IRB Administration Offices
UH IRB Phone: 216.844.1529
CWRU IRB Phone: 216.368.6925

APPROVAL

Principal Investigator:	Stephen Ruedrich
Title:	Phase II, Multicenter, Sixteen-Week, Randomized, Double Blind, Placebo-Controlled Evaluation of the Efficacy, Tolerability and Safety of Memantine Hydrochloride on Enhancing the Cognitive Abilities of Adolescents and Young Adults with Down Syndrome
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The IRB reviewed this submission.

- Per Federal regulation, changes MAY NOT be made to any element of the current research without prior IRB approval, except to eliminate an immediate and apparent hazard to subjects enrolled in the study.
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does not require an Approval End date, the institution may require a yearly "check-in" to confirm the status of the study.

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PROTOCOL TITLE:

Phase II, Multicenter, Sixteen-Week, Randomized, Double Blind, Placebo-Controlled Evaluation of the Efficacy, Tolerability and Safety of Memantine Hydrochloride on Enhancing the Cognitive Abilities of Adolescents and Young Adults with Down Syndrome

PRINCIPAL INVESTIGATOR:

Stephen Ruedrich, M.D.
Department of Phsyciatry
Walker Bldg 1st Flr Ste 1162
10524 Euclid Ave
Cleveland OH, 44106
216-844-2400

RESEARCH PRINCIPAL INVESTIGATOR

Alberto Costa, M.D., Ph.D.
Departments of Pediatrics
(216) 844-7395
Alberto.Costa@case.edu

UH FACULTY ADVISOR:

If the principal investigator's primary role at UH is resident, fellow or student, identify a faculty advisor. N/A

Name
Primary Department
Telephone Number
Email Address

OTHER DEPARTMENTS INVOLVED IN THIS STUDY (IF APPLICABLE):

Department of Psychiatry

VERSION NUMBER:

N/A

DATE:

9/18/2018

Objectives

1. *Describe the purpose, specific aims, or objectives*
2. *State the hypotheses to be tested.*

1. *The main objective of this 16-week research study is to determine whether a drug called memantine hydrochloride (memantine) has the potential to help improve episodic memory in adolescents and young adults with Down syndrome. Memantine (Namenda®) is a drug approved by the Food and Drug Administration (FDA) for patients with moderate to severe Alzheimer-type dementia. Two hundred persons of both genders with Down syndrome aged 15-32 years will take part in this study. This is a randomized and double blind study. This means that subjects will have a 50/50 chance of being assigned to receive either the memantine capsules or placebo (inactive capsules). Neither the study participants nor the research personnel will know who is receiving active medication or placebo. Based on memantine's mode of action, current knowledge on brain pathology in persons with Down syndrome, and data from a previous pilot clinical trial, we hypothesize that memantine may improve test scores on a test known as the California Verbal Learning Test-II (CVLT-II) short form in young adults with Down Syndrome. This is a highly used and validated test of episodic memory (which is the collection of past personal experiences occurring at a particular time and place that can be explicitly stated verbally). In addition, we will also investigate the effect of memantine on the performance of the participants in other types of cognitive tests, and continue to investigate the safety and tolerability of memantine in adolescents and young adults with Down syndrome. Accordingly, this research project has four specific aims: 1) investigate whether memantine has the potential to improve test scores on the CVLT-II short form in adolescents and young adults with Down syndrome; 2) investigate whether memantine has the potential to improve test scores of the study participants in other cognitive assessments; 3) determine the usefulness of electrophysiological and neuroimaging methods as potential surrogate efficacy measures; and 4) confirm whether memantine is well tolerated by study participants with Down syndrome.*
2. *We hypothesize that memantine may improve episodic memory in adolescents and young adults with Down syndrome, as assessed by the California Verbal Learning Test-II (CVLT-II) short form.*

Background

1. *Describe the relevant prior experience and gaps in current knowledge describing how it will add to existing knowledge.*
2. *Describe any relevant preliminary data.*

1. *1.1. Introduction. With a rate of live births of 1 in 691 (Parker et al., 2010), and a prevalence of 1 in 1000, Down syndrome, which is the result of the trisomy of Chromosome 21, is the most common genetically defined cause of intellectual disabilities. The combined prevalence of DS in the United States and Brazil is larger than 600,000 (Parker et al., 2010; Brandão et al., 2012). This number is expected to continue rising in both countries due to projected increases in the life expectancy of people with Down syndrome (Bittles and Glasson, 2004). Although the neurodevelopmental disability displayed by individuals with Down syndrome is generally global in nature, disproportionate deficits in hippocampus and prefrontal cortex dependent functions have been well documented (Pennington et al., 2003; Carr 2005; Turner et al., 2008). As the person with Down syndrome ages, he/she will inevitably develop a neuropathology indistinguishable from Alzheimer disease, which initially manifest itself in the mid-thirties to early forties (Zigman et al., 1997; Leverenz and Raskind, 1998). This neurodegenerative process is thought to lead to the observed high prevalence of early-onset dementia in this population, most commonly occurring in the fifth or sixth decade of life (Zigman and Lott, 2007). Given that the life expectancy of persons with Down syndrome is quickly approaching 60 years in the industrialized world (Patterson and Costa, 2005; Zigman and Lott, 2007), mostly due to recent advances in the surgical and clinical management of the various comorbidities associated with Down syndrome (Roizen and Patterson, 2003), it is now reasonable to say that the developmental and neurodegenerative components of the syndrome may presently constitute the two greatest unmet therapeutic needs of this population.*

   1.2. Typical Neuropsychological Profile of Individuals with Down syndrome. The best data available report the mean intellectual quotient (IQ) of school age children with Down syndrome to be in the low to mid 40s (Carr, 1988, Pueschel and Hopmann, 1993, Turner and Alborz, 2003). Individuals with Down syndrome display clear deficits in expressive language, syntactic/morphosyntactic processing, verbal working memory, and digit span (Jarrold et al., 2000; Abbeduto et al., 2001; Vicari et al., 2002, 2004; Brock et al., 2005). Until a decade ago, however, the neuropsychological profile of individuals with Down syndrome was thought to faithfully reflect much of the individual's overall level of intellectual disability. The work by Pennington et al. (2003) has considerably changed this picture. These authors used a comprehensive battery of 18 neuropsychological measures and reported that persons with Down syndrome display disproportional weakness in hippocampus-dependent function, even when their level of intellectual disability is taken into account. The hippocampus-dependent measures (all of which required long-term memory) used by these authors were the List Learning from A Developmental Neuropsychological Assessment (NEPSY), the virtual Morris water maze, the Pattern Recognition and Paired Associates Learning (both parts of the Cambridge Neuropsychological Test Automated Battery; or CANTAB), and the Ecological Memory Questionnaire. Findings from parallel benchmark assessments included measures such as digit span, which is another task in which people with Down syndrome historically

have performed disproportionally poorly (Seung and Chapman, 2000; Brock and Jarrold, 2005), and were in general agreement with the historical Down syndrome literature.

1.3. The glutamatergic hypothesis for Alzheimer disease and memantine. Various neurotransmitter systems have been shown to be affected in Alzheimer disease (Marczynski, 1995; Francis et al., 1999; Chen et al., 2011; Hu et al., 2012). Historically, the so-called cholinergic hypothesis was the first neurotransmitter-based hypothesis for the pathogenesis of Alzheimer disease to arise. It initiated as the result of three reports published in the mid-seventies indicating substantial neocortical deficits in choline acetyltransferase, which is the enzyme responsible for the synthesis of acetylcholine, and subsequent discoveries of reduced choline uptake, acetylcholine release and loss of cholinergic perikarya from the basal forebrain (Francis et al., 1999). Accordingly, the first class of drugs developed to treat patients with Alzheimer disease were anticholinesterase agents (a.k.a., AChE inhibitors), designed to boost the cholinergic system by inhibiting the breakdown of acetylcholine by the enzyme acetylcholinesterase (Tayeb et al., 2012). In comparison to the cholinergic hypothesis, the rationale behind the glutamatergic hypothesis for Alzheimer disease has been less straightforward, and has evolved considerably over the years. One common thread in the many versions of the glutamatergic hypothesis for Alzheimer disease is the very robust experimental observation that excessive amounts of glutamate or excessive calcium permeation through the glutamate receptor subtype known as the N-methyl-D-aspartate (NMDA) receptor can lead to excitotoxic neuronal dysfunction and cell death (Choi, 1992). In addition to Alzheimer disease, excitotoxicity may play an important role in other neurological diseases, such as Parkinson disease, Huntington disease, stroke, amyotrophic lateral sclerosis, and multiple sclerosis (Tilleux and Hermans, 2007; Parsons et al., 2007; Kaindl et al., 2012).

Glutamate is the most abundant excitatory neurotransmitter in the brain, and its receptors are generally categorized into ionotropic and metabotropic receptors (Kew and Kemp, 2005). This classification is based on whether the receptor molecule is a ligand-gated ion channel or whether it is a Guanosine 5'-triphosphate (GTP) binding (G-protein coupled) receptor activated by the neurotransmitter glutamate, respectively. Ionotropic glutamate receptors can be subdivided further into α-amino-3-hydroxy-5-methyl-isoxazole-propionic acid (AMPA), NMDA, and kainate receptors. These receptors were identified originally by electrophysiological and radioligand binding studies before their coding genes were cloned. Therefore, they were named based on their affinity for pharmacological agonist agents that do not occur naturally in the brain.

Excess of glutamate and excessive glutamatergic activity indeed have been shown to be present in Alzheimer disease (Li et al., 1997). This observation has eventually led to the idea that, in Alzheimer disease, glutamate does not exert its physiological role appropriately because NMDA glutamate receptors are tonically overactive, rather than being highly active only during phasic bursts (Danysz et al., 2000). The initial consequence of this dysfunctional state would be the excessive Ca+2 influx through the postsynaptic membrane and increases in "synaptic noise" and impaired neuronal

plasticity (Parsons et al., 2007; Danysz and Parsons, 2012). The chronic persistence of this state of excessive Ca+2 influx through NMDA receptors would then be expected to lead to permanent neuronal damage and cell death. In this view, disturbances in glutamate homeostasis could be potentially triggered by factors such as energy deficits, increased free radical formation, deficits in glutamate uptake and clearance from the synaptic space, and/or the toxic effect of Aβ peptides, Aβ oligomers, and misfolded tau proteins (Parsons et al., 2007; Li et al., 2009; Hu et al., 2012; Danysz and Parsons, 2012).

A unique perspective has been provided by Parsons et al. (2007), who have suggested that alterations in the ability of Mg2+ to regulate the NMDA receptor function may be an important factor in the pathogenesis of Alzheimer disease. Such alterations in the voltage-dependent blockade of NMDA receptors by Mg2+ could be due to partial membrane depolarization, which might be attributable to decreased activity of Na+/K+ ATPase, mitochondrial dysfunction, AD-related changes in blood flow, and decreases in glucose metabolism and brain glucose supply. These authors also cite other factors like impairment of Ca2+ homeostasis, increased glutamate levels, and increased NMDA receptor sensitivity to glutamate.

Memantine is an NMDA receptor antagonist that has been reported to be effective therapeutically in Alzheimer disease. It has been available in Germany as well as in other countries from the European Union for more than two decades. Memantine was approved for the treatment of patients with moderate to severe Alzheimer disease in 2002 in the European Union, and in 2003 in the United States (Parsons et al., 2007). It provides a small, but significant symptomatic improvement in 6-month, placebo-controlled randomized trials assessing cognitive, functional, and global outcomes of inpatients with moderate-to-severe Alzheimer disease (defined as a Mini Mental State Examination score below 20; Seow and Gauthier, 2007).

The chemical name for memantine hydrochloride (see structural formula in Figure 1) is 1-amino-3,5-dimethyladamantane hydrochloride. (The molecular formula for memantine hydrochloride is C12H21N·HCl and the molecular weight is 215.76.) Memantine is an uncompetitive, moderate affinity, antagonist of NMDA receptors. It has been proposed that therapeutic doses of this drug inhibit the pathologic effect of NMDA receptor activation while leaving unaffected NMDA receptor-mediated physiological processes involved in learning and memory. After oral administration, memantine is quickly and completely absorbed through the gastrointestinal tract with bioavailability close to 100%. Food has no impact on the rate of absorption and the time to reach peak serum concentration is 3–8 hours, and its half-life is 60–80 hours (Kornhuber et al., 2007; Parsons et al., 2007). Over 80% of the drug is excreted via the kidneys unchanged in the urine and in patients with severe renal impairment the dose should be limited to 5 mg twice daily. Minimal metabolism occurs in the liver and there is little involvement of hepatic microsomal p450 iso-enzymes, except for selective inhibition of cytochrome CYP2B6, with minimal drug-drug interactions (Kornhuber et al., 2007). In all clinical trials, memantine was found safe and well tolerated, with a favorable profile of adverse effects. These have been described as mild to moderate and comparable to placebo. The

most frequently observed adverse effects in adult trials are dizziness, constipation, headache, hypertension and somnolence (Sani et al., 2012). The tolerability of an NMDAR antagonist depends upon its affinity toward the receptors, unbinding kinetics, and voltage dependency. Memantine is thought to improve the fidelity of glutamatergic synaptic transmission by voltage-dependently binding to the to the NMDA receptor at or near the Mg2+ binding site with an affinity larger than Mg2+ itself. Such action is predicted to provide both neuroprotection and symptomatic restoration of synaptic plasticity by one and the same mechanism (Parsons et al., 2007; Danysz and Parsons, 2012).

1.4. Preclinical results in an animal model for Down syndrome. In recent years, there have been several successful pharmacological studies using mouse models of Down syndrome (see Costa and McKean, 2013, for a recent review). Such studies have demonstrated that, in spite of its underlying complexity, the possibility for the clinical development of drug therapies to tackle the developmental and neurodegenerative components of Down syndrome might be within reach. Moreover, studies in the most widely used mouse model for Down syndrome, known as the Ts65Dn mouse, have provided increasing evidence for a pathogenic role of deregulated NMDA receptor function in the pathogenesis of Down syndrome (Costa, 2014). Of special importance are pharmacological rescuing studies in which memantine has ameliorated, or even completely reversed the learning and memory deficits typically displayed by these animals (Costa et al., 2008; Rueda et al., 2010; Lockrow et al., 2011). In all these studies, the positive effects of memantine involved learning and memory tasks that are acknowledged as being heavily dependent on the functional integrity of the hippocampus, such as contextual fear conditioning, Morris water maze deficits, and novel object recognition. More recently, we have demonstrated that memantine can also correct at least one form of altered hippocampal synaptic plasticity in a brain slice preparation from Ts65Dn mice (Scott-McKean and Costa, 2011). These preclinical findings have furthered the idea that the pharmacological modulation of the activity of NMDA receptors by memantine may be a realistic pathway to improve hippocampus-dependent function in persons with Down syndrome. This is particularly relevant, given that, as aforementioned, hippocampus-dependent cognitive function is an area disproportionally affected in persons with Down syndrome.

