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RESEARCH ARTICLE

Effect of masupirdine (SUVN-502) on cognition in patients with moderate Alzheimer's disease: A randomized, double-blind, phase 2, proof-of-concept study

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Abstract

Introduction: This study explored the efficacy and safety of a serotonin-6 receptor antagonist, masupirdine, as adjunct treatment in patients with moderate Alzheimer's disease (AD) concomitantly treated with donepezil and memantine.

Methods: The effects of masupirdine were evaluated in patients with moderate AD dementia on background treatment with donepezil and memantine. Five hundred thirty-seven patients were expected to be randomized in a 1:1:1 ratio, using permuted blocked randomization. After a 2- to 4-week screening period, the study consisted of a 26-week double-blind treatment period, and a 4-week washout period. The primary efficacy measure was the 11-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog 11). Secondary efficacy measures were Clinical Dementia Rating Scale–Sum of Boxes, Mini-Mental State Examination, 23-item Alzheimer's Disease Co-operative Study Activities of Daily Living, and 12-item Neuropsychiatric Inventory. Changes from baseline were analyzed using a mixed effects model for repeated measures (MMRM). A total of 564 patients were randomized to receive either daily masupirdine 50 mg (190 patients), masupirdine 100 mg (185 patients), or placebo (189 patients). The study is registered at ClinicalTrials.gov (NCT02580305).

Results: The MMRM results showed statistically non-significant treatment differences in change from baseline in ADAS-Cog 11 scores at week 26, comparing each masupirdine dose arm to the placebo arm. No significant treatment effects were observed in the secondary evaluations.

Discussion: Masupirdine was generally safe and well tolerated. Possible reasons for the observed trial results are discussed.

Highlights

- Masupirdine was evaluated in moderate Alzheimer's disease patients.
- First trial in class with background treatment of donepezil and memantine.
- Masupirdine was generally safe and well tolerated.
- Possible reasons for the observed trial results are discussed.

1 | BACKGROUND

Alzheimer's disease (AD) is a progressive neurodegenerative disorder manifested by cognitive and memory deterioration in addition to progressive impairments of activities of daily living and behavior and neuropsychiatric symptoms.[1,2] Commonly used approved AD treatments are acetylcholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and a non-competitive N-methyl-D-aspartic acid receptor blocker (memantine); however, these do not slow the progression of the disease[2–4] and only demonstrate modest efficacy to symptomatically improve or stabilize the clinical trajectory for most patients.[5] Aducanumab, an amyloid-targeting monoclonal antibody, has been shown to remove amyloid plaques and holds promise for producing modest clinical benefits in early AD,[6] but requires monthly infusions and substantial safety monitoring including magnetic resonance imaging (MRI).[7] The modest efficacy and side effects of current treatment options along with a growing elderly population provide an impetus to develop more effective therapeutic agents with a wider range of application.

Serotonin-6 (5-HT$_6$) receptor is a G protein-coupled receptor localized almost exclusively in the central nervous system areas important for learning and memory.[8–10] 5-HT$_6$ receptors localized on gamma-aminobutyric acid (GABA) interneurons tonically modulate the activity of the GABAergic system. Disinhibiting the inhibitory tone increases the output of a variety of neurotransmitters.[11–13] Selective blockade of the 5-HT$_6$ receptor improves learning and memory possibly through the increased output of acetylcholine and glutamate.[12,13] Thus, 5-HT$_6$ receptor antagonists may offer a novel therapeutic strategy for the treatment of memory deficits associated with AD.[14–17]

Several 5-HT$_6$ receptor antagonists have been evaluated in clinical studies targeting cognitive deficits. Idalopirdine and intepirdine were evaluated for potential benefits in the treatment of cognitive impairment associated with AD. In a phase 2 clinical trial, idalopirdine added to donepezil showed benefits on cognition;[18] however, these observations were not replicated in the phase 3 studies.[19] Similar observations were noted with intepirdine.[20,21] Another 5-HT$_6$ receptor antagonist, PF-05212377 (SAM-760), was evaluated for its potential benefits on cognition in patients with mild to moderate AD dementia and neuropsychiatric symptoms but its study was terminated after an interim analysis showed no benefits on cognition or neuropsy-

chiatric symptoms.[22] Landipirdine and intepirdine were evaluated for their potential benefits in Parkinson's disease dementia and dementia with Lewy bodies, respectively.[23,24] No benefits were observed in either disease population. Overall, inconsistent treatment effects were observed on cognition with 5-HT$_6$ receptor antagonists when tested as a standalone treatment or as an adjunct to cholinesterase inhibitors. The failure of idalopirdine and intepirdine may not be solely attributable to the efficacy of these agents. Failure of idalopiridine could be attributed to the significant changes from phase 2 to phase 3 studies (doses, dosing frequency, range of cognitive impairment, type of background therapy, and geography of study locations).[19] However, the intepiridine phase 3 study largely mimicked the phase 2 study, except for the study locations. It is acknowledged that wide geography of study locations can result in heterogeneity.[21] Most 5-HT$_6$ receptor antagonists were generally safe and well tolerated, thus targeting this receptor for the treatment of cognitive deficits could represent a safe and viable option.

Masupirdine is a potent and selective 5-HT$_6$ receptor antagonist. It produced procognitive effects in various animal models. In non-clinical studies, co-administration of masupirdine with donepezil and memantine resulted in procognitive effects that were significantly better than those seen with the combination of donepezil and memantine.[25,26] Considering the potential beneficial effects of masupirdine on cognition in animal models when co-administered with donepezil and memantine, and the wide use of this combination therapy in clinical practice, masupirdine was evaluated as an add-on therapy to donepezil and memantine in patients with moderate stage AD dementia.

