CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
22-525

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA /Serial Number:	22-525
Drug Name:	Memantine ER (Namenda®)
Indication:	Moderate to severe dementia of the Alzheimer's type
Applicant:	Forest Laboratories, INC.
Date of Submission:	August 20, 2009
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
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Key Words: Alzheimer's Disease, SIB, CIBIC-plus, ANCOVA

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Based on the results of Study MEM-MD-50, a therapeutic benefit for memantine ER/AChEI treatment compared to placebo/AChEI treatment was observed for the two co-primary efficacy measures, SIB (Severe Impairment Battery) and CIBIC-plus (Clinician's Interview-Based Impression of Change with Caregiver's Input). However, this reviewer is concerned with the inter-country difference in the treatment effect of SIB.

1.2 Brief Overview of Clinical Studies

This submission includes Study MEM-MD-50 as the pivotal efficacy study.

This study was conducted as a multicenter, randomized, double-blind, placebo-controlled, parallel-group study comparing memantine ER with placebo in outpatients diagnosed with probable Alzheimer's Disease (AD) who are currently taking an AChEI. In total, 677 patients were randomized to the study. It was performed at 83 study centers (38 study centers in the United States, 23 in Argentina, 11 in Chile, and 11 in Mexico). The study consisted of 1 to 2 weeks of single-blind placebo treatment followed by 24 weeks of double-blind treatment.

1.3 Statistical Issues and Findings

The objectives of this study were to evaluate the safety, tolerability, and efficacy of memantine compared with placebo in outpatients diagnosed with moderate to severe dementia of the Alzheimer's type on a concurrent AChEI.

The primary efficacy parameters were the change from baseline to Week 24 in the SIB total score and the CIBIC-plus rating score at Week 24. The study results were considered "positive" if memantine ER demonstrated a statistically significant superiority to placebo ($p \leq .05$) on both primary efficacy parameters at Week 24 (LOCF).

Change from baseline to Week 24 (LOCF) in SIB total score was analyzed using an analysis of covariance (ANCOVA) model with the treatment group and study center as factors and the baseline SIB total score as a covariate. CIBIC-plus rating score at Week 24 (LOCF) was analyzed by the CMH statistic using modified ridit scores (the van Elteren test), controlling for study center.

At Week 24, the LS mean change in the SIB total score from baseline for the memantine ER/AChEI treatment group was 2.2 compared with a LS mean change in the placebo/AChEI treatment group of –0.4 (a positive change indicates an improvement). The LS mean treatment difference of 2.6 between the two groups was statistically significant in favor of memantine ER/AChEI ($p = .001$, ITT, LOCF). The results of the OC analysis and MMRM analysis of the SIB total score were consistent with the LOCF analysis.

The mean CIBIC-plus rating for memantine ER/AChEI–treated patients was 3.8 at Week 24 (LOCF analysis) compared with 4.1 for patients treated with placebo/AChEI. CIBIC-plus is a seven-point ordinal scale (1=marked improvement and 7=marked worsening. The difference between treatment groups was statistically significant (p = .008, ITT, LOCF) in favor of memantine ER/AChEI at Week 24. The results of OC analysis at Week 24 were consistent with those of the LOCF analysis at Week 24.

This reviewer conducted the following additional analyses to investigate the country effect. Please refer to Section 3.1.2 Reviewer's Analysis for details.

- **Baseline and Change from Baseline in SIB by Country and Treatment:** The mean baseline SIB was very similar across different countries and different treatment groups. However, the treatment effects (difference between the mean change from baseline of memantine and mean change from baseline of placebo) for patients in Argentina, Chile and Mexico were 3.3, 1.5, 3.03, respectively, while the treatment effect for patients in USA was only 0.81. This indicates that even though the numeric changes in SIB were in favor of memantine group for both US and non-US patients the treatment effects of SIB for patients in Argentina, Chile and Mexico were higher than that for patients in USA.

- **Premature Discontinuation by Country and Treatment:** It appears that the dropout rate was higher for USA than for other countries, especially the dropout rate for USA placebo patients was close to 33% while the dropout rate for placebo patients in other countries were all below 15%.

- **CIBIC-plus by Country and Treatment:** It seems that mean baseline CIBIC-plus was very similar across different countries and different treatment groups. At week 24, it appears that the treatment effect was numerically similar across different countries.

In summary, for CIBIC-plus, it seems that the treatment effect was numerically similar across different countries. However, for SIB, the treatment effects for patients in Argentina, Chile and Mexico were higher than that for patients in USA.

2 INTRODUCTION

2.1 Overview

Memantine is a moderate affinity, uncompetitive N-methyl-D-aspartate receptor antagonist with strong voltage dependency and rapid blocking/unblocking kinetics. These pharmacologic features allow memantine to block the sustained activation of the receptor hypothesized to occur under pathological conditions such as Alzheimer's disease (AD) and to rapidly leave the N-methyl-D-aspartate channel during normal physiologic activation of the receptor (Parsons et al, 1999).

Memantine is currently available in the United States (Namenda®) and in over 70 other countries, including Argentina, Chile, and Mexico. It is approved by the FDA for the treatment of moderate to severe dementia of the Alzheimer's type at a dosage of up to 20 mg/d (10 mg twice a day).

Memantine has not been systematically evaluated at total daily dosages greater than 20 mg/d in patients with moderate to severe AD. Furthermore, memantine is currently given as 10 mg twice daily, and a once-daily dosing regimen in an AD population would provide additional convenience and simplify administration for the caregiver.

2.2 Data Sources

The sponsor's original electronic submission was stored in the directory of \\Cdsesub1\evsprod\NDA022525\0000 of the center's electronic document room.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 PROTOCOL MEM-MD-50

3.1.1.1 Study Objectives

The objectives of this study were to evaluate the safety, tolerability, and efficacy of memantine compared with placebo in outpatients diagnosed with moderate to severe dementia of the Alzheimer's type on a concurrent AChEI.

3.1.1.2 Study Design

This study was conducted as a multicenter, randomized, double-blind, placebo-controlled, parallel-group study comparing memantine ER with placebo in outpatients diagnosed with probable AD who are currently taking an AChEI.

This study was performed at 83 study centers (38 study centers in the United States, 23 in Argentina, 11 in Chile, and 11 in Mexico).

The study consisted of 1 to 2 weeks of single-blind placebo treatment followed by 24 weeks of double-blind treatment. This study involved a total of seven clinic visits: Screening (Visit 1); Baseline (Visit 2); and end of Weeks 4 (Visit 3), 8 (Visit 4), 12 (Visit 5), 18 (Visit 6), and 24/Final Study Visit (Visit 7) or early termination.

3.1.1.3 Efficacy Measures

The primary efficacy parameters were the change from baseline to Week 24 in the SIB total score and the CIBIC-plus rating score at Week 24.

The secondary efficacy parameter was change from baseline to Week 24 in ADCS-ADL19 total score.

