

MMFS202 and MMFS302 use in ADHD:
An Open-label Pilot Study of Cognitive and Functional Effects

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I. BACKGROUND AND SIGNIFICANCE

There is need to improve management of Attention Deficit Hyperactivity Disorder:

Attention-deficit hyperactivity disorder (ADHD) is a neurobiological disorder associated with high levels of impairment in adulthood¹⁻⁴, and is estimated to affect up to 5% of adults worldwide⁵⁻⁷. While currently approved pharmacotherapies for adults with ADHD are often effective, there are limits to their clinical utility. Stimulants are the mainstay of treatment for adults with ADHD due to larger effects than nonstimulants on ADHD⁸⁻¹¹. Two decades of study by our research team and others, including controlled studies of stimulant medications and open studies of tricyclic, monoamine oxidase inhibitor, and atypical antidepressants, reveal that 20-50% of adults with ADHD are considered pharmacologic nonresponders¹²⁻¹⁴. Moreover, adults who are considered responders clinically often show a 50% or less reduction in the core symptoms of ADHD¹³. In addition to residual ADHD symptom burden, pharmacologically treated patients also have residual burden in other cognitive capacities such as executive function challenges. For example, In a recent study of robust open label dosing with the amphetamine lisdexamfetamine, 40% of adults with ADHD were considered to have unresolved and clinically significant impairment in essential elements of behavioral executive control¹⁵. Therefore there is significant clinical need for interventions that support the self-regulatory challenges that are not managed by current pharmacotherapies.

Investigation into the neurobiological basis of ADHD has identified that a circuit involving prefrontal, subcortical and parietal regions is implicated in the pathological basis of ADHD.¹⁶⁻²⁰ Delay in cortical maturation of cortex might impair executive functions, resulting in the poor working memory, attention, and response inhibition in ADHD children.²¹

Magnesium (Mg) is involved in a wide range of biochemical reactions. Preclinical work demonstrates that L-Threonic acid Magnesium salt (L-TAMS) administration is associated with neurobiological and neurofunctional effects in the following ways: 1) Elevation of brain Mg lead to increase in synapse density and plasticity in PFC and hippocampus in young and old rats^{22, 23}; 2) Elevation of brain Mg leads to enhancement of working memory, short- and long-term memory in rats²³, and 3) Elevation of brain Mg leads to enhance fear memory extinction and reduction of anxiety in rats.²²

There have been two published studies of L-threonate in animals, which identified metabolic interaction with ascorbic acid (Vitamin C) but no evidence of toxicity attributable to L-threonate. One published study of calcium L-threonate pharmacokinetics (single and multiple dose) in humans, found that L-threonate was rapidly absorbed and metabolized with no observed adverse effects. While we are not aware of studies focusing on the effects or safety of magnesium L-threonate itself in humans, in 2007, the European Food Safety Authority reviewed a number of unpublished animal studies involving calcium L-threonate including acute toxicity, subchronic and chronic toxicity, genotoxicity, and reproductive and developmental toxicity studies. The assessment concluded that the use of calcium L-threonate at levels that would result in 2,700 mg/d of L-threonate intake is not a safety concern.

The European Food Safety Authority comments are based on its review effects of Calcium L-threonate on rats and dogs. For reference, “NOAEL” refers to “no adverse effects level” in their comments. In discussing the safety of Calcium L-threonate, this opinion notes that:

“Calcium L-threonate has low oral acute toxicity, with no adverse effects observed at doses as high as 40 g/kg bw in mice or 32 g/kg bw in rats. In sub-chronic studies with calcium L-threonate, the Panel identified a NOAEL of 4 g/kg bw/day in the rat with regard to effects on blood coagulation time and accretion of the thyroid gland, and of 1 g calcium L-threonate/kg bw/day in the dog with regard to hyperplasia of the thyroid gland. The Panel noted that the effects on blood coagulation time and the thyroid gland were reversible and that a mild accretion in the thyroid gland in rats was limited to males only. The Panel further noted that these effects

are likely to be attributed to the high dosage of calcium administered over a long period, as a high concentration of calcium ions can result in accelerated blood coagulation, and can influence intestinal absorption of iodine and reduce/suppress the secretion of thyroxin by the thyroid gland.” The panel also wrote that “Studies using different test systems in vitro and in vivo indicated that calcium L-threonate was not genotoxic. Although no carcinogenicity studies were available, the Panel considered that such studies were not needed given that L-threonate is an endogenous compound in the body and that calcium L-threonate did not show any genotoxic potential. Reproductive and developmental toxicity studies in mice indicated that calcium L-threonate in doses up to 6 g/kg bw/day has no adverse effect on the fertility and the developing fetus, and did not cause maternal toxicity.”

The agency further notes in their statement that “the margin of safety between the estimated human exposure to L-threonate and the amount of L-threonate equivalent to the NOAELs for calcium L-threonate, as demonstrated in sub-chronic toxicity studies in dogs and rats, is 39 – 19 for the dog and 155-77 for the rat. The Panel considers this margin of safety to be sufficiently large given that threonate is an endogenous compound in the body, and that the NOAELs in the dog and rat studies were identified for effects attributable not to L-threonate but to the calcium dosages.”⁴²

Role of Magnesium in ADHD and ADHD management:

Magnesium deficiency, like Vitamin D deficiency, is common, and has been studied among individuals with ADHD. Kozielec and Starobrat-Hermelin (1997) found magnesium deficiency in 95 per cent of children with ADHD across three sources examined, most frequently in hair (77.6 per cent), in red blood cells (58.6 per cent) and in blood serum (33.6 per cent).²⁴ However, a recent study by another group did not find lower serum Mg in children with ADHD. This could be due to poor resolution of serum Mg for evaluation of body.²⁶

