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Evaluation of the efficacy of pimavanserin in the treatment of agitation and aggression in patients with Alzheimer's disease psychosis: A post hoc analysis

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Objectives: Patients with Alzheimer's disease psychosis (ADP) commonly experience concomitant agitation and aggression. We investigated whether a reduction in ADP following pimavanserin treatment conferred a reduction in associated agitation and aggression.

Methods: ACP-103-019 was a 12-week, randomized, double-blind, placebo-controlled study that evaluated the efficacy of pimavanserin (34 mg) in reducing psychotic symptoms in patients with ADP. The primary endpoint was change from baseline in Neuropsychiatric Inventory-Nursing Home Version-Psychosis Score (NPI-NH-PS) at week six. A post hoc analysis examined whether there was a greater reduction in agitation and aggression (NPI-NH domain C [agitation/aggression] and Cohen-Mansfield Agitation Inventory-Short Form [CMAI-SF]) in pimavanserin-treated patients who experienced a reduction of hallucinations and delusions (psychosis responders defined as ≥50% reduction from baseline in NPI-NH-PS, week six) when compared with those who did not (nonresponders).

Results: Pimavanserin-treated patients with ≥50% response in psychotic symptoms (n = 44) showed a greater improvement in agitation and aggression symptoms on the NPI-NH domain C (week six, least squares mean [LSM] difference = −3.64, t = −4.69, P < .0001) and the CMAI-SF (week six, LSM difference = −3.71, t = −2.01, P = .0483) than nonresponders (n = 32). Differences between psychosis responders and nonresponders were also observed in patients with more severe agitation and aggression at baseline on the NPI-NH domain C (responders, n = 26; nonresponders, n = 13; week six, LSM difference = −3.03, t = −2.44, P = .019).

Conclusions: Patients with ADP, who show improvement in psychotic symptoms after pimavanserin treatment, also experience an improvement in concomitant agitation and aggression.

KEYWORDS
aggression, agitation, Alzheimer's disease, Alzheimer's disease psychosis, pimavanserin

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1 | INTRODUCTION

More than 45 million people worldwide are living with dementia, the majority of whom have Alzheimer's disease (AD).[1] While AD is commonly thought of as a memory disorder, behavioral and psychological symptoms of dementia are nearly universal and include psychotic symptoms.[1-3] More than half of patients with AD will experience psychosis during their illness.[4-6] Hallucinations and delusions are frequently distressing to the individual and their caregivers and are associated with worse disease outcomes relative to AD patients without psychosis,[4] including accelerated cognitive decline,[7,8] more rapid progression of functional impairment,[9] increased hospital admissions,[10] earlier admission to institutional care,[8,9] and increased mortality.[9,11] In addition, psychotic symptoms are often antecedent to or comorbid with other neuropsychiatric symptoms like agitation, aggression, and depression, further adding to the impact on the individual and others making Alzheimer's disease psychosis (ADP) more difficult to treat.[2,5,12]

Currently, no treatments have been approved for ADP.[13] The modest benefits provided by anxiolytics or typical/atypical antipsychotics that clinicians prescribe to mitigate hallucinations and delusions in ADP are associated with considerable adverse effects, such as accelerated cognitive decline and increased short-term mortality in elderly populations.[14-16]

Disruptive behaviors and significant impairments in interpersonal relationships and social functioning make agitation and aggression one of the most difficult symptoms to treat.[17,18] However, the underlying causes and mechanisms of agitation and aggression are multifaceted and not well understood.[13,17] Agitation may be due to direct underlying biological or environmental factors (psychosocial stress or intercurrent medication) or may be a consequence of psychosis, major depressive disorder, or other mood or psychiatric disturbances.[16,17] It is unclear whether the symptoms of agitation and aggression associated with ADP are related to psychosis or are independent behavioral symptoms that need to be treated separately. To optimize the treatment of ADP, a greater understanding of how the treatment of psychosis affects agitation and aggression symptoms is needed.