Additional parameters evaluated for efficacy were:

- Changes from baseline in the SIB total score by visit
- CIBIC-plus rating scores by visit
- Change from baseline in the ADCS-ADL19 total score by visit
- Change from baseline in the NPI total score by visit
- Change from baseline in total words from the verbal fluency test by visit
- Change from baseline in the NPI domain scores by visit
- Change from baseline in each ADCS-ADL19 item by visit

3.1.1.4 Statistical Analysis Plan

Planned Analyses

The primary efficacy parameters were the change from baseline to Week 24 in the SIB total score and the CIBIC-plus rating score at Week 24. The study results were considered "positive" if memantine ER demonstrated a statistically significant superiority to placebo ($p \leq .05$) on both primary efficacy parameters at Week 24 (LOCF).

Change from baseline to Week 24 (LOCF) in SIB total score was analyzed using an analysis of covariance (ANCOVA) model with the treatment group and study center as factors and the baseline SIB total score as a covariate.

CIBIC-plus rating score at Week 24 (LOCF) was analyzed by the CMH statistic using modified ridit scores (the van Elteren test), controlling for study center.

The secondary efficacy parameter was change from baseline to Week 24 in ADCS-ADL19 total score, which was analyzed using an ANCOVA model with the treatment group and study center as factors, and the corresponding baseline value as a covariate.

Changes in the Planned Analyses

The following were main changes to the planned analyses:

- For each of the two primary efficacy parameters, a sensitivity analysis using an MMRM based on the observed data (OC) obtained at all postbaseline visits (up to Week 24) was to be performed.

- A rule of pooling small study centers for efficacy analyses was specified, namely, study centers with less than four patients were to be pooled into a collective study center within a country.

3.1.1.5 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

A total of 864 patients were screened. Among them, 677 patients (335 placebo/AChEI–treated patients and 342 memantine ER/AChEI–treated patients) were randomized to double-blind treatment. A total of 676 patients (335 placebo/AChEI–treated patients and 341 memantine ER/AChEI–treated patients) received at least one dose of double-blind study drug (Safety Population). A total of 661 patients (328 placebo/AChEI–treated patients and 333 memantine ER/AChEI–treated patients) had at least one postbaseline efficacy assessment (ITT Population) and were included in the efficacy analyses.

The number of patients in the Randomized Population who prematurely discontinued from the study is shown by treatment group and reason for discontinuation in Table 1.

A total of 272 (81.2%) placebo/AChEI–treated patients and 273 (79.8%) memantine ER/AChEI–treated patients completed the study. The most frequently reported reason for discontinuation was AEs, which were reported by 21 (6.3%) placebo/AChEI–treated patients and 34 (9.9%) memantine ER/AChEI–treated patients.

Table 1: Number (%) of Patients Prematurely Discontinued and Reasons for Discontinuation—Randomized Population

	Placebo/AChEI (N = 335)	***Memantine ER/AChEI (N = 342)***	***Total (N = 677)***
Completed study	272 (81.2)	273 (79.8)	545 (80.5)
Withdrawn from study	63 (18.8)	69 (20.2)	132 (19.5)
Reason for withdrawal			
Adverse event	21 (6.3)	34 (9.9)	55 (8.1)
Insufficient therapeutic response	8 (2.4)	3 (0.9)	11 (1.6)
Protocol violation	6 (1.8)	14 (4.1)	20 (3.0)
Consent withdrawn	18 (5.4)	10 (2.9)	28 (4.1)
Lost to follow-up	5 (1.5)	4 (1.2)	9 (1.3)
Other	5 (1.5)	4 (1.2)	9 (1.3)

AChEI = acetylcholinesterase inhibitor.

Cross-reference: Table 14.1.3A

Source: Table 10.1-1 of sponsor's Clinical Study Report

Demographic and Other Baseline Characteristics

A summary of patient demographic data and other Baseline (Visit 2) characteristics is presented in Table 2.

Table 2: Demographic Characteristics - Safety population

Characteristic	***Placebo/AChEI (N = 335)***	***Memantine/AChEI (N = 341)***	***Total (N = 676)***
Age, y, mean ± SD	76.8 ± 7.8	76.2 ± 8.4	76.5 ± 8.1
Sex, n (%)	—	—	—
Male	92 (27.5)	97 (28.4)	189 (28.0)
Female	243 (72.5)	244 (71.6)	487 (72.0)
Race, n (%)	—	—	—
Caucasian	312 (93.1)	324 (95.0)	636 (94.1)
Black	12 (3.6)	3 (0.9)	15 (2.2)
Asian	0	1 (0.3)	1 (0.1)
Other	11 (3.3)	13 (3.8)	24 (3.6)
Ethnicity, n (%)	—	—	—
Hispanic	233 (69.6)	233 (68.3)	466 (68.9)
Non-Hispanic	102 (30.4)	108 (31.7)	210 (31.1)
Weight, kg, mean ± SD	64.65 ± 13.28	65.09 ± 12.83	64.87 ± 13.05
Height, cm, mean ± SD	158.94 ± 9.98	158.92 ± 9.84	158.93 ± 9.90
BMI, kg/m^2, mean ± SD	25.56 ± 4.54	25.65 ± 4.05	25.60 ± 4.29

Source: Excerpt from Table 11.2-1 of sponsor's Clinical Study Report

A summary of the mean baseline efficacy assessments are presented in Table 3.

Table 3: Summary of Efficacy Assessments and Disease Severity at Baseline – ITT Population

Assessment	*Placebo/AChEI (N = 328)*	*Memantine ER/AChEI (N = 333)*
SIB	75.3 ± 19.3	76.9 ± 17.5
CIBIS	4.5 ± 0.8	4.5 ± 0.9
ADCS-ADL_{19}	32.8 ± 11.0	33.1 ± 11.1
NPI	16.8 ± 15.4	17.2 ± 15.8
Verbal fluency	5.7 ± 3.7	5.8 ± 3.8
MMSE score	10.6 ± 2.9	10.9 ± 2.9
HIS	1.1 ± 1.0	1.1 ± 0.9
FAST score[a]	1.3 ± 2.2	1.2 ± 2.1

a FAST value of –4, –3, –2, ... 11 are assigned to Stage 1, 2, 3, ... 7f, respectively.

AChEI = acetylcholinesterase inhibitor; ADCS-ADL_{19} = 19-Item Alzheimer's Disease Cooperative Study—Activities of Daily Living Inventory; CIBIS = Clinician's Interview-Based Impression of Severity; FAST = Functional Assessment Staging; HIS = Hachinski Ischemia Scale; ITT = intent to treat; NPI = Neuropsychiatric Inventory; SIB = Severe Impairment Battery (test).

Cross-reference: Tables 14.2.1, 14.2.2 and 14.2.5.

Source: Table 11.2.1-1 of sponsor's Clinical Study Report

It seems that the treatment groups were comparable with respect to demographic and other baseline characteristics.

3.1.1.6 Sponsor's Primary Efficacy Results

The primary efficacy parameters were the change from baseline to Week 24 in the SIB total score and the CIBIC-plus rating score at Week 24.

Severe Impairment Parameters (SIB)

A summary of the mean change from baseline at Week 24 for the SIB total score is presented in Table 4.

