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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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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, amnestic 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 ≥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]

	Mean (standard deviation)			
	Pimavanserin		Placebo	
Parameter	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