Pimavanserin is currently approved by the United States Food and Drug Administration (FDA) for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP).[19,20] The positive effect of pimavanserin in improving psychotic symptoms in ADP was also seen in a randomized, double-blind, placebo-controlled trial.[15,21] After 6 weeks of pimavanserin treatment, 51% of patients with ADP, treated with pimavanserin, showed ≥50% improvement compared with baseline in symptoms of psychosis (hallucinations and delusions) on the Neuropsychiatric Inventory-Nursing Home Version-Psychosis Score (NPI-NH-PS).[15]

While the therapeutic benefit of pimavanserin in improving hallucinations and delusions is promising in patients with ADP, treating agitation and aggression symptoms in this group is also an important component of treatment. The goal of this post hoc analysis was to investigate whether decreases in the severity of a patient's hallucinations and delusions while receiving pimavanserin were associated with a reduction in the severity and frequency of the patient's agitation and aggression.

Key points

- Patients with ADP commonly experience concomitant agitation and aggression.
- Patients with ADP who respond to the therapeutic benefit of pimavanserin on psychosis symptoms also experience improvement in agitation and aggression compared with nonresponders.
- Patients with ADP and severe agitation and aggression at baseline who respond to the therapeutic benefit of pimavanserin on psychosis symptoms also show greater improvements in agitation and aggression than nonresponders.

2 | METHODS

2.1 | Study design

Data were collected as a part of the study, ACP-103-019 (NCT02035553), a 12-week, randomized, double-blind, placebo-controlled phase 2 trial conducted in nursing home patients with ADP. Study design and primary results of the study as well as outcomes in patients with more severe psychosis symptoms have been previously published.[15,21] The primary objective of the study was to assess the efficacy of pimavanserin in attenuating ADP-related symptoms, as assessed by NPI-NH-PS, after 6 weeks of treatment.

All procedures were conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Good Clinical Practices, and the United States Code of Federal Regulations. Participants were given 3 weeks of brief psychosocial therapy[22] and were then randomly assigned to receive either pimavanserin 34 mg or placebo administered orally once daily, with stratification by baseline Mini-Mental State Examination (MMSE) total score and NPI-NH-PS.[23] At baseline and after 2, 4, 6, 9, and 12 weeks of pimavanserin treatment or placebo, the NPI-NH[24] and the Cohen-Mansfield Agitation Inventory-Short Form (CMAI-SF)[25] were administered.

2.2 | Patient eligibility

Nursing home patients, 50 years or older, were eligible to participate if they met National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for possible or probable AD[26] and exhibited psychotic symptoms severe enough to warrant treatment with an NPI-NH score of ≥4 in either the delusions or hallucinations domain or a combined score of ≥6 for both measures (delusions + hallucinations). Additional inclusion and exclusion criteria have been published previously.[15]

2.3 | Post hoc analysis

The effect of pimavanserin on agitation and aggression symptoms was compared in patients responsive and nonresponsive to pimavanserin's treatment of psychotic symptoms. Psychosis responders were defined as patients who exhibited ≥50% improvement from baseline in NPI-NH-PS at week six; patients who received pimavanserin but did not meet these improvement criteria were considered nonresponders.

An additional analysis of psychosis responders vs nonresponders was conducted in the subgroup of pimavanserin-treated patients exhibiting more severe agitation and aggression symptoms at baseline, as demonstrated by an NPI-NH agitation/aggression subscale score higher than the midpoint (≥6).

2.4 | Statistical analysis

Baseline characteristics of week six psychosis responders and nonresponders were compared using a *t*-test for continuous parameters or chi-squared test for categorical parameters.

A mixed-effects model for repeated measures was used to determine whether the effect of pimavanserin on agitation and aggression symptoms was related to the therapeutic benefit of pimavanserin on psychosis symptoms. The mean change from baseline in the NPI-NH domain C (agitation and aggression subscale) or the CMAI-SF was analyzed as the dependent variable. The model included fixed effects of baseline MMSE score (<6 vs ≥6), baseline psychosis score (<12 vs ≥12), baseline score of the dependent variable (NPI-NH domain C or CMAI-SF score), group (responder vs nonresponder), study visit (weeks 2, 4, 6, 9, and 12), and group-by-study visit interaction. Group differences are reported as the least square (LS) mean (standard error [SE]) change from baseline for each measure. The association between change from baseline scores in the NPI-NH-PS and change from baseline in agitation and aggression symptoms as measured by both the NPI-NH domain C scores and the CMAI-SF scores at week six was also analyzed using a Spearman's correlation test. All analyses were conducted at the 5% level of significance using two-sided tests.

