Effect of pimavanserin on anxious depression in patients with major depression and an inadequate response to previous therapy: secondary analysis of the clarity study

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In a post hoc analysis, the effect of pimavanserin on anxious depression was determined from CLARITY, a randomized, double-blind, placebo-controlled study in patients with major depression and an inadequate response to previous therapy. Patients were randomized in a 3:1 ratio to placebo or pimavanserin 34 mg daily added to ongoing antidepressant therapy. At 5 weeks, placebo nonresponders were rerandomized to placebo or pimavanserin for an additional 5 weeks. Mean change from baseline to week 5 for the Hamilton depression rating scale (HAMD) anxiety/somatization (AS) factor was examined for all patients and those with a score ≥7 at baseline. Least squares (LS) mean [standard error (SE)] difference between placebo and pimavanserin for the AS factor score was −1.5 (0.41) [95% confidence interval (CI) −2.4 to −0.7; *P* = 0.0003; effect size: 0.634]. Among patients with an AS factor score ≥7 at baseline, LS mean (SE) difference was −2.2 (0.66) (95% CI −3.5 to −0.9; *P* = 0.0013; effect size: 0.781). Response rates (≥50% reduction in HAMD-17 from baseline) were 22.4 and 55.2% (*P* = 0.0012) and remission rates (HAMD-17 total score <7) were 5.3 and 24.1% (*P* = 0.0047), respectively, with placebo and pimavanserin among patients with a baseline AS factor score ≥7. Among patients with anxious major depressive disorder at baseline, adjunctive pimavanserin was associated with a significant improvement. *Int Clin Psychopharmacol* 35: 313–321 Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

The frequency of comorbid anxiety disorders and/or higher levels of anxiety symptoms in people with major depressive disorder (MDD) is approximately 50% (Kessler *et al*., 2003; Fava *et al*., 2004; Ionescu *et al*., 2013; Dold *et al*., 2017; Gasperz *et al*., 2018). Residual anxiety symptoms, high baseline levels of anxiety, or the presence of a comorbid anxiety disorder are known to be risk factors for relapse or recurrence of MDD (Wilhelm *et al*., 1999; Parker *et al*., 2000; Dombrovski *et al*., 2007; Fava *et al*., 2008; Yang *et al*., 2010). Anxious depression also is associated with impaired functioning, higher rates of unemployment, and a greater risk of suicidality (Fava *et al*., 2006; Nelson, 2008; Farabaugh *et al*., 2012). A recent study found that the severity of anxiety at baseline adversely affected depression severity at 12 months and that a reduction of anxiety within the first 3 months of antidepressant treatment led to additional improvements in symptoms of depression (Bair *et al*., 2013). Antidepressant use may actually worsen symptoms in a minority of patients (Jha *et al*., 2018). A standard definition of anxious depression is a Hamilton depression rating scale (HAMD-17; Hamilton, 1960) anxiety/somatization factor subscale score of ≥7 (Fava *et al*., 2008). This definition of anxious depression has been used in previous studies, including secondary analyses of the Sequenced Treatment Alternatives to Relieve Depression trial (Fava *et al*., 2008; Farabaugh *et al*., 2012; Thase *et al*., 2014; Lyndon *et al*., 2019). Based on previous studies, the management of anxious depression should be aimed at treating symptoms of both depression and anxiety (Ionescu *et al*., 2014).

Pimavanserin is a potential 5-hydroxytryptamine$_{2A}$ (5-HT$_{2A}$) receptor antagonist/inverse agonist with less activity as a 5-HT$_{2C}$ antagonist/inverse agonist and no appreciable activity at adrenergic, dopaminergic, histaminergic, or muscarinic receptors (Vanover *et al*., 2006).

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Pimavanserin is approved in the United States by the Food and Drug Administration for treating hallucinations and delusions in patients with Parkinson's disease psychosis. In a phase 2, randomized, placebo-controlled study (CLARITY), adjunctive pimavanserin demonstrated a significant improvement of depressive symptoms in patients with MDD and an inadequate response to previous treatment (Fava *et al.*, 2019). This was a post hoc analysis of CLARITY was undertaken to evaluate the effects of adjunctive pimavanserin vs. placebo in a subgroup of patients with MDD and a baseline score ≥7 on the six-item HAMD-17 anxiety/somatization factor.

Materials and methods

The CLARITY study was conducted in accordance with the International Council of Harmonization guidelines and followed the principles of Good Clinical Practice derived from the Declaration of Helsinki. The study protocol and amendments and informed consent forms were reviewed and approved by an independent ethics committee or institutional review board. Prior to any study procedures, all patients were informed of the risks and benefits of the study and provided written informed consent. The CLARITY study was registered at clinicaltrials.gov: NCT03018340.

