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Featured Article

The **A**lzheimer's disease **THE**rapy with **NE**uroaid (**ATHENE**) study protocol: Assessing the safety and efficacy of Neuroaid II (MLC901) in patients with mild-to-moderate Alzheimer's disease stable on cholinesterase inhibitors or memantine—A randomized, double-blind, placebo-controlled trial

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Abstract

Background: Dementia is a large and growing health care burden globally, and its major cause is Alzheimer's disease (AD). MLC901 (Neuroaid II) is a simplified form of MLC601 (Neuroaid), a Traditional Chinese Medicine with neuroprotective and neuroproliferative properties in cellular and animal models of brain injury. MLC601 has been shown to modulate amyloid precursor protein (APP) processing in human neuroblastoma cell cultures and increase the levels of soluble APPα. In addition, MLC901 has been shown to reduce tau phosphorylation in vitro. Hence, MLC901 may have possible multimodal actions and a disease-modifying effect in AD. In previous clinical studies, MLC601 has shown promising effects in AD.

Objective: To investigate the safety and efficacy of MLC901 add-on therapy to standard treatment in mild-to-moderate probable AD patients stable on standard treatment and to evaluate if MLC901 has a disease-modifying effect in AD.

Methods: This is a 6-month randomized, double-blind, placebo-controlled trial in mild-to-moderate probable AD where MLC901 will be given as an add-on therapy to standard AD treatment, followed by an extension study for another 6 months, where all subjects will be treated with open-label MLC901 in addition to standard treatment. The primary outcome is safety as measured by adverse events, vital signs, electrocardiogram, laboratory tests, and physical and neurological examinations. Secondary outcomes evaluating cognition, behavior, and activities of daily living at various time points include the Alzheimer's Disease Assessment Scale–cognitive subscale, Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory, Neuropsychiatric Inventory, and Mini–Mental State Examination.

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Conclusion: MLC901 has the potential to improve cognition in AD patients. It may also have a role in delaying disease progression. This study will be the first to provide safety and efficacy data for MLC901 in mild-to-moderate probable AD patients already receiving standard therapy.

Keywords: MLC901; Clinical trial; Alzheimer's disease; Disease progression; Neuroaid II

1. Introduction

Dementia is a large and growing health care burden globally and particularly in Asia due to large and rapidly aging populations [1]. The incidence of the disease doubles every 5 years after 65 years of age, with the diagnosis of 1275 new cases per year per 100,000 persons older than 65 years of age [2]. 35.6 million people were estimated to be living with dementia in 2010, with numbers doubling every 20 years reaching 65.7 million in 2030 [3]. According to the World Alzheimer Report 2015, Asia will have the highest burden (4.9 million or 49%) of new dementia cases [4]. The global cost of dementia increased from US$ 604 billion in 2010 to US$ 818 billion in 2015, representing an increase of 35.4% over 5 years and is set to soar by approximately 85% by 2030, based on the predicted increase in the number of people with dementia [5]. Alzheimer's disease (AD) is a chronic neurodegenerative disorder in which the main pathological feature is accumulation of β-amyloid peptide (Aβ) laden cerebral plaques and neurofibrillary tangles in the brain [6]. There is progressive deterioration in cognition, affecting memory, thinking, orientation, learning capacity, and judgment, eventually making the patients fully dependent on their caregivers [7]. To date, only symptomatic treatments exist as licensed therapies for AD. Currently, three acetylcholinesterase inhibitors (AChEIs) are in clinical use (donepezil, rivastigmine, and galantamine) for AD [8,9]. Memantine, an N-methyl-D-aspartate receptor antagonist, is a further therapeutic option used for moderate-to-severe AD and for moderate AD patients who are intolerant of or have contraindications to AChEIs [10,11]. These treatments are primarily symptomatic and do not have a proven effect on delaying disease progression. Moreover, tolerability and compliance are limited by adverse reactions especially at higher doses, which are often required by the patients to achieve a stable effect [8–10].

Disease-modifying treatments that may effectively change the course of AD are being extensively researched, but none have yet been shown to be effective and safe. The pathological hallmark of AD is the accumulation of abnormal proteins in the intracellular (hyper-phosphorylated tau in neurofibrillary tangles) and extracellular (β-amyloid in plaques) compartments of the brain; hence, targeting either or both of these pathogenic processes may halt progression of disease [6]. Treatments that can both improve the symptoms and also delay or halt the progression of the disease would be the optimal management option for AD. Hence, there is a need for further clinical trials of innovative and novel treatments that meet these needs.

