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NUPLAZID® (pimavanserin): Clinical Trials in Major Depressive Disorder

This letter is provided in response to your specific request for information regarding pimavanserin clinical trials in major depressive disorder (MDD).

Pimavanserin is approved by the U.S. Food and Drug Administration (FDA) as an atypical antipsychotic indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis.[1] The efficacy and safety of pimavanserin for the adjunctive treatment of MDD is investigational and have not been established and approved by the FDA.

Summary

- The efficacy and safety of pimavanserin as adjunctive treatment in participants with MDD who had an inadequate response to standard antidepressant therapy with either selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) have been evaluated in one **Phase 2 study (CLARITY)** and two **Phase 3 studies (CLARITY-2 and CLARITY-3)**.[2,3]
- In the 10-week, Phase 2 CLARITY sequential parallel comparison design (SPCD) study (N=207), adjunctive pimavanserin 34 mg **met the primary endpoint** of the weighted average results of Stage 1 and Stage 2 by significantly reducing the 17-item Hamilton Depression Rating Scale (HAMD-17) total score compared to placebo (least squares mean [LSM] [SE] = –1.7 [0.85], p=0.039).[2]
    - The **most common treatment-emergent adverse events (TEAEs)** in the pimavanserin group were dry mouth, nausea and headache, all with frequency of <10%.[2]
- The two identical 6-week, **Phase 3 CLARITY-2 and CLARITY-3 studies** were merged into one study with a pre-specified statistical analysis plan (N=298), in agreement with the FDA.[3,4]
    - The study did not achieve statistical significance on the **primary endpoint** which was the HAMD-17 total score change from baseline to Week 5.[4]
- **TEAEs** occurred in 58.1% (86/148) of pimavanserin-treated and 54.7% (82/150) of placebo-treated patients. The most common TEAE in both groups was headache (pimavanserin, 20.9%; placebo, 18.0%).[4]

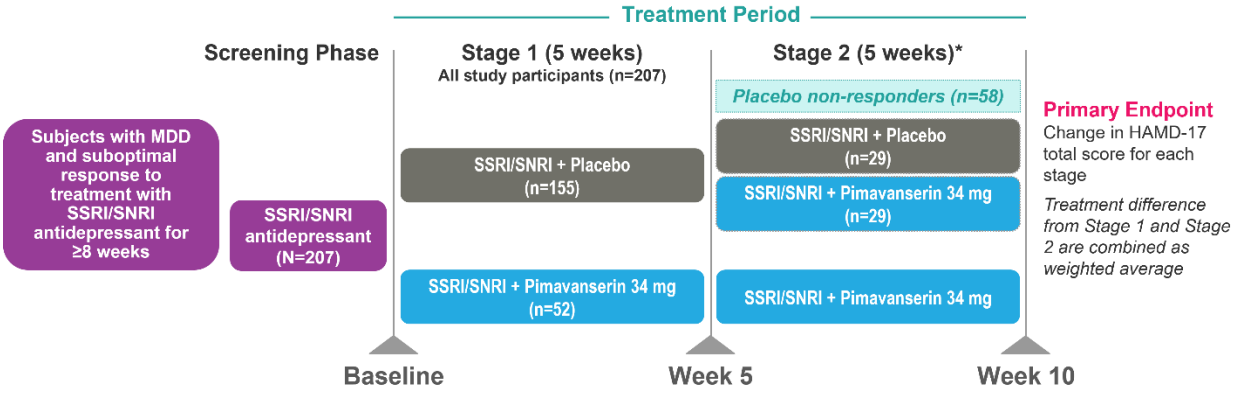
CLARITY (ACP-103-042)

CLARITY was a Phase 2, 10-week, randomized, double-blind, placebo-controlled, multi-center, SPCD study.[2] In the study, 207 adult participants with a confirmed inadequate response to existing first-line SSRI or SNRI therapy for MDD received adjunctive treatment of either pimavanserin 34 mg or placebo, in addition to pre-existing first-line therapy for 5 weeks (Stage 1). Those participants who did not show a response to placebo in Stage 1 were re-randomized to receive either pimavanserin or placebo added to current therapy for a second five-week treatment period (Stage 2).

