CLINICAL REVIEW

Application Type	Efficacy Supplements
Application Number	N-22-525
Priority or Standard	Standard
Submission Date	06 Jan 2014
Received Date	06 Jan 2014
PDUFA Goal Date	06 Jul 2014
Division/Office	DPP/ODE1
Reviewer Name	Mark Ritter, M.D. R.Ph.
Review Completion Date	04 Jun 2014
Established Name	Namenda XR
Trade Name	Memantine HCl
Therapeutic Class	Alzheimer's
Applicant	Forest Pharmaceuticals
Formulation	Capsule
Dosing Regimen	Daily Oral
Indication	Treatment of Core Symptoms of Autism
Intended Population	Children/Adolescents with Autism

Table of Contents

1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT

1.1 Recommendation on Regulatory Action

This reviewer recommends that the Agency APPROVE this New Drug Application (NDA). Although efficacy was not established with memantine administration for the treatment of the core autistic symptom of social communication dysfunction, the efficacy and safety results obtained from the clinical development program should be included in the product labeling to inform clinicians and families of the lack of memantine's effect on the treatment of core symptoms of autism.

1.2 Risk Benefit Assessment

Not applicable.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not Applicable.

1.4 Recommendations for Postmarket Requirements and Commitments

This reviewer recommends that the sponsor conduct a new dissolution study with the 3 and 6mg doses using approved dissolution acceptance criteria due to the sponsor's failure to use approved dissolution acceptance criteria for the 3 and 6mg strengths.

Although the 3 and 6mg capsules are not intended to be marketed by the sponsor, (b) (4) an acceptable dissolution method must be employed.

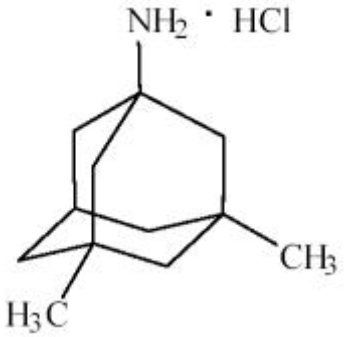
2 INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information

Memantine, an NMDA-receptor antagonist, has been developed as an extended release capsule containing 3 and 6mg of memantine hydrochloride per capsule.

The chemical name for memantine is 3,5-dimethyladamantan-1-amine.

The structural formula of memantine is provided below:



2.2 Tables of Currently Available Treatments for Proposed Indications

There is currently no available Agency- approved treatment for the treatment of core symptoms of autism.

2.3 Availability of Proposed Active Ingredients in the United States

Currently memantine is available as 7, 14 ,21 and 28mg of memantine HCL as extended release capsules for the treatment of Alzheimer's disease.

2.4 Important Safety Issues With Consideration to Related Drugs

There are no known safety considerations with other NMDA-receptor antagonists.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The sponsor submitted an IND (IND 73,075) to the Agency to investigate the effects of memantine for the treatment of core symptoms of autism in 2006. Due to pre-clinical concerns of brain lesions seen in rats that appeared non-dose related, the IND was placed on clinical hold. On 23 Jan 2007, the clinical hold was removed after the sponsor agreed to limit memantine exposure to pediatric patients to no more than 2100 ng*hr/ml, providing a 10-fold safety margin for brain lesions noted in rats.

On 23 Sept 2008, the Agency and sponsor met to discuss the proposed protocol for study MD-57A, which eventually would become the study that provided both pediatric pharmacokinetic data and efficacy data for this submitted NDA.

The Agency ultimately issued a Written Request on 25 Jan 2012 to evaluate the safety and efficacy of memantine treatment in core impairment symptoms in pediatric patients (aged 6-12 years of age). Upon completion of the planned studies to examine memantine's efficacy on the core symptoms of autism, a final pre-NDA meeting was held with the sponsor on 22 Jul 2013 to discuss filing of the clinical data to the Agency.

On 06 Jan 2014, the sponsor formally submitted NDA 22-525 to the Agency for review and pediatric exclusivity.

2.6 Other Relevant Background Information

A summary of the protocol amendments for each of the two clinical efficacy studies is reviewed below.

Study 57A (Original protocol date 31 Oct 2008)

For study 57A, there were seven (7) protocol amendments submitted to the agency during the clinical development program of MEMANTINE for the treatment of autism:

- Amendment 1 dated 16 March 2009: this protocol amendment clarified contraception use for patients and added the inclusion criterion that the SRS raw total score must be >44 for females and >53 for males. In addition, the visit 5 PK visit was changed from a patients home to the clinic and clarified that the secondary measures CATS-S and CAASTS-S was not to be conducted at last visit/ET.
- Amendment 2 dated 26 Aug 2009: This protocol amendment clarified that blood pressure measurements were to be orthostatic measures, as well as defining the intent to treat (ITT) population and correcting typographical errors.
- Amendment 3 dated 29 Dec 2009: This amendment reduced the weight-based doses as originally pre-specified in the original protocol from 18mg to 15mg for groups A, 12mg down to 9mg/day in group B, and a new dose group, Group C, having a dose of 6mg/day. In addition, normal vital sign parameters based on age were added to inclusion/exclusion criteria.
- Amendment 4 dated 11 Aug 2011: This amendment clarified that all new patients were to be enrolled in part 2 as part one had been completed. In addition, dose group D (originally pre-specified as only those patients who completed part 1), was set to enroll patients with a target dose of 3mg/day. Also, the amendment ensured that at least 80 patients that were to be included into the efficacy analysis must have completed 12 weeks of double-blind treatment.
- Amendment 5 dated 08 Dec 2011: This amendment allowed a blinded interim analysis to determine if an increase in study sample size was required in order to comply with initial study power calculations.
- Amendment 6 dated 07 Mar 2012: This amendment changed the primary efficacy analysis from an LOCF-based approach to an MMRM-based modality. It also included two sensitivity analyses for the primary efficacy parameter.
- Amendment 7 dated 12 Jul 2012: This amendment clarified the definition of ITT and the safety population, as well as statistical changes to the interim analysis and clarification of the statistical approach to be used for the primary efficacy analysis.

For study MD-68, there were two (2) protocol amendments:

- Amendment 1 dated 22 Mar 2013- This amendment increased the sample size from 96 patients per treatment arm to 165 based on an unblinded interim analysis of study MD-91.It also allowed patients to use benzodiazepines to reduce stress of discomfort during certain study procedures. Changes were made to add

information on the data safety monitoring board and clarification of appropriate administration of the C-SSRS scale.

- Amendment 2 dated 20 May 2013- This amendment further allowed recruitment greater than 165 per arm, as well as clarification of reporting unintended pregnancies as a serious adverse event. Literature was also updated.

In this reviewer's opinion, the protocol amendments did not significantly affect the overall study results, analyses or conclusions for study 57A or study 68.

3 ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

The Division of Scientific Investigations (DSI) was provided a list of 6 U.S. sites for inspections on Table 2 as shown below:

Table 2: Office of Compliance Inspections

Site Name and #	Number Subjects Study 57A	Number of subjects Study 67	Number of Subjects Study 68	Action Taken
Antonio Hardan,MD Site 02	10	6	2	No Action Indicated (NAI)
Robert Hendren, DO Site 21	13	11	2	NAI
Jeffrey Blumer, Ph.D., MD, Site 13	6	6	--	Verbal Action Indicated (VAI)
Robert Findling, MD Site 13	6	7	--	NAI
Michael Aman, PhD Site 01	8	7	8	VAI
Riaz Baber, MD Site 23	10	8	8	NAI

John Lee, MD from the Office of Scientific Investigations performed the review of the clinical inspections from the above sites. A brief summary from the two sites that were issued FDA form 483 are provided below.

Site 13 (Blumer) was cited on FDA form 483 for enrolling patients while on prohibited medications, thus not adhering to the clinical protocol. Otherwise, the site was adequately monitored.

Site 01 (Aman) was cited on FDA form 483for inadequate maintenance of subject case histories and not adhering to the study protocol.

As noted by the clinical inspection review, these two sites with the deficiencies noted above are likely not have an impact on the overall outcome of the studies. Thus no data integrity issues appeared to have played a role in the outcome of the study results.

3.2 Compliance with Good Clinical Practices

Studies 57A, 68, 69, and 91 were conducted according to the Declaration of Helsinki and amendments. All subject information was documented and stored using Good Clinical Practices (GCP) as delineated in the Health Insurance Portability and Accountability Act (HIPAA) of 1997.

3.3 Financial Disclosures

See Appendix for Financial Disclosure Template.

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry Manufacturing and Controls

Okpo Eradiri, Ph.D. of the Office of New Drug Quality Assurance (ONDQA) performed a review of the Chemistry, Manufacturing and Controls (CMC) section of the supplement on 12 March 2014.

(b) (4)

In his review, Dr. Eradiri noted that the 3 and 6mg capsules exhibit similar dissolution profiles to the already approved adult dose of 28mg. However the proposed dissolution acceptance criteria for the pediatric strengths were not complete. (b) (4)

(b) (4)

Thus, Dr. Eradiri has recommended a COMPLETE RESPONSE of the supplement from a CMC perspective, pending implementation of current dissolution acceptance criteria.

On 30 May, 2014, Dr. Eradiri provided an addendum to his review. Since the 3 and 6mg strengths were manufactured only for clinical trial purposes and not marketing purposes, the division has deemed the modified-dissolution criteria appropriate. As the sponsor is

not seeking an approval for the 3 and 6mg strengths, Dr. Eradiri has recommended APPROVAL of this application.

4.2 Clinical Microbiology

Due to the absence of any clinical microbiological data, a review of such data is not applicable to this submission.

4.3 Preclinical Pharmacology/Toxicology

A pharmacology/toxicology review of this supplement was conducted by Ikram Elayan , Ph.D. on XXXX. A brief summary of this review indicates that no new non-clinical studies were submitted as part of this IND. As there was no additional information related to memantine as part of a literature search, it was Dr. Elayan's recommendation that there are no new non-clinical data or concerns that affect the safety profile of memantine for the treatment of autism, as memantine will not carry an indication for the treatment of autism due to the failed clinical studies.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Memantine is a known N-methyl-D-aspartate (NMDA) receptor antagonist. The NMDA receptor is an ionotropically-gated glutamate synaptic receptor. Since glutamate is a known excitatory neurotransmitter in the brain, antagonism of the NMDA receptor will lead to reduced excitatory effects on synaptic transmission within the brain.

The reduced NDMA effect provided by memantine-induced NMDA receptor antagonism for the treatment of Alzheimer's is hypothesized to be effective for Alzheimer's as excessive glutamatergic activity is believed to underlie the symptomatology of Alzheimer's. However the purported effect memantine would have on the symptoms of autism are unknown.

4.4.2 Pharmacodynamics

Memantine shows antagonist effects to 5-HT3 receptors with potency similar to that seen for the NMDA receptor according to the memantine product label.

4.4.3 Pharmacokinetics

According to the Namenda approved product labeling, memantine has linear pharmacokinetics with a Cmax ranging between 3-7 hours. There is low plasma protein binding, thus resulting a lower volume of distribution of 9-11L/Kg.

Memantine undergoes partial hepatic metabolism with approximately 48% of memantine being excreted in the urine unchanged. The terminal half life of memantine is approximately 60-80 hours.