3 | RESULTS

3.1 | Patients

In the study, 181 patients from 133 care homes across the United Kingdom (UK) were randomized to receive pimavanserin (n = 90) or placebo (n = 91). Efficacy analyses included all patients who received at least one dose of pimavanserin and completed the NPI-NH at baseline and at least one postbaseline study visit (pimavanserin, n = 87). At baseline, patients had an overall mean (standard deviation [SD]) score on the NPI-NH domain C of 4.7 (3.9) and an overall mean (SD) score on the CMAI-SF of 28.6 (8.8) (Table 1). More severe baseline agitation/

aggression symptoms, defined by a score of ≥6 on the NPI-NH domain C subscale, were observed in 43 of 87 (49.4%) pimavanserin-treated patients and 42 of 91 (46.2%) placebo-treated patients.

3.2 | Overall changes in agitation and aggression symptoms

As previously reported, in the overall study population, pimavanserin treatment did not improve agitation and aggression symptoms (relative to placebo) based on either the NPI-NH domain C (pimavanserin: n = 76; LS mean change from baseline [SE], −1.13 [0.414]; placebo: n = 81; LS mean change [SE], −0.47 [0.401]; difference = −0.66, *t* = −1.14; *P* = .2544) or the CMAI-SF (pimavanserin: n = 77; LS mean change [SE], −2.07 [0.846]; placebo: n = 81; LS mean change [SE], −2.36 [0.825]; difference = 0.30, *t* = 0.25; *P* = .8031).[15]

3.3 | Changes in agitation and aggression symptoms in psychosis responders

At the study's primary-efficacy endpoint of 6 weeks, 44 of 87 patients (50.6%) were defined as psychosis responders based on exhibiting a ≥50% reduction on the NPI-NH-PS. Data were not available for 11 patients. Baseline symptoms of agitation and aggression were comparable for psychosis responders and nonresponders, with mean (SE) NPI-NH domain C scores of 5.57 (0.658) for psychosis responders and 4.47 (0.648) for nonresponders and mean (SE) CMAI-SF scores of 28.57 (1.312) for psychosis responders and 28.75 (1.665) for nonresponders (Table 1).

At the study's primary-efficacy endpoint of week six, psychosis responders exhibited a significantly greater improvement in NPI-NH domain C score (LS mean change [SE], −2.85 [0.497]) than nonresponders (LS mean change [SE], 0.79 [0.584]; difference = −3.64; *t* = −4.69; 95% CI, −5.19 to −2.10, *P* < .0001) (Figure 1A). Similarly, psychosis responders exhibited a significantly greater reduction from baseline to week six on the CMAI-SF (LS mean change [SE], −3.73 [1.185]) than nonresponders (LS mean change [SE], −0.02 [1.390]; difference = −3.71; *t* = −2.01; 95% CI, −7.38 to −0.03; *P* = .0483) (Figure 1B).

In the overall study population, change from baseline on the NPI-NH-PS at week six was strongly correlated with the change from baseline in agitation and aggression symptoms, as measured by both the NPI-NH domain C (n = 157; *r* = 0.29, *P* = .0002) and the CMAI-SF (n = 156; *r* = 0.33, *P* < .0001).