2. *1.5. Results from a recent pilot clinical trial of memantine in persons with Down syndrome. As the direct result of the successful pharmacological rescuing studies in the animal model of Down syndrome Ts65Dn described in the previous section, and the safety profile of memantine (which is far superior to the AChE inhibitors that have been used in several clinical trials in persons with Down syndrome), we recently conducted a pilot clinical trial with memantine in adults with Down syndrome. This was a small-scale, randomized, placebo controlled clinical trial of memantine in young adults with Down syndrome (Boada et al., 2012 – see APPENDIX 6). The main aim of this study was to test the hypothesis that a short drug regimen of memantine could be efficacious in improving scores on hippocampus-dependent tasks by participants with Down syndrome. In this double-blind clinical study on memantine (NCT01112683; www.clinicaltrials.gov), we compared the effects of 16-week treatment with either*

memantine or placebo on cognitive and adaptive functions of 40 young adults (aged 18-32 years) with Down syndrome, using a broad and carefully selected set of neuropsychological outcome measures. The primary measures of this study were the Paired Associate Learning (PAL) and Pattern Recognition Memory (PRM) tests. We also included two additional secondary measures associated with the primary hypothesis that memantine therapy would produce improvements in test scores on hippocampus-dependent measures. These additional measures were the short form of the California Verbal Learning Test-II (CVLT-II) and the Rivermead Behavioral Memory Test-Children's version (RBMT). Safety and tolerability were also monitored.
This was the first clinical study in Down syndrome to benefit fully from the lessons learned from preclinical work in animal models and recent neuropsychological findings in persons with Down syndrome. Although no significant differences were observed between the memantine and placebo groups on the two primary outcome measures, we found a significant effect of memantine therapy on the CVLT-II short form. The CVLT-II measures supraspan word learning ability (i.e., word lists with number of words larger than the typical 7±2 span of short term memory) as an index of episodic verbal long-term memory, and is known to be sensitive to posterior hippocampal functioning (based on neuroimaging) and to be impaired in patients with various forms of degeneration or damage to the hippocampus. Additionally, the study showed a P-value <0.10 for one of the primary outcome measures: the number of stages completed in the PAL. This is a measure of non-verbal memory that requires the participant to learn associations between an abstract visual pattern and its location. A P-value <0.10 was also detected for one of the secondary outcome measures, the Recall of Digits test (which is part of the Differential Ability Scales; DAS-II). This is a measure of rote short-term verbal memory in which the participant is asked to repeat, in the same order, an increasingly longer string of single digit numbers verbally presented by the examiner. Memantine was well tolerated, with only infrequent and mild adverse events noted (two participants in the memantine arm showed increased anxiety and one displayed echolalia, as reported to the investigators by their caregivers). With only 37 participants (out of 40 recruited and randomized) completing the study, the small sample size was the obvious limitation of this study.

Recently, results from another clinical trial on memantine in persons with Down syndrome were also published (Hanney et al., 2012). This study was named "Memantine for Dementia in Adults Older than 40 years with Down's Syndrome" (abbreviated as 'MEADOWS'; NCT00240760; www.clinicaltrials.gov). It consisted of a randomized, double-blind, placebo-controlled trial to assess safety and efficacy of memantine on improving broad cognitive and adaptive function in older individuals with Down syndrome. In contrast to our study, the trial design rationale was not based on preclinical findings on mouse models or subsystem-specific neuropsychological assessments in persons with DS. Instead, it followed a more traditional approach, in the sense that it was based on the association between Down syndrome and Alzheimer disease and previous findings by members of the same research team demonstrating a progressive loss of function typically experienced by a subset of individuals with Down syndrome in their forties and beyond. Accordingly, the primary endpoints were changes in cognition and function, as measured through the Down syndrome attention, memory and executive

function scales (DAMES) and the adaptive behavior scale (ABS) parts I and II. These authors found that, although the 1-year-long treatment with memantine was well tolerated in their participant sample, the treatment produced no significant improvement on the scores of their primary or secondary efficacy measures. In this particular study, we posit that, just as it is the case with most clinical trials on idiopathic Alzheimer disease in the general population, the most likely explanation for lack of efficacy probably lies on the fact that various irreversible neurodegenerative cascades were already well underway and the disease process might have reached a point of no return by the time pharmacological treatment was attempted. (For a more complete set of comments on the MEDOWS trial, see Costa 2012).

1.6. A follow-up, phase II clinical trial of memantine in adolescents and young persons with Down syndrome. Because of the promising findings on our pilot study (Boada et al., 2012; APPENDIX 6) with young adults, all the professionals involved in the present project agreed that these findings were encouraging enough, and the risks were small enough, that a follow-up, larger trial was warranted. We are proposing to use the short form of the CVLT-II as the primary efficacy measure in this new study. The main goal of this study is to repeat the same treatment (drug, drug dose, and treatment duration) of the previous study on a larger sample to test whether the memantine treatment indeed produces a significant improvement on this important measure of hippocampus-dependent cognitive performance. Given the P-value <0.10 for the Recall of Digits test, which is potentially a measure of prefrontal cortex-mediated short term memory, we also decided to add two new prefrontal cortex dependent tasks to the new study: the Spatial span from the CANTAB battery, and a simple Go/No-go test. In addition, in this expanded study, we plan to investigate the usefulness of the electrophysiological measure known as mismatch negativity (MMN), as a biomarker of the severity of the cognitive disability in a person with Down syndrome as well as a potential surrogate marker for the efficacy of memantine in persons with Down syndrome. This is a non-invasive, easy to implement test, which involves electroencephalographic (EEG) assessment of the brain wave that occurs after any discriminable deviation in an ongoing repetitive acoustic stimulation with identical tones. The choice of MMN comes from several studies showing that the MMN amplitude is sensitive to modulation of NMDA receptors by pharmacological treatments with the NMDA receptor antagonists such as ketamine (Umbricht et al., 200), phencyclidine, MK-801 (Steinschneider et al., 1996), and memantine (Nikulin at al., 2007; Tikhonravov et al., 2010).

Please add relevant references at the <u>end</u> of the protocol, not at the end of this section.

Inclusion and Exclusion Criteria

1. *Describe how individuals will be screened for eligibility.*
2. *Describe the criteria that define who will be **<u>included</u>** in your final study sample.*

	Inclusion
1.	Subjects will be males or females with Down syndrome aged 15 to 32 years.
2.	The cytogenetic diagnosis should be either “Trisomy 21”, or “Complete Unbalanced Translocation of the Chromosome 21”

3.	Female subjects must be documented not to be pregnant by serum testing at screening.
4.	Laboratory findings will be within normal limits or judged clinically insignificant at baseline. (Any abnormalities must be documented by the investigator as clinically insignificant, i.e., not likely to cause cognitive impairment or medical instability.)
5.	Vital signs must be within normal limits for their age. (Subjects with stable, medically treated hypotension will be allowed.)
6.	Screening ECG must demonstrate predominately normal sinus rhythm. Minor abnormalities (including sinus bradycardia > 50 beats per minute) documented as clinically insignificant by the investigator will be allowed. (Subjects with clinically significant but stable ECG abnormalities may enter the trial only with the permission of the principal investigators.)
7.	Both subject and caregiver must be expected to complete the full course of the study including all efficacy evaluations. In addition, the patient must be able to complete all efficacy evaluations at Baseline.
8.	Subjects and their authorized representative will provide written informed consent as described above.
9.	Subjects will be outpatients without sensory or motor difficulties, which would prevent their participation in any aspect of the study, i.e. compliance with taking medication, travel to the site and completing efficacy and safety assessments. Eyeglasses and hearing aids are allowed.
10.	Subjects must be in general good health and judged by the investigators to be able to fully participate in the trial.
11.	Subjects must be able to swallow oral medication (crushing of capsules will not be permitted).
12.	Subjects must have a reliable caregiver or family member who agrees to accompany the subject to all visits, provide information about the subject as required by this protocol, and ensure compliance with the medication schedule. The same reliable caregiver must accompany the subject on all scheduled visits where caregiver input is required. The subject must have contact at least once a day with the caregiver.
13.	Subjects must be sufficiently proficient in English (in the Cleveland site) or Portuguese (in the São Paulo site) to be capable of reliably completing the study assessments.
14.	For Typically-developing Reference Controls: Subjects will be males or females without Down syndrome aged 15 to 32 years Subjects will be age and gender matched to the age and gender of the subjects with Down syndrome whom they are expected to serve as control, non-Down syndrome subjects Age matching will be within three years

3. *Describe the criteria that define who will be **excluded** in your final study sample.*

	Exclusion
1.	Mosaic Trisomy 21 and partial translocations will be excluded from this study.
2.	Subjects weighing less than 40 kg (to protect subjects from potential medication overdosing).
3.	Any current psychiatric or neurologic diagnosis other than Down syndrome. This includes, but is not limited to, major depressive disorder, schizophrenia, schizoaffective disorder, any other psychotic disorder, bipolar disorder, seizure disorder (no seizures for more than 3 years), autism, Alzheimer disease, Parkinson's disease, cerebrovascular disease, other dementias, brain tumor, or other known structural brain abnormalities.
4.	Subjects who currently are being treated with psychotropic drugs.
5.	Subjects who currently meet or have within the past five years met DSM-IV criteria for drug or alcohol abuse or dependence.
6.	Subjects who, in the judgment of the investigators, currently represent a significant suicide risk or who would require treatment with electro-convulsive therapy (ECT) or with psychotropic drugs during the study or who have received treatment with a depot neuroleptic drug within 6 months of entering the study.
7.	Subjects who are hospitalized or residing in a skilled nursing facility or subjects who are anticipated to enter a nursing home within the next 6 months. (Note: subjects may reside in group homes of other residential settings where they do not require or receive skilled nursing.)
8.	Any active or clinically significant conditions affecting absorption, distribution or metabolism of the study drugs (e.g., inflammatory bowel disease, celiac disease, gastric or duodenal ulcers).
9.	Subjects with significant allergies to or other significant intolerance of memantine therapy, its ingredients, or with contraindications to memantine therapy as stated in the prescribing information.
10.	Subjects who are expected to require general anesthetics during the course of the study
11.	History or presence of encephalitis
12.	Presence or recent history of seizure disorder (no seizures for more than 3 years).
13.	History of malignant neoplasms treated within 3 years prior to study entry (other than basal or squamous cell carcinoma of the skin) or where there is current evidence of recurrent or metastatic disease.
14.	Subjects currently experiencing clinically significant and/or clinically unstable: dermatologic disease, hematologic disease, pulmonary disease, cardiovascular disease, renal disease, hepatic disease, gastrointestinal disease, genitourinary disease, endocrine disease, neurologic disease (other than Down syndrome).
15.	(Note: Subjects with treated hypothyroidism must be on a stable dose of medication for at least 3 months prior to screening and have normal serum T-4 and TSH at screening. Subjects with diabetes mellitus controlled by diet or oral medication or insulin must have an HbA1c of < 8.0% and a random serum glucose value of < 170 mg/dl.)

16.	Severe infections or a major surgical operation within 3 months prior to screening.
17.	History of persistent cognitive deficits immediately following head trauma. (note: remote history of head trauma without cognitive sequelae is not an exclusion.)
18.	Subjects who have donated blood or blood products during the 30 days prior to screening who plan to donate blood while participating in the study or within four weeks after completion of the study.
19.	Subjects who may not be able to comply with the protocol or perform the outcomes measures due to significant hearing (>40 dB hearing loss) or visual impairment (best corrected visual acuity of less than 20/60) or other issues judged relevant by the investigators.
20.	For Typically-developing Reference Controls: Subjects with history of substance abuse, major psychiatric disorder, attention deficit disorder, or learning disability Subjects with Beck Depression Score greater than 10 Exclusion criteria specific to MR scanning: weight inappropriate for height, ferrous objects within the body, low visual acuity, and a history of claustrophobia Pregnancy Neurologic history (e.g., head injury, seizures, stroke)

Number of Research Participants

1. *Indicate the target number of research participants to be accrued locally.*
2. *If this is a multi-site study, indicate the total number of research participants to be accrued across all sites.*

    1. *100 clinical trial participants, 30-60 typically-developing reference controls,*
    2. *200 total clinical trial participants, 30-60 typically-developing reference controls,*

We will have 200 people with Down syndrome taking placebo or medication.

100 will be locally recruited, 100 will be recruited in Brazil.
30-60 out of the 100 recruited locally (with Down syndrome, taking study medication) will also take part in the MRI substudy.

We will have an additional 30-60 control participants recruited locally for just the MRI/EEG substudy (no medication, medical visits or neuropsychological testing)

Vulnerable Populations

1. *Indicate specifically if you will include each of the following special populations by checking the appropriate box:*

    ☒ **Adults unable to consent**

☒ **Minors (infants, children, teenagers)**
- ☐ Wards of the state
- ☐ Foster Children

☐ **Pregnant Women**
☐ **Neonates**
☐ **Neonates of Uncertain Viability**
☐ **Employees of CWRU or UHHS**
☐ **Prisoners**
☐ **Illiterate Individuals**
☒ **Non-English Speaking**
☐ **University Students**

2. *If the research involves individuals that are included in a vulnerable population, describe the additional safeguards included to protect the rights and welfare of the individuals for each population indicated.*

   It is the responsibility of the investigators to obtain written informed consent from each caregiver and subject (or her/his legal representative, if the subject is not capable of giving written informed consent and the caregiver is not her/his legal representative) participating in this study, after providing a clear explanation of the methods, objectives and potential hazards of the study at a appropriate terms for the comprehension level of the subject, authorized representative, and caregiver (who can be the same person as the authorized representative). In the case of subjects with Down syndrome not legally responsible for themselves, consent will be obtained from their legal authorized representative. Even when the subject is not fully capable of giving written informed consent, the subject must assent in writing to participation in the study (this is in addition to obtaining informed consent from her/his legal representative).

