Alzheimer's Disease THErapy With NEuroaid (ATHENE): A Randomized Double-Blind Delayed-Start Trial

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Objectives: Preclinical and clinical studies indicate a role for MLC901 (NeuroAiD II) in Alzheimer's disease (AD). The primary aim was to investigate its safety as add-on therapy to standard treatment and the secondary aims its effect on cognition and slowing disease progression.

Design: Randomized double-blind placebo-controlled delayed-start study.

Setting and Participant: Patients with mild to moderate probable AD by NINCDS-ADRDA criteria, stable on acetylcholinesterase inhibitors or memantine (n = 125), were randomized to receive MLC901 (early starters) or placebo (delayed starters) for 6 months, followed by a further 6 months when all patients received MLC901, in a delayed-start design (clinical trial registration: ClinicalTrials.gov, NCT03038035).

Early starters did not differ significantly on ADAS-Cog from delayed starters at M6 [mean difference (MD) −1.0, 95% CI −3.3 to 1.3] and M12 (MD −2.35, 95% CI −5.45 to 0.74) on intention-to-treat analysis.

This study randomized patients to be either (1) early starters: MLC901 from 0 to 12 months, or (2) delayed starters: placebo from 0 to 6 months, and MLC901 from 6 to 12 months. This resulted in 2 treatment periods: a double-blind placebo-controlled phase from 0 to 6 months, followed by an early vs delayed-start phase during which all patients received MLC901 from 6 to 12 months. During the entire study period of 12 months, study personnel and patients were blinded to each patient's allocation as an early or delayed starter.[24] This study was approved by the National Healthcare Group, Domain Specific Review Board (DSRB), Singapore, and the study was performed according to the Good Clinical Practice guidelines and the Declaration of Helsinki (ClinicalTrials.gov: NCT03038035).

Participants

The participants were male or female patients, aged ≥50 years, diagnosed with probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria,[25] of mild-moderate severity as defined by a Mini-Mental State Examination (MMSE) score of 8 to 26, receiving AChEI or memantine or both during the prior 4 months and on a recommended stable dose defined in the protocol for the prior 2 months.[24] The main exclusion criteria were intake of any investigational product within 60 days or 5 half-lives prior to study entry and the presence of any serious medical or psychiatric condition that might put the patient at risk from participating in the study.

Treatment

MLC901 was provided in a capsule form containing 400 mg of dry extracts from nine herbs (*Radix Astragali*, *Radix Salviae miltiorrhizae*, *Radix Paeoniae rubra*, *Rhizoma chuanxiong*, *Radix Angelicae sinensis*, *Carthamus tinctorius*, *Prunus persica*, *Radix polygalae*, and *Rhizoma Acori tatarinowii*). Matching placebo capsules contained dextrin, turmeric, carmine, and caramel. Both MLC901 and placebo were provided by Moleac Pte Ltd. Standard treatment for AD were continued according to the treating physician's judgment.

Assessments and Outcomes

Occurrence of any AE/SAE, dose of standard treatment for AD, and compliance to study treatment were ascertained at month (M) 1, M3, M6, M7, M9, M12. Vital signs and physical examination at baseline, M3, M6, M9, and M12 and safety laboratory investigations and ECGs at M6 and M12 were performed. For the efficacy endpoints, ADAS-Cog, Alzheimer's Disease Cooperative Study−Clinician's Global Impression of Change (ADCS-CGIC), Alzheimer's Disease Cooperative Study−Activities of Daily Living Scale (ADCS-ADL), Neuropsychiatric Inventory (NPI), and MMSE were administered at baseline, M3, M6, M9, and M12.

Statistics

A sample size of 118 patients (59 per group) was calculated for concluding noninferiority of MLC901 against placebo in the proportion of subjects experiencing SAEs (assuming 5% in each group) at a noninferiority margin of 10% with 80% power at a 5% significance level. This also provided >80% power to detect a treatment effect of 3 points (SD = 6) on the mean ADAS-Cog at a 5% significance level. Hence, it was planned to recruit 150 subjects to allow for a 20% dropout rate.

The safety analyses were performed on the "as-treated" population, which consisted of all patients with documented intake of at least 1 dose of MLC901 or placebo. We calculated the differences in proportions (and their 90% CIs) of patients who experienced an outcome between early and delayed starters using the method of Miettinen and Nurminen[26,27] and compared the upper limit to a prespecified noninferiority margin of 10%.

The secondary efficacy endpoints were analyzed based on the intention-to-treat (ITT) population. Missing data were imputed using the last observation carried forward (LOCF) method. We compared the mean difference (MD) of change from baseline between early and delayed starters using a 2-sample *t* test. ADCS-CGIC was compared using the Mann-Whitney *U* test and the proportions of patients with improvement or no change from baseline in ADCS-CGIC using the chi-squared test. Additionally, as the study was ended early, 14 patients with ongoing follow-up were discontinued before their M12

assessments, in addition to 4 patients who discontinued the open-label phase. Among these 18 patients, 7 were early starters and 11, delayed starters. A per-protocol (PP) analysis that included patients having ≥70% treatment compliance and without major protocol deviations was performed, as well as sensitivity analyses using the ITT population without LOCF and after adjustment for potential confounders.