3.4 | Changes in symptoms of agitation and aggression in patients with more severe baseline symptoms

Among pimavanserin-treated patients who had a week 6 NPI-NH domain C response (n = 39), severe agitation and aggression (NPI-NH

TABLE 1 Baseline characteristics

	Placebo overall (n = 91)	Pimavanserin overall (n = 87)	Pimavanserin responders (n = 44)	Pimavanserin nonresponders (n = 32)	Responders vs nonresponders P value[b]
Female, n (%)	73 (80.2)	71 (81.6)	36 (81.8)	29 (90.6)	.281
Age, mean (min, max) (years)	86.1 (64, 99)	85.6 (68, 99)	85.5 (70, 95)	86.8 (70, 99)	.403
NPI-NH-PS, mean (SD)	10.0 (5.6)	9.5 (4.8)	11.0 (5.0)	8.6 (4.6)	.036
NPI-NH-PS ≥12, n (%)	30 (33.0)	27 (31.0)	21 (47.7)	6 (18.8)	.009
NPI-NH domain C (agitation/ aggression), mean (SD)	4.5 (3.8)	4.9 (4.0)	5.6 (4.4)	4.5 (3.7)	.250
NPI-NH domain C (agitation/ aggression) ≥6, n (%)	42 (46.2)	43 (49.4)	26 (59.1)	13 (40.6)	.112
CMAI-SF total score, mean (SD)	28.9 (8.9)	28.3 (8.7)	28.6 (8.7)	28.8 (9.4)	.931
MMSE, mean (SD)	9.8 (5.0)	10.3 (5.4)	10.7 (5.6)	10.0 (5.0)	.562
MMSE <6, n (%)[a]	15 (17.6)	18 (21.4)	7 (17.1)	7 (21.9)	.605

Abbreviations: CMAI-SF, Cohen-Mansfield Agitation Inventory-Short Form; MMSE, Mini-Mental State Examination; NPI-NH-PS, Neuropsychiatric Inventory-Nursing Home Version-Psychosis Score; SD, SD.

[a]Number of subjects with non-missing data used as the denominator for calculating percentages with each treatment group (Placebo = 85; Pimavanserin = 84; Total = 169).

[b]t test for continuous variables, chi-square test for categorical variables.
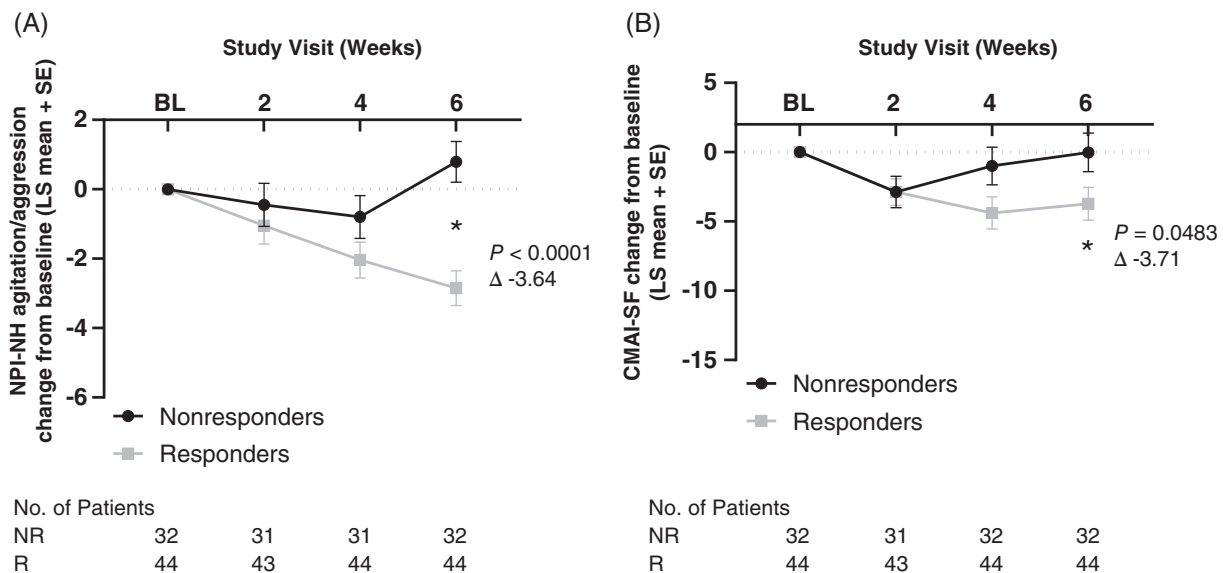

