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A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of Adjunctive Pimavanserin in Patients With Major Depressive Disorder and an Inadequate Response to Therapy (CLARITY)

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ABSTRACT

Objective: Pimavanserin is a 5-hydroxytryptamine-2A antagonist and inverse receptor agonist. This phase 2 study examined the efficacy and safety of pimavanserin as adjunctive therapy in patients with major depressive disorder (MDD).

Methods: This was a multicenter, randomized, double-blind, placebo-controlled study in patients with *DSM-5*-defined MDD and an inadequate response to a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI). Using a 2-stage sequential parallel-comparison design, patients were initially randomized in a 3:1 ratio to placebo or pimavanserin added to ongoing SSRI or SNRI therapy; at 5 weeks, placebo nonresponders were re-randomized to placebo or pimavanserin for an additional 5 weeks. Key endpoints were change from baseline to the end of each stage in 17-item Hamilton Depression Rating Scale (HDRS-17) total score and Sheehan Disability Scale (SDS) score.

Results: Between December 2016 and October 2018, 207 patients were randomized. For the prespecified pooled Sequential Parallel Comparison Design analyses of Stages 1 and 2, the least squares (LS) mean (SE) difference for the HDRS-17 total score was -1.7 (0.85) ($P=.039$) and for the SDS score was -0.8 (0.29) ($P=.004$). At week 5 of Stage 1, LS mean (SE) difference for pimavanserin versus placebo was significant for changes on the HDRS-17 (-4.0 [1.09], $P=.0003$) and SDS (-1.2 [0.40], $P=.0036$) with effect sizes of 0.626 and 0.498, respectively. Early and sustained separation of pimavanserin from placebo ($P<.05$) occurred at 1 week. The most common adverse events with pimavanserin were dry mouth, nausea, and headache.

Conclusions: Pimavanserin demonstrated robust efficacy in patients with MDD and an inadequate response to an SSRI or SNRI. Tolerability was consistent with previous experience.

Trial Registration: ClinicalTrials.gov identifier: NCT03018340

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Major depressive disorder (MDD) affects 300 million persons worldwide,¹ causing substantial morbidity and mortality.² Drug therapy is effective,³ but fewer than one-third of patients achieve remission.⁴⁻⁸ A few atypical antipsychotics are approved by the US Food and Drug Administration (FDA) for use in adjunctive treatment of patients with an inadequate response to antidepressants. Currently available atypical antipsychotics may reduce symptoms⁹; however, their use may be limited by associated weight gain, metabolic effects, and extrapyramidal effects.^{4,10-12} Thus, other options are needed for patients with MDD and inadequate treatment response.¹³

Pimavanserin, approved for treating Parkinson's disease psychosis, is a potent 5-hydroxytryptamine-2A (5-HT_{2A}) receptor antagonist/inverse agonist with lesser activity as a 5-HT_{2C} antagonist/inverse agonist but no activity at adrenergic, dopaminergic, histaminergic, or muscarinic receptors.¹⁴ Activity of some antidepressant drugs has been attributed to blockade of the 5-HT_{2A} receptor.¹⁵ Mixed β -adrenoceptor/5-HT_{1A} antagonists may enhance the clinical action of selective serotonin reuptake inhibitors (SSRI), activity demonstrated with drugs that combine 5-HT reuptake inhibition and partial agonism at 5-HT_{1A} receptors.¹⁶ Pimavanserin demonstrates a receptor-binding profile similar to those of other drugs with antidepressant activity.^{17,18} This report presents data from a phase 2 study (CLARITY; ClinicalTrials.gov identifier: NCT03018340) undertaken to investigate the efficacy and tolerability of pimavanserin administered as adjunctive therapy for patients with MDD and an inadequate response to antidepressant therapy.

METHODS

The study protocol was reviewed 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.

Study Design

This was a multicenter, randomized, double-blind, placebo-controlled study in patients with MDD and

Clinical Points

- An inadequate response to antidepressant treatment is a common cause of poor outcomes in patients with major depressive disorder (MDD), and currently available adjunctive treatments are not adequate.
- For patients with MDD not responding to antidepressant treatment, adjunctive pimavanserin produced a robust treatment response.
- Additional clinical studies with adjunctive pimavanserin are planned in patients with MDD.

inadequate responses to treatment with an SSRI or serotonin-norepinephrine reuptake inhibitor (SNRI). The primary objective was to evaluate efficacy, and secondary objectives were to evaluate safety and tolerability, effects on disability, clinician's global assessment, patient-reported quality of life, perception of treatment, sleepiness, sexual functioning, impulsivity, and irritability of pimavanserin in this patient population. The study consisted of an 8- to 21-day screening period, a 10-week double-blind treatment period, and a 30-day safety follow-up period. To ensure that appropriate patients were enrolled, a remote interview was conducted by Massachusetts General Hospital Clinical Trials Network and Institute raters between the screening and baseline visits. Screening assessments consisted of the SAFER Interview,¹⁹ which included the Montgomery-Asberg Depression Rating Scale (MADRS),²⁰ the Clinical Global Impression-Severity of Illness scale (CGI-S),²¹ and the Massachusetts General Hospital Antidepressant Treatment Questionnaire (MGH ATRQ).²²

The study utilized a 2-stage Sequential Parallel-Comparison Design (SPCD)²³ whereby, following screening, eligible patients were randomized in Stage 1 in a 3:1 ratio to placebo or pimavanserin added to their current SSRI or SNRI therapy for 5 weeks. At the end of 5 weeks, placebo nonresponders (17-item Hamilton Depression Rating Scale [HDRS-17]²⁴ total score >14 and <50% reduction in score from baseline) were re-randomized to placebo or pimavanserin (1:1 ratio) added to current therapy for an additional 5 weeks. All patients assigned to pimavanserin in Stage 1 continued treatment with pimavanserin in Stage 2, whereas responders to placebo in Stage 1 remained on placebo in Stage 2. Patients were randomly assigned via an interactive voice response system to pimavanserin 34 mg once daily or placebo. All patients continued on their SSRI or SNRI at a stable dose for the duration of the study. Patients and investigators and their staff were blinded to treatment assignment.

