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RESEARCH ARTICLE

Effect of Age, Cognitive Impairment Severity, and Duration of Disease on Efficacy of Masupirdine in Moderate Alzheimer's Disease Patients: A Post Hoc Analysis of a Phase-2 Randomized Placebo Controlled Study Results

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ABSTRACT

Background:
Alzheimer's disease (AD) is an age-related progressive neurodegenerative brain disorder with cognitive symptoms as a hallmark phenotype of the disease. Masupirdine, a pure serotonin 6 (5-HT_6) receptor antagonist is being developed for the treatment of cognitive deficits in AD. The objective of the current study is the post hoc analysis of a multicenter, randomized, double-blind, parallel group, 26-week, placebo-controlled phase-2 study (NCT02580305) that evaluated the effects of masupirdine on cognition in patients with moderate AD.

Methods: Masupirdine phase 2 study included AD patients of 50 to 85 years age, mini-mental state examination (MMSE) score of 12 to 20 and diagnosis of probable AD at least 1 year prior to the screening visit. The impact of age, cognitive impairment severity, and duration of disease since diagnosis on efficacy of masupirdine as assessed by 11-item version of the Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-Cog 11) was evaluated. Treatment effects were assessed by Cohen's *d* effect size.

Results: Cohen's *d* effect size for change in ADAS-Cog 11 scores from baseline to week 26 ranged between ~0.2 and 0.4 for the subgroup of population with age ≤ 70 years, MMSE range of 18 to 20, and duration of disease over 4 years (since diagnosis).

Conclusions: Considering the linear relationship between age and cognitive decline, masupirdine effects across the subgroups could be attributed to "slowing of cognitive decline". The study provides important findings for design of future clinical trials. Further research is warranted to confirm the potential beneficial effects of masupirdine on cognition in AD patients.

Keywords: Masupirdine; SUVN-502; 5-HT_6 receptor; Alzheimer's disease; Age; Cognitive impairment severity; Disease duration.

1.0 Introduction

Alzheimer's disease (AD) is an age-related non-reversible progressive neurodegenerative brain disorder. Cognitive symptoms are one of the hallmark phenotype of the disease. Donepezil, rivastigmine, galantamine (cholinesterase inhibitors), and memantine (N-methyl-D-aspartic acid receptor blocker) have been approved to manage cognitive symptoms of the AD.[1] Aducanumab a recently approved amyloid beta-directed antibody reduces the amyloid beta plaques in AD patients and thereby slows clinical decline.[1] Currently approved treatments show modest efficacy on the cognitive symptoms and hence new treatments are desperately needed. However, the new drug development for AD has been challenging because of high failure rates.

Although several clinical trials have been conducted to evaluate the efficacy of investigational Alzheimer's therapeutics, 99% of these trials have not been successful. Several factors are reported to influence the outcomes of AD clinical trials which include but not limited to host factors, population factors, AD diagnosis, clinical trial instrumentation and cultural effects.[2,3] Many of the studies suffered due to confounders such as genetic and phenotypic heterogeneity, population stratification or inaccurate phenotyping. Confounding is generally a "mixing of effects" wherein the effects of the treatment under investigation on a given outcome are mixed with the effects of an additional factor (or set of factors) resulting in a distortion of the true relationship. These factors may mask an actual association or, falsely demonstrate an apparent association between the treatment and outcome when in fact no real association between them exists.[4]

As age is one of the biggest risk factors for Alzheimer's disease, it is often a very difficult parameter that might affect the outcome of the trial. Older adults face a combination of obstacles, including comorbidities, ageism, communication issues (e.g., hearing difficulties that interfere with telephone interviews and impaired vision that affects written surveys) and physical immobility that constrain transportation options.[5]

Similar to the age of the study participants, baseline disease severity is another important confounding factor especially for the clinical trials evaluating drug effects for neurodegenerative disorders. Based on the post-hoc analyses, Maher-Edwards G (2010) reported that the subject groups with a baseline MMSE >18 showed improvements from baseline in ADAS-Cog scale throughout the study with different doses of SB-742457.[6] In contrast, subjects with baseline MMSE ≤ 18 showed worsening or little change with this treatment in the same study. Severity of disease at baseline could be an important factor affecting the outcome of the clinical trials.