We used SAS (version 9.4) in performing all analyses.

Results

From December 2016 to November 2018, 136 patients with AD were screened and 125 were found eligible and randomized (MLC901 n = 62, placebo n = 63). Study recruitment was stopped early because patient retention was better than the anticipated 20% dropout rate and the required sample size for the principal safety (SAE) and efficacy (ADAS-Cog) endpoints was achieved (see study flow diagram in Figure 1). Of the 125 patients randomized, 6 patients discontinued the
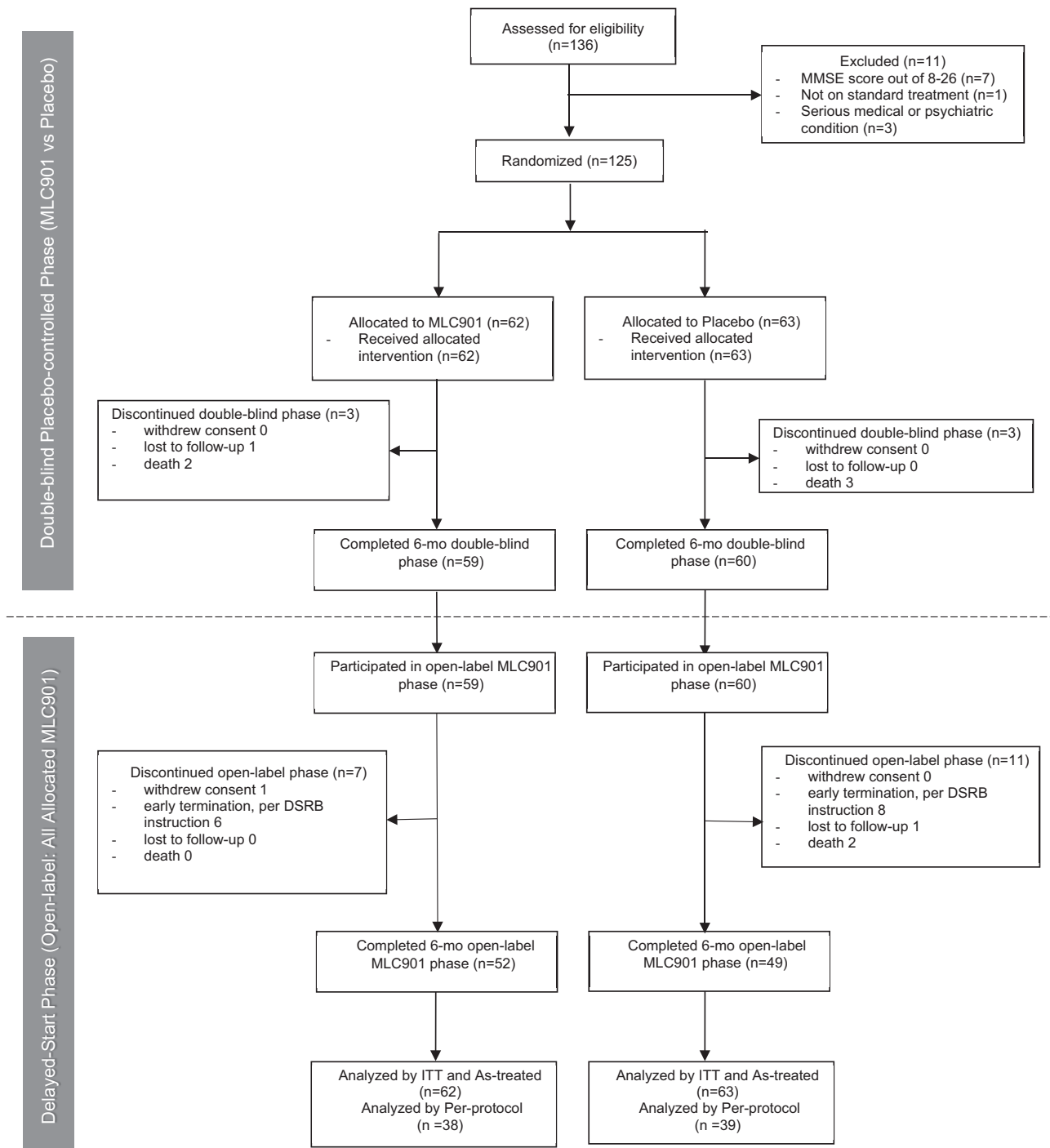

Fig. 1. Study design and patient flow (CONSORT diagram).

double-blind phase. All 119 patients eligible for the open-label extension agreed to participate.

