CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
22-525

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data

NDA:	**22525**
Sponsor:	**Forest Laboratories**
Drug:	**Namenda® XR**
Proposed Indication:	**Alzheimer's Disease**
Material Submitted:	**New Drug Application**
Correspondence Date:	**8/20/09**
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Date Review Completed:	**6/15/10**
Reviewer:	**Ranjit B. Mani, M.D.**

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EXECUTIVE SUMMARY

Recommendation

I recommend the approval of Namenda® XR (7 mg, 14 mg, 21 mg, and 28 mg) for the treatment for moderate to severe dementia of the Alzheimer's type.

Proposed Indication

This New Drug Application (NDA) seeks the approval of a new formulation (Namenda® XR) of memantine hydrochloride for the treatment of moderate to severe dementia of the Alzheimer's type.

The proposed new formulation consists of extended-release capsules of 7 mg, 14 mg, 21 mg, and 28 mg strength, and is intended for once-daily administration.

Memantine hydrochloride (Namenda®) is currently approved as an immediate-release tablet (in 5 mg and 10 strengths) and as an oral solution (2 mg/mL) for the treatment of moderate to severe dementia of the Alzheimer's type. The currently-marketed formulations of memantine are dosed twice daily (except for the initial dose of 5 mg QD) and at a maximum dose of 10 mg BID, as stated in the approved product labeling for those formulations.

Summary Of Clinical Findings

Efficacy

The sponsor has submitted the results of a single efficacy study , MEM-MD-50, to support the approval of the proposed new formulation of memantine, also referred to below as memantine ER. This study was conducted at a total of 83 centers in 4 countries: Argentina, Chile, Mexico, and the United States.

The design and efficacy data for Study MEM-MD-50 are described further below.

Design

This was a randomized, double-blind, placebo-controlled, parallel-arm study of 24 weeks duration.

The three key criteria used for enrolling patients in this study were a diagnosis of Probable Alzheimer's Disease, using the National Institute for Neurological and Communicative Diseases and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, an entry Mini-Mental Status Examination score of 3-14, and use of an acetylcholinesterase inhibitor at a stable daily dose for at least 3 months prior to study entry.

Patients enrolled in this study were randomized to treatment with one of the following regimes for the 24-week period of double-blind, parallel-arm treatment,

- Placebo
- Memantine ER 28 mg QD

Patients assigned to memantine ER were titrated to a dose of 28 mg QD over 3 weeks, beginning with a dose of 7 mg QD and increasing by 7 mg QD every week.

The primary efficacy measures for the study were:

- A measure of cognition, the Severe Impairment Battery (SIB)
- A measure of global function, the Clinician Interview-Based Impression of Change-Plus (CIBIC-Plus).

The study had a single secondary efficacy measure, a 19-item version of the Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale (ADCS-ADL) specially designed for patients with moderate to severe dementia. Additional efficacy measures included a verbal fluency test, the Neuropsychiatry Inventory (NPI) and health outcomes assessments.

Safety measures included adverse events, vital signs, physical examinations, safety laboratory tests, and electrocardiograms.

The primary efficacy parameters were the change from baseline in the total SIB score at Week 24 and the CIBIC-Plus score at Week 24. The primary efficacy analysis was performed on the intent-to-treat dataset at Week 24, using the last-observation-carried-forward method of imputation. The intent-to-treat dataset consisted of all randomized patients who received at least one dose of study medication and had at least one post-baseline evaluation of the SIB or CIBIC-Plus.

The comparison between the 2 treatment groups on the SIB was made using a two-way analysis of covariance with treatment group and center as the 2 factors and baseline SIB score as the covariate. CIBIC-Plus scores at Week 24 were analyzed using the Cochran-Mantel-Haenszel test based on modified ridit scores controlling for study center, to compare the distributions between the two treatment groups.

The results of the study were to be considered "positive," if memantine demonstrated a statistically significant superiority to placebo on both primary efficacy parameters at Week 24.

Results

677 patients were randomized, of whom 545 patients (80.5%) received study drug. The number of patients randomized to, and completing the study in each treatment group is summarized in the following table.

Category	Placebo*	Memantine ER*	Total
Randomized	335	342	677
Completed	272	273	545

*plus acetylcholinesterase inhibitor

Patients actually enrolled in this study had a mean (standard deviation) baseline Mini-Mental Status Examination score in each treatment group as follows.

Treatment Group	Mini-Mental Status Examination score at baseline Mean (SD)
Placebo*	10.6 (2.9)
Memantine ER*	10.6 (2.9)

*plus acetylcholinesterase inhibitor

The results of the primary efficacy analysis revealed the following:

- A mean improvement from baseline (2.2 points [Least Squares means]) in the memantine ER group and a minimal worsening in the placebo group (-0.4 points [Least Squares means]), on the SIB, with the difference between the groups being statistically significant (p = 0.001). Prominent and unexplained inter-country differences were seen in the effect of both memantine ER and placebo on the SIB, but the effect of memantine ER was superior to that of placebo regardless of country.

- A mean score of 3.8 in the memantine group and 4.1 in the placebo group, a statistically significant treatment difference (p = 0.008).

Several sensitivity analyses of the SIB and CIBIC-Plus supported the results of the primary efficacy analysis.

No statistically significant treatment difference was seen for the ADCS-ADL when analyzed in a manner similar to the primary efficacy analysis for the SIB.

Reviewer's Conclusion

The results of Study MEM-MD-50 do provide evidence for the efficacy of Namenda® XR capsules in a dose of 28 mg QD over placebo when used concomitantly with a stable dose of an acetylcholinesterase inhibitor in the treatment of moderate to severe dementia of the Alzheimer's type.

Safety

The safety data reviewed under this application were submitted in the following.

The Integrated Summary of Safety, submitted with the original application
The 120-Day Safety Update

Each of these components is further summarized below.

Integrated Summary Of Safety

Studies included in the Integrated Summary of Safety were in 3 groups, as listed below.

- Group 1, comprising studies of memantine ER in patients with Alzheimer's Disease and including:
    - The randomized, double-blind, placebo-controlled study MEM-MD-50
    - The following open-label uncontrolled studies
        - MEM-MD-51, a 52-week free-standing (i.e., non-extension) study
        - MEM-MD-54, a 28-week extension to MEM-MD-50
        - MEM-MD-82, a still-ongoing extension to MEM-MD-51 and MEM-MD-82.
- Group 2, consisting of studies of the immediate-release formulation of memantine at doses > 20 mg/day (and as high as 80 mg/day). These included controlled and uncontrolled studies in neuropathic pain and bipolar disorder and a drug-drug interaction study with bupropion.
- Group 3, consisting of clinical pharmacology studies of memantine ER.

A total of 775 patients with Alzheimer's Disease and 114 healthy subjects were exposed to memantine ER in the Group 1 and Group 3 studies.

Safety outcome measures in the majority of these studies included adverse events, vital signs, safety laboratory tests, and electrocardiograms.

Information from the above studies was supplemented in the Integrated Summary of Safety by a summary of post-marketing safety data for the immediate-release formulation of memantine and a review of the medical literature by the sponsor.

The cut-off date for data included in the Integrated Summary of Safety was September 30, 2008.

In Study MEM-MD-50, the incidence of all treatment-emergent adverse events and deaths was similar in the 2 treatment groups, while the incidence of serious adverse events and adverse events leading to treatment discontinuation was slightly higher in the memantine ER group than in the placebo group. The only individual adverse event that was substantially more common in the memantine

group than in the placebo group was dizziness which was seen in 4.7% of those treated with memantine as opposed to 1.5% of those treated with placebo. The sponsor-provided descriptions of deaths and serious adverse events that occurred in this study suggested that they were most unlikely to be attributable to memantine. The same applies to adverse events that led to treatment discontinuation, with the exception of dizziness which was more common in those treated with memantine than in those treated with placebo. Other safety data analyzed, including vital signs, safety laboratory tests, and electrocardiograms showed no areas of concern when comparing the memantine group with the placebo group.

Overall data in the Integrated Summary of Safety indicated that the safety profile of the extended-release formulation of memantine, administered in a dose up to 20 mg QD, was broadly similar to that of the immediate-release formulation administered in a dose up to 10 mg BID.

120-Day Safety Update

The contents of the Update included information from the following sources:

- A clinical pharmacology study (MEM-PK-24) completed after the original submission of this application
- The ongoing open-label extension study MEM-MD-82
- A literature search
- Post-marketing experience with the immediate-release formulation of memantine.

While safety data from Study MEM-PK-24 included information about adverse events, vital signs, safety laboratory tests and electrocardiograms, those from Study MEM-MD-82 included only a listing of deaths and other serious adverse events, as well as a description of a single patient who experienced a drug overdose.

The cut-off date for data included in the Update was June 30, 2009.

The contents of the 120-Day Safety Update did not raise any concerns pertinent to the safety and tolerability of memantine ER administered in a dose of 28 mg QD to patients with moderate to severe Alzheimer's Disease.

Pharmacokinetics

The sponsor's summary of the clinical pharmacokinetics of Namenda® XR is based primarily on the results of Study MEM-PK-18, supplemented by the results of Studies MEM-PK-13, MEM-PK-17, and MEM-PK-23. Extended-release formulations of memantine, including, but not limited to, Namenda® XR, were evaluated in all 4 studies.

Study MEM-PK-23 compared the steady-state pharmacokinetics of Namenda® XR capsules in a dose of 28 mg QD with those of Namenda® tablets in a dose of 10 mg BID. As might have been expected:

- Exposure, based on C_{max} and AUC was higher with the extended-release formulation than with the immediate-release formulation.
- Terminal half-life was similar for both formulations
- The T_{max} was greater for the extended-release formulation than for the immediate-release formulation.

The Office of Clinical Reviewer of this submission has found the data submitted by the sponsor to be acceptable in support of the approval of all 4 proposed strengths of Namenda® XR. Among her observations are the following:

- Namenda® XR is bioequivalent under both fed and fasted conditions.
- A patient taking a stable dose of Namenda® tablets of 10 mg BID may transition directly the next day to Namenda® XR capsules taken in a dose of 28 mg QD, based on actual and simulation data.
- A moderate dose dumping effect of alcohol observed *in vitro* is unlikely to be of serious consequence.

Overall Conclusions

The efficacy, safety and pharmacokinetic data for Namenda® XR submitted with the current application support its approval for the treatment of moderate to severe dementia of the Alzheimer's type (moderate to severe Alzheimer's Disease).

1. Background

This New Drug Application (NDA) seeks the approval of a new formulation (Namenda® XR) of memantine hydrochloride for the treatment of moderate to severe dementia of the Alzheimer's type. [Note that the term "moderate to severe Alzheimer's Disease" is considered identical to "moderate to severe dementia of the Alzheimer's type" for regulatory purposes].

The proposed new formulation consists of extended-release capsules of 7 mg, 14 mg, 21 mg, and 28 mg strength, and is intended for once-daily administration.

Memantine hydrochloride (Namenda®) was initially approved, as a tablet formulation, on October 16, 2003, for the treatment of moderate to severe dementia of the Alzheimer's type, under NDA 21487, submitted by the current sponsor. Please refer to reviews of that application for full details. Currently, tablets of that formulation are marketed in 5 mg and 10 mg strengths.

An oral solution formulation of Namenda® (memantine hydrochloride [2 mg/mL]) was then approved for the treatment of moderate to severe dementia of the Alzheimer's type on April 18, 2005. Please also refer to reviews of that application for further details.

The currently-marketed formulations of memantine are dosed twice daily (except for the initial dose of 5 mg QD) and at a maximum dose of 10 mg BID, as per the approved labeling for those formulations.

The key efficacy trial supporting this application (MEM-MD-50), as well as other clinical trials, were conducted under IND 33392.

A Supplemental NDA (NDA 21487; SE1-003) seeking the approval of Namenda® tablets as a treatment of mild to severe dementia of the Alzheimer's type was submitted on September 23, 2004. The application was not approved, the final Not-Approvable letter being issued on May 23, 2006.

The sponsor notes that in this application:

- The term "Namenda® XR" is used interchangeably with the terms "Namenda® ER" and "Memantine ER"

- The currently-approved formulations of memantine are referred to with the "IR" (i.e., immediate-release) appellation.

In this review, the term "modified-release" is also used interchangeably with "extended-release" and the term "memantine IR" is used for the currently-approved immediate-release formulation of memantine.

2. Contents Of Submission

This New Drug Application has been submitted in Electronic Common Technical Document (eCTD) format, in accordance with the Code of Federal Regulations and the pertinent Agency guidance document.

The application is comprised of the following main items.

- The original submission of this application (sponsor letter dated August 20, 2009) containing the following:

    - Clinical and statistical data (with Case Report Forms and Case Report Tabulations)
    - Chemistry, manufacturing, and controls data
    - Clinical pharmacology data
    - Common Technical Document summaries
    - Financial disclosure certification
    - Request for pediatric study waiver
    - Draft Package Insert exclusive to Namenda® XR (with annotations).
    - Other items.

- The 120-Day Safety Update for this application, dated December 17, 2009. (A proposal regarding the contents of the 120-Day Safety Update was submitted by the sponsor on October 30, 2009).

    The submission that contained the 120-Day Safety Update also contained the following:

    - Pharmacokinetic simulation data to support the switch from the immediate-release tablet formulation to the extended-release capsule formulation
    - The completed report for a pharmacokinetic study that was not described in the original NDA submission
    - Updated labeling text with full annotations
    - An alternate packaging design for the patient starter kit/titration pack
    - An addendum to the original Integrated Summary of Safety to include new Post-Marketing Safety data.

- Additional Chemistry, Manufacturing, and Controls data submitted September 14, 2009, September 17, 2009, January 14, 2010, April 2, 2010, and April 16, 2010. These submissions were either spontaneous or in response to requests for information from the Agency

- Additional Clinical Pharmacology data submitted on October 19, 2009, December 2, 2009, January 12, 2010, and March 12, 2010 in response to requests for information from the Agency

- A proprietary name request submitted on October 6, 2009 in response to an Agency communication, with further submissions in the same regard on November 2, 2009, and November 6, 2009.

- A revised Pediatric Study Waiver request submitted on March 25, 2010

- A statement of clarification regarding a discrepancy noted in a clinical data listing for the main efficacy study in this application. This discrepancy was noted during an Agency inspection.

- Responses to other requests for information from the Agency regarding the following items: investigator information; the final protocol for the main efficacy study (MEM-MD-50) contained in this application; financial disclosure forms; and the analysis of a primary efficacy parameter for Study MEM-MD-50.

3. Contents Of Review

The contents of this submission have been reviewed under the following primary headings and in the same order as below:

- History of development of Namenda® XR
- Summary of all clinical studies used to support this application
- Description of main controlled clinical trial of Namenda® XR in Alzheimer's Disease (Study MEM-MD-50)
- Integrated Summary of Safety
- 120-Day Safety Update
- Sponsor's summary of clinical pharmacokinetics of Namenda® XR
- Description of Namenda® XR Drug Product
- Summary of additional agency reviews of current application
- Review of labeling
- Financial disclosure certification
- MEM-MD-50 study site inspection report
- Overall conclusions
- Recommendation.

4. History Of Development Of Namenda® XR

4.1 Rationale For Development Of Namenda® XR

The stated rationale for the development of the extended-release memantine capsule as a treatment for moderate to severe Alzheimer's Disease is that Namenda® XR is intended to be administered once daily only, whereas the currently-approved immediate-release tablet formulation is administered twice daily. Once-daily administration is considered more convenient for both patient and caregiver.

The sponsor-stated primary objective when developing the extended-release formulation of memantine was to provide a rate of absorption that was slower than that of the immediate-release formulation while using a dosage that would provide a higher systemic exposure than that achieved with the currently-approved twice daily administration of the immediate-release formulation.

4.2 Interactions Between Sponsor And Agency Regarding Development of Extended-Release Namenda® Capsule

A single randomized, double-blind, placebo-controlled, parallel-arm study, MEM-MD-50, forms the basis for demonstrating the efficacy of the extended-release formulation of memantine in the current application. The protocol for this study was submitted as serial #452 under IND 33392 on June 7, 2005, was then formally reviewed by this Division, and comments were conveyed to the sponsor in a letter dated December 9, 2005. The Statistical Analysis Plan for this study was formally submitted as serial #515 under IND 33392 on May 24, 2006, and was again formally reviewed by this Division; no comments were felt to be needed at that time.

The Agency agreed after review of the protocol and Statistical Analysis Plan described in the above submissions that the single study MEM-MD-50 would be sufficient in itself to provide evidence for the efficacy of the extended-release formulation of memantine in moderate to severe Alzheimer's Disease.

The planned contents and format of the current NDA were described by the sponsor in a Briefing Package for a Pre-NDA meeting submitted as Serial #587 under IND 33392 on December 12, 2007. After preliminary responses to the sponsor's questions were conveyed by the Agency to the sponsor, the meeting, scheduled for January 17, 2008, was cancelled at the sponsor's request.

Please see my review of the above submissions and the related communications with the sponsor for further details.

5. Summary Table For All Clinical Studies Used To Support This Application

Clinical studies supporting this application fall into 3 groups:

- Efficacy and safety studies of the extended-release formulation of memantine in patients with Alzheimer's Disease. These studies are designated in this submission as Group 1 studies.