Patient Selection

Male or female patients ≥ 18 years of age with a body mass index (BMI) between 19 and 35 kg/m² inclusive were eligible if they had a primary diagnosis of MDD and a current major depressive episode (MDE) defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*), and confirmed by the Structured Clinical

Interview for *DSM-5*, Clinical Trials Version (SCID-5-CT).²⁵

Eligible patients had a history of MDD for ≥ 1 year prior to screening, a MADRS total score >20, and a CGI-S score ≥ 4 (moderately ill or worse) at both screening and baseline. Eligible patients also had a history of inadequate response to 1 or 2 antidepressant treatments during the current depression episode. Inadequate treatment response was determined with the MGH ATRQ, administered during the SAFER interview. Eligible patients were receiving treatment for their current episode with exactly 1 of the following drugs at approved doses: citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline, venlafaxine, or venlafaxine extended-release. The minimum trial duration for inclusion was 8 weeks (with the last 4 weeks on a stable dose).

Eligible women were of non-childbearing potential or agreed to use 2 acceptable methods of contraception throughout the study. A negative serum pregnancy test at screening and urine pregnancy test at baseline were required for inclusion. Patients were excluded for any medical or psychiatric condition or clinically significant laboratory abnormality that could interfere with safety or the conduct of the study. Patients who were actively suicidal or had attempted suicide within the past 2 years were excluded. Complete selection criteria are detailed in Supplementary Table 1.

Study Assessments

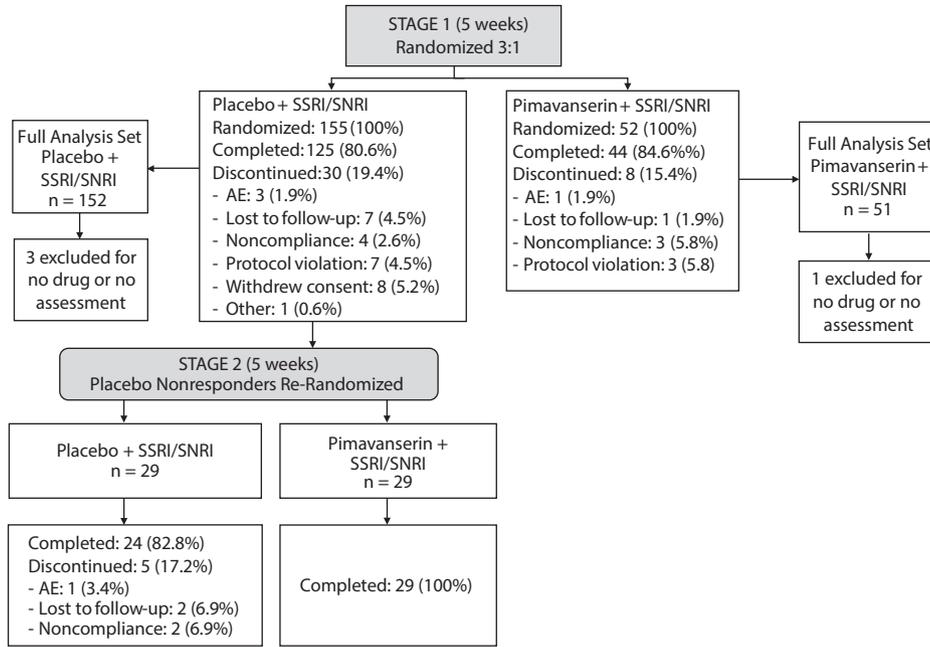
Clinic visits occurred weekly from weeks 1 through 10 (end of study). The MADRS was administered at screening and baseline. The HDRS-17, Sheehan Disability Scale (SDS),²⁶ CGI-S, and Karolinska Sleepiness Scale (KSS)²⁷ were administered at baseline and weekly during the study. The 12-Item Short-Form Health Survey (SF-12),²⁸ Drug Attitude Inventory (DAI-10),²⁹ and MGH Sexual Functioning Index (MGH-SFI)³⁰ were administered at baseline and weeks 5 and 10. The Barratt Impulsiveness Scale (BIS-11)³¹ and Sheehan Irritability Scale (SIS)³² were administered at baseline and weeks 1, 3, 5, 6, 8, and 10. Safety assessments, including adverse events (AEs), physical examination, vital signs, 12-lead electrocardiogram (ECG), and clinical laboratory tests (hematology, chemistry, urinalysis, prolactin), were performed at baseline and routinely during the study. The Columbia-Suicide Severity Rating Scale (C-SSRS)³³ was administered at baseline and weekly, and the Barnes Akathisia Rating Scale (BARS),³⁴ Abnormal Involuntary Movement Scale (AIMS),³⁵ and Simpson-Angus Scale (SAS)³⁶ were administered at baseline and weeks 1, 5, 6, and 10. Treatment response was defined as a $\geq 50\%$ reduction from baseline for the HDRS-17 total score, and remission was defined as a HDRS-17 total score ≤ 7 .