MLC601 (Neuroaid) is a Traditional Chinese medicine (TCM) having neuroprotective and neuroproliferative properties in cellular and animal models of brain injury. It contains 9 herbal and 5 nonherbal components. MLC901 (Neuroaid II) is a simplified formula of MLC601, containing only the 9 herbal components yet showing the same efficacy [12]. They induce neurogenesis and neuroproliferation in rodents and human stem cell cultures. Moreover, both promote cell proliferation, neurite outgrowth, and the development of dense axonal and dendritic networks [12,13]. MLC901 has several differences from MLC601 that may improve patient compliance. First, MLC901 only contains herbal components and excludes the animal ingredients that are present in MLC601, allowing the consumption of less capsules per day and reduces any chance of contaminants or heavy metal toxicity. Second, the capsule shell is made of hypromellose instead of gelatin and hence is suitable for vegetarians. As there are no new ingredients, MLC901 should be as safe as MLC601.

Both MLC901 and its predecessor MLC601 have pharmacological properties relevant to AD. MLC901 activates K-ATP channels in cell cultures under oxygen-glucose deprivation, leading to hyperpolarization and reduced exaggerated Ca influx that reduces excitotoxicity [14]. It also demonstrates protective effects against glutamate-induced cell death on cortical neurons in culture, reduces Bax protein expression (indicating an effect on apoptotic pathways), and reduces levels of lipid peroxidation product malondialdehyde (indicating an antioxidant effect) and hence has neuroprotective properties via multiple mechanisms [13].

MLC601 is a possible modulator of amyloid precursor protein (APP) processing. Using cultures of human neuroblastoma cell line SH-SY5Y, MLC601 increases the level of sAPPα, a nonpathogenic soluble fragment of APP, which is produced by physiological cleavage of APP by α and γ secretase [15]. Furthermore, MLC601 significantly decreases the levels of full-length APP in the media, suggesting a modulatory effect of MLC601 on APP processing [15]. A recently concluded in vitro study shows that MLC901 significantly reduced tau phosphorylation at various epitopes recognized by AT8, AT270, and PHF-13 antibodies. It also showed increased phosphorylation of glycogen synthase kinase 3β along with concurrent decrease in activation of cyclin-dependent kinase 5 [16]. These results provide additional information on the action of MLC901 in reversing tau

phosphorylation and in APP processing, suggesting a possible multimodal disease-modifying action in AD [15,16]. These pharmacological properties in addition to further effects on tau and β-amyloid make MLC901 an attractive candidate as a treatment for AD.

In a recent animal study, MLC901 showed positive effects in cognitive tasks in mice; it promoted extinction in the passive avoidance and reversal learning in Morris water maze and improved the performance in novel object recognition [17]. Increased hippocampal neurogenesis with promoted proliferation, neuronal differentiation, and survival of young neurons were also observed with MLC901. The neurogenesis effect is thought to have contributed to its pro-cognitive effects [17]. This study thus shows that MLC901 improves memory and hence may delay the onset of AD dementia or disease progression.

1.1. Efficacy and safety studies of Neuroaid in AD

MLC601 has shown favorable effects on cognitive function in patients with AD. In a clinical study, patients with mild-to-moderate AD who were unable to tolerate or had failed to benefit from AChEIs were treated with MLC601. Improved cognitive function was observed in the first 6 months, and stabilization of cognitive decline was observed over the remaining 12 months. Adverse events were mainly gastrointestinal and were noted in only 7.3% of patients [18].

These findings led to a multicentre randomized trial where MLC601 efficacy and safety was compared with that of standard AChEIs (donepezil, rivastigmine, galantamine) [19]. MLC601 was shown to have better tolerability and safety profile than standard AChEIs. In addition, its efficacy as a monotherapy was comparable with that of standard AChEIs. These results suggest a symptomatic effect of MLC601 in AD as well as a possible disease-modifying effect. In addition, no safety concerns were raised.

