# Pimavanserin for negative symptoms of schizophrenia: results from the ADVANCE phase 2 randomised, placebo-controlled trial in North America and Europe

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## Summary

**Background** Negative symptoms of schizophrenia are associated with adverse clinical outcomes, but there are few effective treatments. We aimed to assess the effects of pimavanserin, a selective 5-$HT_{2A}$ inverse agonist and antagonist, on negative symptoms of schizophrenia.

**Methods** The ADVANCE study was a phase 2, 26-week, randomised, double-blind, placebo-controlled study of pimavanserin in stable outpatients with schizophrenia aged 18–55 years with predominant negative symptoms. Patients were randomly assigned (1:1) across 83 sites (18 in North America and 65 in Europe) to receive pimavanserin or placebo daily, added to an ongoing antipsychotic medication, per a computer-generated schedule (stratification by geographical region). Eligible patients had a score of at least 20 on the sum of seven Positive and Negative Syndrome Scale (PANSS) Marder negative factor items (and scores of ≥4 on at least three or ≥5 on at least two of negative symptom items). The starting dosage of 20 mg of pimavanserin or placebo could be adjusted to 34 mg or 10 mg within the first 8 weeks of the study, after which dosage remained stable until the end of the study. Both pimavanserin and placebo were administered orally once daily as two individual tablets (pimavanserin tablets were either 10 mg or 17 mg). The primary endpoint was change in total score using the 16-item Negative Symptom Assessment (NSA-16) from baseline to week 26. Primary outcomes were analysed in patients who received at least one dose of the study drug and had NSA-16 assessments at baseline and at least once post-baseline (full analysis set). Safety outcomes were analysed in patients who had received at least one dose of the study drug. This trial is registered with ClinicalTrials.gov, NCT02970305, and is complete.

**Findings** Between Nov 4, 2016, and April 16, 2019, we randomly assigned 403 patients to pimavanserin (n=201; 131 [65%] male; 187 [93%] White) or placebo (n=202; 137 [68%] male, 186 (92%) White), of whom 400 were included in the efficacy analysis (199 in the pimavanserin group, 201 in the placebo group). Mean age was 37·7 years (SD 9·4) in the pimavanserin group and 36·7 (9·2) years in the placebo group. The change in total NSA-16 score from baseline to week 26 was significantly improved with pimavanserin (least squares mean –10·4 [SE 0·67]) versus placebo (least squares mean –8·5 [0·67]; p=0·043; effect size: 0·211). The number of patients with treatment-emergent adverse events (TEAEs) was similar between groups: 80 (40%) patients experienced TEAEs in the pimavanserin group and 71 (35%) in the placebo group. Most TEAEs were headache (6% [n=13] *vs* 5% [n=10]) and somnolence (5% [n=11] *vs* 5% [n=10]). One patient from the placebo group reported severe headache (0·5%), rhinorrhoea (0·5%), cough (0·5%), and influenza (0·5%). In the pimavanserin group, one patient reported severe toothache (0·5%), and two patients had worsening of schizophrenia (1%). Mean change in QTcF interval was higher with pimavanerin (4·5 ms [SD 18·0]) than with placebo (0·0 ms [16·0]).

**Interpretation** Stable patients with predominant negative symptoms of schizophrenia showed a reduction in negative symptoms after treatment with pimavanserin. However, given the small effect size, further investigation with optimised dosing is warranted to determine the clinical significance of this effect.

**Funding** Acadia Pharmaceuticals.



## Introduction

Traditionally, treatment of schizophrenia has focused on positive symptoms, such as hallucinations and delusions. However, most patients with schizophrenia experience negative symptoms that are primary and secondary to the disease and often include social isolation, apathy, and blunted affect. Negative and cognitive symptoms are known to predict disease burden better than positive symptoms[1,2] but, despite this, treatment options are lacking. $D_2$ receptor blockade, one of the main approaches in the treatment of positive symptoms, might complicate management of negative symptoms, and has been shown to produce negative symptoms in healthy subjects.[3] Conversely, antagonism of the serotonin 5-hydroxytryptamine receptor subtype 2A (5-HT2A) blocks the effect of n-methyl-D-aspartate (NMDA)

## Research in context

### Evidence before this study

We searched PubMed for studies investigating treatments that selectively target serotonin receptors in the treatment of negative symptoms of schizophrenia using the terms, "schizophrenia" AND "negative symptoms" AND "5-HT", with search results limited to randomised clinical trials published from database inception to initiation of this study on Nov 4, 2016, and no language restrictions. Our search returned 16 results, none of which were applicable because they investigated treatments that did not selectively target serotonin (eg, treatments with activity at dopamine receptors), were done in patients with an acute psychotic episode, were genetic analyses related to the study of 5-HT receptors, had methodological limitations, or did not investigate negative symptoms (eg, investigations of cognitive symptoms or weight gain). Thus, at the time our study was designed, there were no published data from randomised clinical trials that investigated the treatment of negative symptoms of schizophrenia with a serotonin inverse agonist and antagonist at 5-$HT_{2A}$ receptors. However, preliminary clinical data were available providing limited evidence for the treatment of schizophrenia, in general, with 5-$HT_{2A}$ antagonists and inverse agonists. Pimavanserin is a selective 5-$HT_{2A}$ receptor inverse agonist and antagonist with negligible affinity for dopaminergic, muscarinic, histaminergic, or adrenergic receptors compared with other antipsychotics. In addition to preliminary data for the treatment of patients with schizophrenia, rationale for investigating pimavanserin as a treatment for negative symptoms of schizophrenia came from a small, retrospective case series that reported on ten patients with schizophrenia who responded to pimavanserin. Investigators noted that improvements in negative symptoms were observed in several patients.

### Added value of this study

Our results showed that pimavanserin, added to ongoing antipsychotic medication, resulted in greater improvement of negative symptoms than placebo for the treatment of patients with predominant negative symptoms of schizophrenia of moderate or worse severity. This study was designed to minimise the confounding effects that could have prevented previous clinical trials from showing a meaningful change in negative symptoms. Because changes in positive symptoms or depressive symptoms might mask improvements in negative symptoms, our patient population was selected to include patients with negative symptoms while excluding those with primarily positive or depressive symptoms. We also included eligibility and testing requirements designed to select a patient population with a high likelihood of treatment adherence.

### Implications of all the available evidence

Pimavanserin was well tolerated and, added to ongoing antipsychotic treatment, reduced negative symptoms in patients with stable schizophrenia. Our study provides rationale for further investigation of pimavanserin for the treatment of negative symptoms in schizophrenia.

antagonists and induces striatal and neocortical dopamine release, lending support for the efficacy of atypical antipsychotics in treating the negative symptoms of schizophrenia.[4] Some atypical antipsychotics might be effective for secondary negative symptoms,[5] possibly because of the relatively higher affinity these treatments have for serotonin (5-$HT_2$) receptors over $D_2$ receptors.[2] However, efficacy of atypical antipsychotics for primary enduring negative symptoms remains undetermined.[2] For example, studies of amisulpride and ziprasidone have shown improved effect on negative symptoms, but this improvement could be secondary to effects on secondary negative symptoms. A study of cariprazine showed preliminary activity for the treatment of predominant negative symptoms when compared with risperidone, although the study did not include a placebo control group and further studies of efficacy are needed to confirm these findings. Per a 2018 meta-analysis, antidepressant augmentation might also be beneficial in treating negative symptoms;[6] however, results could have been confounded by secondary negative symptoms, particularly because not all studies restricted the degree of depressive symptoms in enrolled patients. There is a need for more effective treatment options for negative symptoms. Pharmacological treatment options with new mechanisms of action might hold promise.