Study design

The detailed study methodology for CLARITY was previously published (Fava *et al.*, 2019). In brief, this was a multicenter, randomized, double-blind, placebo-controlled study in patients with MDD. Following an 8–21-day screening period, patients entered a 10-week double-blind treatment period, followed by a 30-day safety period to assess safety. The study used a two-stage Sequential Parallel-Comparison Design (Fava *et al.*, 2003). In stage 1, eligible patients were randomized in a 3:1 ratio to placebo or pimavanserin 34 mg once daily added to background treatment with a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) for 5 weeks. Nonresponders to placebo after 5 weeks (HAMD-17 total score >14 and <50% reduction in score from baseline) were rerandomized in a 1:1 ratio to placebo or pimavanserin 34 mg once daily in addition to an SSRI or SNRI 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.

Patient selection

Men or women at least 18 years of age with a BMI of 19–35 kg/m^2 were eligible if they had a primary diagnosis of MDD and a current Major Depressive Episode 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 (First *et al.*, 2016). A history of MDD for ≥1 year prior to screening, a Montgomery–Åsberg Depression Rating Scale (Montgomery and Asberg, 1976) total score >20, a Clinical Global Impression – Severity scale (Guy, 1976) score ≥4 (moderately ill or worse) at screening and baseline visits and a history of inadequate response to one or two adequate treatment trials with an SSRI or SNRI antidepressant during the current depression episode were required. Inadequate treatment response was determined with the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire, and this was confirmed by independent Massachusetts General Hospital Clinical Trials Network and Institute raters during the SAFER [State versus trait, Assessability, Face validity, Ecological validity, and Rule of three Ps (pervasive, persistent, and pathological)] interview. Patients with eating disorder, obsessive-compulsive disorder, attention deficit hyperactivity disorder, panic disorder, acute stress disorder, or posttraumatic stress disorder, according to DSM-5 criteria were excluded.

Study assessments

Clinic visits occurred weekly from weeks 1 to 10 (end of study). The HAMD-17 was administered at baseline and weekly during the study. Safety and tolerability were assessed from adverse events, physical examination, vital signs, and clinical laboratory testing.

Statistical analysis

In this post hoc analysis, anxious depression was defined as a score ≥7 on the six-item HAMD-17 anxiety/somatization factor, which consisted of the sum of items 10 (psychic anxiety), 11 (somatic anxiety), 12 (gastrointestinal somatic symptoms), 13 (general somatic symptoms), 15 (hypochondriasis), and 17 (insight) (Ionescu *et al.*, 2014; Farabaugh *et al.*, 2010). Mean change from baseline to week 5 for the HAMD-17 anxiety/somatization factor was examined for the entire study population. Second, mean change from baseline to week 5 was examined for the subgroup of patients with a baseline score ≥7 for the HAMD-17 anxiety/somatization factor. An analysis was conducted of the mean change from baseline to week 5 among a subgroup with severe MDD at baseline (HAMD-17 total score ≥24) and a HAMD-17 anxiety/somatization factor score ≥7 at baseline. Finally, the effect of a baseline HAMD-17 anxiety/somatization factor score ≥7 on response (≥50% improvement in the HAMD-17 total score from baseline) and remission (HAMD-17 total score ≤7) was examined. Efficacy data were analyzed for the full analysis set for each of the two stages, comprising all randomized patients who received ≥1 dose of blinded study drug and who had a baseline value and at least one postbaseline value for the HAMD-17 total score within each stage.

Least squares (LS) mean [standard error (SE)] was determined from a stage-specific mixed models for repeated measures (MMRM) analysis with change from baseline as the outcome; treatment group, visit, treatment-by-visit

interaction, baseline HAMD-17 anxiety/somatization factor score, and baseline HAMD-17 anxiety/somatization factor score-by-visit interaction as the factors. An unstructured covariance matrix is used to model the within-subject errors. The denominator degrees of freedom were estimated using the Kenward–Roger approximation. A two-sided *P*-value was reported for treatment difference from the stage-specific MMRM analysis. Cohen's *d* effect size was calculated for comparisons between treatments. For response and remission, mean difference for pimavanserin vs. placebo was determined. A Newcombe 95% confidence interval (CI) was calculated on the difference, and *P* values were calculated from a stage-specific Pearson's chi-square test.

Results

In the efficacy population, 152 patients were randomized to placebo and 51 to pimavanserin in stage 1, and 29 patients each were rerandomized to treatment with pimavanserin or placebo in stage 2 (Fava *et al.*, 2019). At week 5 of stage 1, the least squares (LS) mean difference for pimavanserin vs. placebo was –4.0 for the HAMD-17 ($P = 0.0003$).