   In the Cleveland, the site's Research Principal Investigator (Dr. Costa) will explain the research objectives and the design of this clinical trial. This will be done by the Principal Investigator at the São Paulo site. Through an interactive process, subjects will be assessed on whether they are able to perform cognitively and behaviorally the battery of neuropsychological assessments associated with this trial. Caregivers will be inquired about their commitment to oversee drug schedule compliance, attendance to hospital visits, and monitoring/reporting of potential adverse events. All adult subjects and parents/legal guardians will be given a consent form to read and sign. Dr. Costa or the Principal Investigator at São Paulo site (Dr. Ana Claudia Brandão) will explain the consent through an interactive process. The subject and parent/legal guardian, as indicated, will be asked to follow along as the consent is explained and throughout this process will be asked to give his/her interpretation of what is going to be asked of the subject in each of the procedures. All subjects and parents/legal guardians will be given as much time as needed to review the consent and ask questions about any aspect of the research study.

There is no specific cognitive level used to exclude participants. Instead, at the Cleveland and the São Paulo sites, Dr. Alberto Costa or Dr. Ana Claudia Brandão, will make a clinical determination regarding each participant's ability to provide informed consent/assent and cope with the demands of the study. For example, by observing the ability of the participants to sit still during the screening interview, by asking the participants a few simple questions, including questions regarding their overall understanding of the goals of the trial, and by asking the opinion of the parent or guardian about the participant's ability to undergo the procedures involved in the trial. However, this study will not count on one individual's experience alone. Two additional layers of assessment will be used. First, adolescents and adults with Down syndrome will be assessed by an additional experienced physician (Drs. Nancy Roizen, Stephen Ruedrich, or Thomas Scheidemantel at the Cleveland site, and Dr. Patrícia Salmona or Dr. Guilherme de Abreu Silveira at the São Paulo site) who will have the ability to discontinue the participation of a subject with Down syndrome if she/he deems this person not fit to participate fully in the trial. Second, although this will not necessary exclude an individual from participating in the trial, inability to complete the neuropsychological test battery would raise a red flag in terms of the fitness of an individual to participate. At all times, the research staff will assess dissent to participate in the study, and can recommend that a participant be excluded from the study because of any significant, real or perceived, discomfort expressed by the participant or parent/caregiver.

Cognitive function may be impaired from mildly to severely in individuals with Down syndrome. Accordingly, depending on the level of impairment and their legal status, in a few exceptional cases, some studies involving individuals with Down syndrome waives the requirement that a parent/legal guardian signs the informed consent form. Due to the active role of the caregiver in this trial, however, we will require that both the subject and the caregiver sign the consent form, regardless of the level of impairment and their legal status of the adult subjects. For participants 18 years of age and older, the permission of the subject and one parent/legal guardian will be considered sufficient for enrollment in the research project. (Note that, if the legal guardian is not the parent, this person will be required to be at least a next-of-kin with legal guardianship of the participant). For younger subjects, the permission of both parents will be required unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

If excluding pregnant women, illiterate or non-English speaking individuals, provide a scientific rationale for the exclusion. Inconvenience or cost is not an acceptable rationale.

Pregnancy is an exclusion criteria due to the lack of safety data for developing fetuses. Neuropsychological assessments are in English for the Cleveland site, and in Portuguese for the São Paulo site.

Recruitment Methods

1. *Describe the source of the research participants.*

2. *Describe the methods that will be used to identify potential research participants.*
3. *Justify the feasibility of recruiting the required number of suitable research participants within the agreed recruitment period. For example, how many potential research participants do you have access to?*
4. *Describe when, where, and how potential research participants will be recruited.*
5. *Describe materials that will be used to recruit research participants.*

1. *200 persons with Down syndrome from both genders and between the ages of 15 and 32 will be recruited from local and regional communities from each site. In addition, we also expect to recruit 30-60 participants without Down syndrome as typically-developing reference controls in the Cleveland site.*

2. *Prospective subjects and/or caregivers must express interest in learning more about the study and give their contact information to the investigators before investigators will contact them. No "cold-calling"will occur.*

   All prospective subjects with Down syndrome and/or their caregiver will be informally prescreened by telephone to assess probable eligibility for the study. The telephone prescreening questions for will consist of five questions: 1) confirmed diagnosis for Down syndrome? 2) Can the person communicate verbally? 3) What is the person's gender?; 4) What is the person's age?; 5) Is the person taking any new medication or is on a new dose for thyroid medication or for diabetes? At this time, the requirements of the protocol will also be explained briefly to avoid the time and expense of bringing candidates who are unlikely to comply with the requirements of the study to the study site for further evaluation. Provided they meet the prescreening requirements, potential participants and caregivers who appear suitable for the study will be scheduled for a screening visit.

3. *The prevalence of Down syndrome in the general population is 1 in 1000. From the data available, we know that this genetic disorder affects both genders and different ethnic groups equally. During recruitment, we will attempt to involve an equal number of female and male participants. Also, the P.I. will make every effort to include subjects belonging to minority ethnic groups in this study. Given that Brazilians are defined as Hispanic/Latino, according to the National Institutes of Health, we will have a significant number (at least 50%) of participants belonging to this particular ethnic minority group.*

4. *For the Cleveland site of this study, a total of 100 persons with Down syndrome from both genders and between the ages of 15 and 32 will be recruited in conjunction with the regional parent associations (such as the The Up Side of Downs in Cleveland and the Down Syndrome Association of Central Ohio in Columbus), local and regional clinics as well as County Boards of Developmental Disabilities will also be contacted. Depending on the success of (or lack of success of) this traditional approach, we also plan to make use of the online recruiting tools ResearchMatch and DS-Connect™: The Down*

Syndrome Registry. Of these 100 participants, 50 participants will be assigned to be treated with memantine and 50 age- and gender-matched participants will be assigned to the placebo arm of the study. The Up Side of Downs in Cleveland and the Down Syndrome Association of Central Ohio in Columbus have expressed great enthusiasm for this project, and plan to use their membership databases to contact potential subjects for this study. For the majority of participants to be enrolled, all the testing (neuropsychological, medical, clinical laboratory, and electrophysiological tests) will be carried out at University Hospitals. For a subset of 30-60 participants, magnetic resonance imaging (MRI) of the brain will be performed at the Cleveland Clinic.

In addition, we also expect to recruit 30-60 participants without Down syndrome as typically-developing reference controls in the Cleveland site for the magnetic resonance imaging (MRI) assessments. From previous experience, recruiting typically-developing participants for a study involving persons with Down syndrome, we expect to recruit these age and gender matching control participants from the family and friends of the participants with Down syndrome. In case it proves necessary, we may also use ResearchMatch and posting at Case Western Reserve University to recruit this cohort of control, typically-developing participants.

The São Paulo, Brazilian arm of this study will comprise 100 participants with Down syndrome to be recruited through local parent associations and from Drs. Ana Claudia Brandão or Zan Mustacchi's patient database. (Dr. Zan Mustacchi runs a large Down syndrome Clinic in the city of São Paulo and will function as a consultant for this study.) Dr. Ana Claudia Brandão will be responsible for translating this protocol into Portuguese in consultation with Dr. Costa and make the necessary adjustments to comply with Brazilian federal and state laws and regulations.

5. *Materials used to recruit research participants include an advertisement. A poster consisting of pictures of a participant doing some tasks in the clinical trial is used as visual aid during informed consent.*

Setting

1. *Describe the sites or locations where your research team will conduct the research.*
   The study will be conducted at Case Western Reserve University and University Hospitals, Cleveland Ohio, USA (100 subjects), and Hospital Israelita Albert Einstein (English: Albert Einstein Israelite Hospital) in São Paulo, Brazil (100 subjects).

2. *Identify where your research team will identify and recruit potential research participants.*
   See #4 in prior section
3. *Identify the physical location where research procedures will be performed.*

Consent Process

Indicate whether you will be obtaining consent:

☒ Yes ☐ No

If yes describe:

- *Where the consent process will take place*
- *Any waiting period available between informing the prospective subject and obtaining the consent*
- *Any process to ensure ongoing consent*
- *The role of the individuals listed in the application as being involved in the consent process*
- *The time that will be devoted to the consent discussion*
- *Steps that will be taken to minimize the possibility of coercion or undue influence*
- *Steps that will be taken to ensure the research participants' understanding*

Consent will be in a private location. Consent documents are provided to potential participants prior to the informed consent meeting. The Research Principal Investigator at the Cleveland site or the Principal Investigator at the São Paulo site is responsible for obtaining informed consent. Consent discussion continues until the study is fully explained and all questions from the participants have been answered. No monetary reward is offered for participation in the trial to minimize possibility of coercion or undue influence. Informed consent documents and assent documents have been designed to ensure participant's understanding and participants are also encouraged to contact the Investigators and study team regarding any questions they have at any time.

Waiver or Alteration of Consent Process or Documentation (consent will not be obtained, written consent will not be documented)

Indicate which part of the consent process you are requesting be waived or altered:

- ☐ I will obtain consent, but not participant's signature
- ☐ I will obtain consent, but request a waiver for pre-screening purposes
- ☐ I will obtain consent, but request a waiver of some of the elements of consent (e.g. use of deception)
- ☐ I will not obtain consent, and I am requesting a full waiver of consent

1. *Give the rationale for the request of a waiver or alteration of the consent process or documentation.*
2. *If you will obtain consent, but not document consent in writing (e.g. over the phone, verbally, electronic survey, etc.), please describe and provide a rationale.*

   Describe how you will be documenting that a research participant has consented

   Be sure to upload a consent script or information sheet with your study protocol

   N/A

Additional Considerations for Consent Process with Adults

<u>Non English Speakers</u>

- *If research participants who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those research participants will be in that language during initial consent as well as throughout the study. Indicate the language that will be used by those obtaining consent.*

The São Paulo site will use Portuguese

- *List the language(s) other than English that will be included.*
  Portuguese

Adults Unable to Consent

- *Describe the process to determine whether an individual is capable of consent.*

  Cognitive function may be impaired from mildly to severely in individuals with Down syndrome. Accordingly, depending on the level of impairment and their legal status, in a few exceptional cases, some studies involving individuals with Down syndrome waives the requirement that a parent/legal guardian signs the informed consent form. Due to the active role of the caregiver in this trial, however, we will require that both the subject and the caregiver sign the consent form, regardless of the level of impairment and their legal status of the adult subjects.

- *List the individuals from whom permission will be obtained in order of priority (e.g. durable power of attorney for health care, court appointed guardian for health care decisions, spouse, and adult child).*

  For participants 18 years of age and older, the permission of the subject and one parent/legal guardian will be considered sufficient for enrollment in the research project. (Note that, if the legal guardian is not the parent, this person will be required to be at least a next-of-kin with legal guardianship of the participant). For younger subjects, the permission of both parents will be required unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

  - *For research conducted outside of the state, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in the research.*

- *Describe the process for assent of the research participants. Indicate whether:*
  - *Which subjects that are unable to consent will be required to give assent? If not all, explain why.*
  - *Describe whether assent of the research participants will be documented and the process to document assent.*

  In both the Cleveland and the São Paulo sites, the investigators, will make a clinical determination regarding each participant's ability to provide informed consent/assent and cope with the demands of the study. For example, by observing the ability of the participants to sit still during the screening interview, by asking the participants a few simple questions, including questions regarding their overall understanding of the goals of the trial, and by asking the opinion of

the parent or guardian about the participant's ability to undergo the procedures involved in the trial.

Even when the subject is not fully capable of giving written informed consent, the subject must assent in writing to participation in the study (this is in addition to obtaining informed consent from her/his legal representative).

Research Participants Who Are Not Yet Adults (infants, children, teenagers)

1. *Will parental permission be obtained from:*

   ☐ *One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child or*

   ☒ *Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child*

   ☐ *Waiver of parental permission*

2. *Describe whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. Describe the process used to determine these individuals' authority to consent to each child's participation in research.*

   In the case of subjects with Down syndrome not legally responsible for themselves, consent will be obtained from their legal authorized representative.

3. *Indicate whether assent will be obtained from all, some, or none of the children. If assent will be obtained from some children, indicate which children will be required to assent.*
   All
4. *When assent of children is obtained describe how it will be documented.*
   Assent Document

Sharing of Results with Research Participants

Describe whether results (study results or individual subject results such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with the research participants or others (e.g. the subject's primary care physicians) and if so, describe how the results will be shared.

☐ Results will not be shared with research participants

Study results will be shared with research participants at end of the study. Incidental findings, such as laboratory results and genetic reports, can be shared with research participants at any time by request.

Study Design, Procedures and Timeline

1. *Describe and explain the study design.*
   Randomized, Double Blind, Placebo-Controlled

Primary Efficacy Measure

The primary efficacy measure is focused on episodic memory. The choice of the appropriate measure for individuals with Down syndrome was based on results of our pilot clinical trial of the drug memantine in young adults with Down syndrome (Boada et al., 2012; APPENDIX 6). We hypothesize that treatment with memantine will produce significant improvements in the California Verbal Learning Test-II (CVLT-II) short form. The CVLT-II score range is 0 to 36; the baseline and post-intervention scores of the participants with Down syndrome in our pilot study (Boada et al., 2012) were 14.53 ± 1.80 and 20.12 ± 2.10 (mean ± SEM), for the memantine arm, compared to 16.26 ± 1.82 and 13.74 ± 1.63, for the placebo arm of the trial. (Higher score indicates better performance.) As aforementioned, this measure is dependent on the functional integrity of temporal lobe structures such as the hippocampus. Improvement in performance in this measure is expected to be correlated to improvements in the individuals' ability to acquire skills requiring the use of declarative memory. Ultimately, in case we are able to confirm that the administration of memantine is indeed efficacious in improving this cognitive measure in this population, such gains may lead to a measurable improvement in the quality of life of persons with Down syndrome.

Secondary Efficacy Measures

We will include measures for which we have some expectation for a significant improvement on scores from our pilot trial, such as the Paired Associates Learning (PAL; from the CANTAB battery) and the Recall of Digits task (from the DAS). The Pattern Recognition Memory task (PRM; from the CANTAB) will be kept because of its wide use in current studies of hippocampal function involving persons with Down syndrome. Because of the borderline effect of memantine on the Recall of Digits test (P-value <0.10) in our pilot study (Boada et al., 2012; APPENDIX 6), and the fact that this measure is potentially a measure of prefrontal cortex-mediated short term memory, we also decided to add two new prefrontal cortex-dependent tasks to the present study: the Spatial span from the CANTAB battery, and a Go/No-go test. We will also preserve some measures for which we have little or no a priori reason to expect significant changes with memantine treatment, which, therefore, will serve as benchmark measures: receptive vocabulary on the Peabody Picture Vocabulary Test-IV (PPVT-IV); Test for the Reception of Grammar (TROG); and Scales of Independent Behavior Revised (SIB-R). These measures will serve both as benchmarks of overall intellectual functioning and as potential secondary tolerability measures, given that significant decreases in score may be due to subtle adverse events that might not be detectable by a skilled physician in a typical clinical appointment. The electrophysiological assessments of auditory evoked potentials proposed here will also serve a dual purpose: 1) to provide an objective measure of the hearing ability of the persons with Down syndrome participating in this trial through the Auditory Brainstem Response (ABR) Test; and 2) to gauge the potential usefulness of mismatch negativity (MMN) as a biomarker of the severity of the cognitive disability in a person with Down syndrome as well as a potential surrogate marker for the efficacy of memantine.