5 SOURCES OF CLINICAL DATA

5.1 Tables of Studies/Clinical Trials

Table X: Namenda ® Table of Studies

Double-Blind, Placebo Controlled	
MEMANTINE-MD-57A (US) A two phased (A and B) study	Part 1: Single dose pharmacokinetic study in four (4) pediatric patients with autism using a single 3mg dose of memantine. Part 2: A 12-week outpatient, multicenter, double-blind, parallel-group, placebo controlled, randomized (1:1 drug: placebo), flexible-fixed dose study (3-15mg based on weight) of 114 patients (ages 6-12 years of age) with a current clinical diagnosis of autism, PDD-nos or Asperger's with baseline score of 44 or greater for females (53 or greater in males) on the Social Responsiveness Scale (SRS) and an Aberrant Behavior Checklist-I Score of less than 17 at baseline. First Enrollment: 01 May 2009 Last Subject: 02 Aug 2012
Double-Blind, Randomized Withdrawal Study	
MEMANTINE-MD-68 (International)	A 12-week outpatient, multicenter, international (15 countries), double-blind, placebo controlled, randomized treatment withdrawal study of 471 patients (ages 6-12 years of age) with a current clinical diagnosis of autism, PDD-nos or Asperger's who completed at least 12 weeks of exposure to memantine from open-label lead-in study 91 (discussed below) and met responder criterion (a 10 point or greater reduction on the SRS scale) at 2 consecutive visits separated by at least 2 weeks who were then randomized to receive in 1:1:1 fashion either double-blinded full dose memantine, 50% memantine dose (reduced MEMANTINE group), or placebo with primary endpoint of proportion of patients with loss of treatment response (a 10point or greater increase in SRS score) by week 12. First Enrollment: 10 Sep 2012 Last Subject: 11 Sep 2013
OPEN LABEL STUDIES	
MEMANTINE-MD-67 (US)	A 48 week multicenter (6 week double-blind dose titration followed by 42 weeks open label), open-label extension study of study 57A to examine the safety and tolerability of memantine(3-

	15mg/day based on weight) in 95 pediatric patients with autism. First Enrollment: 05 Nov 2009 Last Patient: 01 Feb 2013
MEMANTINE-MD-69 (Ongoing)	A 48 week, multicenter, open-label extension study examining the safety and tolerability of memantine in 275 patients (as of 07 Jun 2013) who have completed studies MD 67, 91 or 68.
MEMANTINE-MD-91 (international)	An up to 48 week, outpatient, multicenter, international, open label extension study of 903 pediatric patients aged 6-12 years) with a current clinical diagnosis of autism, PDD-nos or Asperger's with baseline score of 44 or greater for females (53 or greater in males) on the Social Responsiveness Scale (SRS) and an Aberrant Behavior Checklist-I Score of less than 17 at baseline who (after a minimum of 12 weeks of treatment) meet responder criteria defined as an SRS score reduction of 10 point or greater since baseline will then be enrolled into study MD-68. First Enrollment: 01 Jun 2012 Last Subject: 09 Jul 2013

5.2 Review Strategy

Table 4 below provides a listing of documents that were reviewed during the NDA review process.

Table 4: Items Utilized in this review

SUBMISSION DATE	ITEMS REVIEW
January 6, 2014	• Study reports: 57A, 67, 68, 69, 91 Clinical Safety Summary • Regulatory History • Review of pertinent SAEs and safety data from previously un-reviewed study 2305 • Proposed labeling • Financial Disclosure Certification • Application Summary • Case Report Tabulations (.xpt files) • Case Report Forms

5.3 Discussion of Individual Studies/Clinical Trials

Studies 57A and 68 form the basis of the review for the treatment of autism as the primary endpoints for both studies examined efficacy of autistic patient's treatment with double-blind MEMANTINE treatment when compared to placebo treatment. Studies 67, 69 and 91 are utilized to examine the safety and long-term tolerability of memantine for the treatment of autism.

6 REVIEW OF EFFICACY

Efficacy Summary

Memantine treatment was shown to be INEFFECTIVE for the treatment of core symptoms of autism in patients with autism.

6.1 Studies Pertinent to Claim 1

There are two (2) efficacy studies completed by the sponsor and submitted as part of this NDA package, studies 57A and study MD-68.

6.1.1 Rationale for Selection of Studies for Review

The sponsor has conducted and submitted two (2) efficacy studies to examine whether MEMANTINE treatment in patients with autism is superior to placebo treatment.

6.1.2 Study Summaries

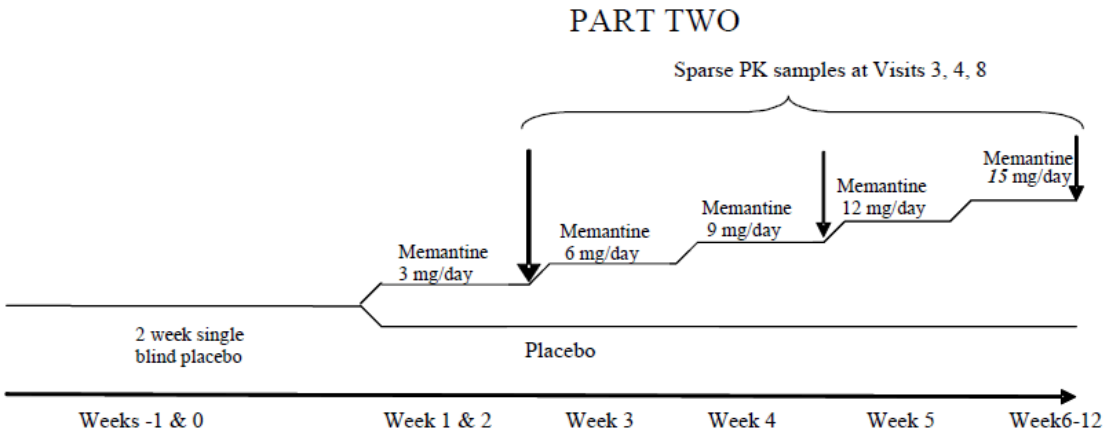
Study 1 (MD-57A)

Methods/Study Design/Analysis Plan
Study MD-57A is a two part, 12-week, randomized, double-blind, placebo-controlled, flexible/fixed dose, parallel group monotherapy study of MEMANTINE in pediatric patients aged 6-12 years of age with autism, PDD-nos or Asperger's disorder. For part 1, the only inclusion criteria for taking part in the open-label, single dose PK study was a diagnosis of autism, Asperger or PDD-nos. Since part 1 of study 57A was an open-label PK study conducted in four (4) patients, results from part 1 will not be reviewed as part of the efficacy review.

For part 2 of study 57A, outpatients with a diagnosis of autism, PDD-nos or Asperger's who are who met DSM-IV criteria for autism using the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R) were given single-blinded placebo for two weeks. Those patients who continued to meet inclusion criteria after two weeks of single-blind placebo were then randomized 1:1 in double-blind fashion two 12 weeks of MEMANTINE or placebo. Patients randomized to MEMANTINE had up to 8 weeks to complete the dosing titration and must have at least 4 weeks of maintenance at a fixed dose. PK data was also taken at three visits during the double blind portion.

The study design schematic is presented below. There are two schematics, one for patients enrolled in part 1 and part 2. However since only 4 patients were enrolled into part 1, only the second schematic is being shown below:

Figure 1: Study MD-57A Study Design Schematic



Patients

The trial protocol pre-specified that patients meeting the following criteria were to be randomized at screening and baseline:

- Subject age 6-12 years of age
- For PART 1: A DSM-IV diagnosis of autism, Asperger or PDD-nos using any of the following validated diagnostic scales:
  - ADI-R
  - ADOS-Social interaction and communication subscale
  - Childhood Autism Rating Scale
  - Gilliam Autism Rating Scale
  - Gilliam Asperger Scale
  - Social Communication Questionnaire
- For PART 2:

- A DSM-IV diagnosis of autism, Asperger or PDD-nos using any of the following validated diagnostic scales:
  - ADOS-Social interaction and communication modules 2 or 3
  - ADI-R
  - an ABC irritability score <17
  - an SRS raw total score >44 for females, >53 for males
  - an IQ (based on standardized IQ testing or Kaufmann Brief Intelligence test KBIT) of 50 or higher.

    - If patients are enrolled in non-pharmacological therapies, all therapies MUST have been continuous for 90 days prior to screening and families intend to maintain the current treatment for the duration of the study and NOT initiation or modify ongoing interventions during the study.
- Normal physical exam, including age appropriate normal vital signs
- Non pregnant females using adequate contraception

Patients were excluded for the following pertinent reasons:

- A history of a movement disorder such as Tourette's or genetic neurological disease such as tuberous sclerosis, fragile X, velocardiofacial syndrome, chromosomal 15q duplication, Angelman syndrome, active epilepsy/seizure disorder, abnormal CT/MRI or brain.
- A history of premature birth, defined as before 35 weeks gestational age of <5lb at birth
- Medical conditions that could interfere with study
- Clinically significant ECG findings
- Patients who are not acceptable in the investigators opinion.
- Having any other Axis 1 diagnosis other than autism
- Taking or have taken psychoactive medication within five half-lives or 4 weeks of screening, whatever is shorter

Primary Objective

The primary objective of this study was to investigate the pharmacokinetics, safety, tolerability and efficacy of MEMANTINE in pediatric patients with autism.

Key Secondary Objective

There were no a priori specified secondary endpoints for this study.
Primary Endpoint for part 2

The primary endpoint for part 2 of study 57A was *a priori* specified to be the mean change from baseline at week 12 on the SRS total raw score in patients administered MEMANTINE and placebo. The SRS is a 65 item, informant-rated instrument that assesses various social domains in a wide range of patients. The SRS has been validated between maternal reported SRS scores and the ADI-R. Although the original SRS was designed to report patient behavior over a previous 6 month time period, the patients previous 6 weeks of behavior was evaluated with this instrument. The scale rates various social behaviors using 65 items rated 1 to 4 by the caregiver informant. These scores are then transposed to a 0 to 3 scales and grouped into 5 social domains. SRS scores can range for 0 to 195.

After discussions with the Dr. Constantino (developer of the SRS scale) and the sponsor, a consensus was reached that a 10 point change on the SRS scale over a 6 week period of

time was considered clinically significant. For this study, the same caregiver was to administer the SRS at baseline, end of week 6, and end of week 12 or early termination.

Key Secondary Endpoint

There was no key secondary efficacy assessment a priori specified. However , the study examined secondary efficacy using the Core Autism Treatment Scale (CATS) and the Children's communication Checklist (CCC). Each instrument is described below,

- Core Autism Treatment Scale (CATS)- The CATS is a validated clinician-rated outcome that has two different, but related, scales. The CATS-Severity scale (CATS-S) contains 14 items scored 1-7 that tests for various areas of social interaction and communication. Scores on the CATS-S are only obtained at baseline and provide an anchor point for the CATS-Improvement (CATS-I). The CATS-I assesses each value obtained on the 14 item CATS-S and allows a clinician to score each item 1 (very much improved) to 7 (very much worse). The CATS-I is administered at the end of week 2, 4, 6, 8, 10 and 12.
- Children's communication Checklist (CCC)- The CCC is a validated informant – related scale with 70 items rated 0(less than once/week or never) to 3 (several time or more than twice a day or always). The 70 items are grouped into 10-seven item subscales useful for measuring changes in various communication domains in children.

Additional Secondary Endpoints
The study also measured changes in core and associated symptoms using the Core and Associated Autism Symptom treatment Scale (CAASTS-S and I). The instrument, anchored by scores on the CAASTS-S and changes noted via administration of the CAASTS-I, is a validated measured used to assess changes in stereotypical behavioral and daily functioning.

The CGI-I and CGI-S, along with changes seen on the Aberrant Behavior Checklist-Community (ABC-C) subscale I (irritability) was also assessed in this study.

Results

Demographics

In general, patients randomized to this study were young (8.9 years), white males with BMI's in the lower end of normal range. The medical history of the patients enrolled into this study.

Metric	**Placebo** **N=61**	**Memantine** **N=60**	**Total** **N=121**

		T	
Age, years (± SD)	8.9 ±2.2	9.0 ±2.2	8.9±2.2
Male %	80.3%	86.7%	83.5%
White	80.3%	83.3%	81.8%
Asian	9.8%	8.3%	9.1%
African American/Black	4.9%	1.7%	3.3%
Height, cm, mean ±SD	137.3±13.9	136.9±12.8	137.1±13.3
Weight, Kg, mean ±SD	35.9±14.6	37.5±13.5	36.7±14.1
BMI, kg/m2. Mean ±SD	18.4±3.9	19.5±4.1	08.9±4.0

Baseline Characteristics
Approximately 90% of all patients had a previous medical condition, with approximately 1/3 of all patients having a psychiatric diagnosis. The most common psychiatric diagnoses in the patient population were anxiety, ADHD and aggression. (see table 14.2.2a).

In addition, prior medication use was similar for both groups, with methylphenidate and melatonin being the two most commonly previously used medications for both groups.

Patients from both groups have very similar IQ's and autism severity.

