Schizophrenia Bulletin Open
https://doi.org/10.1093/schizbullopen/sgac006

ENHANCE: Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Adjunctive Pimavanserin for Schizophrenia in Patients With an Inadequate Response to Antipsychotic Treatment

Dragana Bugarski-Kirola*[,1], Istvan Bitter[2], I-Yuan Liu[3], Brandon Abbs[4,5], and Srdjan Stankovic[4]

[1]Clinical Research, Acadia Pharmaceuticals GmbH, Basel, Switzerland; [2]Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary; [3]Biostatistics, Acadia Pharmaceuticals, San Diego, CA, USA; [4]Clinical Research, Acadia Pharmaceuticals, San Diego, CA, USA
[5]At the time this study was conducted.

*To whom correspondence should be addressed; 12830 El Camino Real Suite #400, San Diego, CA 92130, USA; tel: +41798658317, fax: +41 61 588 21 31; e-mail: dbugarski-kirola@acadia-pharm.com

Inadequate response to antipsychotic treatment is common in patients with schizophrenia. This study evaluated pimavanserin, a 5-HT_{2A} receptor inverse agonist/antagonist, as adjunctive treatment in patients with inadequate response. This was a 6-week, randomized, double-blind, placebo-controlled, study conducted in North America and Europe. Adult outpatients with schizophrenia and inadequate response to current antipsychotic were enrolled. Inclusion criteria included Positive and Negative Syndrome Scale (PANSS) total score ≥65 and ≤110 and retrospective antipsychotic treatment stability of 8 weeks. Pimavanserin 20 mg/day or placebo added to ongoing antipsychotic was tested in a flexible-dose paradigm with dose adjustments allowed during the first 3 weeks. The primary efficacy endpoint, PANSS total score change from baseline to week 6, was not met, although improvement was greater with pimavanserin than placebo (LS mean difference: –2.1, [95% CI: –4.5, 0.4]; *P* = .094). As a hierarchical testing procedure was used, additional efficacy analyses were exploratory. Clear separation from placebo was observed with pimavanserin at week 6 for the PANSS Negative Symptoms subscale (LS mean difference: –0.7, [95% CI: –1.5, 0.0]) and Marder Negative Symptom Factor score (–0.9, [–1.7, –0.1]). Analysis of European sites (81.5% of patients) revealed a difference for pimavanserin versus placebo on PANSS total score (LS mean difference: –3.1, [95% CI: –5.8, –0.4]) and Clinical Global Impressions–Severity score (–0.2, [–0.4, –0.0]). Treatment-emergent adverse events occurred in 39.9% with pimavanserin and 36.4% with placebo. Although statistical significance for the primary endpoint was not met, a trend toward improvement in negative symptoms was observed with pimavanserin, warranting further study.

Key words: serotonin receptor 5-HT2A/treatment nonresponse/antipsychotic agents

Introduction

Second-generation antipsychotics are currently the standard of treatment for schizophrenia.[1] Despite proven efficacy, their use is associated with a high prevalence of residual morbidity due to an inadequate response to antipsychotic treatment. Consequently, a substantial proportion of patients continue to have persistent residual symptoms despite having symptomatic improvement with antipsychotic treatment.[2] These ongoing psychotic symptoms have been associated with a higher risk of relapse and hospitalization[3] and a significant reduction in quality of life and functioning.[4]

Many compounds have been investigated as adjunctive therapies to antipsychotics without demonstrating convincing efficacy in treating nonresponding or residual schizophrenia symptoms.[5] The results of these studies indicate that most types of polypharmacy are not beneficial[6]; however, this is a field that needs further research. While adding medications to antipsychotic drug treatments is common when managing partial response in schizophrenia, no pharmacologic combination has been approved for this indication. Thus, a need exists for treatment options that improve response, remission, and recovery rates as well as safety and tolerability profile compared with current treatments for schizophrenia.

Pimavanserin is a highly selective, 5-hydroxytryptamine $(5\text{-HT})_{2A}$ inverse agonist/antagonist with low appreciable activity at 5-HT_{2C} receptors and no affinity for adrenergic,

dopaminergic, histaminergic, and muscarinic receptors.[7] The rationale for an effect of pimavanserin in psychosis has been well described.[8,9] Beneficial effects of pimavanserin for the treatment of psychosis were seen in previous clinical studies in patients with schizophrenia and with psychosis associated with Parkinson's disease or Alzheimer's disease.[10–12] Pimavanserin is approved in the United States for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis and is currently being investigated in negative symptoms of schizophrenia. The phase 3 ENHANCE study evaluated the efficacy and safety of adjunctive pimavanserin for the treatment of schizophrenia in patients with an inadequate response to current antipsychotic treatment.

Methods

The study protocol was reviewed and approved by an independent ethics committee or institutional review board at each study 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 of Harmonization guidelines. All patients provided written informed consent prior to any study procedures. The study was registered at ClinicalTrials.gov (Identifier: NCT02970292).

Study Design and Participants

This was a 6-week, randomized, double-blind, placebo-controlled, multicenter study conducted in North America and Europe. Adult stable outpatients with schizophrenia defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) and confirmed by a customized module of the Structured Clinical Interview for DSM-5, Clinical Trials Version (SCID-5-CT)[13] were eligible if they had an inadequate response to current antipsychotic treatment.

The study was up to 14 weeks long consisting of a screening period of up to 4 weeks and a 6-week treatment period. Patients who completed the treatment period were eligible to enroll in a 52-week open-label extension phase. For patients who did not enroll in the extension phase or discontinued prematurely from the study, a 4-week safety follow-up (telephone call) was conducted. At baseline, patients were randomized to receive pimavanserin 20 mg/d or placebo added to their ongoing antipsychotic treatment for 6 weeks. Pimavanserin could be increased to 34 mg/d or decreased to 10 mg/d as needed for efficacy or tolerability during the first 3 weeks of treatment.

Men or women ≥18 and ≤55 years of age were eligible if they had a diagnosis of schizophrenia ≥1 year prior to randomization and moderate-to-severe psychotic symptoms, defined as a Positive and Negative Syndrome Scale (PANSS) total score ≥65 and ≤110 with no change >30% between screening and baseline, a PANSS item score ≥4 (moderate or worse) on at least two of the three selected items (P1 delusions, P3 hallucinations, and P6 suspiciousness/persecution), and a Clinical Global Impressions–Severity (CGI-S) score ≥4 at both screening and baseline. To be eligible, patients previously stabilized on an adequate dose of an antipsychotic within the dose range recommended by local regulations for at least 8 weeks prior to screening had to have a partial but inadequate response to treatment established through treatment history and an independent telemedicine interview. Antipsychotic compliance was confirmed by measuring antipsychotic drug levels at screening.

Exclusion criteria included the following: current comorbid psychiatric condition other than schizophrenia; history of resistance to antipsychotic treatment (defined here as minimal response to ≥2 adequate antipsychotic medications at adequate doses for an adequate length of time or treatment with clozapine for refractory psychosis or use of clozapine within 12 weeks of screening); risk of suicide or violent behavior; substance abuse disorder; treatment with three or more antipsychotics within 8 weeks of screening; use of any medication that could prolong the QT interval or history of long QT syndrome or prolonged QRS interval; presence of any medical condition that could interfere with the conduct of the study. A pill count (placebo or pimavanserin) was performed at each visit to document compliance. Patients with <80% or >120% compliance could be discontinued from the study unless there was a justifiable and transient reason for lower compliance, or a case of inadvertent overcompliance, both of which would have been captured as protocol deviations. Complete inclusion/exclusion criteria are listed in Supplementary material S1. Prohibited and restricted therapies and concomitant medications are listed in Supplementary material S2.

