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RESEARCH ARTICLE

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Potential beneficial effects of masupirdine (SUVN-502) on agitation/aggression and psychosis in patients with moderate Alzheimer's disease: Exploratory post hoc analyses

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Abstract

Objectives: The effects of masupirdine on the neuropsychiatric symptoms were explored.

Methods: Masupirdine (SUVN-502) was evaluated for its effects on cognition in patients with moderate AD. The prespecified primary outcome showed no drug-placebo difference. Post hoc analyses of domains of the 12-item neuropsychiatric inventory scale were carried out.

Results: In a subgroup of patients (placebo, $n = 57$; masupirdine 50 mg, $n = 53$; masupirdine 100 mg, $n = 48$) with baseline agitation/aggression symptoms ≥1, a statistically significant reduction in agitation/aggression scores was observed in masupirdine 50 mg (95% confidence interval (CI), −1.9 to −0.5, $p < 0.001$) and masupirdine 100 mg (95% CI, −1.7 to −0.3, $p = 0.007$) treated arms at Week 13 in comparison to placebo and the effect was sustained for trial duration of 26 weeks in the masupirdine 50 mg treatment arm (95% CI, −2.3 to −0.8, $p < 0.001$). Similar observations were noted in the subgroup of patients (placebo, $n = 29$; masupirdine 50 mg, $n = 30$; masupirdine 100 mg, $n = 21$) with baseline agitation/aggression symptoms ≥3. In the subgroup of patients (placebo, $n = 28$; masupirdine 50 mg, $n = 28$; masupirdine 100 mg, $n = 28$) who had baseline psychosis symptoms and/or symptom emergence, a significant reduction in psychosis scores was observed in the masupirdine 50 mg (Week 4: 95% CI, −2.8 to −1.4, $p < 0.001$; Week 13: 95% CI, −3.3 to −1.3, $p < 0.001$) and masupirdine 100 mg (Week 4: 95% CI, −1.4 to 0, $p = 0.046$; Week 13: 95% CI, −1.9 to 0.1, $p = 0.073$) treatment arms in comparison to placebo.

Conclusion: Further research is warranted to explore the potential beneficial effects of masupirdine on NPS.

KEYWORDS
5-HT_6 receptor, agitation/aggression, Alzheimer's disease, clinical trials, masupirdine, NPI-12, psychosis

Key points

- Alzheimer's disease (AD) is a neurodegenerative disorder with manifestations of cognitive decline, functional impairment, and neuropsychiatric symptoms (NPS), with massive unmet need for the safe and effective treatment of NPS.
- Post hoc analyses suggested masupirdine significantly reduced agitation/aggression, and psychosis in subgroup of patients with AD.
- Masupirdine is being evaluated in a phase-3 trial for the treatment of agitation/aggression in patients with AD type dementia.

1 | INTRODUCTION

Alzheimer's disease (AD) is the most common type of neurodegenerative disorder in older people. Cognitive and functional decline and neuropsychiatric symptoms (NPS) are the cardinal clinical features of the disease. Approved treatments currently used in clinical practice (donepezil, rivastigmine, galantamine, memantine, and aducanumab) target the cognitive symptoms of the disease or slows clinical decline. Similar to cognitive symptoms, NPS occur in nearly all patients with AD.[1,2] The negative impact of NPS on caregiver distress is often higher than cognitive and functional impairment.[3] NPS increase the risk for institutionalization resulting in the greater financial burden for caring for these patients.[4–6] Among the NPS, agitation/aggression and psychosis are rated as the most distressing symptoms.[7,8] Currently, there are no approved treatments for the management of NPS associated with AD except for the short term use of risperidone for severe aggression (approved in Europe not in the USA).

Non-pharmacological treatment that is, psychosocial interventions is considered as first-line of treatment for agitation/aggression, and psychosis. However, psychosocial interventions are often helpful, particularly for the treatment of agitation, they have limitations and there is an urgent need for safe and effective pharmacological treatment options.[9] Antipsychotics are the most widely used pharmacological agents for the management of agitation/aggression and psychosis associated with AD. Antipsychotics are reported to show modest efficacy (effect size: 0.2) and the side effects are substantial; they are associated with risks of mortality (black box warning), Parkinsonism, accelerated cognitive decline, sedation, gait disturbance, thrombo-embolic events, respiratory infections and edema.[9–12] Therapies in active clinical development for the potential treatment of agitation/aggression involve a variety of mechanisms of action. These include, but not limited to agents like brexpiprazole, escitalopram, nabilone, AVP-786, AXS-05 and BXCL-501 which are in advanced stages of clinical development (phase-3).[13]

The serotonergic system has been implicated in the control of mood and behavior in patients with dementia.[14,15] In addition, selective serotonin reuptake inhibitors (citalopram and sertraline) are reported to reduce symptoms of agitation and psychosis in dementia patients.[16,17] Among the serotonergic receptors, serotonin 6 (5-HT_6) receptors are widely expressed in the brain regions including cortex, dorsal hippocampus and striatum; brain areas centrally involved in cognition and behavior.[18–20] Studies demonstrate that blockade of 5-HT_6 receptors results in the enhancement of cognition in animal models[21-23]; some but not all clinical trials of 5-HT_6 antagonists in patients with AD have shown cognitive benefit.[24,25] Masupirdine is a selective 5-HT_6 receptor antagonist with favorable physicochemical and ADME properties and improves cognition in animal models.[26–28] Based on the potential effects on cognition; efficacy, safety and tolerability of masupirdine were evaluated in a proof-of-concept trial as an adjunct treatment in moderate AD patients concomitantly treated with donepezil and memantine. Efficacy was assessed by the 11-item Alzheimer's Disease Assessment Scale for Cognitive Behavior subscale (ADAS-Cog 11) after 26 weeks of treatment. The 12-item Neuropsychiatric Inventory (NPI-12) was utilized to assess the effects on behavior. Although, the trial did not meet its primary endpoint,[29] hypothesis-generating observations emerged from the post hoc analyses of the NPI-12. The inventory evaluates the presence and severity of 12 NPS that commonly occur in dementia patients.[30,31] This report describes the post hoc analyses of NPI-12 scores based on the baseline symptoms, or baseline symptoms and/or symptom emergence.