1.2. Other safety studies with Neuroaid

MLC601 did not change hematological, hemostatic, and biochemical parameters in normal subjects and stroke patients in early phase studies [20]. MLC601 has also been investigated in a large randomized controlled trial for stroke recovery, which recruited 1100 acute stroke patients and followed them for up to 24 months after stroke onset. Aside from significantly improving functional independence at 6 to 18 months after a stroke, MLC601 has an excellent safety profile, with adverse events equivalent to placebo [21,22]. Laboratory tests performed in a subgroup of acute ischemic stroke patients during the first 3 months of treatment showed no differences in biochemistry, hematological parameters, and electrocardiogram between the MLC601- and placebo-treated groups [23]. Long-term safety up to 6 months of a 3-month regimen of MLC601 was also assessed in acute ischemic stroke in another study [24]. Mild nausea was observed mainly during the first month of treatment with MLC601, which did not lead to discontinuation. There were no significant changes in mean arterial blood pressure, hemoglobin, renal, or liver laboratory parameters during the 3-month treatment or during the additional follow-up period of 3 months. In a recently concluded traumatic brain injury study, MLC901 was administered for 6 months with a good safety profile [25].

In the proposed study, MLC901 will be given as add-on therapy to standard treatment in patients having mild-to-moderate probable AD.

2. Methods

2.1. Study design

This is a 6-month randomized, double-blind, placebo-controlled trial, followed by an extension study with open-label MLC901 for 6 months in both arms of the study. The total duration of participation in the study is 1 year. The summary of study design is given in Fig. 1.

2.2. Study objectives

2.2.1. Primary objective

To test the hypothesis that the proportion of patients experiencing serious adverse events (SAEs) within the first 6 months after randomization among those who receive MLC901 on top of standard treatments will be no larger than the proportion of SAEs in patients receiving standard treatments alone.

2.2.2. Secondary objectives

To test various exploratory hypothesis (a) that add-on MLC901 will show no increase in occurrence of any adverse event or discontinuation of treatment during 6 months of usage in patients with AD on standard treatment, (b) that add-on MLC901 will be superior to standard treatments alone in cognitive change from baseline to 6 months as measured by Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-Cog) and other cognitive assessments, (c) that add-on MLC901 will show long-term safety, with no increase in occurrence of serious and non-SAEs, during 1 year of usage in patients with AD on standard treatment, and (d) that patients treated with MLC901 from trial onset will show less disease progression on cognitive assessments compared with those started on MLC901 at month 6.

2.3. Enrollment

The study will be conducted in Singapore according to ICH/GCP guidelines. Local ethics committee approval will be obtained before commencing the trial at a site.

2.3.1. Key inclusion criteria

(1) Male or female, age $\geq$50 years, (2) diagnosed with probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's