Baseline Characteristics

The mean age of the overall study population was 78.6 ± 6.7 years with 87 (69.6%) women. Ninety (72%) had hypertension, 87 (69.6%) hyperlipidemia, 45 (36%) diabetes mellitus, and 23 (18.4%) a history of previous stroke. Standard AD treatments were as follows: donepezil, 101 (80.8%); rivastigmine, 18 (14.4%); galantamine, none (0%); and memantine, 9 (7.2%). There was higher educational attainment in the delayed starter group (*P* = .003) (Table 1).

Safety

The number of study capsules consumed and number of dosing days were similar between early and delayed starters. Treatment adherence rate was 76% in both groups.

The numbers of events and patients experiencing SAEs and AEs by study phase are summarized in Table 2 and by system organ classification in Supplementary Table 1. In the placebo-controlled phase (0-6 months) of the study, 14 (22.6%) patients on MLC901 experienced 22 SAEs, whereas 17 (27%) on placebo experienced 19 SAEs with a risk difference of −4.4% and a 90% CI of −16.9% to 8.3%. The upper limit of the CI range fell below the prespecified noninferiority margin of 10% (Figure 2). None of the SAEs were considered related to study treatment. Five deaths were reported in the placebo-controlled phase, 2 were on MLC901 (both from pneumonia), and 3 on placebo (from pneumonia, lung cancer, and ruptured aortic dissection, respectively). Similarly, in the placebo-controlled phase, 38 (61.3%) patients on

MLC901 experienced 79 AEs compared to 38 (60.3%) patients on placebo who experienced 67 AEs. One patient (1.6%) on MLC901 and none on placebo had AE that led to discontinuation of study medication (risk difference 1.6%, 95% CI −4.3%, 8.6%).

Comparable risks of SAE and AE were observed from between-group comparisons (Figure 2). Two other deaths occurred in the delayed-start phase of the study (because of myocardial infarction and pneumonia). Overall, the 6 AEs in 5 patients (8.1%) considered possibly related to MLC901 were all gastrointestinal, nonserious, and resolved.

Toward the end of the study, the DSRB expressed concerns related to high rates of stroke and vascular events (VEs) in the study and decided that the study be discontinued. A specific analysis was performed to address the concern of the DSRB regarding major VEs defined as any stroke, myocardial infarction, aortic aneurysm, hypertensive urgency, and/or death due to vascular cause. Overall, 7 patients in the study experienced a major VE (5 ischemic strokes, 1 myocardial infarction, and 1 ruptured thoracic aortic aneurysm). All 7 patients had combinations of 2 or more vascular risk factors, including hypertension, hyperlipidemia, diabetes mellitus type 2, chronic kidney disease stage 3, sick sinus syndrome, and atrial fibrillation (not anticoagulated due to clinical contraindications). Evidence of VEs evaluated by brain computed tomography or magnetic resonance imaging and computed tomographic angiogram showed vascular occlusion or multiple acute strokes in patients who experienced ischemic strokes.

As the total duration of exposure to MLC901 (82.0 person-years) was longer than placebo (28.6 person-years), we compared the incidence rate of major VE between MLC901 and placebo. The calculated incidence rate of major VE was 6.1 (95% CI 2.3, 13.3) per 100 person-years of exposure to MLC901 compared with 7.0 (95% CI 1.4, 22.3) per 100 person-years for placebo. For stroke alone, the incidence rates

Table 1
Baseline Characteristics of Randomized Patients

Variable	Early Starters (n = 62)	Delayed Starters (n = 63)	Total (N = 125)
Age, y, mean (SD)	78.9 (6.8)	78.3 (6.6)	78.6 (6.7)
Women	44 (71.0)	43 (68.3)	87 (69.6)
Ethnicity			
Chinese	58 (93.5)	53 (84.1)	111 (88.8)
Malay	3 (4.8)	3 (4.8)	6 (4.8)
Indian	1 (1.6)	6 (9.5)	7 (5.6)
Mixed	0	1 (1.6)	1 (0.8)
Education level			
Primary	48 (77.4)	37 (58.7)	85 (68.0)
Secondary	12 (19.4)	11 (17.5)	23 (18.4)
Tertiary	2 (3.2)	15 (23.8)	17 (13.6)
Living situation			
Lives alone	3 (4.8)	5 (7.9)	8 (6.4)
Lives with partner/spouse	25 (40.3)	25 (39.7)	50 (40.0)
Lives with children/relative/friend	26 (41.9)	29 (46.0)	55 (44.0)
Miscellaneous (lives with group/maid/others)	8 (5.6)	4 (6.3)	12 (9.6)
Medical history			
Cerebrovascular event	14 (22.6)	9 (14.3)	23 (18.4)
Ischemic or TIA	14 (22.6)	7 (11.1)	21 (16.8)
Hemorrhagic	0	2 (3.2)	2 (1.6)
Hypertension	47 (75.8)	43 (68.3)	90 (72.0)
Hyperlipidemia	47 (75.8)	40 (63.5)	87 (69.6)
Ischemic heart disease	13 (21.0)	14 (22.2)	27 (21.6)
Diabetes mellitus	26 (41.9)	19 (30.2)	45 (36.0)
ADAS-Cog, mean (SD)	31.1 (11.9)	29.3 (9.5)	30.2 (10.7)
ADCS-ADL23, mean (SD)	44.8 (15.8)	46.1 (15.2)	45.5 (15.4)
NPI, mean (SD)	11.1 (13.9)	11.0 (11.7)	11.0 (12.8)
MMSE, mean (SD)	14.9 (4.2)	15.9 (3.9)	15.4 (4.1)
Standard AD treatment			
Donepezil alone	48 (77.4)	50 (79.4)	98 (78.4)
Rivastigmine alone	10 (16.1)	8 (12.7)	18 (14.4)
Memantine alone	3 (4.8)	3 (4.8)	6 (4.8)
Donepezil + memantine	1 (1.6)	2 (3.2)	3 (2.4)