2 | METHODS

The data from the phase-2, double-blind, multicenter, randomized, parallel group, placebo controlled trial of treatment with masupirdine in patients with moderate AD (NCT02580305) were used in the post hoc analyses. The trial design and the outcome have been reported earlier.[29] The trial was conducted according to the protocol and in compliance with International Council for Harmonisation Guidelines on Good Clinical Practice and in accordance with the Declaration of Helsinki. At each trial center, the protocol, protocol amendments, and informed consent form for this trial were reviewed and approved by an Institutional Review Board or Independent Ethics Committee. The

trial consisted of a 2 to 4 week screening period, a 26 week treatment period, and 1 month follow-up period. Eligible patients were randomly assigned in a 1:1:1 ratio for once daily treatment with placebo or masupirdine 50 mg or masupirdine 100 mg. Safety and efficacy assessments were carried out at baseline and Weeks 4, 13, and 26. Patients returned for a follow-up visit at Week 30.

2.1 | Study population

Patients aged 50–85 years (both inclusive) at screening and living in the community or an assisted living facility were eligible for participation, if they met the diagnostic criteria for probable Alzheimer's disease based on the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria (at least 1 year prior to the screening visit).[32] Patients had moderate cognitive deficits with Mini Mental State Examination (MMSE) scores of 12–20, inclusive at the screening and baseline. Patients were receiving treatment with stable doses of donepezil and memantine for at least 3 months prior to screening visit and were considered likely to have been maintained on their current dose for the duration of the trial. The majority of subjects were White (92.3%) with a similar proportion of White subjects among the 3 treatment arms. The study was conducted exclusively in USA. Detailed study information and additional inclusion and exclusion criteria have been published previously.[29]

2.2 | Post hoc analyses

The effect of masupirdine on the NPS was assessed using NPI-12 scale. The individual domains of the NPI-12 scale were analyzed for potential treatment effects. Additional analyses were carried out on the patient subgroups who had baseline symptoms or baseline symptoms and/or symptom emergence.

2.3 | Statistical analysis

Baseline characteristics of agitation, and psychosis subgroups were compared using Kruskal-Wallis test or chi-squared test.

Mean change in scale scores from baseline to the end of treatment was evaluated in comparison to placebo. A mixed-effects model for repeated measures (MMRM) was used to determine the effect of masupirdine on NPS based on the modified intention to treat (mITT) population. Analyses were based on MMRM including fixed effects for treatment, week, treatment-by-week interaction, baseline NPI score, treatment-by-baseline NPI score interaction, treatment-by-baseline NPI score-by-visit interaction and APO-E4 status (carrier-one allele, carrier-two alleles, and non-carrier), as well as the continuous covariates of age, baseline MMSE score. Psychotropic medication use data was not incorporated in the analysis. Results were not corrected for multiple comparisons due to their exploratory nature of analysis.

3 | RESULTS

3.1 | Study population

A total of 564 patients were enrolled between 1 December 2015 and 21 May 2019 and randomized as per the planned ratio to receive placebo (189 patients) or masupirdine 50 mg (190 patients) or masupirdine 100 mg (185 patients). The mITT population included 543 patients who received at least one dose of study treatment and had at least one post-baseline evaluation of the primary efficacy variable. The mean baseline NPI-12 scale total scores ranged between 9.7 and 10.1 across the treatment arms. The patients had an overall mean (standard deviation [SD]) NPI-12 scores of 9.9 (10.28). The mean baseline agitation/aggression domain scores ranged between 0.8 and 0.9 across the treatment arms. The mean baseline scores ranged between 0.52 and 0.61 for the psychosis domain across the treatment arms (Table 1).

3.2 | Agitation/aggression domain

Effect observed on agitation with masupirdine 50 mg at Week 26 was statistically significant (95% confidence interval (CI), −0.8 to 0, $p = 0.044$) compared to placebo treatment arm in the overall trial population (Figure 1A). As the patients were not included based on the agitation symptoms in the original study, further analyses were carried out in subgroup comprised of patients who had baseline NPI agitation/aggression score (symptoms). Data analysis showed a statistically significant treatment difference in change from baseline in the mean agitation/aggression scores at Week 13 when comparing masupirdine 50 mg (95% CI, −1.9 to −0.5, $p < 0.001$) or masupirdine 100 mg (95% CI, −1.7 to −0.3, $p = 0.007$) to the placebo arm. A statistically significant treatment difference was also observed at Week 26, when comparing the masupirdine 50 mg arm (95% CI, −2.3 to −0.8, $p < 0.001$) to the placebo arm. No drug-placebo differences on the effects of masupirdine 100 mg on agitation/aggression were demonstrated at Week 26 (Figure 1B).

Further analyses were carried out in a subgroup of patients who had baseline NPI agitation/aggression score ≥3. A statistically significant treatment difference in change from baseline in the mean agitation/aggression scores was observed at Weeks 13 (95% CI, −2.1 to −0.3, $p = 0.012$) and 26 (95% CI, −2.1 to −0.1, $p = 0.031$), when comparing masupirdine 50 mg arm to the placebo arm. At Week 13, a statistically significant treatment difference was also noted in the masupirdine 100 mg arm (95% CI, −2.3 to −0.2, $p = 0.024$) compared to placebo. No drug-placebo differences on the effects of masupirdine 100 mg on agitation/aggression were demonstrated at Week 26 (Figure 1C).