Statistical Analyses

A total sample size of 168 evaluable patients was estimated to provide at least 80% power at a 2-sided significance level of .05. Adjusting for a potential non-evaluable rate of up to 10%, approximately 188 patients were planned for randomization. The primary efficacy endpoint, change from baseline to the end

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Figure 1. CONSORT Diagram of Study Flow and Patient Disposition



Abbreviations: AE = adverse event, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

Table 1. Baseline Demographic and Clinical Characteristics^a

Characteristic	Pimavanserin (n = 52)	Placebo (n = 155)
Age, y	48.6 ± 13.3	45.4 ± 15.4
Age range, y	20–69	18–82
Female, n (%)	43 (82.7)	108 (69.7)
Race, n (%)		
White	38 (73.1)	111 (71.6)
Black or African American	9 (17.3)	31 (20.0)
Asian	0	7 (4.5)
American Indian or Alaska Native	1 (1.9)	3 (1.9)
Other	4 (7.7)	3 (1.9)
Body mass index, kg/m ²	28.6 ± 4.6	27.6 ± 4.4
MADRS total score	32.5 ± 5.4	31.1 ± 5.3
HDRS-17 total score	22.8 ± 4.6	22.0 ± 4.2
HDRS-17 score ≥ 24, n (%)	21 (40.4)	50 (32.3)
SDS score	6.3 ± 2.1	6.5 ± 2.1
CGI-S score	4.6 ± 0.7	4.4 ± 0.6

^aValues are shown as mean ± SD unless otherwise noted. Abbreviations: CGI-S = Clinical Global Impressions–Severity of Illness scale, HDRS-17 = 17-item Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, SDS = Sheehan Disability Scale.

of each stage for the HDRS-17 total score, was evaluated using mixed models for repeated measures (MMRM) with effects for treatment group, visit, treatment-by-visit interaction, baseline HDRS-17 total score, and the baseline HDRS-17 total score-by-visit interaction. An unstructured covariance matrix was used, and the Kenward-Roger approximation was used to adjust the denominator degrees of freedom. The treatment effect was assessed as the treatment difference in least squares mean (LS mean) change from baseline to the end of each stage and the corresponding 95% CIs. Cohen *d* effect size was calculated for comparisons between treatments. Similar statistical methods were used to analyze other continuous

endpoints. For the CGI-Improvement scale (CGI-I), baseline CGI-S score was used as the covariate. For the SF-12, DAI-10, and MGH-SFI, which were assessed only at baseline and at the end of the efficacy period, analysis of covariance with effects for treatment group and baseline score was used instead of the MMRM model. For response and remission rates, treatment groups were compared using the Pearson χ^2 test. Overall treatment effects were assessed as the weighted treatment differences in LS mean change for the 2 stages. The number needed to treat (NNT) was calculated for response and remission from the absolute rate of improvement at week 5. Efficacy data were analyzed for the full analysis set (FAS) for each of the 2 stages, comprising all randomized patients who received ≥ 1 dose of blinded study drug and who had a baseline value and at least 1 post-baseline value for the HDRS-17 total score within each stage. The safety analysis set included all patients receiving ≥ 1 dose of blinded study drug for each of the 2 stages.

RESULTS

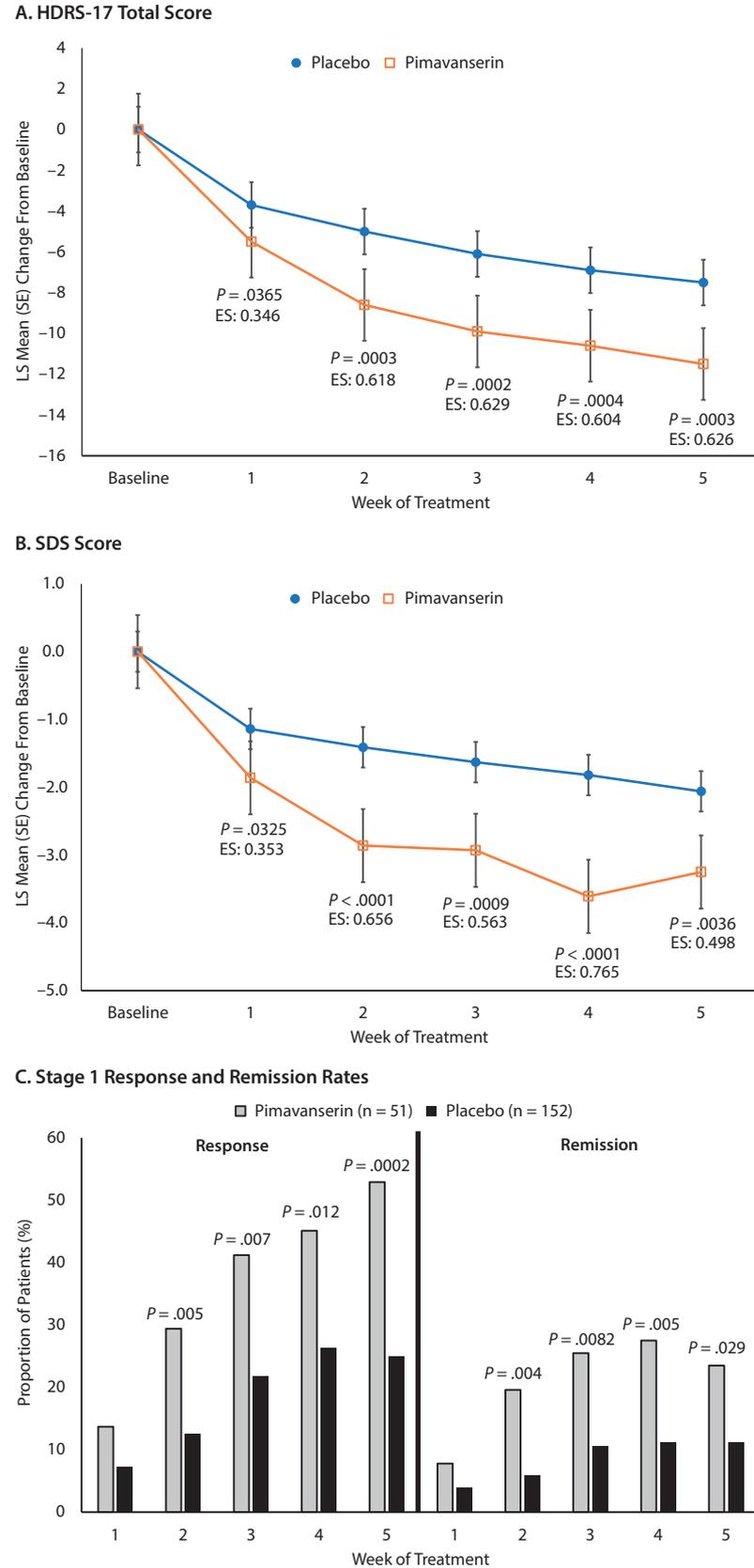
Between December 2016 and October 2018, 207 patients were randomized at 27 study sites and included in the safety population (Figure 1). In Stage 1, 152 (98.1%) and 51 (98.1%) patients in the placebo and pimavanserin groups, respectively, were included in the FAS population; 4 patients were excluded because they did not receive study drug or had no baseline and posttreatment HDRS-17 score. In Stage 2, 29 patients in both placebo and pimavanserin groups were included for the safety and FAS populations.