Safety and Tolerability Assessments

Safety and tolerability will be monitored primarily by physical examinations, electrocardiograms (ECGs), comprehensive clinical laboratory tests, incidence of adverse event recording, and the Screen for Childhood Anxiety Related Emotional Disorders (SCARED), which is a subject and parent self-report instrument used to screen for childhood anxiety disorders including general anxiety disorder, separation anxiety disorder, panic disorder, and social phobia. In addition, it assesses symptoms related to school phobias. The comprehensive clinical laboratory tests will include assessments of liver and kidney function, electrolytes, acid/base balance, and blood glucose and proteins (see Section 7.2., Laboratory Determinations, for a complete description of the laboratory tests to be used). This clinical trial will involve 2 comprehensive clinical laboratory tests per subject (baseline and 16th treatment week). ECGs, with interpretation by the Cardiology Service, and will involve 2, 12-lead, ECGs per subject. Clinical consultations will be performed either by a board certified developmental pediatrician (Dr. Nancy Roizen) or two board certified psychiatrist (Dr. Stephen Reudrich and Dr. Thomas Scheidemantel), or medical residents or fellows under their supervision.

The physical exam will include a health questionnaire addressing the study exclusion criteria. In a checklist format, aspects of the general and neurological exam are to be documented with attention to such aspects as balance, extra ocular movements, optokinetic nystagmus (OKN), tremor, and other movement disorders (see neurological examination checklist).

2. *Provide a description of all study-related **research procedures** being performed including procedures being performed to monitor research participants for safety or minimize risks.*

Visit 1: Baseline physical examination and laboratory tests will be performed by a board certified physician in this visit. Subjects will receive a physical examination, vital signs will be measured, and an electrocardiogram (ECG) will be performed. The subject's medical records also will be reviewed. At the end of the visit, blood samples will be collected for a comprehensive battery of clinical laboratory tests. Below is the list of general procedures to be followed in this visit:

- *Vital Signs*
- *Clinical History Taking*
- *Complete Physical Exam*
- *Neurological Exam*
- *The Screen for Childhood Anxiety Related Emotional Disorders (SCARED)*
- *Concomitant Medication Check*
- *12-lead ECG*
- *Labs (including pregnancy test for females of childbearing potential)*

Visit 2: Baseline neuropsychological assessments will occur one to three weeks after Visit 1. These tests are designed to evaluate the cognitive skills of the participants before the start of the medication. A battery of tests to assess non-verbal reasoning abilities, memory, vocabulary, and language skills will be administered by a trained psychologist. In these interactive tests the participant will be asked to point at a picture, word, or number in response to different requests by the examiner (see description of

"primary and secondary efficacy measures"). In addition, the participant will be asked to perform a few user friendly computer-based tests. The guardian/parent will be asked to complete a questionnaire about the participant everyday behavior and general abilities (the Scales of Independent Behavior Revised - SIB-R). Because we expect the test battery will take approximately two hours to administer, two visits may be required to complete this series of assessments for a few participants. In the next section, we provide a description of the neuropsychological test battery used in this trial. Below is a complete list of the psychometric tests that will be used:

- *California Verbal Learning Test II Short Form (CVLT-II)**
- *Spatial Span (from the CANTAB)*
- *Pattern Recognition Memory (PRM - CANTAB)*
- *Test for Reception of Grammar 2 (TROG-II)*
- *Paired associates task (PAL - CANTAB)*
- *Recall of Digits subtest (DAS)*
- *Matrices subtest (DAS)*
- *Go-No Go test*
- *Spatial working memory (SWM - CANTAB)*
- *Receptive vocabulary on the Peabody Picture Vocabulary Test-IV (PPVT-IV)*
- *Scales of Independent Behavior-Revised (SIB-R)*

** Trial primary measure*

At the end of this visit, a prescription will be submitted to the Investigational Drug Services (IDS) at University Hospitals in the Cleveland site where a study coordinator will dispense a 60-day supply (56 days plus 4 extra days) of either memantine capsules or identically-looking placebo capsules and repeat to the parent/guardian/next-of-kin caretaker the necessary information on the use of the medication. For the 16-week duration of this study, capsules will be taken either once (first week) or twice daily by mouth according to memantine's standard titration schedule. In the São Paulo site, a physician at the Hospital Israelita Albert Einstein (English: Albert Einstein Israelite Hospital) will provide a 60-day supply of either memantine capsules or identically-looking placebo capsules, which will come randomized and prepackaged from the University of Iowa Pharmaceuticals Services.

For a subset of 30-60 participants in the Cleveland site, magnetic resonance imaging (MRI) of the brain will be performed at the Cleveland Clinic in the afternoon, one or two hours after the completion of the neuropsychological test battery. (Note that consent to participate in this particular subset of the study is independent from the overall consent to participate in the study, therefore, the final number of participants here will depend on the number of participants who agree on participating in the clinical trial AND on this component of the study.)

Visit 3: First follow-up medical visit at 8 weeks from the start of the medication. This visit is to ensure that the study medication is being adequately tolerated. The same clinical procedures will be followed as were done during Visit 1. Vital signs will be measured and a physical examination will be performed. At this visit, a final, 60-day, supply of study medication will be dispensed. The general procedures to be followed in this visit are listed below:

- *Vital Signs*
- *Adverse Event Assessment*
- *Medication Compliance Check*
- *Complete Physical Exam*
- *Neurological Exam*
- *Concomitant Medication Check*
- *Urine pregnancy test for females of childbearing potential*
- *Dispensing of Medication*

Once again, at the end of this visit, the subject will be asked to go to Investigational Drug Services (IDS) at University Hospitals in the Cleveland site where a study coordinator will dispense a 66-day supply (56 days plus 10 extra days) of either memantine capsules or identically-looking placebo capsules. For the 16-week duration of this study, capsules will be taken either once (first week) or twice daily (weeks 2-16) by mouth according to memantine's standard titration schedule. In the São Paulo site, a physician at the Hospital Israelita Albert Einstein (English: Albert Einstein Israelite Hospital)s will provide a 60-day supply of either memantine capsules or identically-looking placebo capsules, which will come randomized and prepackaged from the University of Iowa Pharmaceuticals Services.

Visits 4: Primary and Secondary Efficacy Measures at the 16th week from the start of the medication. Various aspects of the subjects' learning, memory, cognition, and adaptive behavior will be assessed again through the same neuropsychological test battery used in visit 2. Again, we expect that the test battery will take approximately two hours to administer. Therefore, two visits may be required to complete this series of assessments for a few participants. Again, for a subset of 30-60 participants in the Cleveland site, magnetic resonance imaging (MRI) of the brain will be performed at the Cleveland Clinic in the afternoon, one or two hours after the completion of the neuropsychological test battery.

Visit 5: Second and final follow-up medical visit at the 16th week from the start of the medication. The purpose of this visit is to ensure again that the study medication is being adequately tolerated. Similarly to visits 1 and 3, vital signs will be measured and a physical examination will be performed. Two blood samples again will be collected for checkup tests (here, the second blood sample is not optional!). In addition, a quantitative assessment of steady-state plasma levels of memantine and Alzheimer's disease biomarkers will be performed in the end of the study, after the unblinding of the randomization codes. The general procedures to be followed in this visit are listed below:

- *Vital Signs*
- *Adverse Event Assessment*
- *Medication Compliance Check*
- *Complete Physical Exam*
- *Neurological Exam*
- *The Screen for Childhood Anxiety Related Emotional Disorders (SCARED)*
- *Concomitant Medication Check*

- *12-lead ECG*
- *Labs (including urine pregnancy test for females of childbearing potential)*

Again, in the Cleveland site, Dr. Costa will perform the electrophysiological assessments of auditory evoked potentials (Auditory Brainstem Response, ABR, Test and Mismatch negativity, MMN) shortly after this visit is completed. (His Research Assistant and one of the Study Coordinators, Ms. Melissa Stasko, may also perform some of these assessments under Dr. Costa's supervision.) In the São Paulo site, these assessments will be carried out by Maria Paula Roberto, M.S., and may require the Brazilian participants to come for an additional visit.

If for some reason the subject withdraws from this study prior to Visit 5, he/she will be asked to return to the clinic for a "Treatment Discontinuation Visit." In addition, if the subject discontinues the medication prior to the end of the study, he/she will be asked to complete a "Retrieved Dropout Visit" on the date that should have represented Visit 5. Study medication will not be provided beyond the study period. The procedures for the "Treatment Discontinuation Visit" will be the same as those described for "Visit 5 (Second follow-up medical visit)."

3.3. Neuropsychological Test Battery

The battery will include measures to assess skills in five major areas: a) memory functioning; b) intellectual functioning; c) language and vocabulary; d) visual and verbal working memory; and e) adaptive/behavioral functioning. The battery includes measures that we expect may be sensitive to changes caused by memantine, given the hypothesized mechanism of action of the drug and previous results from a pilot trial (Boada et al., 2012; APPENDIX 6). Specifically, we hypothesize that the participants will improve in their test scores for declarative memory and, potentially, for working memory capabilities. We have also selected measures of receptive semantics and grammatical understanding that we predict will remain relatively stable, thus acting as benchmark, discriminant measures. Lastly, we have included a comprehensive measure of adaptive functioning that also measures the presence, frequency, and severity of 8 core emotional/behavioral problems. A secondary hypothesis is that memantine may decrease the frequency or severity of behavioral difficulties, although we found no indication of this potential in the previously mentioned pilot trial. All the measures of this battery have been used in research with persons with Down syndrome, and have adequate psychometric properties. What follows is a list of measures, by domain, and a brief description of each.

Memory functioning

A) California Verbal Learning Test-II (CVLT-II) - Short Form: This test is the primary efficacy measure of this clinical trial. It assesses supraspan word learning ability as an index of episodic verbal long-term memory. This type of test is known to be sensitive to posterior hippocampal functioning based on neuroimaging, and has also been shown to be impaired in populations with degeneration or damage to the hippocampus. Participants are provided with an orally presented list of words which are repeated over 5 trials. Short and long delay recall trials as well as a recognition trial follow. The delay interval is 10 minutes. Two dependent variables were selected, based on prior literature,

as indexing hippocampal function: Total number of target items correct summed across learning trials 1-4, and total free recall discriminability for the learning trials, which takes into account hits as well as false positives.

B) Recall of Digits (Differential Ability Scales; DAS-II): This is a measure of rote short-term verbal memory. The participant is asked to repeat, in the same order, an increasingly longer string of single digit numbers orally presented by the examiner. The digits are read at a rate of 2 per second. Number sequences increase in length from 2 to 9 digits. Total number of items correct was used as the dependent variable.

C) Paired Associates Learning (PAL; part of the Cambridge Neuropsychological Test Automated Battery or CANTAB): This is a measure of non-verbal memory that requires the participant to learn associations between an abstract visual pattern and its location. Difficulty is manipulated across learning trials by increasing the number of patterns and locations to be learned from 2 to 8. Participants match pattern to location via a touch screen. Previous research has shown that this task is impaired in participants with hippocampal damage. It has also been shown to be a reliable detector of Alzheimer Disease (Swainson et al. 2001). This subtest has a parallel form to counter practice effects on repeat testing. Two dependent variables have been selected: Total number of items correct on the first trial of each stage, and total number of stages completed.

D) Pattern Recognition Memory (PRM; part of the CANTAB): This is also a measure of non-verbal memory. The participant is presented with a series of visual (non-namable) patterns, and then is asked to identify which of two he or she has seen before by selecting it via touch screen. This subtest has a parallel form to counter practice effects on repeat testing. Total number correct across the two series of items presented will be used as the dependent variable.

Intellectual functioning
Matrices subtest of the Differential Ability Scales-II (DAS-II): a measure of non-verbal reasoning ability that requires subjects to visually inspect a matrix of 4 or 9 pictures that has a missing piece. Participants have to infer a rule or pattern in the stimuli, and select the appropriate response from a range of 4-6 possibilities. Since age norms are not available for individuals older than 17y11m, the ability score will be used as the dependent variable. This is an intermediate score based on Rasch modeling that corrects for different items set being administered to participants.

Linguistic functioning
A) Test for Reception of Grammar 2nd edition (TROG-II): This is a measure of receptive syntax skills (Bishop, 1983). Participants are asked to point to a picture (out of 4) that corresponds to a phrase or sentence spoken by the examiner. Selection of the correct response requires successful interpretation of the grammatical structure presented in the sentence. The internal consistency of this measure is 0.77. The total number of items correct (rather than blocks passed) will be used as the dependent variable, following the administration manual's ceiling rule.

B) Peabody Picture Vocabulary Test-IV (PPVT-IV): This is a measure of receptive semantics, whereby the participant is asked to point to a picture (out of 4) that corresponds to a word spoken by the examiner. As this test has a 0.85 correlation with composite measures of Verbal IQ (i.e. from the Wechsler Intelligence Scale series), it can be used in conjunction with the Matrices subtest to estimate overall intellectual functioning. The total number of items correct was used as the dependent variable, following the administration manual's rules for basals and ceilings.

Executive Functioning
A) Spatial Working Memory (part of the CANTAB): This measure is analogous to the pre-frontally sensitive self-ordered pointing task developed by Petrides and Milner (1982). The test requires participants to search under a series of colored boxes to locate a "blue token" hidden underneath one of them. During a series of trials, the participant is told that the token will be in a new location each time and that they should not go back to a location he or she has looked in previously. This requires participants to keep track of the spatial locations, update this information as new targets are found, and inhibit incorrect (yet prepotent) responses. Two dependent variables were selected: 1) The total number of errors ("between errors"), which indexes the number of times a participant went back to a box where a token had already been found; and 2) a "strategy" score, which indexes the number of times the participant started a search with a different box, the latter being an inefficient strategy (i.e., high strategy scores denote poorer performance).