Table 4: Change from Baseline in SIB Total Score at Week 24 – ITT Population

		Placebo (N=328)		Memantine (N=333)		LS Mean Difference (Memantine-Placebo)	
Visit	Statistics	Baseline	Change	Baseline	Change	(95% CI) [1]	P-value [1]
Week 24: LOCF	Mean	75.2	0.3 (0.627 *)	76.8	2.7 (<0.001 *)		
	SD	19.29	11.48	17.52	11.17		
	SEM	1.07	0.63	0.96	0.61		
	Median	80.0	2.0	82.0	2.0		
	Min, Max	3, 100	-76, 29	9, 99	-30, 37		
	n	327	327	332	332		
	LS Mean (SE)		-0.4 (0.65)		2.2 (0.65)	2.6 [1.0, 4.2]	0.001
Week 24: OC	Mean	76.5	0.5 (0.476 *)	76.1	3.2 (<0.001 *)		
	SD	18.35	10.72	17.78	10.88		
	SEM	1.11	0.65	1.08	0.66		
	Median	81.0	2.0	81.0	3.0		
	Min, Max	13, 100	-48, 29	9, 98	-28, 37		
	n	271	271	270	270		
	LS Mean (SE)		0.0 (0.67)		3.0 (0.69)	3.0 [1.3, 4.6]	<0.001
MMRM at Week 24	LS Mean (SE)		0.1 (0.67)		2.8 (0.67)	2.7 [0.9, 4.6]	0.004

Note: [1] LOCF and OC Analyses are based on change from baseline from an ANCOVA model with treatment group and study center as factors and baseline value as a covariate. MMRM analysis is based on a mixed model for repeated measurements with treatment group, time, treatment group-by-time interaction as factors, baseline value as a covariate and an unstructured covariance matrix. * P-value for within-group change from baseline using paired t-test.
n = Number of patients with available analysis value at both baseline and a specific time point in the ITT Population.
SD = Standard Deviation, SEM = Standard Error of the Mean, Min = Minimum, and Max = Maximum.

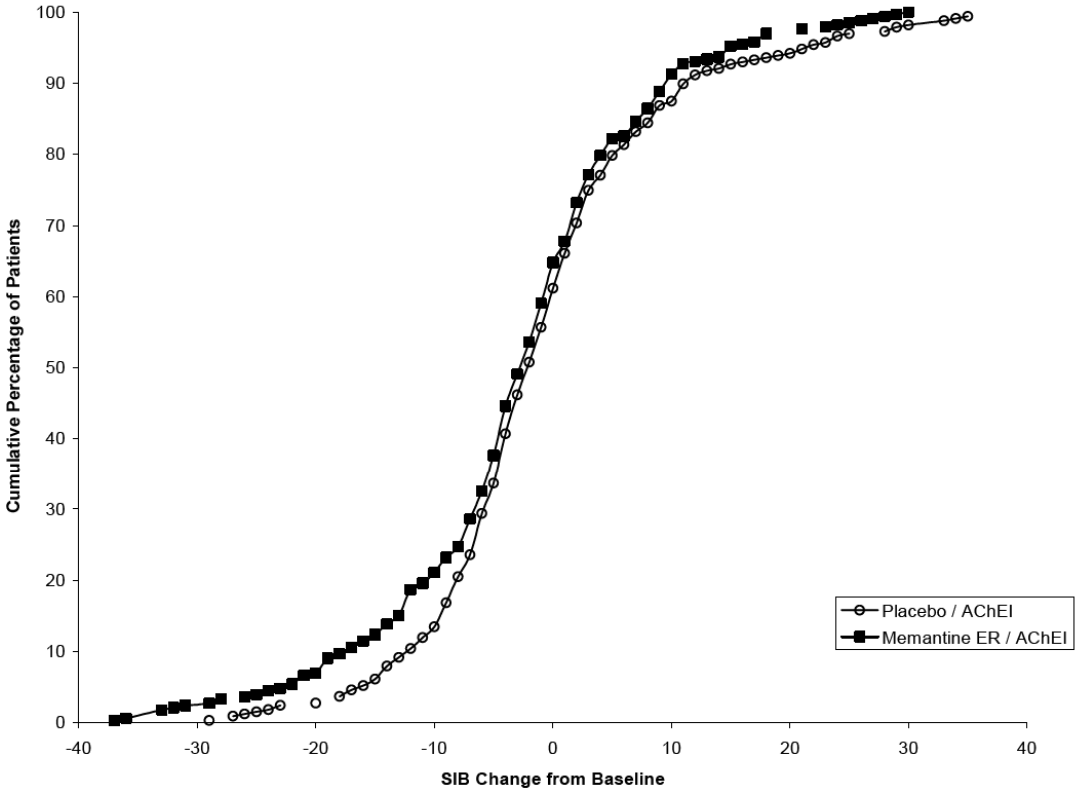
Source: Table 14.4.1.1 of sponsor's Clinical Study Report

At Week 24, the LS mean change in the SIB total score from baseline for the memantine ER/AChEI treatment group was 2.2 compared with a LS mean change in the placebo/AChEI treatment group of –0.4. The LS mean treatment difference of 2.6 between the two groups was statistically significant in favor of memantine ER/AChEI (p = .001).

The results of the OC analysis and MMRM analysis of the SIB total score were consistent with the LOCF analysis.

Figure 1 presents the cumulative percentage of patients from each treatment group who had attained at Week 24 at least the measure of improvement in SIB score shown on the X axis. It appears that the patients in the memantine ER/AChEI treatment group were more likely to show an improvement.

Figure 1: Cumulative Percentage of Patients with Specified Changes from Baseline to Week 24 (LOCF) in Severe Impairment Battery Scores



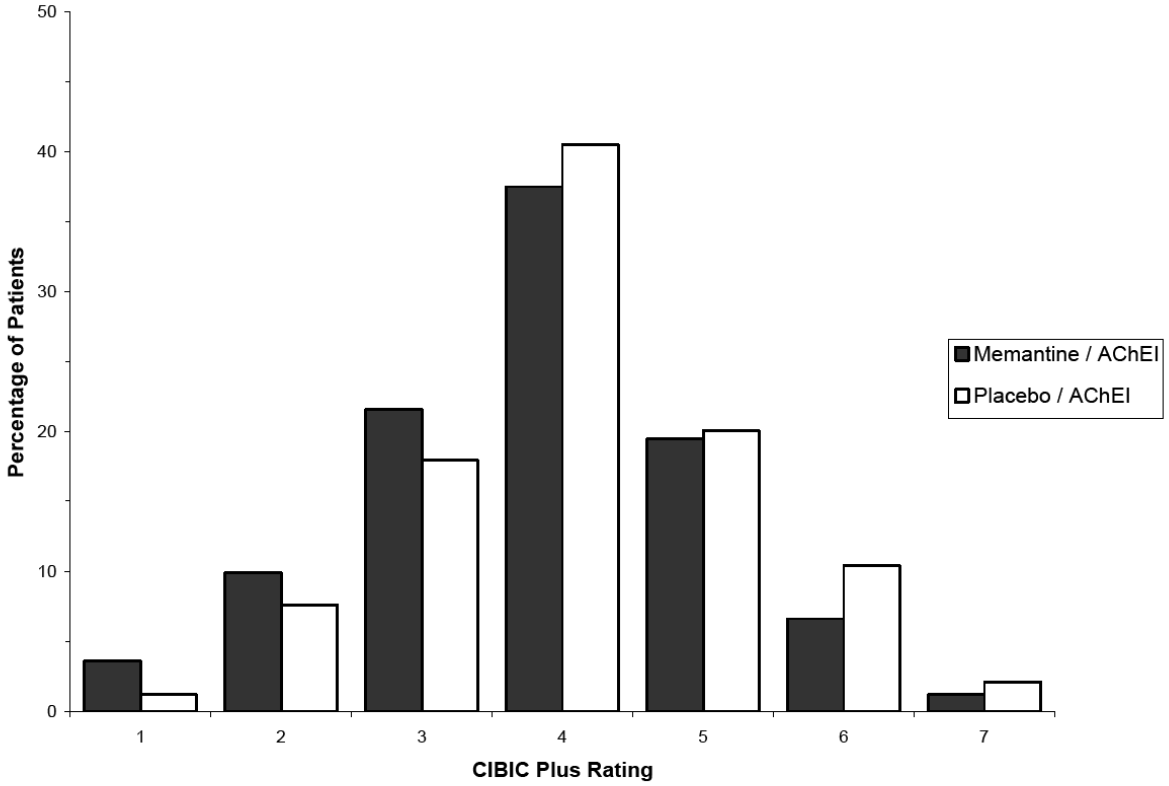
Baseline minus endpoint.
LOCF = last observation carried forward.
Cross-reference: Figure 14.4.4.