Studies have also explored magnesium supplementation in children with ADHD. Another study by Starobrat-Hermelin and Kozielec (1997) recruited 50 hyperactive children, aged 7-12 years, who fulfilled DSM-IV criteria for ADHD, with recognized deficiency of magnesium in the blood (blood serum and red blood cells), and in hair using atomic absorption spectroscopy. Some of the participants had disruptive behavior disorders. Over six months, subjects took magnesium preparations in a dose of about 200 mg/day. Participants received either standard treatment, or standard treatment with a magnesium preparation. For the subgroup of children that did not have other mental disorders coexisting with hyperactivity, there was an increase in the magnesium content in hair and a decrease of hyperactivity, both of which were significant relative to baseline. These changes were also greater than those seen in the control group that was not treated with magnesium.²⁷

A more recent open-label study evaluated the effects of 100 mg of a combined Mg(2+)/vitamin B6 regimen on the behavior of 52 “hyperexcitable” children under the age of 15 and their families. Thirty of the 52 hyperactive children had lower than expected erythrocyte Mg values. Combined Mg(2+)/vitamin B6 intake for 3 to 24 weeks restored expected erythrocyte Mg values, and variables of hyperexcitability were reduced after 1 to 6 months treatment.²⁸

An open-label study conducted by Mousain-Bosc and colleagues followed erythrocyte Mg and symptoms of hyperactivity, hyperemotivity, aggressiveness, and lack of attention at school in 40 children with clinical symptoms of ADHD during a magnesium-vitamin B6 (Mg-B6) regimen (6 mg/kg/d Mg, 0.6 mg/kg/d vit-B6) over at least 8 weeks. Children from the ADHD group showed significantly lower erythrocyte Mg values than control children (n = 36). Over the study, measures of hyperactivity, hyperemotivity/aggressiveness, and attention in school improved, while there was also a significant increase in erythrocyte Mg values. When the Mg-B6 treatment was stopped, ADHD symptoms reappeared within a few weeks, and erythrocyte Mg values decreased.²⁹

Rationale for Magnesium L-Threonate as a support for ADHD and related cognitive deficits:

Preclinical studies suggest that L-Threonic acid Magnesium salt can modulate rat brain function. Slutsky, et al (2010) demonstrated that oral delivery of L-Threonic acid Magnesium salt to rats achieves significantly higher levels than the control feed, whereas magnesium chloride, magnesium orotate, or magnesium gluconate did not. This report also demonstrated increases in synaptic density in hippocampal regions, and reversed task impairment in Alzheimer's-model rodents. Therefore, L-Threonic acid Magnesium salt could be expected to have central nervous system effects in human subjects, including potentially alleviation of ADHD symptoms.²³

The risk profile of magnesium supplementation is favorable relative to that of pharmaceuticals currently available under FDA indication for Attention Deficit Hyperactivity Disorder. In a rat model, magnesium chloride at an intake of up to 2.5% of food resulted in no significant toxic effects.³⁰ In addition, acute and chronic supplementation for hypomagnesemia has been well tolerated with a favorable safety profile.^{31,32}

Magnesium supplements, including L-Threonic acid Magnesium salt, are widely purchased and consumed. The most common side effect of magnesium supplementation may be diarrheic effects. Neurocentria, the makers of the study agent MMFS202 6-hour release and MMFS302 12-hour release, has communicated that in preliminary studies they have not found significant side-effects with 2 g/day of L-Threonic acid Magnesium salt.³³ Some subjects reported sleepiness, but it subsided after a few days. There were also some reports of vivid dreams and restlessness.³⁴

Conventional therapies for ADHD are thought to work in part through reuptake blockade and/or increased release of the catecholamines dopamine and norepinephrine.¹³ L-Threonic acid Magnesium salt, therefore, offers a novel mechanism of modulating cognitive function. If effective and well tolerated, it could offer a novel modality for support of ADHD or related cognitive deficits.

Because L-Threonic acid Magnesium salt could have positive effects on ADHD symptoms, it has not yet been evaluated in adults with ADHD, and is expected to be well tolerated, we propose to conduct an open-label pilot study enrolling 15 adults with ADHD to receive L-Threonic acid Magnesium salt. The study is designed to evaluate tolerability and feasibility of the protocol, and guide development of future more definitive double-blind study of the selected outcomes.

Subjects with moderate levels of ADHD will be enrolled, including individuals on no current treatment and those receiving current pharmacotherapy for ADHD. Six weeks is a typical interval over which stimulant effect on ADHD may be seen, and we will extend observation to 12 weeks to measure L-Threonic acid Magnesium salt effects that might occur during a reasonable time frame for clinical intervention.

II. SPECIFIC AIMS

Aim 1: Assess the safety of the effects of L-Threonic acid Magnesium salt on cognitive functioning when administered to adults with ADHD.

Hypothesis 1: L-Threonic acid Magnesium salt will be well tolerated in adults.

Aim 2: Assess effect of L-Threonic acid Magnesium salt on attention, behavioral control and cognition.

Hypothesis 2: Compared to pre-administration baseline, administration L-Threonic acid Magnesium salt will yield a significant reduction of (2a) attention and behavioral ADHD traits (as measured by the AISRS) and 2b) ratings of clinical global improvement, (2c) symptoms of executive dysfunction (as measured by BRIEF-A subscales).

Hypothesis 3: Compared to pre-administration baseline, performance on individual neuropsychological tests will improve (as measured by a) elements of the Cambridge Neuropsychological Test Automated Battery, and b) tests used to estimate IQ, and c) higher correlation between performance on neuropsychological tasks.

We also will explore whether baseline red blood cell magnesium level, deficits on BRIEF or neuropsychological tests predict improvements on AISRS or BRIEF measures.

These supplements are not known to diagnose, cure, mitigate, treat or prevent ADHD.