Characteristic	**Placebo** **N=61** **Mean ±SD**	**Memantine** **N=60** **Mean ±SD**
K-BIT2 Composite IQ	75.7±19.4	77.9±23.1
K-BIT2 Verbal IQ	36.4±19.4	37.0±16.2
K-BIT2 Non-Verbal IQ	32.1±26.1	26.3±18.1

ADI-R A total	24.5±4.0	23.5±4.4
ADI-R B (V) Total	19.0±4.0	17.7±3.7
ADI-R (NV) Total	11.3±2.9	10.6±2.8
ADI-R C Total	7.0±2.3	7.4±2.5
ADI-R D Total	4.3±0.8	4.2±0.9
ADOS Communication total	6.3±2.1	6.3±2.2
ADOS Social Interaction Tool	11.0±2.8	10.3±2.5
ADOS Communication and Social Interaction Total	17.3±4.5	16.7±4.2
CGI-S Overall Severity	4.8±0.7	4.6±0.6

Metric	**Placebo N=61**	**Memantine N=60 T**	**Total N=121**
Congenital	13.1%	10%	11.6%
Clinodactyly	4.9%	3.3%	4.1%
Eye Disorder	8.2%	10%	9.1%
Photophobia	--	3.3%	1.7%
Strabismus	1.6%	3.3%	2.5%
Myopia	1.6%	1.7%	1.7%
Gastrointestinal	23%	21.7%	22.3%
Constipation	11.5%	11.7%	11.6%
Tooth Malformation	4.9%	3.3%	4.1%

Immune system disorder	41%	23.3%	32.2%
Seasonal Allergy	26.2%	15%	20.7%
Food Allergy	11.5%	11.7%	11.6%
Nervous System Disorder	18%	25%	21.5%
Hypotonia	3.3%	8.3%	5.8%
Psychomotor Activity	--	8.3%	4.1%
Disturbance in Attention	3.3%	3.3%	3.3%
Psychiatric Disorders	29.5%	38.3%	33.9%
Insomnia	4.9%	10%	7.4%
ADHD	9.8%	8.3%	9.1%
Anxiety	1.6%	8.3%	5%
Sleep Disorder	4.9%	6.7%	5.8%
Respiratory, thoracic and mediastinal disorder	23%	26.7%	24.8%
Asthma	8.2%	11.7%	9.9%
Skin and subcutaneous tissue disorders	27.9%	26.7%	27.3%
Eczema	16.4%	8.3%	12.4%

Prior Medication Use

	Placebo **N=61** **%**	**Memantine** **N=60** **%**	**Total** **N=121** **%**
Any Meds	73.8%	80%	76.9%
Systemic Antibacterial	6.6%	6.7%	6.6%
Antihistamines	11.5%	13.3%	12.4%
Psychoactive medications	16.4%	18.3%	17.4%
Methylphenidate	6.6%	11.4%	9%
Fluoxetine	3.3%	5%	4.1%
Obetrol	4.9%	1.7%	3.3%
Psycholeptic Medication	23%	23.3%	23.1%
Melatonin	9.8%	20%	14.9%
Risperidone	9.8%	5%	7.4%

Patient Disposition

Overall 15% of the randomized patient population discontinued the study, with similar proportions of patients discontinuing from the study from placebo and MEMANTINE treatment groups (18% vs. 10% respectively). Adverse events, followed by withdrawal of consent were the two most common reasons for study discontinuation.

	Placebo **N=61** **%**	**Memantine** **N=60** **%**	**Total** **N=121** **%**
Completed Study	82%	90%	86%
Prematurely Discontinued	18%	10%	14%

Discontinued weeks 1-8	11.5%	10%	10.7%
Discontinued after week 8	6.6%	-	3.3%
Reason For Discontinuation			
Adverse event	6.6%	5%	5.8%
Withdrawal of Consent	4.9%	1.7%	3.3%
Lost to Follow-up	-	3.3%	1.7%
Other	3.3%	-	1.7%
Insufficient Therapeutic Response	1.6%	--	0.8%
Protocol Violation	1.6%	--	0.8%

Table 10.1–1. Number (%) of Patients Discontinued From the Study—Part Two Safety Population

	Placebo n (%) (N = 61)	*Memantine n (%) (N = 60)*	*Total n (%) (N = 121)*
Completed study[a]	50 (82.0)	54 (90.0)	104 (86.0)
Prematurely discontinued	11 (18.0)	6 (10.0)	17 (14.0)
Discontinued within Weeks 1-8	7 (11.5)	6 (10.0)	13 (10.7)
Discontinued after Week 8	4 (6.6)	0	4 (3.3)
Reason for discontinuation			
Adverse event	4 (6.6)	3 (5.0)	7 (5.8)
Insufficient therapeutic response	1 (1.6)	0	1 (0.8)
Protocol violation	1 (1.6)	0	1 (0.8)
Withdrawal of consent	3 (4.9)	1 (1.7)	4 (3.3)
Lost to follow-up	0	2 (3.3)	2 (1.7)
Other	2 (3.3)	0	2 (1.7)

Note: Percentages are based on the Safety Population.

a Patients who completed 12 weeks of double-blind treatment were considered completers.

N = number of patients in the Safety Population; n = number of patients in the specified category.

Source: Table 14.1.3A.

Concomitant Medication Use

A majority of patients took medications in addition to study medication during the trial. The majority of medications that were concomitantly taken during the trial were antihistamine, anti-inflammatory medication and psycholeptic medications.

Melatonin was the most commonly concomitant psycholeptic medication given during the trial.

In this reviewers' opinion, the concomitant use of medication in this trial did not significantly alter the efficacy assessments or outcomes for this study.

Concomitant meds	**Placebo** **N=61** **%**	**Memantine** **N=60** **%**	**Total** **N=121** **%**
Any Medications	85.2%	81.7%	83.5%
Analgesics	14.8%	10%	12.4%
Antihistamines (systemic)	26.2%	23.3%	24.8%
Anti-Inflammatory	21.3%	18.3%	19.8%
Psycholeptic	11.5%	25%	18.2%
Melatonin	8.2%	23.3%	15.7%
Lorazepam	--	3.3%	1.7%
Risperidone	--	3.3%	1.7%
Diphenhydramine	1.6%	1.7%	1.7%
Hydroxyzine	1.6%	1.7%	1.7%
Aripiprazole	--	1.7%	0.8%
Clonazepam	--	1.7%	0.8%
Lithium Carbonate	--	1.7%	0.8%
Lithium Citrate	--	1.7%	0.8%

Lithium	1.6%	--	0.8%
Midazolam	1.6%	--	0.8%

Important Protocol Violations

Although slightly more than 1/3 of all patients had a protocol violation, the vast majority of protocol violations was minor in nature and was related to use of a prohibited concomitant medication and did not affect the study results.

The sponsor does report that two patients had their treatment unblinded to an investigator while the investigator was preparing for symposium on his research. At the time of the unblinding, the two patients had already completed the double-blind portion of study 57A and were enrolled into the open-label extension study. Therefore the significance of this protocol violation on overall study efficacy results is negligible.

	Placebo **N=61** **%**	**Memantine** **N=60** **%**	**Total** **N=121** **%**
Patients with at least 1 protocol violation	39.3%	38.3%	38.8%
Patients who took Prohibited concomitant medication	27.9%	35%	31.4%
Failed to meet one or more inclusion/exclusion criteria	13.1%	6.7%	9.9%

Dosing
Dosing for study 57A was based on a patient's body weight. Due to preclinical concerns over neurotoxicity seen in animals given MEMANTINE, the Agency and sponsor agreed to limit total pediatric patient exposure to 10 times the lower limit of the No Observed Adverse Event Level (NOAEL) seen in preclinical studies. This value was set at 2100ng*h/ml.

Initial PK studies in pediatric patients with ADHD given MEMANTINE oral solution of 2.4-20mg/day for 12 weeks conducted by Robert Findling, MD in 2006 (study MD-24) was analyzed with PK data obtained from healthy adults given a single 10mg IR dose of MEMANTINE (PK-07) or 20mg/day (PK-16) to determine a weight based clearance formula.

The sponsor conducted a single dose, escalation dose study in pediatric patients with patients stratified by weight to determine the PK characteristics of MEMANTINE in pediatric patients. Doses of 3, 6, 9, and 15mg were given to patients stratified by weight: Group A (60kg or greater), Group B (40-60kg), Group C (20-39kg) and Group D (<20kg). Results from this study determined that the PK model would estimate that AUC of MEMANTINE in pediatric patients would not exceed the 2100ng*hr/ml limit up to 18mg/day for group a or 15mg/day for group B. Therefore for part two of the study, the maximum dose set for the stratified weight dosing groups for the efficacy studies was set as follows:

- Group A (>60kg): 15mg/day
- Group B (40-60kg): 9mg/day
- Group C (20-39kg): 6mg/day
- Group D (<20kg): 3mg/day

Efficacy Results
Primary Endpoint-SRS

On the primary efficacy endpoint of mean change from baseline in the total SRS raw score at week 12, memantine treatment failed to demonstrate superiority over placebo treatment. A very large placebo-response rate was seen in this study.

Statistic	**Placebo N=53 Mean ±SD**	**Memantine N=54 Mean±SD**	**Memantine-PBO Least Squares Mean Difference (p-value)**
Baseline	(b) (4)		
Week 12 Change from baseline (MMRM)			
Week 12 Change from baseline (LOCF)			

Secondary Endpoints- CATS and CCC

Similar to the results obtained from analysis of the primary efficacy endpoint, memantine treatment failed to demonstrate efficacy over placebo treatment in this study. A large placebo response was again noted.

Metric	Placebo N=53 Mean ±SD	Memantine N=54 Mean±SD	Least Squares Mean (MEMANTINE-PBO)	p-value
CATS-I				
Total Score	(b) (4)			
Social Interaction Subscale				
Communication Subscale				
Speech Subscale				
Syntax subscale				
Semantic subscale				
Coherence subscale				
Initiation subscale				
Scripted language subscale				
Context subscale				
Nonverbal communication				
Social relations				
Interests				

Conclusions

Memantine treatment was not shown to be superior to placebo in improving social communication dysfunction in autistic spectrum disorders. A large placebo response rate was noted in this trial.

One could consider the primary endpoint SRS as potentially not being sensitive to elucidate a treatment effect. However the failure of memantine treatment to show superiority to placebo on the sponsors'-own validated scale precludes this theory.

Study 2 (MD-68 and lead-in Study MD-91)

Methods/Study Design/Analysis Plan

Study MD-68 was a 12-week double-blind, placebo-controlled, randomized withdrawal study in pediatric patients with autistic spectrum disorder that examined efficacy of daily administered MEMANTINE treatment to reduced dose (50% of weight-based dose) MEMANTINE treatment and placebo.

Since study MD-68 was the 12-week double-blind, randomized withdrawal efficacy study, patients who were randomized into study MD-68 were previously enrolled into study MD-91 which was a 12-week open-label lead-in study of MEMANTINE treatment who met 'responder criteria' for entry into study MD-68. Therefore a discussion of the study design, primary objective and patient inclusion/exclusion criteria is germane to the study design and objectives of MD-68.

Lead-in Study MD-91
Study MD-91 was an open-label, up to 52 week safety and tolerability study of MEMANTINE in pediatric patients with autistic spectrum disorder who were dosed by weight as previously discussed in the previously reviewed study MD-57A who were then assessed for treatment effect through administration of the SRS instrument throughout the open-label study.

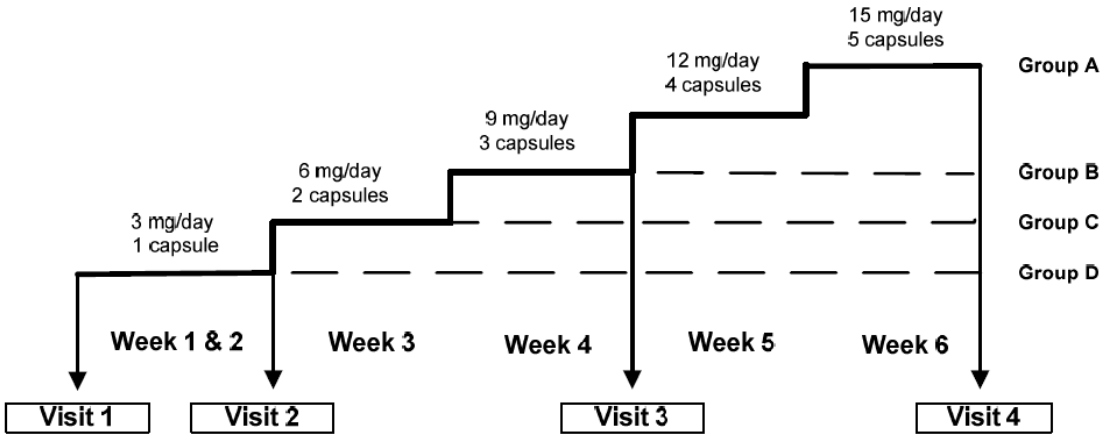
Patients who received AT LEAST 12 weeks of open label MEMANTINE treatment at the weight based dose previously discussed AND met 'responder criteria" for treatment effect based on change from baseline scores on the SRS instrument where then eligible to participate in study MD-68. "Responder Criteria" was defined as at least a 10 point decrease or greater from baseline scores (V1) on the SRS total raw score by at least visit V4A (week 9) with at least a 10-point decrease or greater in the SRS total raw score two weeks later as confirmatory of a treatment "response". This criteria was based on discussions with the Agency, developer of the SRS instrument and the sponsor that a 10-point change on the SRS scale was determined to be clinically significant (and thus incorporated into the Written Request). Patients who did not meet responder criteria be visit 4A continued with open label treatment of MEMANTINE until such patients either met responder criteria and consented to participate into study MD-68; completed the open-label 48 weeks of treatment; or were discontinued from the study.

