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An 8-week open label trial of L-Threonic Acid Magnesium Salt in patients with mild to moderate dementia

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ABSTRACT

Emerging research on the effects of a novel magnesium compound of L-Threonic Acid Magnesium Salt (L-TAMS) containing Vitamins C and D on cognitive performance suggests that supplementation may be of benefit to individuals with Alzheimer's disease (AD). The current open label trial explored L-TAMS effects in patients with mild to moderate probable AD. Fifteen patients with a clinical diagnosis of mild-to-moderate AD underwent 18F-FDG-PET imaging and neuropsychological testing, and blood draws at baseline and after 8 weeks of treatment in order to assess the acute effects of L-TAMS supplementation on cerebral glucose metabolism and cognitive performance. Neuropsychological testing and blood chemistries were also performed after 4 months of L-TAMS discontinuation. We did not find metabolic changes in *apriori* ROIs associated with AD rather, exploratory analyses showed statistical brain maps of cerebral-to-whole brain increases in regions not associated with AD. However, these findings were uncorrected for multiple comparisons and none of the findings survived multiple region comparisons. Although this study was underpowered to detect cognitive changes, a significant increase was found in MMSE scores after 8 weeks of L-TAMS treatment. No significant changes were found on other cognitive measures. The results of this study need to be interpreted with caution given significant study limitations including possible Type I error due to multiple comparisons, no comparison placebo group, and small sample size. Larger and longer, randomized placebo-controlled trials are needed to clarify whether L-TAMS treatment has significant effects on cognitive or relevant biomarkers in persons affected by or at risk for AD.

Introduction

In the United States, there are an estimated 5.2 million cases of Alzheimer's Disease (AD), with AD and other dementias affecting nearly 1 in 3 senior adults [2]. With the mounting financial and emotional toll of care for AD patients, the issue of finding safe and efficacious treatments is ever more pressing. Given the personal and global impact of AD, there is an urgent need for adjunctive or stand-alone treatments aimed at improving the long-term cognitive and functional outcomes by slowing or possibly halting the trajectory of cognitive decline.

Currently, persons with a clinical diagnosis of AD have few therapeutic options and those that are available, show only moderate efficacy in slowing cognitive changes [3–5], marginal clinical improvements [6,7], or temporary functional stabilization [8]. Cholinesterase inhibitors, the most common being donepezil, have been developed as an important and common treatment for people with AD. *N*-methyl-D-aspartate receptor (NMDA) antagonists such as memantine are also commonly used alone or combined with a cholinesterase inhibitor for treatment of AD. Results of treatment with NMDA receptor antagonists are shown to be similar to those of cholinesterase inhibitors [9]. However, neither cholinesterase inhibitors nor NMDA receptor antagonists halt disease progression.

Although data is limited, emerging research on a novel magnesium compound, L-Threonic Acid Magnesium Salt (l-TAMS), suggests that l-TAMS supplementation may have cognitive benefits in patients with AD [1,10–12] or normal elderly with subjective cognitive complaints [13]. The neurobiological effects of l-TAMS treatment have been studied in several studies using AD-like

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animal models [14,15] with findings that suggests a greater bioavailability of l-TAMS in the brain compared to non-significant increases with other magnesium compounds (i.e. magnesium citrate, magnesium chloride).

The current study was an open label, 8-week, proof-of-concept trial to assess whether supplementation with a combination regimen of instant release and sustained release tablets containing l-TAMS resulted in increased cerebral glucose metabolism in regions that are preferentially and progressively affected by AD, measured by 18F-FDG-PET, in patients with a clinical diagnosis of mild to moderate probable AD.

Specifically, we were interested in metabolic changes in regions predominantly affected in AD including the prefrontal cortex, parietotemporal cortex, and posterior cingulate cortex [16]. We also included the medial temporal cortex (including the hippocampus and entorhinal cortex) as a region affected in conversion to AD [17]. In addition to 18F-FDG-PET, we assessed measures of global cognitive functioning and the selected cognitive functions of attention, memory, semantic fluency, visuospatial abilities, and executive functions.

Materials and methods

Subjects

Subjects were recruited through local medical doctor referrals, fliers placed at Stanford clinics and the surrounding community, advertisements in local newspapers, clinical trials registries, and the Alzheimer's Association online clinical trials matching service.