Confounding factors may not be limited to age and disease severity. It is important to investigate the factors that played a role in the trial outcome and address these confounders in future trials. Such exercise may open up new avenues for the design of studies evaluating investigational therapeutics.

Masupirdine is a potent and selective antagonist towards the 5-HT_6 receptors. Masupirdine showed procognitive effects in various animal models.[7,8,9] Based on the results from non-clinical studies, masupirdine was evaluated for its effects on cognition in patients with moderate AD. The phase-2 study did not meet its primary endpoint.[10] Considering the influence of various factors on trial outcome, we explored the effect of patients' age, cognitive impairment severity, and disease duration since AD diagnosis on the effects of masupirdine on cognition in the current post hoc analysis.

2.0 Methods

The primary study evaluated the potential effects of masupirdine on cognition in a double-blind, multicenter, randomized, parallel group, placebo controlled phase-2 trial in patients with moderate AD (NCT02580305) which recruited patients during Nov-2015 to Oct-2018. Detailed study design and methods were previously reported.[10]

The key eligibility criteria were ambulatory or ambulatory-aided male or female patients aged between 50 and 85 years (both inclusive); diagnosis of probable AD based on the national institute of neurological and communicative diseases and stroke/Alzheimer's disease and related disorders association criteria[11] with magnetic resonance imaging or computed tomography scan findings consistent with the dementia due to probable AD at least 1 year prior to the screening visit; patients should have mild to moderate cognitive deficits with Mini Mental Status Examination (MMSE) scores of 12 to 20, and treated with stable doses of donepezil and memantine for at least 3 months prior to the screening visit.

The study was planned to recruit total of 537 subjects randomized into one of three treatment groups, masupirdine 50 mg, masupirdine 100 mg or placebo. This sample size was based on

minimum number required to achieve at least 80% power to detect a 2-point drug-placebo difference on the ADAS-Cog with a standard deviation of 6, assuming a two-sided 5% significance level and a drop-out rate of 20% or less.

Eligible patients were randomized in the ratio of 1:1:1 to one of three treatments. The trial design included a screening period of 2 to 4-weeks, treatment period of 26 weeks, and a 4-week single blind placebo washout period. Each study participants provided written consent and the trial was approved by local or central ethics committees. The trial was conducted according to the protocol and in accordance with the declaration of Helsinki and international conference on harmonization good clinical practice guidelines.

The change in the Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-Cog 11)[12] after 26 weeks of treatment was the primary outcome measure. The treatment duration of 26 weeks was chosen based on the similar contemporary studies evaluating treatment effects of symptomatic agents in AD.[6, 13]

As the outcome of post hoc analysis is presented in the current manuscript, no prospective sample analysis was done. However number of patients was observed to be distributed equally amongst the different treatment arms (Table 1).

2.1 Post Hoc Analyses

The impact of age (≤70 years Vs >70 years), cognitive impairment severity (MMSE 12 to 17 Vs 18 to 20) and duration of disease since AD diagnosis (≤4 years Vs >4 years) on the efficacy of masupirdine was assessed using the Week 26 data of the ADAS-Cog 11 scale. Baseline characteristics were compared using Kruskal-Wallis test or chi-squared test. Cohen's *d* effect size was calculated for the studied subgroups.[14]

3.0 Results

3.1 Study Population

A total of 564 patients were enrolled for the primary study and the modified intent to treat (mITT) population (543 patients) is included in the current analysis. The placebo arm had 183 patients, whereas masupirdine 50 mg and masupirdine 100 mg treatment arms had 184 and 176 patients, respectively. The baseline ADAS-Cog 11 scores ranged between 27.7 and 28.4 (Table 1).

3.2 Effect of Masupirdine Based on Age

In a subgroup of population with age ≤ 70 years, the Cohen's *d* effect size for change in ADAS-Cog 11 scores from baseline was ~0.2 at Week 26. However, no notable effect of masupirdine was observed in the subgroup of patients with age over 70 years (Cohen's *d* effect size ~ 0.03) (Fig 1). No notable differences were observed in the baseline ADAS-Cog 11 scores between the treatment arms (Table 1).