Patients who met inclusion and exclusion criteria and consented for participation into study MD-91 were then administered MEMANTINE based on weight in open-label fashion and returned to the clinic based on a set series of outpatient visits.

The study schematic is provided below:

	Screening Period	Open-label Treatment Period											
		Dose-Titration Period				Maintenance Period							
End of Week	**2 Weeks before V1**	**0**	**2**	**4**	**6**	**9**	**12**	**18**	**24**	**30**	**36**	**42**	**48**
Visit	*V0*	*V1*	*V2*	*V3*	*V4*	*V4A*	*V5*	*V5A*	*V6*	*V6A*	*V7*	*V7A*	*V8/ET*

Dosing during the 6 week dose titration period is delineated below:



Patients

The trial protocol for MD-91 pre-specified that patients meeting the following criteria were to be randomized at screening and baseline. Unlike study MD-57, study patient inclusion criteria differed from MD-57a on the following parameters:

1. that pre-specified that a diagnosis of an autism spectrum disorder be determined via administration of ADOS or ADI-R, study MD-91 pre-specified that all patients must receive a diagnosis of an autism spectrum disorder on BOTH the ADOS and ADI-R.
2. There was no stipulation on the initiation or changing of non-pharmacological therapies

The following are pertinent inclusion criteria:

- A DSM-IV diagnosis of autism, Asperger or PDD-nos on BOTH the following instruments:
  - ADOS-Social interaction and communication modules 2 or 3 (within 6 mos. before screening)
  - ADI-R (within 3 mos. of screening)
- Males and females aged 6-12 years old.
- an SRS raw total score >44 for females, >53 for males
- an IQ (based on standardized IQ testing or Kaufmann Brief Intelligence test KBIT) of 50 or higher.
- Normal physical exam, including age appropriate normal vital signs
- Non pregnant females using adequate contraception

Patients were excluded for the following pertinent reasons:

- Previously enrolled into study 57A
- An ABC irritability subscale score of at least 17 or greater
- A history of a movement disorder such as Tourette's or genetic neurological disease such as tuberous sclerosis, fragile X, velocardiofacial syndrome, chromosomal 15q duplication, Angelman syndrome, active epilepsy/seizure disorder, abnormal CT/MRI or brain.
- A history of premature birth, defined as before 35 weeks gestational age of <5lb at birth
- Medical conditions that could interfere with study
- Clinically significant ECG findings
- Patients who are not acceptable in the investigators opinion.
- Having any other primary Axis 1 diagnosis other than autism
- Taking or have taken psychoactive medication within five half-lives or 4 weeks of screening, whatever is shorter
- Significant risk of suicidality based on ABC-I or a "yes" to question 3, 4 or 5 in the SI section of the C-SSRS.

Primary Objective

The primary objective of the this study was to investigate the safety, tolerability and efficacy of MEMANTINE in pediatric patients with autism who were previously on stable MEMANTINE therapy.

Key Secondary Objective

There were no a priori specified secondary endpoints for this study.

Results

Since study MD-91 was a lead-in open-label study, the demographic and baseline efficacy results from this study will not be formally reviewed in this efficacy section. Only those patients who enrolled into study MD-68 and contributed to eh efficacy assessment for MEMANTINE will be reviewed under study results for study MD-68.

For study MD-91, a total of 1262 patients were screened with 906 patients enrolled with 903 receiving at least 1 dose of open-label MEMANTINE.

Out of an intent to treat population of 868 patients (those patients with at least 1 dose of MEMANTINE and at least one post baseline SRS total raw score assessment), 543 patients were initial SRS responders by week 9, with a further 93 patients meeting response criteria by week 12. Overall, a total of 517 patients (59.6%) were identified as "confirmed SRS responders"; meaning such patients at least a 10 point SRS total raw score decrease by week 9 AND continued to have at least a 10 point decrease two weeks later. More than 90% of confirmed responders had a confirmed response within 12-18

weeks of treatment with a mean time to confirmed SRS response of 97.5 days. A summary of Time to confirmed SRS response is provided below:

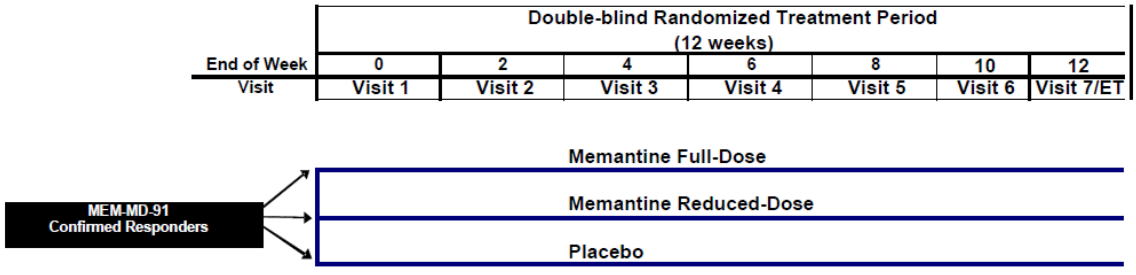
Days to second (confirmed) SRS response	**Confirmed SRS total responders (% based on population of total SRS confirmed responders) Total ITT N=868**
Day 84-125	470 (90.9%)
Das 126-167	35 (6.8%)
Day 168-209	7(1.4%)
Day 201-251	3 (0.6%)
Day 252-293	2 (0.4%)
>294 Days	0
TOTAL Confirmed SRS Responders	517 (100%)

Study MD-68

Study 68 was a 12 week parallel group, multicenter, double-blind, three treatment (full MEMANTINE dose, half MEMANTINE dose, Placebo), randomized withdrawal study to examine the efficacy of stable dose of MEMANTINE administration. As stated above, all patients who were randomized to participate into the double-blind, randomized withdrawal study MD-68 participated in the lead-in study MD-91 and was deemed to be "confirmed SRS responders". A total of 517 patients from study MD-68 were eligible (i.e. were "confirmed SRS responders") to participate in study MD-68 (see above). A total of 92 international study centers participated into the trial.

Patients who were "confirmed SRS responders" from study MD-91 who consented to participate in the randomized withdrawal study MD-68 were then randomized 1:1:1 into either full dose MEMANTINE treatment, half-dose MEMANTINE treatment, or placebo respectively. Patients were administered a baseline SRS prior to double-blind treatment and served as the baseline for efficacy assessments. Thereafter, all patients were administered double-blind study treatment and had bi-weekly visits to the clinic, to include SRS and other efficacy measures.

A schematic of the study design is seen below:



Patients
Please see patient inclusion/exclusion criteria for study MD-91 above for details.

Primary Efficacy Objective
The objective of study MD-68 was to evaluate the safety, tolerability, and efficacy of MEMANTINE treatment compared to placebo in pediatric patients with autism spectrum disorder that were previously on stable MEMANTINE treatment.

Primary Efficacy Variable
The primary efficacy assessment was the proportion of patients with a loss of treatment response (LTR), defined as an increase of at least 10 points in the SRS total raw score at any double-blind visit relative to the SRS total raw score at visit 1 (randomization).

Primary Efficacy Variable Analysis
The primary efficacy variable was analyzed using the Cochrane-Mantel-Haenszel test controlling for autism spectrum disorder subtype. Each treatment arm was compared to placebo treatment arm with an odds ratio of 95% CI with two-sided p-value being reported.

Secondary Efficacy Assessments
The sponsor also examined the proportion of patients whom had a loss of treatment response (defined as at least a 10 point or greater increase in SRS total raw score from baseline) on the Children's communication checklist . Additional efficacy assessments were mean change from baseline scores on CGI-I and CGI-S, and the Aberrant Behavior Checklist-Community Version.

Secondary Efficacy Variables
The sponsor examined additional efficacy variable such as:

- Time to the first LTR, defined as the 1st visit when a patient showed a LTR
    - Kaplan-Meier estimates with hazard ration and 95% CI were employed to examine time to LTR
- Change from baseline in the 10 subscales for the CCC-2 at week 12
    - An ANCOVA analysis using an LOCF approach with an MMRM approach used for sensitivity.

Results

Demographics

Similar to study MD-57A, the majority of patients randomized in study MD-68 were white males approximately 9 years of age with a primary Axis 1 diagnosis of autism (63%), followed by Asperger's (18%) and PDD-NOS (19%). Patients generally were on the lower end of normal BMI curve.

Safety population

Characteristic	Placebo N=160	Memantine Reduced N=160	Memantine Full N=157	Total N=477
Age, Years ±SD	8.9±2.0	9.2±1.9	9.2±1.9	9.1±1.9
Male %	88.8%	82.5%	84.1%	85.1%
White %	86.3%	88.1%	89.2%	87.8%
African American/Black	6.3%	5.6%	4.5%	5.5%
Asian	4.4%	3.1%	5.1%	4.2%
Weight, Kg ±SD	37.64 ±13.85	40.45±16.49	38.07±14.00	38.72±14.85
Height, cm ±SD	139.19±13.33	140.90±13.77	140.02±13.05	140.03±13.38
BMI, kg/m2 ±SD	18.91±4.42	19.70±5.00	18.86±4.21	19.16±4.57

Baseline Characteristics
Baseline levels of autism severity were very similar between the three doing arms.
Study MD-91 Screening for patients in MD-68.

Characteristic	Placebo N=160	Memantine Reduced N=160	Memantine Full N=157	Total N=477
SRS total raw score (screening) ±SD	110.0 ±24.9	111.2±23.6	111.2±24.5	110.8±24.3
SRS total raw score (baseline) ±SD	109.2±23.1	109.0±23.7	112.0±25.3	110.0±24.0
All IQ-tests pooled ±SD	88.7±22.1	88.6±21.2	86.9±23.4	88.0±22.2
KBIT-2 Total Score (screen) ±SD	85.8±21.4 N=25	80.8±20.5 N=30	76.9±18.1 N=27	81.0±20.1 N=82
ABC-I (screening)	8.0±4.7	9.3±5.1	9.0±4.6	8.8±4.8

Study MD-68 Baseline

Characteristic	Placebo N=160	Memantine Reduced N=160	Memantine Full N=157	Total N=477
SRS total raw score ±SD	67.9±24.5	67.8±24.1	72.6±26.9	69.4±25.2
All IQ-tests pooled ±SD	93.3±24.0	93.4±22.7	91.1±25.4	92.6±24.0
KBIT-2 Total Score (screen) ±SD	93.8±24.3 N=135	95.5±22.8 N=130	93.0±26.4 N=130	94.1±24.5 N=395
ABC-I (screening)	7.8±6.9	6.9±5.8	7.6±6.3	7.4±6.4

Generally medical history between the three dosing arms remained quite similar.