Study Design

Consistent with the SPCD design, the study was conducted in two, five-week sequential stages (**Figure 1**).[2] Eligible participants continued receiving their SSRI or SNRI antidepressant at a stable dose for the duration of the study. Participants were randomly assigned (1:3) to pimavanserin 34 mg per day or placebo in Stage 1. Placebo non-responders in Stage 1 (defined as HAMD-17 total score >14 and a percent-reduction from baseline in HAMD-17 total score of <50% at Week 5) were re-randomized (1:1) to Stage 2 to receive pimavanserin 34 mg per day or placebo. Overall treatment effects were assessed as the weighted treatment differences in LSM change for the 2 stages. The primary endpoint was change from baseline in HAMD-17 total score for Stage 1 and Stage 2.

Figure 1. CLARITY Study Design[2]



Note: For Stage 1, baseline is study week 0 and Week 5 is study week 5. For Stage 2, baseline is study week 5 and Week 5 is study week 10.
**Patients who had a response to placebo in Stage 1 continued taking placebo through Week 10.*
Abbreviations: HAMD-17=17-item Hamilton Depression Rating Scale; MDD=major depressive disorder; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor.

Selected inclusion and exclusion criteria are shown in **Table 1**.

Table 1. Selected Inclusion and Exclusion Criteria (ACP-103-042)[5]

Selected inclusion criteria
• Adult participants, aged 18 years and above, with a clinical diagnosis of MDD • Was being treated with one of the following SSRI or SNRI antidepressants as monotherapy: citalopram, escitalopram, paroxetine, fluoxetine, sertraline, duloxetine, venlafaxine, desvenlafaxine, venlafaxine XR • Had a history of inadequate response to 1 or 2 antidepressant treatments during the current depression episode, confirmed with the MGH ATRQ[2] • MADRS total score >20[2] • CGI-S score ≥4 (moderately ill or worse)[2]
Selected exclusion criteria
• Participant had a psychotic disorder other than MDD • Participant had current evidence of serious and/or unstable neurologic, cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematologic, or other medical disorder, including cancer or malignancies, which would affect the participant's ability to participate in the program • Participant had a history or symptoms of long QT syndrome.

Abbreviations: CGI-S=Clinical Global Impression – Severity; MADRS=Montgomery Asberg Depression Rating Scale; MDD=major depressive disorder; MGH ATRQ=Massachusetts General Hospital Antidepressant Treatment Questionnaire; SNRI=serotonin norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor.

Demographics and Baseline Characteristics

Demographics and baseline characteristics are summarized in **Table 2**.

Table 2. Baseline Demographics and Clinical Characteristics (ACP-103-042)[2]

	Placebo (N=155)	Pimavanserin 34 mg (N=52)
Age, years	45.4±15.4	48.6±13.3
Age range, years	18–82	20–69
Female, n (%)	108 (69.7)	43 (82.7)
Race, n (%)		
White	111 (71.6)	38 (73.1)
Black or African American	31 (20.0)	9 (17.3)
Asian	7 (4.5)	0
American Indian or Alaska Native	3 (1.9)	1 (1.9)
Other	3 (1.9)	4 (7.7)
Body mass index, kg/m^2	27.6±4.4	28.6±4.6
MADRS Total Score	31.1±5.3	32.5±5.4
HAMD-17 Total Score	22.0±4.2	22.8±4.6
HAMD-17 Score ≥24, n (%)	50 (32.3)	21 (40.4)
SDS Score	6.5±2.1	6.3±2.1
CGI-S Score	4.4±0.6	4.6±0.7

Note: Values represent mean ± standard deviation unless otherwise noted.
Abbreviations: CGI-S=Clinical Global Impression – Severity; HAMD-17=17-item Hamilton Depression Rating Scale; MADRS=Montgomery Asberg Depression Rating Scale; SDS=Sheehan Disability Scale.

Efficacy Results

Pimavanserin 34 mg met the primary endpoint of the weighted average results of Stage 1 and Stage 2 by significantly reducing HAMD-17 total score compared to placebo (LSM [SE] = –1.7 [0.85], p=0.039).[2,6] In addition, in Stage 1 (n=203; 51 pimavanserin, 152 placebo), LSM change from baseline in HAMD-17 total score was significantly greater (p<0.05) for pimavanserin versus placebo from Week 1 to Week 5. In Stage 2 (n=58; 29 pimavanserin, 29 placebo) results did not demonstrate significant separation in this set of placebo non-responders.