Source: Figure 11.4.1.1.1.1-1 of sponsor's Clinical Study Report

Clinician's Interview-Based Impression of Change with Caregiver Input (CIBIC-plus)

The distribution of CIBIC-plus ratings at Week 24 is displayed in Figure 2. The results for CIBIC-plus ratings at Week 24 (LOCF and OC) are presented in Table 5.

Figure 2: CIBIC-Plus: Distribution of Ratings at Week 24 (LOCF)



1 = marked improvement; 2 = moderate improvement; 3 = minimal improvement; 4 = no change; 5 = minimal worsening; 6 = moderate worsening; 7 = marked worsening.

AChEI = acetylcholinesterase inhibitor; LOCF = last observation carried forward.

Cross-reference: Table 14.4.1.2 and Figure 14.4.1.

Source: Figure 11.4.1.1.2-1 of sponsor's Clinical Study Report

Table 5: CIBIC-Plus Rating Score at Week 24 (ITT)

	Distribution	Placebo (N=328) n (%)	Memantine (N=333) n (%)	Memantine Vs. Placebo p-value [1]
Week 24: LOCF	Marked improvement	4 (1.2)	12 (3.6)	0.008
	Moderate improvement	25 (7.6)	33 (9.9)	
	Minimal improvement	59 (18.0)	72 (21.6)	
	No change	133 (40.5)	125 (37.5)	
	Minimal worsening	66 (20.1)	65 (19.5)	
	Moderate worsening	34 (10.4)	22 (6.6)	
	Marked worsening	7 (2.1)	4 (1.2)	
	Mean	4.1	3.8	
	SD	1.18	1.22	
	SEM	0.07	0.07	
	Median	4.0	4.0	
	Min, Max	1.0, 7.0	1.0, 7.0	
	n	328	333	
Week 24: OC	Marked improvement	4 (1.5)	12 (4.5)	0.051
	Moderate improvement	23 (8.5)	28 (10.4)	
	Minimal improvement	50 (18.4)	55 (20.4)	
	No change	109 (40.1)	107 (39.8)	
	Minimal worsening	54 (19.9)	52 (19.3)	
	Moderate worsening	28 (10.3)	14 (5.2)	
	Marked worsening	4 (1.5)	1 (0.4)	
	Mean	4.1	3.8	
	SD	1.18	1.19	
	SEM	0.07	0.07	
	Median	4.0	4.0	
	Min, Max	1.0, 7.0	1.0, 7.0	
	n	272	269	

Note: [1]: LOCF and OC analysis is based on CMH test (controlling for study center) using modified ridit scores. MMRM analysis is based on a mixed model for repeated measurements with treatment group, time, treatment group-by-time interaction as factors, baseline value (CIBIS) as a covariate and an unstructured covariance matrix.
Percentage is calculated based on the number of patients with assessment.
n = Number of patients with available analysis value at a specific time point in the ITT Population.
Marked Improvement=1 Moderate Improvement=2 Minimal Improvement=3 No Change=4 Minimal Worsening=5
Moderate Worsening=6 Marked Worsening=7.

Source: Table 14.4.1.2 of sponsor's Clinical Study Report

The mean CIBIC-plus rating for memantine ER/AChEI–treated patients was 3.8 at Week 24 (LOCF analysis) compared with 4.1 for patients treated with placebo/AChEI. The difference between treatment groups was statistically significant (p = .008) in favor of memantine ER/AChEI at Week 24.

For OC analysis, the mean CIBIC-plus rating for memantine ER/AChEI–treated patients was 3.8 at Week 24 compared with 4.1 for placebo/AChEI–treated patients. This difference between treatment groups was marginally statistically significant (p = .051) in favor of memantine ER/AChEI.

Reviewer's Comments:

In the Study report, the sponsor also presents the results of MMRM analysis. However, since CIBIC-plus is not a continuous variable, MMRM analysis is controversial and needs justification. .

3.1.1.7 Sponsor's Secondary Efficacy Results

The secondary efficacy parameter was the change from baseline to Week 24 in the ADCS-ADL$_{19}$ score (19-Item Alzheimer's Disease Cooperative Study—Activities of Daily Living Inventory).

A summary of the mean change from baseline after 24 weeks for the ADCS-ADL$_{19}$ is presented in Table 6. At Week 24 (LOCF analysis), the LS mean change from baseline in the ADCS-ADL$_{19}$ for the memantine ER/AChEI treatment group was –1.0 compared with –1.7 in the placebo/AChEI treatment group. It seems that the treatment effect for the memantine ER/AChEI treatment group was numerically better than that for the placebo/AChEI treatment group.

Table 6: Least Square Mean Change from Baseline in ADCS-ADL$_{19}$

	Placebo/AChEI		***Memantine ER/AChEI***	
	N	*Mean*[a]	*N*	*Mean*[a]
Week 24 (LOCF)	328	–1.7	331	–1.0
Week 24 (OC)	272	–1.1	268	–0.3

a Positive change indicates improvement in functioning.

AChEI = acetylcholinesterase inhibitor; ADCS-ADL$_{19}$ = 19-Item Alzheimer's Disease Cooperative Study—Activities of Daily Living Inventory; ER = extended release; ITT = intent to treat; LOCF = last observation carried forward; OC = observed cases.

Cross-reference: Table 14.4.2.1.