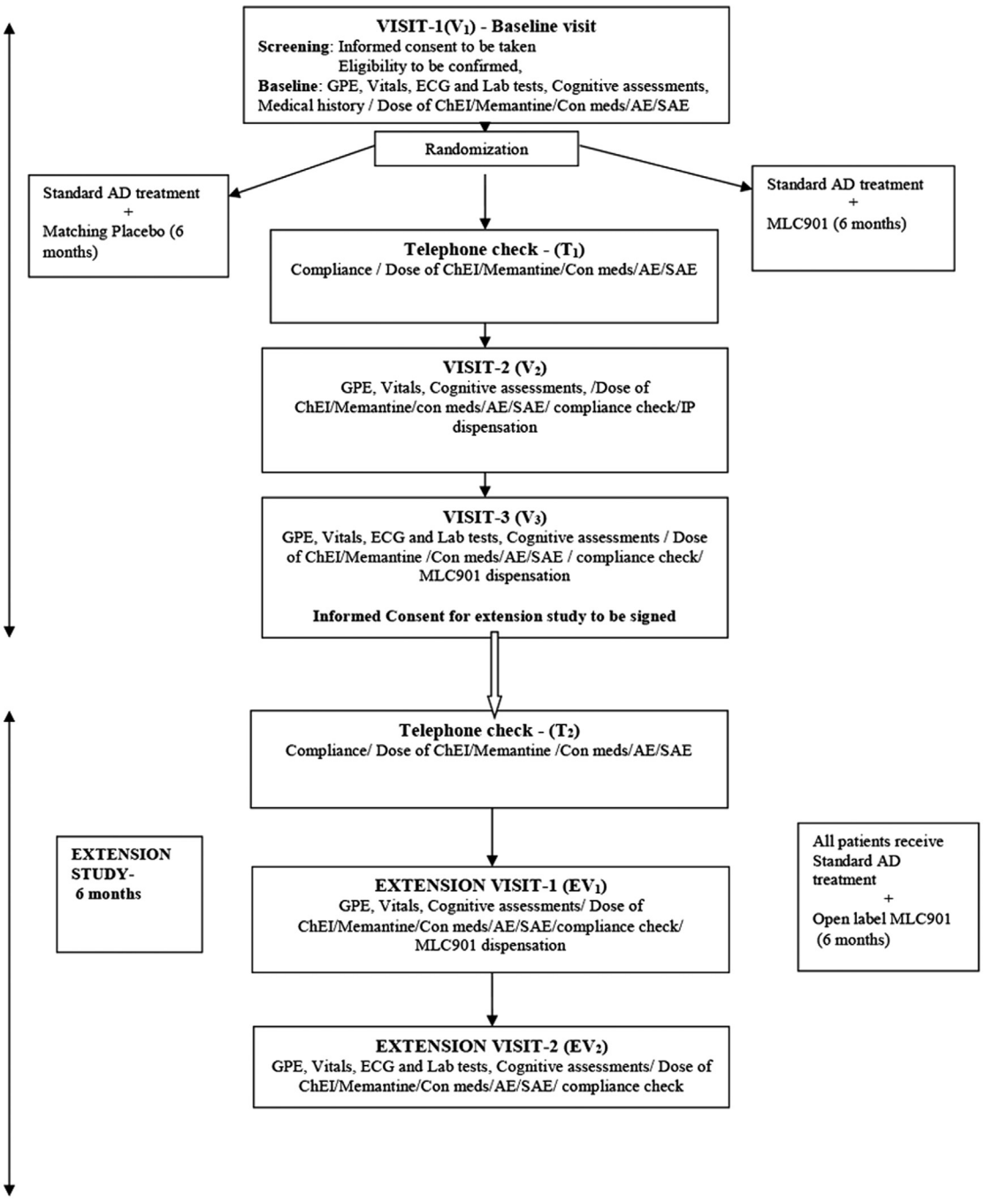

Fig. 1. Summary of study design. Abbreviations: AD, Alzheimer's disease; AE, adverse events; ECG, electrocardiogram; ChEI, cholinesterase inhibitor; SAE, serious adverse events.

Disease and Related Disorders Association (NINCDS-ADRDA) criteria, Mini–Mental State Examination score of 8-26, and (3) receiving the same AChEI or memantine or both for the past 4 months before screening and on a stable dose for the past 2 months (stable dose is defined as 5 to 10 or 23 mg/day for donepezil, 3, 4.5, or 6 mg twice daily for rivastigmine capsules, 4.6 or 9.5 mg for rivastigmine transdermal patch once daily, 8 or 12 mg twice daily for galantamine tablets, 16 to 24 mg once daily for galantamine capsules XL, and 10 mg OD or 10 mg BD for memantine).

2.3.2. Key exclusion criteria

(1) Patients receiving any investigational product within 60 days or 5 half-lives before screening, whichever that is longer and (2) any serious medical or psychiatric condition which in the investigator's judgment may jeopardize the

patient by his/her participation in this study or may hamper his/her ability to perform and complete procedures required in the study.

The diagnosis of probable AD is based on NINCDS-ADRDA criteria for AD [26].

2.4. Randomization

Eligible patients will be given a randomization number that assigns them to one of the treatment groups. Up to 150 subjects will be randomized to MLC901 or placebo treatment according to a balanced randomization scheme of 1:1. To ensure that the treatment assignment is unbiased and concealed from patients and site study personnel, a randomization list will be produced by Moleac Pte Ltd by random assignment of treatment groups to randomization numbers.

At randomization, all patients who fulfill all the inclusion/exclusion criteria will be given the lowest available number on the randomization list and receive a supply of study medication (MLC901 or placebo). Investigators and patients/caregivers will be blinded to treatment allocation. Treatment allocation will be concealed until the end of the study.