Randomization was in a 1:1 ratio using an interactive response system to pimavanserin or placebo stratified by North America versus Europe using a computer-generated permuted-block randomization schedule. Blinding was assured by restricting access of personnel and/or designee to the treatment codes and providing identical tablets and packaging for adjunctive pimavanserin and placebo treatments.

Assessments

The primary efficacy measure was the change from baseline to week 6 in the PANSS total score.[14] The key secondary outcome measure/variable was the mean change from baseline to week 6 for the CGI-S score.[15] The PANSS, including the Informant Questionnaire for the PANSS (IQ-PANSS),[16] and CGI-S were administered at screening, baseline, and weekly, and the Clinical Global Impressions—Improvement scale (CGI-I) was assessed at weeks 1 through 6. The Karolinska Sleepiness Scale (KSS)[17] was administered at baseline and weekly. The

36-Item Short-Form Health Survey (SF-36),[18] Drug Attitude Inventory (DAI),[19] and Personal and Social Performance scale (PSP)[20] were administered at baseline and week 6. The Calgary Depression Scale for Schizophrenia (CDSS)[21] was administered at screening, baseline, and week 6.

All efficacy and safety assessments were performed by certified raters at each site to ensure reliable results. Comprehensive rater training and an in-study assessment program was used to identify discrepant scoring and unusual scoring patterns. Site data monitoring was used to ensure quality of efficacy assessments, reduce variability, and ensure consistency across the sites. Kappa analyses of rater scoring agreement were done based on the prestudy qualification scoring procedure for the PANSS scale study to assess inter-rater reliability both at the group and individual rater level. The proportion of agreement expected based on chance alone was assumed to be 0.7.[22] The methodology for calculating kappa and weighting to correct for chance is in Supplementary text S3. A weighted kappa value of 0.75–1.00 was determined to indicate an excellent level of agreement. Qualified raters were those with good, weighted kappa based on their prestudy qualification rating(s). In the study, overall kappa was 0.906. Individual kappa values also indicated excellent agreement among all raters (individual kappa range, 0.809–0.941).

Safety assessments included adverse events (AEs), physical examination, vital signs (heart rate, blood pressure, respiratory rate, temperature), body weight, 12-lead electrocardiogram, and clinical laboratory tests (hematology, chemistry, urinalysis, prolactin). The Columbia–Suicide Severity Rating Scale[23] was assessed at screening, baseline, and weekly, and the Barnes Akathisia Rating Scale (BARS),[24] Abnormal Involuntary Movement Scale (AIMS),[25] and Simpson–Angus Scale (SAS)[26] were assessed at baseline and weeks 1, 3, and 6.

Statistical Analysis

For sample size determination, it was assumed, based on prior results in a similar population,[10] that a 6.0 difference between pimavanserin and placebo for the mean change in the PANSS total score from baseline to week 6 would be clinically meaningful, and the common standard deviation would be 17.0 points. Thus, 171 evaluable patients per treatment group would provide at least 90% power to detect a difference between pimavanserin and placebo at a significance level of 0.05, using a two-sided *t*-test. Adjusting for a potential nonevaluable rate of up to 10%, approximately 380 patients (190 patients per treatment group) were to be randomized. The safety analysis set included all randomized patients who received at least one dose of study drug and was used for analysis of all safety endpoints. The full analysis set (FAS) included all randomized patients who received at least one dose of study drug and had both a baseline value and at least one postbaseline value for the PANSS total score and was used for analysis of all efficacy endpoints.

The primary outcome of change in PANSS total score was analyzed using mixed-effects model for repeated measures (MMRM) with change from baseline as the dependent variable, and treatment group (pimavanserin or placebo), visit, treatment-by-visit interaction, geographic region (North America, Europe), baseline PANSS total score, and baseline-by-visit interaction as independent variables. The treatment comparison was based on the difference in least squares (LS) mean at week 6 and was tested at an alpha level of 0.05 (two-sided) using the FAS. Exploratory analyses of PANSS total score at each of the other timepoints (weeks 1, 2, 3, 4, and 5) were conducted using the same MMRM model. A hierarchical testing procedure was used to control the type 1 error rate across the primary and key secondary endpoint.

Secondary and exploratory endpoints (CGI-S, PANSS Marder Factor score,[27] PANSS subscales, and KSS) were analyzed using the MMRM model. The CGI-I score at each postbaseline timepoint was analyzed using the MMRM model with CGI-I score as the dependent variable, and treatment group, visit, the treatment-by-visit interaction, geographic region, baseline CGI-S score, and the baseline-by-visit interaction as independent variables. The change from baseline to week 6 for the PSP, Drug Attitude Inventory, CDSS, and SF-36 scores was analyzed using an analysis of covariance model with effects for treatment group and geographic region, and the baseline value as a covariate.

Thus, the proportion of patients with ≥20% or ≥30% reduction in the PANSS total score, and the proportion of patients with a CGI-I score of 1 or 2 were summarized at each timepoint, and treatment groups were compared using a Cochran-Mantel-Haenzel test stratified by geographic region. Observed cases were analyzed in all statistical models. Since the PANSS is an interval scale that lacks a natural zero point (possible scores range from 30 to 210), the percentage change in PANSS total score was calculated based on corrected scores after subtracting 30 points from the raw scores. All analyses were performed using SAS® V9.2 or higher.

Results

A total of 633 patients were screened, and 396 patients were randomized to pimavanserin (n = 198) or placebo (n = 198) at 88 clinical sites in North America and Europe between October 2016 and June 2019. Overall, 88% of pimavanserin and 96% of placebo patients completed the study; the most common reason for study discontinuation was consent withdrawn (Supplementary figure S1). The FAS comprised 196 patients on placebo and 193 on pimavanserin (table 1). At baseline, 222 (57.1%) patients were markedly ill based on a CGI-S score ≥5, and 179 (46.0%) patients had a PANSS total score ≥90.

Table 1. Baseline Characteristics (FAS Population)

	Placebo (n = 196)	Pimavanserin (n = 193)
Age, years[a]	37.5 ± 9.4	36.9 ± 9.5
Male gender, n (%)	120 (61.2)	122 (63.2)
Europe, n (%)	160 (81.6)	157 (81.3)
North America, n (%)	36 (18.4)	36 (18.7)
Race, n (%)		
White	170 (86.7)	172 (89.1)
Black/African American	22 (11.2)	21 (10.9)
Other	4 (2.0)	0
Age at diagnosis, years[a]	26.5 ± 7.4	26.4 ± 7.8
Duration of schizophrenia, years[a]	12.0 ± 8.5	11.5 ± 8.1
Background antipsychotic, n (%)[b]		
Aripiprazole	45 (23.0)	38 (19.7)
Asenapine	--	1 (0.5)
Brexpiprazole	1 (0.5)	4 (2.1)
Capriprazine	1 (0.5)	1 (0.5)
Lurasidone	2 (1.0)	5 (2.6)
Olanzapine	70 (35.7)	69 (35.8)
Risperidone	77 (39.3)	75 (38.9)
PANSS total score[a]	88.1 ± 8.6	88.3 ± 9.4
PANSS positive symptom score[a]	22.8 ± 3.2	23.0 ± 3.4
PANSS negative symptom score[a]	23.1 ± 4.0	23.0 ± 4.1
PANSS general psychopathology[a]	42.2 ± 5.9	42.4 ± 6.2
PANSS Marder Factor Score		
Negative symptoms[a]	22.5 ± 4.2	22.3 ± 4.5
Positive symptoms[a]	27.7 ± 3.4	27.9 ± 3.9
CGI-S [a]	4.6 ± 0.5	4.6 ± 0.6
Karolinska Sleepiness Scale[a]	4.7 ± 1.7	4.6 ± 1.5

Note: CGI-S, Clinical Global Impression–Severity; FAS, full analysis set; PANSS, Positive and Negative Syndrome Scale.
[a] Mean ± standard deviation.
[b] Includes oral and long-acting injectable formulations.