At baseline, treatment groups were generally comparable for demographic and clinical characteristics (Table 1).

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Figure 2. Least Squares (LS) Mean Change From Baseline to Week 5 in (A) HDRS-17 Total Score and (B) SDS Score, and (C) Response and Remission Rate During Stage 1



Abbreviations: ES = effect size, HDRS-17 = 17-item Hamilton Depression Rating Scale, SDS = Sheehan Disability Scale.

Patients in the pimavanserin group tended to have more severe depression based on a greater proportion with a HDRS-17 total score ≥ 24 (40.4% vs 32.3%) and a greater proportion with a score of 5 (markedly ill) or 6 (severely ill) on the CGI-S (48.1% vs 38.7%).

Efficacy

For the prespecified pooled SPCD analyses of Stages 1 and 2, a significantly greater improvement was observed with pimavanserin than placebo for the HDRS-17 total score (LS mean difference [SE] = -1.7 [0.85], $P = .039$) and SDS score (LS mean difference = -0.8 [0.29], $P = .004$). At week 5 of Stage 1, LS mean (SE) change from baseline for the HDRS-17 was -11.5 (0.94) for pimavanserin and -7.5 (0.55) for placebo (LS mean difference = -4.0 [1.09], $P = .0003$; effect size: 0.626), and for SDS, LS mean change was -3.3 (0.35) for pimavanserin and -2.1 (0.20) for placebo (LS mean difference = -1.2 [0.40], $P = .0036$, effect size: 0.498). LS mean change from baseline was significantly ($P < .05$) greater for pimavanserin versus placebo from week 1 to week 5 for both the HDRS-17 and SDS (Figure 2). During Stage 1, response and remission rates were significantly ($P < .05$) greater with pimavanserin versus placebo from week 2 through week 5 (Figure 2). The NNT for response and remission in Stage 1 was 3.6 and 8.1, respectively. In Stage 2, the difference between pimavanserin and placebo was not significant for the HDRS-17 (delta = 0.5; $P = .6940$; Cohen $d = -0.107$).

When data were stratified by baseline HDRS-17 total score < 24 or ≥ 24 , a more robust treatment effect was observed for both the HDRS-17 and SDS in the subgroup with more severe baseline depression (Supplementary Table 2). For the combined Stages 1 and 2, LS mean difference in the severe subgroup was -3.6 (1.4) for the HDRS-17 ($P = .011$) and -1.14 (0.47) for the SDS ($P = .014$). At week 5 in Stage 1, LS mean difference in the severe subgroup was -7.0 (2.1) for the HDRS-17 ($P = .0014$; effect size: 0.933) and -2.0 (0.68) for the SDS ($P = .0054$; effect size: 0.815). No significant differences were observed for HDRS-17 or SDS during Stage 2.

In the prespecified subgroup analyses by background antidepressant, significant differences from placebo ($P < .05$) were observed both for patients receiving an SSRI and for patients receiving SNRI as a

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background therapy from weeks 2 to week 5 in Stage 1 and for the overall treatment effect ($P=.0193$) with effect sizes of 0.43 to 0.61, respectively (data not shown). In a prespecified analysis of patients receiving continuous treatment with pimavanserin or placebo for 10 weeks in Stages 1 and 2, the treatment difference in LS mean change from baseline to week 10 was significant for both the HDRS-17 ($P=.0076$; effect size: 0.497) and the SDS ($P=.0094$; effect size: 0.469) in favor of pimavanserin (Figure 3).