Table 1: Baseline characteristics

Parameters	Placebo	Masupirdine 50 mg	Masupirdine 100 mg	p value^
Age (years), mean (±SD), n	72.9 (7.23), 183	73.4 (8.08), 184	74.4 (6.97), 176	0.15
Female, n (%)	106 (57.92)	95 (51.63)	96 (54.55)	0.48
MMSE, mean (±SD), n	16.53 (2.48), 183	16.86 (2.21), 184	16.99 (2.47), 176	0.14
ADAS-Cog 11, mean (±SD), n	28.41 (8.16), 183	27.72 (6.92), 184	27.89 (8.62), 176	0.49
Age subgroup, ≤70 years				
Age (years), mean (±SD), n	64.8 (4.47), 64	64.0 (5.32), 61	64.4 (4.24), 42	0.66
Female, n (%)	41 (64.06)	36 (59.02)	26 (61.90)	0.84
MMSE, mean (±SD), n	16.39 (2.35), 64	16.49 (2.13), 61	17.34 (2.37), 42	0.06
ADAS-Cog 11, mean (±SD), n	29.47 (9.54), 64	29.05 (7.04), 61	26.71 (9.70), 42	0.19
Age subgroup, >70 years				
Age (years), mean (±SD), n	77.3 (3.95), 119	78.1 (4.14), 123	77.5 (4.09), 134	0.25
Female, n (%)	65 (54.62)	59 (47.97)	70 (52.24)	0.58
MMSE, mean (±SD), n	16.71 (2.47), 119	17.05 (2.24), 123	16.85 (2.47), 134	0.62
ADAS-Cog 11, mean (±SD), n	27.84 (7.30), 119	27.07 (6.79), 123	28.26 (8.26), 134	0.62
MMSE subgroup, 12 to 17				
Age (years), mean (±SD), n	72.8 (7.85), 109	73.2 (8.38), 106	74.4 (6.65), 88	0.43
Female, n (%)	58 (53.21)	55 (51.89)	47 (53.41)	0.97
MMSE, mean (±SD), n	14.84 (1.63), 109	15.33 (1.54), 106	15.00 (1.86), 88	0.10
ADAS-Cog 11, mean (±SD), n	31.74 (7.74), 109	29.63 (7.04), 106	32.02 (8.52), 88	0.06

Parameters	Placebo	Masupirdine 50 mg	Masupirdine 100 mg	p value^
MMSE subgroup, 18 to 20				
Age (years), mean (±SD), n	73.1 (6.27), 74	73.7 (7.71), 78	74.4 (7.32), 88	0.37
Female, n (%)	48 (64.86)	40 (51.28)	49 (55.68)	0.23
MMSE, mean (±SD), n	19.02 (0.94), 74	18.95 (0.87), 78	18.99 (0.88), 88	0.92
ADAS-Cog 11, mean (±SD), n	23.50 (6.04), 74	25.13 (5.87), 78	23.76 (6.52), 88	0.18
AD duration since diagnosis, ≤4 years				
Age (years), mean (±SD), n	72 (7.13), 118	73 (8.76), 125	74 (7.19), 127	0.33
Female, n (%)	66 (55.93)	64 (51.20)	69 (54.33)	0.75
MMSE, mean (±SD), n	16.65 (2.45), 118	16.94 (2.10), 125	16.91 (2.56), 127	0.60
ADAS-Cog 11, mean (±SD), n	27.73 (7.88), 118	27.40 (6.89), 125	27.31 (7.74), 127	0.69
AD duration since diagnosis, >4 years				
Age (years), mean (±SD), n	74 (7.40), 65	75 (6.25), 59	76 (6.08), 49	0.29
Female, n (%)	40 (61.54)	31 (52.54)	27 (55.10)	0.58
MMSE, mean (±SD), n	16.31 (2.53), 65	16.71 (2.44), 59	17.20 (2.24), 49	0.13
ADAS-Cog 11, mean (±SD), n	29.65 (8.58), 65	28.41 (6.99), 59	29.39 (10.52), 49	0.81

AD - Alzheimer's disease; MMSE - mini mental state examination; ADAS-Cog 11 - 11-item Alzheimer's disease Assessment scale-cognitive subscale. ^ - Kruskal-Wallis test or χ^2 test

3.3 Effect of Masupirdine Based on Severity of Cognitive Impairment

Cognitive impairment was categorized based on the baseline MMSE scores. In the subgroup of population with MMSE range of 18 to 20, the Cohen's *d* effect size for change in ADAS-Cog 11 scores from baseline was ~0.2 and 0.4 at Week 26 for the masupirdine 50 mg and 100 mg treatment arms, respectively. The effects were not prominent in the subgroup of patients with MMSE in the range of 12 to 17 (Cohen's *d* effect size ~ 0.02) (Fig 1). There were no notable differences in the baseline ADAS-Cog 11 scores between the treatment arms of the subgroups studied (Table 1).