Despite some encouraging phase 2 trial results, no drug is approved for the treatment of negative symptoms of schizophrenia.[7,8] Many trials are investigating novel mechanisms of action. Preliminary data from the 5-$HT_{2A}$ receptor antagonists and inverse agonists M100907, volinanserin, and SR46349B (eplivanserin) provide limited evidence for efficacy.[9–11] Ritanserin, a selective 5-$HT_{2A/2C}$ inverse agonist and antagonist, showed specific efficacy in reducing negative symptoms.[12,13] These data support use of 5-$HT_{2A}$ receptor inverse agonists as therapy for psychosis and negative symptoms of schizophrenia.

Pimavanserin is a selective 5-$HT_{2A}$ receptor inverse agonist and antagonist with negligible affinity for dopaminergic, muscarinic, histaminergic, or adrenergic receptors compared with other antipsychotics.[14] Pimavanserin is approved by the US Food and Drug Administration (FDA) for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis. It is hypothesised that adding pimavanserin to atypical antipsychotic drugs with lower selectivity for 5-$HT_{2A}$ receptors than $D_2$ receptors might allow titration of the level of 5-$HT_{2A}$ receptor occupancy relative to $D_2$ receptor occupancy for optimal clinical efficacy, without compromising occupancy at other important targets or increasing risk of extrapyramidal side effects (appendix

See Online for appendix

p 1). Negative symptoms were alleviated in a case series of ten patients with schizophrenia who were treated with pimavanserin.[15] Based on data from compounds with similar receptor profiles,[12,13] we hypothesised that pimavanserin provides additional benefit in adults with negative symptoms of schizophrenia whose treatment benefit has been maximised on ongoing second-generation antipsychotics via its additional effects on neocortical dopamine release.[16] The phase 2 ADVANCE trial evaluated efficacy and safety of adjunctive pimavanserin compared with placebo in adults with schizophrenia and predominant negative symptoms while on optimised background antipsychotic therapy.

## Methods

### Study design and participants

In this randomised, double-blind, placebo-controlled, multicentre study, adult outpatients with predominant negative symptoms of schizophrenia were randomly assigned to receive once-daily doses of pimavanserin or placebo added to an ongoing antipsychotic. Investigators recruited patients from outpatient clinics (hospital and community settings) at 33 North American and 69 European sites (appendix p 8). The study had a 4-week screening period, 26-week treatment period, and 4-week follow-up (apart from patients who enrolled in an extension phase or discontinued prematurely). Patients who completed treatment could enrol in a 52-week open-label extension phase.

Eligible participants included male and female outpatients aged 18–55 years who met DSM–5 criteria for schizophrenia as confirmed by the structured clinical interview for DSM-5 clinical trials version (SCID-CT). Inclusion criteria included a schizophrenia diagnosis for at least 1 year and medical stability based on the investigator's judgement for at least 12 weeks before screening (appendix p 10). To select patients with predominant negative symptoms and attenuate secondary improvement in negative symptoms related to improvement in other symptom domains, additional inclusion criteria were: a score of at least 20 on the sum of the seven Positive and Negative Syndrome Scale (PANSS) Marder negative factor items (and scores ≥4 on at least three of the seven PANSS items or ≥5 on at least two of the seven PANSS items), and a score of no more than 22 on the sum of the eight PANSS Marder positive factor items (of which no more than two of the selected items were rated 4, and none ≥5, at screening and baseline [P1 delusions, P3 hallucinatory behaviour, and P6 suspiciousness or persecution]). Severity of negative symptoms required a score of at least 4 (moderately ill or worse) at screening and baseline on the negative symptoms subscale of the Clinical Global Impression of Schizophrenia Scale-Severity (CGI-SCH-S). Eligible patients had to have had at least 8 weeks of treatment with an adequate dose of antipsychotic (aripiprazole, aripiprazole long-acting injectable (LAI), asenapine, brexpiprazole, cariprazine, lurasidone, olanzapine, risperidone, or risperidone LAI) before screening and antipsychotic blood concentrations above the lowest measurable quantity level per laboratory cut-off to confirm treatment adherence. Eligibility was confirmed using a well-established method of independent adjudication[17] consisting of a structured telemedicine interview with raters of the Massachusetts General Hospital Clinical Trials Network and Institute. No dose changes were allowed within 4 weeks of screening for participants treated with oral antipsychotics or concomitant medications or within 16 weeks for participants treated with LAI antipsychotics. Background antipsychotic drugs were restricted to atypical antipsychotics that did not have a warning for prolongation of the corrected QT interval (QTc) in their label to reduce the potential compounding effect on QTc when combined with pimavanserin. Typical antipsychotics were not included in the list of permitted antipsychotics due to data suggesting efficacy when adjunctive pimavanserin was given with risperidone 2 mg per day but not when given with haloperidol,[18] the low rate of use of typical antipsychotics, and the potential for increased QTc prolongation with the use of haloperidol in combination with pimavanserin. The final list of background antipsychotic treatments was prepared in agreement with the FDA.[18] Patients were excluded if they had any active comorbid psychiatric disorder other than schizophrenia or a disorder that would interfere with completion of study assessments. Participants were also excluded if they had a score of 3 or 4 for any single movement on the Abnormal Involuntary Movement Scale (AIMS), a total score of 2 or more on the Barnes Akathisia Rating Scale (BARS), a total score of 5 or more on the Simpson-Angus Extrapyramidal Side Effects Scale (SAS), or a total score of nine or more on the Calgary Depression Scale for Schizophrenia (CDSS). Complete inclusion and exclusion criteria are listed in the appendix (p 10). Patients were required to provide signed written informed consent and have a designated caregiver to provide input required to complete assessments and support compliance with the study. This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by local independent ethics committees or institutional review boards. The protocol and statistical analysis plan are in the appendix (pp 20–255).

### Randomisation and masking

Eligible patients were randomised 1:1 to receive pimavanserin or placebo added to their current antipsychotic. Randomisation assignment was determined by a computer-generated permuted-block sequence and was stratified by region (North America or Europe). Assignments were double-blinded. Patients, the study sponsor, study statisticians, vendors and sponsor designees, and site investigators and personnel were masked to

treatment group assignments. Blinding was assured by restricting access to treatment assignment and providing identical tablets and packing for pimavanserin and placebo treatments. Statisticians were unblinded after the database lock upon initiation of the statistical analysis.

### Procedures

ADVANCE used a flexible dosing design. The starting dosage of pimavanserin was 20 mg administered orally in two tablets once a day, which was previously shown to be effective and safe.[18] Dosage could be adjusted to 34 mg or 10 mg once daily until study week 8, based on the investigator's evaluation of efficacy and tolerability (appendix p 1). The aim of increasing the pimavanserin dose was to try to maximise improvement in negative symptoms that would lead to increased communication, affective engagement, self-care, and interest in social involvement or daily activities, as reported by patient and caregiver and observed by study staff. Dose reduction was allowed in the case of adverse events considered by the investigator to be related to the study drug, while considering the severity and frequency of these adverse events. Dosing changes were not allowed after week 8. Treatment adherence was assessed on the basis of the pill quantity returned at each visit. Dose adjustments for the background antipsychotic were not permitted within 4 weeks of screening or throughout the study. Limited use of hypnotics, anticholinergics, or anxiolytics was allowed for insomnia, anxiety, or extrapyramidal symptoms. For patients undergoing psychotherapy during screening, no changes in the frequency of visits were allowed during the study, unless worsening of schizophrenia symptoms required an increase in frequency. Initiation of new therapy was not allowed. The screening evaluation consisted of the SCID-CT neuropsychiatric interview, medical and psychiatric histories, physical examination, measurement of vital signs, electrocardiogram (ECG), and laboratory tests. Scales that assessed psychopathology included the 16-item Negative Symptom Assessment (NSA-16; primary endpoint), CGI-SCH-S, CGI-SCH-Improvement scale (CGI-SCH-I), PANSS and all PANSS subscales, Brief Assessment of Cognition in Schizophrenia Scale (BACS), and Calgary Depression Scale for Schizophrenia (CDSS). Scales that assessed functioning included the Personal and Social Performance scale (PSP; key secondary endpoint), 36-item Short-Form Health Survey (SF-36), Drug Attitude Inventory (DAI-10), and Karolinska Sleepiness Scale (KSS). All of the scales were administered by certified raters. Additional study procedures, including a description of assessment scales, schedule of efficacy assessments, and reasons for study removal, are shown in the appendix (p 1). Three protocol amendments were made after enrolment of the first patient: amendment 2 (Nov 28, 2016), amendment 3 (March 31, 2017), and amendment 3-CZ (Jan 31, 2018). A list of the changes made are provided in the appendix (p 19).

