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-HT2A) receptor antagonist/inverse agonist with less activity as a 5-HT2C antagonist/inverse agonist and no appreciable activity at adrenergic, dopaminergic, histaminergic, or muscarinic receptors (Vanover et al., 2006).
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/m² 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 (MMRMR) analysis with change from baseline as the outcome; treatment group, visit, treatment-by-visit interactions and all other fixed effects, and residual error as random effects.
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                                                                                |
| N        | 152                                                                                                                         | 51                                                                                          |
| Baseline mean (SE)                                                                 | 6.6 (0.18)                                                                                   | 6.9 (0.38)                                                                                  |
| Change from baseline to week 5                                                                                                      |                                                                                             |
| LS mean (SE)                                                                                                                         | −2.1 (0.21)                                                                                | −3.7 (0.36)                                                                                 |
| 95% CI of LS mean                                                                                                                  | (−2.5 to −1.7)                                                                              | (−4.4 to −3.0)                                                                              |
| 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-valueb                                                                                                                             | 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)                                                                                | (−1.4 to −0.1)                                                                              |
| 95% CI of weighted difference                                                                                                       |                                                                                             |
| P-valueb                                                                                                                             | 0.0186                                                                                      |                                                                                             |
| HAMD anxiety/somatization factor ≥7 at baseline                                                                                  |                                                                                             |
| N                                                                                                                                     | 76                                                                                          | 29                                                                                          |
| Baseline mean (SE)                                                                                                                  | 8.5 (0.15)                                                                                 | 8.8 (0.28)                                                                                 |
| Change from baseline to week 5                                                                                                       |                                                                                             |
| LS mean (SE)                                                                                                                         | −2.8 (0.35)                                                                                | −5.0 (0.56)                                                                                 |
| 95% CI of LS mean                                                                                                                  | (−3.5 to −2.1)                                                                              | (−6.1 to −3.8)                                                                              |
| 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-valueb                                                                                                                             | 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)                                                                                | (−2.0 to −0.1)                                                                              |
| 95% CI of weighted difference                                                                                                       |                                                                                             |
| P-valueb                                                                                                                             | 0.027                                                                                       |                                                                                             |
| HAMD total score ≥24 and HAMD anxiety/somatization factor ≥7 at baseline                                                           |                                                                                             |
| N                                                                                                                                     | 36                                                                                          | 17                                                                                          |
| Baseline mean (SE)                                                                                                                  | 276 (0.41)                                                                                 | 276 (0.70)                                                                                 |
| Change from baseline to week 5                                                                                                       |                                                                                             |
| LS mean (SE)                                                                                                                         | −9.3 (1.40)                                                                                | −17.4 (1.97)                                                                               |
| 95% CI of LS mean                                                                                                                  | (−12.1 to −6.5)                                                                             | (−21.4 to −13.4)                                                                            |
| LS Mean (SE) difference (pimavanserin 34 mg-placebo)                                                                              | −8.1 (2.42)                                                                                | −4.9 (2.3)                                                                                 |
| 95% CI of difference                                                                                                               | (−13.0 to −3.2)                                                                             | (−7.2 to 2.3)                                                                              |
| P-valueb                                                                                                                             | 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)                                                                                | −8.5 to −2.0                                                                               |
| 95% CI of weighted difference                                                                                                       |                                                                                             |
| P-valueb                                                                                                                             | 0.014                                                                                       |                                                                                             |

ANCOVA, analysis of covariance; CI, confidence interval; HAMD, Hamilton depression rating scale; LS, least squares; SE, standard errors.

bTwo-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.
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
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.

Fig. 4

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