III. SUBJECT SELECTION

We plan to recruit until we enroll 15 male or female subjects between the ages of 18-55 in the study. We will recruit subjects from the pool of existing adult subjects and new referrals to the Pediatric Psychopharmacology and Adult ADHD Program at the MGH. No pediatric subjects will be recruited for this study. If a potential subject's clinician ascertains that the patient has an interest in study participation, the clinician will offer him/her contact information for the study coordinator. The patient can then contact the study coordinator *independently* for more information on the study. If a subject is enrolled from among an investigator's own patients through the aforementioned referral process, the process of informed consent must be completed by a physician colleague who is on the approved study staff and whom the potential subject has not seen for clinical care. Under no circumstances will a physician investigator complete informed consent with his or her own patient. All subjects that enter the study will undergo standard screening and diagnostic procedures. Clinical records are not scanned in order to recruit subjects. Subjects who have completed a previous medication trial in our program may be eligible to participate in this study. Other medical records on a subject will not be used at any point, unless explicit written permission is provided by the subject.

The majority of subjects referred to our program first participate in our general screening protocol entitled, "Screening Protocol for Adults with Attention Deficit Hyperactivity Disorder" (Protocol # 2002-P-001856). This protocol includes a phone screen and clinical interviews tailored to identifying subjects eligible for research in our program. After participating in this screening protocol, subjects are triaged to specific studies based upon eligibility requirements (i.e. age, prior medication efficacy or tolerability).

Study Entry Criteria

Inclusion Criteria:

1. Male or female adults ages 18-55 years of age.
2. A diagnosis of childhood-onset ADHD, meeting the DSM-V criteria for ADHD in adulthood, including at least 5 current symptoms of inattentive or impulsive-hyperactive traits, and childhood onset by age 12, defined as two symptoms of inattentive or of impulsive/hyperactive traits by the age of 12.
3. A score of 20 or more on the Adult ADHD Investigator Symptom Report Scale (AISRS), and, for those individuals stably treated with stimulants, a CGI-ADHD severity score of no greater than 4 ("moderately ill").
 - i. Subjects on a stable dose of stimulant medication must be treated on the same dose for at least 1 month prior to study entry.

Exclusion Criteria:

1. A history of intolerance to magnesium supplementation, or the ingredients in MMFS202 (6-hour release) AND MMFS302 (12-hour release).
2. Pregnant or nursing females.
3. A known unstable medical illness including hepatic, renal, gastroenterological, respiratory, cardiovascular (including hypertension $\geq 140/90$ mmHg at screening), endocrinologic (e.g. thyroid), neurologic (e.g. seizure), immunologic, hematologic, or psychiatric (other than ADHD) disorder. Individuals with kidney dysfunction will be excluded, as dysfunctional kidneys may have difficulty clearing the magnesium from the body (which can result in dangerously high magnesium levels). Individuals with heart block will be excluded from the study.
4. Any medical condition that the Principal Investigator (PI) believes will be exacerbated by study participation.
5. A history of cancer (except localized skin cancer without metastases or *in situ* cervical cancer) within 5 years prior to screening.
6. A known history of narrow-angle glaucoma.
7. Current (within 3 months) DSM-V criteria for abuse or dependence with any psychoactive substance other than nicotine.
8. IQ<80 (based on the Wechsler Abbreviated Scale of Intelligence-II Full Scale IQ calculation)
9. Multiple adverse drug reactions.
10. Any other concomitant medication with primarily central nervous system activity as specified in Concomitant Medication portion of the protocol.
11. Current use of MAO Inhibitor or use within the past two weeks.
12. Current use of antibiotics, as the study agent may reduce the absorption of antibiotics.
13. Subjects may not take any of the following substances for at least 7 days prior to baseline and throughout the study:
 - a. Calcium channel blockers including:
 - i. Felodipine (Plendil®)
 - ii. Amlodipine besylate (Norvasc®).
 - b. Any psychoactive medications including:
 - i. Antipsychotics
 - ii. Anxiolytics
 - iii. Antidepressants
 - c. Any medications known to interact with magnesium including:
 - i. Potassium-sparing diuretics such as Amiloride (Midamor), Spironolactone (Aldactone®), and triamterene (Dyrenium®), as they may increase magnesium levels;
 - ii. Loop and thiazide diuretics such as Furosemide (Lasix®) and Hydrodiuril (Microzide ®, Esidrix®, Hydrodiuril®) as they may decrease magnesium levels;

- iii. Muscle relaxants such as Carisoprodol (Soma®), Pipecuronium (Arduan®), Orphenadrine (Banflex®, Disipal®, Norflex ®), Cyclobenzaprine (Flexeril®, Fexmid®, Amrix ®), Gallamine (Flaxedil®), Atracurium (Tracrium®), Pancuronium (Pavulon®), and Succinylcholine (Anectine ®, Quelicin®);
- iv. Penicillamine (Cuprimine®, Depen ®)
- v. Corticosteroids (Prednisone or Deltasone®)
- vi. Magnesium containing antacids including Maalox®, Mylanta®, Milk of Magnesia, Tums® and Rolaids
- d. Supplemental magnesium or any magnesium-containing products
- e. All dietary or herbal supplements or products including those purported to improve memory, improve sleep, or decrease stress.

Any subject found to be taking these substances during the study will be evaluated by the PI for ongoing eligibility.

14. Investigator and his/her immediate family; defined as the investigator's spouse, parent, child, grandparent, or grandchild.

There will be two categories of individuals presenting with ADHD that will participate in the study: (1) those that have residual ADHD symptoms despite benefit from well-tolerated standard of care ADHD pharmacotherapy (stimulant medication or Atomoxetine); and (2) those that are not on medication for ADHD. Because the study is a pilot study, we will recruit a sample of subjects, and have not specified a ratio of participants in these two groups to be enrolled.