2.5. Study treatments

The trial consists of two parts: In the first part, the subjects will be randomly assigned to receiving a 6-month course of either MLC901 or placebo along with the standard AD treatment. In the second part, all patients who complete the first part of study will be offered to participate in open-label extension study where all subjects will receive MLC901 along with the standard AD treatment. MLC901 consists of dry extract of herbs in capsule form to be taken orally at a dose of 2 capsules 3 times per day. Each capsule weighs 0.4 gm and contains extracts of 9 herbs (Radix Astragali, Radix Salviae miltiorrhizae, Radix Paeoniae rubra, Rhizoma chuanxiong, Radix Angelicae sinensis, Carthamus tinctorius, Prunus persica, Radix polygalae, Rhizoma Acori tatarinowii).

MLC901 and placebo will be manufactured by Poli Medical Company Pte Ltd. The placebo consists of dextrin, turmeric, carmine, and caramel to ensure that it has the same appearance as the active treatment. Both MLC901 and placebo will be provided by Moleac Pte Ltd.

2.6. Primary outcome

The primary outcome is the safety of MLC901 as an add-on treatment for 6 months in patients with mild-to-moderate probable AD who are on standard treatment with AChEIs or memantine.

2.7. Secondary outcomes

1. Effect of MLC901 as add-on therapy to standard treatments for 6 months on cognitive function in patients with mild-to-moderate AD.
2. Long-term safety of MLC901 as add-on treatment to standard treatments for up to 1 year in an open extension study.
3. Long-term effect of MLC901 on disease progression as an add-on treatment to standard treatments for up to 1 year in an open extension study.

2.8. Study flow

At screening and baseline visit (V1), all patients will be evaluated for eligibility as per the inclusion/exclusion criteria. Demographic data, medical history, concomitant medication, physical examination, and vital signs will be collected. Baseline cognitive assessments and safety evaluation will be done. Safety and efficacy assessments will be conducted at month 3 (visit 2) and month 6 (visit 3). In addition, electrocardiogram and laboratory tests will be performed at the month 6 visit. The details of study visits and assessments are in Table 1.

Safety will be assessed by physical examination, adverse events/SAEs reporting, electrocardiogram, and laboratory investigations (complete blood count, blood urea, serum creatinine, serum uric acid, blood glucose, serum alkaline phosphatase, serum glutamic-oxaloacetic transaminase, serum glutamic pyruvic transaminase, serum bilirubin, serum electrolytes, total proteins with albumin and globulin).

Efficacy of MLC901 will be evaluated by improvements in cognition, activities of daily living, and disease progression. The following tests will be done: ADAS-Cog, Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory, Neuropsychiatric Inventory, and Mini–Mental State Examination at month 3 (M3), M6, M9, and M12. Telephone-based assessments have been shown to improve subject retention and minimize missing data in longitudinal studies and hence have been included in our study [27].

At month 1, telephone assessment (T1) will be performed for adverse events, concomitant medications, dose of standard treatment, and treatment compliance.

At the month 6 (visit 3), the patient will be offered participation in the open-label extension study. If they agree, an informed consent form for extension study will be signed and MLC 901 will be dispensed to the participants.

2.8.1. Extension study

The month 6 data of the trial will serve as the baseline for extension study. At month 7, telephone assessment (T2) will be performed for any adverse events, concomitant medications, dose of standard treatment, and study treatment compliance.

Safety and efficacy evaluations will be done at month 9 (EV1) and month 12 (EV2). In addition, electrocardiogram and laboratory tests will be performed at the month 12 visit. An independent data safety monitoring board will monitor

Table 1
Study visits and assessments

Placebo-controlled randomized controlled trial					Extension study (EXT)		
Visit number	Screening and baseline (V1)	Month 1 -telephone check (T1)	Month 3 (V2)	Month 6 (V3)	Month 7 telephone check (T2)	Month 9 (EV1)	Month 12 (EV2)
Signed informed consent	✓			✓(for EXT study)			
Demographics	✓						
Medical history	✓						
Vital signs	✓			✓		✓	✓
Physical examination	✓		✓	✓		✓	✓
ECG and laboratory tests	✓			✓			✓
Inclusion/exclusion criteria	✓						
Randomization	✓						
MMSE	✓		✓	✓		✓	✓
ADAS-Cog	✓		✓	✓		✓	✓
ADCS-ADL23	✓		✓	✓		✓	✓
ADCS-CGIC	✓		✓	✓		✓	✓
NPI	✓		✓	✓		✓	✓
Study drug dispensation	✓		✓				
Dose of AChEIs/memantine	✓	✓	✓	✓	✓	✓	✓
Other concomitant medications	✓	✓	✓	✓	✓	✓	✓
Compliance and drug accountability		✓	✓	✓	✓	✓	✓
Neuroaid open-label (MLC901) dispensation-extension study				✓		✓	
Adverse events/serious adverse events	✓	✓	✓	✓	✓	✓	✓