On the key secondary endpoint Sheehan Disability Scale (SDS) score, pimavanserin demonstrated statistically significant reductions compared to placebo for the weighted average results of Stage 1 and Stage 2 (LSM [SE] –0.84 [0.29], p=0.004).[2,6]

Weighted treatment differences for Stage 1 and Stage 2 were statistically significant for seven of the eleven other secondary endpoints: Clinical Global Impression-Severity (CGI-S; p=0.0084), Clinical Global Impression-Improvement (p=0.0289), Short Form-12 Mental Component Summary (p<0.0001), Karolinska Sleepiness Scale (p=0.0205), Massachusetts General Hospital Sexual Functioning Index (p=0.0003), Barratt Impulsiveness Scale (p=0.0075), as well as response rates (p=0.0065) defined as a 50% or greater reduction on the HAMD-17 total score from baseline. Secondary endpoints in which there was no significant separation from placebo include: Short Form-12 Physical Component Summary, Drug Attitude Inventory-10 Total Score, Sheehan Irritability Scale, and remission rates defined as HAMD-17 total score less than or equal to 7.[2,6]

Safety Results

Treatment-related TEAEs occurred in 27.1% and 48.1% of participants in the placebo and pimavanserin groups, respectively, during Stage 1 and in 3.4% and 13.8% of participants in the placebo and pimavanserin groups, respectively, during Stage 2. The most common TEAEs in the pimavanserin group were dry mouth, nausea and headache, all with frequency of <10%. One participant in the placebo group experienced 2 serious TEAEs (bladder stones and prostate cancer), and 1 participant in the pimavanserin group experienced 1 serious TEAE (acute myocardial infarction); all were considered unrelated to therapy and participants remained on study drug. During Stage 1, 3 participants (1.9%) discontinued the study due to an AE in the placebo group and 1 (1.9%) in the pimavanserin group. Additionally, 1 participant (3.4%) discontinued placebo during Stage 2. No deaths occurred, and no clinically relevant changes in vital signs, clinical laboratory testing, or electrocardiogram findings were observed.[2]

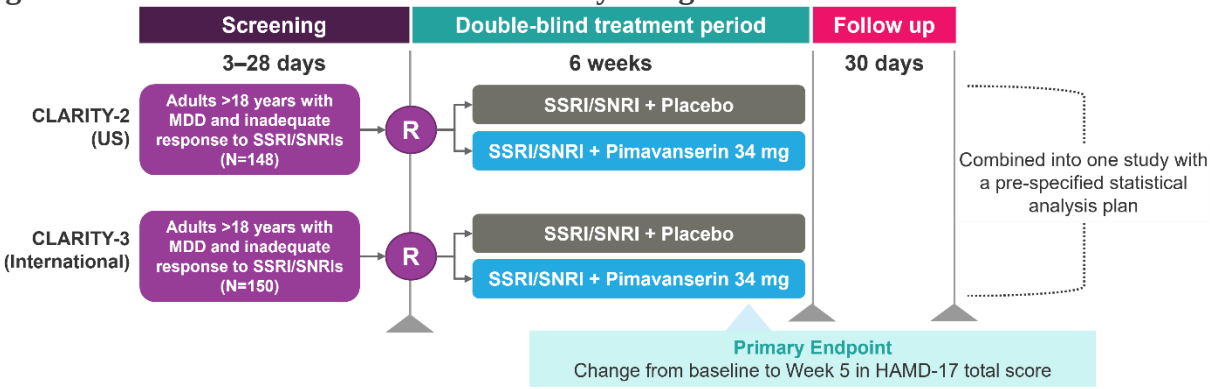
CLARITY-2 (ACP-103-059) and CLARITY-3 (ACP-103-054)