Inclusion criteria included adults of either gender > 60 years of age (women had to be post-menopausal), a diagnosis of probable AD from their physician, a Mini-Mental State Examination (MMSE) between 14 and 24, adequate visual and auditory acuity to allow for neuropsychological testing, at least 12 years of education (or a GED to allow consistency of the sample), and willingness to or having a representative willing to sign the informed consent prior to enrollment into the study (for those subjects unable to sign or understand informed consent, assent to participate in the study was required), and agreeing to discontinue vitamins, minerals, or dietary/herbal supplements for at least 7 days prior to study entry and until after study completion.

Exclusion criteria included having one or more of the following medical conditions: Active heart disease, uncontrolled high blood pressure ($\geq$140/90 mmHg), hepatic or renal dysfunction as evidenced by ALT, AST, AP being $\geq$2 times the upper limit of normal or serum creatinine value $\geq$2.0 mg/dl or other clinically significant abnormal clinical laboratory value per primary investigator (PI) discretion, type I diabetes, unstable thyroid disease, unstable psychiatric illness or psychiatric hospitalization within the past year or, history of drug or alcohol abuse, immune disorder (such as HIV/AIDS), history of TIAs, carotid bruits, verified lacunes, significant pulmonary disease, history of cancer (except localized skin cancer without metastases or in situ cervical cancer) within 5 years prior to screening, or any medical condition or abnormality that, in the opinion of the PI would compromise the safety of the subject or the quality of the study data. Subjects were also excluded if they had participated in another research study within 30 days prior to the screening visit or had any contraindication for PET imaging including those unable or unwilling to lie down for 1 h.

Further exclusion criteria included use of any medications that are known to interact with magnesium including potassium-sparing diuretics because they could increase magnesium levels, loop and thiazide diuretics because they could decrease magnesium levels, muscle relaxants, chelating agents, anticholinergic medications, narcotics, antipsychotics, Parkinsonian medications, anticonvulsants, corticosteroids, anticoagulants, glutamate blockers (including memantine), use of an unstable dose of medication (defined as fewer than 90 days at the same dose), magnesium containing antacids, supplemental magnesium or any magnesium containing products, use of all dietary or herbal supplements or products including those purported to improve memory, improve sleep or decrease stress, having an allergy or sensitivity to any ingredient in the test product, or use of any medication deemed exclusionary by PI. Because the study product could reduce the absorption of antibiotics a washout period of 2 weeks was required for study participation. The PI evaluated any subject using calcium channel blockers. Although as needed benzodiazepine use was allowed, regular benzodiazepine use was not allowed during study participation. Use of cholinesterase inhibitors was not an exclusion criterion for this study.

Procedures

This was an open label trial of l-Threonic acid Magnesium containing Vitamin C and Vitamin D. While l-TAMS has been sold as a commercial supplement and is on the FDA Generally Recognized as Safe (GRAS) list, it has not been optimized for individuals with AD. The dosing schedule and formulations in this trial were designed specifically for AD patients. The daily dosage of l-TAMS was 1800 mg as follows: 1) 600 mg of 6-h sustained release l-TAMS (clinical code MMFS-201) in the morning and 2) one MMFS-201 tablet and one 600 mg instant release tablet (clinical code MMFS-101) in the evening. It is suggested that this sustained release formulation (MMFS-201) may serve to maintain elevated levels of l-TAMS in the periphery.

Subjects underwent 18F-FDG-PET imaging, neuropsychological testing, and blood draws for clinical data at baseline (Time 1; T1) and 8 weeks of MMFS-201-101 treatment (Time 2; T2). Neuropsychological testing was repeated 4 months after discontinuation of MMFS-201-101 treatment (Time 3; T3).

Clinical laboratory tests

Blood draws were conducted prior to treatment initiation to assess kidney and liver function, complete blood count, fasting plasma insulin, and red blood cell magnesium.

Neuropsychological testing

Neuropsychological testing was performed by study personal with expertise in the administration of neuropsychological measures. The following measures were utilized:

Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-COG; [19]). This is a widely used cognitive measure of global abilities in clinical trials of AD and used with permission from the NIA Alzheimer's Disease Cooperative Study (NIA Grant AG10483).

Delis-Kaplan Executive Function System (D-KEFS; [20]). This is a standardized battery that assesses higher order abilities (executive functioning). Two selected subtests were utilized.