The mITT population included patients with no agitation/aggression at any time during the trial, patients with agitation/aggression at baseline, and patients who did not have agitation/aggression at

TABLE 1 Baseline characteristics

Parameters	Placebo	Masupirdine 50 mg	Masupirdine 100 mg	*p* value[a]
NPI, mean (±SD), *n*	10.1 (10.25), 183	9.7 (10.25), 182	9.8 (10.38), 176	0.99
NPI-Agitation/Aggression, mean (±SD), *n*	0.9 (1.78), 183	0.9 (1.75), 184	0.8 (1.65), 176	0.71
NPI-Psychosis, mean (±SD), *n*	0.54 (1.62), 183	0.61 (1.86), 184	0.52 (1.45), 176	0.99
Psychotropics use, *n* (%)	96 (52.46)	99 (53.80)	89 (50.57)	0.83
NPI-A/A (≥1), mean (±SD), *n*	3.0 (2.04), 57	3.2 (1.88), 53	2.9 (2.00), 48	0.61
Age (years), mean (±SD)	74 (6.85)	75 (7.93)	74 (6.46)	0.33
Female, *n* (%)	38 (66.67)	31 (58.49)	27 (56.25)	0.51
MMSE, mean (±SD)	16.56 (2.52)	16.55 (2.32)	16.81 (2.57)	0.83
ADAS-Cog 11, mean (±SD)	28.18 (7.97)	28.66 (8.24)	28.69 (9.88)	0.91
APO-E4 carrier status, *n* (%)	40 (70.18)	27 (50.94)	28 (58.33)	0.15
Psychotropics use, *n* (%)	36 (63.16)	37 (69.81)	31 (64.58)	0.75
NPI-A/A (≥3), mean (±SD), *n*	4.5 (1.72), 29	4.5 (1.38), 30	4.7 (1.65), 21	0.77
Age (years), mean (±SD)	74 (6.73)	75 (7.95)	75 (5.64)	0.53
Female, *n* (%)	20 (68.97)	16 (53.33)	13 (61.91)	0.47
MMSE, mean (±SD)	16.28 (2.51)	16.37 (2.34)	16.62 (2.22)	0.90
ADAS-Cog 11, mean (±SD)	28.97 (9.06)	29.37 (7.78)	28.29 (9.57)	0.74
APO-E4 carrier status, *n* (%)	19 (65.52)	15 (50.00)	11 (52.38)	0.48
Psychotropics use, *n* (%)	20 (68.97)	22 (72.33)	15 (71.43)	0.93
NPI-Agitation/Aggression, (baseline symptoms and/or symptoms emergence), mean (±SD), *n*	1.8 (2.14), 95	1.8 (2.12), 91	1.5 (2.04), 91	0.5
Age (years), mean (±SD)	73 (7.33)	74 (8.11)	75 (6.63)	0.52
Female, *n* (%)	60 (63.16)	42 (46.15)	48 (52.17)	0.06
MMSE, mean (±SD)	16.20 (2.64)	16.59 (2.33)	17.13 (2.51)	0.04
ADAS Cog 11, mean (±SD)	28.79 (8.35)	28.15 (7.67)	27.70 (9.15)	0.30
APO-E4 carrier status, *n* (%)	64 (67.36)	52 (57.14)	56 (60.87)	0.37
Psychotropics use, *n* (%)	58 (61.05)	59 (64.84)	53 (57.61)	0.60
NPI-Psychosis (≥1), mean (±SD), *n*	3.5 (2.59), 28	4.0 (3.04), 28	3.3 (2.10), 28	0.77
Age (years), mean (±SD)	73 (7.85)	75 (8.02)	75 (4.80)	0.72
Female, *n* (%)	17 (60.71)	12 (42.86)	16 (57.14)	0.37
MMSE, mean (±SD)	16.00 (2.79)	16.18 (2.25)	16.14 (2.65)	0.90
ADAS Cog 11, mean (±SD)	29.79 (8.57)	31.36 (8.52)	31.68 (10.07)	0.73
APO-E4 carrier status, *n* (%)	20 (71.43)	19 (67.86)	23 (82.14)	0.37
Psychotropics use, *n* (%)	17 (60.71)	14 (50)	20 (71.43)	0.26
NPI-Psychosis (baseline symptoms and/or symptom emergence), mean (±SD), *n*	1.7 (2.53), 57	2.3 (3.05), 48	1.8 (2.26), 50	0.54
Age (years), mean (±SD)	73 (7.71)	75 (8.45)	76 (5.28)	0.24
Female, *n* (%)	34 (59.65)	26 (54.17)	27 (54.00)	0.80
MMSE, mean (±SD)	15.65 (2.62)	16.31 (2.42)	16.12 (2.49)	0.36
ADAS Cog 11, mean (±SD)	29.44 (8.14)	29.63 (8.14)	31.40 (9.17)	0.52

TABLE 1 (Continued)

Parameters	Placebo	Masupirdine 50 mg	Masupirdine 100 mg	*p* value[a]
APO-E4 carrier status, *n* (%)	39 (68.42)	28 (58.33)	38 (76.00)	0.10
Psychotropics use, *n* (%)	33 (57.90)	26 (54.16)	35 (70)	0.24

Abbreviations: ADAS-Cog 11, 11-item Alzheimer's disease assessment scale-cognitive subscale; APO-E4, Apolipoprotein E4; MMSE, mini mental state examination; NPI, Neuropsychiatric inventory.

[a]Kruskal-Wallis test or $\chi 2$ test.