Abbreviations: V, visit; ECG, electrocardiogram; MMSE, Mini–Mental State Examination; ADAS-Cog, Alzheimer's Disease Assessment Scale–cognitive subscale; ADCS-ADL23, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory; ADCS-CGIC, Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change; NPI, Neuropsychiatric Inventory; AChEIs, acetylcholinesterase inhibitors.

the patient safety and efficacy during the course of the trial. The initial data safety monitoring board meeting will be scheduled once first 50 patients complete the study. Subsequent meetings will be held as decided by the data safety monitoring board chair during the course of the trial. An emergency meeting may be called at anytime by the chairperson or the principal investigator should question of the patient safety arise.

2.9. Sample size

Based on data in earlier trials, we assume that the proportion of subjects who are stable on standard treatment experiencing SAEs is 5%. To achieve a power of 80% and a 5% type I error, 118 subjects (59 per group) are required to exclude a difference of more than 10% in the proportion of subjects experiencing SAEs between the treatment groups. To allow for a maximum 21% dropout rate, up to 150 subjects will be recruited. Furthermore, using this sample size, the study will have a >80% power to detect a difference of 3 points (28 vs. 25) on the ADAS-Cog between the two treatment groups using a standard deviation of 6 at a 5% level of significance.

2.10. Statistical analysis

Three population sets will be considered: (1) intention-to-treat population defined as patients who have taken at least one dose of study medication, (2) as-treated population defined by the actual medication the patients receive, and (3) per-protocol population defined as the subset of the as-treated population but including only those who completed the study without major protocol deviations. Demographic and baseline characteristics will be summarized according to the intention-to-treat population, safety data will be analyzed according to the as-treated population, whereas efficacy data will be analyzed according to both intention-to-treat and per-protocol populations. For safety evaluation, the proportions of patients who experience a SAE or an adverse event or discontinue medication because of either will be compared between the two groups. The difference in proportion will be estimated by a 95% confidence interval, which will be compared to a prespecified noninferiority margin of 10%. Specifically, if the upper limit of the 95% confidence interval for the difference in proportion does not exceed 10%, then noninferiority of MLC901 is established. Continuous variables including laboratory tests, vital signs, the mean change from baseline on ADAS-Cog and other cognitive tests will be compared using a two-sample *t*-test with a two-tailed significance level of 5%. Logistic and linear regression will also be performed as a sensitivity analysis to adjust for baseline characteristics, which may potentially be confounding factors to the treatment effect.

3. Conclusions

MLC901 has shown promise in both preclinical and clinical studies for the treatment of AD. It has the potential to be an add-on to the current standard treatment of AD, due to possible symptomatic and disease-modifying effects. This

study will be the first to provide safety and efficacy data for MLC901 in mild-to-moderate probable AD patients already receiving standard therapy.

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RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using the traditional sources. MLC601 has shown to modulate amyloid precursor protein processing, and MLC901 has shown positive effect on tau phosphorylation as well as cognitive tasks in mice. Two clinical studies with MLC601 in Alzheimer's disease (AD) showed improved cognition along with good safety profile. These relevant articles are appropriately cited.
2. Interpretation: The ATHENE study is a 6-month double-blind, placebo-controlled trial followed by 6-month open-label extension in both arms that is aimed at evaluating the safety and efficacy of MLC901 in AD. The total duration of study is 1 year.
3. Future directions: Limited treatment options are available for AD, and they are primarily symptomatic and do not have proven effect on delaying disease progression. Moreover, the adverse reactions make them intolerable. MLC901 has the potential to be an add-on to the current standard treatment of AD, due to possible symptomatic and disease-modifying effects.

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