Color-Word Test. This test is comprised of 4 subtests including Color Naming, Word Reading, Inhibition, and Inhibition/Switching.

Trail Making Test. This is a graphomotor test comprised of 5 conditions including Visual Scanning, Number Sequencing, Letter Sequencing, Number Letter Switching, and Motor Speed. Condition 4 (Number Letter Switching) is a measure of cognitive flexibility.

Mini Mental Status Examination (MMSE; [21]). This is a brief global measure of cognitive functioning.

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; [22]). This is a neuropsychological battery used in the assessment of dementia and has been utilized in numerous clinical trials. It is composed of 11 subtests that measure attention, processing speed, naming, semantic fluency, visual perception, visuospatial/constructional ability, verbal learning and memory, and visual memory. Subtests are combined into index scores of attention, language, visuospatial/constructions, immediate, and delayed memory. It has 2 alternative forms A and B. Since there are only 2 alternate forms, forms were counterbalanced between patients. That is, half of the patients were administered Form A at baseline and the other half were administered Form B at baseline with alternating forms used at subsequent assessments.

Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV; [23]) Digit Span subtest. This subtest assesses both simple and complex verbal attention.

18F FDG-PET

18F FDG-PET imaging was used to examine the cerebral metabolic rate of glucose (CMRgl) change before and after treatment. Following a fast of at least 4 h confirmed by a fasting serum glucose level below 150 mg/dL, a 10-min PET scan was performed, on GE Discovery 600 or 690 scanners (GE Healthcare, Waukesha, WI), in the 3D mode 45 min after the intravenous (IV) administration of 5 mCi of 18F-FDG together with a CT scan for attenuation correction purposes. PET images were reconstructed using ordered subset expectation maximization (OSEM) with 4 iterations, 16 subsets, and 5.0 mm cutoff filter. CT scan utilized 120 kV and "smart current."

Statistical analyses

The MATLAB-based package SPM (http://www.fil.ion.ucl.ac.uk/spm/) was used to spatially realign baseline and follow up scans, to deform these individual images to the MNI template coordinate space and to smooth them with 8 mm Gaussian kernel. The CMRg was calculated with whole brain as reference. Voxel-wise paired *t*-test to assess the CMRgl changes was conducted especially for each of the regions known to be affected by AD using the small volume correction (SVC) procedure to correct for multiple comparisons. As an exploratory analysis, we investigated the correlation between the MMSE change and the CMRgl change at the peak voxel (with the most significant p-value) where CMRgl increases were detected independent of any behavior change.

Additionally, we assessed increases in a statistical region of interest (sROI) that has been shown to track progressive AD-related CMRgl declines with improved power and freedom from Type I error associated with multiple regional comparisons [18] to examine the MMFS-201-101 treatment effects on CMRgl free of the multiple comparisons. Finally, we examined the relationship between the changes from baseline in 18F-FDG-PET based CMRgl and the changes from baseline in MMSE score using Pearson correlation coefficient.

Repeated measure analyses were conducted on cognitive variables between T1, T2, and T3. Baseline age was used as a covariate for individual RBAN scores and other cognitive variables with the exception of the RBAN index scores. These latter scores were derived from RBANS manual and already adjusted for age.

Results

Thirty-three subjects were screened for the study, 14 subjects did not meet study criteria, 1 subject declined to participate, 1 subject dropped out prior to enrolling secondary to transportation difficulties and 17 subjects were then enrolled into the study. Two subjects were dropped from the study; one due to low sodium level at T1 and the other subject developed mild gastrointestinal discomfort after taking MMFS-201-101. Besides the patient who developed GI symptoms, no other adverse events occurred. Therefore, 15 subjects (8 men and 7 women) completed the T2 assessment (See Fig. 1). Fourteen subjects completed T3 assessment; one female subject did not want to discontinue MMFS-201-101 and therefore was not included in the T3 analyses. See Table 1 for T1 age, education, MMSE, and magnesium levels for T2 completers. Only 1 subject was using donepezil in conjunction with the MMFS-201-101 treatment during the study.