Characteristic	Placebo N=160	Memantine Reduced N=160	Memantine Full N=157	Total N=477
Age, Years ±SD	8.9±2.0	9.2±1.9	9.2±1.9	9.1±1.9
Male %	88.8%	82.5%	84.1%	85.1%
White %	86.3%	88.1%	89.2%	87.8%
African American/Black	6.3%	5.6%	4.5%	5.5%
Asian	4.4%	3.1%	5.1%	4.2%
Weight, Kg ±SD	37.64 ±13.85	40.45±16.49	38.07±14.00	38.72±14.85
Height, cm ±SD	139.19±13.33	140.90±13.77	140.02±13.05	140.03±13.38
BMI, kg/m2 ±SD	18.91±4.42	19.70±5.00	18.86±4.21	19.16±4.57

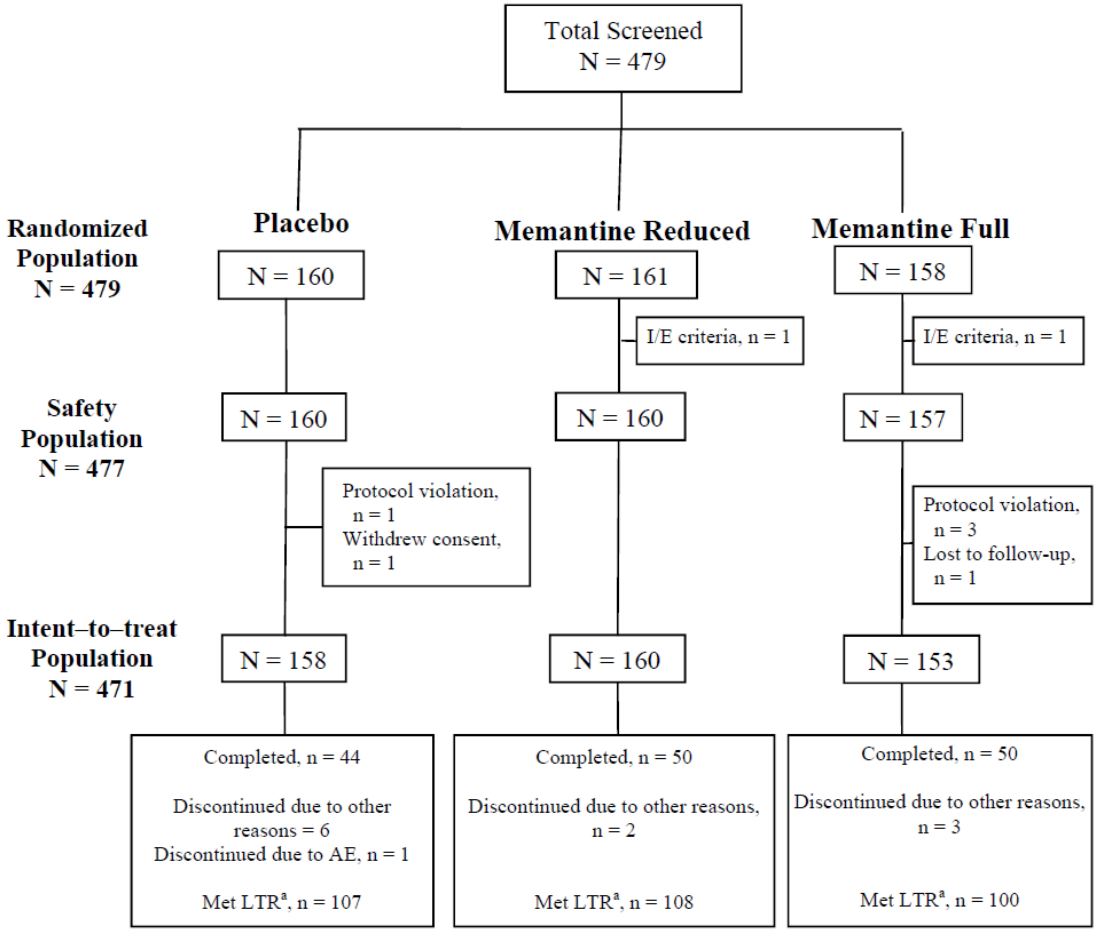
Prior medication use was generally very similar between doing groups. Overall 80 of patients previously took medication of some kind.

Characteristic	Placebo N=160	Memantine Reduced N=160	Memantine Full N=157	Total N=477
Any medication	82%	76%	81%	80%
Analgesics	19%	16%	17%	17%
Antihistamines	21%	22%	29%	24%
Anti-inflammatory	5%	6%	6%	6%
Obstructive airway disease drugs	7%	12%	12%	10%
Psychoanaletics	49%	46%	43%	46%

Methylphenidate	17%	12%	15%	15%
Guanfacine	11%	9%	11%	10%
Fluoxetine	4%	4%	6%	5%
Lisdexamfetamine	5%	6%	3%	5%
Dexmethylphenidate	4%	4%	4%	4%
Sertraline	11%	7%	4%	8%
Psycholpetics	30%	33%	30%	31%
Melatonin	15%	17%	15%	16%
Risperidone	7%	13%	8%	9%
Aripiprazole	4%	3%	6%	4%

Patient Disposition

Out of the 517 patients from study MD-91 that were eligible to participate in study MD-68, 479 patients were screened and randomized into study MD-68 with 471 patients receiving one dose of study medication and 1 post randomized SRS assessment (ITT population). To further delineate the 471 patients that were used to assess the efficacy of MEMANTINE, 158 patients received placebo, 160 received reduced MEMANTINE (50% full dose); and 153 patients continued to receive the full, pre-randomized MEMANTINE dose they had received from study MD-91 respectively.



a A total of 315 patients discontinued due to loss of therapeutic response (LTR) by SRS criterion per the termination page of the electronic case report form. Four additional patients met the LTR criterion based on an increase of SRS total raw score of at least 10 points relative to Visit 1 (randomization) by end of study, but discontinued from the study for Other Reasons (eg, Adverse Event [AE], Withdrawal of Consent).

I/E = inclusion/exclusion; N = number of patients in the Randomized Population; n = number of patients in the specified category.

Concomitant Medication Use (ask sponsor to combine meds)

Rates of concomitant medication use were similar to that seen in study MD57A and are similar amongst all treatment arms. In this reviewers' opinion, the use of concomitant medication likely had little significant on efficacy assessments and conclusions.

Characteristic	Placebo N=160	Memantine Reduced N=160	Memantine Full N=157	Total N=477
Any medication	82%	78%	83%	81%
Analgesics	15%	14%	15%	15%
Antihistamines	20%	24%	29%	24%
Anti-inflammatory	5%	7%	8%	7%

Obstructive airway disease drugs	8%	13%	13%	11%
Psychoanaletics	48%	47%	42%	46%
Methylphenidate	16%	12%	15%	15%
Guanfacine	11%	11%	11%	11%
Fluoxetine	<1%	2%	5%	3%
Lisdexamfetamine	5%	7%	3%	5%
Dexmethylphenidate	4%	4%	4%	4%
Sertraline	11%	7%	4%	8%
Psycholpetics	31%	33%	31%	32%
Melatonin	16%	18%	15%	16%
Risperidone	7%	13%	8%	9%
Aripiprazole	4%	3%	6%	4%

Important Protocol Violations

Major Protocol Deviation	**Placebo N=160**	**Memantine reduced N=161**	**Memantine Full N=158**	**Total N=479**
Patient with one more major protocol deviation	12 (7.5%)	16(10%)	13(8.2%)	41 (8.6%)
Categories				
Randomization	4 (2.5%)	6 (3.7%)	4 (2.5%)	14 (3%)
Eligibility	1 (0.6%)	3(1.9%)	6(3.8%)	10(2.1%)
Informed Consent	2(1.3%)	4(2.5%)	--	6(1.3%)
Concomitant medication	--	2(1.3%)	2(1.3%)	4(0.8%)
Study drug compliance	2(1.3%)	1(0.6%)	1(0.6%)	4(0.8%)
Study procedure	3(1.9%)	--	1(0.6%)	4(0.8%)
Visit Schedule	1(0.6%)	--	--	1(0.2%)

Dosing

For dosing, please refer to study MD-57A. Patients who were randomized to the reduced MEMANTINE arm had their MEMANTINE dose reduced by 50. For those patients who received a full dose of 3mg/day, the reduced dose group received 3mg MEMANTINE every other day with placebo alternating.

Efficacy Results
On the primary endpoint of proportion of patients with loss of therapeutic response by week 12, both memantine full dose and reduced dose memantine failed to demonstrate efficacy over placebo treatment. Again, a very large placebo response was seen in this study.

Primary analysis	Placebo N=158	Memantine Reduced N=160	Memantine full N=153
LTR	(b) (4)		
Non-LTR			
LTR Rate difference			
Odds Ratio			
95% CI			
p-value			

Results from the sensitivity MMRM analysis provided nearly identical results.

Conclusions

Memantine treatment failed to demonstrate superiority over placebo treatment in a randomized withdrawal double blind study. Essentially the proportion of patients who lost a therapeutic response was nearly identical for patients who received placebo.

One possibility for the similar proportion of memantine treated patients who lost a treatment response compared to placebo could be related to only a 12 week period of response required from the lead in study 91 prior to randomization. It is possible that a 12 week period of a 'therapeutic response' may not be long enough to demonstrate longer-term, consistent and thorough efficacy response, which could explain the similar proportion of LTR seen with placebo-responders.

One may consider using a longer lead-in study design prior to randomization.

6.1.3 Crosscutting Issues

Subgroup Analyses

For the double blind studies, the sponsor conducted a post-hoc analysis of the data utilizing different definitions of "responder criteria", which was originally defined by the Agency and sponsor as a post baseline SRS total raw score that is at least lower than 10 point relative to baseline and "sustained responder", defined as at least two post baseline SRS total raw scores this is at least 10 points relative to baseline obtained at least two weeks apart.

Various post hoc analyses were conducted to examine for treatment effects associated with memantine administration. IN study 57A, a post-hoc analysis that examined the

treatment response of patients who were "responders" (i.e. at least a 10 point decrease in SRS score from baseline) at weeks 6 and 12 suggests that slightly more proportion of patients who received memantine continued to have a treatment response at week 12 compared to placebo treatment (b) (4) placebo respectively). However, a greater proportion of placebo patients who responded at week 6 became "non responders" at week 12 when compared to memantine treatment ((b) (4) respectively). Stated another way, (b) (4) of memantine patients who were responders at week 6 continued to be responders at week 12, whereas only (b) (4) of placebo patients who were reconsiders at week 6 were responders at week 12. This suggests that memantine treatment may potentially allow for a sustained effect.

This reviewer feels that this post-hoc analysis result, combined with a very large placebo treatment effect seen, should be incorporated into future clinical trial designs for the ASD population. One recommended design implementation is to incorporate a single blind/double blind phase 12 weeks prior to randomization into the double-blind phase. An approach that could be used is to allow "randomization" of all patients at baseline to either treatment yet in fact all patients would receive placebo treatment for at least 12 weeks, unbenounced to both investigators and patients. Based on responder criteria set for the clinical study, those patients who then met 'responder criteria' at week 12 based on an interim analysis would be excluded from randomization, with only those patients considered 'non-responders' undergoing formal randomization to study drug or placebo for the remained of the trial.

In addition, an analysis of patients who were sustained responders at both week 6 and week 12 in study 57A suggests that a greater cumulative proportion of patients treated with memantine had an SRS total raw score change of -5 to -35 points from baseline than placebo treated patients. Analyzing data from patients who completed the trial, a nearly two fold increase in the proportion of patients who were treated with memantine was seen when threshold criteria for 'responder' status was set at -20 point change from baseline in total SRS raw score was compared to placebo treatment based on patients who had a -20 point change either at week 6 or week 12, as well as patients who had a -20 point change from baseline at both week 6 and week 12. A nearly three-fold increase in the proportion of patients treated with memantine compared to placebo treatment had at least a -30 point decrease in total SRS raw score form baseline at either week 6, 12 AND at both week 6 and week 12. The sponsor concludes that more restrictive responder thresholds should be considered for future trials in order to demonstrate separation between drug treatment and placebo. Although the number of patients who met responder criteria of at least -20 or -30 points on the SRS was very small, this reviewer does concurs with the sponsor that utilizing a more restrictive threshold for responder criteria should be employed into future drug trials in the ASD population that are deigned to examine treatment effects on core autism symptomatology.

Sustained SRS Responders (at both week 6 and Week 12)-Autism ITT population

SRS Responder Threshold (based on patients who has either week 6 or week	Placebo N=53 N(%)	Memantine N=54 n(%)

12 SRS assessment)-Observed Cases		
-10	(b) (4)	
-20		
-30		
(patients who had BOTH week 6 and week 12 SRS assessment)-observed cases		
-10		
-20		
-30		

Dose Response

An analysis of dose response cannot be performed under this clinical development program, since memantine dosage was based upon patient body weight, thus precluding a dose-response assessment.

Key Secondary Variables

SECONDARY EFFICACY

The time to first loss of therapeutic response during the double blind period was nearly identical between the three treatment groups with no statistically significant difference between both memantine treatment arms vs. placebo treatment. Generally time to first LTR was 31 days.