- Clinical studies in populations other than those with Alzheimer's Disease (those with painful diabetic neuropathy, post-herpetic neuralgia, and acute mania associated with bipolar I disorder) in which doses of the immediate-release formulation of memantine exceeding the currently-approved maximum dose of 20

mg/day were administered; in these populations, the doses investigated ranged from 30 to 80 mg/day. Also included in this group is a drug-drug interaction study between memantine and bupropion in healthy subjects in doses of immediate-release memantine up to 30 mg/day was used. These studies are designated in this submission as Group 2 studies.

- Clinical Pharmacology studies of the extended-release formulation of memantine. These studies are designated in this submission as Group 3 studies.

The sponsor's table summarizing all these studies is copied below.

Type of Study	*Study Identifier*	*Location of Study Report*	*Objective(s) of the Study*	*Study Design and Type of Control*	*Test Product(s); Dose Regimen; Route of Administration*	*Number of Subjects**	*Healthy Subjects or Diagnosis of Patients*	*Duration of Treatment*	*Study Status; Type of Report*
BA	MEM-PK-13 An Open-Label, Randomized, Four-Way Crossover Bioavailability Study Comparing Memantine Modified Release Capsules to Immediate Release Tablet in Human Subjects	Module 5.3.1.2.1	To compare the bioavailability of three memantine extended release (ER) capsules to an immediate release (IR) tablet	Single-center, randomized, open label, single-dose, four-way crossover study	20-mg IR tablet; 40-mg single dose; oral 40-mg ER capsule, Formulation I; single dose; oral 40-mg ER capsule, Formulation II; single dose; oral 40-mg ER capsule, Formulation III; single dose; oral	24	Healthy subjects	Single dose (4 days; 1 day per treatment)	Completed; Full
BA/BE	MEM-PK-17 A Randomized, Open-Label, Three-Way Crossover, Single-Dose Bioequivalence and Food-Effect Study of the Clinical Formulation and the to-Be-Marketed Modified-Release Formulation of Memantine HCl in Healthy Human Subjects	Module 5.3.1.2.2	1. To evaluate the bioequivalence of the memantine ER (ER I, Inwood) clinical formulation and the to-be-marketed ER capsule formulation (ER II, Ireland) 2. To evaluate the effect of food on the bioavailability of the memantine to-be-marketed ER capsule formulation (ER II, Ireland)	Single-center, randomized, open-label, single-dose, three-way crossover, study	28-mg ER capsule (clinical formulation, Inwood); single dose, fasted; oral 28-mg ER capsule (to-be-marketed, Ireland); single dose, fasted and fed; oral	24	Healthy subjects	Single dose (3 days; 1 day per treatment))	Completed; Full
Type of Study	*Study Identifier*	*Location of Study Report*	*Objective(s) of the Study*	*Study Design and Type of Control*	*Test Product(s); Dose Regimen; Route of Administration*	*Number of Subjects**	*Healthy Subjects or Diagnosis of Patients*	*Duration of Treatment*	*Study Status; Type of Report*
BA/PK	MEM-PK-23 Evaluation of memantine pharmacokinetics following single- and multiple-dose administration of a memantine HCl extended-release capsule and immediate-release tablet in human subjects	Module 5.3.1.2.3	Primary objective: To evaluate the pharmacokinetics of memantine at steady state following multiple doses of 28-mg memantine ER capsules once daily and 10-mg IR tablets twice daily. Secondary objective: To evaluate the pharmacokinetics of memantine following single dose administration of 28-mg ER capsule and 10-mg IR tablet.	Single-center, randomized, open-label, multiple-dose, two-way crossover study	10-mg IR tablet; single and multiple dose every 12 hours; oral 14-mg, 21-mg and 28-mg ER capsules; single and multiple dose every 24 hours; oral	26	Healthy subjects	54 days (27 days per treatment)	Completed; Full
PK	MEM-PK-18 A Multiple-Dose, Open-Label Study Evaluating the Pharmacokinetics of a Memantine HCl Modified-Release (MR) Capsule at Steady-State in Healthy Human Subjects	Module 5.3.3.1.1	To evaluate the steady-state pharmacokinetics of memantine following administration of an ER capsule formulation of memantine HCl in healthy subjects.	A single-center, single-treatment, open-label, multiple-dose study	7-mg, 14-mg, 21-mg and 28-mg ER capsules; multiple dose every 24 hours; oral	24	Healthy subjects	29 days	Completed; Full

Type of Study	*Study Identifier*	*Location of Study Report*	*Objective(s) of the Study*	*Study Design and Type of Control*	*Test Product(s); Dose Regimen; Route of Administration*	*Number of Subjects**	*Healthy Subjects or Diagnosis of Patients*	*Duration of Treatment*	*Study Status; Type of Report*
Efficacy and Safety	MEM-MD-50 A Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Memantine in Patients with Moderate-to-Severe Dementia of the Alzheimer's Type	Module 5.3.5.1.1	To evaluate the safety, tolerability, and efficacy of memantine compared with placebo in outpatients with moderate to severe dementia of the Alzheimer's type on a concurrent acetylcholinesterase inhibitor (AChEI)	Multinational, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group	Placebo Memantine 7-mg Extended Release (ER) capsules administered orally once a day. Total daily dose titrated to 28-mg	676 (335 Pbo/ 341 Mem)	Patients with moderate to severe Alzheimer's disease	26 Wks (1-2 weeks Pbo followed by 24 weeks double-blind mem)	Completed; Full
Safety	MEM-MD-51 An Open-Label Evaluation of the Safety of Memantine in Patients with Moderate-to-Severe Dementia of the Alzheimer's Type	Module 5.3.5.2.1	To evaluate the safety and tolerability of memantine in outpatients with moderate-to-severe dementia of the Alzheimer's type	Open-Label, Multicenter	Group 1: Memantine 7-mg Extended Release (ER) capsules, titrated to 28 mg/day (QD), oral administration Group 2: Memantine 28-mg Extended Release (ER) capsules, 28-mg/day (QD), oral administration	164 (Group 1: 128, Group 2: 36)	Patients with moderate-to-severe Alzheimer's disease	52 Wks	Completed; Full
Safety	MEM-MD-54 An Open-Label Extension Study Evaluating the Safety and Tolerability of Memantine in Patients with Moderate-to-Severe Dementia of the Alzheimer's Type	Module 5.3.5.2.2	To evaluate the safety and tolerability of memantine in outpatients with moderate-to-severe dementia of the Alzheimer's type	Multi-National, Multicenter, Open-Label, Extension Study	Memantine 7-mg Extended Release (ER) capsules, titrated to 28mg/day (QD), oral administration	491 (245 Pbo/Mem, 246 Mem/Mem)	Patients with moderate-to-severe Alzheimer's disease	28 weeks	Completed; Full

Type of Study	*Study Identifier*	*Location of Study Report*	*Objective(s) of the Study*	*Study Design and Type of Control*	*Test Product(s); Dose Regimen; Route of Administration*	*Number of Subjects**	*Healthy Subjects or Diagnosis of Patients*	*Duration of Treatment*	*Study Status; Type of Report*
Efficacy and Safety	MEM-MD-06A Double-Blind Comparison of Memantine and Placebo in the Treatment of Chronic Pain in Patients with Diabetic Neuropathy	Module 5.3.5.4.1	To compare the efficacy and safety of Memantine and Placebo in diabetic patients with painful peripheral neuropathy.	Multicenter, Randomized, Double-Blind, Parallel Group, Flexible-Dose	Placebo Memantine 5-mg Immediate Release (IR) tablets, started at 10-mg/day, titrated to 40-mg/day over first 4 weeks, administered orally	525 (266 Pbo/259Mem)	Diabetic patients with neuropathic pain	17 weeks (1 week Pbo followed by 16 weeks double-blind mem)	Completed; Full
Safety and Long-Term Efficacy	MEM-MD-06B Open-Label Extension of Memantine Treatment in Patients with Painful Diabetic Neuropathy	Module 5.3.5.4.2	To assess the safety of up to one (1) year of open-label Memantine treatment in diabetic patients with painful peripheral neuropathy. A secondary objective was to investigate the long-term efficacy of Memantine treatment in diabetic patients with	Multicenter, Open-Label Extension Study	Memantine 5-mg Immediate Release (IR) tablets, started at 10-mg/day, titrated to 40-mg/day over first 4 weeks, administered orally	393 (210 Pbo/Mem, 183 Mem/Mem)	Diabetic patients with neuropathic pain	40 weeks	Completed; Full
Efficacy and Safety	Comparing the Efficacy and Safety of Daily Doses of 40 mg, 60 mg, and 80 mg of Memantine in Patients with Painful Diabetic Neuropathy	Module 5.3.5.4.3	objective was to investigate the safety and tolerability of these daily doses of Memantine in diabetic patients with painful peripheral neuropathy	Double-Blind, Parallel Group, Fixed-Dose, Extension Study	(IR) tablets, daily doses of 40-mg, 60-mg, or 80-mg; adminstered orally	(40-mg: 26, 60-mg: 25, 80-mg: 26)	patients with neuropathic pain	16 weeks	Full

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Type of Study	*Study Identifier*	*Location of Study Report*	*Objective(s) of the Study*	*Study Design and Type of Control*	*Test Product(s); Dose Regimen; Route of Administration*	*Number of Subjects**	*Healthy Subjects or Diagnosis of Patients*	*Duration of Treatment*	*Study Status; Type of Report*
Efficacy and Safety	MEM-MD-19 Randomized, Double-Blind, Placebo-Controlled, Flexible-Dose Study of the Efficacy and Safety of Memantine in Comparison to Gabapentin in Patients with Painful Diabetic Neuropathy	Module 5.3.5.4.4	To compare the efficacy and safety of Memantine, Gabapentin, and Placebo in diabetic patients with painful peripheral neuropathy	Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Flexible-Dose	Placebo Gabapentin (300 and 400 mg capsules administered orally) Memantine 5-mg, 10-mg, and 20-mg Immediate Release (IR) tablets; started at 10-mg/day and escalated to 60-mg/day over first 5 weeks of double-blind treatment	158 (52 Pbo, 55 GAB, 51 Mem)	Diabetic patients with neuropathic pain	18 weeks (1 week Pbo followed by 17 weeks double-blind mem)	Completed; Full
Efficacy and Safety	MEM-MD-20 Randomized, Double-Blind, Placebo-Controlled, Flexible-Dose Study of the Efficacy and Safety of Memantine in Comparison with Gabapentin in Patients with Postherpetic Neuralgia	Module 5.3.5.4.5	To compare the efficacy and safety of Memantine with Gabapentin, and Placebo in patients with Postherpetic Neuralgia (PHN)	Multicenter, Randomized, Double-Blind, Placebo-Controlled, Flexible-Dose	Placebo Gabapentin (300 and 400 mg capsules administered orally with a maximum daily dosage of 2400 mg) Memantine 5-mg, 10-mg, and 20-mg Immediate Release (IR) encapsulated tablets; started at 10 mg/day and escalated to 60 mg/day over first 5 weeks of double-blind treatment	145 (46 Pbo, 48 Gab, 51 Mem)	Patients with Postherpetic Neuralgia (PHN)	18 weeks (1 week Pbo followed by 17 weeks double-blind mem)	Completed; Full

Type of Study	*Study Identifier*	*Location of Study Report*	*Objective(s) of the Study*	*Study Design and Type of Control*	*Test Product(s); Dose Regimen; Route of Administration*	*Number of Subjects**	*Healthy Subjects or Diagnosis of Patients*	*Duration of Treatment*	*Study Status; Type of Report*
Safety and Efficacy	MEM-MD-27 A Pilot Evaluation of the Safety and Efficacy of Memantine in Patients with Acute Mania Associated with Bipolar I Disorder	Module 5.3.5.4.6	To evaluate the safety, efficacy, and tolerability of open-label Memantine monotherapy (20, 30, and 40mg/d) in the acute management of adults with Bipolar I Disorder hospitalized for mania	Multicenter, Open-Label, Cohort-Sequential, Dose-Escalation, Inpatient	Memantine 10-mg Immediate Release (IR) tablets, 20- to 50-mg/day, administered orally Cohort 1: a targeted dose of 20 to 30 mg/day; Cohort 2: a targeted dose of 20 to 40 mg/day Cohort 3: a targeted dose of 30 to 50 mg/day	35 (Cohort 1: 12, Cohort 2: 12, Cohort 3: 11)	Patients with acute mania associated with Bipolar I Disorder	3 weeks	Completed; Abbreviated
Safety/PK	MRZ 90001-0519/1 A Single Centre, Randomized, Double-Blinded, Placebo-Controlled, Multiple Dose, Three-Period One-Sequence Cross-Over Study of the Pharmacokinetic Interaction of 30 mg Memantine on CYP2B6 with its Substrate Bupropion in Healthy Male Volunteers	Module 5.3.5.4.7	Investigation of the effect of memantine on CYP2B6 by the use of bupropion hydroxylation as a specific probe reaction for CYP2B6 activity. A secondary objective was to evaluate the pharmacokinetic interactions of bupropion and memantine.	Randomized, Double-Blind, Placebo-Controlled, Multiple Dose, Three-Period, One-Sequence Cross-Over Study	100 mg Wellbutrin (bupropion HCl) tablet; single dose on Day 1 and Day 27; oral Placebo; multiple dose twice daily; oral 10 mg Axura (Memantine HCl) tablet; titrated from 5 mg twice daily to 15 mg twice daily; oral	24 (8 Pbo/ 16 Mem)	Healthy Males	30 days (26 days on mem)	Completed; Full

* = Safety Population

BA = Bioavailability; BE = Bioequivalence; Pbo = Placebo; Mem = Memantine; Gab = Gabapentin; ER = Extended Release; IR = Immediate Release

6. Description Of Main Controlled Clinical Trial Of Namenda® XR In Alzheimer's Disease (Study MEM-MD-50)

6.1 Final Study Protocol

6.1.1 Title

A Randomized, Double-Blind, Placebo-Controlled Evaluation Of The Safety And Efficacy Of Memantine In Patients With Moderate-To-Severe Dementia Of The Alzheimer's Type

6.1.2 Primary Objective

To evaluate the safety, tolerability, and efficacy of memantine versus placebo in outpatients diagnosed with moderate to severe Alzheimer's Disease on a concurrent acetylcholinesterase inhibitor.

6.1.3 Design, Duration, Sample Size, And Duration

This is a randomized, double-blind, placebo-controlled, parallel-arm study.

The study will have 2 treatment arms:

- Memantine (using the modified-release formulation)
- Placebo.

The study has 24 weeks of double-blind, parallel-arm treatment, preceded by 1 to 2 weeks of single-blind placebo treatment.

600 patients are to be randomized in equal proportions to the 2 treatment groups

Memantine will be used in this study in the form of modified-release capsules of 7 mg strength.

Dosing with memantine or matching placebo will be once daily.

All patients assigned to memantine will be titrated to a target dose of 28 mg/day as follows.

Week	Dose of modified-release memantine
1	7 mg QD
2	14 mg QD
3	21 mg QD
4	28 mg QD

Adjustments to the dose and titration schedule are to be permitted for those with dose-limiting adverse events.

Patients unable to tolerate a dose of 21 mg/day of memantine by Week 8 will be discontinued from the trial.

6.1.4 Key Inclusion Criteria

- Male or female outpatients ≥ 50 years of age
- If female, must be at least 2 years post-menopausal or surgically sterile
- Probable Alzheimer's Disease, according to NINCDS-ADRDA and DSM-IV-TR criteria
- Mini-Mental Status Examination score of 3-14 at entry

- CT or MRI of brain, within 12 months prior to randomization, compatible with a diagnosis of Probable Alzheimer's Disease
- Physical examination, laboratory data and electrocardiogram results form screening visit must be normal or abnormal findings must be judged not to be clinically significant
- Ability to walk, at least with an assistive device
- Vision and hearing sufficient to comply with testing
- Informed consent from patient, or legal guardian (if applicable) and a caregiver
- **Use of an acetylcholinesterase inhibitor at a stable daily dose for at least 3 months prior to study entry.**

6.1.5 Key Exclusion Criteria

- Vitamin B_{12} or folate deficiency that is considered clinically significant
- Clinically significant and active pulmonary, gastrointestinal, renal, hepatic, endocrine or cardiovascular system disease. Patients with controlled hypertension, partial or complete right bundle branch block, and pacemakers may be included in the study. Patients with thyroid disease may also be included in the study, provided they are euthyroid on treatment. Patients with controlled diabetes mellitus may also be included
- Other neurological disorders, including but not limited to stroke, Parkinson's Disease, seizure disorder, or head injury with loss of consciousness within the past 5 years
- DSM-IV Axis I disorder other than Alzheimer's Disease, including amnestic disorders, schizophrenia or schizoaffective disorder, bipolar disorder, current major depressive episode, psychosis, panic, or post-traumatic stress disorder
- CT scan or MRI evidence of hydrocephalus, stroke, a space-occupying lesion, cerebral infection, or any other clinically significant central nervous system disease
- Dementia complicated by another organic disease
- Dementia complicated by the presence of predominant delusions
- Patients with a hematological malignancy or solid tumor who are undergoing treatment, who have completed treatment within the past 6 months, or who still have evidence of active disease
- Modified Hachinski Ischemic Scale score of > 4 at screening
- Sitting systolic blood pressure > 180 mm Hg or < 90 mm Hg; sitting diastolic blood pressure > 105 mm Hg or < 50 mm Hg (at screening or baseline visits)
- Known or suspected history of alcohol or drug abuse within the preceding 10 years
- Patients or caregivers unwilling or unable to abide by visit schedule and other study requirements
- Any condition that would, in the opinion of the investigator, make the patient or caregiver unsuitable for the study

- Participation in an investigational drug study or use of an investigational drug within 30 days (or 5 half-lives of that drug, whichever is longer) of the screening visit
- Treatment with a depot typical neuroleptic within 6 months of the screening visit
- Positive test for a prohibited medication on the urine drug screen
- Use of memantine within 1 month of screening
- Known hypersensitivity to memantine, neramexane, rimantadine, or amantadine
- Use of any unapproved concomitant medication that cannot be discontinued or changed to an allowable alternative prior to the minimum allowable interval before baseline
- Patients who are likely to be placed in a nursing home within the next 6 months
- Patients whose acetylcholinesterase inhibitor therapy is likely to be interrupted or discontinued within the next 6 months
- Patients in whom acetylcholinesterase inhibitor treatment is contraindicated
- Treatment with more than one acetylcholinesterase inhibitor
- Patients who cannot perform a minimum of one item of the Severe Impairment Battery at baseline.