MMFS-201-101 Treatment: T1 to T2

Subjects exhibited 8-week regional-to-whole brain CMRgl increases in precuneus ($p = 0.001$), occipital ($p = 0.001$), and frontal ($p = 0.005$) regions, all uncorrected. However, none of these findings survived SVC for multiple comparison correction. To visualize the effects of MMFS-201-101 treatment on CMRgl of this small study in an exploratory manner, voxel-wise results were displayed with very liberal uncorrected $p = 0.01$ (Bottom row, Fig. 2). We noted the increase in occipital regions was bilateral although this finding must be interpreted with caution given the inflated type-I error. Interestingly, we also found a significant increase in several cerebellar regions including crus 1, 2 and vermis uncorrected at the $p = 0.005$ level. We noted that some of the regions where the increase was observed were outside of what FDG-PET AD literature often referred to as the 'spared' regions. In addition to the observed increases, exploratory analyses also noted CMRgl declines in precuneus and inferior parietal regions anterior to those that have

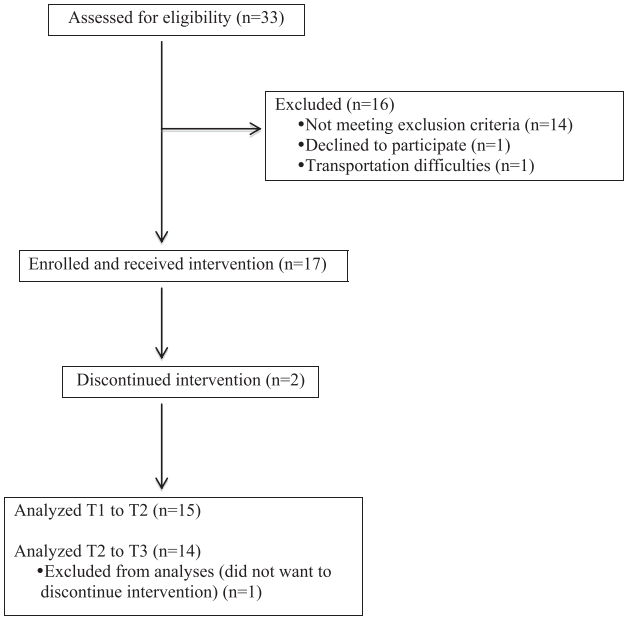

Fig. 1. Study flow chart.

Table 1
Baseline demographic and clinical variables of study completers.

	N	Range	Mean	SD
Age	15	63–87	77.00	5.86
Education	15	12–21	16.80	2.51
MMSE	15	14–26	23.00	3.87
L-TAMS level T1	15	4.00–6.20	4.94	0.63

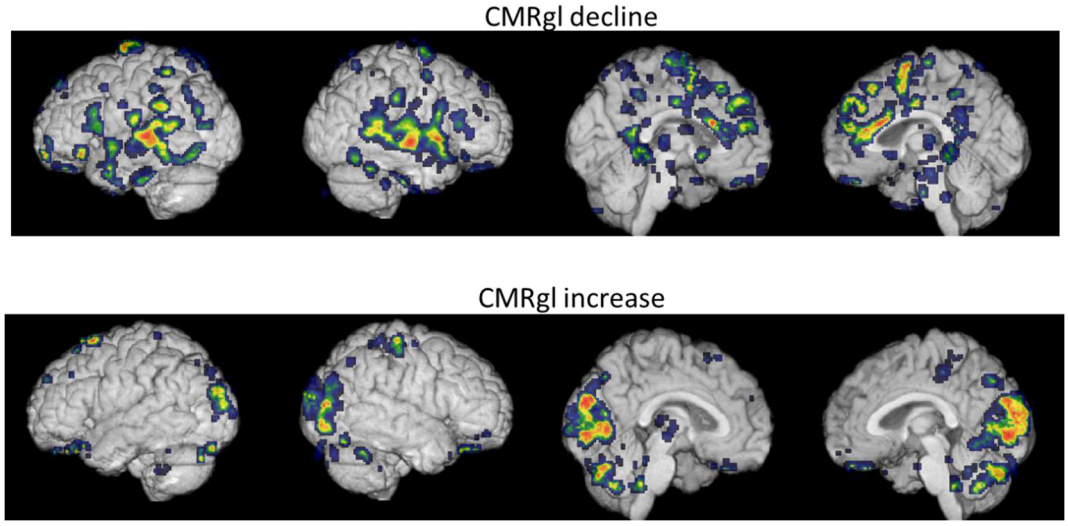

Fig. 2. Increases and decreases in regional cerebral metabolism with FDG PET pre- and post- L-TAMS treatment (paired t-tests, $p < 0.05$).

been shown to be preferentially affected by AD (uncorrected $p = 0.005$) (See top row, Fig. 2). Overall however, the declines were more anterior compared to what is typically seen in AD patients. As part of our cautious note and considering the exploratory nature of the 18F FDG-PET findings, we note again that none of these findings survived the SVC procedure for multiple comparison correction.

