STATISTICAL REVIEW AND EVALUATION
Clinical Studies

NDA/Supplement Number: 22,525 (S-005)

Drug Name: Namenda (Memantine hydrochloride) XR

Indication: Autism

Applicant: Forest Research Institute, Inc.

Dates: Date of Sponsor's Submission: January 6, 2014

PDUFA Due Date: July 6, 2014

Review Priority: Priority

Biometrics Division: Biometrics I

Statistical Reviewer: Yeh-Fong Chen, Ph.D.

Concurring Reviewers: Peiling Yang, Ph.D. & H.M. James Hung, Ph.D.

Medical Division: Division of Psychiatry Products

Clinical Team: Mark Ritter, M.D. & Robert Levin, M.D.

Project Manager: Kofi Anash, Pharm.D.

Table of Contents

1. EXECUTIVE SUMMARY

The sponsor submitted two clinical study reports and data for Studies MEM-MD-57A and MEM-MD-68 to fulfill the requirement of a Written Request (WR) for Namenda XR extended release capsules. Although neither studies provided support for the efficacy of Namenda as a treatment for children's Autism Spectrum Disorder, the statistical reviewer determined that both trials were conducted following the terms listed in the FDA's Written Request. Therefore, the efficacy component of the WR is deemed to be satisfactory.

2. INTRODUCTION

2.1 OVERVIEW

Forest Laboratories Inc. submitted a supplement to New Drug Application (NDA) for Namenda (Memantine Hydrochloride) XR Extended Release Capsules to fulfill the requirements of a Written Request (WR), which was issued by the Agency on January 25, 2012 and amended on May 29, 2013, to obtain pediatric information on Memantine in children 6-12 years old with Autism Spectrum Disorder (ASD).

The sponsor's Memantine program included two double-blind, placebo-controlled studies conducted in patients aged 6-12 years who met the DSM-IV-TR criteria for autistic spectrum disorder (ASD), including Asperger's Disorder and pervasive developmental disorder not otherwise specified (PDD-NOS). Both studies evaluated Memantine doses of 3-15 mg/day, using a weight-based dosing regimen. The studies were titled:

- MEM-MD-57A: (Part One) An open-label, single-dose study of the pharmacokinetics of Memantine in pediatric patients with autism; (Part Two) a 12-week, double-blind, placebo-controlled, parallel-group study of the efficacy and safety of Memantine in pediatric patients with autism.

- MEM-MD-68: A 12-week double-blind, placebo-controlled, randomized-withdrawal study of the safety and efficacy of Memantine in pediatric patients with autism, Asperger's Disorder, or PDD-NOS previously treated with Memantine.

Of note, for Study MEM-MD-57A, no efficacy analyses were performed in Part one and for Study MEM-MD-68, patients were recruited from those who previously received stable memenatine therapy in open-label lead-in Study MEM-MD-91. Neither efficacy studies provided support for the efficacy of Memantine as a treatment for pediatric patients with autism, Asperger's Disorder, or PDD-NOS previously treated with Memantine.

2.2 DATA SOURCES

The sponsor's original submission including data files and clinical study reports are stored in the following link: \\CDSESUB1\evsprod\NDA022525\0053. During the evaluation, we asked the sponsor to clarify why some patients who met the responder criteria were not randomized to Study MEM-MD-68 from Study MEM-MD-91. Their response was stored in the link of \\CDSESUB1\evsprod\NDA022525\0061.

3. STATISTICAL EVALUATION

3.1 DATA AND ANALYSIS QUALITY

The statistical reviewer found the sponsor's data and analysis quality acceptable.

3.2 EVALUATION OF EFFICACY

The following description of the study, including the sponsor's design, endpoints, analysis methods and results were mostly extracted from the submitted clinical study reports. If there is any discrepancy between the study protocols and reports, it will be discussed in the Section of 3.2.4: Statistical Reviewer's Findings and Comments.

3.2.1 Study MEM-MD-57A

This study is titled 'An Open-label (Part One) and a Randomized, Double-blind, Placebo Controlled (Part Two) Study of the Pharmacokinetics, Safety, Efficacy, and Tolerability of Memantine in Pediatric Patients with Autism'. The study was conducted from May 1 of 2009 to August 2 of 2012 and one interim analysis was performed on May 2 of 2012. There were five centers screening patients in Part one and twenty-two centers screening patients in Part Two of the study. All centers were located in the United States.

3.2.1.1 Study Design and Objectives

This was a multicenter, 2-part study in four weight groups (Group A: $\geq$ 60 kg; Group B: 40 to 59 kg; Group C: 20 to 39 kg; Group D: < 20 kg). Since Part I was an open-label, single-dose 1-week pharmacokinetics study, the focus of this trial in this statistical review is only on Part II. The objective of Part Two of this study was to investigate the safety, efficacy, and tolerability of memantine in pediatric patients with autism aged 6 to 12 years.

Part Two was a multicenter, randomized double-blind, placebo-controlled, parallel-group, flexible- and fixed-dose, 14-week study comparing memantine with placebo in pediatric outpatients who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for autism using modules 2 and 3 of the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R). The part two of the study consisted of 2 weeks of single blind placebo treatment followed by 12 weeks of double-blind treatment (up to 8 weeks of flexible-dose titration followed by 4 weeks of maintenance at a fixed dose). Blood samples were collected in Part Two at Visits 3, 4, and 8.