CLARITY-2 and CLARITY-3 were identical 6-week, Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies designed to evaluate the efficacy and safety of pimavanserin as adjunctive treatment in participants with MDD who had an inadequate response to standard antidepressant therapy with either SSRIs or SNRIs.[4] The FDA agreed to a merger of the two studies into one study with a pre-specified statistical analysis plan. The two phase 3 studies concluded with slightly more than 50% enrollment.[3]

Study Design

Participants in both studies were randomized 1:1 to receive six weeks of oral treatment with either 34 mg of pimavanserin or placebo, once daily, in addition to their existing SSRI or SNRI during the double-blind period (**Figure 2**). The primary endpoint in both studies was the change from baseline to Week 5 in the HAMD-17 total score.[4]

Figure 2. CLARITY-2 and CLARITY-3 Study Designs[4]



Abbreviations: HAMD-17=17-item Hamilton Depression Rating Scale; MDD=major depressive disorder; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor.

Selected inclusion and exclusion criteria are shown in **Table 3**.

Table 3. Selected Inclusion and Exclusion Criteria (ACP-103-059/054)[4]

Selected inclusion criteria
• Male or female ≥18 years of age • Clinical diagnosis of MDD with or without anxious distress by DSM-5 criteria • Was being treated with one of the following SSRI or SNRI antidepressants as monotherapy: citalopram, escitalopram, paroxetine, fluoxetine, sertraline, duloxetine, venlafaxine, desvenlafaxine, venlafaxine XR • Inadequate response to SSRI/SNRI antidepressant treatment, confirmed with the MGH ATRQ through SAFER remote interview • MADRS total score >20 at both screening and baseline • CGI-S score ≥4 (moderately ill or worse) for depression at both screening and baseline
Selected exclusion criteria
• History of schizophrenia or other psychotic disorder, MDD with psychotic features, or bipolar type 1 or 2 disorder. Patients who were being treated or require treatment for posttraumatic stress disorder, acute stress disorder, panic disorder, or obsessive-compulsive disorder were also not eligible. • Current primary diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, or histrionic personality disorder, according to DSM-5 criteria • Current evidence of delirium and/or unstable neurologic, cardiovascular, respiratory, gastrointestinal, renal, hepatic, hematologic, or other medical disorder, including cancer or malignancies, which would affect the participant's ability to participate in the program • Known personal or family history of long QT syndrome or family history of sudden cardiac death

Abbreviations: CGI-S=Clinical Global Impression – Severity; DSM-5= Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; MADRS=Montgomery Asberg Depression Rating Scale; MDD=major depressive disorder; MGH ATRQ=Massachusetts General Hospital Antidepressant Treatment Questionnaire; SAFER= State versus trait, Assessability, Face validity, Ecological validity, and Rule of 3 Ps (pervasive, persistent, and pathological); SNRI=serotonin norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor.

Demographics and Baseline Characteristics

Demographics and baseline characteristics are summarized in **Table 4**.

Table 4. Baseline Demographics and Clinical Characteristics (Full Analysis Set; ACP-103-059/054)[4]

	Placebo (n=150)	Pimavanserin 34 mg (n=148)	Total (n=298)
Age, mean (SE)	44.5 (1.22)	47.2 (1.11)	45.8 (0.83)
Female, n (%)	112 (74.7)	96 (64.9)	208 (69.8)
Race, n (%)			
White	137 (91.3)	137 (92.6)	274 (91.9)
Black or African American	8 (5.3)	6 (4.1)	14 (4.7)
Asian	2 (1.3)	1 (0.7)	3 (1.0)
American Indian or Alaska Native	0	1 (0.7)	1 (0.3)
Other	3 (2.0)	3 (2.0)	6 (2.0)
Hispanic or Latino, n (%)	14 (9.3)	15 (10.1)	29 (9.7)
Antidepressant, n (%)			
SSRI	116 (77.3)	111 (75.0)	227 (76.2)
SNRI	34 (22.7)	37 (25.0)	71 (23.8)
Prior number of antidepressants, n (%)			
0	43 (28.7)	39 (26.4)	82 (27.5)
1[a]	41 (27.3)	32 (21.6)	73 (24.5)
2	31 (20.7)	25 (16.9)	56 (18.8)
3	14 (9.3)	21 (14.2)	35 (11.7)
4+	21 (14.0)	31 (20.9)	52 (17.4)
MDD with anxious distress, n (%)	80 (53.3)	78 (52.7)	158 (53.0)