No individual will be removed from an effective and stable treatment regimen for the purposes of participating in the study. Individuals who enter the study on medication for ADHD must be on an effective, well tolerated, and stable dose of a prescription indicated by the FDA for ADHD for at least one month prior to entry. Efficacy and tolerability will be determined by the study clinician, and subjects must have a Clinical Global Impression-ADHD severity rating of no greater than 4 ("moderately ill"), because a score greater than 4 indicates that their ADHD symptoms are unlikely to be effectively treated by their current medication regimen.

IV. SUBJECT ENROLLMENT

Informed consent will be obtained prior to the performance of any protocol procedures and prior to administration of study drug. The informed consent document will be used to explain in simple terms the risks and benefits of study participation to the subject. The nature of the study will be fully explained to the subject by a board-certified physician who is either the primary investigator or a co-investigator. The subject will be encouraged to ask questions pertaining to their participation in the study and the subject may take as much time as they feel is necessary to consider his/her participation in the study as well as consult with family members or their physicians. Participation in this study is voluntary and the subjects may withdraw from the study at any time. The IRB-approved informed consent documents will be signed and dated by the subject and the physician obtaining consent.

V. STUDY PROCEDURES

We will conduct a 12-week open label pilot clinical trial exploring the cognitive effects and tolerability of L-Threonic acid Magnesium salt in adults with ADHD. We will recruit up to 25 subjects, and enrollment will stop once 15 subjects are expected to complete the study.

After providing study information and obtaining IRB approved informed consent, participants will undergo a comprehensive assessment including a psychiatric assessment reviewing current and lifetime DSM-V Axis I conditions, medical history including history of any cardiac symptoms or abnormalities reported on routine clinical exams, and a neuropsychological evaluation which will include confirmation of an IQ greater than 80 (which can be completed at the screening or baseline visit for scheduling flexibility). If a subject has never had a cardiac physical exam a clinician will conduct one. The information obtained at this visit will be reviewed to assure that all inclusion and exclusion criteria are met prior to receiving study agent at the baseline visit. Subjects who do not meet all the criteria for enrollment after these assessments will be discontinued.

We anticipate that subjects may enter this trial following completion of withdrawal from other protocols in our office, and that there may be procedural overlap. So as to not burden subjects with redundant time commitments, we will use the following *diagnostic* data previously collected: If a subject has completed an evaluation with one of the study clinicians within the previous year prior to entrance into this study, they will not be asked to repeat any overlapping diagnostic procedures; if a subject has completed a neuropsychological evaluation within the last 3 months they will not have to repeat this. With subjects' permission, we will use the diagnostic data that had been previously collected. However, the study clinician will review the interval time period to assess for clinically significant medical or psychiatric history, to ensure that the subject meets appropriate study entrance criteria.

Medication Washout:

If clinically appropriate, any subjects taking medication exclusionary to the study must be tapered off this medication prior to baseline visit for the length of 5 half-lives of the medication, corresponding to 95% of the agent leaving the participant's system), plus several days to assess the participant off medication. Discontinuation or taper off of a current medication will be recommended only for subjects with inadequate response to a current treatment. Subjects will not enter the study if it would require tapering a medication that is optimally and comfortably managing a clinical concern. Medication tapers will be monitored by the study clinician in agreement with the research subject and in consultation with the prescribing physician. The prescribing physician will be contacted to discuss feasibility and correctness of removing a subject from current medications and will be asked to monitor the subject's response to the medication change. If the prescribing physician does not find medication discontinuation appropriate or if they do not agree to monitor the subject's response to stopping medications, then the subject will not be enrolled. No subject will be removed from a stable and effective treatment regimen for the purposes of participating in the study.

Participants who fulfill the inclusion and exclusion criteria will participate for 12 weeks, or until withdrawing or terminating participation.

Safety Assessments:

Vital signs (blood pressure, pulse, weight) will be measured at every in-office visit. Height will be measured at baseline and at the end of the study. A urine drug screen will be performed at screening, week 6, and week 12. If the participant is found to have taken an illicit drug, he/she will have a discussion with the doctor to determine if he/she can be in the study. Subjects will be discontinued if there is suspicion of ongoing substance use. For safety purposes, an EKG will be conducted during screening and at the endpoint of the study. Females who are able to have children will also have a urine pregnancy test at screening, week 6, and week 12.

If a participant has a positive pregnancy test she will not be able to take part in the study. Female subjects of childbearing potential must agree to use a medically acceptable form of birth control (such as male for female condoms with or without spermicidal agent, diaphragm or cervical cap with spermicide, medically prescribed IUD, hormonal contraceptives like birth control pills, or abstinence) while they are receiving study agent and for 1 month after the last dose of study agent. In the event that a subject becomes pregnant, we will ask the subject's permission to obtain information about the outcome of the pregnancy and the condition of the newborn. Those subjects who terminate study participation before the completion of the study will be asked to complete all tasks scheduled to take place on the final study visit at the time of study discontinuation.

We will draw blood samples at the screening visit and at study endpoint to determine erythrocyte (red blood cell or RBC) levels of magnesium and calcium. Samples will be analyzed by LabCorp through services provided by the Harvard Clinical and Translational Science Center. Each sample volume will be approximately 3 teaspoons, for a total of 6 teaspoons drawn over the entire study.

All efforts will be made to protect subject privacy, and samples will be labeled with codenames and medical record numbers. The sponsor will not have access to information that identifies participants' samples. Results from laboratory testing (i.e. laboratory values) may become a part of the subjects' MGH medical records, however no information regarding participation in the study will become a part of the medical record.