Metric	Placebo N=158	Memantine reduced	Memantine Full N=153
Number censored	(b) (4)		
Number of events			
Crude rate event			
Median survival days (95% CI)			
Hazard Ratio			
P-value			

Note: 1 p1 is the p-value for the treatment comparison between memantine full-dose and placebo based on log-rank test stratified by Autism Spectrum Disorder subtype.

2 p2 is the p-value for treatment comparison between memantine reduced-dose and placebo based on log-rank test stratified by Autism Spectrum Disorder subtype

CCC

Similar to the primary efficacy variable, no differences were noted between memantine treatment compared to placebo at week 12 compared to baseline on the CCC instrument

	Placebo (N = 158)		*Memantine Reduced (N = 160)*		*Memantine Full (N = 153)*	
	n	***Mean ± SD***	***n***	***Mean ± SD***	***n***	***Mean ± SD***
Speech						
Baseline						(b) (4)
Change at Week 12						
LSMD (95% CI)						
Syntax						
Baseline						
Change at Week 12						
LSMD (95% CI)						
Semantics						
Baseline						
Change at Week 12						
LSMD (95% CI)						
Coherence						
Baseline						
Change at Week 12						
LSMD (95% CI)						
Initiation						
Baseline						
Change at Week 12						
LSMD (95% CI)						
Scripted Language						
Baseline						
Change at Week 12						
LSMD (95% CI)						
Context						
Baseline						
Change at Week 12						
LSMD (95% CI)						
Nonverbal Communication						
Baseline						(b) (4)
Change at Week 12						
LSMD (95% CI)						

	Placebo (N = 158)		*Memantine Reduced (N = 160)*		*Memantine Full (N = 153)*	
	n	*Mean ± SD*	*n*	*Mean ± SD*	*n*	*Mean ± SD*
Social Relations						
Baseline	[redacted]					
Change at Week 12						
LSMD (95% CI)						
Interests						
Baseline						
Change at Week 12						
LSMD (95% CI)						

(b) (4)

Note: Analyses are based on MMRM model for change from baseline with treatment group, ASD subtype, visit, and treatment-group-by visit interaction as fixed effects and baseline value and baseline value-by-visit interaction as the covariate.

CCC-2 = Children's Communication Checklist, US Edition; ITT = intent-to-treat; MMRM = mixed-effect model for repeated measures; N = number of patients in the ITT Population; n = number of patients with a CCC-2 assessment at the specified timepoint.

Additional Secondary Endpoints

In addition to the SRS scale, the sponsor had convened a panel of experts from within academia and industry to develop two clinician-rated instruments as described below:

- The Core Autism Treatment Scale (CATS) : a measure of core symptoms of autism and rate of change in response to treatment between pre-treatment and (CATS-Severity) and during treatment (CATS-Improvement) scores. Both scales contained 14 items that test for social interaction and communication with each item being scored from 1 (normal) to 7 (among the most extremely ill patients).
- Core and Associated Autism Symptom Treatment Scale (CAASTS): a measure of core symptoms of autism and rate of change in response to treatment between pre-treatment and (CAASTS-Severity) and during treatment (CAATS-Improvement) scores. Both scales contained 23 items that test for stereotyped behaviors and restricted interested, associated maladaptive behaviors, and daily function with each item being scored from 1 (normal) to 7 (among the most extremely ill patients). In addition, the CAASTS-S contains 3 free-format open ended patients' summaries.

As seen with the efficacy results obtained with the SRS instrument, results obtained from administration of each of these instruments demonstrated that treatment effects seen in study 57A were not related to memantine treatment.

Secondary Analysis: Change From Baseline to Week 12 in the CATS-I Total Score and Subscales and CCC-2 Subscales (MMRM)—Autism ITT Population

	Placebo (N = 53) Mean ± SD	*Memantine (N = 54) Mean ± SD*	*LSMD (Memantine – Placebo) (95% CI)*	*p-Value[a]*
CATS-I				
Total score				(b) (4)
Social interaction subscale				
Communication subscale				
CCC-2				
Speech subscale				
Syntax subscale				
Semantics subscale				
Coherence subscale				
Initiation subscale				
Scripted language subscale				
Context subscale				
Nonverbal communication				
Social relations				
Interests				

a The p-values were obtained from MMRM.

CATS-I = Core Autism Treatment Scale–Improvement; CCC-2 = Children's Communication Checklist-2; ITT = intent to treat; LSMD = least squares mean difference; MMRM = mixed-effects model for repeated measures.

Effect Size

Due to the very high rate of placebo responders seen in both double-blind studies despite an equally high rate of treatment response in memantine-treated patients, an analysis of the size regarding memantine's treatment effect is moot.

Long-Term Efficacy

Results from study 68 demonstrated that MEMANTINE treatment was not associated with a long term treatment effect despite 24 weeks of treatment with MEMANTINE.

Pediatric Development

The sponsor does not plan to develop MEMANTINE for the treatment of any pediatric indications at this time.

6.1.4 Efficacy Conclusions Regarding Claim 1

Memantine was not found to be effective for the treatment of the core symptoms of autism when compared to placebo treatment.

7 REVIEW OF SAFETY

Safety Summary

Generally memantine treatment was well tolerated during the clinical development program. This reviewer recommends that the common-drug related adverse events that occurred during the clinical development program be included into the product labeling.

7.1 Methods

The Summary of Clinical Safety (SCS), which includes safety data obtained from the two double-blind, placebo-controlled studies, safety and tolerability data from studies MD-57A and MD-68, and data from the open label studies MD-67 and MD-91 as well as serious adverse events from an additional ongoing open label study (study MD-69-an extension study to MD-67, 68 and 91) were reviewed as part of the safety summary. In addition, safety results from the individual studies were also reviewed for the summary of safety.

The cut-off date for safety data used in the integrated summary of safety was 07 Jun 2013 as agreed to by the Agency and the sponsor.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Please see section 7.1 above.

7.1.2 Categorization of Adverse Events

Adverse events were characterized by system and preferred term according the most recent MedDRA update. Adverse events were then displayed by system organ class and by preferred term by proportion of patients receiving lurasidone or placebo who reported the MedDRA-coded adverse event term.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

As agreed to by the Agency and the sponsor, a summary of pooled data from studies MD-57A, 67 and 91 based on the overall safety population was compiled to examine for incidence of treatment emergent adverse events (TEAE). The sponsor did not pool data from the double-blind, treatment withdrawal study MD-68 as the safety data from these patients were included as part of these patients' enrollment into the 12 week titration study MD-91 and thus included as data from study MD-91. However, safety data from MD-68 was provided separately from the pooled safety analysis.

Data pooled form studies 57A, 67 and 91 were presented in three ways:

- 6 months or greater exposure

- Less than 6 months exposure
- Overall safety population

7.2 Adequacy of Safety Assessments

A review of the safety assessments was conducted for all of the submitted efficacy and safety studies. In addition, a review of IQ testing that was performed baseline and at end of study was adequate.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The overall exposure of memantine based on body weight was appropriate to examine for adverse events and safety parameters.

7.2.2 Explorations for Dose Response

Since the doses used in these trials were used based on body weight and not fixed doses, an exploration for dose response is not possible.

7.2.3 Special Animal and/or In Vitro Testing

The reader is referred to the pharmacology/toxicology review for further details.

7.2.4 Routine Clinical Testing

After reviewing the clinical protocols of the submitted studies and clinical study reports, this reviewer is of the opinion that clinical testing was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

The reader is referred to the clinical pharmacology review for further details.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There are no other NMDA receptor antagonists approved for other indications that could be used to evaluate for class-related adverse events.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths that occurred during the clinical development program for MEMANTINE, either during IND protocols or ongoing trials.

7.3.2 Nonfatal Serious Adverse Events (SAEs)

During the entire clinical development program, there were ten (10) SAEs that occurred. Six of the SAEs occurred with less than six months exposure to MEMANTINE, whereas only one occurred with 6 months or greater MEMANTINE exposure. Overall, the majority of SAEs appear to be non-related to memantine treatment. For those cases where agitation or psychiatric SAEs occurred and a stronger relationship to memantine treatment exists, the SAEs were similar to adverse events seen in the clinical trials, with resolution of the SAEs without sequelae. The cases are summarized below.

- Study 57A: Patient 0133001 was a 10 year old male, randomized to memantine receiving a final dose of 6mg/day. On day 29 of double-blind treatment, the patient experienced worsening of aggressive behavior and started on Lithium 150 TID but allowed to continue into the study. 9 days later, the aggressive behavior continued and the patient was hospitalized. The patient remained in the hospital for 6 days and discharged in stable condition with lithium and clonazepam.
- Study 68: Patient 8049103 was a 7 year old Ukrainian male who received MEMANTINE and was randomized to the memantine reduced dose group receiving 3mg/day for 36 days when the patient was hospitalized for a furuncle of the nasal bridge. The patient was treated with IV antibiotics for 8 days and was discharged home in stable condition.
- Study 91: Patient 01999105 was a 7 yo male who was hospitalized for disinhibit ion while on day 117 of MEMANTINE open label. The patient's condition slowly improved after 4 weeks post MEMANTINE treatment.
- Study 91: Patient 0849101 was an 8 year old male who was discontinued on day 55 of MEMANTINE treatment for disruptive and combative behavior. The event was classified as an SAE by the investigator though the patient was not hospitalized and did not discontinue MEMANTINE treatment for 13 more days. Three days after cessation of MEMANTINE, the abnormal behavior resolved.
- Study 91: Patient 0989103 was an 11yo male who was hospitalized for 'abnormal behavior" on day 25 of the open label study, though this was 10 days after discontinuation of MEMANTINE as parents withdrew consent. An apparent trigger for the abnormal behavior was an event that occurred in the patient's home.
- Study 91: Patient 1019107 was a 6 year old male receiving open label MEMANTINE when he was found in the bathroom with two empty bottles of memantine with capsules noted in the toilet. Although it was unclear if the patient ingested the tablets, the patient was treated at the emergency room with activated charcoal, sorbitol, and Zofran. After an overnight observation stay, the patient was discharged home.
- Study 91: patient 1329102was a 6 yo male who was admitted to the hospital on day 84 of open label memantine treatment for gastroenteritis. The patients stayed in the hospital for 24 hours then were discharged home.
- Study 91: Patient 3819107 was a 6 yo male was hospitalized for constipation 14 days after starting open label memantine.

- Study 91: Patient 7029103 was an 11 yo male who was hospitalized for removal of a skin mass in his shoulder that was present prior to the start of memantine treatment open-label.
- Study 67: Patient 0232004 was a 12 yo male with history of pulmonary stenosis who received 83 days of placebo treatment in study 57A, who was then started on open label memantine treatment in the open label study 67. On day 197 of treatment with open label memantine, the patient developed lobar pneumonia and was hospitalized. After inpatient treatment with IV antibiotics, the patient's condition stabilized and the lobar pneumonia resolved on day 210 of the study.
-

7.3.3 Dropouts and/or Discontinuations

Since drug-related drop-outs and discontinuation rates are the focus of this review, dropouts and discontinuations that occurred in the placebo controlled studies 57A and 68 will be reviewed. A brief summary of clinically important discontinuations and dropouts that occurred in the open-label studies will be provided as well.

Study 57A

In study 57A part two (double-blind), there were seven (7) patients total that discontinued from the study due to adverse events. The rate of dropout between placebo and memantine treated subject were similar.

	Placebo N=61	**Memantine N=60**	**Total N=121**
Completed study	82%	90%	86%
Prematurely discontinued Study	18%	10%	14%
Reason for discontinuation			
Adverse Event	6.6%	5%	5.8%
Insufficient therapeutic response	1.5%	--	0.8%
Protocol Violation	1.6%	--	0.8%
Withdrawal of Consent	4.9%	1.7%	3.3%
Lost to follow up	--	3.3%	1.7%
Other	3.3%	--	1.7%

Adverse events that led to discontinuation in the MEMANTINE treated group were irritability (patient 0052003), aggression, mood swings and stereotypy after first dose (pt. 0172001), and aggression 29 days after taking MEMANTINE (pt. 0173006).

Study MD-68
For the randomized withdrawal study 68, there was only one patient (1) who discontinued the study for an adverse event. This patients was taking placebo.