In the safety analysis population, the last dose in the study was 34 mg for 55% of patients (218 of 396; pimavanserin, n = 105; placebo, n = 113), 20 mg for 42% (168 of 396; pimavanserin, n = 88; placebo, n = 80), and 10 mg for 3% (10 of 396; pimavanserin, n = 5; placebo, n = 5). Of randomized patients, 4 patients (2%; 2 from each treatment group) were discontinued because of noncompliance with the study drug (returned >20% of provided tablets). Nonantipsychotic concomitant medication used in the study is summarized in Supplementary table S1. Anticholinergics used during the study by placebo and pimavanserin groups were biperiden hydrochloride (2.0% and 4.0%), trihexyphenidyl (3.0% both), biperiden (2.0% both), benztropine (1.0% and 1.5%), and benztropine mesylate (1.0% both), respectively.

Efficacy

The change from baseline to week 6 on the primary efficacy endpoint (PANSS total score) was numerically greater in the pimavanserin group compared with the placebo group, however, the difference was not statistically significant (LS mean difference: –2.1, 95% confidence interval [CI]: –4.5, 0.4; P = .094). This difference was also smaller than what was hypothesized to be clinically significant at the time of sample size calculation. Gradually increasing separation from placebo was observed from week 3 onward (figure 1).

As there was no evidence of superiority of pimavanserin versus placebo with respect to the primary efficacy endpoint, formal testing for the key secondary endpoint and other efficacy endpoints was not performed. The results of all analyses of these endpoints were therefore exploratory. For the CGI-S, the change from baseline to week 6 also indicated a nonsignificant treatment difference in favor of pimavanserin versus placebo (LS mean difference: –0.1, 95% CI: –0.3, 0.0; table 2). Nominal differences were observed at week 3 (LS mean difference: –0.1, 95% CI: –0.2, –0.0), week 4 (–0.2, 95% CI: –0.4, –0.1), and week 5 (–0.2, 95% CI: –0.3, –0.0) (figure 1).

A prespecified analysis by region (Europe: 81.5%; North America: 18.5%) revealed a difference at week 6 for pimavanserin versus placebo on both the PANSS total score (LS mean difference: –3.1, 95% CI: –5.8, –0.4) and the CGI-S score (LS mean difference: –0.2, 95% CI: –0.4, –0.0) in the European region (figure 2 and table 3). Notable improvements on the CGI-S were observed in the pimavanserin group versus placebo at weeks 3 (LS mean difference: –0.1, 95% CI: –0.3, –0.0), 4 (–0.3, 95% CI: –0.4, –0.1), and 5 (–0.2, 95% CI: –0.4, –0.0) for the European region (figure 2).

In the FAS, a difference favoring pimavanserin versus placebo was observed at week 6 for the PANSS Negative Symptoms subscale (table 2) and for the PANSS Marder Negative Symptom Factor score (table 3). This difference was more pronounced at European sites, where a greater separation of pimavanserin from placebo was observed from week 2 onward for the PANSS Marder Negative Symptom Factor score compared with separation at weeks 3 and 4 for the PANSS Marder Positive Symptoms Factor score (figure 3). Similarly, a difference in favor of pimavanserin versus placebo was observed at week 6 in the European region (LS mean difference: –1.1, 95% CI: –1.9, –0.2) on the PANSS Negative Symptoms subscale. No significant differences between treatment groups were observed for either positive or negative symptoms for North America.

For the CGI-I (score of 1 or 2), response rates were 39.3% and 34.4% with pimavanserin and placebo, respectively (difference: 4.9%, 95% CI: –5.0, 14.7) at week 6. The

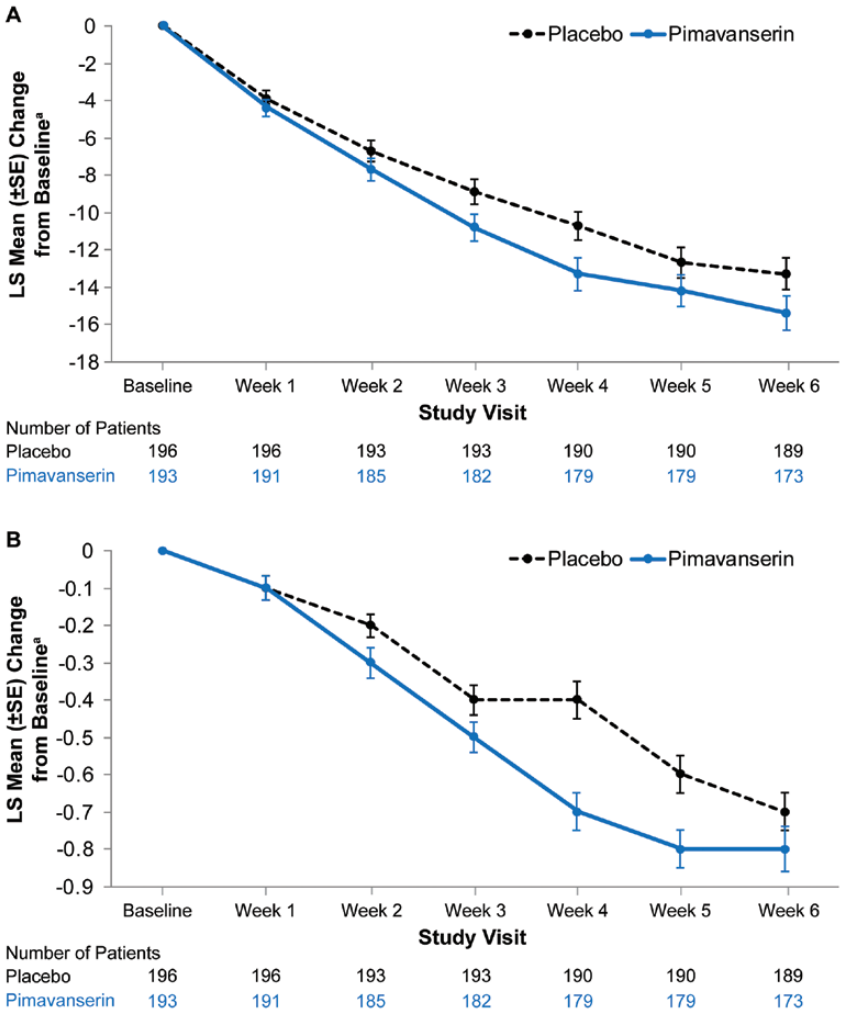

Fig. 1. Mean change from baseline for PANSS total score (A) and CGI-S score (B). FAS population. [a] LS mean from MMRM with fixed effects of region (North America, Europe), planned treatment (adjunctive pimavanserin, adjunctive placebo), study visit (weeks 1, 2, 3, 4, 5, 6), treatment-by-visit interaction, baseline score, and baseline-by-visit interaction. An unstructured covariance matrix is used to model the within-subject errors. The denominator degrees of freedom are estimated using the Kenward-Roger approximation; CGI-S, Clinical Global Impressions–Severity; FAS, full analysis set; LS, least squares; MMRM, mixed-effect model for repeated measures; PANSS, Positive and Negative Syndrome Scale; SE, standard error.

proportion of responders at week 6 (≥20% improvement in PANSS total score) was 63.0% with pimavanserin versus 52.4% with placebo (difference: 10.6%, 95% CI: 0.4, 20.5). Response rates for the PANSS total score in the European region were consistently higher with pimavanserin versus placebo beginning at week 2 (figure 4).