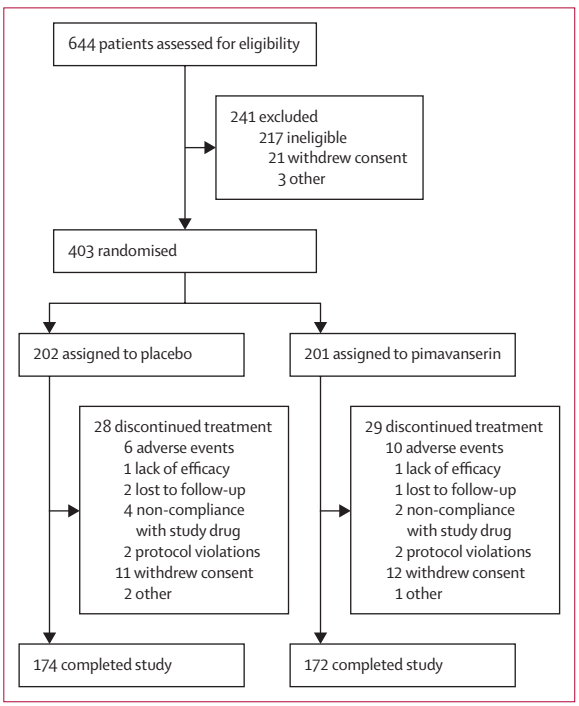


*Figure 1:* **Trial profile**

### Outcomes

The primary efficacy measure was the change in NSA-16 total score from baseline to week 26.

The key secondary endpoint was the change in PSP score from baseline to week 26. Other secondary endpoints at week 26 were the proportions of NSA-16 (multiple criteria) and CGI-SCH-I (score of 1 or 2) responders, and the change from baseline to week 26 in NSA-16 global negative symptoms rating, NSA-16 domain scores, CGI-SCH-S negative symptoms score, PANSS total and subscale scores, BACS score, DAI-10 score, and KSS score. Responder criteria for NSA-16 are in the appendix (p 4).

Safety assessments, including adverse events, physical examination, vital signs, body weight, 12-lead ECG, and clinical laboratory tests were done at baseline and routinely during the study. Safety was also assessed with the Columbia–Suicide Severity Rating Scale (C-SSRS) at each visit, and the BARS, AIMS, and SAS at baseline and weeks 2, 8, 14, and 26. Results from pharmacokinetic analyses will be published separately.

### Choice of primary measure

We chose the NSA-16 as our primary measure as it is a reliable and valid measure of negative symptoms of schizophrenia in the clinical trial setting.[19,20] This scale covers a wide range of negative symptoms and has well-defined items, anchor points for rating symptom severity, a semi-structured interview format, and is sensitive to changes over brief time periods, such as weeks. Importantly, the NSA-16 retains good reliability

| | Placebo (n=202) | Pimavanserin (n=201) |
|---|---|---|
| Age, years | 36·7 (9·2) | 37·7 (9·4) |
| Sex | | |
| Male | 137 (68%) | 131 (65%) |
| Female | 65 (32%) | 70 (35%) |
| Region | | |
| Europe | 177 (88%) | 177 (88%) |
| North America | 25 (12%) | 24 (12%) |
| Race | | |
| White | 186 (92%) | 187 (93%) |
| Black/African American | 15 (7%) | 10 (5%) |
| Asian | 0 | 2 (1%) |
| American Indian or Alaska Native | 1 (<1%) | 0 |
| Native Hawaiian or other Pacific Islander | 0 | 1 (<1%) |
| Other | 0 | 1 (<1%) |
| Body mass index, kg/m² | 26·6 (4·2) | 27·0 (4·1) |
| Age at diagnosis, years | 26·0 (8·4) | 26·8 (7·6) |
| Duration of schizophrenia, years | 11·7 (7·8) | 11·9 (8·0) |
| Diagnosed with schizophrenia for >5 years | 151 (75%) | 151 (75%) |
| Duration of negative symptoms | | |
| <1 year | 20 (10%) | 22 (11%) |
| 1–5 years | 93 (46%) | 84 (42%) |
| >5 years | 89 (44%) | 95 (47%) |
| Time since first antipsychotic, years | 11·0 (7·7) | 11·0 (7·9) |
| Background antipsychotic* | | |
| Aripiprazole | 69 (34%) | 63 (31%) |
| Asenapine | .. | .. |
| Brexpiprazole | .. | .. |
| Cariprazine | .. | .. |
| Lurasidone | 2 (1%) | 2 (1%) |
| Olanzapine | 62 (31%) | 50 (25%) |
| Risperidone | 69 (34%) | 86 (43%) |
| NSA-16 total score | 60·9 (8·7) | 61·7 (8·5) |
| PSP score | 46·7 (10·8) | 47·3 (11·7) |
| Schizophrenia negative symptoms | | |
| NSA-16 total score ≤55 | 55 (27%) | 49 (24%) |
| NSA-16 total score >55 | 147 (73%) | 152 (76%) |
| CGI-SCH-S | 4·7 (0·6) | 4·6 (0·6) |
| CGI-SCH-S score ≥5 | 120 (59%) | 106 (53%) |
| PANSS total score | 79·4 (8·7) | 77·3 (9·9) |
| PANSS positive symptoms subscore | 13·7 (3·1) | 13·1 (3·3) |
| PANSS negative symptoms subscore | 27·5 (3·5) | 27·5 (3·7) |

Data are mean (SD) or n (%). CGI-SCG-S=Clinical Global Impression of Schizophrenia Scale – Severity. NSA-16=16-item Negative Symptom Assessment. PANSS=Positive and Negative Syndrome Scale. PSP=Personal and Social Performance scale. *Includes oral and long-acting injectable formulations.

***Table 1:*** **Baseline characteristics (safety population)**

across multiple languages and cultures;[21] the NSA-16 has also been found to have better cross-cultural agreement and pooled variance than other instruments that are often used for measuring negative symptoms (PANSS negative subscale and PANSS Marder negative factor).[21] In 2009, a group including representatives from academia, the pharmaceutical industry, and the FDA concluded that the NSA-16, SANS, and PANSS subscales were all reliable and valid measures of negative symptoms for clinical trials.[22,23] In 2016, when ADVANCE was designed, some experts recommended the use of newer scales, but the FDA and other regulatory agencies did not yet recognise those for registration trials and validated translations were not available for a global trial. Additional discussion of our choice of primary measure is available in the appendix (p 1).

### Statistical analysis

We determined the sample size based on an estimated common standard deviation of 12·8 for NSA-16 total scores. We estimated 171 evaluable patients per treatment group would provide at least 90% power to detect a difference of 4·5 points in the mean change in NSA-16 total from baseline to week 26 between pimavanserin and placebo at a significance level of 0·05 (two sided t-test). Adjusting for a potential non-evaluable rate of up to 10%, we decided to randomly assign approximately 380 patients (190 patients per treatment group). Because ADVANCE investigated adjunctive treatment in the absence of previous data, the sample size was expanded to approximately 400 patients (200 per treatment group) to improve power for detecting a change in negative symptoms.