Subject Visits:

Subjects will be evaluated in the office at baseline (week 0), and weeks 3, 6, 9 and 12. Subjects will be contacted by phone each week between these visits (weeks 1, 2, 4, 5, 7, 8, 10, and 11 by a member of the study staff who will inquire about study drug adherence. The phone visit at Week 1 will be conducted by a study clinician, who will collect Adverse Events. The clinician's assessment of adverse events will inform the decision to alter the dosing instructions and timing, if necessary. Subsequent phone calls will be conducted by a study research assistant to assess medication compliance. At any time, contact can occur by phone or in person as needed with a clinician or research assistant, based on the judgment of the clinician, or by needs of the subjects as they arise. Study clinicians are also available to subjects 24 hours each day by pager. At each office visit, assessments of safety and efficacy will be obtained by administering measures of efficacy (CGI, GAF, AISRS), tolerability (adverse events), and safety (vital signs). At weeks 0, 6, and 12, the clinician will additionally assess for adverse events specifically related to any discontinued medications for the purpose of enrollment. CGI, GAF, and adverse events will not be collected at screening. Neuropsychological assessments will be repeated at week 6 and study endpoint, excluding the WASI-II, which will be repeated only at study endpoint.

Assessments and Instruments:

During the study, the following, assessments and instruments will be used:

Demographic/Background Interview:

- A brief demographic interview to obtain information used to calculate socioeconomic status and information about head injury and traumatic experiences. This will take place during the Screening Visit, after subjects have signed consent.

Brief neuropsychological measures (at screening or baseline, depending on scheduling flexibility, unless otherwise noted):

- Wechsler Abbreviated Scale of Intelligence- II (WASI-II) Vocabulary and Matrix: to calculate verbal performance, and full-scale IQ. This will be used to ensure that subjects have an IQ greater than 80, and will be repeated at study endpoint to assess change in performance.

- The Delis-Kaplan Executive Function System Trail-making subtest, which measures flexibility of thinking on a visual-motor sequencing task (conducted at screening or baseline, Week 6, and Week 12).

Cambridge Neuropsychological Test Automated Battery (CANTAB) (at screening or baseline, week 6 and week 12): CANTAB is a computer-based system designed to look at frontal lobe (executive functioning). Select subtests will include the following:

- Spatial Working Memory (SWM), tests comprehension, learning and reversal.
- Stockings of Cambridge (SOC), assesses spatial planning and motor control.
- Intra-Extra Dimensional Set Shifting (IED), tests rule acquisition and attentional set shifting.
- Reaction Time (RTI), measures speed of response.
- Rapid Visual Information Processing (RVP), tests sustained visual attention.
- Affective Go/No-go (AGN) assesses information-processing biases for positive and negative stimuli.
- Verbal Recognition Memory (VRM), assesses immediate free recall, and immediate and delayed recognition memory
- Cambridge Gambling task (CGT), to assess decision-making and risk-taking behavior.

Clinician rated assessments (rated at each in-office study visit, unless otherwise noted):

- Global Assessment of Functioning (GAF) scale. The GAF will assess global functioning using a scale from 1 (worst) to 100 (best). This will be collected at all study visits, excluding the screening visit.
- Clinical Global Impressions (CGI) scale for ADHD. The CGI is a measure of illness severity, improvement, and efficacy of treatment.
- Adult ADHD Investigator Symptom Rating Scale (AISRS). Each of the individual symptoms of ADHD is rated 0 to 3 on a scale of severity.
- Adverse Experiences (collected at all visits excluding the screening and baseline visits) and Concomitant Medications.

Subject rated scales (all scales rated at baseline, week 6, and week 12 or drop visit, unless otherwise noted):

- The 18-item ADHD Self Report Rating Scale (ASRS) to evaluate frequency of ADHD symptoms on a scale of 0 to 4.
- The 86-item Behavior Rating Inventory of Executive Function – Adult Form (BRIEF-A) to assess levels of executive function deficits.³⁶ This will be collected at baseline and at Week 12.
- The Adult Self-Report Form (ASR) to measure a wide range of psychiatric syndromes (i.e., depressive problems, anxiety problems, antisocial personality problems) in adults. The ASR provides dimensional scale scores for each syndrome that are age- and gender-normed.³⁷
- The 16-item Quality of Life Enjoyment & Satisfaction Questionnaire (Q-LES-Q) to measure overall satisfaction across different aspects of daily life.³⁸
- The 25-item Endicott Work Productivity Scale (EWPS) to measure behaviors and feelings likely to reduce productivity and efficiency in work activities.³⁹

Data Collection:

Self-report and clinician-rated measures will be collected using DatStat Illume™, a platform for electronic data capture that streamlines data collection and management, and ensures data integrity, resulting in improved data quality. The DatStat™ software allows researchers to design and implement study surveys for collecting, storing, retrieving, and manipulating data electronically. Participants and/or research staff enter survey responses into electronic assessment forms, and the responses are then transmitted securely via encrypted connection and stored in a secured database. This electronic data capture obviates the need for subsequent data entry by staff, thus minimizing human error. Efforts will be made to have all surveys completed in-office, but if needed participants may complete them from home.

Survey respondents will log in to the secure data-collection system at the study site, on a desktop computer provided by MGH staff, or from home, using a personal computer with Internet access. All responses will be transmitted to and stored in a secure database via an encrypted connection. This electronic data capture system obviates the need for the physical transportation of paper source data as well as the entry of paper source data by staff, thus minimizing human error. All data collected via DatStat™ are immediately available for analysis by a statistical package.

All collected data are stored automatically and securely on a Microsoft SQL Server, accessed over an industry standard SSL 128 bit RSA encrypted connection during data transfers. Data is routinely backed up locally onto a redundancy server and stored in a separate database. Individual computers designated for data capture do not store participants' identifying information nor study data. All collected data will be systematically checked by the Project Coordinator.

In the event that the electronic data capture system is unavailable during a study visit (due to technical issues), rating scales will be collected on paper and then entered into the program manually once the system becomes available.

The DatStat Illume™ and Discovery™ Electronic Data Capture Platform has been approved for use at Massachusetts General Hospital by Partners Health Care System Research Computing, Enterprise Research Infrastructure and Services (ERIS) Department. The data collection, transmission, and storage methods are secure and in compliance with Partners policies and procedures. In addition, it is in compliance with the HIPPA HITECH ACT because data is hosted and stored internally (PHS IS Data Center) and managed by Partners Employees.