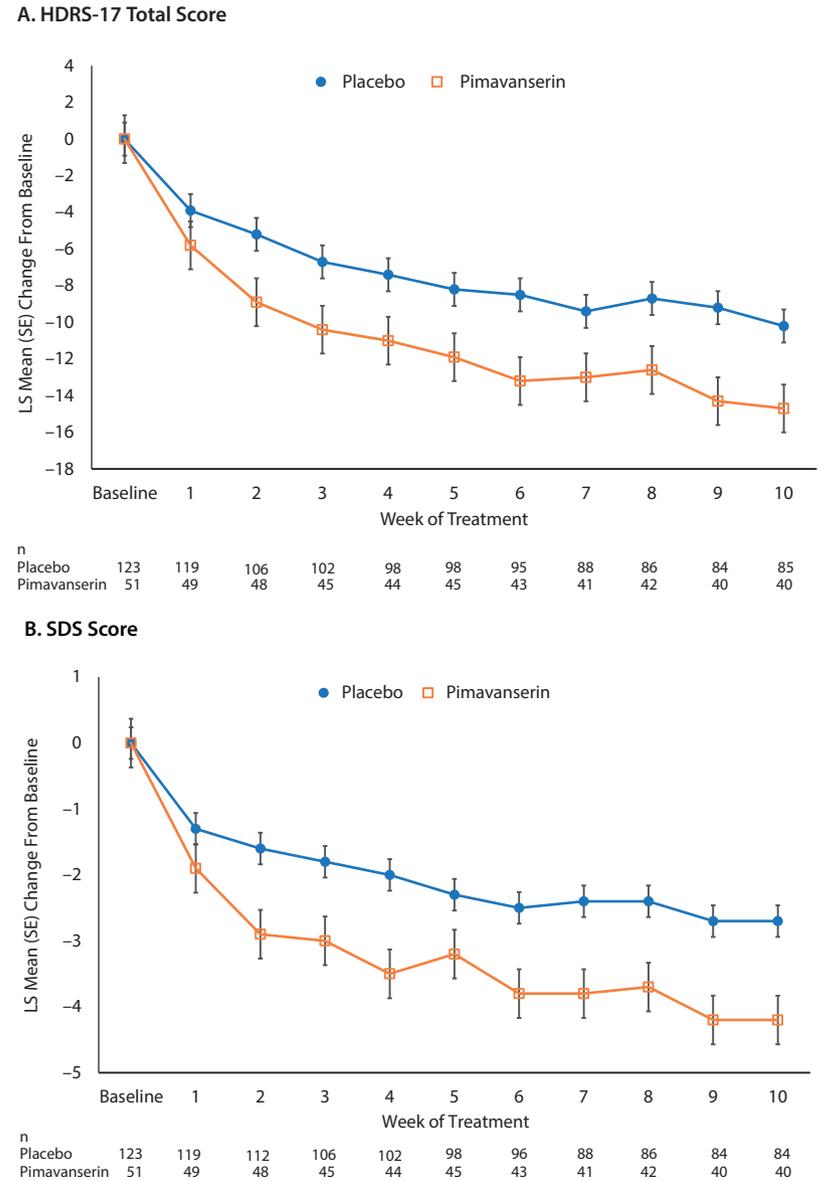
For secondary efficacy endpoints in Stage 1, significant LS mean differences in favor of pimavanserin were observed at week 5 for the CGI-S ($P=.0001$), CGI-I ($P=.001$) (Supplementary Table 2).

Safety and Tolerability

Treatment-related AEs occurred in 27.1% and 48.1% of patients in the placebo and pimavanserin groups, respectively, during Stage 1 and in 3.4% and 13.8% of patients in the placebo and pimavanserin groups, respectively, during Stage 2 (Table 2). The most common AEs in the pimavanserin group were dry mouth, nausea, and headache, all with frequency of less than 10%. Two serious AEs (bladder stones, prostate cancer) occurred in the placebo group and 1 (acute myocardial infarction) in the pimavanserin group; all were considered unrelated to therapy, and patients remained on study drug. During Stage 1, 3 patients (1.9%) discontinued the study due to an AE in the placebo group and 1 (1.9%) in the pimavanserin group. Additionally, 1 patient (3.4%) discontinued placebo during Stage 2 (Figure 1). No deaths occurred, and no clinically relevant changes in vital signs, clinical laboratory testing, or ECG findings were observed. Mean changes from baseline for plasma glucose and lipid parameters were minimal and not clinically significant in either treatment group (Supplementary Table 3). At week 5, the mean change from baseline for serum prolactin levels was 10.2 (9.5) $\mu\text{IU/mL}$ for placebo and -28.4 (15.6) $\mu\text{IU/mL}$ for pimavanserin (Supplementary Table 3). A low rate of extrapyramidal symptoms was observed; 2 events (1.3%) of akathisia occurred with placebo during Stage 1; 1 event (3.4%) of bradykinesia and 1 (3.4%) of cogwheel rigidity occurred with pimavanserin occurred during Stage 2.

For the MGH-SFI at week 5 of Stage 1, the LS mean difference from baseline for pimavanserin versus placebo was -0.6

Figure 3. Least Squares (LS) Mean Change From Baseline to Week 10 in (A) HDRS-17 Total Score and (B) SDS Score^a



^aHDRS-17: $P=.0076$, effect size: 0.497; SDS: $P=.0094$, effect size: 0.469. Abbreviations: HDRS-17 = 17-item Hamilton Depression Rating Scale, SDS = Sheehan Disability Scale.

(0.17) ($P=.0002$; effect size: 0.614), indicating superior sexual functioning among pimavanserin-treated patients. For the KSS at week 5 of Stage 1, LS mean difference from baseline for pimavanserin versus placebo was -1.1 (0.30) ($P=.0003$; effect size: 0.627), indicating less somnolence among pimavanserin-treated subjects (Supplementary Table 2). In Stage 1, no difference from baseline to week 5 for the BIS-11 score was observed for pimavanserin versus placebo (Supplementary Table 2). In Stage 2 and the overall weighted analysis of Stages 1 and 2 for the BIS-11, a significant improvement from baseline was observed with pimavanserin versus placebo. In Stage 1, a significant improvement for the SIS from baseline to week 5 was observed with pimavanserin versus placebo (Supplementary Table 2). In Stage 2 and overall, no difference from baseline to week 5 in SIS score was observed between pimavanserin and placebo.