2 | METHODS

2.1 | Study design and patient population

The phase 2, proof-of-concept (POC), 26-week, double-blind, multicenter, randomized, parallel group, placebo controlled study compared the efficacy and safety of masupirdine (50 or 100 mg) to placebo treatment in patients with moderate AD. The study population consisted of patients with Mini-Mental State Examination (MMSE)[27] score range of 12 to 20 (both inclusive) recruited at 90 study sites located within the United States. The study recruited ambulatory or ambulatory-

aided male or female patients aged between 50 and 85 years (both inclusive) with a diagnosis based on the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria,[28] with MRI or computed tomography scan findings consistent with the diagnosis of dementia due to probable AD. Patients were treated for at least 3 months with donepezil HCl (10 mg, qd) and either memantine HCl (10 mg, bid) or Namenda XR (28 mg memantine HCl extended-release, qd) or the combination therapy, Namzaric (28 mg memantine HCl extended-release/10 mg donepezil HCl, qd) prior to the screening visit. A detailed list of inclusion/exclusion criteria is included in the Appendix.

The study consisted of a 2- to 4-week screening period, followed by a 26-week double-blind treatment period, and an end of study 4-week washout period. The baseline visit occurred 14 to 28 days after screening. During the 26-week treatment period, patient and caregivers had study visits at weeks 4, 13, and 26. Patients who completed the 26-week treatment underwent a 4-week single-blind washout period and safety follow-up at week 30.

The study was conducted according to the protocol and in compliance with International Council for Harmonization guidelines on Good Clinical Practice and other applicable regulatory requirements. At each study center, the protocol, protocol amendment, and informed consent forms were reviewed and approved by an institutional review board or independent ethics committee. Patients eligible for the study or their legally authorized representative and their caregiver provided the informed consent before the patient was admitted to the study.

All data were maintained electronically in the electronic case report form (eCRF).

2.2 | Outcome measures

The primary efficacy measure for the study was the 11-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog 11).[29] Secondary efficacy measures were Clinical Dementia Rating Scale–Sum of Boxes (CDR-SB),[30] MMSE,[27] 23-item Alzheimer's Disease Co-operative Study Activities of Daily Living (ADCS-ADL23)[31] and 12-item Neuropsychiatric Inventory (NPI-12).[32,33] External quality oversight methods (including central review of scale administration) were applied for consistent and accurate ratings.

2.3 | Randomization, intervention, blinding, and sample size

Eligible patients were randomized to receive one of three treatments: masupirdine 50 mg, masupirdine 100 mg, or placebo in a 1:1:1 ratio, using permuted blocked randomization. Randomization was balanced by site with block size of six. For randomization of patients, the investigator used an interactive voice response system which assigned patients in a double-blind manner to a treatment group. All study staff were blind to patient randomization. The study drug and placebo were administered as identical tablets to be taken orally once daily. With an

RESEARCH IN CONTEXT

1. Systematic Review: We reviewed the literature reporting serotonin-6 receptor antagonist for the symptomatic treatment of cognitive deficits in dementia. Idalopirdine, intepirdine, and PF-05212377 (SAM-760) have been evaluated in Alzheimer's disease (AD) patients. Landipirdine and intepirdine have been studied for potential benefits in Parkinson's disease dementia and dementia with Lewy bodies, respectively. These relevant publications are appropriately cited.

2. Interpretation: Findings from the present study demonstrate that masupirdine was generally safe and well tolerated. The prespecified primary outcomes showed no drug-placebo difference. Possible reasons for the observed trial results are discussed.

3. Future Directions: Based on the outcome of post hoc subgroup analysis of the NPI-12 domains, masupirdine is currently being studied for the management of agitation in patients with dementia of the AD type.

expected sample size of 537, there was at least 80% power to detect a 2-point drug–placebo difference on the ADAS-Cog 11 scores with a standard deviation of 6,[34] assuming two-sided 5% significance level and a drop-out rate of 20% or less.

2.4 | Safety monitoring

Safety was assessed by monitoring adverse events (AEs), blood pressure, echocardiogram (ECG), physical and neurological examinations, blood and urine sampling for laboratory evaluations, and suicidality using the Columbia-Suicide Severity Rating Scale (C-SSRS).[35]

2.5 | Pharmacokinetics

Blood samples were collected at screening, and week 4 and week 26 of treatment. Plasma samples were analyzed for levels of masupirdine and its metabolite (M1 of masupirdine), donepezil, and memantine to gather information on population pharmacokinetics and determine compliance with study medication.

2.6 | Statistical analysis

All statistical tests were two-sided and performed at the 5% level of significance, unless otherwise stated. All analyses were conducted using SAS version 9.3 in a secure and validated environment. The primary and secondary analyses compared each treatment of masupirdine to placebo.
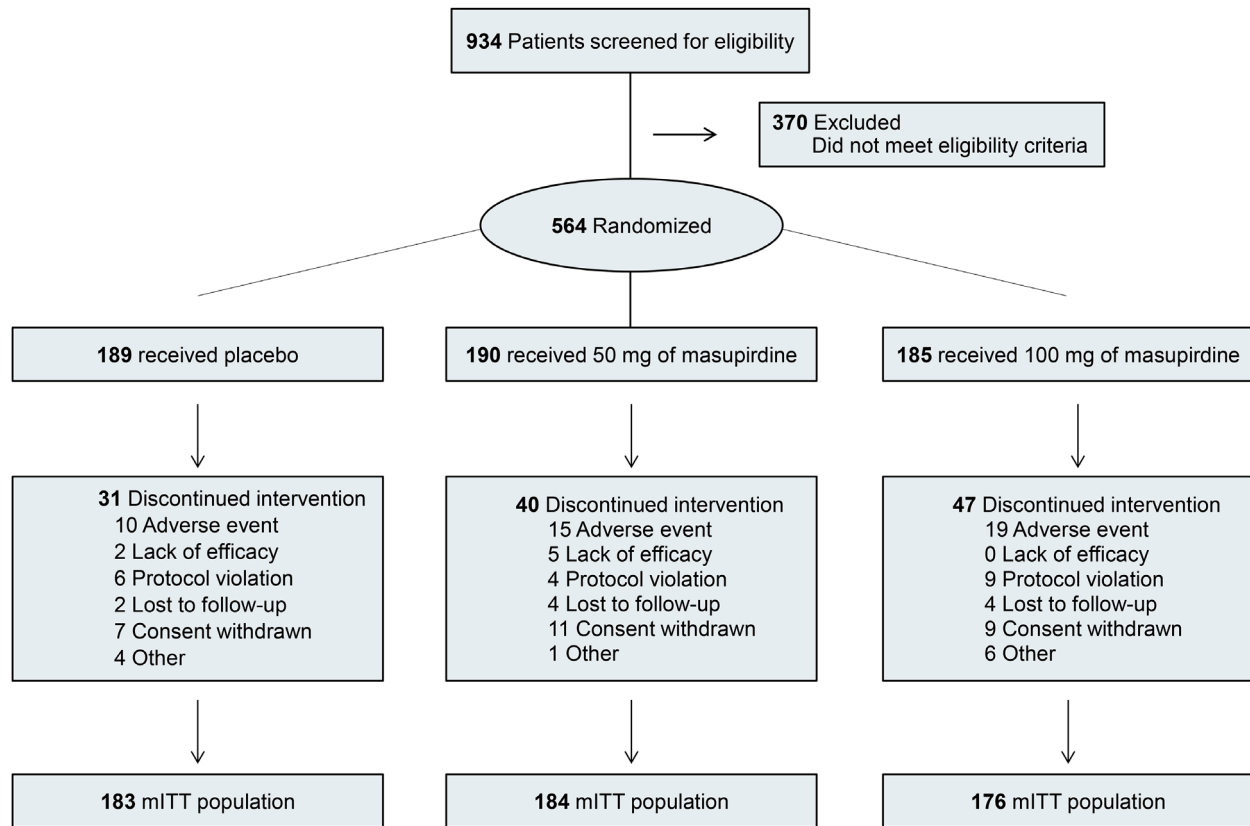
FIGURE 1 Patient disposition. mITT, modified intent to treat population