AD, Alzheimer's disease; TIA, transient ischemic attack.
Unless otherwise noted, values are n (%).

Table 2
Summary of Serious Adverse Events and All Adverse Events by Study Phase

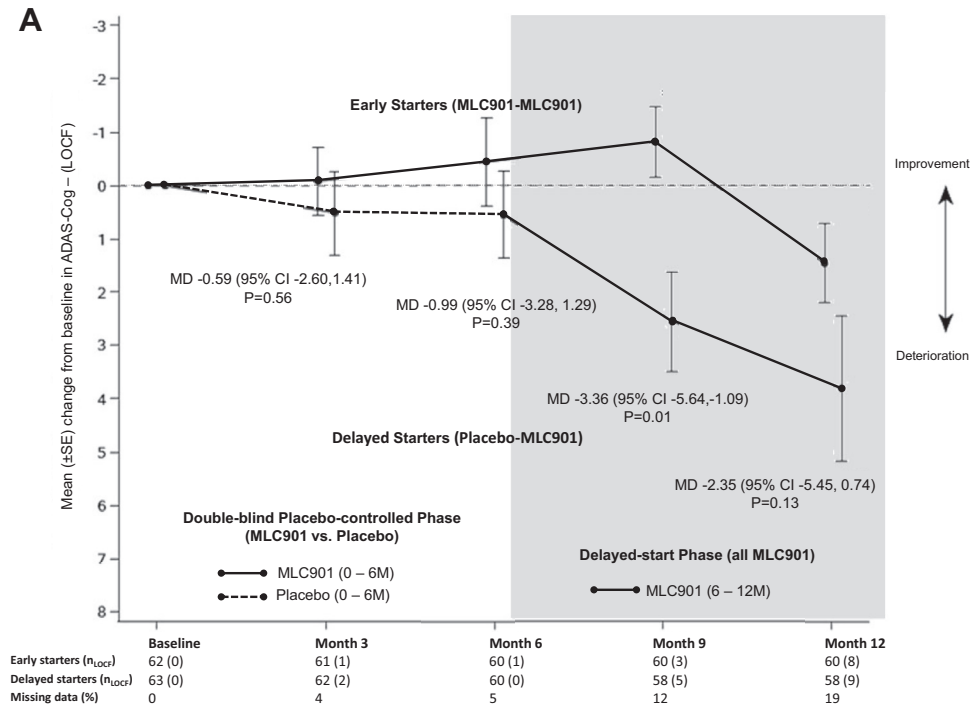|	Placebo-Controlled Phase (0-6 mo)		Delayed-Start Phase (6-12 mo)		Both Phases (0-12 mo)	
	Early Starters (n = 62)	Delayed Starters (n = 63)	Early Starters (n = 59)	Delayed Starters (n = 60)	Early Starters (n = 62)	Delayed Starters (n = 63)
SAEs						
Subjects with any SAE, n (%)	14 (22.6)	17 (27.0)	10 (16.9)	14 (23.3)	21 (33.9)	25 (39.7)
Total number of SAEs	22	19	14	18	36	37
Seriousness criteria of events						
Death	2	3	0	2	2	5
Inpatient/prolonged hospitalization	20	15	14	16	34	31
Important medical event	0	1	0	0	0	1
Causality to study product						
Not related	22	19	14	18	36	37
Action taken on medications, n (%)						
Study product withdrawn	1 (1.6)	0	1 (1.7)	1 (1.7)	2 (3.2)	1 (1.6)