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Table 2. Incidence of Treatment-Emergent Adverse Events (AEs)^a

Adverse Event	Stage 1 (5 Weeks)		Stage 2 (5 Weeks)	
	Pimavanserin (n=52)	Placebo (n=155)	Pimavanserin (n=29)	Placebo (n=29)
At least 1 treatment-emergent AE	38 (73.1)	85 (54.8)	14 (48.3)	6 (20.7)
At least 1 treatment-related AE	25 (48.1)	42 (27.1)	4 (13.8)	1 (3.4)
Serious AE	0	1 (0.6)	0	0
AE leading to discontinuation	1 (1.9)	3 (1.9)	0	1 (3.4)
Most common AE (> 5%) in any group				
Dry mouth	5 (9.6)	4 (2.6)	0	0
Nausea	5 (9.6)	7 (4.5)	0	0
Sinusitis	3 (5.8)	0	2 (6.9)	0
Upper respiratory infection	3 (5.8)	7 (4.5)	2 (6.9)	0
Urinary tract infection	3 (5.8)	1 (0.6)	0	0
Increased appetite	3 (5.8)	0	0	0
Headache	5 (9.6)	14 (9.0)	0	0
Dizziness	4 (7.7)	9 (5.8)	0	0
Sedation	4 (7.7)	4 (2.6)	0	0
Arthralgia	0	0	2 (6.9)	0

^aValues are shown as n (%).

DISCUSSION

The results of this phase 2 study overall showed statistically significant and clinically relevant improvements in the HDRS-17 total score and SDS score with pimavanserin. Particularly robust efficacy was observed during the all-inclusive Stage 1 of the study in which all initially randomized patients are analyzed. The observed effect sizes for measures of depressive symptoms and function at week 5 of Stage 1 were in the range of 0.6 and 0.5, respectively. Additionally, in this study, pimavanserin has demonstrated early separation from placebo at week 1 during Stage 1 for both the HDRS-17 and the SDS. Moreover, significant improvements were observed for a number of secondary endpoints, including sexual functioning, daytime sleepiness, and mental health-related quality of life. The safety and tolerability profile of pimavanserin was consistent with the existing product labeling, and no new safety findings were reported.

One challenge when conducting randomized controlled trials in MDD is the unpredictable and often substantial placebo response, which can undermine the ability to detect a statistically significant difference between drug and placebo groups.³⁷⁻³⁹ The SPCD was developed as a clinical trial methodology to mitigate risk in such instances, reducing the effect of placebo in Stage 2 with the use of a double-blind antidepressant-placebo lead-in in Stage 1.²³ The SPCD is especially useful in drug development as a method to reduce sample size, provide a consistent pool of patients, and reduce variability. Given that it is very challenging to identify depressed patients who are likely to respond to placebo,⁴⁰ by identifying and removing placebo responders during Stage 1 with the SPCD methodology, treatment differences are typically expected to be more detectable in patients who continue into Stage 2 and are re-randomized to staying on placebo or go on active treatment. An additional advantage of the SPCD methodology is the fact that it offers “2 shots on goal” within the same trial to enhance the probability of detecting an effect. This was, in fact, the case in our study, in which the robustness of the effect detected in Stage 1 of SPCD led to overall efficacy despite the lack of effect in Stage 2. The latter was probably due to the markedly smaller than expected sample size of Stage 2 and to the fact that Stage 2 was probably enriched with refractory (and therefore less informative) depressed patients, as a result of the dual requirement for re-randomization.

In the present trial, significant differences were observed between pimavanserin and placebo for the prespecified pooled SPCD analyses for the HDRS-17 total score and the SDS score. When each stage is analyzed separately, particularly robust efficacy results with pimavanserin were observed in Stage 1 with significant mean change from baseline to week 5 for the HDRS-17 and SDS and substantial effect sizes of 0.626 and 0.498, respectively. In contrast, studies^{10,11} with atypical antipsychotics as adjunctive therapy in patients with MDD report effect sizes of 0.27 to 0.43 symptoms. However, because, unexpectedly, few placebo nonresponders—approximately half of the anticipated number—were re-randomized to Stage 2, no statistical separation was observed in this group of re-randomized patients. Additionally, relatively stringent re-randomization criteria may have led to inclusion of a group of subjects with less capacity to improve in Stage 2 and thus contributed to this observation.

As a further indication of robust benefit of pimavanserin adjunctive therapy, a prespecified analysis of 10-week efficacy for patients who received the same, originally assigned treatment through both stages of the study (n = 178, 126 placebo and 52 pimavanserin) showed statistically significant and clinically robust separation from placebo on the HDRS-17 and SDS with the effect sizes of 0.497 and 0.469, respectively. Significant improvement in function on the SDS suggests potentially broader beneficial effects of pimavanserin as adjunctive treatment. Few studies with atypical antipsychotics in MDD included assessment of functional improvement.

This study included the SDS as a key secondary endpoint to assess functional disability, and improvement in workplace function has been demonstrated with antidepressant therapy in patients with MDD.⁴¹ The SDS is well validated and widely accepted for assessing functional outcomes in patients with MDD.⁴² In a systematic review of studies that assessed functional outcomes, the authors suggested that improvements in function (SDS) should be considered for inclusion as co-endpoints with symptomatic assessments when evaluating treatments for MDD.⁴³ Routine assessments of both symptoms and function could be helpful for minimizing residual effects that increase the risk for relapse or recurrence.⁴³

Pimavanserin was well tolerated in this study. The AE profile was consistent with those of previous studies of pimavanserin for Parkinson's disease psychosis and Alzheimer's disease psychosis,^{44,45} and discontinuations for AEs were lower with pimavanserin than with placebo. Importantly, pimavanserin was associated with

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low rates of daytime sleepiness, weight gain, metabolic changes, and sexual dysfunction. In contrast, use of atypical antipsychotics may be limited by weight gain, metabolic disturbances (glucose intolerance, diabetes, lipid disorders, hyperprolactinemia), and daytime sleepiness.^{10,46–48} In addition, most conventional antidepressants are well known to cause sexual dysfunction in at least 50% of patients with MDD.⁴⁹

Limitations of this study include a relatively short length of treatment as well as a small sample size, particularly in Stage 2. A longer duration of treatment in MDD may be necessary to more completely elucidate the full effect of drug treatment.⁵⁰ However, this study was designed to establish an acute signal of efficacy for pimavanserin in an MDD population, and the SPCD design permitted use of a smaller sample size to ascertain efficacy.