All efficacy analyses were performed on the modified intent to treat (mITT) population. All randomized subjects who received at least one dose of study drug and had one post-baseline evaluation of the primary efficacy measure were considered the mITT population. Changes from baseline were analyzed using a mixed effects model for repeated measures (MMRM) based on the mITT population. The model included fixed categorical factors for treatment, week, treatment-by-week interaction, and apolipoprotein E (*APOE*) ε4 status, as well as a continuous covariate of baseline score, the baseline score by week interaction, age, and baseline MMSE score. Pooled sites were included as a random effect. All randomized patients who received at least one dose of study drug were considered the safety population. AEs were coded using MedDRA (version 18.1). Pharmacokinetic and safety analyses were performed on the safety population.

Sensitivity analyses to assess the impact of missing data were conducted. Missing total scores were imputed using the z-score last observation carried forward (zLOCF) approach prior to analysis.

3 | RESULTS

3.1 | Patient demographics and baseline disease characteristics

Study patients were enrolled between December 1, 2015 and May 21, 2019. A total of 564 patients were randomized as per the planned ratio

to receive masupirdine 50 mg (190 patients), masupirdine 100 mg (185 patients), or placebo (189 patients). A total of 543 (96.3%) patients who were randomized to specific treatment sequence were included in the mITT analysis. A total of 556 (98.6%) randomized patients were included in the safety population (Figure 1).

The median age was similar across treatment arms (masupirdine 50 mg: 75.0 years; masupirdine 100 mg: 76.0 years, and placebo: 74.0 years). The majority of patients (at least 85.8%) were in the $\geq$65 years of age category. A higher proportion of female than male patients were enrolled in the study (54.7% female vs. 45.3% male patients). Overall, the majority of patients were White (92.3%) with a similar proportion of White patients among the treatment arms. The median basal metabolic index was similar in all treatment arms (26.24 kg/m^2, 26.57 kg/m^2, and 25.48 kg/m^2 for masupirdine 50 mg, masupirdine 100 mg, and placebo, respectively). At baseline, the median ADAS-Cog 11 score ranged from 26.0 to 28.0 across the treatment arms. The median MMSE score was similar across the treatments and ranged from 17.0 to 17.5. The median CDR-SB score was 6.0 in all three study arms. The proportion of *APOE* ε4 carriers was similar across all three treatment arms (54.8% vs. 62.5% vs. 65%). Overall, the study enrolled a sample representative of patients with moderate AD dementia and had demographics and baseline disease characteristics that were balanced across treatment groups (Table 1).

The proportion of patients who completed week 30 follow-up was higher in the placebo arm (83.5%) compared to the masupirdine 50 mg (78.6%) and masupirdine 100 mg (74.3%) arms. A similar proportion

TABLE 1 Baseline characteristics

Baseline characteristics	Placebo (n = 183)	Masupirdine (n = 360)		P value[a]
		50 mg (n = 184)	100 mg (n = 176)	
Age (years)[#]	72.9 (7.23)	73.4 (8.08)	74.4 (6.97)	.15
Age group distribution*				.81
Age group (< 65 years)	26 (14.2)	25 (13.6)	21 (11.9)	
Age group (≥65 years)	157 (85.8)	159 (86.4)	155 (88.1)	
Male*	77 (42.1)	89 (48.4)	80 (45.5)	.48
White*	168 (91.8)	171 (92.9)	162 (92.0)	.91
BMI (kg/m^2)[#]	26.35 (4.97)	26.63 (5.00)	26.92 (5.36)	.63
APOE ε4 distribution*				.18
APOE ε4 carrier status (one allele)	84 (45.9)	77 (41.8)	79 (44.9)	
APOE ε4 carrier status (two allele)	35 (19.1)	24 (13.0)	31 (17.6)	
MMSE[#]	16.5 (2.48)	16.9 (2.21)	17.0 (2.47)	.14
ADAS-Cog 11[#]	28.4 (8.16)	27.7 (6.92)	27.9 (8.62)	.49
ADCS-ADL23[#]	54.4 (12.79)	55.6 (11.60)	55.4 (13.27)	.56
CDR-SB[#]	7.03 (2.90)	6.51 (2.58)	6.75 (2.74)	.35
NPI-12[#]	10.1 (10.25)	9.7 (10.25)	9.8 (10.38)	.99
Time since diagnosis (years)[#]	3.74 (2.67)	3.78 (2.69)	3.65 (2.82)	.79
Duration of donepezil use (years)[#]	2.72 (2.14)	2.73 (2.22)	2.85 (2.69)	.85
Duration of memantine use (years)[#]	2.01 (2.03)	1.84 (1.94)	1.98 (2.49)	.59
Psychotropics use*	96 (52.46)	99 (53.80)	89 (50.57)	.83