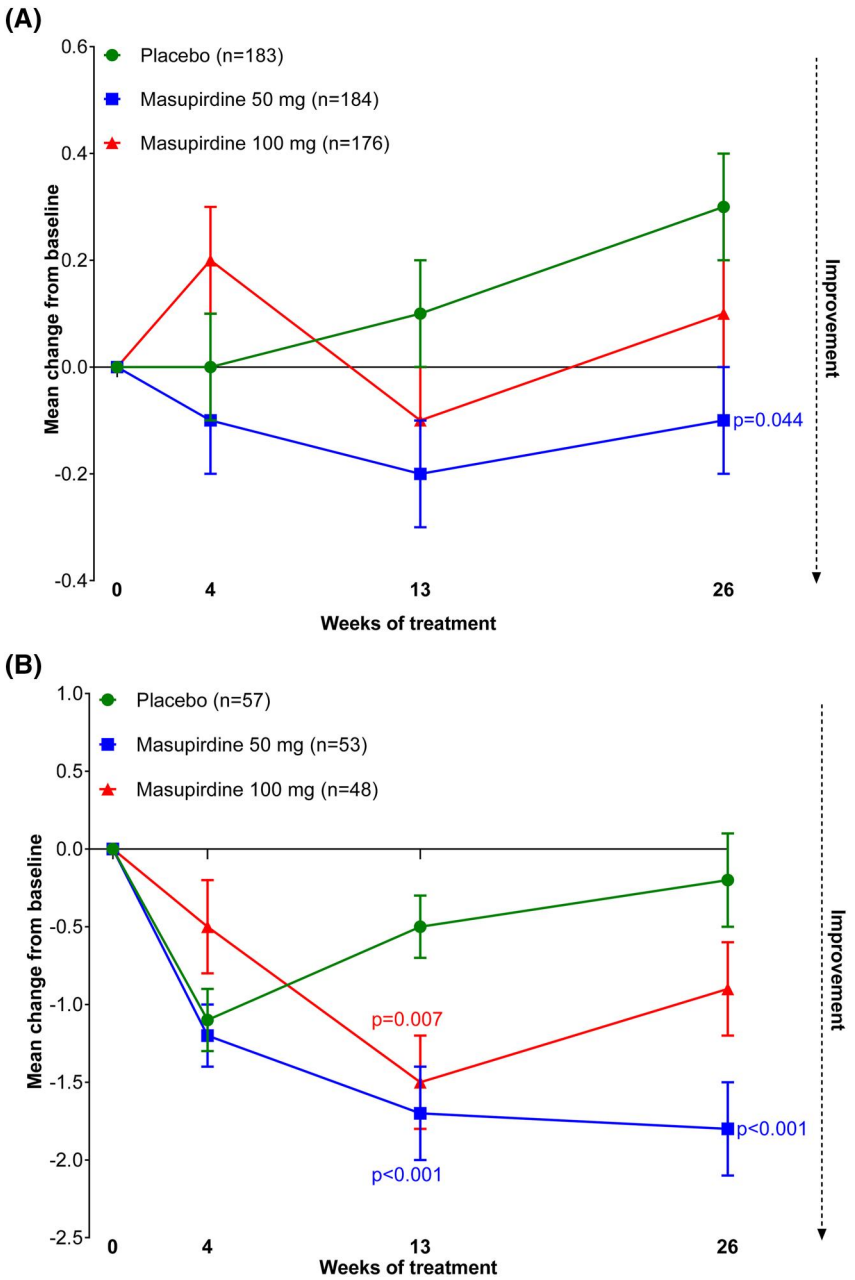

FIGURE 1 (A) Mean change in agitation/aggression domain of NPI-12 (modified intention to treat (mITT)); Error bars represent standard error of mean; NPI-12: 12-item Neuropsychiatric Inventory scale; mITT—modified intent to treat population. (B) Mean change in agitation/aggression domain (baseline ≥1) of NPI-12 (mITT); Error bars represent standard error of mean; NPI-12: 12-item Neuropsychiatric Inventory scale; mITT—modified intent to treat population. (C) Mean change in agitation/aggression domain (baseline ≥3) of NPI-12 (mITT); Error bars represent standard error of mean; NPI-12: 12-item Neuropsychiatric Inventory scale; mITT—modified intent to treat population. (D) Mean change in agitation/aggression domain (baseline symptom and/or symptom emergence) of NPI-12 (mITT); Error bars represent standard error of mean; NPI-12: 12-item Neuropsychiatric Inventory scale; mITT—modified intent to treat population