	Placebo (n=150)	Pimavanserin 34 mg (n=148)	Total (n=298)
HAMD-17 total score, mean (SE)	22.7 (0.34)	23.1 (0.36)	22.9 (0.25)
HAMD-17 total score ≥24, n (%)	60 (40.0)	66 (44.6)	126 (42.3)
SDS score, mean (SE)	6.9 (0.13)	7.0 (0.13)	7.0 (0.09)
CGI-S score, mean (SE)	4.8 (0.05)	4.9 (0.04)	4.8 (0.03)

[a]One participant in study 059 was not included in the full analysis set because they did not have a postbaseline HAMD-17 score. This participant had 1 prior antidepressant at baseline and was randomly assigned to receive placebo.
Abbreviations: CGI-S=Clinical Global Impression – Severity; HAMD-17=17-item Hamilton Depression Rating Scale; SDS=Sheehan Disability Scale; SNRI=serotonin norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor.

Efficacy Results

The study did not achieve statistical significance on the primary endpoint which was the HAMD-17 total score change from baseline to Week 5. Pimavanserin 34 mg (N=138), given once-daily as an adjunctive treatment to standard antidepressant therapy was associated with an LSM (SE) change from baseline to Week 5 in HAMD-17 total score of -9.0 (0.58) compared to -8.1 (0.58) for placebo as an adjunctive treatment (N=135). The LSM (SE) treatment difference was -0.9 (0.82), p=0.2956, effect size 0.12. Positive results were observed on the key secondary endpoint, the CGI-S score, a clinician assessment of a patient's severity of depression (nominal p=0.0419, effect size 0.24).[4]

Safety Results

TEAEs occurred in 58.1% (86/148) of pimavanserin-treated and 54.7% (82/150) of placebo-treated patients (**Table 5**).[4] The most common TEAE in both groups was headache (pimavanserin, 20.9%; placebo, 18.0%). Discontinuations due to TEAEs were 2.7% for both pimavanserin and placebo. Two participants in each of the pimavanserin and placebo groups reported serious TEAEs. There were no changes from baseline to Week 6 in the individual observed CGI-S items of the Extrapyramidal Symptom Rating Scale–Abbreviated (parkinsonism, dystonia, dyskinesia, and akathisia) in either group. Mean (SE) change from baseline to Week 6 in QT interval using Fridericia's correction method (QTcF) was 4.0 (1.35) in the pimavanserin group and 2.6 (1.17) in the placebo group.

Table 5. Summary of TEAEs (Safety Analysis Set; ACP-103-059/054)[4]

	Placebo (N=150) n (%)	Pimavanserin (N=148) n (%)
Any TEAE	82 (54.7)	86 (58.1)
Any serious TEAE	2 (1.3)	2 (1.4)
Any related TEAE	27 (18.0)	47 (31.8)
Any related serious TEAE	0	0
Any TEAE leading to discontinuation or study termination	4 (2.7)	4 (2.7)
Any TEAE resulting in death	0	0
TEAEs occurring in ≥5% in either group		
Headache	27 (18.0)	31 (20.9)
Nasopharyngitis	9 (6.0)	5 (3.4)
Diarrhea	4 (2.7)	12 (8.1)
Dry mouth	4 (2.7)	11 (7.4)

Abbreviation: TEAE=treatment-emergent adverse event.

References

1. NUPLAZID® (pimavanserin) [package insert]. San Diego, CA. Acadia Pharmaceuticals Inc. [**Link**].
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4. Dirks B, Fava M, Atkinson SD, et al. Adjunctive Pimavanserin in Patients with Major Depressive Disorder: Combined Results from Two Randomized, Double-Blind, Placebo-Controlled Phase 3 Studies. *Psychopharmacol Bull*. 2022;52(4):8-30. **[PubMed]**
5. National Institutes of Health. Study to evaluate the efficacy and safety of adjunctive pimavanserin in major depressive disorder (CLARITY). **[Link]**.
6. Acadia Pharmaceuticals Inc. Data on file. ACP-103-042 Clinical Study Report. 2019.