[#]Mean (SD).
*n (%).
Abbreviations: ADAS-Cog 11, 11-item Alzheimer's Disease Assessment Scale-Cognitive subscale; ADCS-ADL23, 23-item Alzheimer's Disease Cooperative Study Activities of Daily Living; APOE, apolipoprotein E; BMI, body mass index; CDR-SB, Clinical Dementia Rating scale Sum of Boxes; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; SD, standard deviation.
[a]Kruskal-Wallis test or χ^2 test.

of patients in the masupirdine 50 mg (13.4%), masupirdine 100 mg (16.4%), and placebo (13.8%) arm withdrew from the study drug and did not complete week 30 follow-up. The proportion of patients who discontinued the study was higher in the masupirdine 100 mg and 50 mg arms compared to the placebo arm (25.7% vs. 21.4% vs. 16.5%). AEs were the most frequently reported reason for discontinuation among patients in the treatment arms. Between treatment arms, the proportion of patients who discontinued due to an AE was higher in the masupirdine 100 mg arm (10.4%) compared to masupirdine 50 mg (8.0%) and placebo arms (5.3%).

3.2 | Efficacy

A summary of efficacy outcomes is presented in Table 2. The MMRM results showed no statistically significant treatment differences in change from baseline in ADAS-Cog 11 scores at week 26. At week 4 and week 13, the mean ADAS-Cog 11 scores remained similar to baseline across the treatment arms. At week 26, there was an increase in the mean ADAS-Cog 11 scores from baseline, which were similar across the treatment arms (Figure 2). The study results remained unchanged

for sensitivity analyses. A subgroup analysis based on the APOE ε4 carrier status (carriers and non-carriers) revealed no treatment effects of masupirdine in the change from baseline ADAS-Cog 11 scores compared to the placebo treatment arm (data not shown). The effects on MMSE (Figure S1 in supporting information), CDR-SB (Figure S2 in supporting information), and ADCS-ADL23 (Figure S3 in supporting information) were consistent with the primary efficacy results. Numerical superiority was observed for masupirdine over placebo treatment in the 12-item NPI scale (Figure S4 in supporting information).

The plasma concentrations of masupirdine and M1 of masupirdine were detectable at week 4 and week 26. A higher mean masupirdine concentration was observed in 100 mg than 50 mg at both of the weeks (Table S1 in supporting information).

3.3 | Safety and tolerability

A total of 968 treatment emergent adverse events (TEAE) were reported in 316 patients (Table 3). Of participants, 56.8% had at least one TEAE. Between treatment groups, at least one TEAE was reported in a similar proportion of patients across the treatment arms

TABLE 2 Summary of efficacy outcomes

| Assessment	Time-frame	Mean (SD)			Change from baselineLS mean (SE)			Masupirdine Difference to placebo; -mean (95% CI)		P value	
		Placebo	Masupirdine		Placebo	Masupirdine		50-mg	100-mg	50 mg	100-mg
			50-mg	100-mg		50-mg	100 mg				
ADAS-Cog 11	Baseline	28.4 (8.16)	27.7 (6.92)	27.9 (8.62)	–	–	–	–	–	–	–
	Week-4	27.7 (8.64)	27.4 (7.72)	27.8 (9.51)	−0.7 (0.4)	−0.6 (0.4)	0 (0.4)	0.2 (−0.8, 1.1)	0.8 (−0.2, 1.7)	.74	.12
	Week 13	28.7 (9.09)	28.7 (7.51)	28.6 (8.86)	0.1 (0.4)	0.8 (0.4)	1.0 (0.4)	0.6 (−0.4, 1.7)	0.8 (−0.2, 1.9)	.21	.11
	Week 26	30.8 (9.74)	29.6 (8.18)	29.6 (9.83)	2.6 (0.5)	2.0 (0.5)	2.5 (0.5)	−0.5 (−1.8, 0.7)	−0.1 (−1.4, 1.2)	.41	.90
MMSE	Baseline	16.5 (2.48)	16.9 (2.21)	17.0 (2.47)	–	–	–	–	–	–	–
	Week-4	16.5 (3.43)	16.9 (3.43)	16.9 (3.52)	0.0 (0.2)	0.1 (0.2)	−0.1 (0.2)	0.1 (−0.4, 0.6)	−0.1 (−0.6, 0.4)	.77	.79
	Week 13	16.2 (3.83)	16.5 (3.48)	16.6 (3.37)	−0.4 (0.2)	−0.4 (0.2)	−0.3 (0.2)	0.0 (−0.6, 0.6)	0.0 (−0.6, 0.6)	.97	.96
	Week 26	15.7 (4.07)	15.9 (3.91)	15.9 (4.17)	−1.0 (0.3)	−1.1 (0.3)	−1.1 (0.3)	−0.1 (−0.8, 0.6)	0.0 (−0.7, 0.7)	.79	.92
CDR-SB	Baseline	7.03 (2.90)	6.51 (2.58)	6.75 (2.74)	–	–	–	–	–	–	–
	Week-4	7.08 (2.81)	6.74 (2.60)	6.83 (2.77)	0.1 (0.1)	0.2 (0.1)	0.0 (0.1)	0.1 (−0.2, 0.4)	0.0 (−0.3, 0.2)	.46	.88
	Week 13	7.49 (3.08)	7.36 (2.92)	7.22 (3.15)	0.4 (0.1)	0.8 (0.1)	0.4 (0.1)	0.4 (0.0, 0.7)	0.0 (−0.4, 0.4)	.04	.99
	Week 26	8.13 (3.44)	7.81 (3.05)	7.67 (3.40)	1.2 (0.2)	1.3 (0.2)	1.0 (0.2)	0.2 (−0.3, 0.6)	−0.2 (−0.6, 0.3)	.46	.48
ADCS-ADL23	Baseline	54.4 (12.79)	55.6 (11.60)	55.4 (13.27)	–	–	–	–	–	–	–
	Week-4	54.0 (12.49)	55.2 (11.82)	54.8 (13.36)	−0.7 (0.4)	−0.4 (0.4)	−0.6 (0.4)	0.3 (−0.8, 1.3)	0.0 (−1.0, 1.1)	.63	.95
	Week 13	52.3 (12.52)	53.1 (12.68)	53.8 (13.26)	−2.5 (0.5)	−2.6 (0.5)	−1.6 (0.5)	−0.1 (−1.4, 1.2)	0.9 (−0.5, 2.2)	.85	.20
	Week 26	51.1 (13.08)	51.2 (13.27)	52.7 (14.19)	−4.4 (0.6)	−4.6 (0.6)	−3.4 (0.6)	−0.2 (−1.9, 1.5)	1.0 (−0.7, 2.7)	.83	.24
NPI-12	Baseline	10.1 (10.25)	9.7 (10.25)	9.8 (10.38)	–	–	–	–	–	–	–
	Week-4	10.3 (10.73)	8.4 (8.78)	9.1 (10.12)	0.4 (0.6)	−1.6 (0.6)	−0.8 (0.6)	−1.9 (−3.5, -0.4)	−1.2 (−2.7, 0.4)	.01	.14
	Week 13	10.4 (11.15)	8.8 (9.09)	9.9 (10.65)	0.4 (0.6)	−0.8 (0.7)	−0.2 (0.7)	−1.2 (−2.8, 0.4)	−0.6 (−2.2, 1.1)	.15	.50
	Week 26	11.8 (13.74)	10.0 (12.24)	9.8 (10.74)	2.1 (0.8)	0.5 (0.8)	0.4 (0.9)	−1.6 (−3.7, 0.6)	−1.7 (−3.9, 0.5)	.17	.14