Source: Excerpt from Table 11.4.1.2.1-1 of sponsor's Clinical Study Report

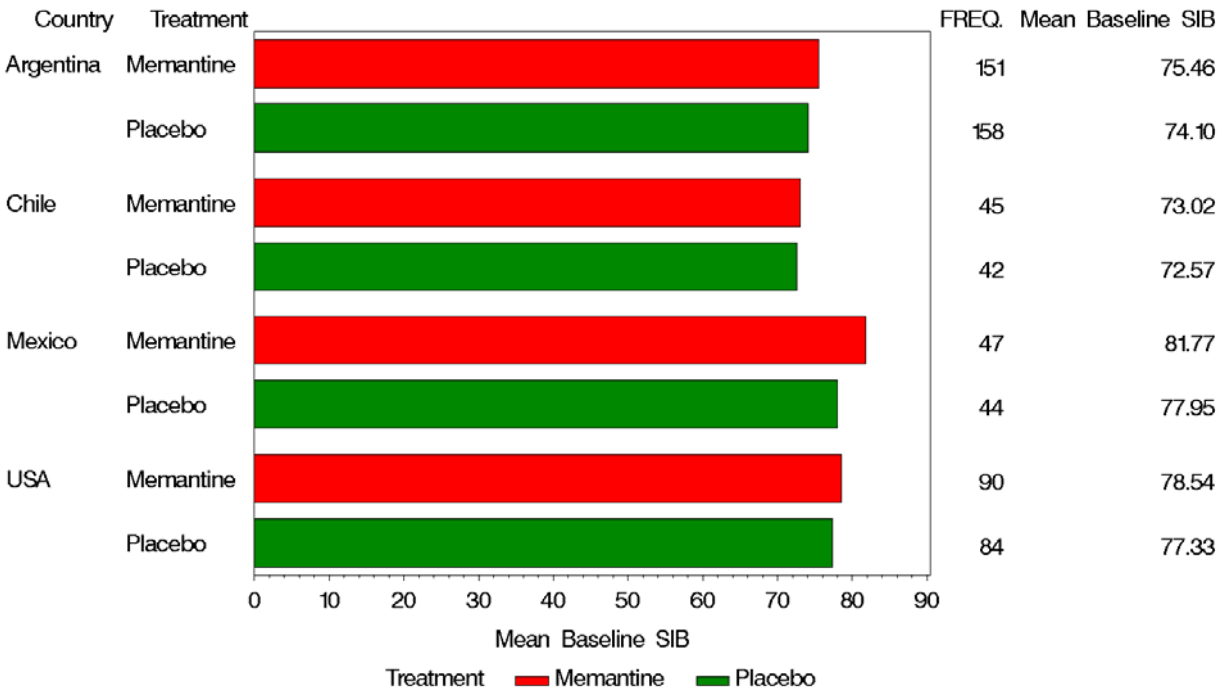
3.1.2 REVIEWER'S ANALYSIS

This reviewer verified sponsor's efficacy analysis presented in this review. In addition, this reviewer conducted the following analyses to investigate the effect of country.

3.1.2.1 Baseline and Change from Baseline in SIB by Country and Treatment

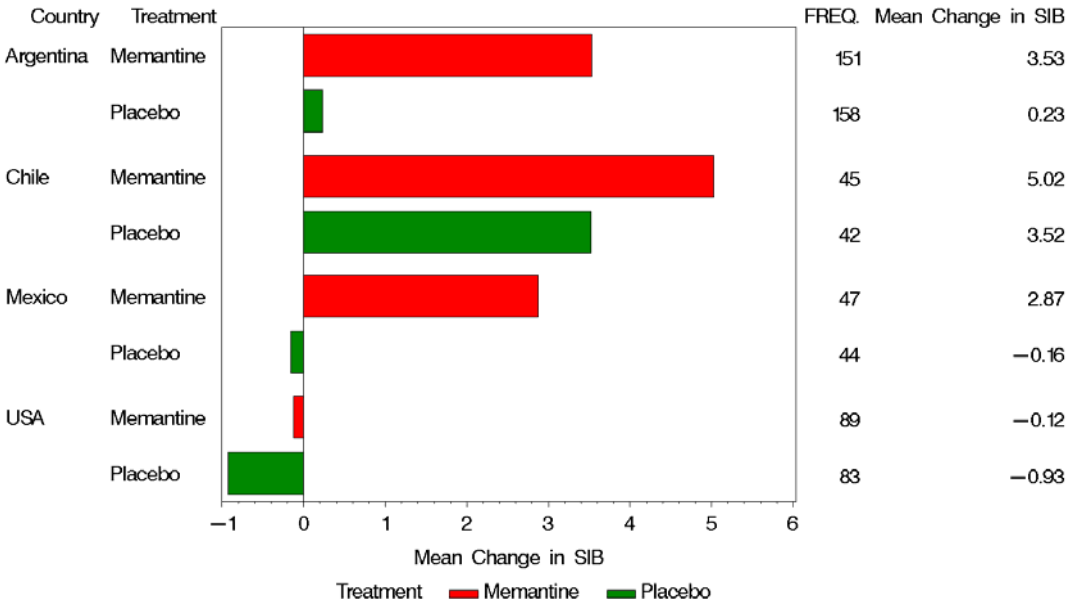
Figure 3 and Figure 4 display mean baseline and mean change from baseline in SIB by country and treatment, respectively. The mean baseline SIB was very similar across different countries and different treatment groups. However, the treatment effects (difference between the mean change from baseline of memantine and mean change from baseline of placebo) for patients in Argentina, Chile and Mexico were 3.3, 1.5, 3.03, respectively, while the treatment effect for patients in USA was only 0.81. This indicates that even though the numeric changes in SIB were in favor of memantine group for both US and non-US patients the treatment effects of SIB for patients in Argentina, Chile and Mexico were higher than that for patients in USA. In addition, for patients in Argentina, Chile and Mexico, the mean changes from baseline in memantine group were 3.53, 5.02, 2.87, respectively, while for patients in USA, the mean change from baseline in memantine group was -0.12, which indicates a slight worsening from baseline. However, based on this reviewer's discussion with the Medical Division, this slight worsening is not uncommon for Alzheimer's Disease clinical trials.

Figure 3: Mean Baseline in SIB by Country and Treatment (ITT, LOCF)