For the KSS, separation from placebo was observed with pimavanserin beginning at week 4, and the difference between treatments favored pimavanserin (LS mean difference: –0.3, 95% CI: –0.6, –0.0) at week 6 (table 2). Changes for the CDSS, SF-36, DAI, and the PSP were similar between placebo and pimavanserin groups (table 3).

Safety

Pimavanserin was well tolerated, with treatment-emergent adverse events (TEAEs) occurring in 79 (39.9%) patients with pimavanserin versus 72 (36.4%) with placebo (table 4). The most common TEAEs were somnolence (6.6%), headache (6.6%), and insomnia (5.1%) with pimavanserin, and headache (9.1%) with placebo. The most common treatment-related TEAEs with pimavanserin were somnolence (11 patients, 5.6%), nausea (5 patients, 2.5%), insomnia (5 patients, 2.5%), headache (3 patients, 1.5%), and anxiety (3 patients, 1.5%). Serious TEAEs occurred in 2 (1.0%) patients with pimavanserin (schizophrenia, hallucinations, suicidal ideation) and 2 (1.0%) patients with placebo (schizophrenia, psychotic symptoms, self-injurious ideation). Five (2.5%) patients discontinued pimavanserin for 7 TEAEs (palpitations, psychogenic visual disorder, suicidal ideation [n = 2], hallucinations [n = 2], schizophrenia). No patients discontinued placebo for TEAEs. No deaths occurred in either group.

Table 2. Baseline and Mean Change at Week 6 for Primary and Secondary Outcomes (FAS Population)

Endpoint	Placebo (N = 196)		Pimavanserin (N = 193)			
	Mean (SE) baseline	LS mean (SE) change at week 6	Mean (SE) baseline	LS mean (SE) change at week 6	LS mean (SE) difference 95% CI	Cohen's d effect size
Primary						
PANSS total score	88.1 (0.61)	–13.3 (0.86)	88.3 (0.68)	–15.4 (0.89)	–2.1 (1.24) [–4.5, 0.4]	0.173
Secondary						
Clinical Global Impressions-Severity	4.6 (0.04)	–0.7 (0.05)	4.6 (0.04)	–0.8 (0.06)	–0.1 (0.08) [–0.3, 0.0]	0.200
PANSS Positive Symptoms Subscale	22.8 (0.23)	–4.9 (0.30)	23.0 (0.25)	–5.4 (0.31)	–0.5 (0.43) [–1.4, 0.4]	0.120
PANSS Negative Symptoms Subscale	23.1 (0.29)	–2.0 (0.26)	23.0 (0.29)	–2.8 (0.27)	–0.7 (0.37) [–1.5, –0.0]	0.206
Personal and Social Performance	51.6 (0.78)	5.6 (0.62)	51.8 (0.79)	6.9 (0.64)	1.3 (0.89) [-0.5, 3.0]	0.148
Drug Attitude Inventory –10	5.8 (0.23)	0.4 (0.18)	5.6 (0.24)	0.4 (0.18)	–0.0 (0.25) [–0.5, 0.5]	–0.015
Karolinska Sleepiness Scale Score	4.7 (0.12)	–0.2 (0.10)	4.6 (0.11)	–0.5 (0.10)	–0.3 (0.14) [–0.6, –0.0]	0.232

Note: FAS, full analysis set; LS, least squares; PANSS, Positive and Negative Syndrome Scale; SE, standard error; SF-36, 36-Item Short-Form Health Survey.

No clinically significant effects of pimavanserin were reported on clinical laboratory tests or vital signs. Bodyweight increased ≥7% from baseline in 3/191 (1.6%) patients on placebo and 5/189 (2.6%) patients on pimavanserin. Elevations >500 ms in the QTcB or QTcF interval at any time postbaseline were not reported in any patients, and a >60 ms change from baseline in the QTcB interval was reported for 1/195 (0.5%) patient on placebo and 2/189 (1.1%) patients on pimavanserin. Six (3.0%) patients in each group reported postbaseline suicidal ideation on the Columbia–Suicide Severity Rating Scale, and no patients had suicidal behavior.

The incidence of extrapyramidal symptoms was low in this study. Mean (standard deviation) change from baseline to week 6 with adjunctive pimavanserin and placebo for the AIMS (–0.1 [0.83], –0.1 [0.41]), BARS (–0.1 [0.52], 0.0 [0.60]), and SAS (–0.3 [1.11], 0.0 [0.84]) was minimal (Supplementary table S2). No patients in placebo and pimavanserin groups experienced dyskinesias when defined as a score of ≥3 on any of the first seven AIMS items or ≥2 on any two of the first seven AIMS items. Among patients without akathisia at baseline, 1/189 (0.5%) on placebo and 4/186 (2.2%) on pimavanserin experienced akathisia at any postbaseline visit using a score of ≥2 on BARS as the cutoff. Among patients without Parkinsonism at baseline, 4/182 (2.2%) on placebo and 3/181 (1.7%) on pimavanserin had signs of Parkinsonism (SAS total score >3) at any postbaseline visit (Supplementary table S3).

Discussion

In this multicenter, randomized, double-blind, placebo-controlled study in patients with an inadequate response to ongoing antipsychotic treatment, neither the primary endpoint of change in PANSS total score at 6 weeks nor the key secondary endpoint of change in CGI-S at 6 weeks was met. However, increasing separation from placebo was apparent with pimavanserin at later timepoints with exploratory efficacy analyses suggesting a trend toward improvement in all symptoms of schizophrenia, notably more in negative symptoms.

The overall improvement in the PANSS total score with pimavanserin treatment (LS mean [standard error; SE]: –15.4 [0.89]) was comparable to that reported in similar studies of adjunctive treatment in stable schizophrenia patients with a partial response to antipsychotic treatment (mean: –11.2 with cannabidiol after 6 weeks of treatment; –10.5 to –14.4 for bitopertin after 12 weeks of treatment).[28,29] However, the placebo group in the ENHANCE study (LS mean [SE]: –13.3 [0.86]) demonstrated a stronger response than the placebo groups in these prior studies (mean: –8.8 after 6 weeks of treatment in the cannabidiol study; –11.65 to –14.1 after 12 weeks of treatment in the 3 bitopertin studies).[28,29]