Abbreviations: ADAS-Cog 11, 11-item Alzheimer's Disease Assessment Scale-Cognitive subscale; ADCS-ADL23, 23-item Alzheimer's Disease Cooperative Study Activities of Daily Living; CDR-SB, Clinical Dementia Rating scale Sum of Boxes; CI, confidence interval; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; SD, standard deviation; SE, standard error.

TABLE 3 Overview of treatment emergent adverse events

| Treatment emergent adverse events | Placebo $n = 188$ | Masupirdine | | | |
		50 mg $(n = 187)$	100 mg $(n = 181)$	Total $(N = 556)$	P value[a]
Number (%) of subjects with	n (%)	n (%)	n (%)	n (%)	
Any TEAE	108 (57.4)	101 (54.0)	107 (59.1)	316 (56.8)	.60
Any treatment related TEAE	21 (11.2)	29 (15.5)	38 (21.0)	88 (15.8)	.04
Any serious TEAE	12 (6.4)	10 (5.3)	14 (7.7)	36 (6.5)	.65
Any treatment related serious TEAE	0	1 (0.5)	1 (0.6)	2 (0.4)	.60
Any TEAE leading to study discontinuation	10 (5.3)	14 (7.5)	19 (10.5)	43 (7.7)	.17
Any TEAE with fatal outcome	1 (0.5)	3 (1.6)	2 (1.1)	6 (1.1)	.60

[a]χ^2 test.
Abbreviation: TEAE, treatment emergent adverse event.
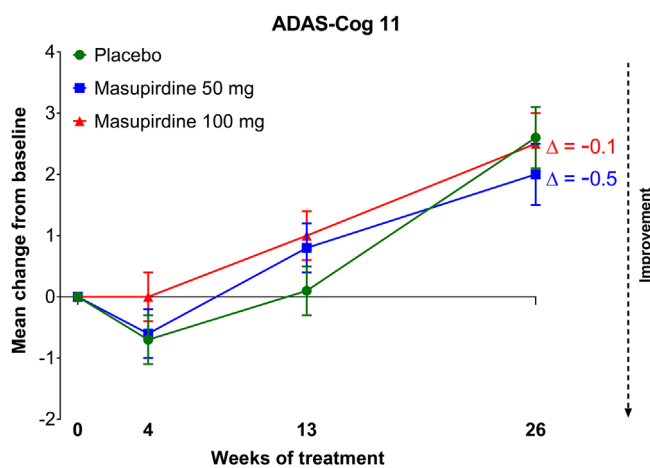
FIGURE 2 Adjusted mean change in ADAS-Cog 11 (mITT); error bars represent standard error of mean; ADAS-Cog 11, 11-item Alzheimer's Disease Assessment Scale, Cognitive Subscale; mITT, modified intent to treat population

(masupirdine 50 mg: 54.0%, masupirdine 100 mg: 59.1%, and placebo: 57.4%, respectively). A total of 153 TEAEs ascribed to the study treatment were reported in 88 patients (15.8%). Between treatment groups, a higher proportion of patients in the masupirdine 100 mg group had at least one TEAE attributed to the study treatment compared to masupirdine 50 mg group and placebo group (21.0% vs. 15.5% vs. 11.2%; $P = .04$). Between treatment groups, the proportion of patients who reported serious TEAEs was similar across treatment groups (10 patients [5.3%] in masupirdine 50 mg, 14 patients [7.7%] in masupirdine 100 mg, 12 patients [6.4%] in placebo). Overall, 43 patients (7.7%, 61 TEAEs) discontinued due to TEAEs. Between treatment groups, a similar proportion of patients reported TEAEs that led to discontinuation from the study: 14 patients (7.5%) in masupirdine 50 mg group, 19 patients (10.5%) in masupirdine 100 mg group, and 10 patients (5.3%) in placebo group. The frequently reported TEAEs leading to discontinuation from study treatment were agitation, mental status changes, alanine aminotransferase (ALT) increase, aspartate aminotransferase (AST) increase, diarrhea, fall, and atrial fibrillation. Overall,

6 patients (1.1%) had at least one TEAE that was fatal, masupirdine 50 mg group—3 patients (1.6%, 3 TEAEs); masupirdine 100 mg group—2 patients (1.1%, 3 TEAEs); placebo group—1 patient (0.5%, 1 TEAE). All deaths were considered by the investigators to be unrelated to the treatment. The most frequent TEAEs (occurring in more than 2% patients in any arm) were urinary tract infection, fall, diarrhea, headache, elevated liver enzyme, nasopharyngitis, nausea, upper respiratory tract infection, agitation, depression, cough, bronchitis, anxiety, back pain, dizziness, vomiting, dehydration, rash, decreased appetite, hypertension, confusional state, mental status changes, arthralgia, and bundle branch block (Table 4). The most frequent serious AEs (at least 1% in any arm) were pneumonia, sepsis, syncope, acute kidney injury and dehydration; of these serious events, dehydration was considered related to the study treatment (Table S2 in supporting information).