For quality control purposes, clinician-administered measures completed during the visits may be audio taped, with subjects' permission. These recordings will be used to monitor quality control and inter-rater reliability in this study by the PI. Each digital audio file will be coded with subject initials and number to maintain confidentiality. These files will be de-identified and stored on a password-protected, encrypted computer within the Partners firewall, and will be accessed only by the appropriate study staff.

Study Completion:

Upon completion of the study, participants can choose to pursue follow-up care, as possible, at our MGH practice or continue treatment with their primary care physician. Study clinicians may also offer psychiatric referrals to treaters in their communities. All subjects will be offered two free follow-up visits in the clinic.

ADHD Pharmacotherapy:

If a subject enters the study on pharmacotherapy for ADHD, they will be maintained on this agent during the study by a study clinician, and will receive L-Threonic acid Magnesium salt in addition. With

written permission of the subject, prior to beginning the study, subjects' treaters will be contacted by mail (followed by a phone call) before the study clinician initiates treatment.

Subjects who are not on pharmacotherapy for ADHD as they enter the study will take only L-Threonic acid Magnesium salt during the study. No individual will be removed from an effective and stable treatment regimen for the purposes of participating in the study.

Those subjects who are treated for ADHD prior to their enrollment in the study will continue to be responsible for the cost of their medication, as they will be instructed to take this medication as usual. The study drug will be provided at no cost to study participants.

Study Agent and Dosing:

L-Threonic acid Magnesium salt will be provided as MMFS202 (6-hour release) and MMFS302 (12-hour release). Neurocentria, the makers of MMFS202 (6-hour release) and MMFS302 (12-hour release), will provide a detailed Certificate of Analysis attesting to the contents of the product.

Neurocentria has provided the following list of ingredients for MMFS202 (6-hour release) and MMFS302 (12-hour release):

- Active ingredients: Magtein ® (L-Threonic acid Magnesium salt). L-Threonic acid Magnesium salt is a magnesium salt of L-Threonic acid, having a molecular formula of $Mg(C_4H_7O_5)_2$. MMFS202 will release the active ingredient at a constant rate over 6 hours. MMFS302 will release the active ingredient over a 12 hour period.
- Inactive ingredients: polyvinyl pyrrolidone, microcrystalline cellulose, silicon dioxide, talc, and magnesium stearate

Both MMFS202 (6-hour release) and MMFS302 (12-hour release) will be provided in 0.5-gram tablets. Participants will be instructed to take one tablet of MMFS302 (12-hour release) in the morning and one tablet of MMFS202 (6-hour release) in the evening for one week 2 hours before bedtime. After one week, if well tolerated subjects will start a regimen of two tablets of MMFS302 (12-hour release) in the morning and two of MMFS202 (6-hour release) in the evening. Therefore, subjects will take up to 2 grams per day of L-Threonic acid Magnesium salt during the course of the study. However, study agent dosing will be flexible. If individual subjects display patterns of adverse effects or drug effects that suggest an alternative dosing schedule would be preferred, this will be allowed, including dose reduction to only one of either MMFS202 (6-hour release) or MMFS302 (12-hour release). The study clinician can increase or decrease the dose based on tolerability and reinstate higher doses after a decrease if tolerability increases. No subject will take more than two MMFS202 (6-hour release) or more than two MMFS302 (12-hour release) 0.5-gram tablets a day, and subjects will be instructed not to take more than two tablets at a time or to take more than four tablets in a day total. Subjects will be encouraged to spread out the daily dose into at least two doses several hours apart.

This approach to dosing will allow us the flexibility to maintain subject comfort and convenience during study participation.

The active ingredient in MMFS202 (6-hour release) and MMFS302 (12-hour release), L-Threonic acid Magnesium salt has been granted GRAS status by the FDA. Neurocentria produces MMFS202 (6-hour release) and MMFS302 (12-hour release) using good manufacturing practices.

Study clinicians, or research assistants under the supervision of a study clinician, will be responsible for dispensing MMFS302 (12-hour release) and MMFS202 (6-hour release) at our research office. The MGH Clinical Trials Pharmacy will receive and label and distribute the product for dispensing during the study.

Study clinicians, in cooperation with the subject and the subject's treater, may develop a plan for continued MMF302 (12-hour release) and MMF202 (6-hour release) treatment after the completion of the study, if appropriate. At each visit, measures of safety and effectiveness will be administered and subjects will be evaluated for response and side effects to the treatment. To assess and increase adherence to dosing of the agent, the study agent and any concurrent ADHD medication treatment will be returned and counted at office visits.

Concomitant Medications / Treatments:

A detailed past and present treatment history will be taken as part of initial screening. Concomitant medications with primarily central nervous system activity, other than ADHD pharmacotherapy as noted above, are not allowed in this study. No subject will be tapered from medication that is useful to him or her. Non-pharmacological treatments such as individual, family or group therapy will be allowed if they were in place before the patient joined the study. Any such therapy regimen must remain the same throughout the study. If a subject is asked to stop a medication with central nervous system activity for participation in the study, sufficient time will pass off the medication prior to baseline visit, based on the pharmacokinetics of the agent, to ensure that it has been eliminated from the patient's system.

Subjects will be instructed not to take any medications or supplements that contain any forms of magnesium compounds to avoid unsafe levels of magnesium. All new medications and supplements started during the study will be reviewed by the PI, and subjects may be dropped from study participation, but their data will be retained in the safety and intent-to-treat analyses with PI discretion.

In addition, any subject found to be taking medication listed as exclusionary during the course of the study or the seven days prior to baseline will be evaluated by the PI for ongoing eligibility.