Change in standard treatment	1 (1.6)	4 (6.3)	0	0	1 (1.6)	4 (6.3)
All AEs						
Subjects with any AE, n (%)	38 (61.3)	38 (60.3)	29 (49.2)	28 (46.7)	47 (75.8)	47 (74.6)
Total number of AEs	79	67	56	46	135	113
Causality to study product						
Possibly related	3	0	3	0	6	0
Not related	76	67	53	46	129	113
Action taken on medications, n (%)						
Study product withdrawn	1 (1.6)	0	1 (1.7)	1 (1.7)	2 (3.2)	1 (1.6)
Change in standard treatment	1 (1.6)	4 (6.3)	2 (3.4)	0	2 (3.2)	4 (6.3)
Major VEs						
Subjects with any VE, n (%)	2 (3.2)	2 (3.2)	2 (3.4)	1 (1.7)	4 (6.5)	3 (4.8)
Total number of VEs	2	2	2	1	4	3
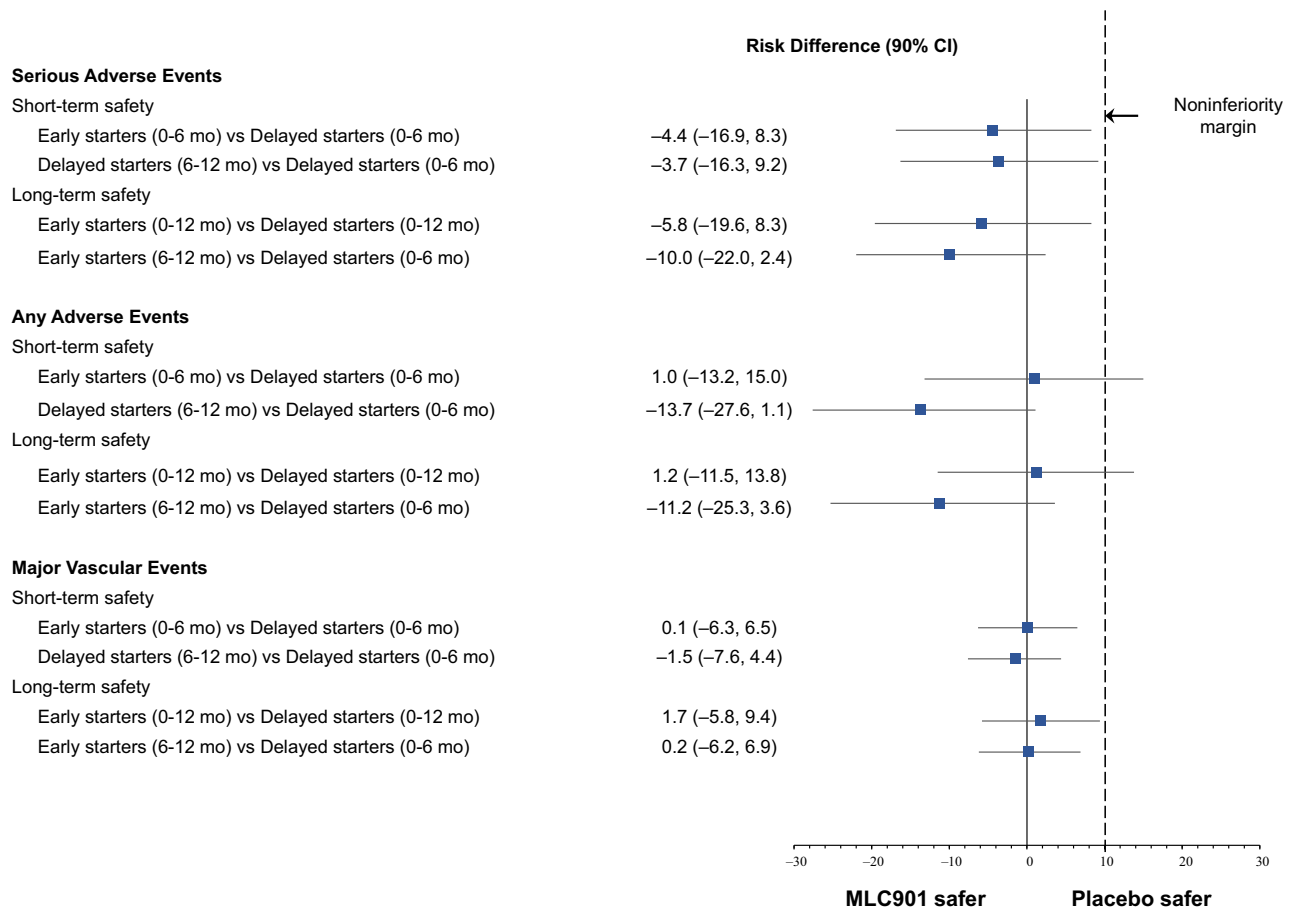
Fig. 2. Risk differences and 90% CIs of the proportions of serious adverse events, any adverse events, and major vascular events between early and delayed starters in the double-blind phase (0-6 months), delayed-start phase (6-12 months), and overall (0-12 months).