Most patients in the overall safety population had normal vital signs and electrocardiographic parameters at baseline, and there were no clinically relevant changes in vital signs throughout the study. The changes were similar across three treatment groups. Throughout the study, no meaningful increase in number of patients for different parameters of C-SSRS was observed across all treatment groups. In the overall safety population, no meaningful differences were observed between patients in the masupirdine treatment groups and in placebo group on hematology, biochemistry, endocrinology, and urinalysis parameters.

4 | DISCUSSION

This is the first published report for a double-blind, placebo controlled, POC study evaluating the potential benefits of adding masupirdine, a 5-HT$_6$ receptor antagonist, to stable doses of donepezil and memantine in patients with moderate AD.

Treatment with masupirdine showed non-significant differences from placebo in primary efficacy measure, change from baseline to week 26 in ADAS-Cog 11 scores. Secondary evaluations were consistent with primary efficacy results; numerical superiority was observed

TABLE 4 TEAEs reported in at least 2% of patients in either treatment group by preferred term

		Masupirdine			
Preferred term	**Placebo** **(n = 188)**	**50 mg** **(n = 187)**	**100 mg** **(n = 181)**	**Total** **(N = 556)**	**P value[a]**
Number (%) of subjects with	*n (%)*	*n (%)*	*n (%)*	*n (%)*	
Urinary tract infection	19 (10.1)	15 (8)	21 (11.6)	55 (9.9)	.51
Fall	11 (5.9)	11 (5.9)	10 (5.5)	32 (5.8)	.99
Diarrhea	3 (1.6)	12 (6.4)	9 (5)	24 (4.3)	.06
Headache	7 (3.7)	12 (6.4)	4 (2.2)	23 (4.1)	.12
Elevated liver enzymes	3 (1.6)	7 (3.7)	9 (5)	19 (3.4)	.19
Nasopharyngitis	6 (3.2)	4 (2.1)	5 (2.8)	15 (2.7)	.82
Nausea	4 (2.1)	4 (2.1)	6 (3.3)	14 (2.5)	.71
Upper respiratory tract infection	8 (4.3)	0	5 (2.8)	13 (2.3)	.02
Agitation	5 (2.7)	3 (1.6)	5 (2.8)	13 (2.3)	.72
Depression	6 (3.2)	5 (2.7)	2 (1.1)	13 (2.3)	.39
Cough	4 (2.1)	4 (2.1)	3 (1.7)	11 (2.0)	.93
Bronchitis	4 (2.1)	4 (2.1)	2 (1.1)	10 (1.8)	.69
Anxiety	7 (3.7)	1 (0.5)	2 (1.1)	10 (1.8)	.05
Back pain	3 (1.6)	3 (1.6)	4 (2.2)	10 (1.8)	.88
Dizziness	4 (2.1)	1 (0.5)	3 (1.7)	8 (1.4)	.41
Vomiting	2 (1.1)	4 (2.1)	2 (1.1)	8 (1.4)	.62
Dehydration	1 (0.5)	3 (1.6)	4 (2.2)	8 (1.4)	.39
Rash	2 (1.1)	5 (2.7)	1 (0.6)	8 (1.4)	.20
Decreased appetite	1 (0.5)	4 (2.1)	2 (1.1)	7 (1.3)	.37
Hypertension	3 (1.6)	0	4 (2.2)	7 (1.3)	.14
Confusional state	1 (0.5)	1 (0.5)	4 (2.2)	6 (1.1)	.20
Mental status changes	4 (2.1)	0	1 (0.6)	5 (0.9)	.08
Arthralgia	4 (2.1)	1 (0.5)	0	5 (0.9)	.08
Bundle branch block left	4 (2.1)	0	0	4 (0.7)	.02

[a]χ^2 test.
Abbreviation: TEAE, treatment emergent adverse event.

in the 12-item NPI scale for masupirdine over placebo treatment. The available exposure data of masupirdine and M1 of masupirdine from this study were consistent with the pharmacokinetic studies in preclinical species[25] and healthy humans.[36] Concentrations achieved in this study were equivalent or higher than the concentrations observed to be efficacious in the animal models of cognition. The observed trough plasma concentrations of masupirdine, M1 of masupirdine, donepezil, and memantine suggest that the patients were generally compliant to the study medication and background therapy, thus allowing an adequate test of the null hypothesis in the current study.

TEAEs reported in this study ranged from mild to severe in intensity and most resolved by the end of study. These observations are consistent with the data from the phase 1 safety and tolerability studies.[36] The TEAEs were comparable in all arms with a trend of higher incidence in the masupirdine arms. All TEAEs were manageable and there was no indication of additive toxicity when used in combination of donepezil and memantine.

The study participants were only from the United States, thus limiting the variability associated with the multi-country trials. Moreover, patients participating in this trial were on stable doses of memantine, which is approved only for the treatment of cognitive deficits associated with moderate–severe AD. Thus, the enrolled patients are representative of typical moderate AD dementia population. More than 50% of the population in each treatment arm was a carrier of *APOE ε*4 alleles, which is consistent with the distribution observed in studies of patients with known AD pathology[19] and indicates that the trial was successful in enrolling patients with AD.