3.4 Effect of Masupirdine Based on Duration of Disease Since Diagnosis

The Cohen's *d* effect size for change in ADAS-Cog 11 scores from baseline was ~0.2 and 0.4 at Week 26 for the masupirdine 50 mg and 100 mg treatment arms, respectively for the subgroup of patients with duration of disease since diagnosis over 4 years. No prominent effects of masupirdine was observed in the subgroup of population with duration of disease lesser than 4 years (Cohen's *d* effect size ~0.01-0.03) (Fig 1). There were no notable differences in the baseline ADAS-Cog 11 scores between the treatment arms of the subgroups studied (Table 1).

3.5 Safety and Tolerability

Safety and tolerability findings of the study evaluating masupirdine in AD patients (NCT02580305) have been reported earlier.[10] The observations from the current study are in agreement with the earlier report in AD patients.

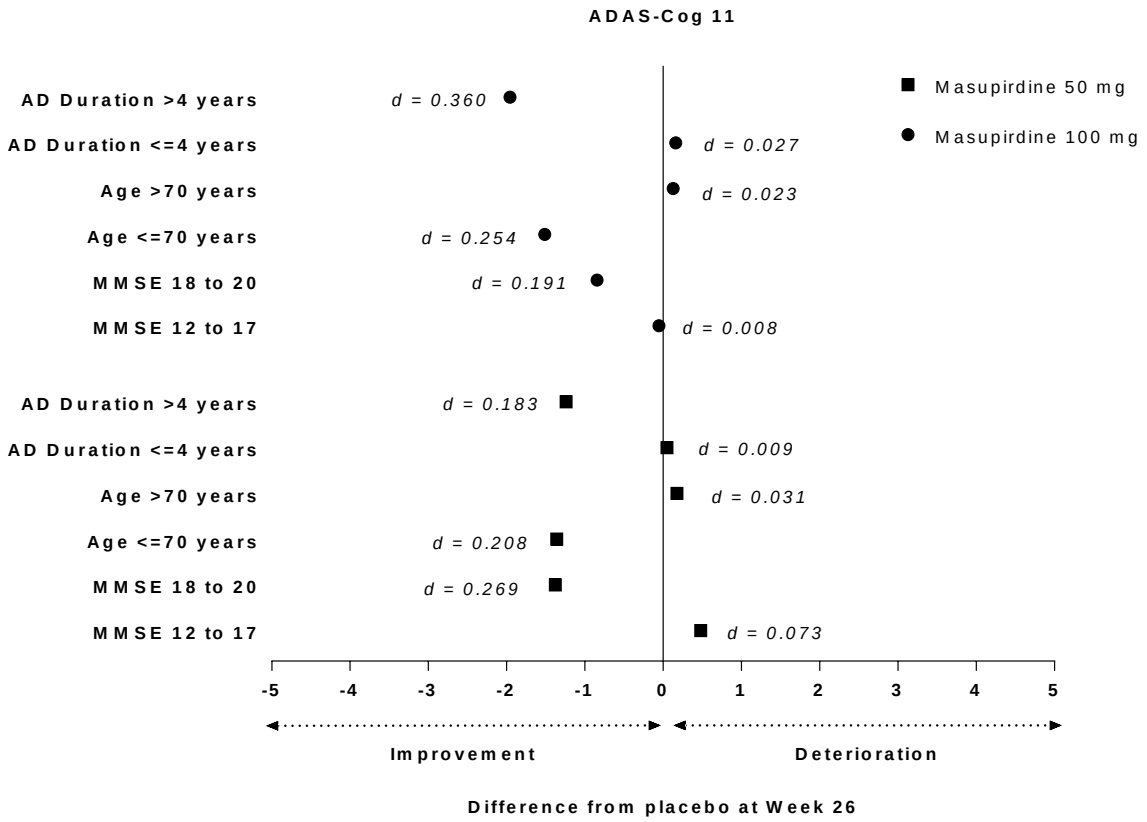
4.0 Discussion

The current investigation involved subgroup analyses of the masupirdine phase-2 study with an objective to understand the variables that might have affected the study outcome. Post hoc subgroup analyses for the current investigation were focused on age, severity of cognitive impairment and duration of disease since diagnosis.