FIGURE 1 Changes in agitation and aggression symptoms among psychosis responders vs nonresponders as assessed by (A) NPI-NH domain C or (B) CMAI-SF. *P < .05. Δ = difference in LS mean change from baseline ((Responders LS mean change from baseline) − (Nonresponders LS mean change from baseline)). BL, baseline; CMAI-SF, Cohen-Mansfield Agitation Inventory-Short Form; LS, least square; NPI-NH-PS, Neuropsychiatric Inventory-Nursing Home Version-Psychosis Score; NR, nonresponders; R, responders; SE, standard error

domain C score ≥ 6) were observed at baseline in 26 psychosis responders and 13 nonresponders (Table 1). Psychosis responders and nonresponders in this subset of patients exhibited comparable baseline mean (SE) NPI-NH domain C scores (psychosis responders: 8.69 [0.489]; nonresponders: 8.00 [0.784]) and baseline mean (SE) CMAI-SF scores (psychosis responders: 32.38 [1.724]; nonresponders: 35.31 [1.848]).

At the study's primary-efficacy endpoint of week six, this subset of psychosis responders exhibited a significantly greater reduction on the NPI-NH domain C score (LS mean change [SE], −4.86 [0.688])

than nonresponders (LS mean change [SE], −1.83 [0.993]; difference = −3.03; t = −2.44; 95% CI, −5.54 to −0.52; P = .0190) (Figure 2A). A statistical difference was not observed at 6 weeks on the CMAI-SF; however, this subset of psychosis responders appeared to show a numerically greater reduction compared with nonresponders (LS mean change [SE], −6.57 [1.827] vs −1.75 [2.618], difference = −4.82, t = −1.47; P = .1484) (Figure 2B).

In patients with severe agitation and aggression at baseline, change from baseline on the NPI-NH-PS at week six was correlated
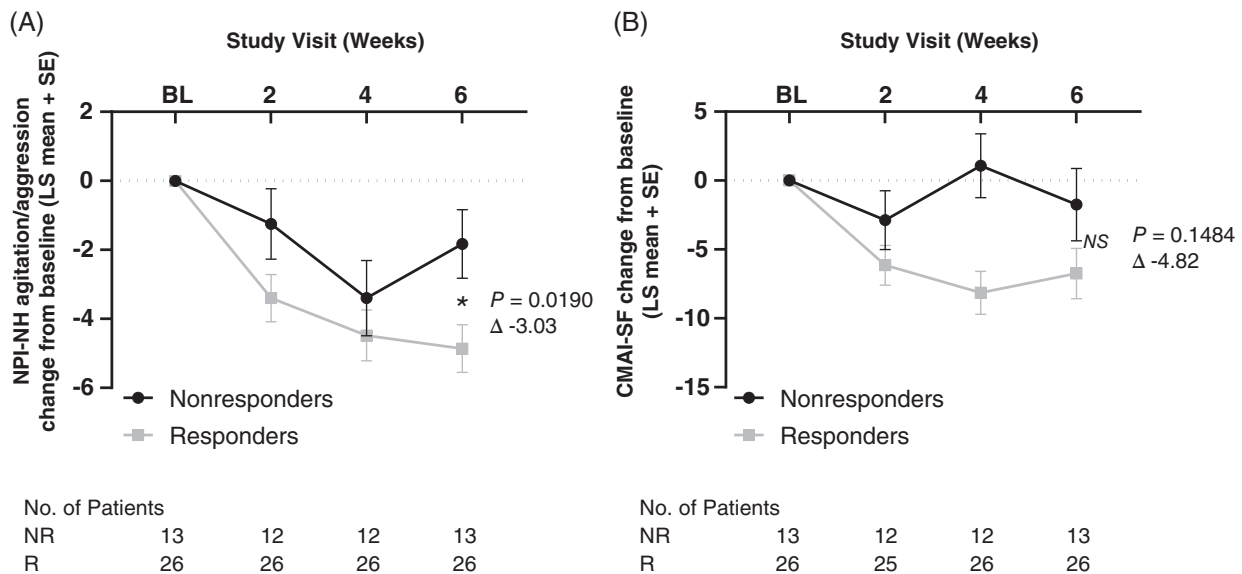
FIGURE 2 Changes in agitation and aggression symptoms among psychosis responders with more severe symptoms of agitation and aggression at baseline as assessed by (A) NPI-NH domain C or (B) CMAI-SF. *$P < .05$. Δ = difference in LS mean change from baseline ([responders LS mean change from baseline] – [nonresponders LS mean change from baseline]). BL, baseline; CMAI-SF, Cohen-Mansfield Agitation Inventory-Short Form; LS, least square; NPI-NH-PS, Neuropsychiatric Inventory-Nursing Home Version-Psychosis Score; NR, nonresponders; R, responders; SE, standard error