Study Discontinuation Criteria

Subjects who: 1) develop intolerable AE(s) despite dose adjustments; 2) have (a) clinically relevant serious AE(s) as determined by the investigator; 3) have worsening ADHD symptoms (much worse or very much worse as rated on CGI-Improvement at two consecutive visits); or 4) have emergent adverse mental health state including psychosis, suicidality, substance use, or worsening mood and/or anxiety; 5) are non-adherent to study procedures or withdraw from the study; 6) intend to be or become pregnant will no longer continue in the study. If study participation is discontinued due to safety reasons, participants will receive two follow-up visits, giving adequate time for appropriate psychiatric referrals to treaters in their communities.

Subjects found to be taking substances listed as exclusionary during the course of the study may be discontinued based on PI evaluation of their eligibility.

VI. BIOSTATISTICAL ANALYSIS

As this is a single-arm, open study designed to evaluate the effectiveness and safety/tolerability of L-Threonic acid Magnesium salt, formal power analyses are not warranted.

Data processing and management will follow procedures developed by the investigators and used in ongoing studies. 15 subjects will receive L-Threonic acid Magnesium salt. Changes in outcome ratings within and between study groups will be tested. All analyses will be intention to treat (ITT), utilizing.

Our exploratory hypotheses are as follows. Our primary test of Hypothesis 1 will be review of the occurrence of moderate or severe adverse events. Hypothesis 2 will be tested by evaluating whether over the course of L-Threonic acid Magnesium salt administration the following are seen: a) at least a 25% reduction in ADHD as rated by the AISRS total score; b) CGI of much or very much improved, c) reduced symptoms of executive dysfunction (defined by a 0.5 standard deviation improvement on BRIEF-A self-report total or subscale scores). Hypothesis 3 predicts that there will be measurable improvement in cognitive function, as

measured by a) statistically significant improvement on CANTAB tasks, and b) improvement in performance on the WASI matrix, used to estimate IQ, and c) increased correlation between performance on domains of function.

For ADHD AISRS, BRIEF, and CANTAB evaluations, we will compare pre-treatment and study visit values of measures using paired t-tests, via an intention-to-treat analysis with the last observation carried forward (LOCF) for subjects who did not complete the full study. Alpha will be set at 0.05 for all comparisons.

We will also explore descriptively whether baseline erythrocyte magnesium level, or deficits in BRIEF or CANTAB ratings as measured against norms predict improvement on AISRS or BRIEF ratings.

VII. RISKS AND DISCOMFORTS

All efforts are made to minimize risks to subjects. Consistent with good clinical practice, safety will be monitored by the Principal Investigator, and will reflect the oversight of co-investigator study clinicians. Adverse events will be recorded and reported according to institutional policies. Risks of the study agent have been incorporated into the exclusionary criteria for this proposal.

Study clinician evaluation and subject questionnaires:

Some questions may make subjects feel uncomfortable. Subjects may refuse to answer any question they wish. In the event that a participant reports risk of harm to himself or herself, or to another person, study clinicians will assess the level of risk, and take appropriate actions, including disposition of an immediate referral to a local Psychiatric Emergency Room.

Study Agents –MMF202 (6-hour release) and MMF303 (12-hour release):

The active ingredient in MMF202 (6-hour release) and MMF303 (12-hour release) is L-Threonic acid Magnesium salt, is considered a dietary supplement that the manufacturer has self-certified as fulfilling the US Food and Drug Administration criteria for agents that are Generally Regarded as Safe. There are few risks to taking L-Threonic acid Magnesium salt orally. Magnesium is known to cause gastrointestinal discomfort, nausea, vomiting, or diarrhea. Although occurrences are rare, very large amounts of magnesium might cause hypermagnesemia with symptoms including thirst, hypotension, drowsiness, confusion, loss of tendon reflexes, muscle weakness, respiratory depression, cardiac arrhythmias, coma, cardiac arrest, and death. There have been only two reports of death from hypermagnesemia that we found record of.⁴³ The dose prescribed to subjects as part of this study will unlikely lead to hypermagnesemia, as extremely high doses of magnesium are required to produce this effect.

ADHD Pharmacotherapies:

Some individuals will enter the study taking medication for ADHD and continue in the study on this medication. Only subjects taking FDA approved agents for treatment of ADHD in adults (stimulants-class medication or Atomoxetine) will be enrolled. The risks to these subjects are not expected to change with the addition of L-Threonic acid Magnesium salt to their treatment regimen.

Commonly observed side effects associated with the use of these FDA-approved stimulants include insomnia, decreased appetite, dry mouth, headache, or increased pulse. Other less common side effects include irritability, stomach pain, onset of tics, or mood changes. Stimulants have also been associated with more rare, but serious, adverse effects such as sudden death, stroke, and heart attack in adults with a history of heart disease.

Side effects of Atomoxetine are similar to those of stimulants, but notably include fatigue, nausea, increase in heart rate, increase in blood pressure, sexual side effects, agitation or changes in mood. The label for Atomoxetine carries warnings about rare reports of liver failure and of suicidal ideation. Subjects receiving ADHD pharmacotherapy prior to trial entry will continue their regimen as usual, with treatment managed by the study clinicians.

Washout:

During the washout period, if the subject stops taking his/her medications, his/her symptoms might get worse. Medication washout will be monitored by the study clinician in agreement with the research subject and in consultation with the prescribing physician. No subject will be removed from a stable and effective treatment regimen for the purposes of participating in the study. All medications that are discontinued for the purpose of enrollment will be thoroughly documented, and the PI will regularly evaluate the subject's status off the drug and document any subsequent adverse events. This will be done at Week 0, 6, and 12, although all adverse events will be documented throughout the study, including any relation to medication washout. If the investigator determines that it would be beneficial to the subject to resume their previous medication, they will be withdrawn from the study and referred for clinical care.