Though increasing age does not cause AD, but it is considered as one of the most important risk factors for this neurodegenerative disorder. The risk of AD increases with age.[15-18] Hence, age was considered as a factor for subgroup analysis.

Literature evidences also suggest that the effect of pharmacological interventions can vary with the levels of cognitive impairment in AD. Donepezil (cholinesterase inhibitor) is effective in mild, moderate and severe cognitive stages of AD.[19] However, the other cholinesterase inhibitor galantamine is approved only for the treatment of mild to moderate cognitive deficits. The effects of galantamine in severe form of cognitive deficits are unclear.[20] In similar lines, cholinesterase inhibitor rivastigmine is approved only for the treatment of mild to moderately severe cognitive deficits.[21] The amyloid beta-directed antibody aducanumab is indicated for the treatment of mild cognitive impairment.[22,23] These observations indicate that the severity of cognitive deficits is an important variable influencing the efficacy of medicament, irrespective of the mechanism of action. Considering the above, the stage of cognitive impairment was considered another factor for subgroup analysis. In the current study, MMSE scores of about 40% subjects were in the range of 18 to 20 which can be considered as mild AD. considered as mild AD.

Figure 1: Effect of masupirdine on ADAS-Cog 11 based on age, MMSE and AD duration since diagnosis



Although, some of the clinicians/ researchers define mild AD with MMSE scores more than 20, there is no fixed criteria below which one can be considered as moderate. In one study, the researchers considered MMSE score of 20 and above as mild and MMSE score of 19 and below as moderate. 24 The current study included subjects with MMSE scores of 12 to 20 and we considered subject having MMSE scores 18 to 20 as mild AD subjects for this post hoc analysis.

Scientific reports suggest differences observed in terms of disease between the longer and shorter AD duration population.[25] The shorter AD duration is associated with the sporadic form of the disease whereas the longer AD duration is associated with the familial forms. Considering the above, we also evaluated the efficacy of masupirdine in the subgroups based on the duration of disease since diagnosis.

Effect sizes can often be informative in small population analyses.[26] The effect size of 0.2 is considered as a minimal efficacy signal.[14] Therefore, we considered effect size of ~0.2 as a positive signal/trend for these post hoc observations. Since these post hoc observations are not powered for statistical significance, a positive trend in efficacy outcome can be considered as important signal that can be proved in a larger trial. The effect size of ~0.2 and above were achieved in the subgroup of population with age ≤ 70 years or MMSE range of 18 to 20 or duration of disease since diagnosis over 4 years. These observations suggest treatment effect heterogeneity.

Age factor may be important for cognitive dysfunction considering the association between the fall in MMSE score with increasing age.[27] In addition increase in the amyloid burden with age may also account for the association between cognitive deficits and age. [28,29] Although there is association between age and cognitive decline, the rate of cognitive decline is higher for the lower age group.[30, 31] Therefore, the observations of beneficial effects with masupirdine in the subgroup of age ≤ 70 years, and MMSE range of 18 to 20 suggest that masupirdine may show beneficial effects on cognition by slowing cognitive decline. Masupirdine being a 5-HT_6 receptor antagonist produces its beneficial effects possibly through the modulation of neurotransmitters like acetylcholine and the severity of the disease might affect the neurotransmitter modulations. Results of present

subgroup analysis indicating MMSE scores at baseline had effects on the ADAS-Cog outcomes were also supported by similar exercises of various other clinical trials. For example, SB-742457 showed mean improvements from baseline in ADAS-Cog outcomes in subjects with baseline MMSE >18, whereas worsening or little change from baseline in subjects with MMSE ≤18.[6] This further supports the hypothesis that disease severity at baseline is an important confounding factor in clinical trials.