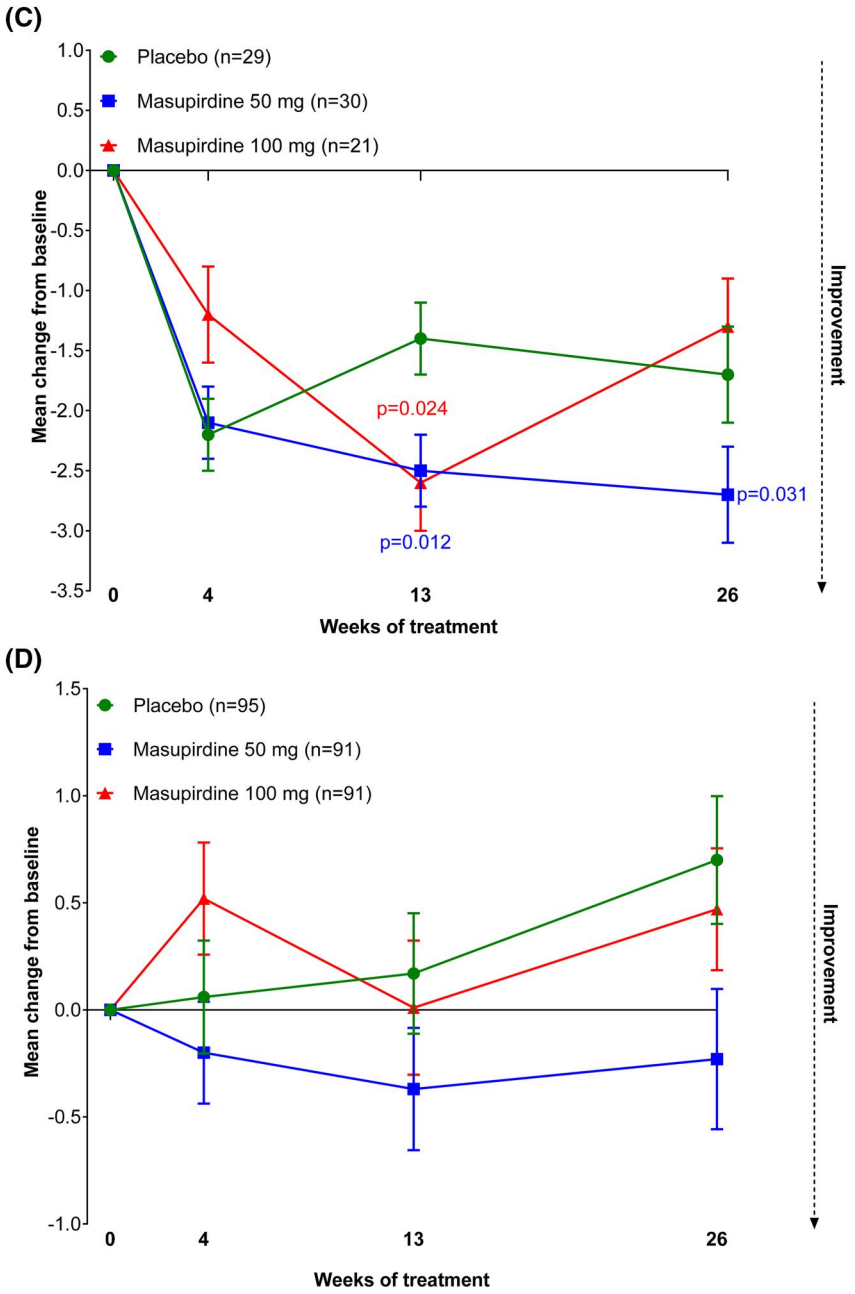

FIGURE 1 (Continued)

baseline but in whom these symptoms emerged in the course of the trial. In the subgroup of patients who had baseline agitation/aggression symptoms and/or agitation/aggression symptom emergence in the course of the trial, no significant effect was observed when comparing masupirdine treatment arms to the placebo arm ($p > 0.05$) (Figure 1D).

In the subgroup of patients with baseline symptoms of agitation or baseline symptoms and/or symptom emergence, no notable differences were observed in the ADAS-Cog 11 or MMSE scores when comparing masupirdine treatment arms to the placebo arm ($p > 0.05$) (data not shown).

3.3 | Psychosis domain

No statistically significant effects were observed with masupirdine treatment when compared to placebo treatment arm in the overall trial population (Figure 2A). Further analyses were carried out in subgroup of patients who had baseline psychosis score (symptoms). Data analyses showed a statistically significant treatment difference in change from baseline in the mean psychosis scores at Week 4 for masupirdine 50 (95% CI, −2.8 to −1.4, $p < 0.001$) and masupirdine 100 mg (95% CI, −1.4 to 0.0, $p = 0.046$), and Week 13 for masupirdine 50 mg (95% CI, −3.3 to