In the post hoc analysis, pimavanserin produced a significantly greater effect on the HAMD-17 anxiety/somatization factor score vs. placebo in stage 1 ($P = 0.0003$) and across stages 1 and 2 using prespecified weighting ($P = 0.0166$), but not in stage 2 ($P = 0.980$) (Table 1). At week 5 in stage 1, the LS mean (SE) difference between placebo and pimavanserin for the anxiety/somatization factor score was –1.5 (0.41) (95% CI –2.4 to –0.7; $P = 0.0003$; Cohen's *d* effect size: 0.634) (Fig. 1).

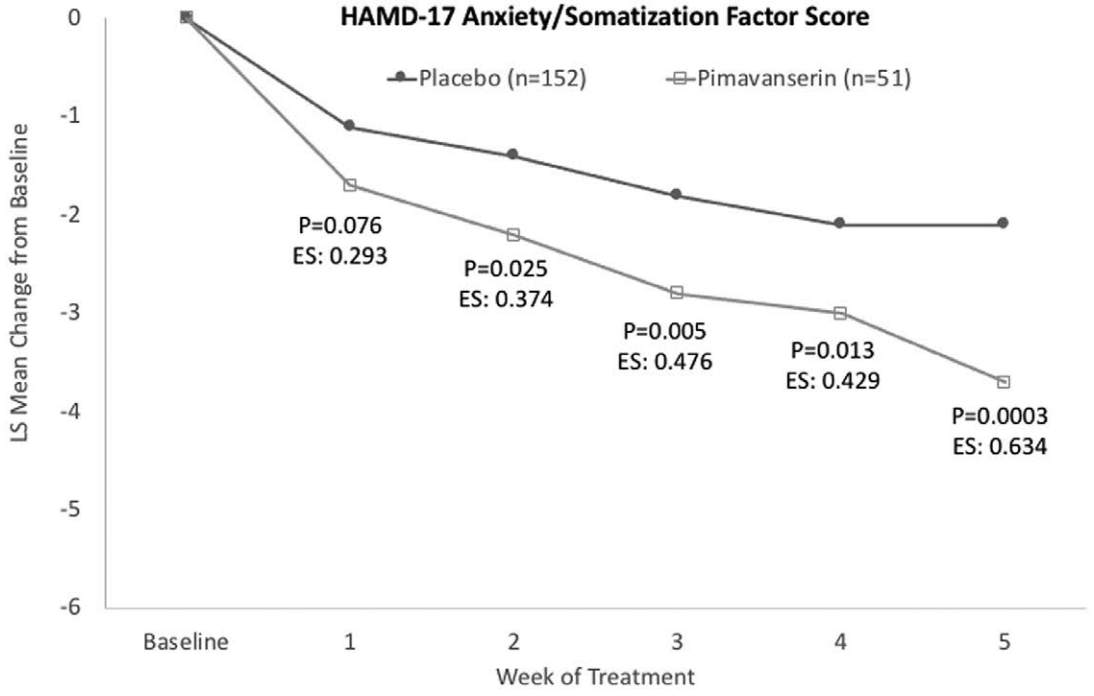
For the subgroup of patients (placebo 75, pimavanserin 29) with a baseline HAMD-17 anxiety/somatization factor score ≥7, pimavanserin significantly reduced the HAMD-17 anxiety/somatization factor score in stage 1 ($P = 0.0013$) and across stages 1 and 2 using prespecified weighting ($P = 0.027$), but not in stage 2 ($P = 0.847$) (Table 1). In stage 1, among patients with a baseline HAMD anxiety/somatization factor score ≥7, the LS mean (SE) difference at

Table 1 Mean baseline and least squares mean change and treatment difference between pimavanserin and placebo for study outcomes