Among the four locations (peak voxels) at which CMRgl improvement was observed, precuneus, occipital, frontal cortex and the cerebellar peak voxels, none of the corresponding CMRgl associations with MMSE was significant. However, a trend level CMRgl change was associated with MMSE change in the peak voxel within the cerebellum ($p = 0.055$ and $R = 0.544$) without correction for multiple comparisons.

Repeated measures analyses revealed significant improvement in MMSE score with MMFS-201-101 treatment (mean change = 1.73 points, SD = 2.49, $p = 0.035$). When age was added as a covariate, findings remained significant ($p = 0.043$; Fig. 3). No significant treatment changes were seen on any RBANS index scores or individual RBANS subtests with age as a covariate. Similarly, there were no significant changes on ADAS-Cog, D-KEFS subtests, or WAIS Digit Span (Table 2). Furthermore, many of the subjects were unable to complete the D-KEFS subtests therefore results from these measures was limited due to very small sample size.

Positive correlations between the change of MMSE and the change of CMRgl were observed in the inferior orbital frontal ($p = 0.026$), precuneus ($p = 0.032$), thalamus ($p = 0.028$), middle cingulate ($p = 0.028$), and multiple cerebellum locations ($p < 0.005$), all uncorrected for multiple comparisons. Again, none of these survived multiple comparison correction. Finally, we examined CMRgl changes using our summary index sROI which is free of the multiple comparison concern. The mean sROI change 0.0093 (SD = 0.031) was not statistically significant ($p = 0.265$) and somewhat consistent with the voxel-wise weak CMRgl decline pattern as well as increases of CMRgl in some regions. The lack of CMRgl decline measured by sROI may be indicative of MMFS-201-101 effects, but may also be due to the limited sample size, short trial duration, and lack of a comparison to a placebo group.

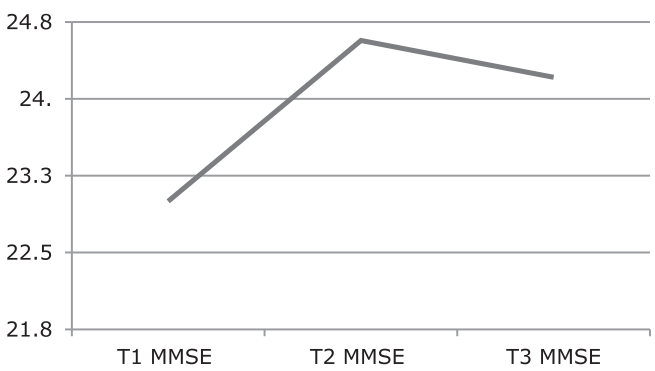

Fig. 3. Change in mean MMSE over time.

MMFS-201-101 discontinuation: T2 to T3

No significant or trend level difference was found in MMSE score (Fig. 3) or on any other cognitive variables 4 months after MMFS-201-101 discontinuation.

Discussion

The current pilot, proof-of-concept study assessed the regional metabolic change in 18F-FDG-PET imaging before and after 8 weeks of treatment with MMFS-201-101, and the association between the metabolic change and MMSE in a sample of subjects with mild to moderate dementia. We did not find metabolic changes in our primary endpoints, *i.e. apriori* ROIs [24] associated with AD. Rather, exploratory analyses showed statistical brain maps of cerebral-to-whole brain increases in regions not associated with AD. However, these findings were uncorrected for multiple comparisons and none of the findings survived multiple region comparisons. Therefore, we cannot rule out that these latter findings were due to Type I error.