6.1.6 Concomitant Medications

A comprehensive table listing permitted and prohibited concomitant medication is copied below from the final study protocol.

Drugs Allowed (Y) and Drugs Not Allowed (N) as Concomitant Medications

Drug Class	*Drug Usage*		*Restrictions*
	Episodic (p.r.n.)	*Chronic*	
Acetylcholinesterase inhibitors	N	Y	All AChEIs are allowed and should have been taken daily on a stable dose for 3 months prior to Screening (Visit 1). It is preferred that the dose be kept stable during the study. Patients may take only one AChEI at a time during the study. Any changes in AChEI therapy must be discussed with the Study Physician.
Analgesics	Y	Y	Only non-opioid-containing analgesics may be administered chronically. Combination products containing codeine, hydrocodone or oxycodone may be used on a p.r.n. basis only (not to exceed 5 consecutive days) and not within 24 hours of a clinic visit.
Anesthetics *General* *Local*	 N Y	 N N	If patient requires surgery contact Study Physician.
Anorexics	N	N	
Antacids	Y	Y	Cisapride is not allowed. Calcium or aluminum containing compounds such as Maalox are allowed prn only and only if given at least 2 hours before or after study drug administration.
Antianginal agents	Y	Y	
Antiarrhythmics	Y	Y	Only digoxin, sotalol, and amiodarone are allowed. Dose must be stable for 3 months prior to Screening. For other medications, contact Study Physician for prior approval.
Antiasthma agents	Y	Y	
Antibiotics	Y	Contact Study Physician	Linezolid use is not allowed.

Drug Class	*Drug Usage*		*Restrictions*
	Episodic (p.r.n.)	*Chronic*	
Anticholinergics	N (See Qualifications)	N	Benztropine and tolteradine are allowed but dose must be stable 1 month prior to Screening. Only anticholinergics biperiden and trihexyphenidyl may be used acutely, but only briefly and not within 48 hours prior to clinic visit. Belladonna alkaloids are also allowed for short-term use, but not within 48 hours of a clinic visit. If patient is taking any of these medications for other reasons, contact the Study Physician.
Anticonvulsants	N	Y	Lamotrigine and topiramate not allowed. Other anticonvulsants used for conditions other than for seizures, are allowed provided the dose has been kept stable for 1 month prior to Screening.
Antidepressants	N	Y	Only SSRIs, trazadone, bupropion, and the SNRIs duloxetine and venlafaxine are allowed. Dose and medication must be stable for 1 month prior to Screening. Monoamine oxidase inhibitors not allowed. For tricyclic use, please contact Study Physician.
Antiemetics	Y	Y	Metoclopramide, scopolamine and sedating (H1) antihistamines are not allowed.
Antifungal agents *Systemic* *Topical*	 N Y	 N Y	
Antihistamines	Y	Y	Sedating (H1) antihistamines are not allowed. Use nonsedating agents such as fexofenadine, cetirizine, loratadine, and desloratadine. Doxepin is not allowed.
Antihypertensives	N	Y	Reserpine, clonidine, prazosin, guanabenz, guanfacine, and methyldopa are not allowed. For all others (such as β-blockers), medication and dose must be stable for 1 month prior to Screening.
Anti-inflammatory	Y	Y	Indomethacin and systemic corticosteroids are not allowed.

Drug Class	*Drug Usage*		*Restrictions*
	Episodic (p.r.n.)	*Chronic*	
Anti-neoplastics	N	Y	Hormone modulators such as tamoxifen, aromatase inhibitors, (including letrozole), Lupron, anti-androgen agents, LHRH antagonists are allowed. Dose must be stable for 3 months prior to Screening. Other chemotherapeutics are not allowed.
Anti-obesity	N	Y	Only orlistat is allowed. Dose must be stable for at least 1 month prior to Screening. For all others please contact Study Physician.
Anti-Parkinson's	N	N	For antiparkinsonian agents prescribed for indications other than Parkinson's (e.g. topinerole for restless leg syndrome) please contact Study Physician.
Antipsychotics	N	Y	Atypical antipsychotics are allowed. The dose must be stable for at least 1 month prior to Screening. Use of the following Typical agents are allowed: haloperidol, fluphenazine and chlorpromazine.
Antiviral agents	Y	Contact Study Physician	Use of nucleoside analogues are allowed (valcyclovir, famciclovir and acyclovir). Amantadine and rimantadine are not allowed during the study. Call Study Physician for use of ostelamivir or other agents.
Anxiolytics	Y (See Restrictions)	Y (See Restrictions)	Buspirone is allowed. Lorazepam, alprazolam or diazepam may be used episodically, but only briefly, and use is not permitted 48 hours prior to clinical testing. Lorazepam, alprazolam and diazepam may be used chronically if stable for one month prior to Screening. If used chronically, no dosing modification should occur 48 hours prior to testing. For use of other benzodiazepines, contact the Study Physician.
Cough/Cold preparations	Y	Contact Study Physician	Decongestants containing dextromethorphan or narcotics are not allowed. Preparations containing pseudoephedrine or phenylpropanolamine are not allowed within 24 hours of a study visit. *See Antihistamines*

Drug Class	*Drug Usage*		*Restrictions*
	Episodic (p.r.n.)	*Chronic*	
Diuretics	Y	Y	One month stability prior to Screening preferred.
Gingko biloba	N	Y	Dose must be stable for at least one month prior to Screening.
H_2 blockers	Y	Y	
Hormones	N	Y	Medication and dose must be stable for 3 months prior to Screening.
Hormone suppressants	N	Y	Only finasteride is allowed. Dose must be stable for 3 months prior to Screening. Contact Study Physician for all other hormonal antisuppressant use.
Hypoglycemic agents	Y	Y	
Muscle relaxants	N	N	
Psychotropic drugs not otherwise specified (including herbal products)	N	N	
Sedatives/hypnotics	Y	Y	Only zolpidem (maximum dose 10 mg/day), zaleplon (maximum dose 10 mg/day), zopiclone (maximum dose 7.5 mg/day), eszopiclone (maximum dose 3 mg/day) and trazodone (maximum dose 100 mg/day) are allowed for sleep. Avoid introduction of these agents or any dose modifications 48 hours prior to cognitive testing. Contact Study Physician for brief use of benzodiazepines.
Steroids *Systemic* *Topical* *Inhalant*	 N Y Y	 Y Y Y	For special circumstances call Study Physician.
Stimulants	N	N	Includes modafinil, amphetamines, any methylphenidate preparations, pemoline.
Tocopherol (vitamin E)	N	Y	Dose must be stable for at least 1 month prior to Screening.
Vaccines	Y	N/A	

Note that the study protocol states the following in reference to concomitant acetylcholinesterase inhibitor therapy: "*It is preferred that the dose be kept stable during the study. Patients may take only one acetylcholinesterase inhibitor at a time during the study. Any changes in acetylcholinesterase inhibitor therapy must be discussed with the Study Physician*."

6.1.7 Schedule

The study schedule is summarized in the following table, which I have copied from the final study protocol. The table is self-explanatory.

	Visit 1 (Screening)	*Visit 2 (Baseline)*	*Visit 3*	*Visit 4*	*Visit 5*	*Visit 6*	*Visit 7 (Final)*
	Run-in Phase	**Double-Blind Treatment Phase**					
Study Week	*-2 to -1*	*0*	*4*	*8*	*12*	*18*	*24*
Informed Consent	x						
Medical/Neurological and Surgical History	x						
NINCDS-ADRDA and DSM-IV-TR criteria	x						
Physical/Neurological Exam	x						x
Vital Signs[1, 2]	x[1]	x	x	x	x	x	x[1]
ECG	x						x
Clinical Lab Determinations[3]	x						x
Inclusion/Exclusion Criteria	x	x					
CT/MRI[4]	x						
Hachinski	x						
MMSE	x	x					
FAST	x						
SIB		x	x	x	x	x	x
CIBIC-Plus		x[5]	x	x	x	x	x
NPI		x		x	x	x	x
ADCS-ADL$_{19}$		x	x	x	x	x	x
MRUD-Lite		x			x		x
Verbal Fluency Test		x	x	x	x	x	x
CPBQ		x	x		x		x
AEs		x	x	x	x	x	x
Concomitant Medications	x	x	x	x	x	x	x
Drug Dispensing	x	x	x	x	x	x	
Medication Compliance		x	x	x	x	x	x
Final Assessment[6]							x

[1] Orthostatic evaluations will be performed at Screening (Visit 1) and Week 24/final study visit (or early termination.
[2] Height is measured at Screening (Visit 1) only.
[3] Includes urine drug screen at Screening (Visit 1) only.
[4] Neuroimaging must be conducted if patient has not had a CT or MR scan within the 12 months prior to Screening (Visit 1).
[5] Clinician's Interview-Based Impression of Severity (CIBIS) at Baseline.
[6] Final evaluation includes all procedures scheduled at the final study visit or upon early termination.

6.1.8 Outcome Measures

6.1.8.1 Primary Efficacy Measures

Severe Impairment Battery (SIB)
Clinician Interview-Based Impression of Change-Plus (CIBIC-Plus)

6.1.8.2 Secondary Efficacy Measures

Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale (ADCS-ADL)

6.1.8.3 Additional Efficacy Measures

Verbal Fluency Test: Animal Naming

Neuropsychiatry Inventory (NPI)

6.1.8.4 Health Outcomes Assessments

Modified Resource Utilization in Dementia-Lite (MRUD-Lite)

Alzheimer's Disease Caregiver Perceived Burden Questionnaire (CPBQ)

6.1.8.5 Safety Measures

Adverse events, vital signs, physical examinations, safety laboratory tests, electrocardiograms

6.1.9 Further Description Of Main Efficacy Outcome Measures

The following are descriptions of the primary and secondary outcome measures for this study.

6.1.9.1 Severe Impairment Battery (SIB)

This scale has been developed to assess cognitive function in severely demented patients. It is divided into 9 sub-scales assessing attention, orientation, language, memory, praxis, visuospatial perception, construction, social skills and orientation to name. The tests that comprise the Severe Impairment Battery involve simple 1-step commands that may be presented with gestural cues that can be repeated if necessary; 51 such tests are assessed altogether. Total scores range from 0 to 100 points with higher scores indicating better cognitive function.

The SIB has been used as the primary (cognitive) efficacy measure in a main pre-approval efficacy trial of the immediate-release formulation of memantine conducted in patients with moderate to severe Alzheimer's Disease.

The SIB is designated as a primary efficacy measure for this study.

6.1.9.2 Clinician Interview-Based Impression of Change-Plus (CIBIC-Plus)

The format for this instrument consists of the assessment, at baseline and at all subsequent visits, of an independent clinician based on observation of the patient at an interview, and information provided by the caregiver. The clinician is blinded to the results of other study assessments. The clinician's overall impression of the global change in disease severity, compared with baseline, is rated. A 7-point categorical rating scale is used, ranging from a score of 1 indicating "markedly improved", to a score of 7 indicating "markedly worse", and with a score of 4 indicating "no change".

Domains assessed include, but are not limited to, concentration, orientation, memory, language, behavior, social functions, and activities of daily living.

The CIBIC-Plus is designated as a primary efficacy measure for this study.

The baseline rating of severity of disease by an independent clinician is referred to as the Clinician Interview-Based Impression of Severity (CIBIS). It is rated on a 7-point scale.

6.1.9.3 Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale (ADCS-ADL)

This is a rating scale used to assess basic and instrumental activities of daily living. In the full version of the scale, 45 items are rated by the investigator using information supplied by the caregiver. Each item has a score range varying from 0-3 to 0-7. Higher scores indicate better function.

In Study MEM-MD-50, a modified version of the ADCS-ADL is to be used consisting of a subset of 19 of the above 45 items. These 19 items, selected to fit the expected activities of daily living profile of patients with moderate-to-severe dementia, consist of the following:

Eating	Ability to watch TV	Ability to be left alone
Walking	Making conversation	Ability to turn a faucet on
Toileting	Clearing a table	Ability to turn a faucet off
Bathing	Locating belongings	Ability to turn a light on
Grooming	Obtaining a beverage	Ability to turn a light off
Dressing	Litter disposal	
Use of a telephone	Traveling outside the home	

For the modified ADCS-ADL, a sum score is calculated by adding the scores for the individual items, and used as a primary efficacy measure. The sum score can range from 0 to 54, with higher scores indicating better function.

The modified ADCS-ADL is designated as a secondary efficacy measure for this study. The same instrument has been used as a primary efficacy measure in a

main pre-approval efficacy trial of the immediate-release formulation of memantine conducted in patients with moderate to severe Alzheimer's Disease.

6.1.10 Analysis Plan

6.1.10.1 Patient Populations

The sponsor has defined the following patient populations for purposes of analysis.

6.1.10.1.1 Randomized Population

This population will consist of all patients randomized into the study.

6.1.10.1.2 Safety Population

This population will consist of all randomized patients who receive at least one dose of double-blind study medication.

6.1.10.1.3 Intent-To-Treat Population

This population will consist of all those in the safety population who complete at least one post-baseline efficacy evaluation of the SIB or CIBIC-Plus.

6.1.10.1.4 Donepezil Intent-To-Treat Population

This population will consist of all patients in the intent-to-treat population whose background treatment with an acetylcholinesterase inhibitor both at baseline and during the study consists of donepezil.

6.1.10.2 Demographic And Other Baseline Characteristics

Demographic parameters and other baseline characteristics will be summarized by treatment group, using descriptive statistics for continuous variables and frequency distributions for categorical variables.

The treatment groups will be compared as follows:

- Continuous variables will be analyzed using a 2-way analysis of variance model with treatment and study center as factors
- Categorical variables will be analyzed using a Cochran-Mantel-Haenszel test controlling for study center.

6.1.10.3 Extent Of Exposure And Dosing Compliance

Extent of exposure to study drug will be presented in terms of treatment duration and mean daily dose. A summary table will be provided for dosing compliance.

6.1.10.4 Prior And Concomitant Medication

Both prior and concomitant medication will be summarized.

6.1.10.5 Efficacy Analyses

6.1.10.5.1 General

All efficacy analyses will be based on the intent-to-treat population; primary analyses will be performed using the intent-to-treat population: the last-observation-carried-forward approach at Week 24 will be used for imputation.

Supportive analyses will use the Observed Cases and last-observation-carried-forward approach at each visit.

All statistical tests will be 2-sided and a p-value of < 0.05 will be considered statistically significant.

In all efficacy analyses, study centers with less than 4 patients will be pooled into one collective center within a country.

6.1.10.5.2 Primary Efficacy Parameters

The primary efficacy parameters will be the change from baseline in the total SIB score at Week 24 and the CIBIC-Plus score at Week 24.

The results of the study will be considered “positive,” if memantine demonstrates a statistically significant superiority to placebo on both primary efficacy parameters at Week 24.

The primary efficacy analysis will be performed on the intent-to-treat dataset at Week 24, using the last-observation-carried-forward method of imputation, as follows.

- The comparison between the 2 treatment groups on the SIB will be made using a two-way analysis of covariance with treatment group and center as the 2 factors and baseline SIB score as the covariate. The results of this analysis will be summarized using least squares means for each treatment group and the point estimate, 95% confidence interval and the p-value corresponding to the between-treatment difference in least square means.

  In addition, a mixed model for repeated measures analysis based on the observed data up to Week 24 will be performed as a secondary analysis to compare treatment effects at Week 24. That model will include treatment group, visit, and treatment group-by visit interaction as factors and baseline SIB total score as a covariate. An unstructured covariance matrix will be used to model the correlation over time in change from baseline values

- CIBIC-Plus scores at Week 24 will be analyzed using the Cochran-Mantel-Haenszel test based on modified ridit scores controlling for study center, to compare the distributions between the two treatment groups. In addition, a mixed model for repeated measures analysis based on the observed data up to Week 24 will be performed as a sensitivity analysis to compare treatment effects at Week 24. That model will include treatment group, visit, and treatment group-by visit interaction as factors and baseline CIBIS rating score as a covariate. An unstructured covariance matrix will be used to model the correlation over time in change from baseline values

The change from baseline to each post-baseline visit in the SIB score and the CIBIC-Plus score at each visit will be analyzed as above.