	Stage 1		Stage 2	
	Placebo	Pimavanserin	Placebo	Pimavanserin
HAMD anxiety/somatization factor at baseline	*N* = 152	*N* = 51	*N* = 29	*N* = 29
Baseline mean (SE)	6.6 (0.18)	6.9 (0.36)	6.0 (0.43)	6.5 (0.49)
Change from baseline to week 5				
LS mean (SE)[a]	−2.1 (0.21)	−3.7 (0.36)	−0.6 (0.35)	−0.6 (0.33)
95% CI of LS mean	(−2.5 to −1.7)	(−4.4 to −3.0)	(−1.3 to 0.1)	(−1.3 to 0.0)
LS mean (SE) difference (pimavanserin 34 mg-placebo)		−1.5 (0.41)		0 (0.48)
95% CI of difference		(−2.4 to −0.7)		(−1.0 to 1.0)
P-value[b]		0.0003		0.980
Effect size (Cohen's *d*)		0.634		−0.007
Overall treatment comparison at week 5 (linear combination test)				
Weighted difference in LS mean (SE)				−0.8 (0.32)
95% CI of weighted difference				(−1.4 to −0.1)
P-value[b]				0.0166
HAMD anxiety/somatization factor ≥7 at baseline	*N* = 76	*N* = 29	*N* = 18	*N* = 19
Baseline mean (SE)	8.5 (0.15)	8.8 (0.28)	7.1 (0.54)	7.5 (0.59)
Change from baseline to week 5				
LS mean (SE)[a]	−2.8 (0.35)	−5.0 (0.56)	−1.5 (0.49)	−1.3 (0.44)
95% CI of LS mean	(−3.5 to −2.1)	(−6.1 to −3.8)	(−2.5 to −0.5)	(−2.3 to −0.4)
LS Mean (SE) difference (pimavanserin 34 mg-placebo)		−2.2 (0.66)		0.1 (0.66)
95% CI of difference		(−3.5 to −0.9)		(−1.2 to 1.5)
P-value[b]		0.0013		0.847
Effect size (Cohen's *d*)		0.781		−0.067
Overall treatment comparison at week 5 (linear combination test)				
Weighted difference in LS mean (SE)				−1.0 (0.47)
95% CI of weighted difference				(−2.0 to −0.1)
P-value[b]				0.027
HAMD total score ≥24 and HAMD anxiety/somatization factor ≥7 at baseline	*N* = 36	*N* = 17	*N* = 8	*N* = 10
Baseline mean (SE)	27.6 (0.41)	27.6 (0.70)	24.0 (1.20)	22.0 (1.90)
Change from baseline to week 5				
LS mean (SE)[a]	−9.3 (1.40)	−17.4 (1.97)	−1.3 (1.68)	−3.7 (1.43)
95% CI of LS mean	(−12.1 to −6.5)	(−21.4 to −13.4)	(−4.9 to 2.3)	(−6.8 to −0.6)
LS mean (SE) difference (pimavanserin 34 mg-placebo)		−8.1 (2.42)		−2.4 (2.22)
95% CI of difference		(−13.0 to −3.2)		(−7.2 to 2.3)
P-value[b]		0.0018		0.295
Effect size (Cohen's *d*)		1.037		0.536
Overall treatment comparison at week 5 (linear combination test)				
Weighted difference in LS mean (SE)				−5.2 (1.64)
95% CI of weighted difference				−8.5 to −2.0)
P-value[b]				0.0014

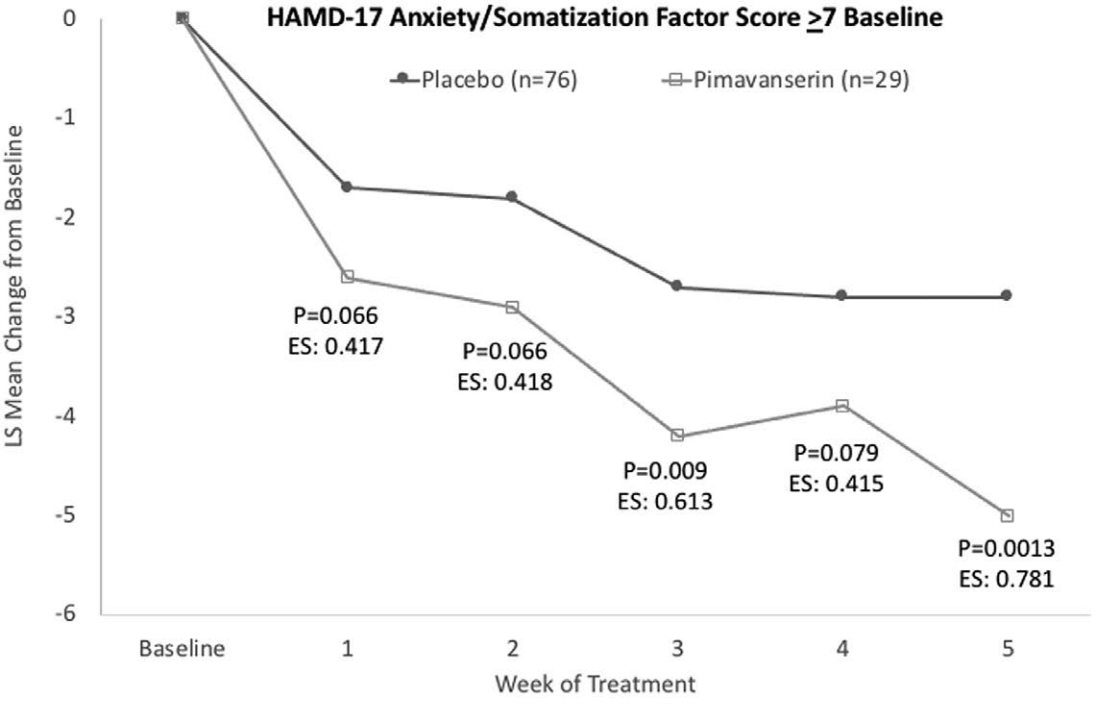
ANCOVA, analysis of covariance; CI, confidence interval; HAMD, Hamilton depression rating scale; LS, least squares; SE, standard errors.
[a]LS mean from the stage-specific ANCOVA analysis with the change from baseline as the outcome, treatment group as a factor, and the corresponding baseline value as a covariate.
[b]Two-sided *P*-value for treatment difference from the stage-specific ANCOVA analysis.