The safety analysis set included all randomly assigned patients who received at least one dose of study drug with patients classified by actual treatment received. The full analysis set included all randomly assigned patients who received at least one dose of study drug and had both a baseline value and at least one post-baseline value for the NSA-16 total score, with patients classified by randomised treatment assignment.

All statistical analyses were predefined in the statistical analysis plan (appendix p 189). NSA-16 total score was analysed using mixed-effect model repeated measures (MMRM), with change from baseline as the dependent variable, and treatment (pimavanserin or placebo), visit (categorical variable: study week), treatment-by-visit interaction, region (North America or Europe), baseline NSA-16 total score (continuous covariate), and baseline-by-visit interaction as independent variables. An unstructured covariance matrix was used with the Kenward-Roger approximation to adjust the denominator degrees of freedom. Treatment comparison was based on the difference in least squares mean at week 26 and was tested at α level of 0·05 (two-sided) using the full analysis set. PSP score was analysed using the same methodology. A hierarchical testing procedure was used to control for type I errors across the primary and key secondary endpoints. Additional details regarding the statistical analysis, including sensitivity analyses and analyses of other endpoints are in the appendix (pp 5–6). All analyses were done using SAS version 9.2 or higher. Exploratory endpoints included the change from baseline to week 26 in PANSS Marder factor score,

CDSS, and SF-36. The study is registered at ClinicalTrials.gov (NCT02970305).

### Role of the funding source

The funder designed the study with collaboration from investigators and had a role in data analysis, data interpretation, and writing of the report.

## Results

From Nov 4, 2016, to April 16, 2019, 644 patients were screened, of whom 241 (37%) were determined to be ineligible (figure 1). The remaining 403 patients were randomised (201 to the pimavanserin group and 202 to the placebo group) and, of these, 346 (86%) completed the study. All randomised patients received their assigned treatment and were included in the safety analysis set. The full analysis set included 400 patients (199 in the pimavanserin group, 201 in the placebo group). The majority of patients were White (187 [93%] pimavanserin, 186 [92%] placebo) and men (131 [65%], 137 [68%]; table 1). Mean duration of schizophrenia in the overall population was 11·8 years (SD 7·9). Although demographics and baseline characteristics were comparable between treatments, more than 50% of patients had marked negative symptoms, with mean CGI-SCH-S scores for negative symptoms of 4·6 (pimavanserin) and 4·7 (placebo). The most commonly used antipsychotics were risperidone, aripiprazole, and olanzapine. Concomitant medications other than antipsychotics are summarised in the appendix (p 12).

Based on the MMRM analysis, change in NSA-16 total score from baseline to week 26 was significantly greater with pimavanserin versus placebo (least squares mean difference –1·9 [standard error (SE) 0·95]; p=0·043; Cohen's d effect size 0·211; figure 2; table 2). Sensitivity analyses of the primary endpoint were similar to the primary analysis (appendix p 13). Pimavanserin was not significantly different from placebo in the evaluation of the key secondary efficacy endpoint of change in the PSP score from baseline to week 26 (MMRM least squares mean difference 0·0 [SE 1·00]; p=0·98; effect size: 0·003; table 2). For other secondary efficacy endpoints, the proportion of patients who were NSA-16 responders at week 26 with at least 20% improvement was 93 (53% ) of 174 patients in the pimavanserin group versus 84 (49%) of 173 patients in the placebo group (p=0·30); the number with at least 30% improvement was 56 (32%) versus 51 (29%; p=0·50; appendix p 14). The number of patients who were CGI-SCH-I responders (score of 1 or 2) was 47 (27%) in the pimavanserin group versus 40 (23%) in the placebo group (p=0·36). Of all NSA-16 domains, only the social involvement domain score showed an improvement: –2·0 (0·17) with pimavanserin and –1·4 (0·17) with placebo (least squares mean difference –0·6; [95% CI –1·1 to –0·1]; unadjusted p=0·011; effect size 0·269; table 2).

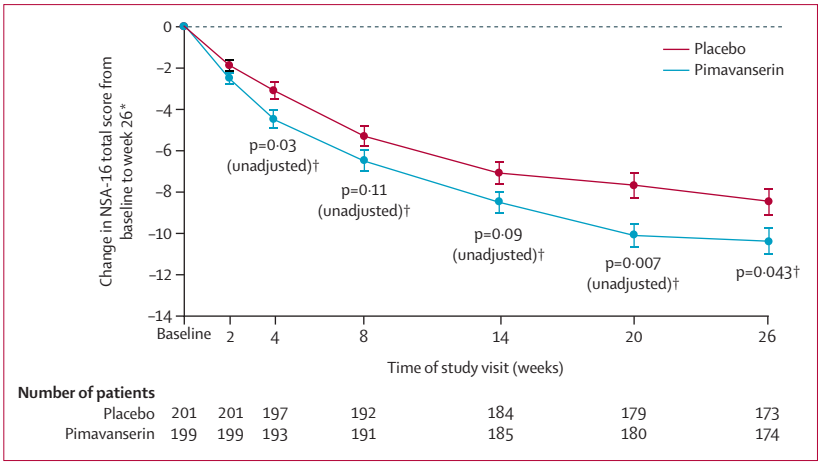


***Figure 2:*** **Least squares mean change in the NSA-16 total score from baseline to week 26 on the full analysis set**

MMRM=mixed-effect model repeated measures. NSA-16=16-item Negative Symptom Assessment. *Least squares mean from MMRM with fixed effects of region (North America or Europe), planned treatment (pimavanserin or placebo added to background antipsychotic treatment), study visit (weeks 2, 4, 8, 14, 20, or 26), treatment-by-visit interaction, baseline score, and baseline-by-visit interaction. †Two-sided p-value for treatment difference at specified visit from MMRM analysis.

Prespecified subgroup analyses of the primary endpoint in the full analysis population showed that, of those patients who were enrolled in Europe, male, of White race, and had baseline body mass index (BMI) of less than 25 kg/m², greater improvements in NSA-16 total score were seen in patients treated with pimavanserin than in patients treated with placebo (figure 3). Similarly, of the patients with a schizophrenia duration of more than 5 years, those with a duration of negative symptoms of more than 5 years, and those who were markedly or severely ill by negative symptoms based on a CGI-SCH-S score of at least 5, greater improvement in NSA-16 total score was observed in those treated with pimavanserin than in those treated with placebo. The related clinical subgroups for these stratifications showed a similar magnitude of treatment effects for pimavanserin, but differences between treatment groups were smaller due to higher responses in the placebo treatment group than in the pimavanserin group.

The incidence of any treatment-emergent adverse event (TEAE) was 71 (35%) of 202 patients in the placebo group and 80 (40%) of 201 patients in the pimavanserin group (table 3). The most common TEAEs were headache (10 [5%] of 202 in the placebo group and 13 [6%] of 201 in the pimavanserin group) and somnolence (10 [5%] *vs* 11 [5%]). There were no fatal TEAEs and the incidence of serious TEAEs was 1 (<1%) with placebo and 4 (2%) with pimavanserin, and all were classified as psychiatric disorders. TEAEs leading to discontinuation occurred in 6 (3%) of 202 patients in the placebo group and 10 (5%) of 201 patients in the pimavanserin group. Most of the TEAEs were mild or moderate in severity. One patient from the placebo group reported severe headache (<1%), rhinorrhoea (<1%), cough (<1%), and influenza (<1%). In