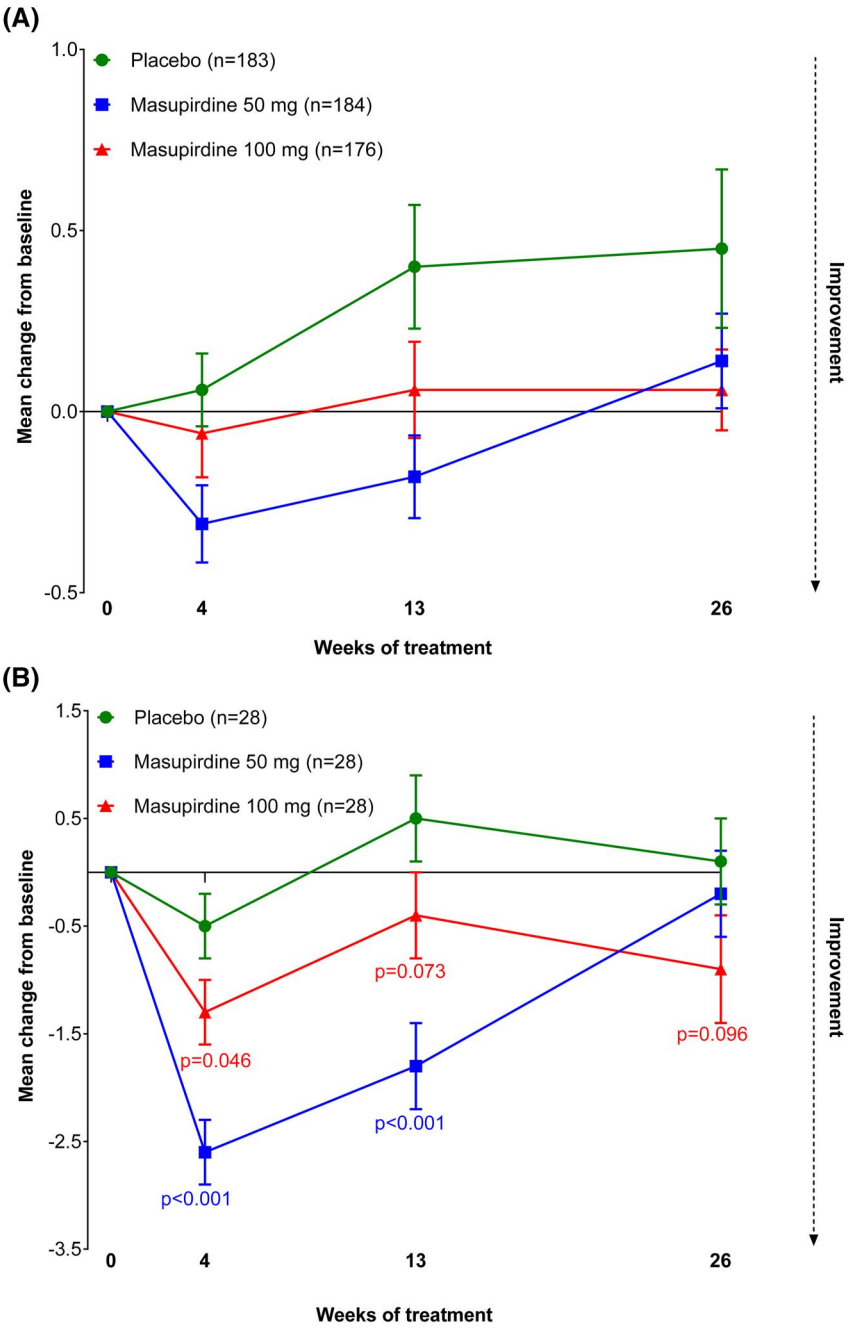

FIGURE 2 (A) Mean change in psychosis domain of NPI-12 (modified intention to treat (mITT)); Error bars represent standard error of mean; NPI-12: 12-item Neuropsychiatric Inventory scale; mITT - modified intent to treat population. (B) Mean change in psychosis domain (baseline ≥1) of NPI-12 (mITT); Error bars represent standard error of mean; NPI-12: 12-item Neuropsychiatric Inventory scale; mITT—modified intent to treat population. (C) Mean change in ADAS-Cog 11 scores in patients with psychosis (baseline ≥1) of NPI-12 (mITT); Error bars represent standard error of mean; ADAS-Cog 11: 11 item Alzheimer's Disease Assessment Scale–Cognitive subscale; NPI-12: 12-item Neuropsychiatric Inventory scale; mITT—modified intent to treat population. (D) Mean change in psychosis domain (baseline symptom and/or symptom emergence) of NPI-12 (mITT); Error bars represent standard error of mean; NPI-12: 12-item Neuropsychiatric Inventory scale; mITT—modified intent to treat population. (E) Mean change in ADAS-Cog 11 scores in patients with psychosis (baseline symptom and/or symptom emergence) of NPI-12 (mITT); Error bars represent standard error of mean; ADAS-Cog 11: 11 item Alzheimer's Disease Assessment Scale–Cognitive subscale; NPI-12: 12-item Neuropsychiatric Inventory scale; mITT—modified intent to treat population

−1.3, $p < 0.001$) when comparing to the placebo treated arm. A trend towards improvement was observed in the masupirdine 100 mg treatment arm at Weeks 13 (95% CI, −1.9 to 0.1, $p = 0.073$) and 26 (95% CI, −2.3 to 0.2, $p = 0.096$) when compared to the placebo treated arm (Figure 2B). Analysis of ADAS-Cog 11 scores in patients with baseline psychosis symptoms showed a statistically significant (95% CI, −7.1 to −0.6, $p = 0.021$) treatment difference in change from baseline in

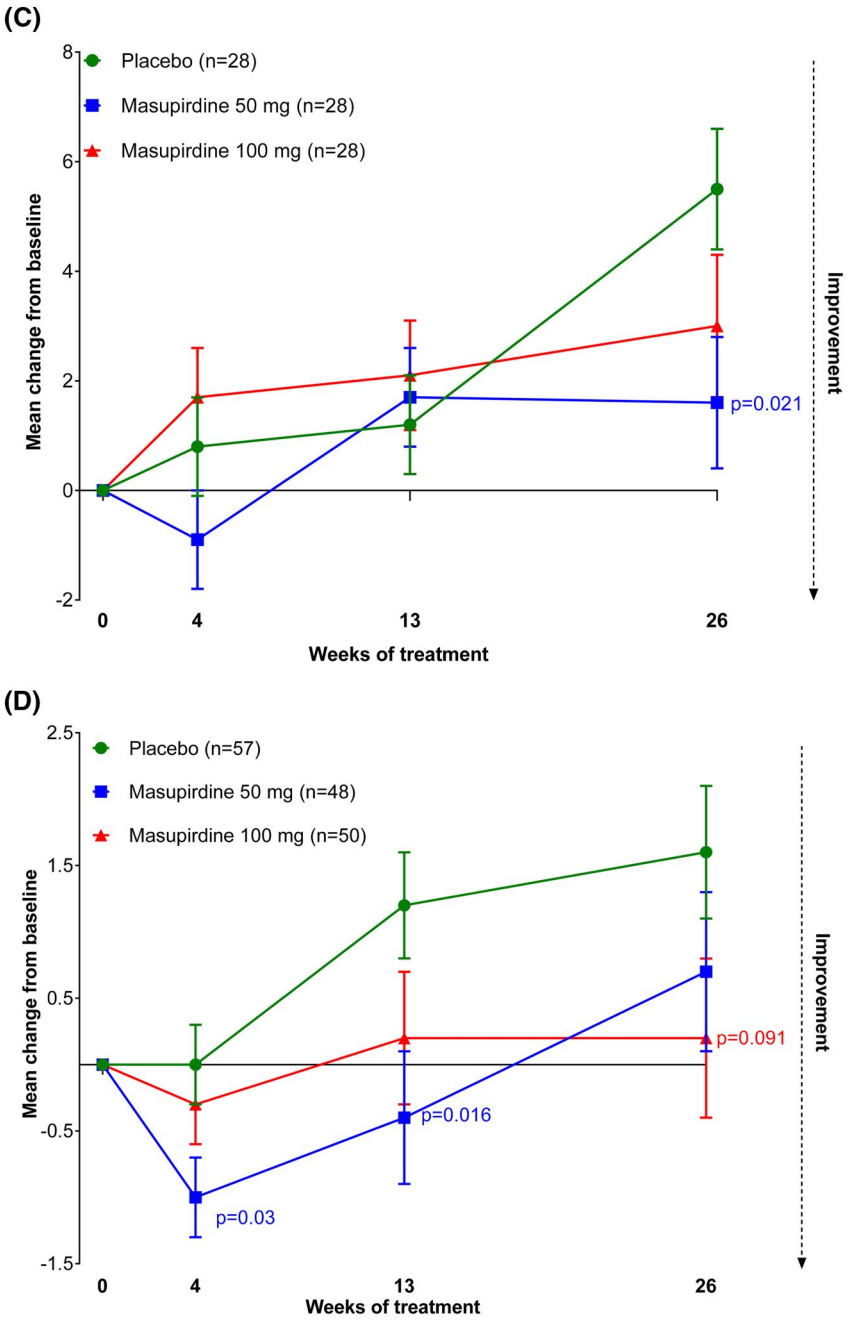

FIGURE 2 (Continued)

ADAS-Cog 11 scores at Week 26, when comparing masupirdine 50 mg arm to the placebo arm (Figure 2C). No notable differences were observed in the MMSE score (data not shown).