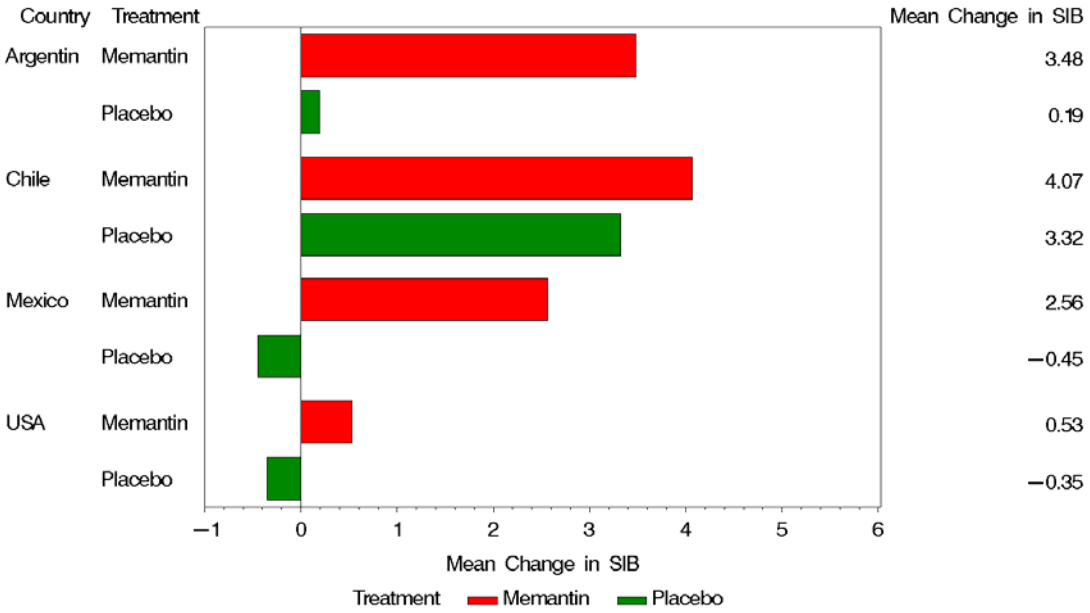
Source: Reviewer's Analysis

Figure 4: Mean Change from Baseline in SIB by Country and Treatment (ITT, LOCF)



Source: Reviewer's Analysis

Figure 5: Mean Change from Baseline in SIB by Country and Treatment (ITT, LOCF, New Model)



Source: Reviewer's Analysis

In the information request sent to the sponsor via email on April 8, 2010, the Agency asks the sponsor if they have explanation for the inter-country difference in treatment effect of SIB. In the response received by the Agency on April 20, the sponsor states that the observed difference between countries in SIB may be a reflection of the inter-country difference on the patient demographics, baseline characteristics, and on baseline SIB and CIBIS values. This reviewer used the same model specified by the sponsor in the April 20 response to estimate the treatment effect by country and treatment. That is, the ANCOVA analysis of SIB change from baseline score (ITT, LOCF at Week 24) includes Treatment, Country, age, ethnicity, duration of education, BMI, and Hachinski Ischemia Scale total score, baseline SIB total score, and baseline CIBIS as factors/covariates. The only factor this reviewed added to the ANCOVA model was country by treatment term in order to estimate the mean change from baseline after adjusting for all of the variables stated above (the treatment by country term was not statistically significant, p=0.61). Figure 5 displays mean change from baseline in SIB by country and treatment based on the aforementioned new model. It seems that Figure 5 exhibits the similar pattern as Figure 4. Therefore, this reviewer is not convinced by the sponsor's explanation regarding the inter-country difference in the treatment effect of SIB.

3.1.2.2 Premature Discontinuation by Country and Treatment

Table 7 presents the number and percent of patients prematurely discontinued by country and treatment. It appears that the dropout rate was higher for USA than for other countries, especially the dropout rate for USA placebo patients was close to 33% while the dropout rate for placebo patients in other countries were all below 15%.

Table 7: Number (%) of Patients Prematurely Discontinued by Country and Treatment – Randomized Population

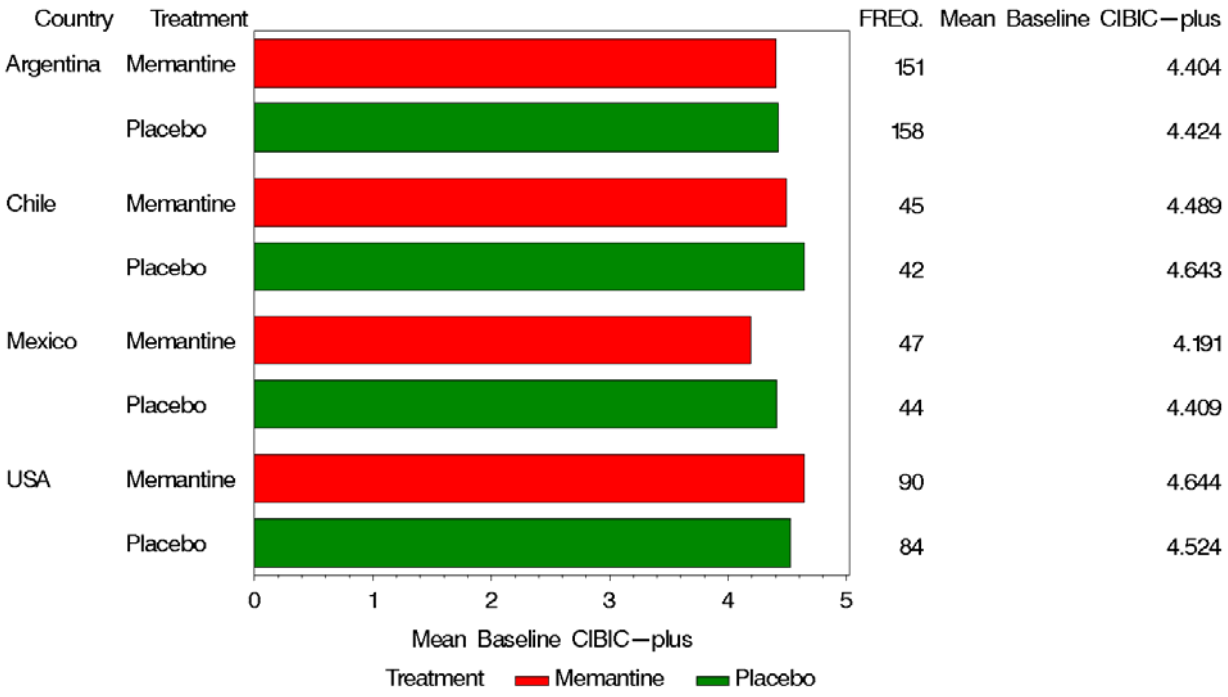
Country	Memantine	Placebo
Argentina	16 (10.5%)	23 (14.6%)
Chile	11 (24.9%)	5 (11.4%)
Mexico	12 (24.5%)	7 (14.6%)
USA	29 (31.2%)	28 (32.9%)