B) Spatial Span (part of the CANTAB): This measure is a computerized version of the Corsi Blocks task, a long-standing neuropsychological test. It is an analogue to the verbal digit span task (or in our battery the DAS Recall of Digits task), as it measures how long a sequence of locations of visually presented tokens can be held in short-term memory over a brief interval. Although it does not require the participant to manipulate information in short-term memory, it does rely on working memory and attention to some extent, and thus is thought to invoke frontal circuitry in addition to occipito-parietal systems. The CANTAB manual describes it as a working memory task, but it differs from the Spatial Working Memory task in that it does not require updating of information from trial to trial. The participant is shown a pattern of white boxes on a screen. Some of the boxes change color, one by one, in a variable sequence. The lowest level starts with a sequence of 2, and it increases to 9. At the end of a sequence, the participant is asked to touch the locations of the boxes that changed color, in the same order as they were originally presented. Once the participant correctly reproduces the sequence at one level, he or she will move onto the next level. If the participant fails three trials at a particular level, the test stops. Two dependent variables were selected for this test: 1) span length, which is the longest sequence of numbers recalled accurately (possible score ranges from 2 to 9); and 2) total usage errors, which represents the number of times a subject selects a box no in the sequence being recalled (scores range from 0 - 39).

C) The Go – No Go task: This is a measure of inhibitory control, often used as a marker for prefrontal-striatal function integrity. Specifically, it measures the participant's ability to inhibit pre-potent behavioral responses that have been established by provision

of prior "go" or "no-go" cues in a classical conditioning paradigm. The cognitive model that underlies the Go - No Go task emphasizes the anticipatory nature of inhibitory and activational mechanisms of control. Thus, it is much harder to inhibit a behavioral response to a target after a "go" cue has been given, than it is to inhibit a response to a target when a "no-go" cue has been given. The task works as follows: Two types of cues are given in the form of a horizontal or vertical rectangle on a computer screen. A black framed vertical rectangle (on a white background) is the "go" cue, which is followed 80% of the time by the "go" target (the rectangle turning green). A black framed horizontal rectangle (on the same white background) acts as a "no-go" cue, as it is followed by the "no-go" target (the rectangle turning blue) 80% of the time. Participants press a computer key only when the green rectangle ("go" target) appears. In contrast, participants have to suppress a response when the "no-go" blue target appears. Responses to "go" cues are of particular interest. Go cues generate response prepotency which speeds reaction time to "go" (green) targets. However, participants must overcome this response pre-potency in order to inhibit a response if a "no-go" (blue) target is subsequently displayed. Failures to inhibit responses to "no-go" targets are more frequent following "go" cues compared with "no-go" cues. The ability to inhibit the pre-potent response has been noted to be particularly sensitive to pharmacological effects in prior studies using this paradigm (Fillmore et al., 2006). This particular version of the Go – No Go task is well suited for participants with Down syndrome because it does not use verbal or letter stimuli; it is administered completely in the visual modality. Two dependent variables were selected: 1) the proportion of no-go targets in which a subject fails to inhibit a response under the go-cue (pre-potent) condition; and 2) speed of response execution to Go targets.

Adaptive/Behavioral Functioning
Scales of Independent Behavior-Revised (SIB-R): Scales of Independent Behavior-Revised (SIB-R): This is a measure of adaptive functioning that integrates information from 13 different domains (e.g., gross motor, social interaction, eating, toileting, dressing, personal self-care, etc.). It is in a questionnaire format, which a caregiver can complete while the participant is being tested. The following composite scores are derived: Motor Skills, Social Interaction and Communication Skills, Personal Living Skills, and Community Living Skills. There is also an overall Broad Independence Score. The SIB-R also has a Maladaptive Index, where caregivers report the presence of maladaptive behaviors, such as hurtful to self, hurtful to others, destruction of property, disruptive behavior, unusual or repetitive habits, socially offensive behavior, withdrawal/inattentive behavior, and uncooperative behavior. Standard scores for all indices will be derived from age norms that extend from birth to age 80, as these will be used as dependent variables.

Duration of the Testing Procedure and Quality Control: The test battery will take approximately two hours to administer, not counting breaks, time for prompts and rewards, or time needed to acquaint the participant with the testing situation. Factors such as mental age and cooperativeness of the participant will also influence total testing time. In this study, we will target individuals who have a mental age of at least 5 years. In the pilot memantine study performed in Colorado (Boada et al., 2012; APPENDIX 6),

the average mental ages of the study participants, as assessed by the PPVT-III, were 6.1 years for those in the placebo group, and 7.6 years for those in the memantine group. Given that the PPVT-III correlates with the Wechsler series Full Scale IQ with a correlation coefficient of r=0.85, the cognitive abilities of our sample was consistent with the literature. In addition to the 4th edition of the PPVT (PPVT-IV), here we will use the SIB-R as a means of assessing adaptive skills and as a proxy for mental age in this present study. Clinically, a verbal and interactive person with Down syndrome, with a reasonable level of impulse control to sit through several minutes of interview and/or neuropsychological assessments is very likely to have a mental age of 5 years or above. It has been our experience that individuals with mental ages significantly below this cutoff will have significant difficulty understanding and completing the various tasks in this battery (especially the memory tasks). We feel quite confident that we will obtain the data necessary to complete this project. Dr. Boada, the overall co-P.I. of this study, has had extensive experience in testing individuals with Down syndrome, which has been demonstrated by the publication of our pilot study on memantine. He will provide specific training on the neuropsychological assessment of individuals with Down syndrome to both the Cleveland and São Paulo teams and will monitor the neuropsychological data collection in both sites to assure standardization of the procedures. Dr. Boada is not only an accomplished neuropsychologist, but also is fluent in Portuguese and Spanish, which will be instrumental in assuring reliable communication between the Cleveland and São Paulo teams.

Dr. Boada currently collaborates with Dr. Bruce Pennington, who has done some instrumental work in understanding the cognitive profiles of children with Down syndrome. Dr. Pennington's neuropsychology laboratory at the University of Denver, where Dr. Boada trained, has tested children with Down syndrome ages 11-19 on a very similar neuropsychological battery (Pennington et al, 2003). Dr. Boada is also the co-principal investigator on a longitudinal NIH funded study examining the relationship between speech, language, and reading skills. As part of that study, he has tested over 250 five-year-old children on a 6 hour neuropsychological battery. These children, due to the nature of the disorders being studied, are difficult to understand and have significant language and attentional impairments.

In addition to Dr. Boada's expertise, we will count on the decades of neuropsychological experience of Dr. H. Gerry Taylor who will be one of the Cleveland site's co-principal investigators. Dr. Taylor is a Professor of Pediatrics and Psychology at Case Western Reserve University, and former Chief of the Division of Psychology, Speech and Language of the Department of Pediatrics. Dr. Taylor has been the P.I. and co-PI of more than 20 projects involving typical and atypical brain development, including several clinical trials. Dr. Taylor will work in close collaboration with Dr. Boada in the implementation of the neuropsychological battery associated to this clinical trial, will perform neuropsychological data analysis, and will provide direct supervision to Ms. Anne Birnbaum (who will function as the main psychometrist for the Cleveland site).

Once the battery of tests is ready for implementation, including the computerized procedures, we will be running appropriate practice subjects (i.e., same mental age) through the protocol in order to ensure that administration glitches are identified and solved prior to testing actual study participants. All protocol-specified evaluations will be

conducted at approximately the same time of day (with start time between 9 and 11 AM), and in the same test order and by the same examiner at each subject visit. This is intended to lessen variability in subject, caregiver and examiner responses, which may be influenced by time of day, order of test administration, and examiner. In the Cleveland site, only Ms. Birnbaum and one other trained psychometrician will be testing participants. In the Brazilian site, Ms. Veridiana Barrionuevo (who is an accredited psychologist in the state of São Paulo) will be the main psychometrist. Recently, she has received intense training by Dr. Boada at the Colorado Children's Hospital. Although Dr. Boada has deemed her capable of applying the test battery, he will be spending at least another week in São Paulo providing further training and supervision to Ms. Barrionuevo to assure inter-site reliability of testing procedures.

Unless, it is practically impossible (due to disease, strong personal reasons, or inclement weather), in both sites, the same tester will administer the complete testing session for each participant, as well as the follow-up testing 16 weeks later. We will schedule all testing sessions to begin at the same time each morning. In the Cleveland Site, all the participants in the study will be tested at the Rainbow Child Development Center. In the São Paulo site, the participants in the study will be tested at testing facilities in the Hospital Israelita Albert Einstein (English: Albert Einstein Israelite Hospital). At both sites, we have dedicated testing rooms for research participants. Since the current protocol requires computer administered tests (via CANTAB), all the testing will be completed in the same testing room for all participants. The various tests in the battery will be administered according to a standard set of instructions, which will be written out before hand and accessible in the testing room at all times. Subjects will be given practice trials on the various measures, as allowed by each instrument, before beginning the stimulus trials. Responses will be either written down verbatim by the examiner, or otherwise saved by the computer software.

Electrophysiological and Imaging Studies

Auditory Evoked Potentials: We propose to investigate the usefulness of the electrophysiological measure known as mismatch negativity (MMN), as a biomarker of the severity of the cognitive disability in a person with Down syndrome as well as a potential surrogate marker for the efficacy of memantine in persons with Down syndrome. This is a non-invasive, easy to implement test, which involves electroencephalographic (EEG) assessment of the brain wave that occurs after any discriminable deviation in an ongoing repetitive acoustic stimulation with identical tones. The repetitive standard stimuli are thought to generate a memory template, and any incoming stimulus is compared against it. If the incoming stimulus does not match the template, a MMN is generated (Näätänen, 1995). Since MMN occurs whether or not stimuli are being attended, it is supposed to reflect an automatic, i.e., preattentive process for detecting change (Picton et al., 2000). Therefore, the MMN represents context-dependent information processing at the level of the auditory sensory cortex (Näätänen et al., 2001). The prevailing position among electrophysiologists is that the MMN of the event-related potential and magnetic field (ERP and ERF, respectively) are memory-based processes and not merely reflections of the activity of fresh afferent neuronal populations (Näätänen, 1995). Interestingly, the MMN amplitude is sensitive to

modulation of NMDA receptor function, which can be altered by pharmacological treatment with the NMDA receptor antagonists such as ketamine (Umbricht et al., 200), phencyclidine, MK-801 (Steinschneider et al., 1996), and memantine (Nikulin at al., 2007; Tikhonravov et al., 2010). Therefore, the two dependent variables that will be assessed here are MMN peak amplitude and latency.

We will also assess Auditory Brainstem Responses (ABRs) to provide an objective measure of the hearing abilities of the persons with Down syndrome participating in this trial. Because of the high prevalence of middle ear infections (otitis media), mild hearing loss is not uncommon in persons with Down syndrome (Roizen and Patterson, 2003). However, because moderate to severe hearing losses are likely to impact the participant's performance on the neuropsychological assessments, including their ability to comprehend verbal instructions, a cutoff of 40 dB of hearing loss will be used as an exclusion criterion for this trial. In case it turns out that the participant has had a recent episode of otitis media, a tympanometry, and a second ABR assessment a week or two later will be performed.

In this project, we will evaluate ABR and MMN in all trial participants using a simple 4-Channel Evoked Potential System (Intelligent Hearing Systems, Miami, FL), which will allow the recording of these cognition-dependent auditory evoked potentials, plus ABRs in the participants with Down syndrome within 15 to 20 minutes. This system is certified to meet or exceed the FDA QSR Part 820 and ISO 13485:2003 standards. Its operation is simple enough that investigators with little previous experience in recording evoked potentials can use it to generate reliable and reproducible results. A vertical montage (high forehead [active or positive], earlobes or mastoids [reference right & left or negative], low forehead [ground] will be used for both ABR and MMN recordings, which will speed up the session. Sound will be delivered by earphones.

In the Cleveland site, Dr. Costa, a trained physician who also has a Ph.D. in biophysics and extensive experience in electrophysiological recordings in general and neurophysiological assessments in persons with Down syndrome in particular (see, for example, Costa 2011a; 2011b), will be in charge of recording MMNs and ABRs from the participants shortly following the screening visit, and consent and assent signing in his office at University Hospitals. This should reduce the burden of an additional visit to the participants and their families. In the São Paulo site, however, these assessments will be carried out by Maria Paula Roberto, M.S., an audiologist with decades of practice in the application of ABR and other types of auditory evoked potentials (her Master thesis at the University of São Paulo focused on the audiological evaluation of babies with Down syndrome). Because Ms. Roberto may not be on site following the screening visit, these assessments may require the Brazilian participants to come for an additional visit to the Hospital Israelita Albert Einstein (English: Albert Einstein Israelite Hospital). In both sites, a second ABR and MMN assessment will be performed on the day of the final medical appointment (Visit 5). These tests involve no risk beyond the minimal risks associated with typical EEG recordings, which are described in the consent form. No sedation will be used in this study.

High-Density EEG Recordings of Evoked Potentials: Because of a simple four-lead EEG recording might not have enough spatial resolution to detect the source of MMN alteration, we plan to use high-density EEG recordings in all the participants at the

Cleveland site to identify precisely the source of any potential significant difference in peak amplitude and latency of MMNs in persons with Down syndrome in relation to typically developing persons without Down syndrome, and before and after memantine treatment. For these participants, Visual evoked potentials will also be recorded as benchmark, discriminant measures, given that we have no a priori reason to suspect that memantine will change the amplitude or delay of these evoked potentials. These assessments will be performed by Dr. Costa, using a 128 Channel Geodesic EEG System 400, with a Source Analysis Package Featuring GeoSource 2.0 and Geodesic Photogrammetry System 2.0 (Electrical Geodesics; EGI, Inc., Eugene, OR). This system uses 128 electrodes evenly spaced over the entire scalp, cheeks, and back of the neck, Geodesic EEG provides dense and even sampling, allowing the detection of brain activity at high spatial resolution, without having to interpolate between widely spaced sensors. The HydroCel Geodesic Sensor Net (HCGSN) provides a simple method to apply dense arrays of sensors quickly and easily (one can apply up to 256 sensors in just a few minutes). The HCGSN gently holds each silver/silver chloride electrode sensor in place without the need for excessive head measurements or glues; no scalp abrasion is necessary to get high-quality EEG data. It can be used with a simple saline solution (i.e., it does not require any special glue or paste) for short recordings such as the ones proposed here. The result is a comfortable and low stress experience for the participants. This system has been used extensively in infants, children, and populations with behavioral challenges. Again, these tests involve no risk beyond the minimal risks associated with typical EEG recordings, which are described in the consent form. No sedation will be used in this study.