3.2.1.2 Efficacy Endpoints and Analyses

The primary efficacy endpoint is the change from baseline in Social Responsiveness Scale (SRS) total raw score at Week 12, which was analyzed using a mixed model for repeated measures (MMRM) approach with treatment group, study center, visit, and treatment group-by-visit interaction as fixed effects and baseline SRS total raw score and baseline SRS total raw score-by-visit interaction as the covariates. An unstructured covariance matrix was used to model the covariance of within-patient scores. The Kenward-Roger approximation was used to estimate denominator degree of freedom. These analyses were performed based on all post-baseline scores using only the observed cases without imputation of missing values.

Two sensitivity analyses were also performed for the primary efficacy parameter. The first sensitivity analysis was based on the LOCF approach using an ANCOVA model with treatment group and study center as the factors and baseline value as the covariate. The LOCF approach was used to impute missing post-baseline values, provided that at least one post-baseline assessment was available.

In the second sensitivity analysis, a pattern-mixture model based on non–future-dependent missing value restrictions (Kenward et al, 2003) was performed to assess the robustness of the primary MMRM analysis results to the possible violation of the missing-at-random assumption. The non–future-dependent missing value restriction states that the probability of drop-out at a specific visit can only depend on the observed value and the possibly missing value up to that visit, but not future values beyond that visit.

An interim analysis plan for MEM-MD-57A Part Two was adopted on Jan 06, 2012. The purpose of the interim analysis was to confirm that the study had a sufficient number of subjects to detect a 10-point difference between drug and placebo in the primary efficacy parameter. The plan was amended on Mar 07, 2012 and on Apr 27, 2012. A single, blinded, independent interim analysis, based on the final amended interim analysis plan, was executed on May 02, 2012 after > 90% planned enrollment was completed.

The original study sample size was to have an 85% power to detect an effect size of 0.68. The study power to detect a 10-point treatment difference in the primary efficacy endpoint may be below 85% if the population standard deviation of the primary efficacy parameter, for which the true value is unknown in the literature, is greater than 14.8.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

Patient populations are shown in Figure 1. The sponsor noted that the Part One of the study was intended to supply patients directly into Part Two; however the time taken to analyze the drug levels and review these levels with the FDA precluded this; thus, it ended up having fewer patients entering Part Two from Part One than originally planned.

Tables 2 and 3 summarize patients' demographic characteristics in Part Two for the autism ITT Population and the Safety Population respectively.

5

Table 2 Demographics and Baseline Characteristics Based on ITT Population for
Study MEM-MD-57A

Parameter	Placebo (N=53)	Memantine (N=54)	Total (N=107)
Age, mean (SD)	8.9 (1.9)	8.9 (2.0)	8.9 (2.0)
Sex, n (%)			
Male	43 (81.1)	47 (87.0)	90 (84.1)
Female	10 (18.9)	7 (13.0)	17 (15.9)
Race, n (%)			
White	44 (83.0)	46 (85.2)	90 (84.1)
All Other Races	9 (17.0)	8 (14.8)	17 (15.9)
Black or African American	1 (1.9)	1 (1.9)	2 (1.9)
Asian	5 (9.4)	5 (9.3)	10 (9.3)
American Indian or Alaska Native	0	0	0
Native Hawaiian/ Other Pacific Islander	1 (1.9)	0	1 (0.9)
Other	2 (3.8)	2 (3.7)	4 (3.7)
Ethnicity, n (%)			
Hispanic or Latino	7 (13.2)	4 (7.4)	11 (10.3)
Not Hispanic or Latino	46 (86.8)	50 (92.6)	96 (89.7)

Source: Sponsor's Table 14.2.1E of CSR

Figure 1. Patient Populations for Part One and Part Two of Study MEM-MD-57A
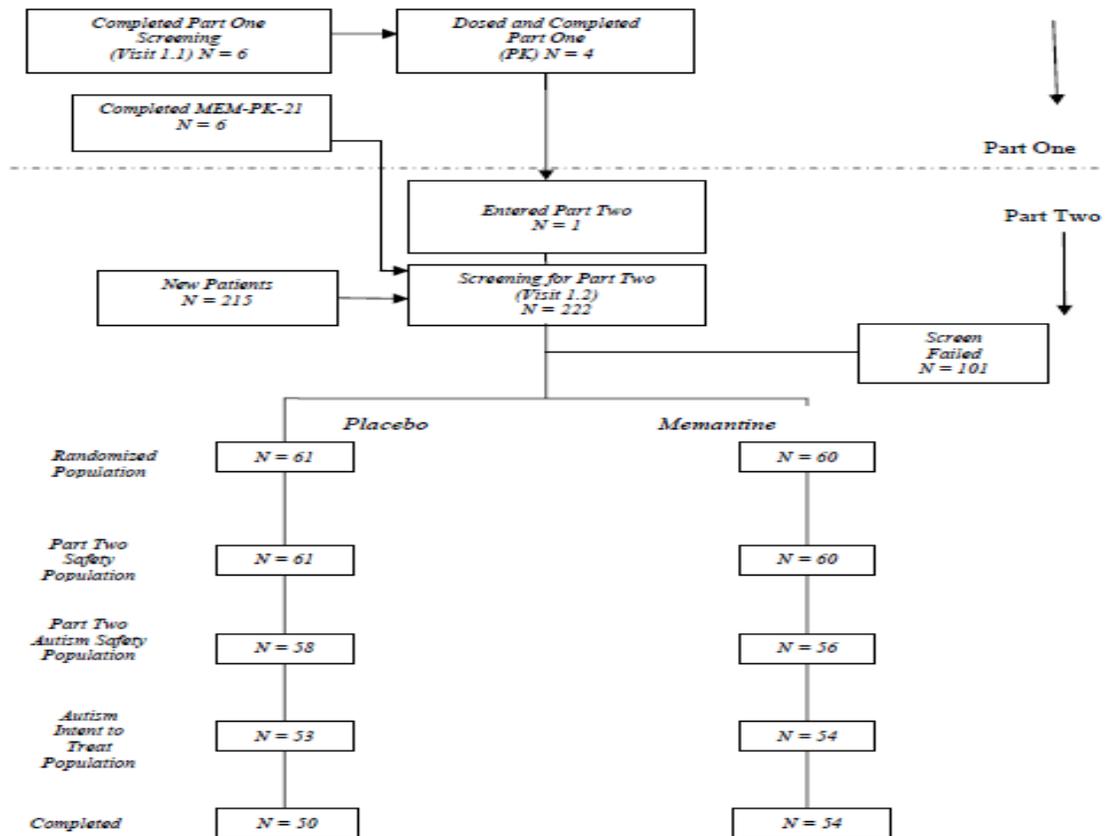
Source: Sponsor's 10.1-1 of CSR