TABLE 2 Treatment-emergent adverse events in responders and nonresponders

	Responders (n = 44)	Nonresponders (n = 32)
Summary of adverse events, n (%)		
Any adverse event	44 (100)	30 (93.8)
Any serious adverse event	4 (9.1)	7 (21.9)
Any adverse event causing discontinuation	1 (2.3)	1 (3.1)
Adverse events by preferred term, n (%)[a]		
Fall	9 (20.5)	11 (34.4)
Urinary tract infection	9 (20.5)	8 (25.0)
Lower respiratory tract infection	9 (20.5)	3 (9.4)
Contusion	5 (11.4)	6 (18.8)
Agitation	5 (11.4)	11 (34.4)
Anemia	4 (9.1)	5 (15.6)
Blood urea increased	4 (9.1)	3 (9.4)
Aggression	3 (6.8)	5 (15.6)
Edema peripheral	3 (6.8)	4 (12.5)
Cellulitis	3 (6.8)	3 (9.4)
Anxiety	2 (4.5)	2 (6.3)
Behavioral and psychiatric symptoms of dementia	3 (6.8)	2 (6.3)
Blood potassium increased	2 (4.5)	3 (9.4)

[a]Number of adverse events occurring in at least 5% of patients.[15]

with the change from baseline in agitation and aggression symptoms, as measured by both the NPI-NH domain C (n = 77; $r = 0.23$, $P = .048$) and the CMAI-SF (n = 77; $r = 0.26$, $P = .021$).

3.5 | Safety

Pimavanserin was well tolerated in both psychosis responders and nonresponders. Adverse events occurred in 44 (100%) psychosis responders and 30 (93.8%) nonresponders; serious adverse events occurred in 4 (9.1%) psychosis responders and 7 (21.9%) nonresponders. Rates of individual adverse events were similar between psychosis responders and nonresponders (Table 2).

4 | DISCUSSION

This post hoc responder analysis suggests improvements in psychotic symptoms in patients receiving pimavanserin treatment were associated with an improvement in agitation and aggression symptoms. Patients showing ≥50% improvement from baseline in psychotic symptoms after 6 weeks of pimavanserin treatment exhibited a greater improvement in agitation and aggression symptoms than nonresponders. This effect was observed on two distinct measures, the NPI-NH domain C score and the CMAI-SF score.

In patients with ADP, experiencing severe agitation and aggression symptoms at baseline (baseline NPI-NH domain C score ≥ 6), the

therapeutic benefit of pimavanserin on psychosis was associated with an improvement in agitation and aggression symptoms on the NPI-NH domain C score. Psychosis responders also exhibited an improvement from baseline in CMAI-SF score at week six, although the difference between responders and nonresponders was not statistically significant. This may be explained by the relatively low patient numbers in the severe subgroups and by a slight improvement in CMAI-SF score for nonresponders between weeks four and six.