Despite these limitations, pimavanserin demonstrated robust and clinically meaningful efficacy in MDD patients with inadequate response to antidepressant therapy. Importantly, pimavanserin was not associated with significant metabolic dysregulation, sexual dysfunction, or extrapyramidal symptoms. Thus, pimavanserin may offer an effective alternative as adjunctive therapy for patients with MDD and an inadequate response to antidepressant treatment without the safety and tolerability concerns of atypical antipsychotics. A phase 3 program of adjunctive pimavanserin in patients with MDD inadequately responsive to SSRI or SNRI therapy has been initiated.

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Supplementary Material

Article Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of Adjunctive Pimavanserin in Patients With Major Depressive Disorder and an Inadequate Response to Therapy (CLARITY)

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List of Supplementary Material for the article

1. [Table 1](#) Inclusion and Exclusion Criteria
2. [Table 2](#) LS mean (SE) change from baseline during Stage 1 and Stage 2 for primary and secondary endpoints
3. [Table 3](#) Baseline and mean (SD) change from baseline to Week 5 for clinical laboratory values

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Table 1. Inclusion and Exclusion Criteria.

Inclusion Criteria

A subject must meet all of the following inclusion criteria to be eligible for participation in the study:

1. Is a male or female ≥ 18 years of age at time of Screening.
2. Is able to understand and provide signed informed consent, and is able to sign and date a Health Insurance Portability and Accountability Act (HIPAA) authorization form or subject privacy form, if appropriate.
3. Is able to understand the nature of the trial and follow protocol requirements (in the opinion of the Investigator), and is willing to comply with study drug administration requirements and discontinue prohibited concomitant medications (including sedative hypnotic agents).
4. Is able to complete subject-reported outcome measures and can be reliably rated on assessment scales (in the opinion of the Investigator).
5. Has a DSM-5 primary diagnosis of an MDE as part of MDD (confirmed using the SCID-5-CT).
6. Is being treated with only one of the following SSRI or SNRI antidepressants at a dose within the FDA-approved dose range. Subjects who are currently taking a second antidepressant or antidepressant augmentation agent are not eligible for the study.
 - a. Citalopram
 - b. Escitalopram
 - c. Paroxetine
 - d. Fluoxetine
 - e. Sertraline
 - f. Duloxetine
 - g. Venlafaxine
 - h. Desvenlafaxine
 - i. Venlafaxine XR
7. Has been treated with SSRI/SNRI monotherapy during the current MDE for at least 8 weeks, with the same adequate dose over the last 4 weeks, and the dose level is expected to remain stable throughout the study.
8. Has a history of inadequate response during the entire current MDE to 1 or 2 adequate antidepressant treatments, including current treatment, as confirmed by the MGH ATRQ through the SAFER interview.
9. Has a history of MDD diagnosis ≥ 1 year prior to Screening. To satisfy this criterion, the current MDE either represents a recurrent episode and the MDD was diagnosed >1 year ago, OR, if this is the first episode, its duration must be of greater length than 1 year.
10. Was medically stable within the month prior to Screening (in the opinion of the Investigator).
11. Has a Montgomery-Asberg Depression Rating Scale (MADRS) total score >20 at both Screening and Baseline.
12. Has a Clinical Global Impression – Severity (CGI-S) score ≥ 4 (moderately ill or worse) at both Screening and Baseline.
13. Is not actively suicidal (including, on the Columbia Suicide Severity Rating Scale [C-SSRS], an answer of “no” to question 4 or 5 [current or over the last 6 months]) and has not attempted suicide in the 2 years prior to Screening.

14. If the subject is a female, she must be of non-childbearing potential (defined as either surgically sterilized or at least 1 year postmenopausal) OR must agree to use TWO clinically acceptable methods of contraception throughout the study and for 1 month following study completion. Clinically acceptable methods of contraception include oral, injectable, transdermal, or implantable contraception, an intrauterine device (IUD), and a condom, diaphragm, cervical cap, or sponge with spermicide. Only one of the two clinically acceptable methods can be a hormonal method.
15. If the subject is a female of childbearing potential, she must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline.
16. Must have a detectable blood level of SSRI/SNRI monotherapy identified at Screening.

Subject Exclusion Criteria

A subject must meet none of the following exclusion criteria to be eligible for the study:

1. Is inappropriate for the study (in the opinion of the Investigator or the Medical Monitor).
2. Has any condition that would interfere with the ability to comply with study instructions or might confound the interpretation of the study results or put the subject at undue risk (in the opinion of the Investigator).
3. Has a body mass index (BMI) <19 or >35 at Screening.
4. Has clinically significant laboratory abnormalities that would jeopardize the safe participation of the subject in the study (in the opinion of the Investigator).
5. Has current evidence, or a history within the previous 3 months prior to Screening, of a serious and/or unstable neurologic, cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematologic, or other medical disorder, including cancer, that would jeopardize the safe participation of the subject in the study (in the opinion of the Investigator).
6. Has a known history of a positive hepatitis C virus (HCV) or human immunodeficiency virus (HIV) test.
7. Has laboratory evidence of hypothyroidism at Screening, as measured by thyroid stimulating hormone (TSH) and reflex free thyroxine (T4). If TSH is abnormal and the reflex free T4 is normal, the subject may be enrolled.
8. Has current unstable diabetes or glycosylated hemoglobin (HbA1c) >8% at Screening.
9. Has a history of delirium, dementia, amnesic disorder, cognitive disorder, schizophrenia or other psychotic disorder, or bipolar I or II disorder. Subjects who are currently being treated for eating disorder, obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), panic disorder, acute stress disorder, or posttraumatic stress disorder (PTSD), according to DSM-5 criteria, are also not eligible.
10. Has a current primary diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, or histrionic personality disorder, according to DSM-5 criteria.
11. Has met DSM-5 criteria for substance use disorders within the last 6 months prior to Screening, except for disorders related to the use of caffeine or nicotine.
12. Has a positive test for an illicit drug or cannabis at Screening or Baseline. Subjects who test positive for a controlled substance and who have a valid prescription may be retested if they agree to abstain from the medication for the length of their participation in the study. The repeat test, and any other tests, must be negative for them to participate in the study.
13. Has a history of seizure disorder or of neuroleptic malignant syndrome/serotonin syndrome. Single, absence, or febrile seizures are not exclusionary.