Imaging Studies: The primary purpose of these magnetic resonance imaging (MRI) studies will be to provide precise source localization for the high-density EEG recordings of auditory evoked potentials to be performed by Dr. Costa in a subset of 30-60 participants of this trial. In addition, to morphometric data suitable for source localization, in the 30-minute MRI scan these experiments will also produce high resolution sagittal slice images of the hippocampus and simple connectivity data sets that may produce additional biomarkers for the severity of the cognitive disability associated to Down syndrome and for the efficacy of the memantine treatment. This study will be performed by Dr. Katherine Koenig, an Assistant Professor at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, and Project Staff in Imaging Sciences at the Cleveland Clinic. Dr. Koenig has extensive experience with acquisition, reconstruction, quality control, and analysis of imaging data. In addition, she is very familiar with the special issues related to working with the imaging individuals with developmental disabilities, including Down syndrome. This study will comprise 30-60 MRI scan sessions before the memantine treatment and 30-60 scans after the treatment for 30-60 participants with Down syndrome. In addition, 30-60 single MRI scan sessions will be performed on chronological age and gender matched typically developing control participants to provide a baseline for this measure. In order to provide familiarity and comfort to the 30-60 participants with Down syndrome before going inside the MRI scanner, Dr. Koenig is planning to perform one 30-minute long "practice" MRI session on a MRI mock scanner (which is also expected to decrease the amount of movement-related artifacts, and, therefore, improve the quality of the resulting

imaging data). In order to obtain reference control data, we will recruit a group 30-60 of age and gender matching participants without Down syndrome, who will undergo a single session of both the High-Density EEG Recordings of Evoked Potentials and imaging studies. As with the electrophysiological assessments, no sedation will be used in this study.

Complete Physical and Neurologic Examinations
Blood pressure will be measured in the sitting position with a standardized mercury manometer or appropriately calibrated digital manometer, according to the American Heart Association recommendations.

Heart rate will be determined by palpation of radial pulse in the sitting position.

Weight (kg), height (cm), and temperature (oral, °C) will be recorded;

General physical well-being will be assessed by evaluation of the head, eyes, ears, nose, throat, neck, heart, chest, lungs, abdomen, extremities, peripheral pulses, skin, and other physical conditions of note.

A standard Neurological Examination will be performed to include an assessment of frontal release signs (grasp reflex, glabellar tap, snout reflex, and tone) to assess paratonia, rigidity; cog wheeling, and impairment of postural reflexes; and extra ocular movements, OKNs, tremor, and movement disorders.

3.6. The Screen for Childhood Anxiety Related Emotional Disorders (SCARED)
The SCARED is a child and parent self-report instrument used to screen for childhood anxiety disorders including general anxiety disorder, separation anxiety disorder, panic disorder, and social phobia. In addition, it assesses symptoms related to school phobias. The SCARED consists of 41 items and 5 factors that parallel the DSM-IV classification of anxiety disorders. The child and parent versions of the SCARED have moderate parent-child agreement and good internal consistency, test-retest reliability, and discriminant validity, and it is sensitive to treatment response. Designed for children ages 8-18 years, is used by clinicians and psychiatrists, and takes approximately 10 minutes to Administer. Typically, the questionnaire is completed by the patient and parents. For the scoring, the severity of symptoms for the past three months is rated using a 0 to 2-point rating scale with 0 meaning not true or hardly ever true, 1 meaning sometimes true, and 2 meaning true or often true. It is available in both English and Portuguese, in addition to six other languages. Given that one of the adverse events noted by Boada et al. (2012; APPENDIX 6) was increased anxiety in two participants in the memantine arm, as reported to the investigators by their caregiver, we decided to include the SCARED questionnaire as a means of quantifying this potentially important adverse event related to the use of memantine in persons with Down syndrome.

Laboratory Determinations

A fast of at least 2 hours from food and beverages except water is required prior to collection of blood samples. All clinical laboratory testing in Cleveland will be conducted by the University Hospitals' central clinical laboratory facility, and by a single accredited clinical laboratory to be contracted by Dr. Mustacchi in São Paulo.

Hematology: red blood cell count, hemoglobin, hematocrit, indices, white blood cell count (with differential), and platelet count.

Clinical Chemistry: sodium, potassium, chloride, glucose, urea nitrogen, creatinine, calcium, total bilirubin, total protein, albumin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and lactate dehydrogenase.

Thyroid Function: total T4, free T4, and TSH at screening; and TSH after treatment.

Routine Urinalysis: pH, protein, glucose, ketones, hemoglobin or blood, specific gravity, and microscopic examination of the sediment.

Additional Labs: β-HCG (females) and serum Hemoglobin A1c (HbA1c) for all subjects with diabetes (at screening only).

12-Lead Electrocardiogram

The electrocardiogram (ECG) will be a complete, standard 12-lead recording. A copy of the ECG and the evaluation report by the Department of Cardiology at University Hospitals or a Board Certified Cardiologist in São Paulo will be kept in the investigator's subject file and appended to the Case Report Form (CRF)(see Appendix 3).

Karyotype

If results of previous karyotyping are not available this must be performed at the baseline visit (Visit 1). A copy of the results, whether conducted prior to baseline visit or at the baseline visit, must be appended to the subjects CRF and the appropriate page of the CRF completed. If this has been done previously, all efforts should be made to obtain the medical records.

At the end of Visit 2 ("Baseline neuropsychological assessments"), subjects will receive either memantine or placebo. Assignment to a treatment group will be according to a computer-generated randomization schedule. The drug dosage will follow memantine's standard titration schedule (i.e., 5 mg/d week one, 5 mg/BID week two, 5 & 10 mg/d divided dose week three, 10mg/BID week four).

ONCE THE SUBJECT HAS COMPLETED THE WEEK 8 VISIT, THE DOSAGE 0F STUDY DRUG MAY BE DECREASED AT ANY TIME BECAUSE OF MILD/MODERATE ADVERSE EXPERIENCES. If the subject cannot tolerate 20 mg/day MEMANTINE or placebo, the dosage should be reduced temporarily to 10 mg/day MEMANTINE or placebo. The subject should be re-challenged with 20 mg/day MEMANTINE or placebo within 7-10 days. If the subject cannot tolerate 20 mg

MEMANTINE or placebo after re-challenge, the subject will be dropped from the study and an early termination visit will be completed.

3. *Describe:*
   - ☒ *Procedures performed to lessen the probability or magnitude of risks*
   - ☒ *List all drugs and devices used in the research and the purpose of their use and their regulatory approval status (more detailed information is requested in the section on Drugs and Devices at the end of this document.)*
   - ☒ *The source records, including medical or educational records, which will be used to collect data about subjects*

The trial medication will consist of: 5 mg memantine HCl capsules and 10 mg memantine HCl capsules (from commercial grade memantine to be donated by Forest Pharmaceuticals and encapsulated by the University of Iowa Pharmaceuticals); and Placebo, capsules to match (also to be produced by the University of Iowa Pharmaceuticals).
Test drugs are defined as any treatments given for investigational purposes, including placebo or comparative drugs, or any agents given in conjunction with them in order to enhance the therapeutic effect. In this study, the test drugs are memantine HCl and placebo.

To ensure safety at screening, subjects will be evaluated by a standard battery of clinical tests, including a medical history, physical examination, neurological exam, electrocardiogram, and laboratory screen. These procedures are described in Sections 3.4 through 3.6. A routine physical examination, neurological exam, 12-lead ECG, and laboratory studies will be conducted again at the final or discontinuation visit. Vital sign measurements, routine physical examination, and neurological exam will be conducted at each visit.

These or other safety measurements can be conducted more frequently if clinically indicated, or at the discretion of the investigators. The reason for additional observations will be provided in the Comments section of the CRF.

In addition to the scheduled measurements, inquiries will be made at each evaluation period as to the presence of any adverse experiences by asking general questions such as, "How are you feeling? Have you had any problems since the last visit? Have you been sick or gone to the doctor? Are you taking any new medicines?" Should information on adverse experiences be elicited during this questioning, the information will be recorded in the CRF.
In addition to expert medical evaluations during the medical visits (Visits 1, 3, and 5), periodic review of adverse events in this trial will be performed. The function of the DSMB is to monitor the safety data being generated by the clinicians in this trial to determine if the risk/benefit ratio is acceptable to continue this trial. Dr. Costa will participate in the open portion of meetings to be appraised of the group decisions and any suggestions to improve the safety and reliability of trial procedures (made during their closed deliberations), but he will not have any say in terms of the appropriateness of the continuation of the trial. The formal charter of the DSMB will be prepared and approved at the DSMB organizational meeting. Written reports will be generated annually, in case no serious adverse event (SAE) is reported. In addition to its annual meeting, the board may also meet within 48 hours of the occurrence of a severe adverse event (SAE) to plot an appropriate course of action for the remainder of the trial, and should generate a detailed report of their decision within one week from the time a SAE has been noted and properly reported. DSMB meetings may occur more often than annually at the discretion of the DSMB Chairperson.

In case of a serious adverse event (SAE), the subject will be dropped immediately from the study, and the investigators will notify the Institutional Review Board (IRB) within 24 hours and file a form 3500A – Medwatch SAE form with the FDA. (Form 3500A – Medwatch is appended to the Case Report Form - CRF) (see APPENDIX 4).

SAE monitoring and reporting for the São Paulo site will follow the same general standard operating procedures. In addition, the São Paulo site will have to comply with Brazilian federal, state, and local rules and regulations for the performance of clinical trials.

In line with the relatively long half-life of the compound, the safety databases from the FDA and European Union do not list any signs or symptoms of withdrawal after discontinuation of memantine treatment; however, this issue has not been systematically evaluated. In addition, no cases of memantine abuse have been reported to date. However, the caregivers for all participants will be instructed in the consent form that the participants need to be referred to their primary care provider in the unlikely event of behavioral deterioration following discontinuation of memantine treatment in this study.

Describe when research procedures will take place and the duration of an individual subject's participation in the study. Use of the descriptive table listing the study procedures that indicates the visit/week of the interventions below is encouraged.

TABLE 1	**SCREENING VISIT**	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4**	**VISIT 5**
	Informal Interview, Informed Consent, EEG	**Baseline Medical and Formal Screening**	**Baseline Neuropsychological Evaluation, MRI**	**Week 8, Follow-up Medical Evaluation**	**Week 16, Final Neuropsychological Evaluation, MRI**	**Week 16, Final Medical Evaluation**
Explanation of Trial Procedures	X					
Informed Consent/Assent	X					
Medical History	X	X				
Electrophysiological Assessments	X					X
Karyotyping	X (obtain copy of results if available)	X (collect blood if necessary)				
Physical Exam		X		X		X
Vital Signs		X		X		X
Clinical Lab Tests		X				X
Screen for Childhood Anxiety Related Emotional Disorders (SCARED)		X				X
Pregnancy Test		X (blood)		X (urine)		X (urine)
ECG		X				X
Concomitant Meds	X	X		X		X
Adverse Events Monitoring				X		X
California Verbal Learning Test – CVLT II Short Form			X (AM)		X (AM)	
Spatial Span (CANTAB)			X (AM)		X (AM)	
Pattern Recognition Memory – PRM (CANTAB)			X (AM)		X (AM)	

Test of Receptive Grammar 2 – TROG-2			X (AM)		X (AM)	
Par Associates Learning – PAL (CANTAB)			X (AM)		X (AM)	
Recall of Digits (DAS-II)			X (AM)		X (AM)	
Spatial working memory (CANTAB)			X (AM)		X (AM)	
Matrices subtest of the (DAS-II)			X (AM)		X (AM)	
Go-No Go task			X (AM)		X (AM)	
Receptive vocabulary (PPVT-IV)			X (AM)		X (AM)	
SIB-R			X (AM)		X (AM)	
MRI Neuroimaging of a selected group of 30-60 participants			X (PM)		X (PM)	
Medication Compliance Check				X		X

Radiation and Radioactive Substances

1. Does the research involve the use of radiation or radioactive substances?
   ☐ Yes ☒ No – leave rest of the section blank

   If yes, answer the following questions.
   Please note that you must receive Radiation Safety Committee (RSC) prior to IRB submission.
2. Is the radiation use only for the purposes of the research study (e.g. over and above standard of care)
   ☐ Yes ☐ No

3. Does the protocol use radionuclides?
   ☐ Yes ☐ No

4. Provide justification for the additional risk associated with the research radiation use.

ClinicalTrials.gov Information

Has this study been registered on ClinicalTrials.gov?

☒ Yes. Provide the following:

i. The ClinicalTrials.gov identifier: NCT02304302
ii. Investigator/sponsor responsible for registering: Dr. Alberto Costa

☐ No. Explain if there are plans to register or why registration is not required (i.e., the study is not NIH funded, registration is in process, or does not meet the definition of a clinical trial)

List of Data to be Collected

1. *Indicate what identifiers you will collect*

- ☒ Name
- ☒ Address
- ☒ Dates related to an individual *(e.g., Date of admission, birth, surgery, etc.)*
- ☒ Telephone number
- ☐ Fax number
- ☒ Email address
- ☐ Social security number
- ☒ Medical record number
- ☐ Health plan beneficiary number
- ☐ Account number
- ☐ Certificate/license number
- ☐ Any vehicle or other device serial
- ☐ Device identifiers or serial numbers
- ☐ Web URL
- ☐ Internet protocol (IP) address
- ☐ Finger or voice prints
- ☒ Photographic images
- ☐ Other: Any characteristic that would uniquely identify the individual

2. *List all other data to be collected for the research study (e.g. laboratory values, physician notes, length of stay, etc.). Laboratory values, test results*

Data Analysis Plan

1. *Describe the data analysis plan, including any statistical procedures. Provide a power analysis if applicable.*

2. *If applicable, describe the primary and secondary study endpoints including safety endpoints.*

STATISTICAL CONSIDERATION AND ANALYTICAL PLAN

Sample Size

The sample size for this project was calculated from power analyses performed on the data from our pilot study (Boada et al., 2012; APPENDIX 6). One hundred (100) subjects per treatment group will provide approximately 99.9% power to detect a between-group mean difference of 4 points on the California Verbal Learning Test II short form (CVLT-II short form) with respect to change from baseline to week 16 endpoint with a one-tail, paired design, and an alpha = 0.025. These calculations were performed using the PASS 12 software (Version 12.0.3; NCSS, LLC. Kaysville, Utah, USA. www.ncss.com). Sixty (60) subjects per treatment group (the Cleveland site) are already expected to produce approximately 99% conditional probability of rejecting the null hypothesis. Therefore, in case any unanticipated (technical or regulatory) issues happen to impede or delay the performance of the trial in the São Paulo site, the Cleveland site should provide enough power to confirm or reject our previous observations in the pilot

study. Obviously, the larger the study, the greater the conditional probability of rejecting the null hypothesis, therefore, our intent is to combine the data from both sites into one large dataset.