In the subgroup of patients who had baseline psychosis symptoms and/or psychosis symptom emergence, a significant drug-placebo difference was observed in change from baseline in the mean psychosis scores at Weeks 4 (95% CI, −1.9 to 0.1, $p = 0.03$) and 13 (95% CI, −2.8 to −0.3, $p = 0.016$) when comparing masupirdine 50 mg treatment arm to the placebo arm. A trend towards improvement was observed in the masupirdine 100 mg (95% CI, −3.0 to 0.2, $p = 0.091$) treatment arm at Week 26 when compared to the placebo treated arm (Figure 2D). Analysis of ADAS-Cog 11 scores in these patients suggested a trend (95% CI, −5.2 to 0.2, $p = 0.067$) towards improvement in the change from baseline score at Week 26, when comparing masupirdine 50 mg arm to the placebo arm, favoring masupirdine treatment (Figure 2E). No notable differences were observed in the MMSE scores (data not shown).

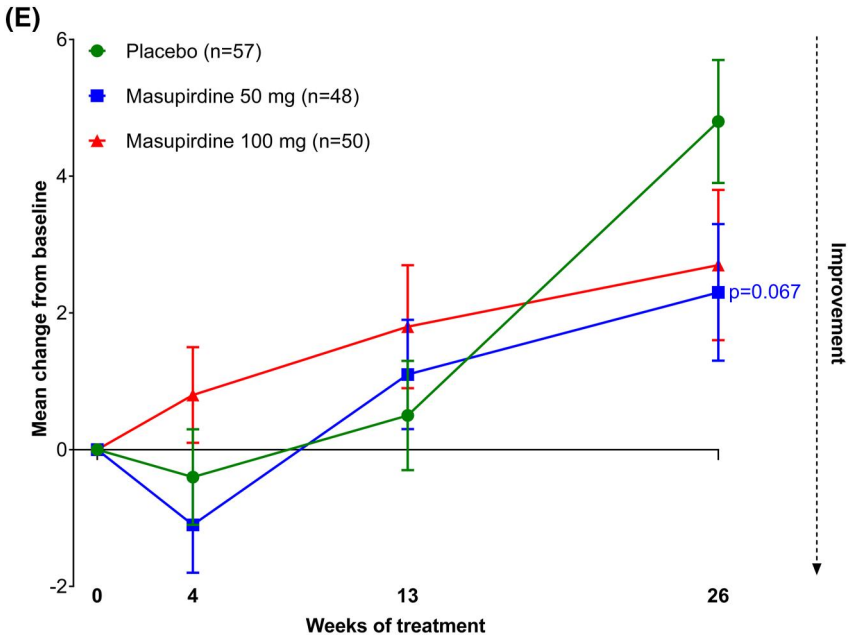

FIGURE 2 (Continued)

3.4 | Safety

Safety and tolerability findings of the trial have been previously published.[29] Overall, adverse event profiles for the patient populations reported in this analysis were in accord with the published safety profile of masupirdine (Supplementary Table S1). Masupirdine was safe and well tolerated.

4 | DISCUSSION

The current post hoc analyses were based on the observed numerical superiority in the NPI-12 scale for masupirdine over placebo in the phase-2 trial (NCT02580305).[29] Based on the observed trends in the NPI-12 sub-domains, the analyses were focused on the agitation/aggression and psychosis domains of the NPI-12 scale. Post hoc analyses included patients exclusively having baseline symptoms or baseline symptoms and/or symptom emergence in the course of the trial.

Approximately one-third patients in masupirdine trial had agitation/aggression symptoms at baseline. In the subgroup of the trial patients having agitation/aggression scores of ≥1 or ≥3 at baseline, a significant beneficial effect of masupirdine 50 mg was observed at Weeks 13 and 26. The observed drug-placebo difference was 1.5 (Cohen's $d = 0.66$ for baseline ≥1 subgroup) or 1.1 (Cohen's $d = 0.60$ for baseline ≥3 subgroup) at the end of 26 weeks. The drug placebo difference for the masupirdine 50 mg treatment for the subgroup's agitation/aggression was greater than 0.4 standard deviation, a common threshold used to determine the minimum clinically important difference.[33,34] The effect observed with masupirdine on agitation/aggression was consistent across all levels of agitation. On the contrary, post hoc analyses have suggested severity of agitation as one of the factors that influenced treatment outcome for agents like citalopram[35] and ELND005.[36] No notable differences were observed on agitation/aggression between placebo and masupirdine treatment arms in the subgroup of patients who had baseline symptoms and/or symptom emergence in the course of the trial. This may be because of the lower baseline scores (mean baseline scores for placebo: 1.78, masupirdine 50 mg: 1.95 and masupirdine 100 mg: 1.6) and low rate of symptom emergence (mean Week 26 scores for placebo: 2.31, masupirdine 50 mg: 1.53 and masupirdine 100 mg: 1.93).

Approximately 15% patients in the masupirdine trial had baseline psychosis. In the subgroup of patients having baseline psychosis scores, a significant effect of masupirdine 50 mg was observed at Weeks 4 and 13, however only a trend (positive) was observed with masupirdine 100 mg treatment. At Week 26, no effects were observed with masupirdine 50 mg treatment, but the trend observed with the masupirdine 100 mg treatment persisted. Similar observations were also noted in the subgroup of patients having psychosis symptoms and/or symptom emergence. Approximately 30% patients in the masupirdine trial had baseline psychosis and/or symptoms emergence. Overall, the effects of masupirdine on psychosis were consistent across the subgroups.