6.1.10.5.3 Secondary Efficacy Parameters

The secondary efficacy parameter is the change from baseline to each post-baseline visit in the 19-item ADCS-ADL total score.

This parameter will be analyzed in a manner similar to the primary analysis of the SIB, as well as using a mixed model repeated measures approach similar to that used for the CIBIC-Plus.

6.1.10.5.4 Additional Efficacy Parameters

These parameters are as follows:

- Change from baseline in total Neuropsychiatry Inventory score by visit
- Change from baseline in Neuropsychiatry Inventory domain scores by visit
- Change from baseline to each visit in total words on the Verbal Fluency Test.

For these additional parameters, a between treatment group comparison will be performed by visit using an analysis of covariance model with treatment group and study center as factors, and the corresponding baseline value as a covariate.

6.1.10.5.5 Efficacy Analysis For The Donepezil Intent-To-Treat Population

Since it is projected that more than 65% of randomized patients will have been concomitantly treated, the efficacy analyses described above are to be performed on the donepezil intent-to-treat population.

However, the planned analyses for the co-primary efficacy parameters for the donepezil intent-to-treat population will be performed only if the planned primary efficacy analyses demonstrate statistically significant effects favoring memantine over placebo.

6.1.10.5.6 Sub-Group Analyses

The consistency of the treatment effects seen on the primary and secondary efficacy parameters in major sub-groups is to be examined in the Week 24 last-observation-carried-forward population. The subgroups are to be based on the following:

- Gender
- Age (< 75 years versus ≥ 75 years)
- Race (Caucasian versus non-Caucasian)
- Country (US versus non-US)

For each of the above subgroups, the analysis of change from baseline in SIB and ADCS-ADL total score is to be performed using an analysis of covariance model with treatment group, subgroup, and treatment group-by-subgroup interaction as factors and baseline total score as a covariate. The subgroup-based analysis of the CIBIC-Plus at Week 24 will be performed using an analysis of variance model with treatment group, sub-group, and treatment group-by-subgroup interaction as factors.

6.1.10.5.7 Health Outcomes Assessments

Parameters to be derived and methods of performing analyses of Modified Resource Utilization in Dementia-Lite (MRUD-Lite) and Alzheimer's Disease Caregiver Perceived Burden Questionnaire (CPBQ) are described in the submission.

6.1.10.6 Safety Parameters

Safety analyses will be performed using the safety population as defined above.

For adverse events:

- The number and percentage of patients with treatment-emergent adverse events, serious adverse events, and discontinuations due to adverse events, will be tabulated by body system, preferred term and treatment group
- Listings will be provided for all patients with serious adverse events and discontinuations due to adverse events.

For laboratory parameters and vital signs

- The number and percentage of patients with post-baseline potentially clinically significant values will be tabulated by treatment group. Listings will be provided for all such patients. Criteria for potentially clinically significant laboratory tests are provided
- For each parameter, summary statistics will be provided by treatment group at each visit.

For electrocardiograms

- The number and percentage of patients with post-baseline potentially clinically significant values will be tabulated by treatment group
- For each parameter summary statistics will be provided by treatment group for each visit.

For physical examinations in each body system, the number and percentage of patients with transitions from normal or not done at baseline to abnormal post-baseline will be presented by treatment group.

6.1.10.7 Sample Size Rationale

The sample size calculation is based on the change from baseline to Week 24 in the SIB and the Week 24 score on the CIBIC-Plus.

The assumptions underlying the sample size estimate are as follows:

- Effect size (treatment group difference relative to pooled standard deviation) of 0.40 for SIB, and 0.24 for the CIBIC-Plus
- 83% power
- Alpha of 0.05 (2-sided).

Based on the above assumptions 300 patients will be needed per treatment group.

6.1.10.8 Interim Analysis

No interim analysis is to be performed

6.2 Results

[All references to “memantine ER” and “placebo” groups below should be considered to imply that patients in both groups were also taking a stable dose of an acetylcholinesterase inhibitor].

This study was conducted at 83 centers in 4 countries, distributed as indicated in the table below.

Country	Number of Centers
United States	38
Argentina	23
Chile	11
Mexico	11

6.2.1 Patient Disposition

677 patients were randomized, of whom 545 (80.5%) completed the study. 132 patients (19.5%) withdrew prematurely from the study.

The distribution of the above randomized patients by treatment group, and reasons for withdrawal (again, by treatment group) are highlighted in the following table, which I have copied from the submission.

	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.

6.2.2 Protocol Deviations

The number of patients with protocol deviations in specific categories in the randomized population are listed in the table below, which I have created from data included in the submission.

Category	Placebo*	Memantine ER*	Total
Randomized	335	342	677
Deviation from entry criteria	9	15	24
Failure to be withdrawn from study despite satisfying withdrawal criteria	5	2	7
Received wrong study drug or incorrect dose of study drug	0	3	3
Received clinically relevant excluded concomitant medications	13	15	28
Received study drug prior to baseline CIBIS rating	3	0	3
CIBIC-Plus rater unblinded to post-baseline information	8	10	18

*plus acetylcholinesterase inhibitor

As the above table indicates, the number of protocol deviations was small and evenly matched between treatment groups in the most commonly occurring category (“received clinically relevant excluded concomitant medications”).

6.2.3 Efficacy Analysis

6.2.3.1 Datasets Analyzed

The number of patients in each pre-specified analysis population, by treatment group is in the following sponsor table.

	Placebo/AChEI	*Memantine ER/AChEI*	*Total*
Patients screened	—	—	864
Not randomized	—	—	187
Patients randomized	335	342	677
Did not receive study drug	0	1	1
Safety Population[a]	335	341	676
No postbaseline efficacy data	7	8	15
ITT Population[b]	328	333	661
Donepezil ITT Population[c]	224	232	456

a All patients who received at least one dose of study drug.
b All patients who received at least one dose of study drug and had one baseline and at least one primary postbaseline efficacy assessment performed.
c All patients in the ITT Population who were concurrently taking donepezil.
AChEI = acetylcholinesterase inhibitor; ER = extended release; ITT = intent to treat.

6.2.3.2 Demographic And Other Baseline Characteristics

6.2.3.2.1 Demographics

Demographic characteristics of the safety population, which were comparable between the two treatment groups are in the following table, which I have copied from the submission.

Characteristic	*Placebo/AChEI (N = 335)*	*Memantine/AChEI (N = 341)*	*Total (N = 676)*	*p-Value*[a]
Age, y, mean ± SD	76.8 ± 7.8	76.2 ± 8.4	76.5 ± 8.1	0.150
Sex, n (%)	—	—	—	0.893
Male	92 (27.5)	97 (28.4)	189 (28.0)	
Female	243 (72.5)	244 (71.6)	487 (72.0)	
Race, n (%)	—	—	—	0.117
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 (%)	—	—	—	0.852
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	0.714
Height, cm, mean ± SD	158.94 ± 9.98	158.92 ± 9.84	158.93 ± 9.90	0.992
BMI, kg/m^2, mean ± SD	25.56 ± 4.54	25.65 ± 4.05	25.60 ± 4.29	0.899

a p-Values for continuous variables (age, weight, height, and BMI) are from a two-way ANOVA with treatment group and study center as factors; p-values for categorical variables (sex, race, ethnicity) are from a CMH test, controlling for study center.
AChEI = acetylcholinesterase inhibitor; ANOVA = analysis of variance; BMI = body mass index; CMH = Cochran-Mantel-Haenszel (test).

6.2.3.2.2 Disease Severity

Baseline assessments of disease severity were comparable between the treatment groups as indicated by the following sponsor table (mean values ± standard deviation).

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).

6.2.3.3 Concomitant Acetylcholinesterase Inhibitor Use

The specifics of concomitant acetylcholinesterase inhibitor use, both at baseline and during the study, are summarized in the following sponsor table, which is self-explanatory.

	Placebo/AChEI (N = 335)	*Memantine ER/AChEI (N = 341)*
Donepezil/Donepezil hydrochloride, n (%)	**227 (67.8)**	**236 (69.2)**
Mean treatment duration at baseline, wks	76.1	73.6
Mean daily dose at baseline, mg	7.76	8.03
Mean dose at end of study, mg	7.76	8.07
Galantamine/Galantamine hydrobromide, n (%)	**66 (19.7)**	**72 (21.1)**
Mean treatment duration at baseline, wks	61.9	69.8
Mean daily dose at baseline, mg	13.52	13.52
Mean dose at end of study, mg	13.52	13.52
Rivastigmine/Rivastigmine tartrate, n (%)	**41 (12.2)**	**32 (9.4)**
Mean treatment duration at baseline, wks	73.0	75.5
Mean daily dose at baseline, mg	6.84	6.80
Mean dose at end of study, mg	6.95	6.80

AChEI = acetylcholinesterase inhibitor; ER = extended release.

As the above table indicates, the most commonly used acetylcholinesterase inhibitor in study patients in both treatment groups was donepezil.

6.2.3.4 Primary Efficacy Analysis

6.2.3.4.1 SIB

The following sponsor table displays the results of the analyses performed on the intent-to-treat population. As the table indicates, for the primary last-observation-carried-forward analysis there was a mean improvement from baseline in the memantine ER group and a minimal worsening in the placebo group, with the difference between the groups being statistically significant.

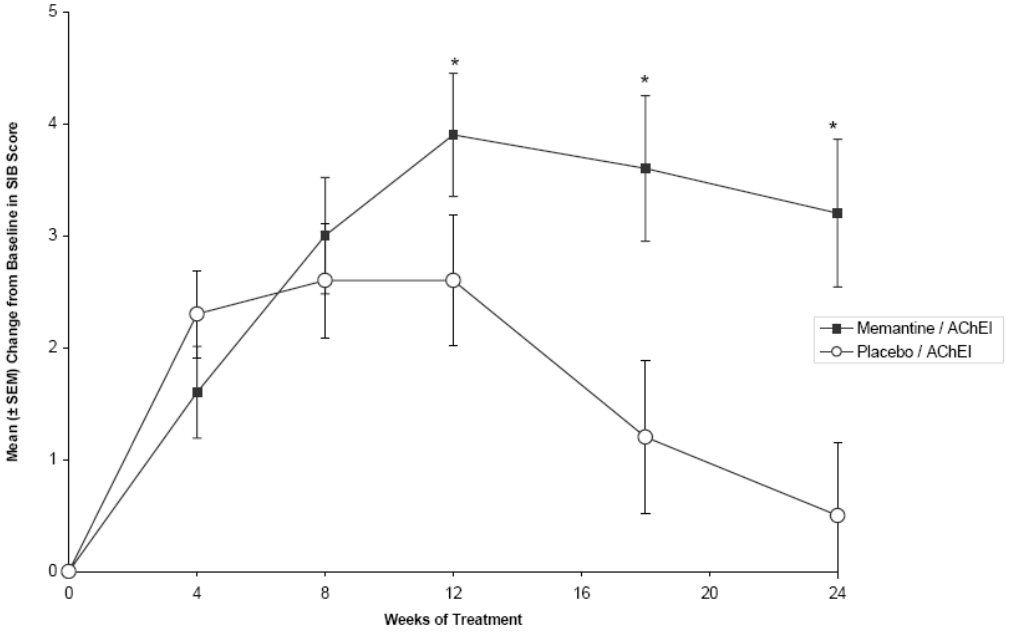
	Placebo/AChEI		*Memantine ER/AChEI*		*p-Value*
	N	*LS Mean*[a]	*N*	*LS Mean*[a]	
Week 24 (LOCF)	327	–0.4	332	2.2	.001
Week 24 (OC)	271	0.0	270	3.0	< .001
Week 24 (MMRM)	—	0.1	—	2.8	.004

a A positive change indicates improvement from baseline.

AChEI = acetylcholinesterase inhibitor; ITT = intent to treat; LOCF = last observation carried forward; LS = least square; MMRM = mixed model for repeated measures; OC = observed cases.

Similar effects were seen on the non-primary Week 24 Observed cases and mixed model repeated measures analyses.

The change from baseline in Severe Impairment Battery score by visit for the Observed Cases population is shown in the following sponsor figure.



* p < .05.

6.2.3.4.2 CIBIC-Plus

The following sponsor table displays the results of the analyses performed on the intent-to-treat population. As the table indicates, for the primary last-observation-carried-forward analysis there was a statistically significant treatment difference between the two groups favoring memantine ER over placebo.

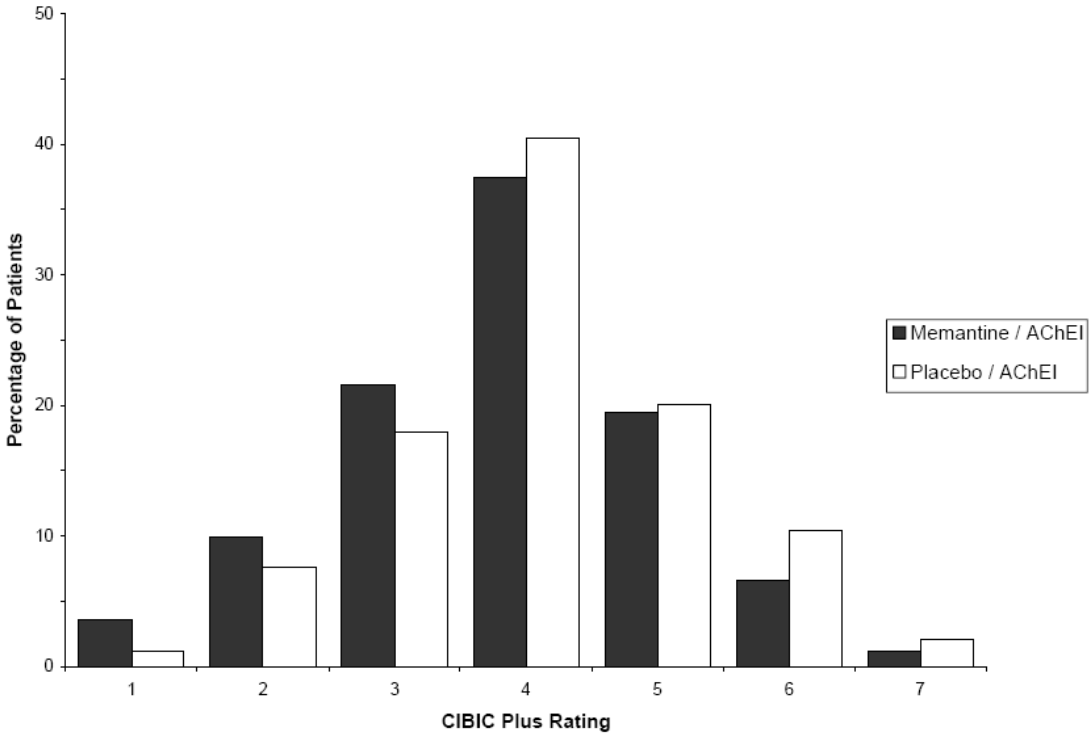
	Placebo/AChEI		*Memantine ER/AChEI*		*p-Value*
	N	Mean[a]	N	Mean[a]	
Week 24 (LOCF)	328	4.1	333	3.8	.008
Week 24 (OC)	272	4.1	269	3.8	.051
MMRM	—	4.1[b]	—	3.8[b]	.003

a Based on a scale of 1 to 7, where 1 = marked improvement, 4 = no change, and 7 = marked worsening.

b LS mean for MMRM.

AChEI = acetylcholinesterase inhibitor; ER = extended release; ITT = intent to treat; LOCF = last observation carried forward; LS = least square; MMRM = mixed model for repeated measures; OC = observed cases.

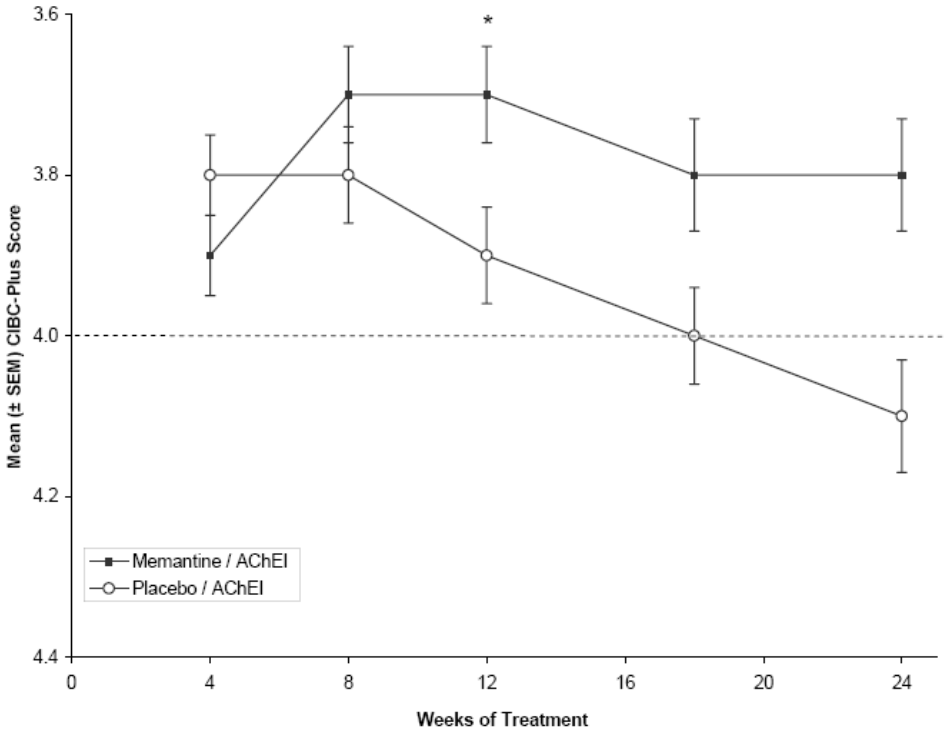
The distribution of CIBIC-Plus ratings by treatment group is in the figure below which I have copied from the submission, which indicates that in all the improved categories, there was a higher proportion of patients receiving memantine than placebo. The figure is for the last-observation-carried-forward population.