| | Placebo (n=201) | | Pimavanserin (n=199) | | | | |
|---|---|---|---|---|---|---|---|
| | Mean baseline | LS mean change at week 26 | Mean baseline | LS mean change at week 26 | LS mean difference (pimavanserin – placebo; 95% CI) | p value | Cohen's d effect size |
| Primary endpoint | | | | | | | |
| NSA-16 total score*†‡ | 61·0 (0·61) | −8·5 (0·67) | 61·8 (0·60) | −10·4 (0·67) | −1·9 (0·95; −3·8 to −0·1) | 0·043 | 0·211 |
| Secondary endpoints | | | | | | | |
| Personal and Social Performance*†‡ | 46·7 (0·76) | 8·1 (0·70) | 47·2 (0·83) | 8·1 (0·70) | 0·0 (1·00; −1·9 to 2·0) | 0·98 | 0·003 |
| NSA-16 global negative symptoms rating*†‡ | 4·8 (0·05) | −0·6 (0·05) | 4·7 (0·05) | −0·7 (0·05) | −0·1 (0·08; −0·2 to 0·1) | 0·37 | 0·095 |
| NSA-16 domain scores*†‡ | | | | | | | |
| Communication | 12·3 (0·21) | −2·0 (0·19) | 12·3 (0·22) | −2·3 (0·19) | −0·4 (0·27; −0·9 to 0·1) | 0·15 | 0·153 |
| Emotion or affect | 12·5 (0·15) | −1·6 (0·16) | 12·7 (0·14) | −1·9 (0·16) | −0·3 (0·22; −0·7 to 0·1) | 0·16 | 0·148 |
| Social involvement | 12·6 (0·18) | −1·4 (0·17) | 13·1 (0·16) | −2·0 (0·17) | −0·6 (0·24; −1·1 to −0·1) | 0·011 | 0·269 |
| Motivation | 16·6 (0·18) | −2·2 (0·21) | 16·7 (0·18) | −2·5 (0·21) | −0·3 (0·29; −0·9 to 0·3) | 0·30 | 0·109 |
| Retardation | 7·0 (0·12) | −1·5 (0·12) | 7·0 (0·12) | −1·7 (0·12) | −0·2 (0·16; −0·5 to 0·1) | 0·22 | 0·128 |
| CGI-SCH-S*†‡ | 4·7 (0·04) | −0·6 (0·05) | 4·6 (0·04) | −0·7 (0·05) | −0·1 (0·08; −0·2 to 0·1) | 0·47 | 0·075 |
| PANSS total score§¶‖ | 79·4 (0·62) | −8·4 (0·75) | 77·2 (0·70) | −8·9 (0·75) | −0·5 (1·07; −2·6 to 1·6) | 0·61 | 0·055 |
| PANSS positive symptoms subscale§¶‖ | 13·7 (0·22) | −0·7 (0·19) | 13·1 (0·24) | −0·7 (0·19) | 0·0 (0·27; −0·5 to 0·5) | 0·96 | −0·006 |
| PANSS negative symptoms subscale§¶‖ | 27·5 (0·25) | −3·8 (0·30) | 27·5 (0·26) | −4·0 (0·30) | −0·2 (0·43; −1·0 to 0·7) | 0·68 | 0·045 |
| PANSS general psychopathology subscale§¶‖ | 38·2 (0·40) | −3·7 (0·41) | 36·6 (0·44) | −4·4 (0·41) | −0·7 (0·58; −1·8 to 0·5) | 0·24 | 0·126 |

Data are mean (SE) unless otherwise stated. ANCOVA=analysis of covariance. CGI-SCH-S=Clinical Global Impression of Schizophrenia Scale-Severity. LS=least squares. MMRM=mixed-effect model for repeated measures. NSA-16=16-item Negative Symptom Assessment. PANSS=Positive and Negative Syndrome Scale. *Least squares mean from MMRM with fixed effects of region (North America or Europe), planned treatment (pimavanserin or placebo added to background antipsychotic treatment), study visit (weeks 2, 4, 8, 14, 20, or 26), treatment-by-visit interaction, baseline score, and baseline-by-visit interaction. An unstructured covariance matrix was used to model the within-subject errors. The denominator degrees of freedom were estimated using the Kenward-Roger approximation. †Difference between LS mean changes for pimavanserin and placebo (pimavanserin – placebo) at the specified visit from MMRM analysis. ‡Two-sided p-value for treatment difference at specified visit from MMRM analysis. §LS mean from ANCOVA analysis with region (North America or Europe) and planned treatment (pimavanserin or placebo) as factors and baseline score as a continuous covariate. ¶Difference between LS mean changes for pimavanserin and placebo (pimavanserin – placebo) at the specified visit from ANCOVA analysis. ‖Two-sided p-value for treatment difference at specified visit from ANCOVA analysis.

***Table 2:*** **Baseline and mean change at week 26 for primary and secondary outcomes in the full analysis set**

the pimavanserin group, one patient reported severe toothache (<1%), and two patients reported worsening of schizophrenia (1%). The incidence of TEAEs was generally similar between men and women, although women treated with pimavanserin had a numerically higher incidence of any TEAE than men. Rates of serious TEAEs and discontinuation due to TEAEs were similar between men and women.

No clinically relevant effects were observed for pimavanserin versus placebo on vital signs, weight, plasma glucose, or lipids. Mean changes from baseline to week 26 were greater with pimavanserin than placebo for serum prolactin (mean change 24·69 [SD 521·56] *vs* −9·27 [369·48]) and creatine kinase (mean change 29·4 [SD 195·3] *vs* −16·5 [247·2]). No serious TEAEs or study discontinuations were associated with these increases. Mean change in BMI was 0·13 (SD 1·16) kg/m² with placebo and 0·06 (1·24) kg/m² with pimavanserin. Body weight increases of 7% or more from baseline occurred in 7 (4%) of 189 patients in the placebo group, and 11 (6%) of 188 patients in the pimavanserin group. Mean change in the QTcF interval was higher for pimavanserin than placebo (4·5 [SD 18·0] ms *vs* 0·0 [16·0] ms), as was the change in QTcB interval (4·5 [21·1] ms *vs* 0·1 [22·3] ms), and the QT interval (4·6 [27·8] ms *vs* −0·1 [22·9] ms). No patient had a QTcF value of more than 500 ms; change from baseline in QTcF greater than 60 ms was reported in one patient (<1%) in the pimavanserin group and none in the placebo group. Shifts in ECG from normal at baseline to abnormal post-baseline were reported in 13 (7%) patients in the placebo group and 11 (6%) patients in the pimavanserin group.

The incidence of extrapyramidal symptoms was relatively low in this study. Mean changes from baseline to week 26 were small and similar for both the pimavanserin and placebo groups (appendix p 17). Dyskinesia was reported in one (0·5%) patient in the pimavanserin group (appendix p 18). Suicidal ideation on the C-SSRS was reported in two (1%) and six (3%) patients in the placebo and pimavanserin groups, respectively.

Of the patients treated with pimavanserin in the full analysis set, 107 (54%) of 199 underwent dose escalation to 34 mg of pimavanserin as their last dose, 89 (45%) had a last dose of pimavanserin at 20 mg, and only 3 (2%) required the lower 10 mg dose of pimavanserin. In a post hoc analysis of change in NSA-16 from baseline to week 26 by last pimavanserin dose, improvement in NSA-16 score was significantly greater in those who received a last dose of 34 mg of pimavanserin (99 [57%] of 174 participants) than those who received placebo (least squares mean difference −3·1 [95% CI −5·3 to −0·9]; unadjusted p=0·0065; effect size=0·339). The change in NSA-16 score for patients whose last dose was pimavanserin 20 mg was similar to those who received placebo (least squares mean difference −0·5 [95% CI −2·9 to 1·9]; p=0·6847; effect size=0·055). Results of all