	Placebo N=160	Memantine reduced N=161	Memantine full N=158	Total N=479
Completed study	27.5%	31.1%	31.6%	30.1%
Discontinued due to Loss of Therapeutic Response	66.9%	67.1%	63.3%	65.8%
Other reasons for Discontinuation	5.6%	1.9%	5.1%	4.2%
Did not meet inclusion/exclusion criteria	-	0.6%	0.6%	0.4%
Adverse event	0.6%	--	--	0.2%
Insufficient response	--	0.6%	--	0.2%
Protocol violation	2.5%	--	2.5%	1.7%
Withdrawal of consent	1.3%	--	1.3%	0.8%
Lost to follow up	0.6%	--	0.6%	0.4%
Other reasons	0.6%	0.6%	--	0.4%

Study MD-91
Out of the enrolled population of 903 patients, 765 patients completed the open label study MD-91. Out of the `138 patients that did not complete the open-label study, the majority of discontinuations were due to adverse events (60 patients, 6.6% of total population). Discontinuations due to adverse events followed an inverse relationship to weight (group A 1.4%, group b 5.3%, group c 7.5%, group D 17.6%).

A review of the 60 patients that were discontinued from the study revealed that the majority of patients were discontinued for irritability and/or aggression. Emotional liability was also noted as an adverse event leading to discontinuation. No clinically significant or impairing adverse events were noted that led to discontinuation from the study.

Study MD-67
Out of 95 patients that received at least one dose of MEMANTINE during this open-label trial (safety population), 60 patients (63.2%) completed the study with 35 discontinuing prematurely. Adverse events and lost to follow up were the two most common reasons for discontinuation.

	Total N=95
Completed Study	63.5%
Prematurely Discontinued	36.8%

Reasons for Discontinuation	
Adverse Event	9.5%
Lost to follow up	9.5%
Withdrawal of consent	7.4%
Insufficient therapeutic response	5.3%
Other	3.2%
Inclusion/Exclusion	1.1%
Protocol Violation	1.1%

Adverse events leading to discontinuation are summarized below:

- Patient 0011001: Irritability on day 47 of MEMANTINE treatment
- Patient 0033005: negativism on day 201 of MEMANTINE treatment
- Patient 0033010: agitation/aggression, impulsive behavior and stereotypy on day 115 of MEMANTINE treatment
- Patient 0113001: abnormal behavior and affective disorder on day 40 of MEMANTINE treatment
- Patient 0113002: irritability on day 39 of MEMANTINE treatment
- Patient 0142002: disturbance in attention on day 49 of MEMANTINE treatment
- Patient 0173002: aggression on day 266 of MEMANTINE treatment
- Patient 0173004: pseudologia and psychomotor hyperactivity on day 147 of MEMANTINE treatment
- Patient 0173005: aggression on day 69 of MEMANTINE treatment

7.3.4 Significant Adverse Events

During the clinical development program, there were no clinically significant adverse events that were noted.

7.3.5 Submission Specific Primary Safety Concerns

Due to preclinical evidence of neuronal damage with MEMANTINE exposure, neuronal development was specifically assessed during the clinical development program for MEMANTINE. Baseline measured of Intelligence Quotient (IQ) testing and mean change from baseline values were measured and assessed. Review of mean changes from baseline values in IQ testing for all clinical studies failed to demonstrate any cessation or reduction in IQ with MEMANTINE administration.

Therefore there is little clinical evidence that at the doses and duration of MEMANTINE treatment given during the clinical development program, MEMANTINE had any clinical effect on neuronal development.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

This reviewer recommends including common adverse events that occurred in study 57A and the randomized withdrawal study 68 is included into product labeling should this NDA obtain approval. A summary of common adverse events for each study in briefly reviewed below.

Study 57A

Those adverse events which occurred in at least 2% or greater of MEMANTINE-treated patients AND at least twice the rate of placebo were agitation, influenza, affective disorder, ear infection, laceration, allergic rhinitis, frequent bowel movements and enuresis. Although the proportion of MEMANTINE-treated patients with aggression was higher than placebo treatment, the rate was not quite twice the rate of placebo (8.3% v. 4.9% respectively)

Table XX: Study 57A Adverse Events Occurring ≥2% and Twice the Rate of Placebo

Adverse Event	Placebo N=61	MEMANTINE N=60
Influenza	3.3%	6.7%
Ear Infection	1.6%	3.3%
Laceration	1.6%	3.3%
Agitation	1.6%	6.7%
Affective Disorder	--	3.3%
Enuresis	--	3.3%
Allergic Rhinitis	1.6%	3.3%
Frequent bowel movements	--	3.3%

With regards to common adverse events occurring based on weight categories (group a, b, c, d), the majority of patients in the study were dosed in the group C category (65%), with rates of MEMANTINE-treated patients v. placebo patient-related TEAEs similar to those seen in the above table. Visual inspection of adverse events from MEMANTINE-treated patients v. placebo from groups a, b, and d reveals a similar pattern of adverse event from the combined table listed above.

Study 68

Common and drug-related adverse events were mild and of little clinical significance during the randomized, withdrawal study. There also did not appear to be any dose-related adverse events. However an analysis of dose-related adverse events is severely limited for study 68 as all patients had at least 12 weeks of exposure to MEMANTINE during the preceding study 91, thereby allowing patients to acclimate to the systemic effects to MEMANTINE.

Adverse Event	Placebo	Memantine	Memantine Full

	N=160	Reduced N=160	N=157
Vomiting	--	5.1%	--
Viral Gastroenteritis	--	2%	3%
Rhinitis	--	2%	--
Streptococcal Infection	--	2%	--
Increased Appetite	--	--	2%
Oropharengeal Pain	--	1%	2%

7.4.2 Laboratory Findings

Generally MEMANTINE treatment was not associated with any clinically significant changes in clinical laboratory parameters. There were changes in potentially clinically significant (PCS) values from baseline in BUN, proteinuria and creatinine that were noted in patients exposed to MEMANTINE for greater than 6 months, however creatinine levels that were PCS were elevated in less than 6 mos. exposure compared to greater than 6 months exposure. Although ALT was noted to be increased in a few patients exposed to MEMANTINE for less than 6 months, no Hy's law cases were noted, nor any clinically significant changes in hepatic functioning was noted.

This reviewer contacted the primary regulatory medical officer Ranjit Mani, MD of the division of neurology to determine whether or not a signal for increased BUN or proteinuria has been noted in geriatric patients exposed to MEMANTINE for the treatment of Alzheimer's. In the opinion of Dr. Mani, neither renal signal nor clinically significant renal events have been noted from current use of MEMANTINE for the treatment of Alzheimer's.

Based on the lack of a renal signal or clinically significant renal events with MEMANTINE exposure with currently labeled use and the lack of any clinically significant renal events during the autism clinical development program, the increase in PCS BUN, creatinine and proteinuria is likely of little clinical significance and does not require labeling as the medication is not being indicated for use in pediatric patients.

Laboratory Parameter, unit	PCS criterion	<6 mos. MEMANTINE Exposure N=892	≥6 mos. continuous MEMANTINE exposure (N=112)
Eosinophil's %	>10%	25/761 (3.3%)	4/108 (3.7%)
Lymphocyte %	>60%	2/776 (0.3%)	5/109 (4.6%)
WBC	<2500	1/788 (0.1%)	2/109 (1.8%)
Alanine Aminotransferase (ALT) , U/l	≥3 X ULN	3/789 (0.4%)	1/109 (0.9%)
Albumin, G/l	>1.1 X ULN	1/800 (0.1%)	8/102 (7.8%)

Blood Urea Nitrogen, mmol/l	≥1.2 X ULN	10/787 (1.3%)	7/107 (6.5%)
Cholesterol, Total mmol/l	>1.3 X ULN	15/785 (1.9%)	1/106 (0.9%)
Glucose, nonfasting, mmol/l	>1.4 X ULN	5/796 (0.6%)	0/108
Urinalysis			
Protein	≥1.0g/l or at least 2+	10/797 (1.3%)	5/110 (4.5%)

The proportion of patients with PCS criteria from the two randomized, double-blind placebo controlled studies were similar between placebo treated and MEMANTINE treated groups.

57A

Laboratory Parameter, unit	**PCS criterion**	**Placebo N=58**	**Memantine N=56**
Eosinophils %	>10%	2/44 (4.5%)	1/49 (2.0%)
Lymphocyte %	>60%	0/44	2/49 (4.1%)
Alanine Aminotransferase (ALT) , U/l	≥3 X ULN	0/51	1/51 (2%)
Albumin, G/l	>1.1 X ULN	2/45 (4.4%)	4/48 (8.3%)
Blood Urea Nitrogen, mmol/l	≥1.2 X ULN	1/48 (2.1%)	3/49 (6.1%)
Triglycerides	>1.2 X ULN	8/43 (18.6%)	5/38 (13.2%)
Urinalysis			
Protein	≥1.0g/l or at least 2+	0/48	0/51

Study 68

Laboratory Parameter, unit	**PCS criterion**	**Placebo N=160**	**Memantine reduced N=160**	**Memantine full N=157**
Eosinophils %	>10%	4/142 (2.8%)	5/148 (3.4%)	7/138 (5.1%)
Lymphocyte %	>60%	0/147	0/152	3/142 (2.1%)
WBC	<2500	1/148 (0.7%)	0/153	1/143 (0.7%)
Alanine Aminotransferase (ALT) , U/l	≥3 X ULN	0/149	1/152 (0.7%)	0/144
Blood Urea Nitrogen, mmol/l	≥1.2 X ULN	1/149 (0.7%)	3/153 (2.0%)	3/140 (2.1%)
Cholesterol, Total mmol/l	>1.3 X ULN	1/147 (0.7%)	1/149 (0.7%)	3/140 (2.1%)

Glucose, nonfasting, mmol/l	>1.4 X ULN	1/150 (0.7%)	0/153	2/145 (1.4%)
Urinalysis				
Protein	≥ 2+	0/152	1/153 (0.7%)	3/147 (2.0%)

7.4.3 Vital Signs

Since memantine is not being indicated for any pediatric indication, this reviewer does not recommend that vital sign changes that were noted in patients during the clinical studies be included into the product labeling. The following are vital sign changes noted during the clinical trials:

There was a slight increase in proportion of patients who developed PCS criterion for increased diastolic blood pressure in patients who received MEMANTINE for over 6 months.

Laboratory Parameter, unit	**PCS criterion**	**<6 mos. MEMANTINE Exposure N=892**	**≥6 mos. continuous MEMANTINE exposure (N=112)**
Systolic Blood Pressure, mmHg	High (≥130 and increase ≥20 from baseline)	22/886 (2.7%)	4/112 (3.6%)
	Low (≤75 and decrease ≥20)	5/886 (0.6%)	1/112 (0.9%)
Diastolic Blood pressure, mmHg	High (≥90 and increase ≥15 from baseline)	24/886 (2.7%)	6/112 (5.4%)
	Low (≤35 and decrease ≥15)	3/886 (0.3%)	0/112
Pulse Rate, bpm	High (≥130 and increase ≥15)	7/886 (0.8%)	3/112 (2.7%)
	Low (≤55 and decrease ≥15)	10/886 (1.1%)	3/112(2.7%)

In the double-blind study 57, 9% of MEMANTINE treated patients developed PCS criteria for elevated diastolic blood pressure.

Laboratory Parameter, unit	**PCS criterion**	**Placebo N=58**	**Memantine N=56**
Systolic Blood Pressure, mmHg	High (≥130 and increase ≥20 from baseline)	3/57 (5.3%)	3/55 (5.5%)
	Low (≤75 and decrease ≥20)	1/57 (1.8%)	--

Diastolic Blood pressure, mmHg	High (≥90 and increase ≥15 from baseline)	1/57 (1.8%)	5/55 (9.1%)
	Low (≤35 and decrease ≥15)	--	--
Pulse Rate, bpm	High (≥130 and increase ≥15)	--	2/55 (3.6%)
	Low (≤55 and decrease ≥15)	1/57 (1.8%)	--

For the randomized withdrawal study 68, a small proportion of patients who received MEMANTINE had PCS criteria for elevated DBP. However the elevation did not appear to be dose related.