Source: Reviewer's Analysis

3.1.2.3 CIBIC-plus by Country and Treatment

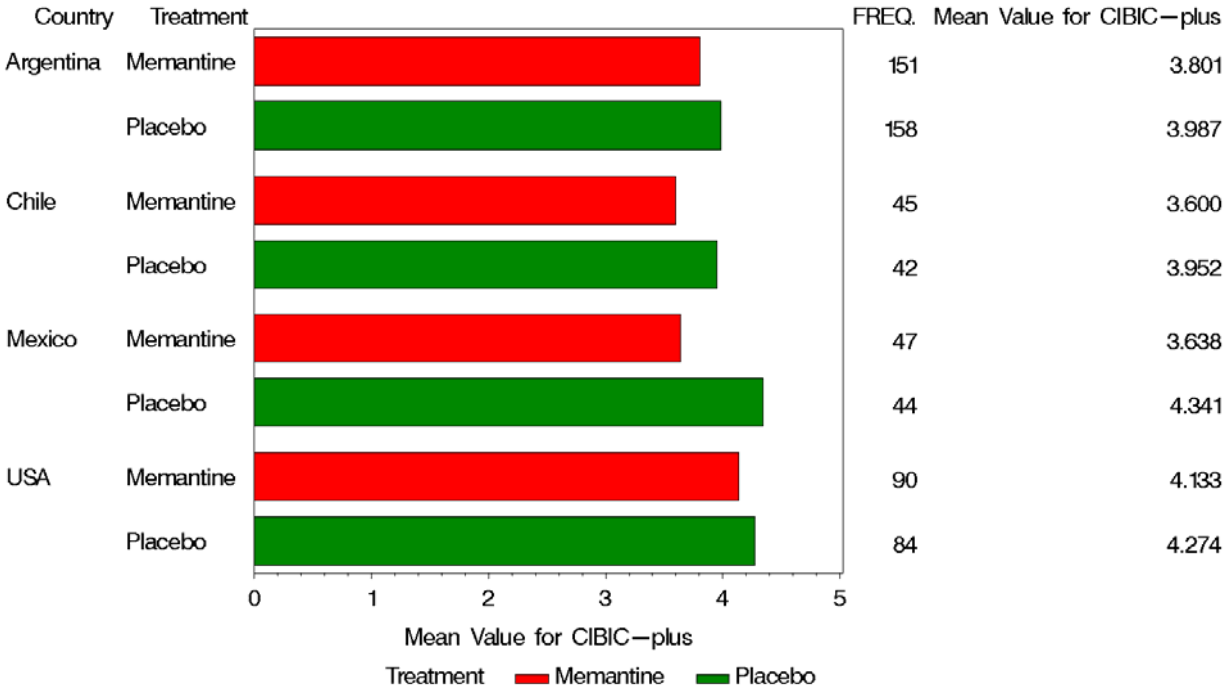
Figure 6 and Figure 7 present mean baseline CIBIC-plus and mean CIBIC-plus at week 24 by country and treatment group. It seems that mean baseline CIBIC-plus was very similar across different countries and different treatment groups. At week 24, it appears that the treatment effect was numerically similar across different countries.

Figure 6: Mean Baseline in CIBIC-plus by Country and Treatment (ITT, LOCF)



Source: Reviewer's Analysis

Figure 7: Mean CIBIC-plus at Week 24 by Country and Treatment (ITT, LOCF)



Source: Reviewer's Analysis

3.1.2.4 Summary of Analyses for Country Effect

The primary efficacy parameters for this study were the change from baseline to Week 24 in the SIB total score and the CIBIC-plus rating score at Week 24.

For CIBIC-plus, it seems that the treatment effect was numerically similar across different countries.

For SIB, the mean baseline SIB was very similar across different countries and different treatment groups. However, the treatment effects for patients in Argentina, Chile and Mexico were much higher than that for patients in USA. Further analysis shows that the dropout rate was higher for USA than for other countries, especially for the placebo group.

3.2 Evaluation of Safety

Please read Dr. Mani's review for safety assessment.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender and Ethnic group

4.1.1 STUDY MEM-MD-50

4.1.1.1 Effects of Age

The results of the analyses of the effectiveness of memantine ER/AChEI treatment in patients stratified into two age subgroups, < 75 years old and ≥ 75 years old, are presented in Table 8.

Table 8: Efficacy Results by Age

Parameter	*Placebo/AChEI*		*Memantine ER/AChEI*	
SIB: change from baseline at Week 24 (LOCF)				
	N	Mean Change (SD)	N	Mean Change (SD)
< 75 y	103	0.16 (10.63)	117	4.70 (11.67)
≥ 75 y	224	0.38 (11.88)	215	1.55 (10.75)
CIBIC-plus: rating scores at Week 24 (LOCF)				
	N	Mean (SD)	N	Mean (SD)
< 75 y	103	4.23 (1.03)	118	3.60 (1.22)
≥ 75 y	225	4.04 (1.24)	215	3.97 (1.20)
ADCS-ADL$_{19}$: Change from baseline at Week 24 (LOCF)				
	N	Mean Change (SD)	N	Mean Change (SD)
< 75 y	103	–1.14 (7.99)	118	0.16 (6.39)
≥ 75 y	225	–1.44 (7.52)	213	–1.15 (7.17)

AChEI = acetylcholinesterase inhibitor; ADCS-ADL$_{19}$ = 19-Item Alzheimer's Disease Cooperative Study—Activities of Daily Living Inventory; CIBIC-plus = Clinician's Interview-Based Impression of Change With Caregiver Input; LOCF = last observation carried forward; SIB = Severe Impairment Battery.

Cross-reference: Tables 14.4.5.1B, 14.4.5.2B, and 14.4.5.3B.

Source: Table 11.4.1.5.1-1 of sponsor's Clinical Study Report

It seems that the numeric scores in all parameters were in favor of memantine ER/AChEI for both age subgroups.

4.1.1.2 Effects of Sex

The results of the analyses of the effectiveness of memantine ER/AChEI treatment in male versus female patients are presented in Table 9.

Table 9: Efficacy Results by Sex

Parameter	*Placebo/AChEI*		*Memantine ER/AChEI*	
SIB: change from baseline at Week 24 (LOCF)				
	N	Mean Change (SD)	N	Mean Change (SD)
Male	91	1.07 (10.71)	93	4.37 (11.17)
Female	236	0.02 (11.77)	239	2.00 (11.12)
CIBIC-plus: rating score at Week 24 (LOCF)				
	N	Mean (SD)	N	Mean (SD)
Male	91	4.16 (1.18)	94	3.76 (1.22)
Female	237	4.08 (1.19)	239	3.87 (1.22)
ADCS-ADL$_{19}$: change from baseline at Week 24 (LOCF)				
	N	Mean Change (SD)	N	Mean Change (SD)
Male	91	–1.13 (6.44)	93	0.31 (7.30)
Female	237	–1.42 (8.09)	238	–1.07 (6.74)

AChEI = acetylcholinesterase inhibitor; ADCS-ADL$_{19}$ = 19-Item Alzheimer's Disease Cooperative Study—Activities of Daily Living Inventory; CIBIC-plus = Clinician's Interview-Based Impression of Change With Caregiver Input; ER = extended release; LOCF= last observation carried forward; SIB = Severe Impairment Battery.

Cross-reference: Tables 14.4.5.1A, 14.4.5.2A, and 14.4.5.3A.

Source: Table 11.4.1.5.1-1 of sponsor's Clinical Study Report.

It appears that the numeric scores in all parameters were in favor of memantine ER/AChEI for both males and females. However, for both SIB and ADCS-ADL$_{19}$, the point estimates for males were larger than that for females.

4.1.1.3 Effects of Race

The results of the analyses of the effectiveness of memantine ER/AChEI treatment in Caucasian versus non-Caucasian patients are presented in Table 10.