| | All patients | | Male | | Female | |
|---|---|---|---|---|---|---|
| | Placebo (n=202) | Pimavanserin (n=201) | Placebo (n=137) | Pimavanserin (n=131) | Placebo (n=65) | Pimavanserin (n=70) |
| Any TEAE | 71 (35%) | 80 (40%) | 46 (34%) | 47 (36%) | 25 (38%) | 33 (47%) |
| Drug-related TEAEs | 18 (9%) | 33 (16%) | 13 (9%) | 22 (17%) | 5 (8%) | 11 (16%) |
| Serious TEAEs | 1 (<1%) | 4 (2%) | 0 (0) | 4 (3%) | 1 (2%) | 0 |
| Discontinuation due to TEAE | 6 (3%) | 10 (5%) | 4 (3%) | 7 (5%) | 2 (3%) | 3 (4%) |
| TEAEs occurring in ≥2% of either placebo or pimavanserin group | | | | | | |
| Headache | 10 (5%) | 13 (6%) | 6 (4%) | 6 (5%) | 4 (6%) | 7 (10%) |
| Somnolence | 10 (5%) | 11 (5%) | 5 (4%) | 9 (7%) | 5 (8%) | 2 (3%) |
| Insomnia | 6 (3%) | 6 (3%) | 5 (4%) | 4 (3%) | 1 (2%) | 2 (3%) |
| Influenza | 1 (<1%) | 4 (2%) | 0 | 2 (2%) | 1 (2%) | 2 (3%) |
| Nasopharyngitis | 9 (4%) | 4 (2%) | 7 (5%) | 4 (3%) | 2 (3%) | 0 |
| Dizziness | 5 (2%) | 4 (2%) | 4 (3%) | 3 (2%) | 1 (2%) | 1 (1%) |
| Weight increase | 4 (2%) | 7 (3%) | 1 (1%) | 7 (5%) | 3 (5%) | 0 |
| Anxiety | 6 (3%) | 6 (3%) | 3 (2%) | 5 (4%) | 3 (5%) | 1 (1%) |
| Schizophrenia | 3 (1%) | 6 (3%) | 1 (1%) | 4 (3%) | 2 (3%) | 2 (3%) |
| Irritability | 5 (2%) | 1 (<1%) | 4 (3%) | 0 | 1 (2%) | 1 (1%) |
| Fatigue | 3 (1%) | 4 (2%) | 1 (1%) | 3 (2%) | 2 (3%) | 1 (1%) |
| Seasonal allergy | 0 | 2 (1%) | 0 | 0 | 0 | 2 (3%) |
| Upper respiratory tract infection | 2 (1%) | 2 (1%) | 2 (1%) | 0 | 0 | 2 (3%) |
| Blood prolactin increased | 0 | 3 (1%) | 0 | 1 (1%) | 0 | 2 (3%) |
| Rhinorrhoea | 1 (<1%) | 3 (1%) | 0 | 1 (1%) | 1 (2%) | 2 (3%) |
| Oropharyngeal pain | 0 | 2 (1%) | 0 | 0 | 0 | 2 (3%) |

Data are n (%). TEAE=treatment-emergent adverse event.

***Table 3:*** **Incidence of treatment-emergent adverse events in the safety population**

other prespecified secondary and exploratory analyses revealed no significant differences between treatment groups (appendix pp 14–15).

## Discussion

In this 26-week study of patients with predominant negative symptoms of schizophrenia, adding pimavanserin to ongoing antipsychotic treatment resulted in significantly greater improvement of negative symptoms than did adding a placebo, as assessed with the NSA-16 total score. However, no significant differences were observed in secondary outcomes. Post-hoc analyses showed greater improvement in patients on a final pimavanserin dose of 34 mg daily than patients whose final dose was 20 mg. Pimavanserin once daily over a 26-week treatment period was generally safe and well tolerated when added to the antipsychotics used in this study.

In patients with schizophrenia, morbidity and decreased functioning are strongly associated with negative symptoms.[24,25] However, detecting negative symptoms is a challenge because of their resemblance to depressive or extrapyramidal symptoms. Changes in either of these or changes in positive symptoms can influence the interpretation of treatment effects on negative symptoms,[26] which could limit the conclusions that can be drawn from clinical trials.[27] Thus, the design of our study—to select patients with primarily negative symptoms and exclude those with prominent positive or depressive symptoms—was chosen to evaluate the effect of pimavanserin on negative symptoms, independent of effects on other symptom domains. Rigorous control of confounding symptoms at enrolment and negligible changes in those symptoms at week 26 support our conclusion that pimavanserin had an independent effect on negative symptoms. We also excluded the possibility that the improvement in negative symptoms was due to the background antipsychotic through the requirement for a minimum of 8 weeks of treatment with the background antipsychotic before screening.

Although pimavanserin showed greater improvement in the social involvement domain of the NSA-16 than placebo, change in PSP score, the key secondary outcome measure for psychosocial functioning, was not statistically different from placebo. There were no significant differences between treatment groups in other secondary and exploratory endpoints. Despite our use of patient selection criteria that were intended to reduce variability in the population, the small treatment differences between pimavanserin and placebo in secondary outcomes could be attributed to a higher than expected placebo response in those measures[28] and heterogeneity of response among patients with schizophrenia with potentially different underlying disease mechanisms.[29]