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.

The mean CIBIC-Plus rating by visit for the Observed Cases population is in the following figure, again taken from the submission.



*p < .05

6.2.3.5 Analysis Of Secondary Efficacy Measure (ADCS-ADL)

The following sponsor table displays the results of the analyses performed on the intent-to-treat population. As the table indicates, no statistically significant difference between treatment groups was seen on the ADCS-ADL in either the Observed Cases or last-observation-carried-forward populations.

	Placebo/AChEI		***Memantine ER/AChEI***		***p-Value***
	N	*Mean*[a]	*N*	*Mean*[a]	
Week 24 (LOCF)	328	–1.7	331	–1.0	0.177
Week 24 (OC)	272	–1.1	268	–0.3	0.155

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.

6.2.3.6 Additional Efficacy Analyses

The results of several (but not all) of the many additional efficacy analyses performed by the sponsor are below.

- Nominally statistically significant differences favoring the memantine ER over the placebo group were seen on the NPI total score (p = 0.005), and Verbal Fluency Test (p = 0.004) in the last-observation-carried-forward population at Week 24

- For the donepezil intent-to-treat population (i.e., the intent-to-treat population subset that was concomitantly using donepezil), a nominally statistically significant difference favoring the memantine ER over the placebo group was seen on the SIB in the last-observation-carried-forward population at Week 24 (least squares mean difference between groups of 3.2; p = 0.001), but not on the CIBIC-Plus rating (mean difference between groups of 0.2; p = 0.165) or the ADCS-ADL (mean difference between groups of 0.1; p = 0.894)

6.2.3.7 Sub-Group Analyses

6.2.3.7.1 Efficacy Results By Gender

Efficacy results by sex are summarized in the following table, which I have copied from the submission

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.

The sponsor observes that:

- The numeric changes on both the SIB and CIBIC-Plus favored memantine ER over placebo in both men and women

- There was no statistically significant treatment group-by-gender interaction (p-values of 0.520 and 0.328 for the change from baseline in the SIB total score and in the CIBIC-Plus score, respectively).

6.2.3.7.2 Efficacy Results By Age

The efficacy of memantine by age was evaluated using two age-delineated subgroups, < 75 years and ≥ 75 years. The results are summarized in the next sponsor table.

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.

The sponsor points out that:

- The numeric scores on both the SIB and CIBIC-Plus favored memantine ER over placebo in both subgroups
- The subgroup analysis using age group (stratified as above) as a categorical variable provided treatment-by-age interaction p-values of 0.067, 0.005, and 0.364 for SIB change score, CIBIC-Plus rating score, and ADCS-ADL change score, respectively.
- A further post-hoc subgroup analysis using age as a continuous variable provided treatment-by-age interaction values of 0.145, 0.083, and 0.563 for SIB change score, CIBIC-Plus rating score, and ADCS-ADL change score, respectively.

These and additional exploratory analyses have suggested to the sponsor that a consistent treatment-by-age interaction was not seen.

6.2.3.7.3 Efficacy Results By Race

Analyses intended to evaluate the efficacy of memantine in Caucasian patients as compared with non-Caucasian patients are summarized in the following table, which I have copied from the submission.

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.

While the number of non-Caucasians enrolled in these studies was very small, the sponsor has concluded that the numeric changes on the SIB, CIBIC-Plus, and ADCS-ADL all favored memantine ER over placebo, in both Caucasians and non-Caucasians.

6.2.3.7.4 Efficacy Results By Country

The sponsor has analyzed the effect of country on the efficacy results of this study by comparing US with non-US patients. The results are summarized in the following table.

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.

From the above data, the sponsor has concluded that the numeric changes in SIB, CIBIC-Plus and ADCS-ADL were in favor of memantine ER for both US and non-US patients. The sponsor also notes that there was no statistically significant treatment group-by-country interaction (p values of 0.281 and 0.415 for the change from baseline in the SIB and CIBIC-Plus, respectively).

6.2.4 Safety Analysis

6.2.4.1 Exposure

Descriptive statistics for the duration of treatment – in days- in the 2 treatment groups are summarized in the following table, which I have copied from the submission. The duration of treatment was comparable between the groups.

	Placebo* n = 335	Memantine ER* n = 341
Mean (days)	154.9	148.6
Standard deviation (days)	45.85	50.32
Median (days)	168	168
Minimum, Maximum (days)	3, 294	1, 295

Descriptive statistics for the mean daily dose in the memantine group are in the next table.

	Memantine ER* n = 341
Mean (mg)	24.6
Standard deviation(mg)	3.79
Median (mg)	26.1
Minimum, Maximum (mg)	6, 27

6.2.4.2 Adverse Events

6.2.4.2.1 Summary Of All Adverse Events

A sponsor table summarizing all adverse events that occurred during the study, in the safety population, is copied below.

	Placebo/AChEI (N = 335)	***Memantine ER/AChEI (N = 341)***
TEAEs	214 (63.9)	214 (62.8)
Deaths	5 (1.5)	4 (1.2)
SAEs	21 (6.3)	28 (8.2)
AEs resulting in premature discontinuation	21 (6.3)	34 (10.0)

AChEI = acetylcholinesterase inhibitor; AE = adverse event; ER = extended release; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

As the table indicates, the incidence of all treatment-emergent adverse events and of deaths was similar between the groups, whereas the incidence of serious adverse events and adverse events leading to treatment discontinuation was slightly higher in the memantine ER group than in the placebo group.

6.2.4.2.2 Deaths

Deaths that occurred either while on treatment with study drug or within 30 days of study drug discontinuation are listed in the following table, which I have copied from the submission. As the table below, and the preceding table indicate, there were 5 such deaths in the placebo group and 4 such deaths in the memantine ER group. The narratives, supplemented by Case Report Forms where needed, for each death suggest that all were likely attributable to incidental illnesses common in the study population, or to the consequences of worsening Alzheimer's Disease, or both, and were not attributable to the study drug.

Patient ID	*Age, y*	*Sex*	*Day of Death*[a]	*Days Off Study Drug*[c]	*Preferred Term*	*Relationship*
Placebo/AChEI						
1125002	71	M	57	0	Drowning	Not related
1205007	97	M	132	5	Pneumonia aspiration	Not related
					Cardiac arrest	Not related
					Respiratory arrest	Not related
1225010	77	F	125	1	Cardio-respiratory arrest	Possibly related
2115002	91	F	48	17	Myocardial infarction	Not related
3015003	87	M	58	2	Intracranial hematoma	Not related
Memantine ER/AChEI						
0065003	81	F	76	7	Metastatic carcinoma of the bladder	Not related
0245001	86	F	68	8	Cerebrovascular accident	Not related
1055009	91	M	97	1	Pneumonia aspiration	Not related
1085006[b]	78	M	214	43	Dementia Alzheimer's type	Not related
					General physical health deterioration	Not related

a Day of death is in relationship to date of first dose (Day 1).
b The fatal SAE of dementia of the Alzheimer's type occurred during the double-blind treatment phase, and the fatal SAE general health deterioration occurred within 30 days of the last dose of study drug.
c At the time of death.
AChEI = acetylcholinesterase inhibitor; ER = extended release; M = male; F = female.

6.2.4.2.3 Serious Adverse Events

As already indicated, 21 patients (6.3%) in the placebo group and 28 patients (8.2%) in the memantine group, developed serious adverse events (including the fatal serious adverse events listed earlier) in the safety population.

A review of the narratives for each serious adverse event, supplemented by Case Report Forms where needed, suggest that all were likely attributable to illnesses common in the study population, or to the consequences of worsening Alzheimer's Disease, or both, and were not attributable to the study drug. They are not described in further detail here.

6.2.4.2.4 Discontinuations Due To Adverse Events

As an earlier table indicated, 21 patients (6.3%) in the placebo group and 34 patients (10.0%) in the memantine group, developed adverse events leading to treatment discontinuation, in the safety population. The following sponsor table also lists adverse events that led to treatment discontinuation in > 1 patient in either treatment group.

Adverse Event	*No. (%) of Patients*	
	Placebo/AChEI (N = 335)	*Memantine ER/AChEI (N = 341)*
Patients with ≥ 1 AE leading to discontinuation	21 (6.3)	34 (10.0)
Dizziness	0	5 (1.5)
Agitation	1 (0.3)	3 (0.9)
Depression	1 (0.3)	2 (0.6)
Cerebrovascular accident	0	2 (0.6)
Pneumonia	0	2 (0.6)
Cardiac failure congestive	2 (0.6)	0
Urinary tract infection	2 (0.6)	0

AChEI = acetylcholinesterase inhibitor; AE = adverse event; ER = extended release.

Again, a perusal of the narratives for each adverse event that led to treatment discontinuation, supplemented by Case Report Forms where needed, suggest that most, with the exception of dizziness, were likely attributable to incidental illnesses common in the study population. They are, therefore, not described further in this review.

6.2.4.2.5 All Adverse Events

The most frequent treatment-emergent adverse events are listed in the following table, which I have copied from the submission; those listed are ones which occurred at a frequency approximating or greater than 5% in either treatment group.

TEAE	*No. (%) of Patients*	
	Placebo/AChEI (N = 335)	*Memantine ER/AChEI (N = 341)*
Fall	26 (7.8)	19 (5.6)
Headache	17 (5.1)	19 (5.6)
Urinary tract infection	24 (7.2)	19 (5.6)
Diarrhea	13 (3.9)	17 (5.0)
Dizziness	5 (1.5)	16 (4.7)
Insomnia	16 (4.8)	14 (4.1)

AChEI = acetylcholinesterase inhibitor; ER = extended release; TEAE = treatment-emergent adverse event.

I have reviewed the sponsor's table for all adverse events that occurred during this study. The incidence of the vast majority of individual adverse events was either small and/or comparable between treatment groups; the incidence of dizziness was, however, notably higher in the memantine group than in the placebo group. Only 9.6% of adverse events in the memantine ER group and 5.8% in the placebo group were severe; the rest were mild or moderate. In no individual instance, was the incidence of a specific adverse event disturbing.

6.2.4.3 Vital Signs

There were no prominent or noteworthy differences in the mean change from baseline to endpoint in vital sign parameters between the 2 treatment groups, and the incidence of potentially clinically significant abnormalities in vital signs was very low in both treatment groups. The data presented by the sponsor have been reviewed in detail, but reveal no items of clinical concern.

The proportion of patients who experienced treatment-emergent postural hypotension was higher in the placebo group (9.8%) than in the memantine group (7.7%).

6.2.4.4 Safety Laboratory Tests

There were no clinically significant differences in the mean change from baseline to endpoint in laboratory parameters between the 2 treatment groups, and the incidence of potentially clinically significant abnormalities in laboratory data very low and/or comparable between treatment groups. While the data presented by the sponsor have been reviewed in detail, they do not warrant further description here.

6.2.4.5 Electrocardiograms

The changes from baseline to endpoint in electrocardiographic parameters were small and comparable between treatment groups.

Potentially clinically significant electrocardiographic abnormalities, when present, did not occur in more than 1 patient in the memantine group.

6.2.4.6 Physical Examinations

47 patients (15.6%) in the placebo group and 29 patients (9.4%) in the memantine group had a change in physical examination results from "normal/not done" at screening to "abnormal" at the final visit.

6.3 Sponsor's Overall Conclusions Regarding Efficacy And Safety

The memantine ER formulation in a dose of 28 mg QD showed a statistically significant superiority to placebo, in patients with moderate to severe Alzheimer's Disease concomitantly taking acetylcholinesterase inhibitors, on pre-specified primary measures of efficacy.

There was evidence for the safety and tolerability of memantine ER in a dose of 28 mg QD in the treatment of moderate to severe Alzheimer's Disease.

6.4 Agency Biometrics Reviewer's Comments

6.4.1 Overall Conclusion

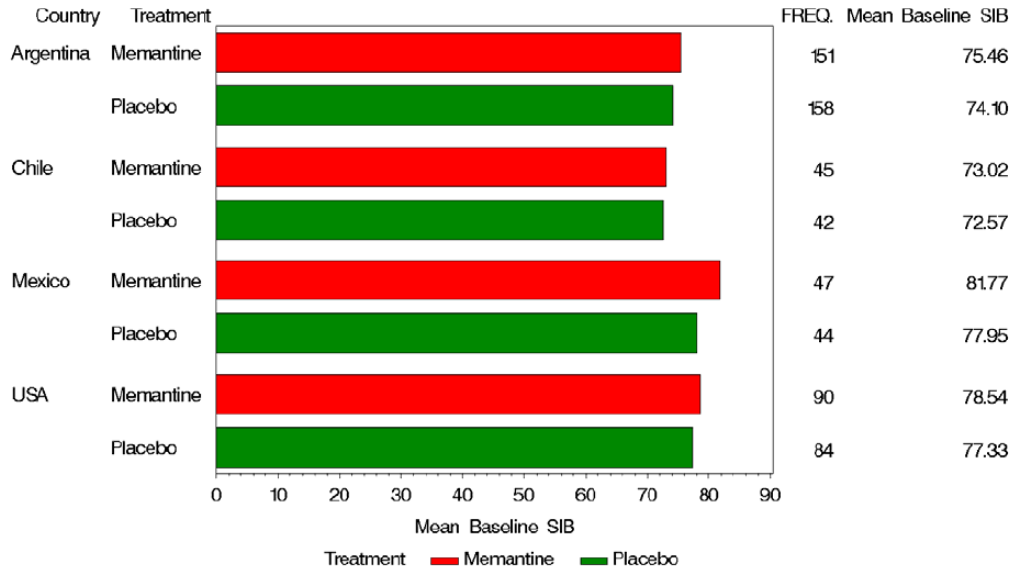
The Agency Biometrics reviewer of this submission is Jingyu (Julia) Luan, PhD. She reviewed the efficacy data for Study MEM-MD-50. Please read her review for full details.

She has concluded that the results of Study MEM-MD-50 did demonstrate a therapeutic benefit for memantine ER (combined with an acetylcholinesterase inhibitor) over placebo (combined with an acetylcholinesterase inhibitor) on the two co-primary efficacy measures, the SIB and the CIBIC-Plus.

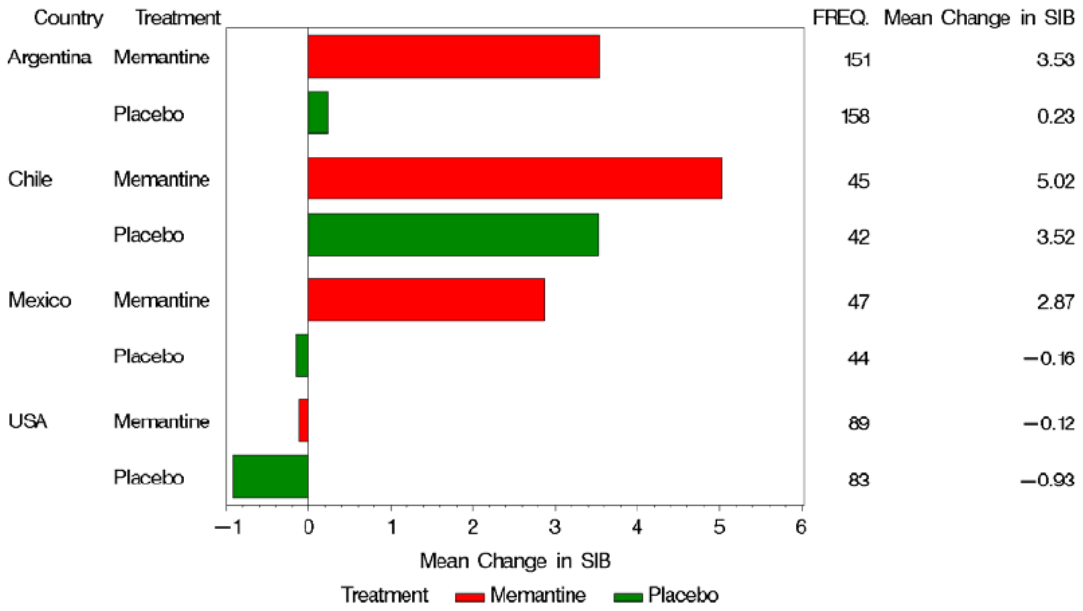
6.4.2 Concern About Inter-Country Differences In Treatment Effect On Severe Impairment Battery

Notwithstanding her overall conclusion above, Dr Luan was concerned about inter-country differences in the effect of treatment on the SIB; such differences were <u>not</u> seen for the treatment effect on the CIBIC-Plus. Her concern is further explained below.