Randomization Method

A computer generated, blinded randomization list will be used. Subjects will be paired according to age and gender. At the baseline visit subjects will be assigned to one of the two treatment regimens (memantine or placebo). The random code will assign subjects to treatments in a 1:1 ratio.

Replacement Policy for Subjects Withdrawn from the Study

To minimize missing data points in this paired-design study, replacement of an individual in memantine/placebo age-gender matched pairs will be acceptable until such subject complete the 16 weeks on the study medication; a special age-gender matching code will be created for the replacement subject to indicate that he/she has replaced one of the subject in a memantine/placebo pair. Data on any adverse event that may have caused the subject to drop from the study will be recorded and reported in the manuscript describing the study findings. After the subject start taking the study medication, if the subject drops from the study due to a severe adverse event, he/she will not be replaced.

Study Populations

An "intention-to-treat" approach will be used in the statistical analyses, so that data from all subjects will be included regardless of subject eligibility or adherence to the protocol. The intent-to-treat (ITT) population is defined as all subjects who received at least one dose of medication and at least one evaluation at the start of double-blind treatment irrespective of compliance and protocol violations.

An "efficacy evaluable" population will be determined based on blinded application of protocol criteria, and a statistical assessment of this group will also be performed, and 80% or greater medication compliance and no major protocol violations will be required for a subject to be "efficacy evaluable." Repeated measures mixed models (MIXED) from SPSS will be used to deal with missed data.

Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment, and simple comparisons of the mean numerical values of these characteristics between memantine and placebo groups will be performed using the two-tailed unpaired t test. Comparability of treatment groups at baseline will be tested for the efficacy parameters in the analysis of efficacy.

Efficacy Parameters

The two primary efficacy endpoints are the comparison of the effects of memantine and placebo on the California Verbal Learning Test II short form (CVLT-II short form). The CVLT-II short form score range is 0 to 36; the baseline and post-intervention scores of the participants

with Down syndrome in our pilot study (Boada et al., 2012; APPENDIX 6) were 14.53 ± 1.80 and 20.12 ± 2.10 (mean ± SEM), for the memantine arm, compared to 16.26 ± 1.82 and 13.74 ± 1.63, for the placebo arm of the trial. (Higher score indicates better performance.) This measure is dependent on the functional integrity of temporal lobe structures such as the hippocampus. Improvement in performance in this measure is expected to be correlated to improvements in the individuals' ability to acquire skills requiring the use of declarative memory. Ultimately, in case we are able to confirm that the administration of memantine is indeed efficacious in improving this cognitive measure in this population, such gains may lead to a measurable improvement in the quality of life of persons with Down syndrome.

Changes from baseline scores of the following secondary efficacy parameters at the post-baseline visit will also be used to compare the memantine and placebo groups:

1. Spatial Span (CANTAB)
2. Pattern Recognition Memory (PRM - CANTAB)
3. Test for Reception of Grammar 2 (TROG)
4. Paired associates task (PAL - CANTAB)
5. Recall of Digits subtest (DAS)
6. Matrices subtest (DAS)
7. Go-No Go test
8. Spatial working memory (SWM - CANTAB)
9. Receptive vocabulary on the Peabody Picture Vocabulary Test-IV (PPVT-IV)
10. Scales of Independent Behavior-Revised (SIB-R)
11. Neurophysiological Assessments: Auditory Brainstem Response (ABR) Test and Mismatch negativity (MMN)
12. Brain morphometric Magnetic Resonance Imaging (MRI) of a subset of 30-60 participants will be performed for source localization for EEG evoked potential studies, quantitative hippocampal morphometry, and generation of hippocampal connectivity datasets.

Because the test scores of most participants in our pilot study were well below the standardized means of the adult versions of the neuropsychological instruments used here, we had to use the children's version of many of these instruments. We plan to do the same in the current study. Hence, instead of using the standard scores for most of the measures (which are based on the participant's age), all test scores will be expressed as "z-transformed" raw scores computed with sample mean and sample standard deviation (which will yields the Student's t-statistic for each measure). This method of standardization of the measures will allow us to compare drug effect across the various neuropsychological measures without changing the significance calculations for the drug effect on each individual measure.

It is very common in neuropsychology that each individual measure is typically subdivided into several sub-measures (sometimes more than a dozen sub-measures per test). Although eventually we plan to run comprehensive a posteriori analyses of the data to inform future studies, in the first report describing the analysis of the data of this trial, we intend to focus on the following sub-measures of the primary measure:

- California Verbal Learning Test II, short form: "Total Free Recall Discriminability" and "Free recall correct for learning trials".

To examine the relations among outcome variables, Pearson's r correlations for each time point will be computed across the whole sample. Point biserial correlation will be used to explore the relationship between the outcome variables and gender.

Statistical Models

For all continuous measures, therapeutic effects will be assessed using repeated measures mixed models (MIXED) from SPSS, including effects for treatment group, the baseline value (the covariance) and treatment by baseline interaction (if statistically significant), with change from baseline as the dependent variable. MIXED handles correlated data and unequal variances. Correlated data are very common in such situations as repeated measurements of survey respondents or experimental subjects. MIXED extends repeated measures models in generalized linear model (GLM) to allow an unequal number of repetitions. The other advantage of MIXED models is that it can handle missing data, which GLM repeated measures cannot. A to-be-named statistician from the Biostatistics, Epidemiology & Research Design core of the Case Western Reserve University Clinical & Translational Science Collaborative (CTSC) will be responsible for the analysis of the data from both the Cleveland and the São Paulo sites.

Confidentiality of Specimens and Banking

☐ I am not storing specimens in this research project – *please leave the rest of this section blank*

Describe:

☒ *The source of the specimens*
☒ *Where the specimens will be stored*
☒ *How long the specimens will be stored*
☒ *How the specimens will be labeled*
☒ *How the specimens will be accessed*
☒ *Who will have access to the specimens*
☒ *When and how will the specimens be destroyed*
☒ *How will the specimens be transported (Please note if transporting specimens, a Material Transfer Agreement (MTA) is required).*

An optional urine sample for potential future studies will be asked from the subjects. Cells will be grown from urine samples and used and stored for scientific studies of the properties of such cells after being transformed into induced pluripotent cells (iPSCs), including DNA (gene) studies. This sample can also be collected in any subsequent visit. Refusal to provide this additional samples will not affect the subject's participation in this study. These cells will be stored in a central laboratory freezer for potential future studies. This sample will not have the research participant's name on it. Instead, it will be de-identified. If research participant informs study team they no longer wish to have their cells used, Research Principal Investigator will have the cells destroyed according to Case Western Reserve University's regulations. De-identified cells

lines may be shared with other researchers and will be shipped by Case Western Reserve University hazardous materials shipper trained personnel.

Describe:

☒ *The procedures to release specimens including:*

i. The process to request a release
ii. Approvals required for a release
iii. Who can obtain specimens
iv. The data to be provided with specimens, including if the data will be identifiable to others

De-identified cells lines may be shared with other researchers at the discretion of Dr. Alberto Costa and with the permission of the research participants as documented on the Informed Consent. Additional data may be provided with cell lines such as medical conditions or baseline neuropsychological test results which will not be identifiable.

☒ *For genomic data, please include an attestation of no master list and no attempt will be made to re-identify the specimens.*

Are you storing the specimen for future use for other research projects?

☒ Yes
☐ No

Confidentiality of Data

1. To maintain the confidentiality of the data:
   ☒ I will use a unique study identifier (not derived from the participants personal identifiers) to code individuals' data and I will store this ID log separate from study data.
   ☐ Other (please explain)

2. How are you storing your electronic data?
   ☐ UH Redcap
   ☒ CWRU Redcap
   ☐ Secure Research Environment (SRE)
   ☐ CWRU Box
   ☐ OnCore
   ☐ UH Secure Network Drive
   ☐ CWRU Secure Network Drive
   ☒ Other - List storage method and provide justification:

   Computer data will be coded with a numerical/letter code and only this code will be used to identify the subject during the data recording procedures. Computer databases with identifying information will be stored on the hard drive of the Research Principal Investigators' computers and will only be accessible with a password. Private health information in the form of clinical and cytogenetic records will be obtained and protected in accordance to the Privacy Provisions of the Health Insurance Portability and Accountability Act (HIPAA) and appropriate regulatory procedures by the UHCMC IRB.

For the Cleveland site, no personal health information (PHI) will be shared with members of institutions other than Case Western Reserve University, University Hospitals, and the Cleveland Clinic. For the São Paulo site, no personal health information (PHI) will be shared with members of institutions other than Case Western Reserve University, University Hospitals, Hospital Israelita Albert Einstein (English: Albert Einstein Israelite Hospital), and other medical institutions in which Drs. Ana Claudia Brandão, Guilherme de Abreu Silveira and/or Patrícia Salmona have hospital privileges, such as the Darci Vargas Hospital and the Albert Einstein Hospital.

3. ☒ I acknowledge that paper research data and documents will be stored in a double-locked secure environment in the following location:
   Location: locked filing cabinet, UH Hospitals, Wearn 214

4. If sharing data, describe:
   - *The exact data elements that will be shared*
   - *How data will be sent*

(Please note if sharing data, a Data Use Agreement (DUA) is required.

HIPAA Authorization

If you are going to be accessing PHI (Protected Health Information), indicate how HIPAA authorization will be obtained (check all that apply):

☒ HIPAA authorization is in the consent form
☐ Requesting a full or partial waiver of HIPAA for prescreening
☐ Requesting a full or partial waiver of HIPAA

1. *Describe why the study cannot be completed without the specified identifiable information.*
2. *If the identifiable information will be used or disclosed by anyone other than the research team, please state who those individuals/entities are and provide justification for the disclosure.*
3. *Describe how long identifiers will be kept for in relation to study length and data collection and analysis.*
   Health data is collected to ensure safety of the participants. Identifiable information may only be released to non-research team members with express permission of legally authorized representative. Identifiers will be kept as long as required by law and hospital regulations regarding record keeping for clinical trials.
   ☒ I assure that protected health information collected for purposes of this research study will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use of disclosure of protected health information for which an authorization or opportunity to agree or object is not required by 45 CFR 164.512

Risks to Research Participants

1. *List the reasonably foreseeable risks such as breach of confidentiality, discomforts, hazards, or inconveniences to the research participants related to their participation in the research. Include a description of the probability, magnitude, duration, and*

reversibility of the risks. Include the physical psychological, social, legal, and economic risks.

2. *If applicable, indicate which experimental procedures may have risks to the research participants that are currently unforeseeable.*
3. *If applicable, indicate which procedures may have risks to an embryo or fetus should the research participant or their partner be or become pregnant.*
4. *If applicable, describe the risks to others who are not research participants.*
5. *Describe the availability of medical or psychological resources that research participants might need.*

1. In large placebo-controlled trials in which patients with dementia received doses of MEMANTINE up to 20 mg/day, the likelihood of discontinuation because of an adverse event was the same in the MEMANTINE group as in the placebo group (see Namenda® Package Insert). In such studies, no individual adverse event was associated with the discontinuation of treatment in 1% or more of MEMANTINE-treated patients and at a rate greater than placebo. In other words, there are no known major side effects of MEMANTINE to date. However, as with any drug, there may be side effects, including the risk of death, which we do not know about at present.

Adverse Events Reported in Controlled Trials: The reported adverse events in MEMANTINE trials reflect experience gained under closely monitored conditions in a highly selected patient population (i.e., elderly individuals with Alzheimer disease). No adverse event occurred at a frequency of at least 5% and twice the placebo rate. Adverse events occurring with an incidence of at least 2% in MEMANTINE-treated patients, but at a greater or equal rate on placebo, were agitation, fall, inflicted injury, urinary incontinence, diarrhea, bronchitis, insomnia, urinary tract infection, influenza-like symptoms, walking abnormalities, depression, upper respiratory tract infection, anxiety, peripheral edema, nausea, anorexia, and joint pain. The overall profile of adverse events and the incidence rates for individual adverse events in the subpopulation of patients with moderate to severe Alzheimer disease were not different from the profile and incidence rates described above for the overall population of individuals with dementia. In our pilot study with young adults with Down syndrome (Boada at al., 2012; APPENDIX 6), increased anxiety (2 participants out of 18, i.e., 11.1%) and increased frequency of echolalia (1 participant out of 18, i.e., 5.6%), were reported by the participants' caregivers.

The subject and caregivers will be given a list of phone numbers for contact in the event that emergency treatment is necessary.

Other Risks and Discomforts
ECG risks: The glue used to keep the small discs in place during the ECG may irritate the skin. The ECG discs can also make the skin around the area close to the discs red, but this should wear off after a few hours.

EEG risks: EEG measurements are considered very safe. We will use a glue-free method in which we wet the leads with saline solution. The participant may get a bit bored, and parts of the skin under the EEG cap may turn a little red, but this should also wear off after a couple of hours.

Risks of Having Blood Taken

In this study we will need to get about 6 tablespoons of blood in two visits. The participant may feel some pain from the needle, but the discomfort is brief. A day or two later, the participant may have a small bruise where the needle went under the skin. Infections, dizziness, or fainting can also happen. To minimize these risks, only experienced medical personnel will draw blood.

Questionnaire risks
Participants may be embarrassed by some of the questions we ask. Participants who do not wish to answer a question, may skip it and go to the next question. Participants can refuse to answer any of the questions. Participants may feel bored or tired after the physical exams and psychological testing.

The risks of the MRI study are the same as those for a routine MRI scan. MRI has no known long term effects. A small number of participants, less than 5% complain of claustrophobia. The noise made by the machine may bother some participants, but protective headphones will be used to reduce the noise.