6

Results shown in both populations are consistent. The typical Part Two patients were approximately 9 years of age and most of them were white. The male patients were comprised approximately 84% of the study population. According to the sponsor's results, there were no statistically significant differences between the treatment groups with respect to age, sex, race, ethnicity, height, weight, or body mass index.

Table 3 Demographic Characteristics for Part Two Safety Population of Study MEM-MD-57A

Parameter	Placebo (N=61)	Memantine (N=60)	Total (N=121)
Age, mean (SD*)	8.9 (2.2)	9.0 (2.2)	8.9 (2.2)
Sex, n (%)			
Male	49 (80.3)	52 (86.7)	101 (83.5)
Female	12 (19.7)	8 (13.3)	20 (16.5)
Race, n (%)			
White	49 (80.3)	50 (83.3)	99 (81.8)
All Other Races	12 (19.7)	10 (16.7)	22 (18.2)
Black or African American	3 (4.9)	1 (1.7)	4 (3.3)
Asian	6 (9.8)	5 (8.3)	11 (9.1)
American Indian or Alaska Native	0	0	0
Native Hawaiian/ Other Pacific Islander	1 (1.6)	0	1 (0.8)
Other	2 (3.3)	4 (6.7)	6 (5.0)
Ethnicity, n (%)			
Hispanic or Latino	8 (13.1)	5 (8.3)	13 (10.7)
Not Hispanic or Latino	53 (86.9)	55 (91.7)	108 (89.3)

Note that the SD denotes standard deviation. Source: Sponsor's Table 11.2.2.1-1 of CSR

3.2.1.4 Efficacy Results

3.2.1.4.1 Sponsor's Results for Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline to Week 12 in the SRS total raw score. The sponsor's results for the primary efficacy analysis are displayed in Table 4. As seen from the table, the primary efficacy parameter showed no statistically significant difference between the treatment groups. Their sensitivity analysis results using LOCF and pattern-mixture approaches yielded similar findings.

Table 4 Sponsor's Results for Primary Efficacy Endpoint Based on ITT Population for Study MEM-MD-57A

Descriptive Statistics	Placebo (N=53)	Memantine (N=54)	Memantine-Placebo LSMD (95% C.I.) p-Value
	Mean ± SD*	Mean ± SD*	
Baseline			(b) (4)
Change from baseline			
MMRM (primary analysis)			
LOCF			

7

Descriptive Statistics	Placebo (N=53)	Memantine (N=54)	Memantine-Placebo LSMD (95% C.I.) p-Value
Pattern-mixture model			
Shift Parameter	LS Mean (SE)	LS Mean (SE)	(b) (4)

Note that the SD denotes standard deviation. Source: Sponsor's Table 11.2.4.1.1-1 of CSR.

3.2.1.4.2 Sponsor's Results for Secondary Efficacy Endpoints

The secondary efficacy parameters for this study are CATS-I total score and subscales (social interaction and communication) at Week 12, and the change from baseline to Week 12 in 10 subscales of the CCC-2 scores. Additional efficacy parameters included CGI-S Overall severity and subscales, CGI-I overall severity and subscales, CAASTS-I subscales, ABC subscales, or SRS subscales. The sponsor's results for most of the aforementioned secondary efficacy endpoints are displayed in Table 5 (a &b).

Table 5a Sponsor's Results for Secondary Efficacy Endpoints Based on ITT Population for Study MEM-MD-57A

	Placebo (N=53) Mean ± SD	Memantine (N=54) Mean ± SD	LSMD (Memantine - Placebo) (95% C.I.)	p-Value
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				
CGI-S**				
CGI-S Overall Severity				
CGI-S Social Interaction				
CGI-S Communication				
CGI-S Integrated Social Interaction and Communication				
Behaviors and Restricted Interests				
CGI-S Associated Maladaptive Behaviors				

 * The p-values were obtained from MMRM.
**For the analysis of the CGI-S subscales, only ANCOVA (OC) model was used.
 Source: Sponsor's Tables 11.2.4.1.2-1 and 11.2.4.1.3-1 of CSR.

8

Table 5b Sponsor's Results for Secondary Efficacy Endpoints for Autism ITT Population for Study MEM-MD-57A

	Placebo (N=53) Mean ± SD	Memantine (N=54) Mean ± SD	LSMD (Memantine - Placebo) (95% C.I.)	p-Value
CGI-S** Daily Function				(b) (4)
CGI-I Overall Improvement				
CGI-I Social Interaction				
CGI-I Communication				
CGI-I Integrated Social Interaction and Communication				
CGI-I Stereotyped Behaviors and Restricted Interests				
CGI-I Associated Maladaptive Behaviors				
CGI-I Daily Function				
CAASTS-I Stereotyped Behaviors and Restricted Interests				
CAASTS-I Associated Maladaptive Behaviors				
CAASTS-I Daily Function				
ABC Irritability				
ABC Lethargy				
ABC Stereotypy				
ABC Hyperactivity				
ABC Inappropriate Speech				
SRS Social Awareness				
SRS Social Cognition				
SRS Social Communication				
SRS Social Motivation				
SRS Autistic Mannerisms				

Note that the SD denotes standard deviation.
** For the analysis of the CGI-S subscales, only ANCOVA (OC) model was used.
Source: Sponsor's Table 11.2.4.1.3-1 of CSR.