- The mean baseline SIB score was similar across countries and treatment groups, as indicated by the following figure (for the intent-to-treat, last-observation-carried-forward population) which I have copied from Dr Luan's review.



- While the difference between treatment groups on the change from baseline to endpoint (intent-to-treat; last-observation-carried-forward) favored memantine in both US and non-US patients, that treatment effect was more pronounced in each of the foreign countries where the study was conducted (Argentina, Chile, and Mexico) than in the US. In addition, the group treated with memantine showed a mean improvement from baseline to endpoint in each of the three foreign countries listed above, whereas the memantine group showed a minimal worsening from baseline to endpoint in the United States. These effects are displayed in the next figure which I have also copied from Dr Luan's review.



The sponsor was asked by the Agency if an explanation could be provided for the above inter-country differences in effect on the SIB in a request for information sent on April 8, 2010.

The sponsor responded to the above request for information on April 20, 2010 as follows:

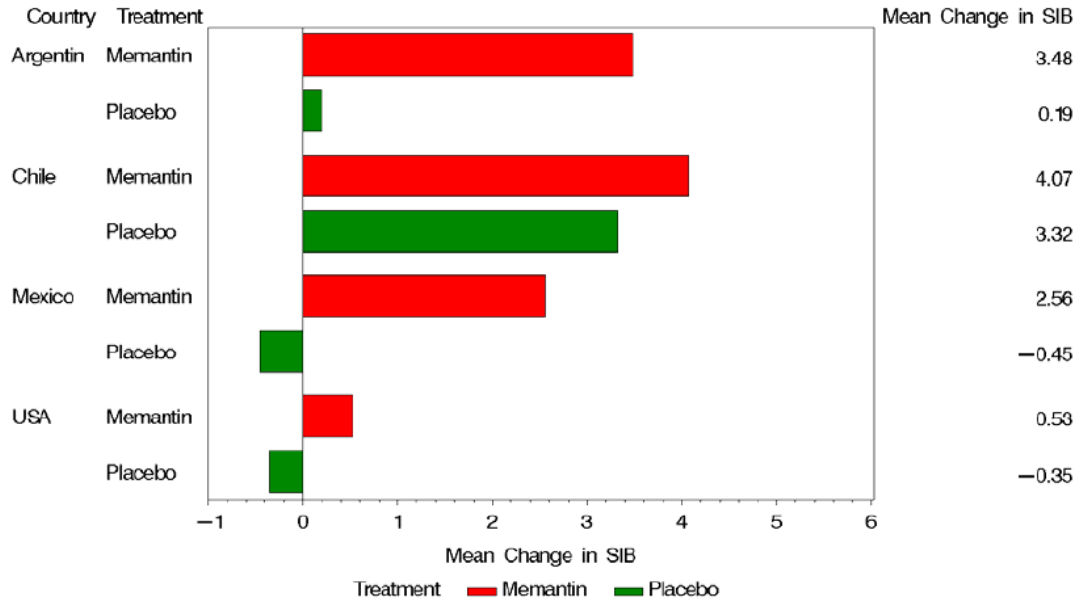
- Inter-country differences in efficacy responses are not uncommon, in general, and are attributed to differences in the demographic and other baseline characteristics of patients across countries.

- Statistical tests were performed comparing all pre-specified demographic and other baseline characteristics, as well as efficacy measure scores at baseline, across countries for Study MEM-MD-50. Imbalances ($p < 0.05$) were seen for the following variables at baseline: age, ethnicity, duration of education, weight, Body Mass Index, height, modified Hachinski Ischemic Scale score, SIB, and CIBIS.

- To evaluate the effect of the above imbalances on the SIB results by country, an exploratory analysis of covariance was performed on the change from baseline to Week 24 SIB score (intent-to-treat; last-observation-carried-forward). Treatment and country were included in the model as factors, and all prespecified demographic and other baseline characteristics (except weight and height which are correlated with Body Mass Index), as well as baseline efficacy measure scores were included in the model as covariates. The results of this analysis revealed that after adjusting for the imbalanced demographic and baseline characteristics, and baseline efficacy measures, the country effect was not statistically significant ($p = 0.2451$).

- The last analysis indicates that the above differences between countries in the effect of study drug on the SIB may be an indication of differences in demographic and other baseline characteristics as well as baseline SIB and CIBIS values.

Dr Luan has reviewed the sponsor's response and has used an analysis of covariance model similar that specified by the sponsor to assess the treatment effect by country; Dr Luan did, however, add the country by treatment term to the model used by the sponsor in order to estimate the mean change from baseline after adjusting for all the variables that were part of the model (the treatment by country term was not statistically significant [$p = 0.61$]). Her results are displayed in the following figure which I have copied from her review.



Dr Luan points out that the results of her second analysis are similar to those of her original analysis of inter-country differences in the effect of treatment on the SIB. She, therefore, does not find the sponsor's explanation for these differences convincing.

6.5 Reviewer's Summary And Conclusions

6.5.1 Summary Of Study MEM-MD-50

The sponsor has submitted the results of a single efficacy study , MEM-MD-50, to support the approval of the proposed new formulation of memantine, Namenda® XR, also referred to as memantine ER.

The design and efficacy data for Study MEM-MD-50 are described further below.

This study was conducted at a total of 83 centers in 4 countries: Argentina, Chile, Mexico, and the United States.

6.5.1.1 Design

This was a randomized, double-blind, placebo-controlled, parallel-arm study of 24 weeks duration.

The two key criteria used for enrolling patients in this study were a diagnosis of Probable Alzheimer's Disease, using the National Institute for Neurological and Communicative Diseases and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, a baseline Mini-Mental Status Examination score of 3-14, and use of an acetylcholinesterase inhibitor at a stable daily dose for at least 3 months prior to study entry.

Patients enrolled in this study were randomized to treatment with one of the following regimes for the 24-week period of double-blind, parallel-arm treatment,

- Placebo
- Memantine ER 28 mg QD

Patients assigned to memantine ER were titrated to a dose of 28 mg QD over 3 weeks, beginning with a dose of 7 mg QD and increasing by 7 mg QD every week.

The primary efficacy measures for the study were:

- A measure of cognition, the Severe Impairment Battery (SIB)
- A measure of global function, the Clinician Interview-Based Impression of Change-Plus (CIBIC-Plus)

The study had a single secondary efficacy measure, a 19-item version of the Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale (ADCS-ADL) specially designed for patients with moderate to severe dementia. Additional efficacy measures included a verbal fluency test, the Neuropsychiatry Inventory (NPI) and health outcomes assessments.

Safety measures included adverse events, vital signs, physical examinations, safety laboratory tests, and electrocardiograms.

The primary efficacy parameters were the change from baseline in the total SIB score at Week 24 and the CIBIC-Plus score at Week 24. The primary efficacy analysis was performed on the intent-to-treat dataset at Week 24, using the last-observation-carried-forward method of imputation, as follows. The intent-to-treat dataset consisted of all randomized patients who received at least one dose of study medication and had at least one post-baseline evaluation of the SIB or CIBIC-Plus.

The comparison between the 2 treatment groups on the SIB was to be made using a two-way analysis of covariance with treatment group and center as the 2 factors and baseline SIB score as the covariate. CIBIC-Plus scores at Week 24 will be analyzed using the Cochran-Mantel-Haenszel test based on modified ridit scores controlling for study center, to compare the distributions between the two treatment groups.

The results of the study were to be considered "positive," if memantine demonstrated a statistically significant superiority to placebo on both primary efficacy parameters at Week 24.

6.5.1.2 Results

6.5.1.2.1 Efficacy Results

677 patients were randomized of whom 545 patients (80.5%) received study drug. The number of patients randomized to, and completing the study in each treatment group is summarized in the following table.

Category	Placebo*	Memantine ER*	Total
Randomized	335	342	677
Completed	272	273	545

*plus acetylcholinesterase inhibitor

Patients actually enrolled in this study had a mean (standard deviation) baseline Mini-Mental Status Examination score in each treatment group as follows.

Treatment Group	Mini-Mental Status Examination score at baseline Mean (SD)
Placebo*	10.6 (2.9)
Memantine ER*	10.6 (2.9)

*plus acetylcholinesterase inhibitor

The results of the primary efficacy analysis revealed the following:

- A mean improvement from baseline (2.2 points [Least Squares means]) in the memantine ER group and a minimal worsening in the placebo group (-0.4 points [Least Squares means]), on the SIB, with the difference between the groups being statistically significant (p = 0.001). Prominent and unexplained inter-country differences were seen in the effect of both memantine ER and placebo on the SIB, but the effect of memantine ER was superior to placebo regardless of country.

- A mean score of 3.8 in the memantine group and 4.1 in the placebo group, a statistically significant treatment difference (p = 0.008).

Several sensitivity analyses of the SIB and CIBIC-Plus supported the results of the primary efficacy analysis.

No statistically significant treatment difference (even one that was nominally statistically significant) was seen for the ADCS-ADL when analyzed in a manner similar to the primary efficacy analysis for the SIB.

6.5.1.2.2 Safety Results

The incidence of all treatment-emergent adverse events and deaths was similar in the 2 treatment groups, while the incidence of serious adverse events and adverse events leading to treatment discontinuation was slightly higher in the memantine ER group than in the placebo group.

The only individual adverse event that was substantially more common in the memantine group than in the placebo group was dizziness which was seen in 4.7% of those treated with memantine as opposed to 1.5% of those treated with placebo.

The sponsor-provided descriptions of deaths and serious adverse events that occurred in this study suggested that they were most unlikely to be attributable to memantine. The same applies to adverse events that led to treatment discontinuation, with the exception of dizziness which was more common in those treated with memantine than in those treated with placebo.

Other safety data analyzed including vital signs, safety laboratory tests, and electrocardiograms showed no areas of concern when comparing the memantine group with the placebo group.

6.5.2 Reviewer's Conclusions

The results of Study MEM-MD-50 do provide evidence, according to pre-specified criteria agreed to by the Agency, for the efficacy of memantine ER – in a dose of 28 mg QD - over placebo when used concomitantly with a stable dose of an acetylcholinesterase inhibitor in the treatment of moderate to severe dementia of the Alzheimer's type, according to pre-specified criteria agreed to by the Agency. While the inter-country differences in the effect of both memantine ER and placebo on the SIB are quite prominent and unexplained, the overall results of the primary efficacy analysis are not negated, especially since the effect of memantine was superior to that of placebo across countries.

The results of the study did not indicate that there were any safety concerns in regard to memantine ER when administered to patients with moderate to severe Alzheimer's Disease at a dose of 28 mg QD.

Note that Agency inspections of two large sites for this study (both in Argentina) revealed no deviations, as has also been summarized in a later section of this review.

7. Integrated Summary Of Safety

The cut-off date for data included in the Integrated Summary of Safety was September 30, 2008.

The contents of the Integrated Summary of Safety are outlined under the following headings. The methods used in the creation of the Integrated Summary of Safety are consistent with those presented to the Agency in the Pre-NDA Briefing Package, and were found acceptable by the Agency at that time.

The sponsor has also conducted a search of the medical literature. The methods used for the literature search are described in the submission. 25 articles, which are provided

in the submission, were considered to contain information regarding the safety of memantine. After reviewing these articles, the sponsor has concluded that no new safety concerns were delineated in their text.

7.1 Description Of Study Groups And Individual Studies Included In Integrated Summary Of Safety

7.1.1 Group 1 (Studies Of Memantine ER In Alzheimer's Disease)

In this group of studies, all conducted in patients with Alzheimer's Disease, memantine was administered as the extended-release formulation and in a maximum daily dose of 28 mg/day. The designs of individual studies in this group are further outlined below.

7.1.1.1 Placebo-Controlled Clinical Study

The placebo-controlled study in this group was MEM-MD-50. The design of this study has already been fully described in Section 6.1.

7.1.1.2 Open-Label Uncontrolled Clinical Studies

The open-label uncontrolled studies in this group are outlined in the following paragraphs.

7.1.1.2.1 Study MEM-MD-51

This was an open-label uncontrolled free-standing (i.e., non-extension) safety study of 52 weeks duration in patients with moderate to severe Alzheimer's Disease.

Patients not previously treated with immediate-release memantine tablets received memantine ER once daily as follows: 7 mg/day for the first week followed by dose escalation to 28 mg/day in weekly increments over the next 3 weeks. Patients previously treated with immediate-release memantine tablets in a dose of 10 mg BID received memantine ER in a dose of 28 mg QD from the beginning of the study.

Safety parameters included adverse events, vital signs, electrocardiograms, safety laboratory tests and physical examinations.

This study is now complete.

7.1.1.2.2 Study MEM-MD-54

This was an open-label uncontrolled 28-week safety extension to Study MEM-MD-50; eligible patients completing the latter could be enrolled in the open-label extension study.

Regardless of treatment assignment in the preceding double-blind study, all patients memantine ER once daily as follows in the extension study: 7 mg/day for the first week followed by dose escalation to 28 mg/day in weekly increments over the next 3 weeks.

Safety parameters included adverse events, vital signs, electrocardiograms, safety laboratory tests and physical examinations.

This study is now complete.

7.1.1.2.3 Study MEM-MD-82

This is an open-label uncontrolled 52-week safety extension to Studies MEM-MD-51 and MEM-MD-54, open to all patients who completed Study MEM-MD-51 or Study MEM-MD-54 at a memantine ER dose of 28 mg/day.

Safety parameters include adverse events, vital signs, electrocardiograms, safety laboratory tests and physical examinations.

This study is currently ongoing.

7.1.2 Group 2 (Studies Of Memantine IR At Doses > 20 Mg/Day)

The designs of individual studies in this group are further outlined below. All studies listed below are complete.

7.1.2.1 Placebo-Controlled Clinical Studies In Patients

7.1.2.1.1 Study MEM-MD-06A

This was a randomized, double-blind, placebo-controlled, parallel-arm study of 16 weeks duration in patients with painful diabetic neuropathy, aged 18 to 80 years.

Memantine was begun in a dose of 10 mg/day and escalated to 40 mg/day over the initial 4 weeks of treatment. A dose of 40 mg/day was then maintained.

Safety parameters included adverse events, vital signs, electrocardiograms, safety laboratory tests, physical examinations, and ophthalmological assessments, as well as measurements of nerve conduction velocity.

7.1.2.1.2 Study MEM-MD-19

This was a randomized, double-blind, placebo-controlled, parallel-arm study of 17 weeks duration in patients with painful diabetic neuropathy, aged 18 to 75 years. The parallel treatment arms in this study were: memantine, gabapentin, and placebo.

Memantine was begun in a dose of 10 mg/day and escalated to 60 mg/day over the initial 5 weeks of treatment. The dose of memantine used in this study was flexible.

Safety parameters included adverse events, electrocardiograms, safety laboratory tests, vital signs, and physical examinations.

7.1.2.1.3 Study MEM-MD-20

This was a randomized, double-blind, placebo-controlled, parallel-arm study of 17 weeks duration in patients with painful diabetic neuropathy, aged 18 to 80 years. The parallel treatment arms in this study were: memantine, gabapentin, and placebo.

Memantine was begun in a dose of 10 mg/day and escalated to 60 mg/day over the initial 5 weeks of treatment. The dose of memantine used in this study was flexible.

Safety parameters included adverse events, electrocardiograms, safety laboratory tests, vital signs, and physical examinations.

7.1.2.2 Open-Label Uncontrolled Clinical Studies In Patients

7.1.2.2.1 Study MEM-MD-06B

This was a 40-week open-label uncontrolled extension to Study MEM-MD-06A intended to evaluate the safety of memantine in patients with painful diabetic neuropathy.

The starting dose of memantine in this study was 10 mg/day, regardless of what dose was administered in the preceding double-blind study; the dose was increased weekly by 10 mg/day to a maximum of 40 mg/day.

Safety parameters included adverse events, vital signs, electrocardiograms, safety laboratory tests, physical examinations, and ophthalmological assessments.

7.1.2.2.2 Study MEM-MD-27

This was an open-label sequential-cohort, dose-escalation study in patients with acute mania associated with bipolar I disorder.

There were 3 sequential cohorts (numbered 1, 2, and 3, in sequence), each consisting of unique subjects, treated as follows.

Cohort 1: 20 to 30 mg/day for 21 days (starting dose of 20 mg/day)

Cohort 2: 20 to 40 mg/day for 21 days (starting dose of 20 mg/day)

Cohort 3: 30 to 50 mg/day for 21 days (starting dose of 30 mg/day).

Subjects enrolled were men and women, aged 18 to 65 years.

Safety parameters included adverse events, safety laboratory tests, vital signs, and physical examinations.

7.1.2.3 Dose-Blinded Extension Study In Patients

7.1.2.3.1 Study MEM-MD-06C

This study was a dose-blinded extension of 16 weeks to Study MEM-MD-06B. Eligible patients were randomized in equal proportions to receive immediate-release memantine in doses of 40 mg/day, 60 mg/day, or 80 mg/day.