Table 10: Efficacy Results by Race

Parameter	*Placebo/AChEI*		*Memantine ER/AChEI*	
SIB: change from baseline at Week 24 (LOCF)				
	N	Mean Change (SD)	N	Mean Change (SD)
Caucasian	304	0.50 (11.33)	316	2.86 (11.11)
Non-Caucasian	23	–2.26 (13.37)	16	–1.31 (11.98)
CIBIC-plus: rating scores at Week 24 (LOCF)				
	N	Mean (SD)	N	Mean (SD)
Caucasian	305	4.11 (1.17)	317	3.84 (1.21)
Non-Caucasian	23	4.04 (1.30)	16	3.81 (1.42)
ADCS-ADL$_{19}$: change from baseline at Week 24 (LOCF)				
	N	Mean Change (SD)	N	Mean Change (SD)
Caucasian	305	–1.42 (7.75)	315	–0.75 (7.00)
Non-Caucasian	23	–0.26 (6.36)	16	0.63 (5.07)

AChEI = acetylcholinesterase inhibitor; ADCS-ADL$_{19}$ = 19-Item Alzheimer's Disease Cooperative Study—Activities of Daily Living Inventory; CIBIC-plus = Clinician's Interview-Based Impression of Change With Caregiver Input; ER = extended release; LOCF = last observation carried forward; SIB = Severe Impairment Battery.

Cross-reference: Tables 14.4.5.1C, 14.4.5.2C, and 14.4.5.3C.

Source: Efficacy Results by Race

The number of non-Caucasians was very small, but the numeric changes in the SIB, CIBIC-plus, and the ADCS-ADL$_{19}$ rating were in favor of memantine ER/AChEI for both Caucasians and non-Caucasians. . However, for SIB, the point estimate for Caucasians was larger than that for non-Caucasians.

4.2 Other Subgroup Populations

The results of the analyses of the effectiveness of memantine ER/AChEI treatment in US and non-US patients are presented in Table 11.

Table 11: Effects of Country

Parameter	*Placebo/AChEI*		*Memantine ER/AChEI*	
SIB: change from baseline at Week 24 (LOCF)				
	N	Mean Change (SD)	N	Mean Change (SD)
US	83	–0.93 (12.57)	89	–0.12 (10.38)
Non-US	244	0.73 (11.08)	243	3.68 (11.29)
CIBIC-plus: rating scores at Week 24 (LOCF)				
	N	Mean (SD)	N	Mean (SD)
US	84	4.27 (1.03)	90	4.13 (1.03)
Non-US	244	4.05 (1.22)	243	3.73 (1.27)
ADCS-ADL$_{19}$: change from baseline at Week 24 (LOCF)				
	N	Mean Change (SD)	N	Mean Change (SD)
US	84	–1.17 (8.43)	89	–1.13 (7.22)
Non-US	244	–1.40 (7.40)	242	–0.51 (6.81)

AChEI = acetylcholinesterase inhibitor; ADCS-ADL$_{19}$ = 19-Item Alzheimer's Disease Cooperative Study—Activities of Daily Living Inventory; CIBIC-plus = Clinician's Interview-Based Impression of Change With Caregiver Input; ER = extended release; LOCF = last observation carried forward; SIB = Severe Impairment Battery.

Cross-reference: Tables 14.4.5.1D, 14.4.5.2D, and 14.4.5.3D.

Source: Table 11.4.1.5.4-1 of sponsor's Clinical Study Report

This reviewer conducted additional analyses to evaluate the effect of country.

For CIBIC-plus, it seems that the treatment effect was numerically similar across different countries.

For SIB, the mean baseline SIB was very similar across different countries and different treatment groups. However, the treatment effects for patients in Argentina, Chile and Mexico were much higher than that for patients in USA. Further analysis shows that the dropout rate was higher for USA than for other countries, especially for the placebo group.

Please refer to Section 3.1.2 Reviewer's Analysis or details.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The objectives of this study were to evaluate the safety, tolerability, and efficacy of memantine compared with placebo in outpatients diagnosed with moderate to severe dementia of the Alzheimer's type on a concurrent AChEI.

The primary efficacy parameters were the change from baseline to Week 24 in the SIB total score and the CIBIC-plus rating score at Week 24. The study results were considered "positive" if memantine ER demonstrated a statistically significant superiority to placebo ($p \leq .05$) on both primary efficacy parameters at Week 24 (LOCF).

Change from baseline to Week 24 (LOCF) in SIB total score was analyzed using an analysis of covariance (ANCOVA) model with the treatment group and study center as factors and the baseline SIB total score as a covariate. CIBIC-plus rating score at Week 24 (LOCF) was analyzed by the CMH statistic using modified ridit scores (the van Elteren test), controlling for study center.

At Week 24, the LS mean change in the SIB total score from baseline for the memantine ER/AChEI treatment group was 2.2 compared with a LS mean change in the placebo/AChEI treatment group of –0.4. The LS mean treatment difference of 2.6 between the two groups was statistically significant in favor of memantine ER/AChEI ($p = .001$, ITT, LOCF). The results of the OC analysis and MMRM analysis of the SIB total score were consistent with the LOCF analysis.

The mean CIBIC-plus rating for memantine ER/AChEI–treated patients was 3.8 at Week 24 (LOCF analysis) compared with 4.1 for patients treated with placebo/AChEI. The difference between treatment groups was statistically significant ($p = .008$, ITT, LOCF) in favor of memantine ER/AChEI at Week 24. The results of OC analysis at Week 24 were consistent with those of the LOCF analysis at Week 24.

This reviewer conducted the following additional analyses to investigate the country effect. Please refer to Section 3.1.2 Reviewer's Analysis for details.

- **Baseline and Change from Baseline in SIB by Country and Treatment:** The mean baseline SIB was very similar across different countries and different treatment groups. However, the treatment effects (difference between the mean change from baseline of memantine and mean change from baseline of placebo) for patients in Argentina, Chile and Mexico were 3.3, 1.5, 3.03, respectively, while the treatment effect for patients in USA was only 0.81. This indicates that even though the numeric changes in SIB were in favor of memantine group for both US and non-US patients the treatment effects of SIB for patients in Argentina, Chile and Mexico were higher than that for patients in USA.

- **Premature Discontinuation by Country and Treatment:** It appears that the dropout rate was higher for USA than for other countries, especially the dropout rate for USA placebo patients was close to 33% while the dropout rate for placebo patients in other countries were all below 15%.

- **CIBIC-plus by Country and Treatment:** It seems that mean baseline CIBIC-plus was very similar across different countries and different treatment groups. At week 24, it appears that the treatment effect was numerically similar across different countries.

In summary, for CIBIC-plus, it seems that the treatment effect was numerically similar across different countries. However, for SIB, the treatment effects for patients in Argentina, Chile and Mexico were higher than that for patients in USA.

5.2 Conclusions and Recommendations

Based on the results of Study MEM-MD-50, a therapeutic benefit for memantine ER/AChEI treatment compared to placebo/AChEI treatment was observed for the two co-primary efficacy measures, SIB (Severe Impairment Battery) and CIBIC-plus (Clinician's Interview-Based Impression of Change with Caregiver's Input). However, this reviewer is concerned with the inter-country difference in the treatment effect of SIB.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22525	ORIG-1	FOREST LABORATORIES INC	NAMENDA XR(MEMANTINE HCL)ER CAPSULES

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JINGYU J LUAN
05/07/2010

KUN JIN
05/07/2010
I concur with this review.

KOOROS MAHJOOB
05/07/2010
The NDA review was dicussed with me and my comments are incorporated in this version. I concur with this review.