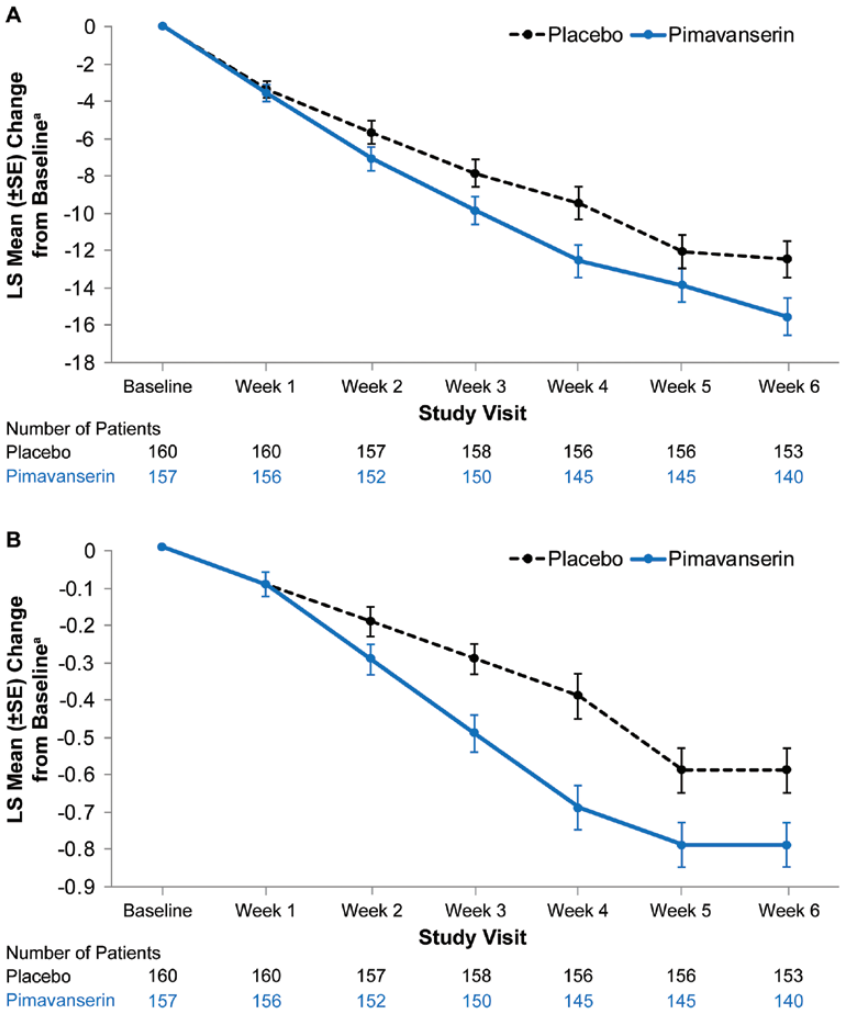

Fig. 2. Mean change from baseline among prespecified subgroup of patients enrolled in Europe for PANSS total score (A) and CGI-S score (B). FAS population. [a] LS mean from MMRM with fixed effects of region (North America, Europe), planned treatment (adjunctive pimavanserin, adjunctive placebo), study visit (weeks 1, 2, 3, 4, 5, 6), treatment-by-visit interaction, baseline score, and baseline-by-visit interaction. An unstructured covariance matrix is used to model the within-subject errors. The denominator degrees of freedom are estimated using the Kenward-Roger approximation; CGI-S, Clinical Global Impressions–Severity; FAS, full analysis set; LS, least squares; MMRM, mixed-effect model for repeated measures; PANSS, Positive and Negative Syndrome Scale; SE, standard error.

Overall safety and tolerability of pimavanserin was comparable to placebo with a very low rate of serious AEs and discontinuation for AEs. No deaths occurred, and no clinically significant differences between pimavanserin and placebo were observed for vital signs, body weight, electrocardiogram findings, or extrapyramidal symptoms. Of randomized patients, only 4 (2%) were discontinued from the study due to noncompliance with study drug, and over 90% of patients in the FAS completed the study.

Several factors, such as a higher than expected placebo response,[30] the inherent variability and heterogeneity of antipsychotic response among individual patients,[31] and a lower responsiveness in patients with multi-episode schizophrenia[31] may have contributed to the lack of a statistically significant effect of pimavanserin on the primary endpoint. In this study, while the proportion of responders at week 6 who had minimal clinical improvement (defined as ≥20% improvement in PANSS total score),[32] was 56.5% with pimavanserin, the proportion of responders in the placebo group (50.5%) was also high, representing a substantial placebo effect. Increased clinical attention in weekly visits, along with caregiver support, might have accounted for meaningful improvements in both pimavanserin and placebo arms. Analyses of geographic differences in outcomes from schizophrenia studies have found increased placebo responses and have suggested lower treatment effects in North American studies sites compared with European sites.[33,34] Differences in patient populations, academic versus commercial sites, rates of antipsychotic polypharmacy, and medical practice may explain these differences.[34,35] The large number of investigative sites have been previously associated with greater placebo response.[36] In this study, because of large sample size

Table 3. Baseline and Mean Change at Week 6 for Exploratory Outcomes (FAS Population)

	Placebo (N = 196)		Pimavanserin (N = 193)			
Endpoint	Mean (SE) baseline	LS mean (SE) change at week 6	Mean (SE) baseline	LS mean (SE) change at week 6	LS mean (SE) difference 95% CI	Cohen's d effect size
PANSS total score—Europe	88.8 (0.65) N = 160	–12.5 (0.96)	89.2 (0.72) n = 157	–15.6 (0.98)	–3.1 (1.37) [–5.8, –0.4]	0.261
PANSS total score—North America	84.7 (1.59) n = 36	–16.8 (1.91)	84.7 (1.71) n = 36	–14.2 (1.96)	2.6 (2.74) [–2.8, 8.1]	–0.229
Clinical Global Impressions-Severity—Europe	4.6 (0.04) n = 160	–0.6 (0.06)	4.6 (0.04) n = 157	–0.8 (0.06)	–0.2 (0.09) [–0.4, 0.0]	0.266
Clinical Global Impressions-Severity—North America	4.4 (0.08) n = 36	–0.8 (0.1)	4.6 (0.09) n = 36	–0.7 (0.11)	0.1 (0.15) [–0.2, 0.4]	–0.144
PANSS Positive Symptoms Subscale—Europe	22.7 (0.24) n = 160	–4.7 (0.34)	23.0 (0.28) n = 157	–5.5 (0.35)	–0.8 (0.49) [–1.8, 0.1]	0.195
PANSS Negative Symptoms Subscale—Europe	23.5 (0.31) n = 160	–1.9 (0.29)	23.6 (0.29) n = 157	–2.9 (0.29)	–1.1 (0.41) [–1.9, –0.2]	0.296
Marder Factor Score—Positive Symptoms	27.7 (0.24)	–4.7 (0.33)	27.9 (0.28)	–5.5 (0.34)	–0.8 (0.48) [–1.7, 0.2]	0.162
Marder Factor Score—Negative Symptoms	22.5 (0.30)	–2.5 (0.29)	22.3 (0.33)	–3.4 (0.30)	–0.9 (0.41) [–1.7, –0.1]	0.218
Marder Factor Score—Positive Symptoms—Europe	27.8 (0.26) n = 160	–4.7 (0.37)	28.0 (0.30) n = 157	–5.6 (0.38)	–1.0 (0.53) [–2.0, 0.1]	0.211
Marder Factor Score—Negative Symptoms—Europe	22.8 (0.32) n = 160	–2.2 (0.31)	22.7 (0.33) n = 157	–3.4 (0.32)	–1.3 (0.45) [–2.2, –0.4]	0.330
SF-36 Physical Health Composite	52.8 (0.61)	0.44 (0.47)	52.7 (0.59)	0.46 (0.49)	0.0 (0.68) [–1.3, 1.3]	0.002
SF-36 Mental Health Composite	36.7 (0.79)	4.6 (0.69)	38.0 (0.81)	5.6 (0.72)	0.99 (1.00) [–1.0, 3.0]	0.105
Calgary Depression Scale for Schizophrenia	2.1 (0.19)	–0.4 (0.12)	1.9 (0.15)	–0.6 (0.12)	–0.2 (0.17) [–0.5, 0.2]	0.094

Note: FAS, full analysis set; LS, least squares; PANSS, Positive and Negative Syndrome Scale; SE, standard error; SF-36, 36-Item Short-Form Health Survey.