Improvement of psychosis was correlated with the improvement of agitation and aggression at the study's primary endpoint, in both the overall study population and those with severe agitation and aggression at baseline, supporting the relationship between these two types of symptoms in patients with AD. This correlation is consistent with the observation that patients with severe psychosis symptoms at baseline (NPI-NH psychosis score ≥ 12) in this study had higher agitation and aggression scores than the overall population[21] and with several studies that have reported significant correlations between psychosis and agitation and aggression in patients with dementia.[27]

Collectively, results described here suggest that the improvement in hallucinations and delusions after pimavanserin treatment are related to improvements observed in agitation and aggression.

Mechanisms driving agitation and aggression in AD remain under investigation. However, evidence for unique patterns of underlying brain circuit dysregulation suggests that distinct types of agitation and aggression might require unique treatment approaches.[17,28] Consistent with this, AD patients in one study, exhibiting moderate agitation symptoms, responded dramatically to citalopram treatment for the management of agitation/aggression symptoms; however, in the same study, those exhibiting severe agitation symptoms showed no therapeutic benefit from the same treatment.[16] Our results suggest one potential underlying mechanism of agitation and aggression in AD is related to psychosis and that treating psychosis may provide a more precise approach to treating agitation and aggression in these individuals.

The current analysis was not prespecified and was conducted post hoc. The analysis is further limited by the small sample sizes in subgroups of pimavanserin-treated patients. The comparison of non-randomized groups (psychosis responders and nonresponders) may be a source of bias unaccounted for by the statistical modeling. In addition, the study was limited to AD patients in nursing homes in the United Kingdom. Patients, in this study, were required to have psychosis symptoms at baseline but were not recruited for the presence of agitation and aggression, which may have limited the number of patients with a potential for improvement in agitation and aggression. Further research is needed to confirm the generalizability of these results beyond the United Kingdom, in other subtypes of dementia and in patients recruited for the presence of agitation and aggression.

Safe and effective treatments to address symptoms of psychosis and agitation and aggression are a critical unmet need in patients with dementia. The primary endpoint analysis of the randomized clinical trial demonstrated significant benefit in the treatment of psychosis at 6 weeks, with acceptable safety and tolerability over 12 weeks of treatment in patients with ADP.[15,21] The current analysis indicates additional benefits in the treatment of agitation and aggression among participants with a therapeutic response in the treatment of psychosis.

CONFLICT OF INTEREST

C.G.B. has received grants and personal fees from ACADIA Pharmaceuticals Inc. and Lundbeck and personal fees from Heptares, Roche, Lilly, Otsuka, Orion, GlaxoSmithKline, and Pfizer; B.C., V.A., S.S., E.F. are employees of and may hold stock in ACADIA Pharmaceuticals Inc.

AUTHOR CONTRIBUTIONS

All authors as well as the sponsor were involved in the design and conduct of the study; the collection, analysis, and interpretation of data; in the preparation of the manuscript; and in the review or approval of the manuscript.

DATA AVAILABILITY STATEMENT

Data available upon request from authors: The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

1. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet*. 2017;390(10113):2673-2734.
2. Ballard CG, Gauthier S, Cummings JL, et al. Management of agitation and aggression associated with Alzheimer disease. *Nat Rev Neurol*. 2009;5(5):245-255.
3. Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. *JAMA*. 2002;288(12):1475-1483.
4. Paulsen JS, Salmon DP, Thal LJ, et al. Incidence of and risk factors for hallucinations and delusions in patients with probable AD. *Neurology*. 2000;54(10):1965-1971.
5. Murray PS, Kumar S, Demichele-Sweet MA, Sweet RA. Psychosis in Alzheimer's disease. *Biol Psychiatry*. 2014;75(7):542-552.
6. Ropacki SA, Jeste DV. Epidemiology of and risk factors for psychosis of Alzheimer's disease: a review of 55 studies published from 1990 to 2003. *Am J Psychiatry*. 2005;162(11):2022-2030.
7. Stern Y, Albert M, Brandt J, et al. Utility of extrapyramidal signs and psychosis as predictors of cognitive and functional decline, nursing home admission, and death in Alzheimer's disease: prospective analyses from the predictors study. *Neurology*. 1994;44 (12):2300-2307.
8. El Haj M, Roche J, Jardri R, Kapogiannis D, Gallouj K, Antoine P. Clinical and neurocognitive aspects of hallucinations in Alzheimer's disease. *Neurosci Biobehav Rev*. 2017;83:713-720.