As seen from the table, there were no significant differences observed between the Memantine and placebo in 9 of the 10 CCC-2 subscales. For one CCC-2 subscale (context) there appeared to be a treatment difference in favor of placebo ((b) (4) , but without proper multiplicity adjustment this is most likely to be a chance finding.

3.2.2 Study MEM-MD-68

This study was titled "A Double-Blind, Placebo-Controlled, Randomized Withdrawal Study of the Safety and Efficacy of Memantine in Pediatric Patients with Autism, Asperger's Disorder, or Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) Previously Treated with Memantine". The study was conducted from September 10 of 2012 to September 11 of 2013 and patients were recruited from 92 centers located in 15 countries.

9

3.2.2.1 Study Design and Objectives

This clinical study was a 12-week, multi-center, double-blind, placebo-controlled, randomized withdrawal study in pediatric outpatients with autism, Asperger's Disorder, or PDD-NOS conducted at 92 study centers. Patients who completed at least 12 weeks of exposure to open-label Memantine and met the responder criterion at 2 consecutive visits separated by at least 2 weeks during lead-in study MEM-MD-91 were eligible to enroll into this study. A patient was considered a responder if he/she had at least a 10-point reduction in the SRS total raw score (improvement) in the SRS relative to the MEM-MD-91 Visit 1 total raw score.

At Visit 1 of this study, 479 patients were randomized (1:1:1) to 1 of 3 double-blind treatment groups: Memantine full-dose ("Memantine Full"); Memantine reduced-dose ("Memantine Reduced"); or placebo. Randomization was stratified by ASD subtype in order to provide a balance of autism, Asperger's Disorder, or PDD-NOS diagnoses across the 3 treatment groups.

The SRS was administered at each visit (every 2 weeks) to access whether loss of therapeutic response (LTR) criterion had been met. LTR was defined as worsening (increase) of at least 10 points in the SRS total raw score relative to the score at Visit 1 (randomization) of this study. As soon as the LTR criterion was met, patients were discontinued from this study and all applicable evaluation scheduled for the final visit at the end of Week 12 (Visit 7) were to be completed.

Patients who completed the 12-week double-blind period or discontinued due to meeting the LTR criterion could then be enrolled in an open-label extension study. Figure 2 provides a schematic of the study design.

Figure 2 Study Design for Study Mem-MD-68
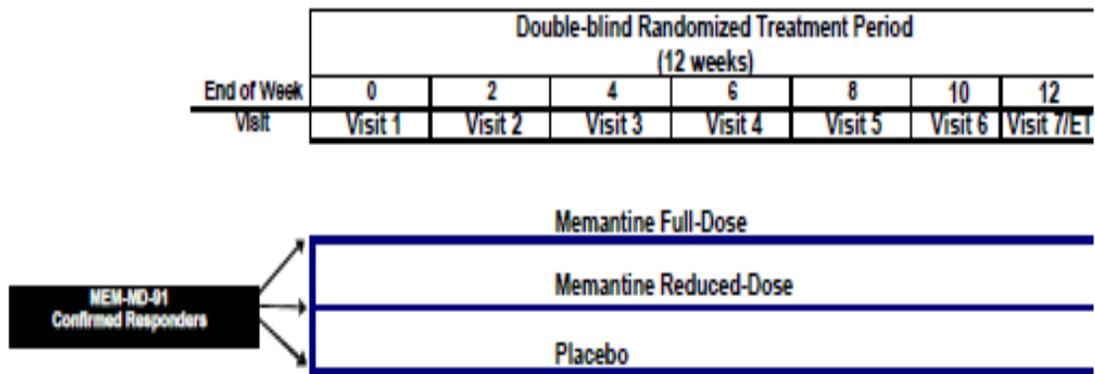
Source: Sponsor's Figure 9.1-1 of CSR

The objective of this study was to evaluate the safety, tolerability, and efficacy of Memantine therapy compared with placebo in pediatric patients with autism, Asperger's Disorder, or PDD-NOS previously on stable Memantine therapy utilizing a randomized-withdrawal paradigm.

3.2.2.2 Efficacy Endpoints and Analyses

The primary efficacy parameter was the proportion of patients with LTR by the end of the study (i.e., by Visit 7/Week 12). LTR was defined as an increase of at least 10 points in the SRS total raw score at any double-blind visit (Visits 2, 3, 4, 5, 6, or 7) relative to the SRS total raw score at Visit 1 (randomization).

The efficacy analyses were based on the ITT Population. Model-based approach or the last-observation-carried-forward (LOCF) approach was used to impute the missing post-baseline values for the change-from-baseline in continuous parameters. For the primary efficacy parameter, analysis was based on the available number of events (i.e., number of patients with LTR) as observed during the study in the ITT Population. Baseline for efficacy was defined as the last non-missing efficacy assessment from lead-in study MEM-MD-91 on or before the date of first dose of double-blind investigational product in this study.