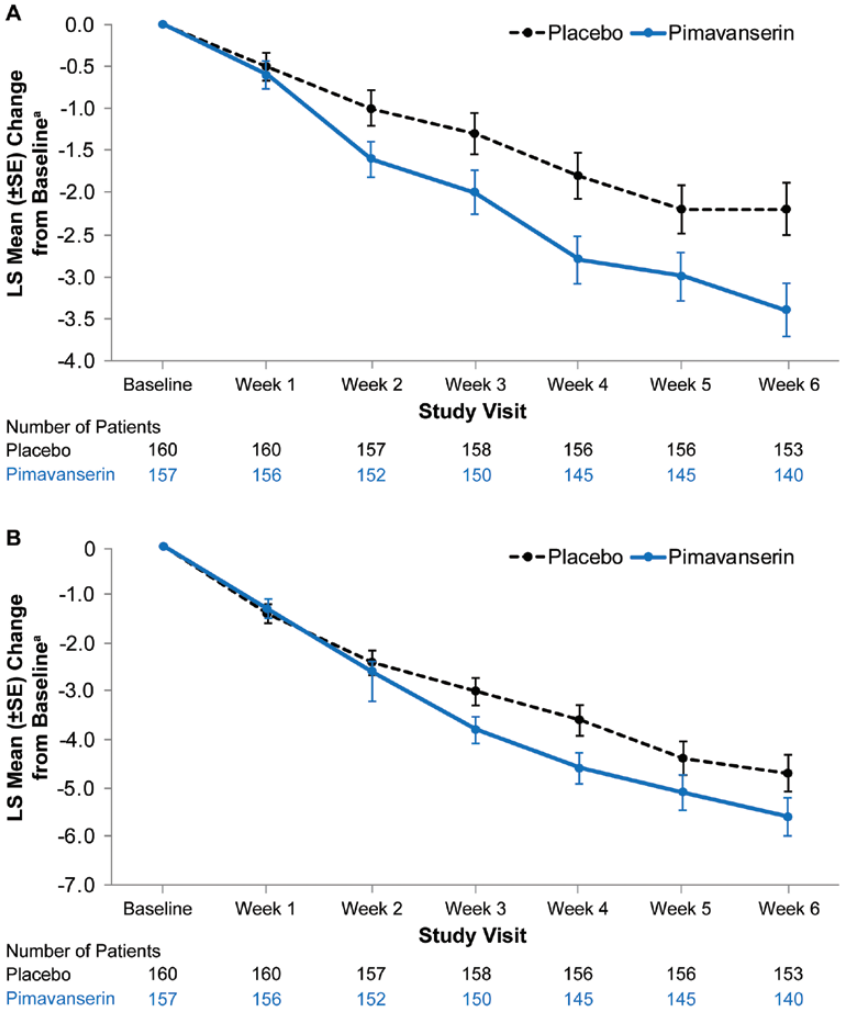

Fig. 3. Mean change from baseline among prespecified subgroup of patients enrolled in Europe for PANSS Marder Factor Score for negative symptoms (A) and positive symptoms (B). FAS population. [a] LS mean from MMRM with fixed effects of planned treatment (adjunctive pimavanserin, adjunctive placebo), study visit (weeks 1, 2, 3, 4, 5, 6), treatment-by-visit interaction, baseline score (continuous covariate), and baseline-by-visit interaction. An unstructured covariance matrix is used to model the within-subject errors. The denominator degrees of freedom are estimated using the Kenward-Roger approximation; FAS, full analysis set; LS, least squares; MMRM, mixed-effect model for repeated measures; PANSS, Positive and Negative Syndrome Scale; SE, standard error.

requirements, 88 investigative sites were engaged. In spite of ongoing rater calibration and quality oversight that reduced the variability of response in our study, their impact on greater placebo response cannot be excluded.

An effort was made to enrich the population by enrolling patients who might be better responders to study treatment based on a broad range of PANSS severity inclusion criteria and focusing on a younger patient population with shorter treatment duration history. Although the mean patient age at screening was younger (37.2 years) than the mean age in comparable studies (39-43 years),[29] with a mean treatment duration of 11 to 12 years since diagnosis, the vast majority (over 84%) of patients enrolled in our study had a history of multiple hospitalizations for schizophrenia (1–5 hospitalizations: 67%; 6–10 hospitalizations: 17.7%). Consequently, despite the effort to recruit patients earlier in their disease course, the actual population enrolled is representative of more severely affected patients who may have already reached the maximum benefit from background antipsychotic therapy.[37] In fact, a good proportion of patients recruited may meet the minimal criteria for treatment resistance based on the TRRIP working group consensus.[38] In addition, while the flexible dose design allowed for dose increases for efficacy, the protocol did not mandate the dosing schedule to start with the highest dose. Consequently, only 55% of the patients received 34 mg as their last dose level, leaving the possibility that potential underdosing may also have contributed to the negative outcome of the study.

Further measures such as inclusion/exclusion criteria designed to select patients with an inadequate response to treatment, confirmation of the adherence to the antipsychotic at screening and throughout the study, and

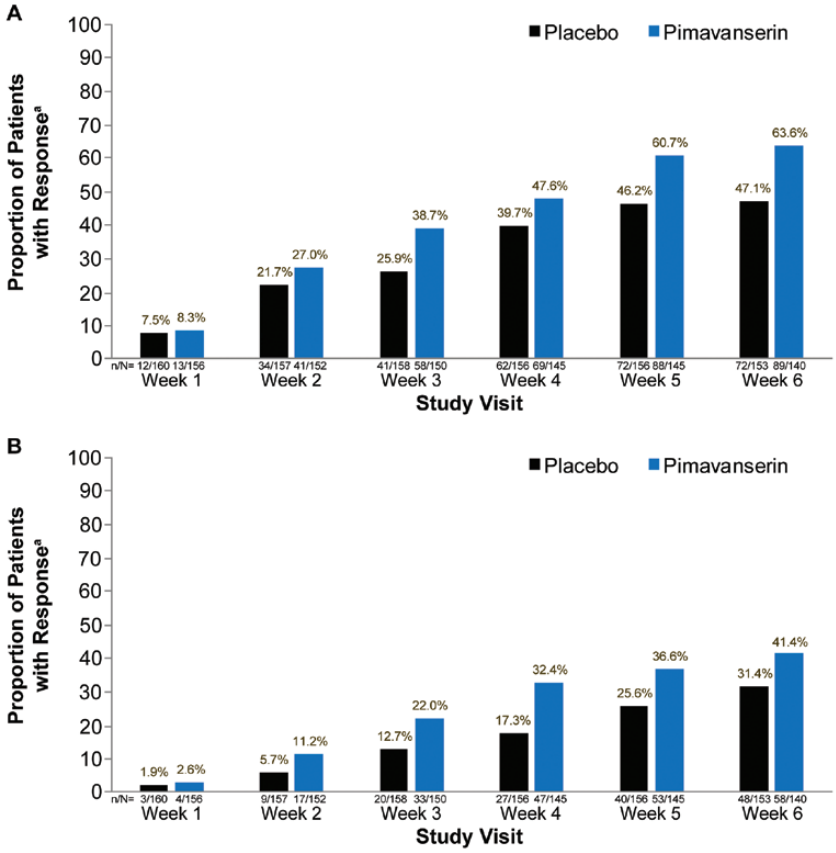

Fig. 4. Response rates for ≥20% improvement from baseline to week 6 (A) and ≥30% improvement from baseline to week 6 (B) on the PANSS total score for the European region. FAS population. *Note:* FAS, full analysis set; PANSS, Positive and Negative Syndrome Scale.