Confidentiality:

All research-related records initiated as a result of a subject's participation in this study that reveal the subject's identity will remain confidential except as may be required by law. Results of urine drug or pregnancy testing will not become part of the subject's medical record. The result of the magnesium and calcium blood test may be entered in the subject's hospital medical record, as Medical Record Numbers may be used by the laboratory to identify samples. This will be explained in the Consent Form so that all subjects are made aware of this.

Information regarding communication with subject's other treater(s) will be explained explicitly in the Consent Form. Should a subject be opposed to study staff communicating with subject's treaters, he/she may refuse consent to participate in the study. Data obtained from this study will not identify the subjects individually. Subjects will be assigned code-names and ID numbers. Data obtained from our studies may be published, but no subjects will be identified individually in these publications. Original research-related records may be reviewed by the Partners Human Research Committee, and regulatory authorities, for the purpose of verifying clinical trial procedures and/or data. Information may be held and processed on a computer. Access to these computerized records will be password protected and restricted to study staff. Subjects will only be contacted regarding future studies if they indicate that they are interested in being contacted by initialing in the specific section of the consent form.

VIII. POTENTIAL BENEFITS

There may be no direct benefit to subjects participating in this study. Potential benefits to the participants include education about ADHD, a trial of a supplement that could be continued after the study, and the opportunity to contribute to medical science and thus help others with similar difficulties.

IX. DATA AND SAFETY MONITORING

At each study visit, the interviewing clinician will evaluate the appropriateness of a subject's continued participation based on presence and severity of adverse events. The study Principle Investigator will review all adverse events that have occurred across all subjects of the study at least monthly to determine if there are

concerning trends in participants' experience that would require discontinuation of study participation or modification of the protocol. The Principal Investigator will confirm that all adverse events are correctly entered into the adverse event log by the coordinator and will be available to answer any questions that the coordinators may have concerning adverse events and notifying the IRB of all serious adverse events and adverse events in accordance with the guidelines outlined on the Partners Human Research Committee web site.

The Principal Investigator will meet regularly with study staff to address procedural issues and the study coordinator will audit each subject's data within 48 hours of each study visit. Furthermore, all data will be audited by the study statistician on a regular basis to ensure the progress of the study and confirm that all necessary data is being collected and can be transitioned to the statistical package smoothly. Co-investigators are actively involved in the monitoring and quality assurance of these trials. Periodic quality assurance audits will insure accuracy and completeness of all subject documents, IRB files and correspondence, and the informed consent documentation.

VIII. Visual Timeline of Key Study Elements

| | Screen | Baseline (Week 0) | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | Week 8 | Week 9 | Week 10 | Week 11 | Week 12 (Drop) |
|-----------------------|----------------|----------------------|----------------|--------|--------|--------|--------|--------|--------|--------|--------|---------|---------|-------------------|
| Consent | X | | | | | | | | | | | | | |
| Eligibility | X | X ^a | | | | | | | | | | | | |
| Procedures | | | | | | | | | | | | | | |
| Blood Pressure | X | X | | | X | | | X | | | X | | | X |
| Pulse | X | X | | | X | | | X | | | X | | | X |
| Weight | X | X | | | X | | | X | | | X | | | X |
| EKG | X | | | | | | | | | | | | | X |
| Height | X | | | | | | | | | | | | | X |
| RBC Mg and Calcium | X | | | | | | | | | | | | | X |
| Urine Drug | X | | | | | | | X | | | | | | X |
| Urine Pregnancy | X | | | | | | | X | | | | | | X |
| Drug accountability | | X ^b | | | X | | | X | | | X | | | X |
| Drug Dispensing | | X | | | X | | | X | | | X | | | |
| Phone Contact | | | X ^c | X | | X | X | | X | X | | X | X | |
| Assessments | | | | | | | | | | | | | | |
| Demographic Interview | X | | | | | | | | | | | | | |
| WASI-II | X ^d | X ^d | | | | | | | | | | | | X |
| D-KEFS Trails | X ^d | X ^d | | | | | | X | | | | | | X |

Study Protocol: MMFS202 and MMFS302 use in ADHD

Amendment 15

Last Modified: 05/10/2017

| | | | | | | | | | | | | | | |
|---|----------------|----------------|---|--|---|--|--|---|--|--|---|--|--|---|
| CANTAB | X ^d | X ^d | | | | | | X | | | | | | X |
| Clinician Evaluation | X | | | | | | | | | | | | | |
| Clinician Rated Scales | | | | | | | | | | | | | | |
| AISRS | X | X | | | X | | | X | | | X | | | X |
| CGIs | X | X | | | X | | | X | | | X | | | X |
| GAF | | X | | | X | | | X | | | X | | | X |
| Adverse Events | | | X | | X | | | X | | | X | | | X |
| Concomitant Medications | X | X | | | X | | | X | | | X | | | X |
| Subject Rated Scales | | | | | | | | | | | | | | |
| BRIEF-A | | X | | | | | | | | | | | | X |
| ASRS | | X | | | X | | | X | | | X | | | X |
| ASR | | X | | | | | | | | | | | | X |
| Q-LES-Q | | X | | | | | | | | | | | | X |
| EWPS | | X | | | | | | | | | | | | X |
| Phone calls to evaluate adherence to study agent dosing and to protocol will occur on weeks 1, 2, 4, 5, 7, 8, 10, and 11. The Week 1 Phone Call will be conducted by a study clinician, who will assess adverse events, and determine if any alterations in study agent dosing are necessary. Phone calls during weeks 2, 4, 5, 7, 10, and 11 will be conducted by a research assistant, who will assess medication compliance. | | | | | | | | | | | | | | |

- (a) Eligibility will be confirmed at baseline.
- (b) Drug accountability will take place at Week 0 only for subjects entering the trial on treatment for ADHD.
- (c) Phone contact at Week 1 will be conducted by the study clinician, who will assess adverse events. Thereafter, contact will be made by a research assistant.
- (d) Can be completed at either screening or baseline visit

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