A

Early Starters (MLC901-MLC901)

MD -0.59 (95% CI -2.60,1.41)
P=0.56

MD -0.99 (95% CI -3.28, 1.29)
P=0.39

MD -3.36 (95% CI -5.64,-1.09)
P=0.01

Delayed Starters (Placebo-MLC901)

MD -2.35 (95% CI -5.45, 0.74)
P=0.13

Double-blind Placebo-controlled Phase
(MLC901 vs. Placebo)

●——● MLC901 (0 – 6M)
●----● Placebo (0 – 6M)

Delayed-start Phase (all MLC901)

●——● MLC901 (6 – 12M)

Mean (±SE) change from baseline in ADAS-Cog – (LOCF)

Improvement

Deterioration

	Baseline	Month 3	Month 6	Month 9	Month 12
Early starters (n_{LOCF})	62 (0)	61 (1)	60 (1)	60 (3)	60 (8)
Delayed starters (n_{LOCF})	63 (0)	62 (2)	60 (0)	58 (5)	58 (9)
Missing data (%)	0	4	5	12	19

were 4.9 (95% CI 1.6, 11.6) and 3.5 (95% CI 0.3, 16.2) per 100 person-years for MLC901 and placebo, respectively. Blinded assessment performed for each event showed that preexisting vascular risk factors were considered plausible reasons for the occurrence of stroke or VE.

As shown in Figure 3A, in ITT analyses with LOCF, the mean change of ADAS-Cog from baseline was −0.4 in early starters and 0.6

in delayed starters at M6 with an MD of −1.0 (95% CI −3.3, 1.3), and 1.5 in early starters and 3.8 in delayed starters at M12 with an MD of −2.4 (95% CI −5.5, 0.7, $P = .13$). Prespecified PP analysis showed an MD of −1.9 (95% CI −4.8, 1.0) at M6 and of −4.8 (95% CI −8.9, −0.6, $P = .026$) at M12 between early starters and delayed starters in favor of MLC901 (Figure 3B). Sensitivity analyses using the ITT population without LOCF as well as after adjusting for potential confounding factors showed similar results as the analysis in ITT with LOCF post hoc ITT (with LOCF) analysis at M3 showed an MD of −0.59 (95% CI −2.60, 1.41) and at M9, −3.36 (95% CI −5.64, −1.09) (Supplementary Table 2).

ADCS-CGIC, ADCS-ADL, NPI, and MMSE

At M6, 8.5% of patients improved on ADCS-CGIC, 59.3% had no change, and 32.2% deteriorated in early starters compared to 10%, 41.7%, and 48.4%, respectively, in delayed starters ($P = .121$) (Supplementary Figure 1). The between-group difference in the proportion of patients who improved or had no change was 16.1% (95% CI −1.4, 32.4) at M6. ADCS-CGIC was comparable between early starters and delayed starters. Similar results were observed in the sensitivity analyses (data not shown) as in the main analysis of ITT with LOCF.

The mean change from baseline was comparable between early starters and delayed starters at M6 and M12 for each of ADCS-ADL, NPI, and MMSE (Supplementary Table 3).

After reviewing all VEs reported as SAEs, the DSRB made the decision to terminate the study because of concern regarding the rate of stroke and major VE that occurred in the study. Subsequently, a formal analysis was performed which showed that the observed rate of stroke and other VEs in ATHENE was no more than expected in an AD pop-ulation. Additionally, no significant difference in the risk of VE be-tween MLC901 and placebo was observed despite an imbalance of vascular risk factors at baseline. Many of the study patients have vascular risk factors for stroke and other VEs at baseline, which is in line with studies showing that patients with AD have more vascular risk factors than nondemented controls.[35,36] Furthermore, patients with AD dementia have higher rates of stroke compared with patients with non-AD dementia even after adjusting for risk factors.[37] The incidence of ischemic stroke in AD cases and non-AD controls has been shown to be 37.8 and 23.2 per 1000 person-years, respectively.[37,38] By comparison, the ATHENE study patients had about 40 ischemic strokes for every 1000 person-years. Hence, there was no evidence that MLC901 increased the risk of stroke and VE in this study population.

In addition to providing more person-years of safety observation of MLC901, the study had a randomized delayed-start design that allowed for the opportunity to observe possible disease-modifying effects.[39−44] From M6, the MLC901 "early starters" continued to improve on mean ADAS-Cog score at M9 and M12. The "delayed starters," on the other hand, exhibited an earlier and more rapid decline at M9 and M12. The difference between treatment arms did not show a clear trajectory of approaching each other, suggesting either a prolonged symptomatic effect of MLC901 or slowing of disease progression by early treatment with MLC901. The effect was more apparent among patients who were compliant to the study medication and in study completers as shown in the PP analysis. These clinical findings are consistent with the reported preclinical pharmacologic properties of MLC901 in AD models.[6,45−48] The 3-point ADAS-Cog change was shown to be an appropriate minimal clinically relevant change in patients with AD.[23] This change was observed as statistically significant difference at M9 between early starters and delayed starters (Figure 3). However, this should be interpreted with caution together with the results at key time points of interest (ie, M6 and M12).

The main strength of this study is the randomized, double-blind, placebo-controlled trial design followed by delayed-start phase. The target recruitment was achieved, and the vast majority (95%) of the subjects in the double-blind phase of the study opted to participate in the delayed-start extension phase. Attrition due to withdrawal of consent and loss to follow-up was minimal.