Fig. 1



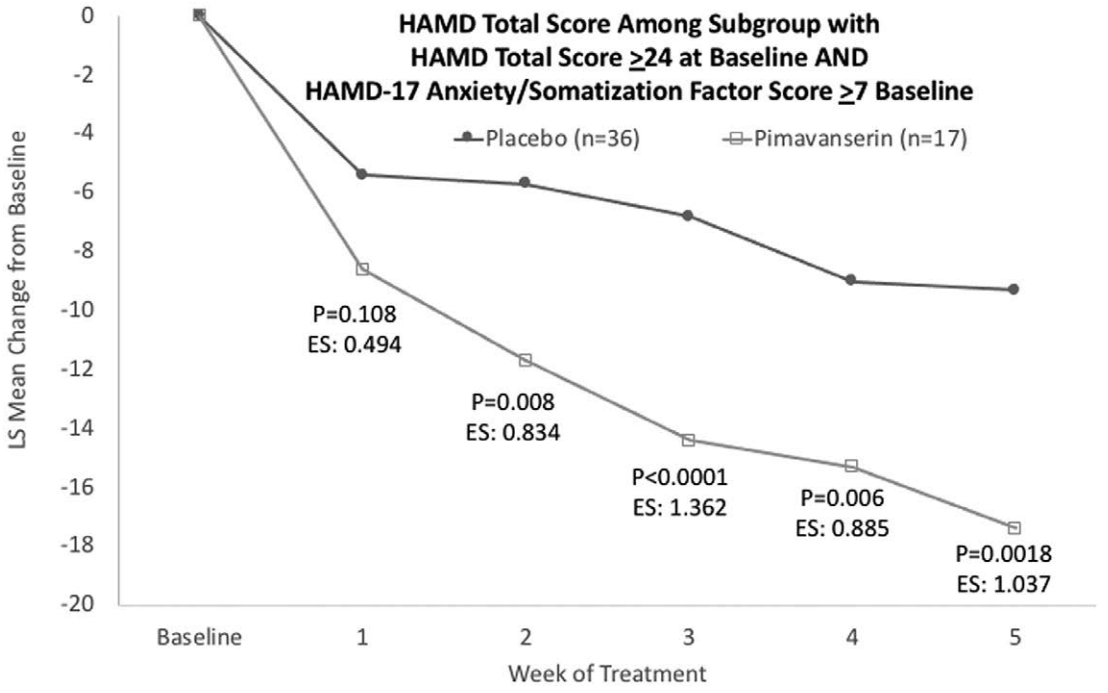
LS mean change from baseline for HAMD-17 anxiety/somatization factor score. HAMD, Hamilton depression rating scale; LS, least squares.

Fig. 2



LS mean change from baseline for patients with a HAMD-17 anxiety/somatization factor score ≥7 at baseline. HAMD, Hamilton depression rating scale; LS, least squares.

Fig. 3



LS mean change from baseline for the HAMD-17 total score among patients with a baseline HAMD-17 total score ≥24 and a HAMD-17 anxiety/somatization factor score ≥7. HAMD, Hamilton depression rating scale; LS, least squares.

week 5 was –2.2 (0.66) (95% CI –3.5 to –0.9; $P = 0.0013$; Cohen's *d* effect size: 0.781) (Fig. 2).

Among the subgroup of patients with a baseline HAMD-17 total score ≥24 indicating severe depression AND a HAMD-17 anxiety/somatization factor score ≥7, pimavanserin significantly reduced the HAMD-17 anxiety/somatization factor score in stage 1 ($P = 0.0018$) and across stages 1 and 2 using prespecified weighting ($P = 0.0014$), but not in stage 2 ($P = 0.295$) (Table 1). In stage 1, the LS mean (SE) difference at week 5 was –8.1 (2.42) (95% CI –13.0 to –3.2; $P = 0.0018$; Cohen's *d* effect size: 1.037) (Fig. 3).