Safety parameters included adverse events, vital signs, electrocardiograms, safety laboratory tests, and physical examinations.

7.1.2.4 Placebo-Controlled Drug-Drug Interaction Study In Healthy Subjects

7.1.2.4.1 Study MRZ 90001-0519/1

This was a randomized, double-blind, placebo-controlled study of the pharmacokinetic interaction between memantine (as an immediate-release formulation) and bupropion.

Healthy men, aged between 18 and 45 years, were randomized to treatment either with memantine or with placebo. They were dosed as follows.

Day 1: Bupropion in a single dose of 100 mg.

Days 5 through 31: Memantine (or placebo). Memantine begun in a dose of 10 mg/day, increased to 30 mg/day over 10 days. Dose of 30 mg/day maintained.

Day 29: Bupropion in a single dose of 100 mg.

Safety parameters included adverse events, vital signs, electrocardiograms, safety laboratory tests and physical examinations.

7.1.3 Group 3 (Clinical Pharmacology Studies Of Memantine ER)

The designs of individual studies in this group are further outlined below.

7.1.3.1 Study MEM-PK-13

This was a randomized, open-label, single-dose, four-way crossover study comparing the bioavailability of three prototype memantine ER capsules, each of

40 mg strength, and that of memantine IR 20 mg twice daily. The periods of dosing were separated by a 21-day washout.

Healthy men and women, aged 18 to 45 years, were enrolled in the study.

Safety parameters included adverse events, vital signs, electrocardiograms, safety laboratory tests and physical examinations.

This study is complete.

7.1.3.2 Study MEM-PK-17

This was a randomized, open-label, single-dose, three-way crossover study comparing the bioavailability of the clinical trial memantine ER capsule (28 mg), and the to-be-marketed memantine ER capsule (28 mg) under fasted conditions, and the effect of food on the bioavailability of the memantine ER capsule (28 mg).

Healthy men and women, aged 18 to 45 years, were enrolled in the study.

Safety parameters included adverse events, vital signs, electrocardiograms, safety laboratory tests and physical examinations.

This study is complete.

7.1.3.3 Study MEM-PK-18

This was an open-label multiple-dose study intended to evaluate the pharmacokinetics of the to-be-marketed memantine ER capsule (28 mg) at steady-state.

Healthy men and women, aged 18 to 45 years, were enrolled in the study.

The memantine ER dosing regime used in this study was as follows:

Study Days	Memantine ER Dose
1 through 3	7 mg QD
4 through 9	14 mg QD
10 through 15	21 mg QD
16 through 29	28 mg QD

Safety parameters included adverse events, vital signs, electrocardiograms, safety laboratory tests and physical examinations.

This study is complete.

7.1.3.4 Study MEM-PK-23

This was a randomized, open-label, multiple-dose, two-way crossover study comparing the pharmacokinetics of memantine ER in a dose of 28 mg QD with memantine IR given in a dose of 10 mg BID, both after administration of single doses and at steady state.

Healthy men and women, aged 18 to 45 years, were enrolled in the study.

The dosing regime for memantine ER used in this study was as follows.

Study Days	Memantine ER Dose
1	28 mg as a single dose
4 through 9	14 mg QD
10 through 15	21 mg QD
16 through 29	28 mg QD

The dosing regime for memantine IR used in this study was as follows.

Study Days	Memantine IR Dose
1	10 mg as a single dose
4 through 9	5 mg BID
10 through 15	10 mg in the morning and 5 mg in the evening
16 through 28	10 mg BID
29	10 mg as a single dose

Safety parameters included adverse events, vital signs, electrocardiograms, safety laboratory tests and physical examinations.

This study is complete.

7.1.3.5 Study MEM-PK-21

This is an open-label single-dose study intended to evaluate the pharmacokinetics of memantine ER in a dose of 3 mg in children aged 6 to 16 years with autistic spectrum disorder.

This study is ongoing.

7.2 Exposure

The overall number of patients and healthy subjects exposed to memantine in all completed studies included in the Integrated Summary of Safety (Groups 1, 2, and 3) is in the following sponsor table, which I have copied from the submission.

	Number of Patients/Subjects[a]	
	Placebo	*Memantine*
Group 1 (Memantine ER Studies in Patients With AD)		
MEM-MD-50	335	341
MEM-MD-51	0	164
MEM-MD-54	0	245 (246)[b]
Total of AD Patients	***335***	***750***
Group 2[c] (Memantine IR Studies Using Dosages > 20 mg/d in Non-AD Patients)		
MEM-MD-06A	266	259
MEM-MD-19	52	51
MEM-MD-20	46	51
MEM-MD-27	0	35
MEM-MD-06B	0	210 (183)[b]
MEM-MD-06C	0	0 (79)[b]
Total of Non-AD Patients	***364***	***606***
Total Patients	**699**	**1356**
Group 3 (Memantine ER Clinical Pharmacology Studies in Healthy Subjects)[d]		
MEM-PK-13	0	24
MEM-PK-17	0	24
MEM-PK-18	0	24
MEM-PK-23	0	26
MRZ 90001-0519/1[e]	8	16
All Healthy Subjects	**8**	**114**

a Patients are counted only once within a treatment group. Patients who received memantine in lead-in studies are not counted in extension studies.
b Number in parenthesis is the number of patients exposed to memantine in lead-in studies.
c Not including Study MRZ 90001-0519/1.
d Subjects in Study MRZ 90001-0519/1 received memantine IR.
e Study MRZ 90001-0519/1 is a Group 2 study in healthy subjects.
AD = Alzheimer's disease; ER = extended release; IR = immediate release.

7.2.1 Group 1

7.2.1.1 Placebo-Controlled Clinical Study

See Section 6.1.10.3.

7.2.1.2 Open-Label Uncontrolled Clinical Studies

Patient exposure to memantine ER in the completed open-label studies MEM-MD-51 and MEM-MD-54 is in the following table, which I have copied from the submission.

	Memantine ER (N = 655)
Treatment duration, days	
Mean	206.5
SD	86.2
Median	196
Min, Max	8, 398
Treatment duration, n (%)	
≥ 1 day	655 (100)
≥ 4 weeks	632 (96.5)
≥ 8 weeks	615 (93.9)
≥ 12 weeks	589 (89.9)
≥ 18 weeks	573 (87.5)
≥ 24 weeks	555 (84.7)
≥ 36 weeks	112 (17.1)
≥ 52 weeks	76 (11.6)
Patient-years	370.3

ER = extended release; Max = maximum; Min = minimum.

7.2.2 Group 2

7.2.2.1 Placebo-Controlled And Open-Label Clinical Studies In Patients

Patient exposure to memantine in these studies is summarized in the following table which I have copied from the submission.

In these studies, most patients received a maximum daily dose of 40 to 50 mg/day. The modal daily dose was 40 mg.

53% of patients in these studies were exposed to memantine IR for at least 24 weeks.

	Memantine IR Study						
	06A (N = 259)	*06B (N = 393)*	*06C (N = 79)*	*19 (N = 51)*	*20 (N = 51)*	*27 (N = 35)*	*Total (N = 606)*
Treatment duration, days							
Mean	95.8	224.0	100.2	88.9	76.0	16.0	213.7
SD	36.5	96.3	30.2	41.2	45.0	6.6	159.4
Median	113	281	113	119	86	21	203
Min, Max	1, 187	8, 353	8, 120	15, 131	4, 127	2, 22	1, 547
Treatment duration, n (%)							
≥ 1 day	259 (100)	393 (100)	79 (100)	51 (100)	51 (100)	35 (100)	606 (100)
≥ 4 weeks	230 (88.8)	374 (95.2)	73 (92.4)	46 (90.2)	42 (82.4)	0	514 (84.8)
≥ 8 weeks	213 (82.2)	355 (90.3)	70 (88.6)	36 (70.6)	29 (56.9)	0	461 (76.1)
≥ 12 weeks	201 (77.6)	334 (85.0)	69 (87.3)	31 (60.8)	27 (52.9)	0	430 (71.0)
≥ 18 weeks	9 (3.5)	301 (76.6)	0	6 (11.8)	2 (3.9)	0	346 (57.1)
≥ 24 weeks	1 (0.4)	287 (73.0)	0	0	0	0	321 (53.0)
≥ 36 weeks	0	266 (67.7)	0	0	0	0	282 (46.5)
≥ 52 weeks	0	0	0	0	0	0	157 (25.9)
Patient-years	68.0	241.0	21.7	12.4	10.6	1.5	354.6

a Does not include Study MRZ 90001-0519/1.

Maximum assigned dosages were 40 mg/d (MEM-MD-06A and MEM-06B); 50 mg/d (MEM-MD-27); 60 mg/d (MEM-MD-19 and MEM-MD-20); and 80 mg/d (MEM-MD-06B).

IR = immediate release; Max = maximum; Min = minimum.

7.2.2.2 Placebo-Controlled Drug-Drug Interaction Study In Healthy Subjects

16 subjects were exposed to memantine for up to 27 days in this study.

7.2.3 Group 3

Patient exposure to memantine ER in the completed clinical pharmacology studies is summarized in the next sponsor table.

	MEM-PK-13[a]	***MEM-PK-17***	***MEM-PK-18***	***MEM-PK-23***[a]
Number of subjects on active drug	24	24	24	26
Total subject-days	92	71	661	1233
Mean days on drug	3.83	2.96	27.5	47.4

a MEM-PK-13 and MEM-PK-23 include subjects taking memantine immediate release (IR).

ER = extended release.

7.3 Demographic And Other Baseline Characteristics

7.3.1 Group 1

7.3.1.1 Placebo-Controlled Clinical Study

See Section 6.1.10.2.

7.3.1.2 Open-Label Uncontrolled Clinical Studies

The demographic and other baseline characteristics for patients enrolled in Studies MEM-MD-51 and MEM-MD-54 are summarized in the following table, which has been created from data provided by the sponsor.

Study	MEM-MD-51	MEM-MD-54
Mean Age	76.0 years	77.5 years
% Female	71.7	62.2
% Caucasian	96.3	91.5
Mean Mini-Mental Status Examination score	10.9 (Range: 3-15)	13.5 (Range: 3-20)

7.3.2 Group 2

7.3.2.1 Placebo-Controlled Clinical Studies In Patients

The demographics of patients enrolled in these studies is summarized in the following sponsor table.

Demographics of Patients in Placebo-Controlled Group 2 Studies—Safety Population[a]

	MEM-MD-06A[b]		*MEM-MD-19*[b]		*MEM-MD-20*[b]	
	Mem IR (N = 259)	*Placebo (N = 266)*	*Mem IR (N = 51)*	*Placebo (N = 52)*	*Mem IR (N = 51)*	*Placebo (N = 46)*
Age, y						
Mean ± SD	60.7 ± 10.0	60.2 ± 10.2	57.7 ± 11.6	56.8 ± 11.4	63.9 ± 12.9	62.8 ± 12.1
Sex, n (%)						
Female	102 (39.4)	109 (41.0)	19 (37.3)	24 (46.2)	28 (54.9)	26 (56.5)
Male	157 (60.6)	157 (59.0)	32 (62.7)	28 (53.8)	23 (45.1)	20 (43.5)
Race, n (%)						
Caucasian	205 (79.2)	219 (82.3)	47 (92.2)	46 (88.5)	44 (86.3)	40 (87.0)
Non-Caucasian	54 (20.8)	47 (17.7)	4 (7.8)	6 (11.5)	7 (13.7)	6 (13.0)
Weight, lb						
Mean ± SD	218.3 ± 45.9	211.7 ± 41.8	198.8 ± 32.8	205.7 ± 40.2	174.0 ± 33.3	172.2 ± 38.7

a Does not include Study MRZ 90001-0519/1.

b For MEM-MD-06A, maximum dosage was 40 mg/d; for MEM-MD-19 and MEM-MD-20, maximum dosage was 60 mg/d.

Mem IR = memantine immediate release (> 20 mg/d).

7.3.2.2 Open-Label Uncontrolled Clinical Studies In Patients

The demographics of patients enrolled in Studies MEM-MD-06B and MEM-MD-06C were reflective of their demographics in the lead-in study MEM-MD-06A and is not repeated here.

In Study MEM-MD-27:

- 16 men and 19 women were enrolled
- The mean patient age was 41.2 years (range: 18 to 66 years)
- 65.7% of patients were Caucasian.

7.3.3 Group 3

In the Clinical Pharmacology studies of memantine ER:

- The 98 enrolled subjects ranged in age from 18 to 45 years
- 63.3% were men
- 80.6% were Caucasian.

7.4 Adverse Events

7.4.1 Group 1

7.4.1.1 Placebo-Controlled Clinical Study

See Section 6.2.4.2.1.

7.4.1.2 Open-Label Uncontrolled Clinical Studies

The most common treatment-emergent adverse events (i.e., adverse events that occurred in ≥ 5% of patients in any treatment group) in Studies MEM-MD-51 and MEM-MD-54 are summarized in the following sponsor table.

	MEM-MD-54 (28 Weeks)		*MEM-MD-51 (52 Weeks)*	*All Patients*
	Pbo/Mem (N = 245)	*Mem/Mem (N = 246)*	*(N = 164)*	*N = 655*
	n (%)	**n (%)**	**n (%)**	**n (%)**
Patients with at least one TEAE	***157 (64.1)***	***143 (58.1)***	***150 (91.5)***	***450 (68.7)***
Fall	15 (6.1)	17 (6.9)	19 (11.6)	51 (7.8)
Urinary tract infection	19 (7.8)	14 (5.7)	17 (10.4)	50 (7.6)
Dizziness	15 (6.1)	8 (3.3)	12 (7.3)	35 (5.3)
Agitation	4 (1.6)	18 (7.3)	11 (6.7)	33 (5.0)
Insomnia	14 (5.7)	9 (3.7)	6 (3.7)	29 (4.4)
Weight decreased	8 (3.3)	6 (2.4)	15 (9.1)	29 (4.4)
Diarrhea	10 (4.1)	9 (3.7)	9 (5.5)	28 (4.3)
Somnolence	11 (4.5)	7 (2.8)	9 (5.5)	27 (4.1)
Constipation	9 (3.7)	6 (2.4)	11 (6.7)	26 (4.0)
Confusional state	7 (2.9)	6 (2.4)	11 (6.7)	24 (3.7)
Hypertension	7 (2.9)	7 (2.8)	9 (5.5)	23 (3.5)
Weight increased	4 (1.6)	3 (1.2)	12 (7.3)	19 (2.9)
Anxiety	3 (1.2)	4 (1.6)	11 (6.7)	18 (2.7)
Depression	2 (0.8)	7 (2.8)	9 (5.5)	18 (2.7)
Nausea	3 (1.2)	3 (1.2)	9 (5.5)	15 (2.3)

Studies MEM-MD-51 and MEM-MD-54
ER = extended release: Mem = memantine; pbo = placebo; TEAE = treatment-emergent adverse event.

The incidence of treatment-emergent adverse events that occurred in ≥ 5% of patients who were exposed to memantine ER for at least 52 weeks either Study MEM-MD-51, or in Studies MEM-MD-50 and MEM-MD-54 combined are summarized in the next sponsor table.

	Memantine ER (N = 214) ***n (%)***
Patients with at least one TEAE	*168 (78.5)*
Fall	19 (8.9)
Urinary tract infection	16 (7.5)
Diarrhea	15 (7.0)
Cough	14 (6.5)
Dizziness	14 (6.5)
Headache	14 (6.5)
Weight decreased	14 (6.5)
Agitation	13 (6.1)
Influenza	13 (6.1)
Weight increased	13 (6.1)
Confusional state	11 (5.1)
Depression	11 (5.1)
Hypertension	11 (5.1)

Studies MEM-MD-50, MEM-MD-51, and MEM-MD-54
ER = extended release; TEAE = treatment-emergent adverse event.

7.4.2 Group 2

7.4.2.1 Placebo-Controlled Clinical Studies In Patients

The incidence treatment-emergent adverse events that occurred in ≥ 5% of memantine-treated patients in these studies is in the following table, which I have copied from the submission.

As the table below indicates, the incidence of dizziness and fatigue were particularly more common in patients treated with memantine than in those treated with placebo.