The primary efficacy parameter was analyzed using the CMH test controlling for ASD subtype as the primary analysis. For each of the two memantine dose groups, the proportion of patients with LTR was compared with that for the placebo group using the CMH test controlling for ASD subtype. The overall Type 1 error rate was controlled at 5% level for the two memantine doses versus placebo comparisons for the primary efficacy parameter using a two-step fixed-sequence testing procedure. Following this procedure, the memantine full-dose group versus placebo was to be tested first at the 5% significance level (2-sided) and the memantine reduced-dose was then to be tested against placebo only if the p-value for testing the memantine full-dose against placebo would be significant in favor of memantine full-dose.

The secondary efficacy parameters included:

- Time to the first LTR, where the first LTR was defined as the first visit when a patient showed an LTR

- Change from baseline in each of 10 subscales of the CCC-2 (speech, syntax, semantics, coherence, initiation, scripted language, context, nonverbal communication, social relations, and interests) at Week 12

11

Time to the first LTR was analyzed by treatment group using Kaplan-Meier estimates. The comparison between the treatment groups in time to first LTR was performed using the log-rank test stratified by ASD subtype. Hazard ratio and 95% CI were estimated for each Memantine dose versus placebo using a Cox model with treatment group and ASD subtypes as explanatory variables.

Statistical Reviewer's Note: The sponsor's analysis plan and results for the change from baseline in each of 10 subscales of CCC-2 at Week 12 are not shown in this review. Because 60% of patients had experienced LTR and discontinued from the study, it is not clear how the results of this type can be interpreted .

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

Figure 3 displays the patient disposition of Study MEM-MD-68. In order to be eligible for participation in this study, patients must have had at least 12 weeks of exposure to open-label Memantine and met the confirmed responder criterion in lead-in study MEM-MD-91.

A total of 479 patients were screened and subsequently randomized into Study MEM-MD-68, of which 477 patients received at least one dose of double-blind investigational product (Safety Population). A total of 471 patients had at least one dose of double-blind investigational product and at least one assessment of the SRS total raw score during the double-blind period (Intent-to-treat Population). According to Figure 3, a total of 144 patients completed the study and 315 patients discontinued due to meeting the LTR criterion. The reasons for discontinuation are presented in Table 6 by treatment group for the Randomized Population.

Table 6 Number and Percentage of Patients Discontinued from the Study in Randomized Population for Study MEM-MD-68

Patient Status	Placebo (N=160) n (%)	Memantine Reduced (N=161) n (%)	Memanine Full (N=158) n (%)	Total (N=479) n (%)
Completed	44 (27.5)	50 (31.1)	50 (31.6)	144 (30.1)
Prematurely Discontinued Due to LTR	107 (66.9)	108 (67.1)	100 (63.3)	315 (65.8)
Prematurely Discontinued Due to Other Reasons	9 (5.6)	3 (1.9)	8 (5.1)	20 (4.2)
Patient did not meet Inclusion/Exclusion Criteria	0	1 (0.6)	1 (0.6)	2 (0.4)
Adverse Event	1 (0.6)	0	0	1 (0.2)
Insufficient Therapeutic Response	0	1 (0.6)	0	1 (0.2)
Protocol Violation	4 (2.5)	0	4 (2.5)	8 (1.7)
Withdrawal of Consent	2 (1.3)	0	2 (1.3)	4 (0.8)
Lost to Follow-up	1 (0.6)	0	1 (0.6)	2 (0.4)
Study or Site Terminated by Sponsor	0	0	0	0
Other Reasons	1 (0.6)	1 (0.6)	0	2 (0.4)

Source: Sponsor's Table 10.1-1 from CSR

12

Figure 3 Patient Disposition for Study MEM-MD-68
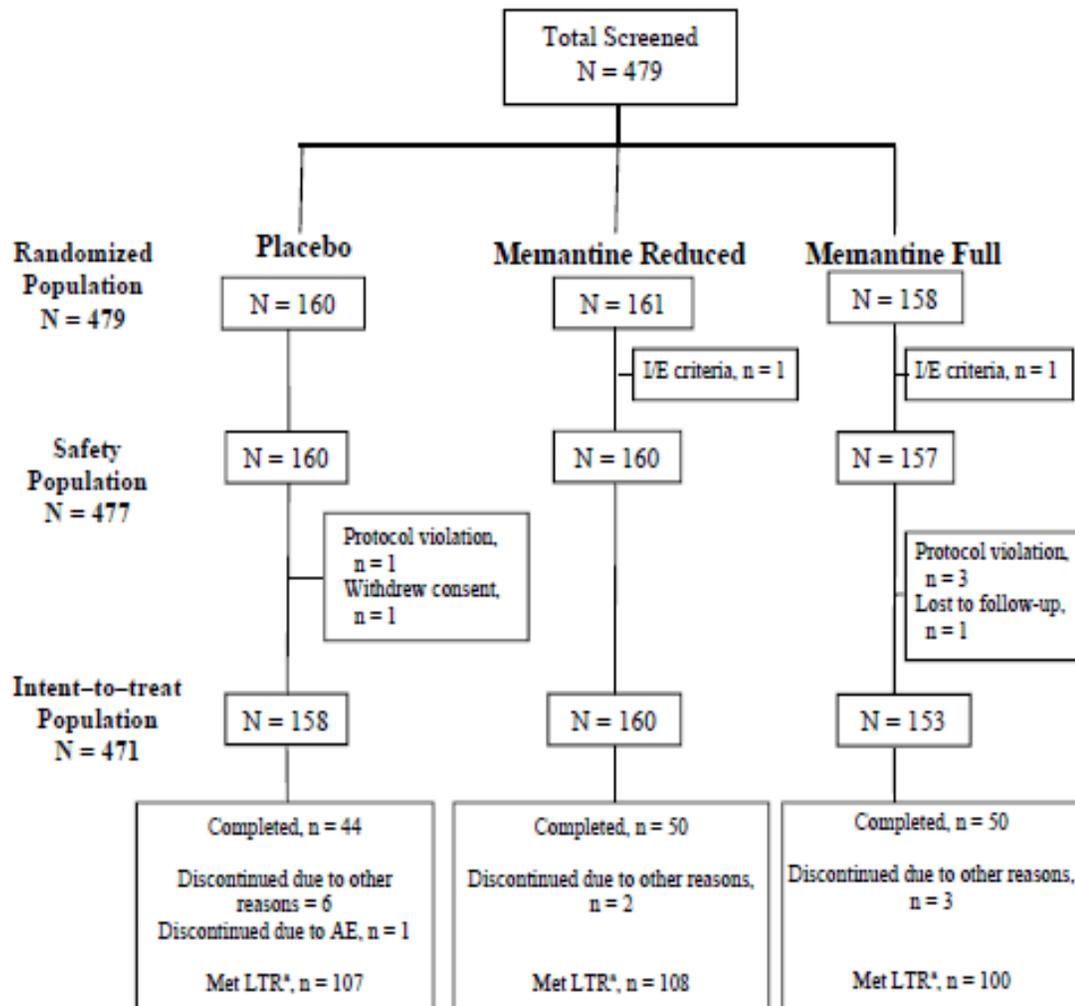
a   A total of 315 patients discontinued due to loss of therapeutic response (LTR) by SRS criterion per the termination page of the electronic case report form. Four additional patients met the LTR criterion based on an increase of SRS total raw score of at least 10 points relative to Visit 1 (randomization) by end of study, but discontinued from the study for Other Reasons (eg, Adverse Event [AE], Withdrawal of Consent).