5-HT$_6$ receptor antagonists like idalopirdine and intepirdine have failed to improve cognition in large phase 3 clinical studies.[19,21] However, there were differences in study designs between phase 2 and phase 3 studies of these agents. Both idalopirdine and intepirdine were studied on a background treatment of cholinesterase inhibitors and recruited patients with mild to moderate AD, whereas masupirdine was studied on a background treatment of donepezil and memantine

in patients with moderate AD. Thus, the outcome of the masupirdine trial may not be generalized to the negative trials associated with other 5-HT$_6$ receptor antagonists. Masupirdine demonstrated robust efficacy in animal models of cognition when tested alone and in combination with donepezil or donepezil plus memantine;[25,26] however, the procognitive effects did not translate to AD patients. 5-HT$_6$ receptor antagonists including masupirdine enhance glutamatergic and cholinergic neurotransmission in the brain. Donepezil mediates its effects on cognition by enhancing cholinergic neurotransmission,[37] which is complementary to the mechanisms of 5-HT$_6$ receptor antagonists. Memantine enhances cognition through its inhibitory effects on the glutamatergic neurotransmission.[38] Donepezil and memantine act through different neurotransmitter systems and show larger improvements in cognition than either treatment alone.[39,40] Effects of masupirdine on the glutamatergic system appear to be counter to those of memantine. Thus, it may be that the opposing pharmacological effects of masupirdine and memantine nullified the effects of masupirdine in AD patients.

Although statistical significance was not observed at the end of 26 weeks treatment, numerical differences were observed on the ADAS-Cog 11 scores between the placebo and masupirdine 50 mg treatment group. A trend toward less decline was observed at week 26. Thus, a longer trial duration may have provided additional information on the potential effects of masupirdine on slowing or delaying cognitive decline. An extended duration of treatment may be necessary for symptomatic agents to show treatment benefits when evaluated on background therapy of multiple agents used as standard-of-care.[5,41] Few symptomatic interventional trials have considered treatment duration beyond 6 months to understand potential long-term treatment effects (e.g., NCT04520412). Characterization of the AD patients based on biomarkers, controlling the population heterogeneity, and identification of a target engagement biomarker to confirm the relevant biologic effect may help in understanding the failures associated with 5-HT$_6$ receptor antagonists. Moreover, most of the studies for symptomatic treatment of cognitive disorders have been limited to ADAS-Cog as the outcome instrument. Other outcomes may be more suitable to characterizing the clinical effects.

A possible limitation of this trial is that the patients' disease was not characterized based on biomarker criteria confirming the AD diagnosis.[42] Previous studies suggest that 70% to 90% of patients clinically diagnosed by experts as AD dementia display AD neuropathologic changes at autopsy or have abnormal amyloid or cerebrospinal fluid amyloid beta protein 42.[43–46] Fifty-four percent to 65% of the trial participants were carriers of the *APOE* gene and have a high probability of amyloid-related disease. The majority of participants included in this trial likely had AD neuropathologic changes.

Cognitive and neuropsychiatric symptoms adversely affect the quality of life of dementia patients and their caregivers. Agents that improve the symptoms may benefit the patient's quality of life (improvement in cognition), caregiver burden, and socioeconomic burden (improvement in neuropsychiatric symptoms). Numerical superiority was observed in the NPI-12 scale for masupirdine over placebo treatment. This observation may suggest a beneficial effect of masupirdine on behavioral symptoms, a hypothesis consistent with mediation of behavior through serotonergic systems[47] and blockade of 5-HT$_6$ receptors.[23,48] This hypothesis-generating observation may warrant exploration in additional trials. Masupirdine is currently being studied for the management of agitation in patients with dementia of the AD type.

CONFLICTS 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. Dr. Alireza Atri has received honoraria for consulting; participated in independent data safety monitoring boards; provided educational lectures, programs, and materials; or served on advisory boards for AbbVie, Acadia, Allergan, the Alzheimer's Association, Axovant, AZ Therapies, Biogen, Eisai, Grifols, Harvard Medical School Graduate Continuing Education, JOMDD, Lundbeck, Merck, Roche/Genentech, Novo Nordisk, Qynapse, Sunovion, Suven, and Synexus. He receives royalties from Oxford University Press for a medical book on dementia. He receives institutional grant/contract funding from NIA/NIH 1P30AG072980, AZ DHS CTR040636, Washington University St. Louis, and Gates Ventures; and his institution receives funding for multiple clinical trial grants, contracts and projects from consortia, foundations, and companies for which he serves as site-PI. Drs. Atri and Cummings did not receive compensation for developing this manuscript. John Ieni has provided consultation services for clinical development to Suven Life Sciences and Oligomerix, Inc. Ramakrishna Nirogi, Vinod Kumar Goyal, Jyothsna Ravula, Satish Jetta, Anil Shinde, Pradeep Jayarajan, Vijay Benade, Veera Raghava Chowdary Palacharla, Dhanunjay Kumar Dogiparti, Venkat Jasti are full-time employees of Suven Life Sciences Ltd.

AUTHOR CONTRIBUTIONS

Jeffrey Cummings was the global coordinating investigator. Jeffrey Cummings, Ramakrishna Nirogi, John Ieni, and Venkat Jasti were involved in the study design. Ramakrishna Nirogi, John Ieni, Venkat Jasti, Vinod Kumar Goyal, Jyothsna Ravula, Satish Jetta, Anil Shinde, Pradeep Jayarajan, Vijay Benade, Veera Raghava Chowdary Palacharla,

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SUPPORTING INFORMATION

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

APPENDIX
Inclusion criteria

1. Male or female subjects aged between 50 and 85 years inclusive at screening.

2. Had a diagnosis of probable Alzheimer's disease (AD) based on the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria at least 1 year prior to the screening visit.

3. Had a score between 12 and 20 inclusive on the Mini-Mental State Examination (MMSE) at the screening and baseline visits.

4. Had a magnetic resonance imaging (MRI) or computed tomography (CT) scan performed within 12 months prior to screening with findings consistent with the diagnosis of dementia due to AD without any other clinically significant comorbid pathologies.