At week 5, response rates (≥50% reduction in HAMD-17 from baseline) were 22.4 and 55.2% ($P = 0.0012$) and remission rates (HAMD-17 total score <7) were 5.3 and 24.1% ($P = 0.0047$), respectively, with placebo and pimavanserin, respectively, among patients with a baseline HAMD anxiety/somatization factor score ≥7 (Fig. 4).

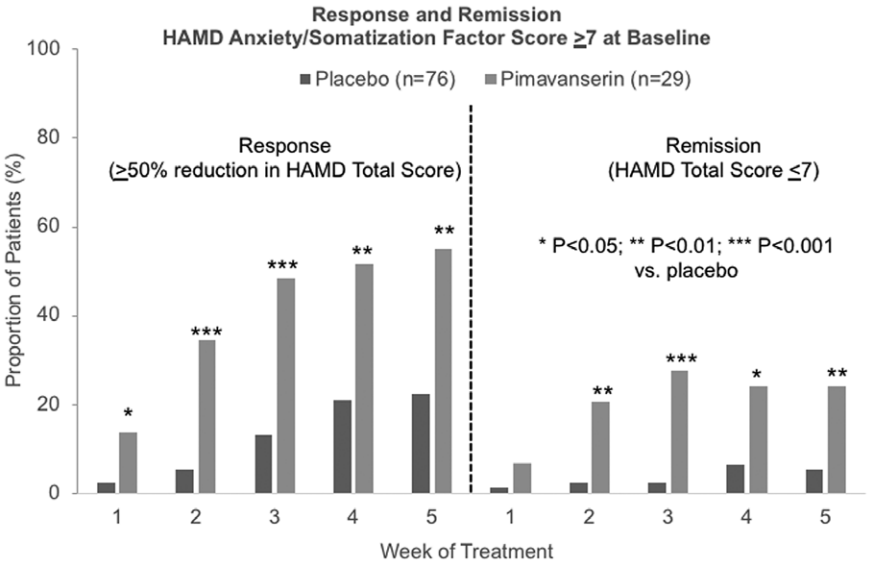
Anxiety was reported as an adverse event in two (1.3%) patients in the placebo group and 1 (1.9%) in the pimavanserin group during stage 1. No anxiety as an adverse event was reported in stage 2.

Discussion

This post hoc analysis of patients with MDD enrolled in the phase 2 CLARITY study found reductions in the HAMD-17 total score as well as the HAMD anxiety/somatization factor score with adjunctive pimavanserin compared with placebo. Significant differences from placebo were observed with adjunctive pimavanserin for the HAMD anxiety/somatization factor score overall and among patients with a baseline HAMD anxiety/somatization factor score ≥7, with effect sizes >0.6 at week 5. Among the subgroup with a baseline HAMD anxiety/somatization factor score ≥7 and a HAMD-17 total score ≥24, representing patients with severe and anxious depression, the HAMD-17 total score was markedly reduced from baseline to week 5 with adjunctive pimavanserin vs. placebo. Of note, significant differences from placebo were observed as early as week 2 with pimavanserin. The lack of significant differences between pimavanserin and placebo in stage 2 may be attributed to the small sample sizes. Among the subgroup of patients with a baseline HAMD anxiety/somatization factor score ≥7, significant improvement in the HAMD-17 response rate was observed at week 1 and the HAMD-17 remission rate at week 2 was observed with pimavanserin vs. placebo. Further, response and remission rates were higher with pimavanserin and lower with placebo in this subgroup of patients with anxious depression compared with the overall study population (Fava *et al.*, 2019).

Anxious depression is reported to occur in approximately 50% or more of patients with MDD (Wiethoff *et al.*, 2010; Papakostas and Larsen 2011). Patients with

Fig. 4



Response and remission rates among patients with a HAMD-17 anxiety/somatization factor score ≥7 at baseline. HAMD, Hamilton depression rating scale.

anxious depression are more likely to experience poor outcomes including increased rates of treatment failure and treatment resistance (Souery *et al.*, 2007; Papakostas and Larsen 2011; Papakostas *et al.*, 2012; Farabaugh *et al.*, 2012; Ionescu *et al.*, 2014; Dold *et al.*, 2017; Gaspersz *et al.*, 2018; Kautzky *et al.*, 2019). Previous studies have found that patients with comorbid anxiety and MDD were less responsive to antidepressant treatment (Souery *et al.*, 2007; Fava *et al.*, 2008; Wiethoff *et al.*, 2010; Kautzky *et al.*, 2019). However, others have found an improved response with SSRI or SNRI antidepressants in depressed patients with anxiety symptoms or anxious depression at baseline (Thase *et al.*, 2014; Lyndon *et al.*, 2019). In this analysis, patients were enrolled who had an inadequate response to SSRI or SNRI treatment, and those with anxious depression experienced a robust response to adjunctive pimavanserin. Thus, consideration should be given to the impact of anxiety symptoms and anxious depression when treating patients with major depression and the potential role of adjunctive therapy in inadequate responders to SSRI or SNRI antidepressants.