Because we powered this pilot proof of concept study only for 18F-FDG-PET results, the significant improvement found in MMSE scores after 8 weeks of MMFS-201-101 treatment was unexpected. No other specific cognitive improvements were expected or found. A previous study showed that in subjects with MMSE scores of 24 or less, that either no change or a maximum of 1 point increase is shown upon MMSE retesting after 2 months [25]. This suggests that in spite of our limited sample size, the finding of a 1.57 improvement after 2 months of MMFS-201-101 treatment may be beyond expectations due to practice effects (improved performance secondary to previous testing) although this finding needs to be interpreted with caution, particularly in patients with the

Table 2
Cognitive variables.

	Time 1		Time 2		Time 3	
	Mean	SD	Mean	SD	Mean	SD
MMSE	23.00	4.02	24.57	4.35	24.21	4.23
ADAS	26.05	10.99	26.69	11.92	25.77	11.84
RBAN Index scores						
Total	76.86	16.52	77.67	16.86	78.21	17.36
Immediate memory	73.93	16.51	75.93	17.57	75.64	19.45
Visuospatial constructions	86.60	21.27	91.47	20.45	93.86	23.76
Language	85.73	21.59	88.40	17.11	85.43	15.67
Attention	93.33	16.39	91.47	15.79	90.64	20.51
Delayed memory	70.29	18.54	66.60	22.02	67.29	20.63
RBANS subtests						
List learning	17.87	5.71	18.13	5.59	16.29	6.88
Story memory	10.20	5.03	11.07	5.26	11.29	4.55
Figure copy	14.47	3.76	14.27	5.48	15.07	4.95
Line orientation	15.93	3.95	16.33	3.35	15.00	6.63
Picture naming	8.93	1.58	9.40	0.99	9.21	1.37
Semantic fluency	13.53	6.03	13.33	5.75	11.36	5.21
Digit span	9.93	2.05	9.60	2.03	9.93	2.37
Coding	29.53	10.84	28.53	12.98	26.00	14.60
List recall	1.27	2.12	1.07	2.46	1.00	1.80
List recognition	16.07	2.87	15.07	3.49	15.07	3.75
Story recall	4.27	3.67	4.53	2.77	4.64	3.67
Figure recall	5.50	4.86	5.07	5.20	5.43	5.43
Other measures						
D-KEFS Trail: Condition 4	175.09	126.29	157.09	96.75	161.50	81.99
WAIS-III: Digit span	14.40	3.40	14.67	3.50	14.07	2.66

higher baseline MMSE scores. Since we only noticed an increase in MMSE with MMFS-201-101 treatment but not with any other measures, we cannot clarify the extent to which those increases were related to natural history or practice effects due to the open label design.

Although limited, previous animal studies and one human study raised the possibility that MMFS-201-101 supplementation might have some beneficial cognitive effects. Improvements in cognition after short-term treatment with MMFS-201-101, including spatial memory and short-term memory retention have been observed in a small exploratory study with wild type rats . A recent placebo controlled randomized clinical trial of MMFS-201-101 supplementation of 51 adults aged 50–70 with mild cognitive impairment indicated a significant improvement in cognitive functioning based on a composite score from measures of executive functioning, working memory, attention, and episodic memory after 12 weeks of treatment [13]. Our MMSE findings showing global rather than specific cognitive domain improvement were consistent with the previous human trial where improvement with MMFS-201-101 supplementation was only detected when a composite score composed of multiple cognitive measures was utilized [13].

As this study was a proof-of-concept study, sample size was limited and tailored to detect regional metabolic change. Therefore we were underpowered to detect changes in cognition. In addition, limitations beyond small sample size existed. Because this was an open label trial, we could not determine whether study findings were the result of a placebo effect. Clearly, larger studies that are double-blinded and placebo-controlled are warranted to evaluate whether MMFS-201-101 can be useful as an effective, easily accessible, and affordable treatment supplement for individuals with AD.

Conclusions

This study sought to evaluate the potential effect of microelements, (specifically, magnesium preparation) on regional cerebral metabolism in patients with AD.

Findings suggest the possibility that MMFS-201-101 supplementation is associated with small increases in cerebral metabolism although not necessarily in the regions associated with AD, as well as possibly improvement in global cognitive functioning. However, the biological and clinical significance of these findings are yet to be determined. Further, replication of study results with large cohorts of patients with AD are warranted before adequate conclusions can be drawn. Considering the preliminary nature of this study, results should be interpreted with caution.

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ADAS-COG used with permission from the NIA Alzheimer's Disease Cooperative Study (NIA Grant AG10483).

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