2. *The study may include risks that are unknown at this time. If any new risks become known in the future, participants will be informed of them.*

3. *The effect of the study medicine on pregnancy and on a fetus is not known. Female subjects must be documented not to be pregnant by serum testing at screening. Females of child-bearing potential who are sexually active must be practicing a reliable method of birth control (oral contraceptives or double-barrier method) which must be documented and the subject and caregiver must be counseled in writing on the importance of not becoming pregnant during the trial. A blood pregnancy test will be done at baseline visit (Visit 1) and must be negative prior to dispensing any medication. Urine pregnancy tests will be done at the two follow-up medical visits (Visit 3 and Visit 5).*
4. *N/A*
5. *The subject and caregivers will be given a list of phone numbers for contact in the event that emergency treatment is necessary.*

Provisions to Protect the Privacy Interests of Research Participants

Describe the steps that will be taken to protect research participants' privacy interests. (consider issues such as physical space, proximity to other, and participant preferences)

Prospective subjects will be approached for consent in a private location, and will be given time and space in which to make their decision. All details and information related to study participation will be discussed in private locations only, and that research records will be kept in a separate location from the regular medical record.

Potential Benefit to Research Participants

1. *Describe the potential benefits that individual research participants may experience from taking part in the research. Include the probability, magnitude, and duration of the potential benefits. Indicate if there is no direct benefit.*

No direct benefit

2. *If no direct benefit, state the potential benefit to society or others. Do not list compensation.*

This is a study of the efficacy and safety of memantine HCl in adolescents and young adults with Down syndrome. Although specific risks have been identified above, as with any medication, it must be emphasized that serious adverse experiences, previously identified or not, may occur. Subjects participating in this study cannot be guaranteed a clinical benefit from the administration of the test drug. Thus, for each subject, the possibility of a positive therapeutic effect and their contribution to the scientific understanding of the properties and actions of memantine HCl in persons with Down syndrome are the only benefits.

Withdrawal of Research Participants

1. *Describe the anticipated circumstances under which research participants will be withdrawn from the research without their consent.*

Adolescents and adults with Down syndrome will be assessed by an additional experienced physician who will have the ability to discontinue the participation of a subject with Down syndrome if she/he deems this person not fit to participate fully in the trial. Although this will not necessary exclude an individual from participating in the trial, inability to complete the neuropsychological test battery would raise a red flag in terms of the fitness of an individual to participate. At all times, the research staff will assess dissent to participate in the study, and can recommend that a participant be excluded from the study because of any significant, real or perceived, discomfort expressed by the participant or parent/caregiver.

In accordance with the Declaration of Helsinki, subjects have the right to withdraw from the study at any time for any reason. The Investigators also have the right to remove subjects from the study. Subjects may be removed from the study for the following reasons:

a. Adverse experience

b. Intercurrent illness that, in the judgment of the Investigators, might place the subject at risk or invalidate the study

c. Request of the subject, his/her legal representative, or Investigators, whether for administrative or other reasons

d. Non-compliance with medication, protocol violation, or unreliable behavior

2. *Describe the procedures that will be followed when research participants withdraw or are withdrawn from the research, including partial withdrawal from procedures with continued data collection.*

If for some reason the subject withdraws or is withdrawn from this study prior to Visit 5, he/she will be asked to return to the clinic for a "Treatment Discontinuation Visit." In addition, if the subject discontinues the medication prior to the end of the study, he/she will be asked to complete a "Retrieved Dropout Visit" on the date that should have represented Visit 5. Study

medication will not be provided beyond the study period. The procedures for the "Treatment Discontinuation Visit" will be the same as those described for "Visit 5 (Second follow-up medical visit)."

Alternatives to Participation

1. *Please list other available clinical treatments.*
   There are no alternative clinical treatments.
2. *Please state if a subject could continue on standard of care therapy and what that might include.*
   Standard therapies include physical, speech, and occupational therapies, and should continue during the study.
3. *If not a clinical trial you may state that the alternative is not to participate. <u>If there is a viable alternative you must list it in the consent.</u>*
   N/A

Costs to Research Participants

☐ There are no costs to research participants or their insurance companies – *please leave the rest of this section blank*

1. *If applicable, describe what costs the research participants will be responsible for because of participation in the research including but not limited to: transportation to study visits, parking for study visits, costs of procedures, lost, broken or stolen devices, costs of drugs or therapy, etc.*

We plan to reimburse all reasonable expenses incurred by the parents/guardians of the participants of this study for travel, hotel accommodations, and parking. The Research Principal Investigator of this study will decide on the amount of reimbursement, based on Case Western Reserve University guidelines for travel reimbursement and availability of receipts to document the expenses. However, depending on how many out-of-town participants we have in this trial, we may reach a point in which funds are not available to reimburse all the expenses. At that point, we will explain the situation to these individuals before they commit to participating in the trial, and will let them decide whether they are willing to incur the expenses for participating in this trial.

2. *You must clearly state if insurance will be charged and who will be responsible if insurance does not pay.*

Insurance will not be charged for the study visits.

3. *List what research procedures and research interventions will be covered by this study.*

Study medication and all testing will be covered by this study.

Research Participant Compensation

☐ There is no compensation for research participants – *please leave rest of this section blank*

1. *Describe the schedule, payment method and payment total of any incentives or compensation that research participants will receive for participation in the research (e.g., gift cards or cash with amounts, t-shirts, devices, bags, swag, etc.)*

No incentives

2. *Describe the schedule, payment method and payment total of any reimbursements that research participants will receive for participation in research (e.g., parking, mileage, meals, etc.)*

   We plan to reimburse all reasonable expenses incurred by the parents/guardians of the participants of this study for travel, hotel accommodations, and parking. The Research Principal Investigator of this study will decide on the amount of reimbursement, based on Case Western Reserve University guidelines for travel reimbursement and availability of receipts to document the expenses.

Compensation for Research Related Injury

Describe who will pay for the costs of medical treatment and/or compensation in the event of a research related injury:

- ☐ Funding agency is providing some/all payment for injury
- ☒ Funding agency is providing no payment for injury
- ☐ Not applicable

Provisions to Monitor the Data to Ensure the Safety of Research Participants

1. *Describe the Data and Safety Monitoring Plan for the proposed study. Describe how often the data will be monitored for completeness, accuracy and adherence to the protocol.*

In addition to expert medical evaluations during the medical visits (Visits 1, 3, and 5), periodic review of adverse events in this trial will be performed through meetings of the Data Safety Monitoring Board (DSMB). The function of the DSMB is to monitor the safety data being generated by the clinicians in this trial to determine if the risk/benefit ratio is acceptable to continue this trial. Dr. Costa will participate in the open portion of meetings to be appraised of the group decisions and any suggestions to improve the safety and reliability of trial procedures (made during their closed deliberations), but he will not have any say in terms of the appropriateness of the continuation of the trial. The formal charter of the DSMB will be prepared and approved at the DSMB organizational meeting.

Written reports will be generated annually in case no serious adverse event (SAE) is reported. In addition to its annual meeting, the board may also meet within 48 hours of the occurrence of a severe adverse event (SAE) to plot an appropriate course of action for the remainder of the trial, and should generate a detailed report of their decision within one week from the time a SAE has been noted and properly reported. DSMB may also meet more often than annually at the discretion of the DSMB Chairperson.

In case of a serious adverse event (SAE), the subject will be dropped immediately from the study, and the investigators will notify the Institutional Review Board (IRB) within 24 hours and file a form 3500A – Medwatch SAE form with the FDA. (Form 3500A – Medwatch is appended to the Case Report Form - CRF) (see APPENDIX 4).

SAE monitoring and reporting for the São Paulo site will follow the same general standard operating procedures. In addition, the São Paulo site will have to comply with Brazilian federal, state, and local rules and regulations for the performance of clinical trials.

It is also understood that monitors appointed by the UHCMC IRB in Cleveland and Ethics Committees in São Paulo will be allowed to inspect the various records of the trial (CRFs and other pertinent data, provided that subject confidentiality is maintained in accord with institutional requirements). IRB/Ethics Committee-appointed monitors will also be able to inspect the CRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered. The monitors must have access to laboratory test reports and other subject records needed to verify the entries on the CRF. The Investigators agree to cooperate with the monitors to ensure that any problems detected in the course of these monitoring visits are resolved.

2. *Is there a formal Data and Safety Monitoring Board/Committee? If yes, provide information about the DSMB/C including the contact information of the committee member(s) (as applicable); whether it is independent from the study sponsor; how often it meets; the type of data that will be used; written reports, etc.*

List of DSMB Members

Mark S. Scher, MD
Professor of Pediatric Neurology
Rainbow Babies & Children's Hospital
11100 Euclid Ave, Cleveland, OH 44106
Phone: 216-844-3691
Fax: 216-844-8966
Email: Mark.Scher@uhhospitals.org
Cell Phone: 216-233-8780

Alan J. Lerner, MD
Professor of Neurology
Director, Brain Healthy and Memory Center
University Hospitals
Cleveland Medical Center
11100 Euclid Avenue
Cleveland, OH 44106-5040
Phone: 216-464-6412
Fax:
Email: alan.lerner@case.edu
Cell Phone: 216-577-9140

Melissa Armstrong-Brine, PhD
Assistant Professor, Psychiatry
Neuropsychologist
MetroHealth Medical Center
2500 MetroHealth Drive
Cleveland, Ohio 44109
Phone: 216-778-4428
Fax:
Email:marmstrongbrine@metrohealth.org
Cell Phone:

Patricia A. Marshall, PhD
Professor of Bioethics
Phone: 216.368.6196
Fax:

Associate Professor of Anthropology
Case Western Reserve University
10900 Euclid Avenue
Cleveland, Ohio 44106

Email: pam20@case.edu
Cell Phone:

Abdus Sattar, PhD (DSMB statistician)
Associate Professor of Biostatistics
Professor of Population and
Quantitative Health Sciences
Case Western Reserve University
Wood Bldg, WG-51A
10900 Euclid Ave
Cleveland, OH 44106, USA

Phone: 216-368-1501
Fax: 216-368-4880
email: sattar@case.edu
Cell Phone:

Drugs or Devices

☐ There are no drugs or devices being utilized in this research project – *please leave rest of this section blank*

1. *If the research involves drugs or device(s), describe your plans to store, handle, and administer those drugs or device(s) so that they will be used only on research participants and be used only by authorized investigators.*

UIP will purchase commercial grade memantine (Namenda®) from Forest Pharmaceuticals, Inc., bulk pack, and ship memantine and placebo to our Investigational Drug Services (IDS) at University Hospitals of Cleveland Case Medical Center (run by Michael J. Banchy R.Ph.). At IDS, the double-blind label bottles of medication will be filled by Dr. Banchy and dispensed by a study coordinator at the site of the trial. The study dosages of memantine and placebo will be individually packaged and labeled.

Additionally, UIP will also perform all the individual packaging, double-blind labeling, and shipping to the São Paulo site. Packaging of the study dosages scheme for memantine and placebo will be identical to the one described above IDS at University Hospitals of Cleveland Case Medical Center. William J. Wilson, R.Ph., Director, Non-Sterile Manufacturing and Maintenance for UIP will be in charge of all packing and labeling procedures related to the São Paulo site.

2. *How will the drug(s) be dispensed (i.e., indicate the pharmacy that will be used)?*

Uh Hospitals Investigational Drug Services in the Cleveland site. William J. Wilson, R.Ph., Director, Non-Sterile Manufacturing and Maintenance for UIP will be in charge of all packing and labeling procedures related to the São Paulo site.

3. *If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), identify the holder of the IND/IDE/Abbreviated IDE*

N/A

Additional Information

If you have any additional information regarding your study not covered in the template, please include it here.

Community-Based Participatory Research

☒ This is not a community-based participatory research project – *please leave rest of this section blank*

If applicable, describe the involvement of the community in the design and conduct of the research.
Note: Community based research is research that is conducted as an equal partnership between academic investigators and members of a community. In Community Based Participatory Research (CBPR) protects, the community participates fully in all aspects of the research process.

International information

☐ This is not an international study – *please leave rest of the section blank*

☒ We will be conducting this research at the following international sites:
1. São Paulo

☒ We are recruiting participants outside of the US from the following locations:
1. São Paulo

☐ We are sending data outside of the US to the following locations:
1.

☒ We are receiving data from outside of the US from the following locations:
1. São Paulo

MULTI-SITE RESEARCH (when UH or CWRU is the IRB of Record)

Does this project have multiple sites?

☒ **Yes**

☐ **No**

Non-Local Site Information for Multi-Site Studies

*If this is a multi-site study where you are the **lead investigator,** list the following information for each relying site:*

1. Name of site: Hospital Israelita Albert Einstein (English: Albert Einstein Israelite Hospital) – FWA IRB00005041 Hospital Israelita Albert Einstein IRB #1 – Biomedical.
2. PI of relying site: Dr. Ana Claudia Brandão
3. Name of IRB contact: Leslie Johnson
4. Phone number of IRB contact: 718.430.2237

5. Email address of IRB contact: leslie.johnson@einstein.yu.edu

Non-Local Recruitment Methods for Multi-Site Studies
*If this is a multi-site study and research participants will be recruited by methods **not under the control of the local site** (e.g. call centers, national advertisements) describe those methods. Local recruitment methods are described above.*
N/A

1. *Describe when, where, and how potential research participants will be recruited.*
2. *Describe the methods that will be used to identify potential research participants.*
3. *Describe the materials that will be used to recruit research participants.*

Multi-Site Research Communication Plan (when you are the lead investigator)
*If this is a multi-site study where you are the **lead investigator**, describe the processes to ensure communication among sites including:*

- *All sites will have the most current version of the protocol, consent document, and HIPAA authorization*
- *All required approvals (initial, continuing review and modifications) have been obtained at each site (including approval by the site's IRB of record)*
- *All modifications have been communicated to sites, and approved (including approval of the site's IRB of record) before the modification is implemented*
- *All engaged participating sites will safeguard data, including secure transmission of data, as required by local information security policies*
- *All local site investigators conduct the study in accordance with applicable federal regulations and local laws*
- *All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy*

Lead and Research Principal Investigator, Dr. Alberto Costa, and relevant members of the local study team have made numerous trips and will continue to travel to Brazil site to train personnel, disseminate translated study documents, and ensure study procedures are implemented as per study protocol. Research Principal Investigator is constantly in direct communication with PI and other study team members of the Brazilian site.

*If this is a multi-site study where you are the **lead investigator,** describe the method for communicating to engaged participant sites:*

- *Problems*
- *Interim results*
- *The closure of the study*

See above

References

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The Following have been uploaded as separate documents:

APPENDIX 1 (Study Advertisement)

APPENDIX 2 (Subject Consent Forms)

APPENDIX 3 (case report form (CRF))

APPENDIX 4 (serious adverse event (SAE) reporting and FDA form 3500A - Medwatch)

APPENDIX 5 (Namenda® package insert)

PPENDIX 6 (Copy of the published article describing the results of the pilot study of memantine in young adults with Down syndrome)

Please reference the Investigator Manual for local institutional requirements.