Laboratory Parameter, unit	**PCS criterion**	**Placebo N=160**	**Memantine reduced N=160**	**Memantine full N=157**
Systolic Blood Pressure, mmHg	High (≥130 and increase ≥20 from baseline)	2/160 (1.3%)	2/160 (1.3%)	4/156 (2.6%)
	Low (≤75 and decrease ≥20)	1/160 (0.6%)	2/160 (1.3%)	0/156
Diastolic Blood pressure, mmHg	High (≥90 and increase ≥15 from baseline)	0/160	3/160 (1.9%)	1/156 (0.6%)
	Low (≤35 and decrease ≥15)	--	--	--
Pulse Rate, bpm	High (≥130 and increase ≥15)	1/160 (0.6%)	--	--
	Low (≤55 and decrease ≥15)	--	1/160 (0.6%)	4/156 (2.6%)

Weight

The majority of patients exposed to MEMANTINE for greater than 6 months met PCS criteria for weight gain at least 10% or greater from baseline. However there were no TEAE-reports of weight increase. The sponsor notes that increases in weight could be attributed to normal growth over time. However standardized growth charts reveal a 0.5-1kg normal increase in weight over a 1 year period during the childhood/adolescent years. Assuming an average weight of 45kg for the population, a 1kg increase over 1 year in a 45kg patient is a 2% increase in weight.

Since memantine is not being indicated for any pediatric indication, this reviewer does not recommend that the change in weight <6 mos. and >6mos of MEMANTINE exposure be included into the product labeling.

Laboratory Parameter, unit	PCS criterion	<6 mos. MEMANTINE Exposure N=892	≥6 mos. continuous MEMANTINE exposure (N=112)
Body weight, kg	≥10% increase	43/884 (4.9%)	66/112 (58.9%)
	≥5% decrease	38/884 (4.3%)	7/112 (6.3%)

Looking at changes in BMI over time when exposed to memantine, patients generally stayed within the baseline BMI category. No significant trends were noted. Highlighted boxes represent no changes from baseline BMI categories

Baseline BMI	<6mos Exposure N=892				≥6 mos. exposure N=112			
	End of study BMI category				End of study BMI category			
	Under	Healthy	Over	Obese	Under	Healthy	Over	obese
Under	28/40 (70%)	11/40 (27.5%)	1/40 (2.5%)	0/40	3/3 (100%)	0/3	0/3	0/3
Healthy	15/495 (3%)	463/495 (93.5%)	17/495 (3.4)	0/495	0/60	57/60 (95%)	3/60 (5%)	0/60
Over	0/138	22/138 (15.9)	103/138 (74.6%)	13/138 (9.4)	0/19	6/19 (31.6%)	11/19 (57.9%)	2/19 10.5%
Obese	0/154	0/154	19/154 (12.3%0	135/154 (87.7%)	0/29	0/29	6/29 (20.7%)	23/29 79.3%

<5th %-ile:Under;≥5th to <85th %-ile:healthy; ≥85th to <95th%-ile:obese; ≥95th%-ile:obese

Very few MEMANTINE-treated patients had changes greater than 10% from baseline BMI.

BMI Percentage Category	<6 mos. exposure N=892	≥6mos exposure
➢ -10%	13/827 (1.6%)	5/111 (4.5)
-10% to <0%	337/827 (40.7%)	32/111 (28.8%)
0 to <10%	454/827 (54.9%)	57/111 (51.4%)
10% to <15%	15/827 (1.8%)	12/111 (10.8%)
15% to <20%	6/827 (0.7%)	3/111 (2.7%)
>20%	2/827 (0.2%)	2/111 (1.8%)

Study 57A and 68

Memantine treatment did not appear to affect significant changes in weight when administered for a short period of time. However weight fluctuations were noted in patients who had received memantine in the double blind randomized withdrawal study.

57A

Laboratory Parameter, unit	PCS criterion	Placebo N=58	Memantine N=56
Body weight, kg	≥10% increase	5/51 (9.8%)	3/53 (5.7%)
	≥5% decrease	2/51 (3.9%)	1/53 (1.9%)

68

Laboratory Parameter, unit	PCS criterion	Placebo N=160	Memantine Reduced N=160	Memantine Full N=157
Body weight, kg	≥10% increase	0/160	6/160 (3.8%)	1/156 (0.6%)
	≥5% decrease	1/160 (0.6%)	1/160 (0.6%)	3/156 (1.9%)

7.4.4 Electrocardiograms (ECG's)

Memantine treatment was not associated with any clinically significant changes in ECG tracings. No patients had treatment emergent adverse events of ECG changes during the clinical development program of MEMANTINE for the treatment of autism.

Two (2) patients who were exposed to memantine for > 6mons met PCS criterion for a QTcB increase of >60 msec from baseline. However there were no clinical sequelae noted in either of these two patients. A review of these two patients is provided below.

- Patient 0151001 was a 9 yo male had an initial QTcB at -127 days of 395 msec. on day -1, the measured QTcB was 461msec, meeting PCS criterion for >60 msec change from baseline. This patient was also noted to have a QTcB of 456msec at day 170. He was treated for 337 days without incident. During the clinical trial, there were no changes in QTcF measurements.
- Patient 1179105 was an 8 yo female who had a QTcB measurement of 382 msec at day -10. On day 252 of the trial, the measures QTcB was 494msec, meeting PCS criterion for QTcB change >60msec from baseline. No clinical sequelae were reported. QTcF measurements were within normal limits.

In patients exposed to memantine for less than 3 months, three (3) patients met PCS criteria for a QTcB increase >60 msec from baseline and 1 patient met PCS criterion for a QTcF increase of >60msec from baseline. In both of these patients, pulse rate were elevated and, in the sponsor's opinion, these PCS changes were not considered clinically significant. A review of these patients is provided below.

- Patient 0829103 was an 11 yo male who had a QTcB value of 381 msec at day -14. On day 172, his QTcB measurement was 443 msec, thereby meeting PCS criterion for >60msec change from baseline and also had a recorded pulse rates of 96bpm. There were no clinical symptoms and the QTcF measurement was within normal limits
- Patient 3819105 was a 6 yo male who had an initial QTcB measure of 383msec at day -14. His QTcB measurement on day 125 was 455msec, meeting PCS

criterion for QTcB change >60msec from baseline with a recorded pulse rate of 110 bpm. There were no reported symptoms and the QTcF measurements were within normal limits.

- Patient 8019102 was a 10 yo female with an initial QTcB measurement of 385msec at day -15. Her recorded QTcB at day 117 was 459msec with a pulse of 105bpm. QTcF measurements were within normal limits and there were no reported symptoms.
- Patient 8079103 was a 6yo male with an initial QTcF of 321msec on day -14. On day 84, the recorded QTcF was 384 msec with a pulse of 123bpm. There were no reported symptoms and the QTcB measurement was within normal limits.

7.4.5 Special Safety Studies/Clinical Trials

Due to preclinical concerns of neurotoxicity, the sponsor conducted baseline and post-baseline IQ testing in all patients to assess for clinically significant changes in cognitive functioning.

Overall, memantine administration was not associated with slower rate of increase or decreases in IQ scores from baseline values although a comparison to patients naïve to memantine and who received placebo could not be assessed. The sponsor used the KBIT-2 and other IQ tests to assess IQ at baseline and at the end of treatment. For the double-blind study 57A, IQ testing was ONLY performed at screening and not post treatment, thus a comparison to placebo could not be obtained. The sponsor did conduct change from baseline IQ testing in the randomized withdrawal study. However the baseline IQ measure was obtained after 12 weeks of memantine treatment from the lead in study 91.

Although no changes in IQ testing were seen with memantine administration, subtle changes in cognitive or neurological functioning are likely not to be observed with standard IQ testing. Therefore this reviewer is unable to definitively state that memantine administration was associated with no subtle neurological or cognitive issues.

	Memantine <6 mos. exposure N=892		**Memantine ≥6mos exposure N=112**	
	N	**Mean ±SD**	**N**	**Mean ±SD**
All IQ tests Pooled				
Baseline	810	88.5±22.3	112	81.1±22.6
Change at end of treatment	810	4.7 ±8.8	112	5.6±19.9
KBIT-2				
Baseline	655	89.8±22.5	105	80.9±22.4
Change at end of treatment	655	5.0±9.1	105	5.8±20.5
All IQ tests Pooled (excluding KBIT-2)				

Baseline	155	82.9±20.1	7	84.1±
Change at end of treatment	155	3.6+7.2	7	2.3±6.2

Study 68

	Placebo N=160		**Memantine reduced N=160**		**Memantine full N=157**	
	N	**Mean ±SD**	**N**	**Mean ±SD**	**N**	**Mean ±SD**
All IQ tests pooled						
Baseline	156	93.5±23.8	160	93.4±22.7	152	91.8±25.3
Change at end of study	156	1.9±6.6	160	1.8±7.6	152	2.9±11.4
KBIT-2						
Baseline	131	94.1±24.1	130	95.5±22.8	125	93.8±26.2
Change at end of study	131	2.2±6.8	130	1.5±7.9	125	3.1±12.3

7.4.6 Immunogenicity

Testing for immunogenicity was not conducted under this efficacy supplement.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Although study 68 provided some information on adverse events related to the administration of MEMANTINE in pediatric patients with autism at full dose and half dose, an analysis of drug-dependent adverse events cannot be conducted since all patients in study 68 received full dose MEMANTINE for at least 12 weeks in the lead-in study 91 prior to randomization into study 68 which precludes any analysis of dose dependent adverse events.

7.5.2 Time Dependency for Adverse Events

Time dependency studies were not performed as there were no long term controlled data that was collected during the clinical development program.

7.5.3 Drug-Demographic Interactions

There were no drug-demographic analyses performed on the data.

7.5.4 Drug-Disease Interactions

No additional studies were performed in patients with clinically significant medical illnesses.

7.5.5 Drug-Drug Interactions

There were no explorations conducted by the sponsor to examine drug-drug interactions in this clinical development program.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity studies were not performed as part of the clinical development program for autism.

7.6.2 Human Reproduction and Pregnancy Data

Human reproductive and pregnancy data is not available for memantine under this clinical development program as no cases of pregnancy were reported during the clinical trials.

Memantine is categorized as a category B drug.

7.6.3 Pediatrics and Assessment of Effects on Growth

Based on clinical safety data, memantine does not appear to affect growth parameters in the pediatric patient population studied. Since memantine will not carry an indication for the treatment of autism or for pediatric use, no additional wording regarding effects or lack thereof on growth should be included into labeling.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No studies have been conducted to examine the drug abuse potential of memantine. In addition, there is no information current available to indicate memantine being a drug of abuse.

7.7 Additional Submissions/Safety Issues

There are no additional safety issues of note.

8 POSTMARKET EXPERIENCE

Postmarketing experience with memantine is not applicable to this submission as memantine is only approved for adult use only.

9 APPENDICES

9.1 Literature Review/References

The sponsor conducted a review of current literature. The updated review of literature did not identify any new safety or tolerability issues with the use of memantine.

9.2 Labeling Recommendations

The Agency is currently in labeling negotiations with the sponsor at this time. Final labeling will be attached to final approval letter.

9.3 Advisory Committee Meeting

No FDA advisory committee meeting was held for this supplemental NDA application.

10. Appendix

Clinical Investigator Financial Disclosure
Review

Application Number: 22-525

Submission Date(s): 6 Jan 2014

Applicant: Forest Pharmaceuticals

Product: Memantine HCL

Reviewer: Mark Ritter, MD

Date of Review: 30 June 2014

Covered Clinical Studies: 57A, 68, 91 and 67

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from applicant)
Total number of investigators identified: : There were 1061 unique investigators identified in the entire clinical development program, consisting of 145 Principle Investigators and 916 Sub-Investigators.		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): There were five (5) unique investigators across the entire clinical development program with disclosable financial interests/arrangements, including two (2) investigators that participated in both studies MEM-MD-57A and MEM-MD-67 as well as one (1) investigator that participated in study MEM-MD-57A, one (1) investigator that participated in study MEM-MD-67, and one (1) investigator that participated in both studies MEM-MD-91 and MEM-MD-68.		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 5 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial	Yes X	No ☐ (Request details from applicant)

interests/arrangements:		
Is a description of the steps taken to minimize potential bias provided:	Yes X	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) There were a total of nine (9) unique investigators with certification of due diligence, including one (1) investigator that participated in study MEM-MD-68, one (1) investigator that participated in both studies MEM-MD-91 and MEM-MD-68, and seven (7) investigators in that participated in study MEM-MD-67.		
Is an attachment provided with the reason:	Yes X	No ☐ (Request explanation from applicant)

The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] The five investigators who had disclosable financial interests did not raise questions about the integrity of the data, particularly since the efficacy studies failed to demonstrate any treatment effects.

After review of the financial interests and arrangements, I find that there appears to be no conflict of interest with the study results and the financial arrangements of the investigators involved in this clinical development program.

[1] See [web address].

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/s/

MARK A RITTER
07/01/2014