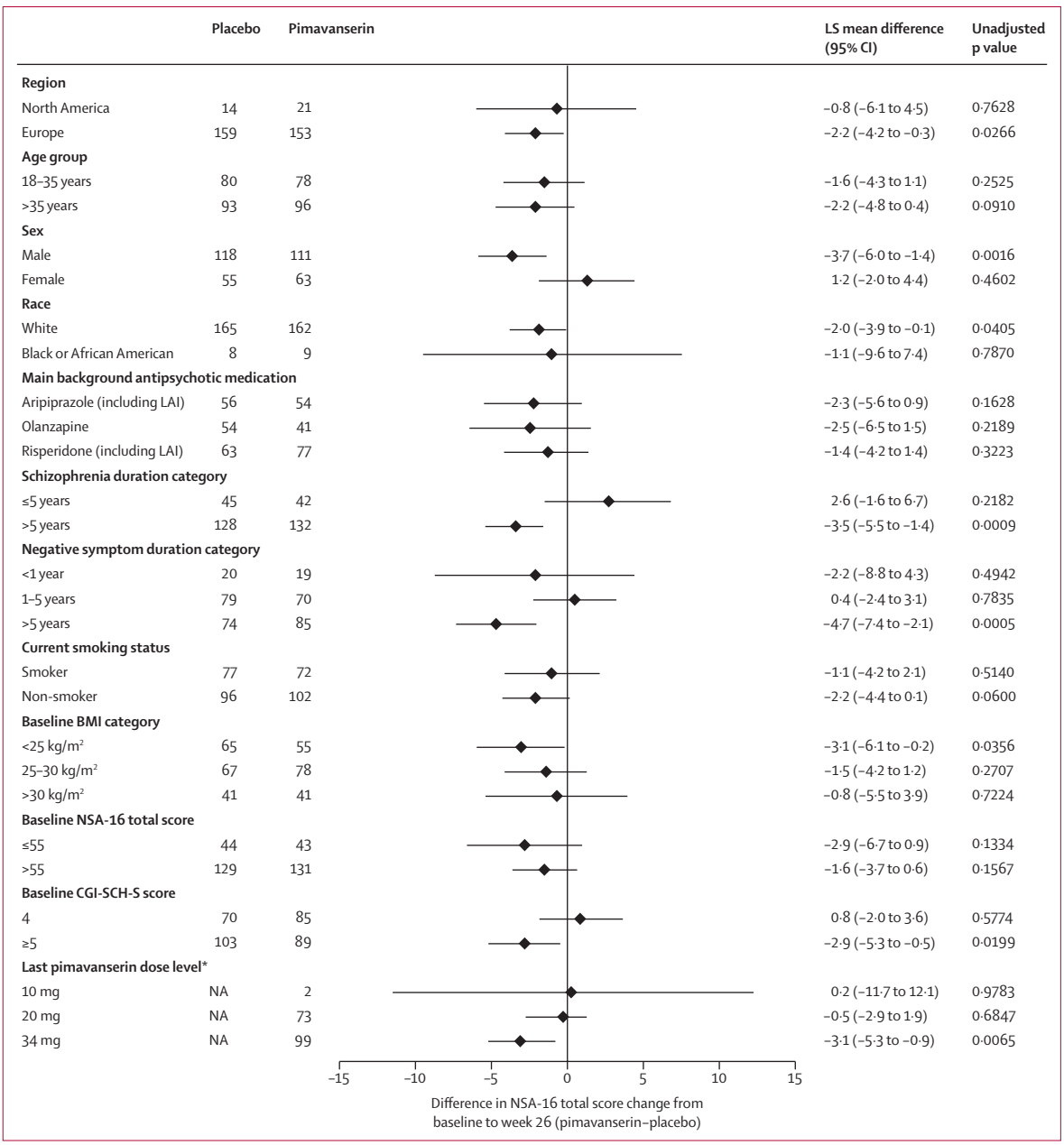


***Figure 3:*** **Change from baseline to week 26 in NSA-16 total score by subgroup in the full analysis set**
BMI=body mass index. CGI-SCH-S=Clinical Global Impression of Schizophrenia Scale–Severity. LAI=long-acting injectables. LS=least squares. NSA-16=16-item Negative Symptom Assessment. *For the least squares mean difference, each pimavanserin dose subgroup was compared with the group of all patients from the placebo group (n=173).

A meta-regression analysis of 18 independent, double-blind, placebo-controlled, randomised clinical trials of negative symptoms in schizophrenia showed the placebo effect was higher in studies with larger numbers of treatment arms, larger numbers of study sites, and in studies that received industry funding than it was in smaller studies that were not funded by industry.[30] In ADVANCE, significant differences in negative symptoms of schizophrenia based on the NSA-16 were observed between placebo and pimavanserin groups, and this effect was greater with pimavanserin 34 mg than 20 mg, in patients with more severe negative symptoms than those with milder symptoms, and in those enrolled at European sites than those enrolled in North America. The NSA-16 results are also consistent with findings from the ENHANCE study, which found more robust effects of adjunctive pimavanserin compared with placebo on negative symptoms of schizophrenia than on total

PANSS score and more robust effects on those enrolled at European sites than on those enrolled in North America.[31] One potential explanation for these subgroup differences might be variation in placebo response rates, which could result from inclusion of patients who were partial non-responders to previous antipsychotic treatment or participation of patients who actively seek out clinical trials, both of which might differ by geographical region.[28]

To date, no previous negative symptoms trials have investigated the use of adjunctive antipsychotic drugs. Recent trials of monotherapies have shown promising results in the treatment of negative symptoms. Cariprazine showed superiority versus risperidone on the PANSS factor score for negative symptoms in a 26-week, randomised, double-blind, phase 3b study of adults with stable schizophrenia and predominant negative symptoms.[32] However, this study did not have a placebo group and dopamine antagonists (eg, risperidone) can produce negative symptoms.[3] MIN-101 (5-$HT_{2A}$, sigma-2, and 5-$HT_{1A}$ antagonist) was compared with placebo in a randomised, controlled study of adults with stable schizophrenia and at least moderately severe negative symptoms after withdrawal from antipsychotic medication.[33] There was a significant reduction in PANSS negative symptom score in the two MIN-101 dose groups compared with placebo. Nonetheless, the extent to which some of the improvement might have been secondary to withdrawal of previous antipsychotics, which might have been different in the two groups, is uncertain. Additionally, a high placebo effect was shown in a phase 3 trial of MIN101 in which neither the primary (reduction in PANSS Marder negative symptoms factor score) nor the key secondary (improvement in PSP total score) endpoints were met.[34] Studies evaluating add-on therapies with other mechanisms of action have been done, but the results obtained from these have often been negative, ambiguous, or difficult to validate.[2]

Overall safety and tolerability of pimavanserin and placebo were similar, with low rates of serious TEAEs and discontinuation from TEAEs, and no reported deaths. No clinically significant differences between pimavanserin and placebo were observed for vital signs, body weight, or extrapyramidal symptoms. Rates of discontinuations due to TEAEs were 5% or less, which is noteworthy for a study with a treatment of two combined antipsychotics and concomitant medications over 6 months, and suggests that this treatment regimen was well tolerated. There was a prolonged QTc in patients who received pimavanserin compared with patients who received placebo; however, shifts in electrocardiogram from normal (baseline) to abnormal (post-baseline) were reported in similar proportions of patients in both groups. Given pimavanserin was administered with an ongoing background antipsychotic, it is noteworthy that there were no observations of QTcF prolongation greater than 500 ms. These findings provide additional understanding of the effect of adjunctive pimavanserin on QTc; however, the dose-response relationship in this setting might require additional investigation.

Safety and efficacy findings are supported by an analysis of treatment adherence from the ADVANCE study.[35] In this analysis, concentrations of both pimavanserin and the background antipsychotic were evaluated in blood samples drawn for pharmacokinetic assessment before randomisation and during the study. The analysis showed that 383 (95%) of 403 patients were considered adherent with their current baseline antipsychotic, and high adherence rates (>90%) were observed for both pimavanserin and the background antipsychotic treatment at weeks 2, 8, 14, and 26, or the end of treatment.[35]

Use of a flexible dosing schedule for pimavanserin was a potential limitation of the ADVANCE study. As the protocol did not require patients to be treated with the maximum dose of 34 mg, some patients might not have received an optimal dose of pimavanserin. Only 54% of patients underwent dose escalation to 34 mg. Changes in pimavanserin dosing were at the discretion of site investigators and were not mandated; therefore, it is possible an increase to 34 mg was not made because symptom improvement and tolerability were adequate. In future studies, encouraging the use of pimavanserin 34 mg could result in an improved response. The potential benefit of selecting a study population with greater severity of negative symptoms to better show functional change has been suggested because of the better treatment responses observed in more severely affected patients than those with milder disease severity.[36] In ADVANCE, selection criteria were specifically designed to select patients with predominant negative symptoms in accordance with regulatory guidance to effectively evaluate treatment effects in this population. Consequently, this criterion might limit generalisability of study findings. In addition, although we aimed for balanced representation of race, sex, and region in the study population, our results were also limited in generalisability due to underrepresentation of non-White races, female patients, and those from North America. Despite one-third of the sites being in North America, only 12% of patients were in North America, compared with 88% from European sites. On the other hand, the range of allowed background antipsychotics and the use of dosing according to local approved label prescribing allows generalisability of findings to the clinical practice setting. We found that pimavanserin reduced negative symptoms across the variety of background antipsychotics used in our patient population. It should be noted, however, that although a variety of background antipsychotics were allowed, only a small number were represented because of scarce regional availability. Our study is strengthened by having independent confirmation of predominant negative symptoms at screening, required participation of a caregiver, evaluation of

treatment adherence that showed high adherence with pimavanserin and background antipsychotic treatments, and an extended trial time of 26 weeks to allow sufficient time to evaluate negative symptoms. This study duration also allowed sufficient time to assess the safety of two combined antipsychotics and the risks associated with potential activating effects and worsening of psychosis. Our study was not specifically designed to evaluate the effect of pimavanserin on cognition, and we did not observe any significant differences on the BACS.

As mentioned in the Introduction, adding pimavanserin to a background antipsychotic might allow titration of the level of 5-$HT_{2A}$ receptor occupancy for optimal clinical efficacy, without increasing the risk of $D_2$-related extrapyramidal side effects. As the 20 mg dose of pimavanserin provides almost full saturation of $5HT_{2A}$ receptors,[37] the efficacy of the 34 mg dose in ADVANCE might be attributed to optimised occupancy that reaches the maximum effect or, alternatively, attributed to additional $5HT_{2C}$ engagement, leading to further induction of neocortical dopamine release.

