21 or more. In contrast, 61% of the patients with Par-

kinson's disease in the current trial had moderate-to-severe dementia. Almost all the patients in the trial were White. Finally, the double-blind phase was planned for 26 weeks of follow-up of each individual patient but was stopped early for efficacy, which contributed to a median duration of exposure during this phase of approximately 18 weeks in the pimavanserin group and 11 weeks in the placebo group.

Common adverse events that occurred more frequently with pimavanserin than with placebo were headache, constipation, and urinary tract infection. The mean change in QTcF in patients who were exposed to pimavanserin in the open-label phase was 5.4 msec, consistent with the current labeling of the drug, and five adverse events involving asymptomatic prolongation of the QT interval were reported.

In this trial that involved patients with psychosis related to several types of neurodegenerative disease and that was stopped early for efficacy, discontinuation of pimavanserin in patients who had previously had a response to the drug led to a higher risk of relapse of psychosis than did continued receipt of pimavanserin.

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