The beneficial effects of masupirdine were also observed in the subgroup of population with duration of disease since diagnosis >4 years. However, considering the observation of beneficial effects of masupirdine subgroup of age ≤ 70 years, and MMSE range of 18 to 20; one may expect the beneficial effect of masupirdine in the subgroup of population with duration of disease since diagnosis ≤4 years. Literature evidences suggest differences in the disease characteristics based on the disease duration.[25] The rate of cognitive decline for familial AD is higher compared to sporadic forms.[32] The subgroup of population with duration of disease since diagnosis >4 years can be a representation of familial AD. Thus, the observed effect with masupirdine in subgroup of population with duration of disease since diagnosis >4 years may be due to slowing of cognitive decline. Overall, masupirdine effects across the subgroups could be attributed to "slowing of cognitive decline"

5.0 Conclusion

Subgroup analysis is a hypothesis generating exercise and it can also serve as a guide for personalized treatment selections i.e., to identify the patient population who may have the greatest potential to respond to investigational drugs. The present study outcome gives an opportunity to formulate a developmental plan for designing clinical trials in AD and also provides important information on the potential of masupirdine as a treatment option for cognitive disorders in AD. The limitation of the current study is that the study patients were not recruited prospectively and the hypotheses generated must be confirmed in a randomized clinical trial. Therefore, further studies will be worthwhile in providing a deeper understanding on the potential beneficial effects of masupirdine on cognition in AD patients.

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7.0 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.

8.0 Declaration of Interests

Ramakrishna Nirogi, Vijay Benade, Ramkumar Subramanian, Satish Jetta, Anil Shinde, Vinod Kumar Goyal, Santosh Kumar Pandey, Pradeep Jayarajan, Venkat Jasti are fulltime employees of Suven Life Sciences Ltd.

9.0 References

1. NIH National Institute on Aging (NIA). How Is Alzheimer's Disease Treated? Accessed May 11, 2022. https://www.nia.nih.gov/health/how-alzheimers-disease-treated.
2. Cummings J, Reynders R, Zhong K. Globalization of Alzheimer's disease clinical trials. *Alzheimers Res Ther*. 2011; 3(4):24.
3. Liyanage SI, Santos C, Weaver DF. The hidden variables problem in Alzheimer's disease clinical trial design. *Alzheimers Dement (N Y)*. 2018; 4: 628-635.
4. Skelly AC, Dettori JR, Brodt ED. Assessing bias: the importance of considering confounding. *Evid Based Spine Care J*. 2012; 3(1): 9-12.
5. Herrera AP, Snipes SA, King DW, et al. Disparate inclusion of older adults in clinical trials: priorities and opportunities for policy and practice change. *Am J Public Health*. 2010; 100 (Suppl 1):S105-S112.
6. Maher-Edwards G, Zvartau-Hind M, Hunter AJ, et al. Double-blind, controlled phase II study of a 5-HT6 receptor antagonist, SB-742457, in Alzheimer's disease. *Curr Alzheimer Res*. 2010; 7(5): 374-385.
7. Nirogi R, Abraham R, Benade V, et al. SUVN-502, a novel, potent, pure, and orally active 5-HT6 receptor antagonist: pharmacological, behavioral, and neurochemical characterization. *Behav Pharmacol*. 2019; 30(1):16-35.
8. Nirogi R, Mudigonda K, Bhyrapuneni G, et al. safety, tolerability and pharmacokinetics of the serotonin 5-HT6 receptor antagonist, SUVN-502, in healthy young adults and elderly subjects. *Clin Drug Investig*. 2018; 38(5): 401-415.
9. Nirogi R, Shinde A, Kambhampati RS, et al. Discovery and development of 1-[(2-Bromophenyl)sulfonyl]-5-methoxy-3-[(4-methyl-1-piperazinyl) methyl] -1H-indole dimesylate monohydrate (SUVN-502): A novel, potent, selective and orally active serotonin 6 (5-HT6) receptor antagonist for potential treatment of Alzheimer's disease. *J Med Chem*. 2017; 60(5): 1843-1859.
10. Nirogi R, Ieni J, Goyal VK, et al. Effect of masupirdine (SUVN-502) on cognition in patients with moderate Alzheimer's disease: A randomized, double-blind, phase 2, proof-of-concept study. *Alzheimers Dement (N Y)*. 2022; 8(1): e12307. doi: 10.1002/trc2.12307.
11. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDSADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*.1984; 34(7): 939-944.
12. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry*. 1984; 141(11):1356-1364.
13. Atri A, Frölich L, Ballard C, et al. Effect of Idalopirdine as adjunct to cholinesterase inhibitors on change in cognition in patients with Alzheimer disease: three randomized clinical trials. *JAMA*. 2018 Jan 9;319(2):130-142.
14. Cohen, J. Statistical Power Analysis for the Behavioral Sciences. 2nd ed. New York: Lawrence Erlbaum Associates; 1988.
15. Guerreiro R, Bras J. The age factor in Alzheimer's disease. *Genome Med*. 2015; 7: 106.
16. Herrup K. Reimagining Alzheimer's disease--an age-based hypothesis. *J Neurosci*. 2010; 30(50): 16755-16762.
17. Terry AV Jr, Buccafusco JJ. The cholinergic hypothesis of age and Alzheimer's disease-related cognitive deficits: recent challenges and their implications for novel drug development. *J Pharmacol Exp Ther*. 2003; 306(3): 821-827.
18. Mesulam MM, Asuncion Morán M. Cholinesterases within neurofibrillary tangles related to age and Alzheimer's disease. *Ann Neurol*. 1987; 22(2): 223-228.
19. Kumar A, Gupta V, Sharma S. Donepezil. In: StatPearls. Treasure Island (FL): StatPearls Publishing; December 22, 2021.
20. Burns A, Bernabei R, Bullock R, et al. Safety and efficacy of galantamine (Reminyl) in severe Alzheimer's disease (the SERAD study): a randomised, placebo-controlled, double-blind trial. *Lancet Neurol*. 2009; 8(1): 39-47.
21. Khoury R, Rajamanickam J, Grossberg GT. An update on the safety of current therapies for Alzheimer's disease: focus on rivastigmine. *Ther Adv Drug Saf*. 2018; 9(3):171-178.
22. Budd-Haeberlein S, Von Hein C, Tian Y, et al. EMERGE and ENGAGE topline results: two phase 3 studies to evaluate aducanumab in patients with early Alzheimer's disease. Paper presented at Clinical Trials on Alzheimer's Disease Conference; December 4-7, 2019; San Diego, CA.