Table 4. Incidence of Treatment-Emergent Adverse Events (Safety Population)

	Number (%) of patients	
	Placebo (n = 198)	Pimavanserin (n = 198)
Any TEAE	72 (36.4)	79 (39.9)
Drug-related TEAE	25 (12.6)	33 (16.7)
Serious TEAE	2 (1.0)	2 (1.0)
Discontinuation for TEAE	0	5 (2.5)
TEAEs occurring in ≥2% of either group, n (%)		
Headache	18 (9.1)	13 (6.6)
Somnolence	7 (3.5)	13 (6.6)
Insomnia	7 (3.5)	10 (5.1)
Dizziness	5 (2.5)	3 (1.5)
Nausea	4 (2.0)	6 (3.0)
Nasopharyngitis	4 (2.0)	5 (2.5)
Anxiety	2 (1.0)	5 (2.5)
Respiratory tract infection	1 (0.5)	5 (2.5)

Note: AE, adverse event; TEAE, treatment-emergent adverse event.

study drug adherence checks at each study visit were undertaken to minimize variability among the study population. Additionally, site data monitoring was employed to ensure quality and consistency across sites and to reduce variability. Despite these measures, the heterogeneity of schizophrenia syndrome remains an obstacle to demonstrating an overall group effect.

Many exploratory analyses were conducted to understand the findings of this study. In particular, most analyses consistently revealed notable differences from

placebo on assessments of negative symptoms of schizophrenia, including the PANSS Negative Symptom subscale and Marder Negative Factor score in the FAS and among European study sites for negative symptoms on the same measures. These results, while interesting, should be interpreted with caution; however, they align with results from a prior study in patients with schizophrenia, where augmenting low-dose risperidone with pimavanserin demonstrated greater efficacy than low-dose risperidone with placebo in all symptom domains, including negative symptoms.[10] It is unclear whether this difference is generalizable across regions, as these effects were more prominent among European patients in this study. Moreover, while the study targeted enrollment of patients with positive symptoms, baseline severity of negative symptoms (measured by PANSS negative subscale) was reflective of a population with predominant negative symptoms (where predominant negative symptoms are defined as a PANSS negative subscale score greater than any occurring positive subscale score[39]). This is important to further understand the potential effect of pimavanserin on negative symptoms, given the retrospective stability of positive symptoms and antipsychotic treatment stability of the enrolled population in the ENHANCE study.

The possible benefit of adjunctive pimavanserin on negative symptoms is encouraging, considering that negative symptoms are poorly responsive to most antipsychotic treatments.[30,40] A meta-analysis of 21 antipsychotic clinical trials of negative symptoms in schizophrenia found significant improvement with amisulpride versus placebo,[41–44] and for cariprazine versus risperidone[45] where the effect size was 0.31.[40] These monotherapy results are similar to the effect sizes that were observed in this adjunctive treatment study for the PANSS Negative Symptoms subscale (0.206 overall; 0.296 among European sites). While this study did not demonstrate a significant difference in the PANSS total score between pimavanserin and placebo treatment groups, future studies of pimavanserin are warranted in clinical trials that target negative symptoms.

Potential limitations of this study include a 6-week treatment period, use of a flexible dosage schedule without requiring that patients achieve a maximum dose, study entry criteria that allowed for patients with different severity of disease, and within label but often high background antipsychotic dose that would imply treatment resistance. Prior pimavanserin studies show a separation from placebo after 2 weeks, but it is possible that a 6-week study in this population of patients with marked severity of illness did not allow sufficient time to observe a significant effect. As mentioned above, the flexible dose design, while resembling clinical practice, did not mandate at least an initiation of treatment with a maximum dose, leaving many patients on a potentially suboptimal dose throughout the whole study. Approximately 55% of patients received dosage escalation to 34 mg at the end of the study; 42% received 20 mg. In future studies, treatment with the 34-mg dose of pimavanserin could demonstrate an improved response.

Conclusion

The primary efficacy endpoint of change in PANSS total score at 6 weeks was not met, indicating lack of significant and clinically meaningful benefit of adjunctive pimavanserin over placebo in schizophrenia patients with inadequate response to antipsychotic treatment. Exploratory analyses identified trends toward improvement in negative symptoms, warranting future study. Overall safety and tolerability of pimavanserin was comparable to placebo.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin Open* online.

Funding

This work was supported by Acadia Pharmaceuticals Inc., San Diego, CA, USA. The funder of the study had a role in study design, data analysis, data interpretation, and writing of the report.

Acknowledgments

The authors acknowledge the editorial assistance of Richard S. Perry, PharmD, in the preparation of this manuscript, which was supported by Acadia Pharmaceuticals Inc., San Diego, CA. DBK worked on the literature search, conducted, collected, and analyzed data (efficacy and safety), data interpretation, and the writing of all parts of the report. IB searched the scientific literature and provided written contribution to the introduction and discussion in the paper. SS led the study design, final analysis, and interpretation of data, and provided input into the discussion and conclusions. I-YL created the statistical analysis plan, delivered data and tables, wrote the statistical analysis section in the paper, and generated data. BA worked on the efficacy data collection and interpretation and relevant literature search. All authors had full access to all the data in the study and had full responsibility for the content of the manuscript for publication. The corresponding author was responsible for the final review and had final responsibility for the decision to submit for publication.

Conflict of interest

Dragana Bugarski-Kirola, I-Yuan Liu, and Srdjan Stankovic are employees of Acadia Pharmaceuticals, Inc. and may be stockholders. Brandon Abbs was an employee of Acadia Pharmaceuticals, Inc. at the time of this study. Istvan Bitter received in the last 5 years honoraria or consultation fees from Angelini, Eli Lilly, Gedeon Richter,

Janssen-Cilag, Lundbeck, Pierre Fabré, PSI (CRO), and Servier.