5. Had a Modified Hachinski Ischemic Scale (MHIS) score of 4 or less.

6. Must have been receiving treatment with stable doses of donepezil HCl (10 mg qd), either as 10 mg donepezil HCl only or part of the combination therapy, Namzaric (28 mg memantine HCl extended-release + 10 mg donepezil HClqd) for at least 3 months prior to screening visit. Subjects were likely to have been maintained on their current dose of donepezil HCl or Namzaric for the duration of the study.

7. Must have been receiving treatment with stable doses of memantine HCl (10 mg bid) or Namenda XR (28 mg memantine HCl extended-release qd) or as part of the combination therapy Namzaric (28 mg memantine HCl extended-release + 10 mg donepezil HClqd) for at least 3 months prior to the screening visit. Subjects were likely to have been maintained on their current dose of memantine HCl, Namenda XR, or Namzaric for the duration of the study.

8. Availability of a person (caregiver) who in the Investigator's judgment had frequent and sufficient contact with the subject, such that this person was qualified, willing, and able to provide accurate information regarding the subject's cognitive and functional abilities and would accompany the subject to study visits. The caregiver should have had face-to-face contact with the subject for a minimum of approximately 12 hours per week spread over 3 to 5 days during the week (for example: 3 hours per day for 4 days a week, or 4 hours per day for 3 days a week).

9. Must have been living in the community or an assisted living facility. No subjects currently residing in a nursing home or anticipated to move into a nursing home during the study were allowed entry into the study.

10. Must have been ambulatory or ambulatory aided (use of cane or walker).

11. Must have had vision and hearing (corrected) ability sufficient to comply with the testing procedures.

12. Both subject and caregiver must have been able to read and understand English or Spanish and had appropriate literacy skills to ensure compliance with the testing and study visit procedures.

13. Was not pregnant or planning to become pregnant during the study. Women of childbearing potential must have had a negative pregnancy test at screening and must have been using oral or injectable contraception (non-childbearing potential was defined as post-menopausal for at least 1 year or surgical sterilization or hysterectomy at least 3 months before study start).

14. Subject (or subject's legally acceptable representative) and caregiver must have signed an Informed Consent to participate in the study.

Exclusion criteria

1. Had a diagnosis of dementia due to other causes, including vascular disease, Parkinson's disease, Lewy body disease, acquired immune deficiency syndrome (AIDS), Creutzfeldt-Jakob disease, fronto-temporal dementia, Huntington's disease, major head trauma, primary or secondary cerebral neoplasia, or other non-Alzheimer disorders. Subjects with major strokes (large cortical/subcortical or in brain areas related to cognition), based on medical history, physical exam or MRI, were excluded.

2. Had a diagnosis of schizophrenia, bipolar disorder or current major depressive disorder (MDD) or subjects whose Cornell Scale for Depression in Dementia scores were suggestive of probable depression (typically scores ≥12). Subjects with history of MDD who were being treated and controlled on medication for at least 6 months may have been enrolled. Subjects taking low doses of antipsychotics for the treatment of sleep disturbances or for agitation or aggression, for which the dose had been stable for at least 1 month and not anticipated to change during the course of the study, were not to be enrolled.

3. Was taking cholinesterase inhibitors other than donepezil HCl, including rivastigmine and galantamine. Subjects who were taking 5 mg of donepezil HCl or taking 23 mg daily doses of donepezil HCl or subjects taking 10 mg daily doses of donepezil HCl for whom the physician contemplated increasing the dose to 23 mg during the conduct of the study, were not to be enrolled.

4. Was taking doses of memantine HCl other than 10 mg bid, Namenda XR (28 mg memantine HCl extended-release qd), or Namzaric (28 mg memantine HCl extended-release + 10 mg donepezil HCl qd).

5. Had uncontrolled cardiac disease or hypertension. This included subjects with history of myocardial infarction within 6 months of the screening visit; congestive heart failure; history of unstable angina within 6 months of the screening visit; clinically significant ECG at the screening visit; and subjects whose hypertension was not controlled on medication for at least 3 months prior to the screening visit.

6. Had a history or current evidence of long QT syndrome, Fridericia's formula corrected QT (QTcF) interval ≥470 ms (for male subjects) or ≥480 ms

(for female subjects), or torsades de pointes, as determined by an ECG read by a central ECG vendor.

7. Had bradycardia (< 50 bpm) or tachycardia (> 100 bpm) on the ECG at screening visit.

8. Had uncontrolled Type 1 or Type 2 diabetes (glycated hemoglobin [HbA1c] above 6.5%). A subject with HbA1c levels up to 7.5% could be enrolled if the Investigator believed the subject's diabetes was under control.

9. Had cancer or a malignant tumor, or had been treated for an active malignancy within the past 5 years. Subjects with stable untreated prostate cancer, localized squamous cell cancer, or basal cell cancer were allowed.

10. Had untreated thyroid disorder. Subjects who were considered euthyroid on medication with normal free thyroxine (T4) were allowed.

11. Had a history of seizure disorder.

12. Had clinically significant renal or hepatic impairment.

13. Had any clinically significant abnormal laboratory values. Subjects with liver function tests (aspartate aminotransferase [AST] or alanine aminotransferase [ALT]) greater than twice the upper limit of normal were excluded.

14. Was treated, or likely to require treatment, during the study with any medication prohibited by the study protocol.

15. Had abnormal vitamin B-12 levels that were lower than normal limits and remained low on repeat testing. Subjects taking vitamin B-12 supplements who were within normal limits or above at screening or within normal limits or above at repeat testing were allowed.

16. Had participated in a previous clinical study within 26 weeks of the screening visit, or had been previously treated with the investigational product, SUVN-502.

17. Subject (or caregiver) was deemed otherwise ineligible for participation in the study in the Investigator's judgment

18. Was at imminent risk of self-harm, based on clinical interview and responses on the C-SSRS, or of harm to others in the opinion of the Investigator. Subjects must have been excluded if they reported suicidal ideation with intent, with or without a plan or method (e.g., positive response to Items 4 or 5 in assessment of suicidal ideation on the C-SSRS) in the past 2 months, or suicidal behavior in the past 6 months.