Source: Sponsor's Figure 10.1-1 of CSR

Demographic and baseline characteristics data for the Safety Population are shown in Table 7. As shown in the table, demographic characteristics for the Safety Population were generally comparable across treatment groups. The sponsor noted that "Mean age was approximately 9 years old; most patients were male (85.1%), white (87.8%), and not Hispanic (87.4%). Distribution by ASD subtype was 62.9%, 18.2% and 18.9% in the autism, Asperger's Disorder, and PDD-NOS subtypes, respectively. Most of the patients in the Safety Population were in the United States (385/477 [80.7%]).

13

Table 7 Demographic and Baseline Characteristics for Safety Population for
Study MEM-MD-68

Characteristic	Placebo (N=160)	Memantine Reduced (N=160)	Memantine Full (N=157)	Total (N=477)
Age, years, Mean ± SD	8.9 ±2.0	9.2 ± 1.9	9.2 ± 1.9	9.1 ± 1.9
ASD Subtype, n (%)				
Autism	101 (63.1)	99 (61.9)	100 (63.7)	300 (62.9)
Asperger's Disorder	30 (18.8)	30 (18.8)	27 (17.2)	87 (18.2)
PDD-NOS	29 (18.1)	31 (19.4)	30 (19.1)	90 (18.9)
Sex, n (%)				
Male	142 (88.8)	132 (82.5)	132 (84.1)	406 (85.1)
Female	18 (11.3)	28 (17.5)	25 (15.9)	71 (14.9)
Race, n (%)				
White	138 (86.3)	141 (88.1)	140 (89.2)	419 (87.8)
All Other Races	22 (13.8)	19 (11.9)	17 (10.8)	58 (12.2)
Black or African American	10 (6.3)	9 (5.6)	7 (4.5)	26 (5.5)
Asian	7 (4.4)	5 (3.1)	8 (5.1)	20 (4.2)
American Indian or Alaska Native	0	1 (0.6)	0	1 (0.2)
Native Hawaiian or Other Pacific Islander	1 (0.6)	1 (0.6)	0	2 (0.4)
Other	4 (2.5)	3 (1.9)	2 (1.3)	9 (1.9)
Ethnicity, n (%)				
Hispanic or Latino	23 (14.4)	22 (13.8)	15 (9.6)	60 (12.6)
Not Hispanic or Latino	137 (85.6)	138 (86.3)	142 (90.4)	417 (87.4)
Weight, kg, Mean ± SD	37.64 ± 13.85	40.45 ± 16.49	38.07 ± 14	38.72 ± 14.85
Height, cm, Mean ± SD	139.19 ± 13.33	140.9 ± 13.77	140.02 ± 13.05	140.03 ± 13.38
BMI, kg/m^2, Mean ± SD	18.91 ± 4.42	19.70 ± 5	18.86 ± 4.21	19.16 ± 4.57
SRS total raw score (screening), Mean ± SD	110 ± 24.9	111.2 ± 23.6	111.2 ± 24.5	110.8 ± 24.3
SRS total raw score (baseline), Mean ± SD	109.2 ± 23.1	109.0 ± 23.7	112 ± 25.3	110 ± 24.0
All IQ tests pooled (including KBIT-2) (screening), Mean ± SD	88.7 ± 22.1	88.6 ± 21.2	86.9 ± 23.4	88 ± 22.2
All IQ tests pooled (excluding KBIT-2) (screening), Mean ± 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
KBIT-2 total score (screening), Mean ± SD	89.2 ± 22.3 n = 135	90.4 ± 21.0 n = 130	88.9 ± 23.8 n = 130	89.5 ± 22.4 n = 395
ABC-I (screening), Mean ± SD	8.0 ± 4.7 n = 160	9.3 ± 5.1 n = 160	9.0 ± 4.6 n = 157	8.8 ± 4.8 n = 477

Note that the SD denotes standard deviation.
Source: Sponsor's Tables 11.2.1-1, 11.2.1-2 & 11.2.3-1 of CSR.