However, we acknowledge some potential limitations in this study. Each phase of the study was planned to last only 6 months primarily to investigate safety. However, AD, being a chronic progressive disease, may require study follow-up of more than a year to sufficiently assess the full effects of disease-modifying treatments. The study was performed in a predominantly Chinese population and hence may not be generalizable to other populations. The diagnosis of AD as study entry requirements was not based on neuroimaging or cerebrospinal fluid biomarkers of amyloid burden; hence, not all study subjects may have AD pathology. Discontinuation of 14 subjects from assessment of efficacy outcomes at M12 might reduce the chance of detecting a potential treatment effect in any of the efficacy outcomes. As this was a small trial and the efficacy outcomes were secondary, future clinical trials of MLC901 in AD are warranted, and these studies should utilize AD biomarkers, larger sample sizes, longer follow-up and sensitive assessments to detect disease modification such as the Clinical Dementia Rating sum of boxes.

Conclusions and Implications

The ATHENE study of 125 persons with dementia found no evidence of a significant increase in adverse events between MLC901 and placebo, thus providing support for further studies on both efficacy and safety. Analyses suggest the potential of MLC901 in slowing down AD progression, but this requires further confirmation in larger and longer studies using biomarkers for AD.

Acknowledgments

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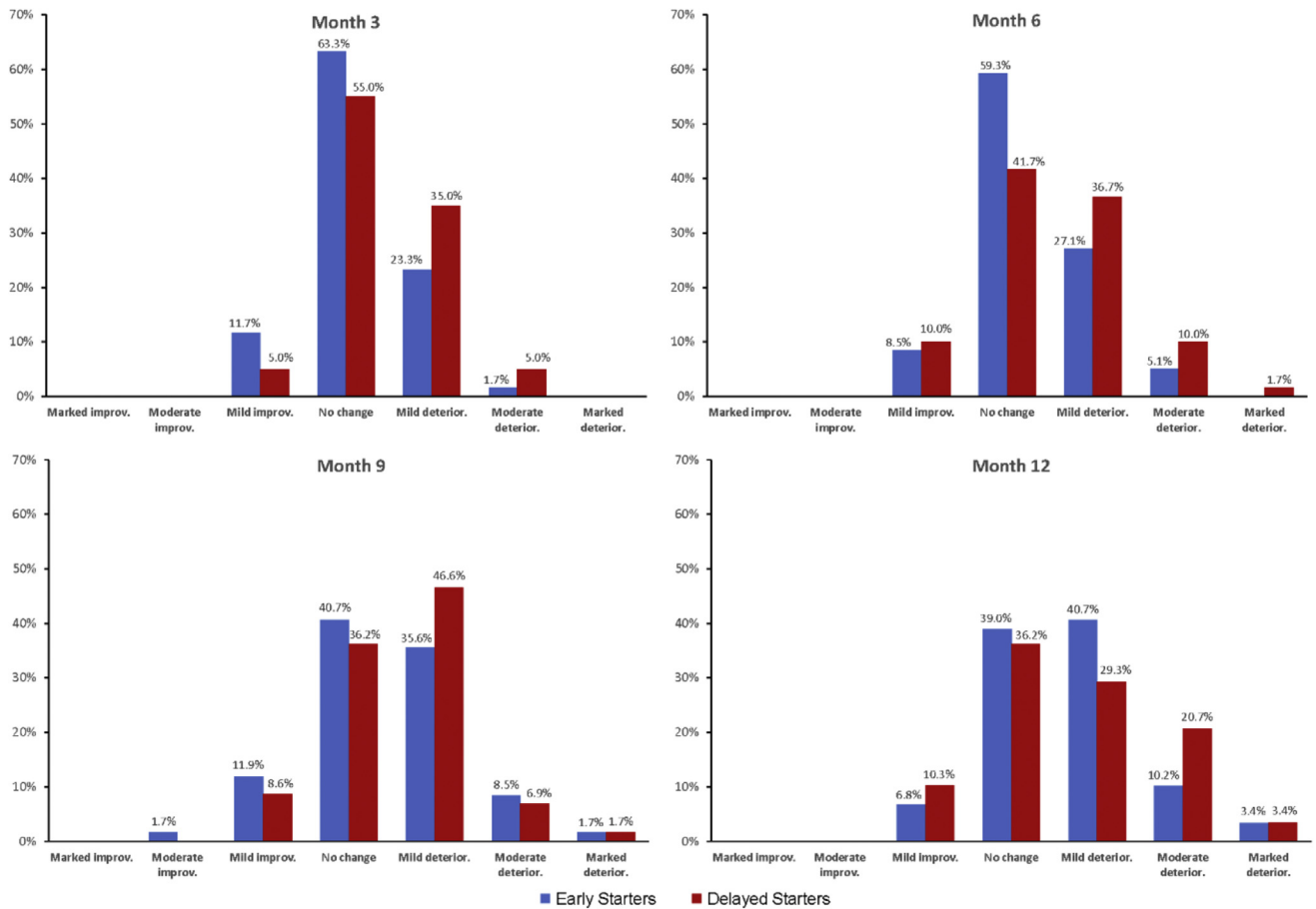
Supplementary Figure 1. Comparison of Alzheimer's Disease Cooperative Study−Clinician's Global Impression of Change (ADCS-CGIC) scores between early and delayed starters at months 3, 6, 9, and 12.