23. Cummings J, Aisen P, Lemere C, et al. Aducanumab produced a clinically meaningful benefit in association with amyloid lowering. *Alzheimers Res Ther*. 2021; 13(1): 98.
24. Wattmo C, Minthon L, Wallin ÅK. Mild versus moderate stages of Alzheimer's disease: three-year outcomes in a routine clinical setting of cholinesterase inhibitor therapy. Alzheimers Res Ther. 2016;8:7.
25. Armstrong RA. Factors determining disease duration in Alzheimer's disease: a postmortem study of 103 cases using the Kaplan-Meier estimator and Cox regression. *Biomed Res Int*. 2014; 2014: 623487.
26. Friedman LG, McKeehan N, Hara Y, et al. Value-Generating Exploratory Trials in Neurodegenerative Dementias. *Neurology*. 2021; 96(20): 944-954.
27. Pradier C, Sakarovitch C, Le Duff F, et al. The mini mental state examination at the time of Alzheimer's disease and related disorders diagnosis, according to age, education, gender and place of residence: a cross-sectional study among the French National Alzheimer database. *PLoS One*. 2014; 9(8): e103630. doi: 10.1371/journal.pone.0103630.
28. Jack CR Jr, Wiste HJ, Weigand SD, et al. Age, Sex, and APOE ε4 effects on memory, brain structure, and β-amyloid across the adult life span. *JAMA Neurol*. 2015; 72(5): 511-519.
29. Jansen WJ, Ossenkoppele R, Knol DL, et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. *JAMA*. 2015; 313(19):1924-1938.
30. Schneider LS, Kennedy RE, Wang G, et al. Differences in Alzheimer disease clinical trial outcomes based on age of the participants. *Neurology*. 2015; 84(11): 1121-1127.
31. Stanley K, Whitfield T, Kuchenbaecker K, et al. Rate of cognitive decline in Alzheimer's disease stratified by age. *J Alzheimers Dis*. 2019; 69(4): 1153-1160.
32. Rosselli MC, Ardila AC, Moreno SC, et al. Cognitive decline in patients with familial Alzheimer's disease associated with E280a presenilin-1 mutation: a longitudinal study. *J Clin Exp Neuropsychol*. 2000; 22(4): 483-495.