A limited number of studies have been published describing the use of antidepressants for treating anxious depression. Greater improvement in symptoms of MDD was observed among those with anxious depression at baseline (Thase *et al.*, 2014; Lyndon *et al.*, 2019), together with higher response and remission rates (Lyndon *et al.*, 2019). However, the majority of studies of patients with comorbid anxiety or anxious depression and MDD found less benefit from antidepressant therapy among patients with anxiety compared with those without anxiety (Nelson, 2008).

Limitations of this analysis include its post hoc design that was not specified a priori in the original analyses, where patients with comorbid anxiety were not prospectively identified, the small sample size, especially among patients with severe MDD at baseline in stage 2, and the short 5-week duration of follow-up in stages 1 and 2. However, limited clinical data are available where antidepressant therapy has been studied in patients with anxious depression. The lack of significant differences between pimavanserin and placebo in stage 2 likely was a result of small sample sizes. Thus, these results add valuable information about anxious depression in patients with MDD.

In summary, these results from a post hoc analysis demonstrated a marked response among patients with anxious depression to adjunctive pimavanserin compared with placebo. Statistically significant and clinically meaningful improvements were observed with pimavanserin vs. placebo within 2 weeks. Reductions in anxiety measured by the HAMD anxiety/somatization factor were associated with significant improvement in response and remission on the HAMD-17 total score. Ongoing phase 3 studies, with adjunctive pimavanserin in patients with MDD, will provide a larger population of patients in which the occurrence of anxious depression and the response to pimavanserin can be examined further. Future studies may also assess whether pimavanserin is specifically efficacious in anxious MDD compared with other subtypes

and whether it may be considered to treat comorbid anxiety disorders, as well as anxious symptoms, in the context of a major depressive episode.

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Conflicts of interest

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References

Bair MJ, Poleshuck EL, Wu J, Krebs EK, Damush TM, Tu W, Kroenke K (2013). Anxiety but not social stressors predict 12-month depression and pain severity. *Clin J Pain* **29**:95–101.

Dold M, Bartova L, Souery D, Mendlewicz J, Serretti A, Porcelli S, *et al.* (2017). Clinical characteristics and treatment outcomes of patients with major depressive disorder and comorbid anxiety disorders - results from a European multicenter study. *J Psychiatr Res* **91**:1–13.

Dombrovski AY, Mulsant BH, Houck PR, Mazumdar S, Lenze EJ, Andreescu C, *et al.* (2007). Residual symptoms and recurrence during maintenance treatment of late-life depression. *J Affect Disord* **103**:77–82.

Farabaugh A, Alpert J, Wisniewski SR, Otto MW, Fava M, Baer L, *et al.* (2012). Cognitive therapy for anxious depression in STAR(*) D: what have we learned? *J Affect Disord* **142**:213–218.

Farabaugh AH, Bitran S, Witte J, Alpert J, Chuzi S, Clain AJ, *et al.* (2010). Anxious depression and early changes in the HAMD-17 anxiety-somatization factor items and antidepressant treatment outcome. *Int Clin Psychopharmacol* **25**:214–217.

Fava M, Alpert JE, Carmin CN, Wisniewski SR, Trivedi MH, Biggs MM, *et al.* (2004). Clinical correlates and symptom patterns of anxious depression among patients with major depressive disorder in STAR*D. *Psychol Med* **34**:1299–1308.

Fava M, Dirks B, Freeman MP, Papakostas GI, Shelton RC, Thase ME, *et al.* (2019) 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). *J Clin Psychiatry* **80**: 19m12928.

Fava M, Evins AE, Dorer DJ, Schoenfeld DA (2003). The problem of the placebo response in clinical trials for psychiatric disorders: culprits, possible remedies, and a novel study design approach. *Psychother Psychosom* **72**:115–127.

Fava M, Rush AJ, Alpert JE, Balasubramani GK, Wisniewski SR, Carmin CN, *et al.* (2008). Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR*D report. *Am J Psychiatry* **165**:342–351.

Fava M, Rush AJ, Alpert JE, Carmin CN, Balasubramani GK, Wisniewski SR, *et al.* (2006). What clinical and symptom features and comorbid disorders characterize outpatients with anxious major depressive disorder: a replication and extension. *Can J Psychiatry* **51**:823–835.