Supplementary Table 1
Adverse Events by MedDRA System Organ Classification by Study Phase

System Organ Classification	Placebo-Controlled Phase (0-6 mo)		Delay-Start Phase (6-12 mo)		Both Phases (0-12 mo)	
	Early Starters (n = 62)	Delayed Starters (n = 63)	Early Starters (n = 59)	Delayed Starters (n = 60)	Early Starters (n = 62)	Delayed Starters (n = 63)
Blood and lymphatic system disorders	2	0	0	1	2	1
Cardiac disorders	0	1	0	2	0	3
Ear and labyrinth disorders	0	1	0	0	0	1
Eye disorders	0	1	0	0	0	1
Gastrointestinal disorders	11	5	8	5	19	10
General disorders and administration site conditions	3	6	3	1	6	7
Hepatobiliary disorders	1	0	0	0	1	0
Immune system disorders	0	0	1	0	1	0
Infections and infestations	14	13	15	8	29	21
Injury, poisoning, and procedural complications	12	15	9	11	21	26
Investigations	3	3	3	3	6	6
Metabolism and nutrition disorders	3	1	0	0	3	1
Musculoskeletal and connective tissue disorders	4	3	0	3	4	6
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	1	0	0	0	1
Nervous system disorders	11	3	1	2	12	5
Product issues	1	0	0	0	1	0
Psychiatric disorders	3	3	1	3	4	6
Renal and urinary disorders	3	1	0	0	3	1
Reproductive system and breast disorders	0	0	2	0	2	0
Respiratory, thoracic, and mediastinal disorders	5	6	5	2	10	8
Skin and subcutaneous tissue disorders	0	1	5	1	5	2
Surgical and medical procedures	0	0	0	1	0	1
Vascular disorders	3	3	3	3	6	6
Total	79	67	56	46	135	113

Supplementary Table 2
Sensitivity Analysis of Mean Difference and 95% CI of Improvement From Baseline in ADAS-Cog Scores Between Early and Delayed Starters at Months 3, 6, 9, and 12 Using the Intention-to-Treat (ITT) Population, Per-Protocol Population (PP), Without Last Observation Carried Forward Method (without LOCF), and After Adjustment for Potential Confounders

	ITT (LOCF)	PP	ITT (Without LOCF)	ITT Adjusted*
Month 3	−0.59 (−2.60, 1.41)	−1.45 (−4.16, 1.27)	−0.61 (−2.67, 1.45)	−0.72 (−2.67, 1.23)
Month 6	−0.99 (−3.28, 1.29)	−1.89 (−4.81, 1.03)	−1.00 (−3.31, 1.31)	−1.09 (−3.33, 1.15)
Month 9	−3.36 (−5.64, −1.09)	−3.66 (−6.42, −0.89)	−3.01 (−5.29, −0.73)	−3.22 (−5.50, −0.94)
Month 12	−2.35 (−5.45, 0.74)	−4.75 (−8.92, −0.59)	−3.06 (−6.61, 0.48)	−2.07 (−4.96, 0.82)

*Adjusted for age, sex, educational level, baseline ADAS-Cog score, baseline MMSE score, and standard AD treatment used.

Supplementary Table 3
Change From Baseline Scores (Mean ± SD) on Alzheimer's Disease Cooperative Study−Activities of Daily Living Scale (ADCS-ADL), Neuropsychiatric Inventory (NPI), and Mini−Mental State Examination (MMSE) Over Time in the ITT Population

	Early Starters (n = 62)	Delayed Starters (n = 63)	Mean Difference (95 CI)
ADCS-ADL			
M3	−1.7 (6.75)	−1.0 (5.61)	−0.74 (−2.95, 1.48)
M6	−3.2 (8.18)	−2.7 (7.29)	−0.52 (−3.32, 2.28)
M9	−3.7 (9.82)	−4.5 (8.47)	0.78 (−2.56, 4.13)
M12	−4.6 (9.28)	−6.1 (9.46)	1.54 (−1.88, 4.95)
NPI			
M3	−0.2 (7.67)	1.0 (10.38)	−1.13 (−4.39, 2.12)
M6	2.7 (12.48)	0.5 (10.51)	2.18 (−1.99, 6.35)
M9	0.9 (13.34)	4.1 (13.18)	−3.20 (−8.04, 1.63)
M12	3.0 (11.64)	3.6 (13.13)	−0.60 (−5.12, 3.92)
MMSE			
M3	0.1 (2.37)	−0.0 (2.79)	0.15 (−0.78, 1.07)
M6	0.1 (2.66)	−0.5 (3.02)	0.57 (−0.46, 1.60)
M9	0.6 (3.24)	−0.1 (2.98)	0.70 (−0.43, 1.84)
M12	−0.4 (3.12)	−1.2 (4.02)	0.81 (−0.50, 2.12)