14. Is experiencing hallucinations, delusions, or any psychotic symptomatology in the current MDE.
15. Has received new-onset psychotherapy or has had a change in the intensity of psychotherapy within the 8 weeks prior to Screening.
16. Has received electroconvulsive therapy (ECT) during the current MDE.
17. Has a known history of long QT syndrome or family history of sudden cardiac death.
18. Has a Screening or Baseline ECG with a QTcF >450 ms when the QRS duration is <120 ms or has a Screening or Baseline ECG with a QTcF >470 ms when the QRS duration is \geq 120 ms. (The ECG may be repeated once at Screening or Baseline in consultation with the Medical Monitor.)
19. Has a significant sensitivity or allergic reaction to pimavanserin or its excipients.
20. Has previously been randomized in any prior clinical study with pimavanserin, and/or has received any other investigational (either approved or unapproved) drug within 30 days or 5 half-lives (whichever is longer) prior to Screening.
21. Has participated in >2 clinical research trials utilizing an investigational product within the previous 2 years.
22. Is an employee of ACADIA Pharmaceuticals Inc. or is a family member of an employee of ACADIA Pharmaceuticals Inc.
23. Has a history of minimal or non-response to adjunctive antipsychotics, such as quetiapine or aripiprazole, for prior MDEs, as clinically assessed by the Investigator.
24. Has a history of myocardial infarction, unstable angina, acute coronary syndrome, or cerebrovascular accident (CVA) within the last 4 months. Has greater than NYHA Class 2 congestive heart failure or Class 2 angina pectoris, sustained ventricular tachycardia (VT), ventricular fibrillation, torsade de pointes, or syncope due to an arrhythmia.

Supplementary Table 2. LS mean (SE) change from baseline during Stage 1 and Stage 2 for primary and secondary endpoints.

	Stage 1 (5 weeks)		Stage 2 (5 weeks)		Overall
	Pimavanserin (n=51)	Placebo (n=152)	Pimavanserin (n=29)	Placebo (n=29)	
HAMD-17 total LSmean (SE) p-value Effect size	-11.5 (0.94) P=0.003 0.626	-7.5 (0.55)	-2.8 (0.89) 0.694 -0.107	-3.3 (0.94)	-1.7 (0.85) 0.039
Sheehan Disability Scale LSmean (SE) p-value Effect size	-3.3 (0.35) 0.0036 0.498	-2.1 (0.20)	-0.9 (0.29) 0.256 0.311	-0.4 (0.30)	-0.84 (0.29) 0.004
CGI-Severity LSmean (SE) p-value Effect size	-1.9 (0.17) 0.0001 0.667	-1.2 (0.10)	-0.5 (0.12) 0.940 0.021	-0.5 (0.16)	-0.4 (0.15) 0.0084
CGI-Improvement LSmean (SE) p-value Effect size	2.2 (0.17) 0.001 0.574	2.8 (0.10)	3.0 (0.18) 0.817 0.063	3.1 (0.19)	-0.4 (0.16) 0.0289
Karolinska Sleepiness Scale LSmean (SE) p-value Effect size	-1.7 (0.26) 0.0003 0.627	-0.6 (0.15)	-0.4 (0.28) 0.842 0.056	-0.3 (0.30)	-0.6 (0.26) 0.0205
MGH-Sexual Functioning Index LSmean (SE) p-value Effect size	-0.8 (0.15) 0.0002 0.614	-0.2 (0.08)	-0.5 (0.14) 0.127 0.412	-0.2 (0.14)	-0.47 (0.13) 0.0003
Sheehan Irritability Scale Score LSmean (SE) p-value Effect size	-19.5 (2.17) 0.0013 0.561	-11.2 (1.28)	-5.7 (2.34) 0.889 -0.039	-6.2 (2.47)	-3.9 (2.12) 0.0672

Barrett Impulsiveness Scale Score					
LSmean (SE)	-4.3 (1.14)	-3.1 (0.66)	-1.9 (0.97)	2.1 (1.04)	-2.6 (0.98)
p-value	0.374		0.0071		0.0075
Effect size	0.152		0.796		

Supplementary Table 3. Baseline and mean (SD) change from baseline to Week 5 for clinical laboratory values. [Table 14.3.3.1]

Parameter	Mean (standard deviation)			
	Pimavanserin		Placebo	
	Baseline N=52	Week 5 N=45	Baseline N=155	Week 5 N=126
Glucose, mmol/L	5.3 (1.1)	0 (1.2) ^a	5.2 (0.9)	0.1 (1.4) ^a
Prolactin, uIU/mL	192.1 (147.5)	-28.4 (104.7)	187.6 (239.0)	10.2 (106.7)
Cholesterol, mmol/L	5.2 (0.14)	-0.14 (0.80)	5.0 (1.0)	0.01 (0.06)
LDL cholesterol, mmol/L	3.2 (0.9)	-0.13 (0.59)	3.2 (0.9)	-0.03 (0.59)
HDL cholesterol, mmol/L	1.5 (0.5)	-0.01 (0.24)	1.4 (0.4)	0.03 (0.19)
Triglyceride, mmol/L	1.6 (1.0)	-0.11 (0.93)	1.6 (0.9)	-0.0 (0.76)

^a N=44 pimavanserin and N=125 placebo