First MB, Williams JBW, Karg RS, Spitzer RL. (2016) *Structured Clinical Interview for DSM-5 Disorders, Clinician Version (SCID-5-CV)*. Arlington, VA: American Psychiatric Association.

Gaspersz R, Nawijn L, Lamers F, Penninx, BWJH (2018). Patients with anxious depression: overview of prevalence, pathophysiology and impact on course and treatment outcome. *Curr Opin Psychiatry* **31**:17–25.

Guy W (1976). *ECDEU Assessment Manual for Psychopharmacology–Revised (DHEW Publ No. ADM 76-338)*. Rockville, MD: 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, 218–222.

Hamilton M (1960). A rating scale for depression. *J Neurol Neurosurg Psychiatry* **23**:56–62.

Ionescu DF, Niciu MJ, Henter ID, Zarate CA (2013). Defining anxious depression: a review of the literature. *CNS Spectr* **18**:252–260.

Ionescu DF, Niciu MJ, Richards EM, Zarate CA Jr (2014). Pharmacologic treatment of dimensional anxious depression: a review. *Prim Care Companion CNS Disord* **16**:PCC.13r01621.

Jha MK, Minhajuddin A, South C, Rush AJ, Trivedi MH (2018). Worsening anxiety, irritability, insomnia, or panic predicts poorer antidepressant treatment outcomes: clinical utility and validation of the concise associated symptom tracking (CAST) scale. *Int J Neuropsychopharmacol* **21**:325–332.

Kautzky A, Dold M, Bartova L, Spies M, Kranz GS, Souery D, *et al.* (2019). Clinical factors predicting treatment resistant depression: affirmative results from the European multicenter study. *Acta Psychiatr Scand* **139**:78–88.

Kessler RC, Sampson NA, Berglund P, Gruber MJ, Al-Hamzawi A, Andrade L, *et al.* (2015). Anxious and non-anxious major depressive disorder in the World Health Organization World Mental Health Surveys. *Epidemiol Psychiatr Sci* **24**:210–226.

Lyndon GJ, Prieto R, Wajsbrot DB, Allgulander C, Bandelow B (2019). Efficacy of venlafaxine extended release in major depressive disorder patients: effect of baseline anxiety symptom severity. *Int Clin Psychopharmacol* **34**:110–118.

Montgomery SA, Asberg M (1979). A new depression scale designed to be sensitive to change. *Br J Psychiatry* **134**:382–389.

Nelson JC (2008). Anxious depression and response to treatment. *Am J Psychiatry* **165**:297–299.

Papakostas GI, Fan H, Tedeschini E (2012). Severe and anxious depression: combining definitions of clinical sub-types to identify patients differentially responsive to selective serotonin reuptake inhibitors. *Eur Neuropsychopharmacol* **22**:347–355.

Papakostas GI, Larsen K (2011). Testing anxious depression as a predictor and moderator of symptom improvement in major depressive disorder during treatment with escitalopram. *Eur Arch Psychiatry Clin Neurosci* **261**:147–156.

Parker G, Wilhelm K, Mitchell P, Gladstone G (2000). Predictors of 1-year outcome in depression. *Aust N Z J Psychiatry* **34**:56–64.

Souery D, Oswald P, Massat I, Bailer U, Bollen J, Demyttenaere K, *et al.*; Group for the Study of Resistant Depression. (2007). Clinical factors associated with treatment resistance in major depressive disorder: results from a European multicenter study. *J Clin Psychiatry* **68**:1062–1070.

Thase ME, Chen D, Edwards J, Ruth A (2014). Efficacy of vilazodone on anxiety symptoms in patients with major depressive disorder. *Int Clin Psychopharmacol* **29**:351–356.

Vanover KE, Weiner DM, Makhay M, Veinbergs I, Gardell LR, Lameh J, *et al.* (2006). 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* **317**: 910–918.

Wiethoff K, Bauer M, Baghai TC, Möller HJ, Fisher R, Hollinde D, *et al.* (2010). Prevalence and treatment outcome in anxious versus nonanxious depression: results from the German Algorithm Project. *J Clin Psychiatry* **71**:1047–1054.

Wilhelm K, Parker G, Dewhurst-Savellis J, Asghari A (1999). Psychological predictors of single and recurrent major depressive episodes. *J Affect Disord* **54**:139–147.

Yang H, Chuzi S, Sinicropi-Yao L, Johnson D, Chen Y, Clain A, *et al.* (2010). Type of residual symptom and risk of relapse during the continuation/maintenance phase treatment of major depressive disorder with the selective serotonin reuptake inhibitor fluoxetine. *Eur Arch Psychiatry Clin Neurosci* **260**: 145–150.