References

1. Huhn M, Nikolakopoulou A, Schneider-Thoma J, *et al.* Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet.* 2019;394(10202):939–951.
2. Lally J, Ajnakina O, Stubbs B, *et al.* Remission and recovery from first-episode psychosis in adults: systematic review and meta-analysis of long-term outcome studies. *Br J Psychiatry.* 2017;211(6):350–358.
3. Csernansky JG, Schuchart EK. Relapse and rehospitalisation rates in patients with schizophrenia: effects of second generation antipsychotics. *CNS Drugs.* 2002;16(7):473–484.
4. Postrado LT, Lehman AF. Quality of life and clinical predictors of rehospitalization of persons with severe mental illness. *Psychiatr Serv.* 1995;46(11):1161–1165.
5. Stroup TS, Gray N. Management of common adverse effects of antipsychotic medications. *World Psychiatry.* 2018;17(3):341–356.
6. Correll CU, Rubio JM, Inczedy-Farkas G, Birnbaum ML, Kane JM, Leucht S. Efficacy of 42 pharmacologic cotreatment strategies added to antipsychotic monotherapy in schizophrenia: systematic overview and quality appraisal of the meta-analytic evidence. *JAMA Psychiatry.* 2017;74(7):675–684.
7. Vanover KE, Weiner DM, Makhay M, *et al.* Pharmacological and behavioral profile of N-(4-fluorophenylmethyl)-N-(1-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy) phenylmethyl) carbamide (2R,3R)-dihydroxybutanedioate (2:1) (ACP-103), a novel 5-hydroxytryptamine(2A) receptor inverse agonist. *J Pharmacol Exp Ther.* 2006;317(2):910–918.
8. Meltzer HY, Roth BL. Lorcaserin and pimavanserin: emerging selectivity of serotonin receptor subtype-targeted drugs. *J Clin Invest.* 2013;123(12):4986–4991.
9. Stahl SM. Mechanism of action of pimavanserin in Parkinson's disease psychosis: targeting serotonin 5HT2A and 5HT2C receptors. *CNS Spectr.* 2016;21(4):271–275.
10. Meltzer HY, Elkis H, Vanover K, *et al.* Pimavanserin, a selective serotonin (5-HT)2A-inverse agonist, enhances the efficacy and safety of risperidone, 2mg/day, but does not enhance efficacy of haloperidol, 2mg/day: comparison with reference dose risperidone, 6mg/day. *Schizophr Res.* 2012;141(2-3):144–152.
11. Ballard C, Banister C, Khan Z, *et al.*; ADP Investigators. Evaluation of the safety, tolerability, and efficacy of pimavanserin versus placebo in patients with Alzheimer's disease psychosis: a phase 2, randomised, placebo-controlled, double-blind study. *Lancet Neurol.* 2018;17(3):213–222.
12. Cummings J, Isaacson S, Mills R, *et al.* Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. *Lancet.* 2014;383(9916):533–540.
13. First MB, Williams JBW, Karg RS, Spitzer RL. *Structured Clinical Interview for DSM-5 Disorders, Clinician Version (SCID-5-CV)*. Arlington: American Psychiatric Association; 2015.
14. Kay SR, Opler LA, Lindenmayer JP. Reliability and validity of the positive and negative syndrome scale for schizophrenics. *Psychiatry Res.* 1988;23(1):99–110.
15. Guy W. *ECDEU Assessment Manual for Psychopharmacology—Revised (DHEW Publ No. ADM 76-338)*. Rockville: US Department of Health, Education, and Welfare Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976;218–222.
16. Opler LA, Ramirez PM. *Informant Questionnaire for the Positive and Negative Syndrome Scale (IQ-PANSS)*. North Tonawanda: Multi-Health Systems Publications, Inc; 2009.
17. Kaida K, Takahashi M, Akerstedt T, *et al.* Validation of the Karolinska sleepiness scale against performance and EEG variables. *Clin Neurophysiol.* 2006;117(7):1574–1581.
18. McHorney CA, Ware JE Jr, Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Med Care.* 1994;32(1):40–66.
19. Hogan TP, Awad AG, Eastwood R. A self-report scale predictive of drug compliance in schizophrenics: reliability and discriminative validity. *Psychol Med.* 1983;13(1):177–183.
20. Morosini PL, Magliano L, Brambilla L, Ugolini S, Pioli R. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. *Acta Psychiatr Scand.* 2000;101(4):323–329.
21. Addington D, Addington J, Maticka-Tyndale E, Joyce J. Reliability and validity of a depression rating scale for schizophrenics. *Schizophr Res.* 1992;6(3):201–208.
22. Cicchetti D, Bronen R, Spencer S, *et al.* Rating scales, scales of measurement, issues of reliability: resolving some critical issues for clinicians and researchers. *J Nerv Ment Dis.* 2006;194(8):557–564.
23. Posner K, Brown GK, Stanley B, *et al.* The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry.* 2011;168(12):1266–1277.
24. Barnes TR. The Barnes Akathisia Rating Scale–revisited. *J Psychopharmacol.* 2003;17(4):365–370.
25. Lane RD, Glazer WM, Hansen TE, Berman WH, Kramer SI. Assessment of tardive dyskinesia using the Abnormal Involuntary Movement Scale. *J Nerv Ment Dis.* 1985;173(6):353–357.
26. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand Suppl.* 1970;212:11–19.
27. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. *J Clin Psychiatry.* 1997;58(12):538–546.
28. McGuire P, Robson P, Cubala WJ, *et al.* Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: a multicenter randomized controlled trial. *Am J Psychiatry.* 2018;175(3):225–231.
29. Bugarski-Kirola D, Iwata N, Sameljak S, *et al.* Efficacy and safety of adjunctive bitopertin versus placebo in patients with suboptimally controlled symptoms of schizophrenia treated with antipsychotics: results from three phase 3, randomised, double-blind, parallel-group, placebo-controlled, multicentre studies in the SearchLyte clinical trial programme. *Lancet Psychiatry.* 2016;3(12):1115–1128.
30. Leucht S, Leucht C, Huhn M, *et al.* Sixty years of placebo-controlled antipsychotic drug trials in acute schizophrenia: systematic review, bayesian meta-analysis, and meta-regression of efficacy predictors. *Am J Psychiatry.* 2017;174(10):927–942.

31. Haddad PM, Correll CU. The acute efficacy of antipsychotics in schizophrenia: a review of recent meta-analyses. *Ther Adv Psychopharmacol.* 2018;8(11):303–318.
32. Leucht S, Kane JM, Kissling W, Hamann J, Etschel E, Engel RR. What does the PANSS mean? *Schizophr Res.* 2005;79(2-3):231–238.
33. Gopalakrishnan M, Zhu H, Farchione TR, *et al.* The trend of increasing placebo response and decreasing treatment effect in schizophrenia trials continues: an update from the US food and drug administration. *J Clin Psychiatry*. 2020;81:19r12960.
34. Mattila T, Wohlfarth T, Koeter M, *et al.* Geographic variation in efficacy of atypical antipsychotics for the acute treatment of schizophrenia—an individual patient data meta-analysis. *Eur Neuropsychopharmacol.* 2014;24(7):1067–1077.
35. Gallego JA, Bonetti J, Zhang J, Kane JM, Correll CU. Prevalence and correlates of antipsychotic polypharmacy: a systematic review and meta-regression of global and regional trends from the 1970s to 2009. *Schizophr Res.* 2012;138(1):18–28.
36. Agid O, Siu CO, Potkin SG, *et al.* Meta-regression analysis of placebo response in antipsychotic trials, 1970-2010. *Am J Psychiatry.* 2013;170(11):1335–1344.
37. Reynolds GP. High dose antipsychotic polypharmacy and dopamine partial agonists—time to rethink guidelines? *J Psychopharmacol.* 2021;35(9):1030–1036.
38. Howes OD, McCutcheon R, Agid O, *et al.* Treatment-resistant schizophrenia: treatment response and resistance in psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology. *Am J Psychiatry.* 2017;174(3):216–229.
39. Rabinowitz J, Berardo CG, Bugarski-Kirola D, Marder S. Association of prominent positive and prominent negative symptoms and functional health, well-being, healthcare-related quality of life and family burden: a CATIE analysis. *Schizophr Res.* 2013;150(2-3):339–342.
40. Krause M, Zhu Y, Huhn M, *et al.* Antipsychotic drugs for patients with schizophrenia and predominant or prominent negative symptoms: a systematic review and meta-analysis. *Eur Arch Psychiatry Clin Neurosci.* 2018;268(7):625–639.
41. Boyer P, Lecrubier Y, Puech AJ, Dewailly J, Aubin F. Treatment of negative symptoms in schizophrenia with amisulpride. *Br J Psychiatry.* 1995;166(1):68–72.
42. Danion JM, Rein W, Fleurot O. Improvement of schizophrenic patients with primary negative symptoms treated with amisulpride. Amisulpride Study Group. *Am J Psychiatry.* 1999;156(4):610–616.
43. Loo H, Poirier-Littre MF, Theron M, *et al.* Amisulpride versus placebo in the medium-term treatment of the negative symptoms of schizophrenia. *Br J Psychiatry*. 1997;170:18–22.
44. Lecrubier Y, Quintin P, Bouhassira M, *et al.* The treatment of negative symptoms and deficit states of chronic schizophrenia. olanzapine compared to amisulpride and placebo in a 6-month double-blind controlled clinical trial. *Acta Psychiatr Scand.* 2006;114(5):319–327.
45. Németh G, Laszlovszky I, Czobor P, *et al.* Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia. A randomised, double-blind, controlled trial. *Lancet*. 2017;389(10074):1103–1113.