In summary, amidst an unmet need for safe and effective treatments for negative symptoms of schizophrenia, pimavanserin added to ongoing antipsychotic treatment resulted in a significant improvement in negative symptoms of schizophrenia and was well tolerated. Treatment efficacy for negative symptoms of schizophrenia was influenced by patients who received pimavanserin 34 mg and was the greatest in men, patients from Europe, those with pronounced symptom severity than those with mild or moderate symptoms, and those who had had schizophrenia and negative symptoms for more than 5 years. Although the primary outcome was statistically significant, further studies are needed to optimise dosing and determine the clinical significance of pimavanserin for the treatment of negative symptoms in schizophrenia.

#### Contributors

DB-K and BA did the literature search. DB-K, I-YL, BA, and SS did the study design and data analysis. DB-K, I-YL, and BA had access to raw data. DB-K, CA, and I-YL wrote and revised the manuscript. MF, HN, BA, and SS revised the manuscript. All authors interpreted the data. DB-K took responsibility for the decision to submit for publication. CA and MF collected the data. I-YL developed the statistical analysis plan and developed the figures. I-YL and BA verified the underlying data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

#### Declaration of interests

DB-K, I-YL, and SS are employees of Acadia Pharmaceuticals and have stock and stock options in Acadia Pharmaceuticals. BA was an employee of Acadia Pharmaceuticals at the time of the study and owns stock in Acadia Pharmaceuticals; he is currently an employee of and owns stock in Praxis Precision Medicines. MF has received research support or equity from, or served in an advisory, consulting, or speaking capacity for, Abbott Laboratories, Acadia Pharmaceuticals, Adamed, Aditum Bio Management Company, Advanced Meeting Partners, Affectis Pharmaceuticals, Alfasigma USA, Alkermes, Altimate Health Corporation, Amarin Pharma, American Cyanamid, American Psychiatric Association, American Society of Clinical Psychopharmacology, Amorsa Therapeutics, Angelini, Aptinyx, Arbor Pharmaceuticals, Aspect Medical Systems, Astella Pharma Global Development, AstraZeneca, Auspex Pharmaceuticals, Avanir Pharmaceuticals, AXSOME Therapeutics, Bayer AG, Belvoir Media Group, Best Practice Project Management, BioClinica, Biogen, Biohaven, BioMarin Pharmaceuticals, BioResearch, BioXcel Therapeutics, Biovail Corporation, Boehringer Ingelheim, Boston Pharmaceuticals, BrainCells, Bristol Myers Squibb, Cambridge Science Corporation, CeNeRx BioPharma, Cephalon, Cerecor, Clarus Funds, Clexio Biosciences, Click Therapeutics, Clintara, CME Institute/Physicians Postgraduate Press, CNS Response, Compellis Pharmaceuticals, Covance, Covidien, Cybin Corporation, Cypress Pharmaceutical, Dainippon Sumitomo Pharma, DiagnoSearch Life Sciences (P), Dr. Katz, Dov Pharmaceuticals, Edgemont Pharmaceuticals, Eisai, Eli Lilly and Company, ElMindA, EnVivo Pharmaceuticals, Enzymotec, ePharmaSolutions, EPIX Pharmaceuticals, Esthismos Research, Euthymics Bioscience, Evecxia Therapeutics; ExpertConnect, FAAH Research, F Hoffmann-La Roche, Fabre-Kramer Pharmaceuticals, Forest Pharmaceuticals, Forum Pharmaceuticals, Ganeden Biotech, Gate Neurosciences, GenetikaPlus, GenOmind, Gentelon, GlaxoSmithKline, Global Medical Education, Grunenthal, Happify, Harvard Clinical Research Institute, H Lundbeck A/S, i3 Innovus/Ingenis, Icon Clinical Research, Imedex, Indivior, Intracellular, Janssen Pharmaceuticals, Janssen R&D, Jazz Pharmaceuticals, JDS Therapeutics, Jed Foundation, Johnson & Johnson Pharmaceutical Research & Development, Knoll Pharmaceuticals, Labopharm, Lichtwer Pharma, Lorex Pharmaceuticals, Lundbeck, Marinus Pharmaceuticals, MedAvante, Merck, MGH Psychiatry Academy/Primedia; MGH Psychiatry Academy/Reed Elsevier, MSI Methylation Sciences, National Alliance for Research on Schizophrenia & Depression (NARSAD), National Center for Complementary and Alternative Medicine (NCCAM), National Coordinating Center for Integrated Medicine (NiiCM), National Institute of Drug Abuse (NIDA), National Institutes of Health, National Institute of Mental Health (NIMH), Naurex, Navitor Pharmaceuticals, Nestle Health Sciences, Neuralstem, Neurocrine Biosciences, Neuronetics, NeuroRx, NextWave Pharmaceuticals, Niraxx Light Therapeutics, Northwestern University, Novartis, Nutrition 21, Opiant Pharmecuticals, Orexigen Therapeutics, Organon Pharmaceuticals, Osmotica, Otsuka Pharmaceuticals, Ovid Therapeutics, Pamlab, Perception Neuroscience, Pfizer, Pharmaceutical Research Associates, Pharmacia-Upjohn, PharmaStar, PharmaTher, Pharmavite, PharmoRx Therapeutics, Photothera, Polaris Partners, Praxis Precision Medicines, Precision Human Biolaboratory, Premiere Research International, Prexa Pharmaceuticals, Protagenic Therapeutics, PPD, Psy Therapeutics, PsychoGenics, Psylin Neurosciences, PThera, Purdue Pharma, Puretech Ventures, RCT Logic (formerly Clinical Trials Solutions), Reckitt Benckiser, Relmada Therapeutics, Rexahn Pharmaceuticals, Ridge Diagnostics, Sanofi-Aventis US, Schering-Plough Corporation, Sentier Therapeutics, Sepracor, Servier Laboratories, Shenox Pharmaceuticals, Shire, Solvay Pharmaceuticals, Somaxon Pharmaceuticals, Somerset Pharmaceuticals, Sonde Health, Stanley Medical Research Institute (SMRI), Sunovion Pharmaceuticals, Supernus Pharmaceuticals, Synthelabo, Taisho Pharmaceuticals, Takeda Pharmaceutical Company, Tal Medical, Tetragenex, Teva Pharmaceuticals, Transcept Pharmaceuticals, TransForm Pharmaceuticals, United BioSource, University of Michigan Department of Psychiatry, Usona Institute, Vanda Pharmaceuticals, Versant Venture Management, VistaGen, and Wyeth-Ayerst Laboratories; holds patents for Sequential Parallel Comparison Sequential Parallel Comparison Design (SPCD, licensed by MGH to Pharmaceutical Product Development (PPD, US_7840419, US_7647235, US_7983936, US_8145504, US_8145505) and for pharmacogenomics of depression treatment with folate (US_9546401, US_9540691); has a patent application for a combination of ketamine plus scopolamine in Major Depressive Disorder (MDD, licensed by MGH to Biohaven); and has a copyright for the MGH Cognitive & Physical Functioning Questionnaire (CPFQ), Sexual Functioning Inventory (SFI), Antidepressant Treatment Response Questionnaire (ATRQ), Discontinuation-Emergent Signs & Symptoms (DESS), Symptoms of Depression Questionnaire (SDQ), and SAFER (Lippincott, Williams & Wilkins; Wolkers Kluwer; World Scientific Publishing). Disclosures for MF can also be viewed at https://mghcme.org/faculty. CA has been a consultant to, provided expert testimony for, or received honoraria or grants from Acadia, Angelini, Boehringer, Gedeon Richter,

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#### Data sharing

Given the ongoing phase 3 study in negative symptoms of schizophrenia, the research data collected for the study, including individual participant data, will not be made available on request at this time.

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