9. Scarmeas N, Brandt J, Albert M, et al. Delusions and hallucinations are associated with worse outcome in Alzheimer disease. *Arch Neurol*. 2005;62(10):1601-1608.

10. Beydoun MA, Beydoun HA, Gamaldo AA, et al. Nationwide inpatient prevalence, predictors, and outcomes of Alzheimer's disease among older adults in the United States, 2002-2012. *J Alzheimers Dis*. 2015; 48(2):361-375.

11. Peters ME, Schwartz S, Han D, et al. Neuropsychiatric symptoms as predictors of progression to severe Alzheimer's dementia and death: the Cache County dementia progression study. *Am J Psychiatry*. 2015;172(5):460-465.

12. Lyketsos CG, Sheppard JM, Steinberg M, et al. Neuropsychiatric disturbance in Alzheimer's disease clusters into three groups: the cache county study. *Int J Geriatr Psychiatry*. 2001;16(11):1043-1053.

13. Cummings J, Ritter A, Rothenberg K. Advances in Management of Neuropsychiatric Syndromes in neurodegenerative diseases. *Curr Psychiatry Rep*. 2019;21(8):79.

14. Cummings J, Zhong K. Trial design innovations: clinical trials for treatment of neuropsychiatric symptoms in Alzheimer's disease. *Clin Pharmacol Ther*. 2015;98(5):483-485.

15. Ballard C, Banister C, Khan Z, et al. Evaluation of the safety, tolerability, and efficacy of pimavanserin versus placebo in patients with Alzheimer's disease psychosis: a phase 2, randomised, placebo-controlled, double-blind study. *Lancet Neurol*. 2018;17(3):213-222.

16. Schneider LS, Frangakis C, Drye LT, et al. Heterogeneity of treatment response to citalopram for patients with Alzheimer's disease with aggression or agitation: the CitAD randomized clinical trial. *Am J Psychiatry*. 2016;173(5):465-472.

17. Sano M, Soto M, Carrillo M, et al. Identifying better outcome measures to improve treatment of agitation in dementia: a report from the EU/US/CTAD task force. *J Prev Alzheimers Dis*. 2018;5(2):98-102.

18. Cummings JL, Lyketsos CG, Peskind ER, et al. Effect of dextromethorphan-quinidine on agitation in patients with Alzheimer disease dementia: a randomized clinical trial. *JAMA*. 2015;314(12): 1242-1254.

19. Cummings J, Isaacson S, Mills R, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. *Lancet*. 2014;383(9916):533-540.

20. Mathis MV, Muoio BM, Andreason P, et al. The US Food and Drug Administration's perspective on the new antipsychotic Pimavanserin. *J Clin Psychiatry*. 2017;78(6):e668-e673.

21. Ballard C, Youakim JM, Coate B, Stankovic S. Pimavanserin in Alzheimer's disease psychosis: efficacy in patients with more pronounced psychotic symptoms. *J Prev Alzheimers Dis*. 2019;6(1):27-33.

22. Ballard C, Brown R, Fossey J, et al. Brief psychosocial therapy for the treatment of agitation in Alzheimer disease (the CALM-AD trial). *Am J Geriatr Psychiatry*. 2009;17(9):726-733.

23. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198.

24. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. *Neurology*. 1994;44(12):2308-2314.

25. Cohen-Mansfield J, Marx MS, Rosenthal AS. A description of agitation in a nursing home. *J Gerontol*. 1989;44(3):M77-M84.

26. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology*. 1984;34(7):939-944.

27. Shub D, Ball V, Abbas AA, Gottumukkala A, Kunik ME. The link between psychosis and aggression in persons with dementia: a systematic review. *Psychiatry Q*. 2010;81(2):97-110.

28. Charu V, Rosenberg PB, Schneider LS, et al. Characterizing highly benefited patients in randomized clinical trials. *Int J Biostat*. 2017;13 (1).20160045