3.2.2.4 Efficacy Results

3.2.2.4.1 Sponsor's Results for Primary Efficacy Endpoint

The sponsor's results for the primary efficacy analysis are summarized in Table 8. The primary efficacy parameter was the proportion of patients with LTR at the end of the study. LTR was defined as worsening (increase) of at least 10 points in the SRS total raw score relative to the score at Visit 1 (randomization) of this study. As shown on Table 8, Memantine full-dose did not demonstrate statistical significance over placebo [(b) (4)] for the primary efficacy parameter. Thus, according to the multiplicity adjustment strategy, no formal statistical testing between Memantine reduced-dose and placebo was performed. The sponsor also performed two sensitivity analyses and those results were similar to the

14

primary analysis results. No significant differences (nominal) were observed (at the nominal 5% significance level) in these sensitivity analyses.

Table 8 Sponsor's Results for Primary Efficacy Endpoint for Study MEM-MD-68

	Placebo (N = 158) n (%)	Memantine Reduced (N = 160) n (%)	Memantine Full (N=153) n (%)
Primary Analysis			
LTR LTR rate difference Odds ratio (95% CI) p-value			(b) (4)
Sensitivity Analysis (Based on Multiple Imputation)			
Missing at Random LTR LTR rate difference Odds ratio (95% CI) p-value			(b) (4)
Not Missing at Random LTR LTR rate difference Odds ratio (95% CI) p-value			

Source: Sponsor's Table 11.4.1.1-1 of CSR

3.2.2.4.2 Sponsor's Results for Secondary Efficacy Endpoint

The sponsor's results for the time to first LTR endpoint are summarized in Table 9. The first LTR was defined as the first visit when a patient showed an LTR. As seen from the table, neither memantine dose group demonstrated significant differences from placebo (nominal p-value ≥0.6) while controlling for the effect of ASD subtype.

.

Table 9 Sponsor's Results for Time to First LTR Endpoint for Study MEM-MD-68

	Placebo (N=158)	Memantine Reduced (N=160)	Memantine Full (N=153)
Number censored Number of events			(b) (4)
Crude rate of event (%) Median Survival, days (95% C.I.)			
Hazard ratio (Memantine vs Placebo) (95% C.I.)			
p-value			

Source: Sponsor's Table 11.4.1.2.1-1 of CSR.

15

3.2.3 Sponsor's Conclusion

As part of the Written Request, the sponsor conducted two randomized, double-blind, placebo-controlled studies, MEM-MD-57A and MEM-MD-68, to evaluate the safety and efficacy of memantine in the treatment of the core features of autism or ASD.

Study MEM-MD-57A studied pediatric patients with autism with respect to 2 of the 3 core symptoms (social interaction and communication). It was summarized by the sponsor that "*Patients in the memantine and placebo groups showed clinically important improvements in SRS total raw scores from baseline and CATS-I of a magnitude that are not commonly seen in clinical practice. However, there were no statistically significant differences in improvement between the patients treated with memantine and patients treated with placebo for the primary and secondary endpoints.*"

Study MEM-MD-68 was a randomized-withdrawal trial, with a placebo, a memantine reduced-dose arm, and a memantine full-dose arm. Similar to Study MEM-MD-57A, it was summarized by the sponsor that "*No statistically or nominally significant difference between either the memantine full-dose or reduced-dose groups and placebo was observed for the primary efficacy parameter, the proportion of patients with LTR (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) by the end of the double-blind treatment period. No statistically significant differences (nominal) were observed between the memantine treatment groups and placebo for any of the secondary efficacy parameters.*"

The sponsor concluded that "*Both studies were designed with at least 85% statistical power to detect a clinically meaningful treatment effect of memantine compared with placebo at the conventional 5% significance level (2-sided). However, neither study showed a positive treatment effect for memantine over placebo in the treatment of autism or any of the ASD subtypes.*"

3.2.4 Statistical Reviewer's Findings and Comments

For both Studies MEM-MD-57A and MEM-MD-68, the statistical reviewer confirmed the sponsor's analysis results for the primary and major secondary endpoints and did not find significant deficiency. For Study MEM-MD-68, however, the statistical reviewer noted that several patients who did not meet the responder criteria were randomized to the study, and many patients who indeed met the responder criteria were not randomized to the study. Therefore, during the review cycle, an official letter was issued to the sponsor for clarification.

In the sponsor's response, they noted that there were eleven patients randomized into Study MEM-MD-68 without meeting the complete eligibility criteria and a total of 49 patients in Study MEM-MD-91 met the above criteria but were not included in the Randomized Population of Study MEM-MD-68. For these 49 patients, they enclosed a list of detailed reasons why those patients were not randomized into Study MEM-MD-68, where the majority of them were due to the closeout of the enrollment.

16

The statistical reviewer carefully studied the sponsor's response. Because 479 patients were randomized in Study MEM-MD-68, the impact of those 11 patients, who were erroneously randomized and included the study, would be minimal. On the other hand, the main reason why most patients who met the responder criteria but were not randomized was due to the closeout of the enrollment of Study MEM-MD-68, which is reasonable. Therefore, the statistical reviewer accepts the sponsor's response and does not have any further concern about this issue.

3.3 EVALUATION OF SAFETY

The safety evaluation is not performed in this review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 GENDER, RACE AND AGE

Both Studies MEM-MD-57A and MEM-MD-68 randomized pediatric patients with the majority of them white males; thus, the sponsor did not conduct any demographic subgroup analysis.