No significant differences were observed in the ADAS-Cog 11 or MMSE scores between placebo and masupirdine treatment arms for agitation/aggression subgroups. However in the psychosis subgroups, a significantly lower (better) or a trend towards slower decline in ADAS-Cog 11 scores was observed with masupirdine 50 mg or

100 mg treatment compared to placebo at Week 26. The effect of masupirdine on ADAS-Cog 11 scores was consistent in the psychosis subgroups. No notable differences were observed in the MMSE scores in either of the psychosis subgroups. Overall, post hoc analyses of the data from the NCT02580305 trial suggest that masupirdine may have potential beneficial effects on agitation/aggression and psychosis in AD patients.

Few 5-HT_6 receptor antagonists have been evaluated for the utility in the treatment of NPS; post hoc analyses from the current clinical study identified a drug-placebo difference favoring masupirdine as a potential therapy for agitation and psychosis of AD. Supportive results were observed in an idalopirdine trial where a trend towards amelioration of anxiety and hallucinations were noted.[37] In a post hoc analysis, landipirdine treatment was associated with potential improvements in apathy, sleep, anxiety, and irritability/lability in patients with Parkinson's disease dementia.[38] Both idalopirdine and landipirdine block 5-HT_{2A} receptors in addition to 5-HT_6 receptors. Masupirdine is a potent and selective 5-HT_6 receptor antagonist with >1200 fold selectivity for 5-HT_6 receptors over 5-HT_{2A} receptors.[27,28] Based on the observations with masupirdine, 5-HT_6 receptors may also had a role on effects observed with landipirdine and idalopirdine on NPS.

In the agitation subgroups, the effects observed with masupirdine were not dose dependent (masupirdine 50 mg treatment appeared better than masupirdine 100 mg treatment). In addition, effects at the end of 26 weeks were not pronounced compared to Week 4 or Week 13 in the psychosis subgroups. Prior researches suggest the existence of unique types of agitation/aggression[39] and psychosis[40] due to the underlying brain circuit dysregulation resulting in differential responses to treatment. Non-dose response relation could also be due to lower symptom severity compared to those that were recruited specifically for the presence of agitation/aggression or psychosis symptoms,[41–43] resulting in ceiling effects.

No notable treatment effects of masupirdine were observed in the ADAS-Cog 11 scores for the agitation/aggression subgroup. In contrast, a significant effect or trend of masupirdine on slowing cognitive decline was observed in the psychosis subgroups. The placebo decline in ADAS-Cog 11 scores of about 5 points was observed for both the psychosis subgroups at Week 26. This change is higher when compared with the studies of similar nature[25] or overall masupirdine trial population.[29] Literature evidences suggest rapid cognitive decline in AD patients with agitation/aggression and psychosis.[2,44–48] Thus, the psychosis subgroup could be a representation of general patients with AD and psychosis. However, ADAS-Cog 11 scores of the agitation/aggression subgroup was comparable to masupirdine phase-2 trial population, which is contrary to the research reports. Reasons for divergent results in terms of cognitive outcomes can be attributed to the possible differences in the epidemiology and neurobiology of agitation and psychosis.[44,49,50] Although effect of masupirdine was observed in the ADAS-Cog 11 scale in psychosis subgroups, no notable effect was observed in the MMSE scale. An annual decline of 3 points was observed in AD patients on the MMSE scale[51] and a decline of 3 points is suggestive of meaningful decline for moderate AD patients.[52,53] Decline observed in the overall masupirdine trial population was approximately 1 point at the end of 26 weeks.[29] The change observed in the MMSE scale could be low to decipher the treatment effects on the MMSE scale. Although the effect of masupirdine on the ADAS-Cog 11 scores has to be interpreted with caution, the observations suggest potential differential effects of masupirdine on cognition in patients with AD psychosis.

The main limitation of post hoc analyses is that the trial patients were not recruited prospectively based on agitation/aggression or psychosis criteria. The post hoc sample size was smaller compared to the studies constructed to assess treatment effects on agitation/aggression or psychosis. These analyses sets did not have the symptom severity comparable to those that were recruited specifically for the presence of agitation/aggression or psychosis symptoms.[41-43] Patients with more severe symptoms may exhibit a different response profile than that observed in this post hoc analyses. Despite the above limitations, the analyses suggest potential treatment effects of masupirdine on agitation/aggression and psychosis symptoms. Additional clinical trials are warranted to explore hypothesis-generating observations regarding potential effects of masupirdine on agitation/aggression and psychosis. Currently, masupirdine is being evaluated in a phase-3 trial for the treatment of agitation/aggression in patients with AD dementia (NCT05397639).

AUTHOR CONTRIBUTIONS

All authors were involved in the design and conduct of the study. Authors critically reviewed the manuscript, commented on drafts, and approved the final manuscript.

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CONFLICT OF INTEREST

Dr. Cummings has provided consultation to AB Science, Acadia, Alkahest, AlphaCognition, ALZPathFinder, Annovis, AriBio, Artery, Avanir, Biogen, Biosplice, Cassava, Cerevel, Clinilabs, Cortexyme, Diadem, EIP Pharma, Eisai, GatehouseBio, GemVax, Genentech, Green Valley, Grifols, Janssen, Karuna, Lexeo, Lilly, Lundbeck, LSP, Merck, NervGen, Novo Nordisk, Oligomerix, Ono, Otsuka, PharmacotrophiX, PRODEO, Prothena, ReMYND, Renew, Resverlogix, Roche, Signant Health, Suven, Unlearn AI, Vaxxinity, VigilNeuro pharmaceutical, assessment, and investment companies.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the author (Ramakrishna Nirogi—nvsrk@suven.com) upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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