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

4.2.1 ASD Subtype for Study MEM-MD-68

The following Tables 9 displays the sponsor's subgroup analysis results by patients' ASD subtype. As shown in the table, there do not appear to be clinically meaningful differences between treatment groups in ethese ASD subtypes.

Table 9 Sponsor's Subgroup Analysis Results by ASD Subtype for Study MEM-MD-68

ASD Subtype	Placebo (N=158) n/N1 (%)	Memantine Reduced (N=160) n/N1 (%)	Memantine Full (N=153) n/N1 (%)
Autism			
LTR	73/100 (73.0)	66/99 (66.7)	63/98 (64.3)
Difference in LTR rate		6.3	8.7
Asperger's Disorder			
LTR	18/30 (60.0)	21/30 (70.0)	19/26 (73.1)
Difference in LTR rate		-10.0	-13.1
PDD-NOS			
LTR	18/28 (64.3)	21/31 (67.7)	20/29 (69.0)
Difference in LTR rate		-3.5	-4.7

Note that N1 denotes the number of patients within the specific ASD subtype
Source: Sponsor's Table 11.4.1.4.1-1 of CSR

4.2.2 Region

The following Table 10 displays the sponsor's subgroup analysis results by patients' ASD subtype. As shown in the table, the regional analysis suggested substantial heterogeneity. In

17

particular, a numerical difference was observed in the non-US population between each Memantine dose group (reduced-dose group: 51.4%, full-dose group: 50.0%) and placebo (80.8%). Due to the small sample size in the subgroups of non-US patients, we should keep in mind that these results are difficult to interpret.

Table 10 Sponsor's Subgroup Analysis Results by Region and also ASD Subtype under Regions for Study MEM-MD-68

Region	Placebo (N=158) n/N1 (%)	Memantine Reduced (N=160) n/N1 (%)	Memantine Full (N=153) n/N1 (%)
United States			
LTR	88/132 (66.7)	90/125 (72.0)	88/123 (70.7)
Difference in LTR rate		-5.3 (-16.6, 5.9)	-4.1 (-15.4, 7.3)
Autism			
LTR	54/76 (71.1)	53/74 (71.6)	53/74 (71.6)
Difference in LTR rate		-0.6 (-15.0, 13.9)	-0.6 (-15.0,13.9)
Asperger's Disorder			
LTR	17/29 (58.6)	19/27 (70.4)	17/23 (73.9)
Difference in LTR rate		-11.7 (-36.6, 13.1)	-15.3 (-40.7, 10.1)
PDD-NOS			
LTR	17/27 (63.0)	18/24 (75.0)	17/26 (65.4)
Difference in LTR rate		-12.0 (-37.2, 13.1)	-2.4 (-28.2, 23.4)
Non-US			
LTR	21/26 (80.8)	18/35 (51.4)	15/30 (50.0)
Difference in LTR rate		29.3 (6.9, 51.8)	30.8 (7.3, 54.2)
Autism			
LTR	19/24 (79.2)	13/25 (52.0)	10/24 (41.7)
Difference in LTR rate		27.2 (1.7, 52.6)	37.5 (11.9, 63.1)
Asperger's Disorder			
LTR	1/1 (100.0)	2/3 (66.7)	2/3 (66.7)
Difference in LTR rate		33.3 (-20.0, 86.7)	33.3 (-20.0, 86.7)
PDD-NOS			
LTR	1/1 (100.0)	3/7 (42.9)	3/3 (100.0)
Difference in LTR rate		57.1 (20.5, 93.8)	0

Note that N1 denotes the number of patients within the specific ASD subtype
Source: Sponsor's Table 11.4.1.4.2-1 of CSR

5. SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

For both Studies MEM-MD-57A and MEM-MD-68, the statistical reviewer confirmed the sponsor's analysis results for the primary and major secondary endpoints and did not find significant deficiency. For Study MEM-MD-68, however, the statistical reviewer noted that several patients who did not meet the responder criteria were randomized to the study, and many patients who indeed met the responder criteria were not randomized to the study. Therefore, during the review cycle, an official letter was issued to the sponsor for clarification.

In the sponsor's response, they noted that there were eleven patients randomized into Study MEM-MD-68 without meeting the complete eligibility criteria and a total of 49 patients in Study MEM-MD-91 met the above criteria but were not included in the Randomized Population of Study MEM-MD-68. For these 49 patients, they enclosed a list of detailed reasons why those patients were not randomized into Study MEM-MD-68, where the majority of them were due to the closeout of the enrollment.

The statistical reviewer carefully studied the sponsor's response. Because 479 patients randomized in Study MEM-MD-68, the impact of those 11 patients, who were erroneously randomized and included the study, would be minimal. On the other hand, the main reason why most patients who met the responder criteria but were not randomized was due to the closeout of the enrollment of Study MEM-MD-68, which is reasonable. Therefore, the statistical reviewer accepts the sponsor's response and does not have any further concern about this issue.

5.2 CONCLUSIONS AND RECOMMENDATIONS

Although both Studies MEM-MD-57A and MEM-MD-68 failed to support the efficacy of Namenda as a treatment for children's Autistic Spectrum Disorder, the statistical reviewer determined that both trials were conducted thoroughly following the terms listed in the FDA's Written Request. Therefore, the efficacy component of the WR is deemed to be satisfactory.

_____
Yeh-Fong Chen, Ph.D.
Mathematical Statistician

cc: NDA 22,525
HFD-130/Dr. Mathis
HFD-130/Dr. Levin
HFD-130/Dr. Ritter
HFD-130/Mr. Anash
HFD-700/Ms. Patrician
HFD-710/Dr. Mahjoob
HFD-710/Dr. Hung
HFD-710/Dr. Yang

19

Reference ID: 3517485