	MEM-MD-06A[b]		***MEM-MD-19***[b]		***MEM-MD-20***[b]	
	Mem IR (N = 259)	*Placebo (N = 266)*	*Mem IR (N = 51)*	*Placebo (N = 52)*	*Mem IR (N = 51)*	*Placebo (N = 46)*
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Patients with at least one TEAE	***196 (75.7)***	***205 (77.1)***	***35 (68.6)***	***36 (69.2)***	***41 (80.4)***	***31 (67.4)***
Dizziness	55 (21.2)	11 (4.1)	15 (29.4)	1 (1.9)	16 (31.4)	2 (4.3)
Fatigue	18 (6.9)	12 (4.5)	7 (13.7)	1 (1.9)	6 (11.8)	1 (2.2)
Headache	21 (8.1)	18 (6.8)	8 (15.7)	4 (7.7)	2 (3.9)	5 (10.9)
Upper respiratory tract infection	11 (4.2)	17 (6.4)	4 (7.8)	0	0	2 (4.3)
Diarrhea	10 (3.9)	16 (6.0)	3 (5.9)	2 (3.8)	1 (2.0)	3 (6.5)
Nasopharyngitis	14 (5.4)	14 (5.3)	3 (5.9)	0	4 (7.8)	1 (2.2)
Edema peripheral	14 (5.4)	13 (4.9)	3 (5.9)	1 (1.9)	0	1 (2.2)
Nausea	10 (3.9)	14 (5.3)	5 (9.8)	4 (7.7)	7 (13.7)	1 (2.2)
Back pain	5 (1.9)	8 (3.0)	4 (7.8)	1 (1.9)	0	0
Urinary tract infection	6 (2.3)	4 (1.5)	3 (5.9)	3 (5.8)	0	0
Balance disorder	5 (1.9)	2 (0.8)	1 (2.0)	0	4 (7.8)	0
Somnolence	4 (1.5)	5 (1.9)	2 (3.9)	0	4 (7.8)	3 (6.5)

a Does not include Study MRZ 90001-0519/1.

b For MEM-MD-06A, maximum dosage was 40 mg/d; for MEM-MD-19 and MEM-MD-20, maximum dosage was 60 mg/d.

Mem IR = memantine immediate release (> 20 mg/d); TEAE = treatment-emergent adverse event.

7.4.2.2 Open-Label Uncontrolled Clinical Studies In Patients

Dizziness, fatigue and blurred vision were the most common adverse events seen in Studies MEM-MD-06B and MEM-MD-06C.

In Study MEM-MD-06C, the incidence of dizziness at various doses of memantine was as follows:

- 30.8% of patients who received a dose of 80 mg/day
- 12.0% of patients who received a dose of 60 mg/day
- 7.1% of patients who received a dose of 40 mg/day.

In Study MEM-MD-27, the most common adverse events were nausea (17%), constipation (17%) and headache (11%).

7.4.2.3 Placebo-Controlled Drug-Drug Interaction Study In Healthy Subjects

Adverse events reported in at least 2 subjects treated with memantine included headache, dizziness, cough, somnolence, fatigue, and dysphonia.

7.4.3 Group 3

Adverse events that occurred in at least 2 subjects in any Clinical Pharmacology study of memantine ER are in the following table, which I have copied from the submission.

	MEM-PK-13[a] ***(N = 24)***	***MEM-PK-17 (N = 24)***	***MEM-PK-18 (N = 24)***	***MEM-PK-23***[a] ***(N = 26)***
	n (%)			
Subjects with at least one TEAE	**20 (83.3)**	**8 (33.3)**	**15 (62.5)**	**19 (73.1)**
Dizziness	15 (62.5)	3 (12.5)	4 (16.7)	5 (19.2)
Headache	7 (29.2)	4 (16.7)	11 (45.8)	9 (34.6)
Somnolence	1 (4.2)	0	9 (37.5)	1 (3.8)
Nausea	3 (12.5)	0	2 (8.3)	2 (7.7)
Back pain	1 (4.2)	0	0	5 (19.2)
Paresthesia	3 (12.5)	0	1 (4.2)	0
Vomiting	1 (4.2)	1 (4.2)	2 (8.3)	1 (3.8)
Viral upper respiratory tract infection	0	0	0	3 (11.5)
Pharyngolaryngeal pain	0	0	1 (4.2)	2 (7.7)
Sedation	2 (8.3)	0	0	0
Flushing	2 (8.3)	0	0	0
Rash	0	0	2 (8.3)	0

a MEM-PK-13 and MEM-PK-23 include subjects taking memantine IR.
ER = extended release; IR = immediate release; TEAE = treatment-emergent adverse event.

7.5 Deaths

7.5.1 Group 1

7.5.1.1 Placebo-Controlled Clinical Study

See Section 6.2.4.2.2.

7.5.1.2 Open-Label Uncontrolled Clinical Studies

30 patients died during Studies MEM-MD-51 and MEM-MD-54.

Deaths that occurred in Studies MEM-MD-51 and MEM-MD-54 are listed by the sponsor, with narratives provided for each. None are clearly attributable to study drug; all appear to have been accompanied by illnesses common in this population. A further description (in this review) of the deaths that occurred in these studies is not warranted.

3 deaths occurred in the ongoing open-label extension study MEM-MD-82 through the cut-off date for the Integrated Summary of Safety. Again, based on

the narratives provided in this submission, these adverse events are consistent with illnesses common in the elderly.

7.5.2 Group 2

7.5.2.1 Placebo-Controlled Clinical Studies In Patients

There were no deaths in memantine-treated patients in these studies. A placebo-treated patient in Study MEM-MD-06A died within 30 days of the last dose of study drug after undergoing a craniotomy for subdural hematoma.

7.5.2.2 Open-Label Uncontrolled Clinical Studies In Patients

4 deaths occurred, all in Study MEM-MD-06B, and all in patients who had previously received placebo in Study MEM-MD-06A. In all 4 cases, the deaths appeared unlikely to be attributable to memantine.

7.5.2.3 Placebo-Controlled Drug-Drug Interaction Study In Healthy Subjects

No deaths occurred during this study.

7.5.3 Group 3

No deaths occurred during these studies.

7.6 Non-Fatal Serious Adverse Events

7.6.1 Group 1

7.6.1.1 Placebo-Controlled Clinical Study

See Section 6.2.4.2.3.

7.6.1.2 Open-Label Uncontrolled Clinical Studies

14.8% of patients enrolled in Studies MEM-MD-51 and MEM-MD-54 had at least one non-fatal serious adverse event during those studies. Narratives are provided for these events, none of which are attributable to study drug; all the events described are consistent with incidental illnesses common in older individuals.

Non-fatal serious adverse events are reported to have occurred in 13 patients in the ongoing open-label extension study MEM-MD-82 through the cut-off date for the Integrated Summary of Safety. Their description suggests that they represent incidental illnesses and were not caused by memantine.

7.6.2 Group 2

7.6.2.1 Placebo-Controlled Clinical Studies In Patients

The overall incidence of serious adverse events in these studies was low, and similar in the memantine and placebo groups; individual serious adverse events had a very low incidence. None seem likely to have been caused by memantine, based on review of the listings for these events.

7.6.2.2 Open-Label Uncontrolled Clinical Studies In Patients

Individual serious adverse events in these studies were very infrequent and by their description seemingly unlikely to be related to study drug.

7.6.2.3 Placebo-Controlled Drug-Drug Interaction Study In Healthy Subjects

No serious adverse events occurred during this study.

7.6.3 Group 3

No serious adverse events occurred during these studies.

7.7 Premature Discontinuations Due To Adverse Events

7.7.1 Group 1

7.7.1.1 Placebo-Controlled Clinical Study

See Section 6.2.4.2.4.

7.7.1.2 Open-Label Uncontrolled Clinical Studies

The following sponsor table shows the incidence of individual treatment-emergent adverse events that led to treatment discontinuation and occurred in at least 1% of those in any treatment group in the two completed open-label uncontrolled trials, MEM-MD-51 and MEM-MD-54. As the table indicates, the incidence of individual adverse events in this category was very low, with the majority seemingly unrelated to treatment with memantine.

	MEM-MD-54		MEM-MD-51	All Patients
	Placebo/Mem (N = 245)	Mem/Mem (N = 246)	(N = 164)	(N = 655)
	n (%)	n (%)	n (%)	n (%)
Patients with an ADO	***20 (8.2)***	***25 (10.2)***	***39 (23.8)***	***84 (12.8)***
Agitation	0	3 (1.2)	4 (2.4)	7 (1.1)
Dizziness	2 (0.8)	0	5 (3.0)	7 (1.1)
Dementia Alzheimer's type	3 (1.2)	0	1 (0.6)	4 (0.6)
Pneumonia	3 (1.2)	1 (0.4)	0	4 (0.6)
Aggression	0	0	3 (1.8)	3 (0.5)
Dementia	0	0	3 (1.8)	3 (0.5)
Depression	0	0	2 (1.2)	2 (0.3)
Hip fracture	0	0	2 (1.2)	2 (0.3)
Tremor	0	0	2 (1.2)	2 (0.3)

Studies MEM-MD-51 and MEM-MD-54

ADO = adverse event leading to dropout; ER = extended release; Mem = memantine ER; N = number of patients in treatment group; n = subset of N for the category.

7.7.2 Group 2

7.7.2.1 Placebo-Controlled Clinical Studies In Patients

The following sponsor table shows the incidence of individual treatment-emergent adverse events that led to treatment discontinuation and occurred in at least two patients treated with memantine (immediate-release) in these trials. While the incidence of all individual adverse events was very low in both the memantine and placebo groups in each of these trials, the incidence of dizziness was consistently higher in those treated with memantine than in those treated with placebo in these studies.

	MEM-MD-06A[a]		MEM-MD-19[a]		MEM-MD-20[a]	
	Mem IR (N = 259)	Placebo (N = 266)	Mem IR (N = 51)	Placebo (N = 52)	Mem IR (N = 51)	Placebo (N = 46)
	n (%)		n (%)		n (%)	
Patients with an ADO	***28 (10.8)***	***9 (3.4)***	***11 (21.6)***	***6 (11.5)***	***17 (33.3)***	***6 (13.0)***
Dizziness	7 (2.7)	1 (0.4)	3 (5.9)	1 (1.9)	4 (7.8)	1 (2.2)
Fatigue	1 (0.4)	0	2 (3.9)	0	2 (3.9)	1 (2.2)
Headache	1 (0.4)	0	2 (3.9)	0	1 (2.0)	0
Nausea	1 (0.4)	2 (0.8)	2 (3.9)	3 (5.8)	3 (5.9)	0
Ataxia	3 (1.2)	0	0	0	0	0
Palpitations	2 (0.8)	0	0	0	0	0

a For MEM-MD-06A, maximum dosage was 40 mg/d; for MEM-MD-19 and MEM-MD-20, maximum dosage was 60 mg/d.

ADO = adverse event leading to dropout; Mem IR = memantine immediate release (> 20 mg/d).

7.7.2.2 Open-Label Uncontrolled Clinical Studies In Patients

The following sponsor table shows the incidence of individual treatment-emergent adverse events that led to treatment discontinuation and occurred in at least two patients treated with memantine (immediate-release) in these trials. The incidence of these events was low.

	MEM-MD-06B		***MEM-MD-06C***	***MEM-MD-27***
	Placebo/Mem (N = 210)	*Mem/Mem (N = 183)*	*(N = 79)*	*(N = 35)*
	n (%)	**n(%)**	**n (%)**	**n (%)**
Patients with an ADO	***28 (13.3)***	***9 (4.9)***	***9 (11.4)***	***1 (2.9)***
Dizziness	6 (2.9)	1 (0.5)	3 (3.8)	0
Myocardial infarction	3 (1.4)	0	0	0
Somnolence	3 (1.4)	0	2 (2.5)	0
Asthenia	2 (1.0)	0	0	0
Cerebrovascular accident	2 (1.0)	0	0	0
Blurred vision	2 (1.0)	0	0	0
Fatigue	2 (1.0)	0	1 (1.3)	0

ADO = adverse event leading to dropout; IR = immediate release; Mem = memantine; N = number of patients in treatment group; n = subset of N for the category.

7.7.2.3 Placebo-Controlled Drug-Drug Interaction Study In Healthy Subjects

There were no discontinuations due to adverse events in this study.

7.7.3 Group 3

There were no discontinuations due to adverse events in the clinical pharmacology studies of memantine ER.

7.8 Safety Laboratory Tests

7.8.1 Group 1

7.8.1.1 Placebo-Controlled Clinical Study

See Section 6.2.4.4.

7.8.1.2 Open-Label Uncontrolled Clinical Studies

The incidence in these studies of laboratory abnormalities classed as potentially clinically was very low and of little import in regard to memantine.

7.8.2 Group 2

7.8.2.1 Placebo-Controlled Clinical Studies In Patients

There was no meaningful difference between the memantine and placebo groups in these studies in the incidence of laboratory abnormalities considered potentially clinically significant or in the mean change from baseline to endpoint in individual laboratory parameters.

7.8.2.2 Open-Label Uncontrolled Clinical Studies In Patients

The mean changes from baseline to endpoint in laboratory parameters in these studies were small, and appeared much less likely to be related to memantine than to other factors such as diabetes mellitus. Similar conclusions apply to laboratory findings satisfying the potentially clinically significant criteria.

7.8.2.3 Placebo-Controlled Drug-Drug Interaction Study In Healthy Subjects

A single memantine-treated subject in this study had a slightly elevated alanine aminotransferase level of 69.7 U/L (reference range of 10 to 50 U/L). This subject had a baseline alanine aminotransferase level of 27.9 U/L and the aforementioned abnormality had resolved several days after first detected.

7.8.3 Group 3

Laboratory abnormalities seen in memantine-treated patients in these studies were minor and of no clinical significance.

7.9 Vital Signs

7.9.1 Group 1

7.9.1.1 Placebo-Controlled Clinical Study

See Section 6.2.4.3.

7.9.1.2 Open-Label Uncontrolled Clinical Studies

No vital sign data of concern are apparent either in the mean change from baseline to endpoint or in those judged potentially clinically significant in Studies MEM-MD-51 and MEM-MD-54.

7.9.2 Group 2

7.9.2.1 Placebo-Controlled Clinical Studies In Patients

Changes from baseline to endpoint in vital sign parameters were in general small in these studies and the differences between treatment groups seemingly of little significance as indicated in the following sponsor table, which I have copied from the submission.

Parameter	MEM-MD-06A				MEM-MD-19				MEM-MD-20			
	Placebo (N = 266)		Mem (N = 259)		Placebo (N = 52)		Mem (N = 51)		Placebo (N = 46)		Mem (N = 51)	
	n	mean ± SD	n	mean ± SD	n	mean ± SD	n	mean ± SD	n	mean ± SD	n	mean ± SD
Systolic blood pressure, mm Hg												
Baseline	262	131.9 ± 16.3	256	132.6 ± 14.8	52	127.8 ± 16.1	51	130.6 ± 14.5	44	129.3 ± 14.3	50	131.7 ± 14.5
Change from baseline	262	0.7 ± 15.7	256	0.2 ± 15.6	52	4.5 ± 16.4	51	2.8 ± 16.7	44	−0.8 ± 14.1	50	−2.9 ± 19.9
Diastolic blood pressure, mm Hg												
Baseline	262	76.9 ± 9.8	256	76.0 ± 9.6	52	76.5 ± 10.8	51	77.4 ± 10.5	44	77.8 ± 9.9	50	76.8 ± 9.4
Change from baseline	262	−0.3 ± 9.3	256	0.2 ± 8.7	52	1.4 ± 11.9	51	0.5 ± 11.0	44	0.2 ± 9.4	50	−0.5 ± 10.6
Pulse rate, bpm												
Baseline	262	76.6 ± 10.6	256	74.6 ± 11.1	52	79.1 ± 12.7	51	76.9 ± 9.0	44	71.9 ± 11.9	50	70.4 ± 9.7
Change from baseline	262	−1.3 ± 10.1	256	−1.1 ± 10.6	52	−0.5 ± 9.5	51	−1.0 ± 8.2	44	0.5 ± 12.1	50	0.8 ± 10.5
Weight, lb												
Baseline	233	212.2 ± 42.0	228	219.2 ± 46.8	49	202.3 ± 35.1	48	195.8 ± 30.9	40	169.3 ± 35.7	44	177.0 ± 32.4
Change from baseline	233	0.5 ± 9.0	228	0.5 ± 8.1	49	2.0 ± 5.9	48	1.2 ± 4.7	40	0.3 ± 5.8	44	1.5 ± 5.4

End-of-study value is last observation carried forward.
IR = immediate release.

The incidence of vital sign findings falling into the potentially clinically significant category was very small and not strikingly different between treatment groups as indicated by the next sponsor table.

Parameter	*PCS Criteria*	*MEM-MD-06A*		*MEM-MD-19*		*MEM-MD-20*	
		Placebo (N = 266)	*Mem (N = 259)*	*Placebo (N = 52)*	*Mem (N = 51)*	*Placebo (N = 46)*	*Mem (N = 51)*
		n/N_1 (%)	**n/N_1 (%)**	**n/N_1 (%)**	**n/N_1 (%)**	**n/N_1 (%)**	**n/N_1 (%)**
SBP, mm Hg	≥ 180 and increase ≥ 20	9/262 (3.4)	9/256 (3.5)	3/52 (5.8)	1/51 (2.0)	1/44 (2.3)	2/50 (4.0)
	≤ 90 and decrease ≥ 20	5/262 (1.9)	3/256 (1.2)	1/52 (1.9)	2/51 (3.9)	1/44 (2.3)	3/50 (6.0)
DBP, mm Hg	≥ 105 and increase ≥ 15	2/262 (0.8)	3/256 (1.2)	0/52	0/51	0/44	0/50
	≤ 50 and decrease ≥ 15	2/262 (0.8)	2/256 (0.8)	0/52	3/51 (5.9)	0/44	0/50
Pulse rate, bpm	≥ 120 and increase ≥ 15	1/262 (0.4)	0/256	0/52	0/51	0/44	1/50 (2.0)
	≤ 50 and decrease ≥ 15	0/262	2/256 (0.8)	1/52 (1.9)	0/51	0/44	0/50
Weight, kg	Increase ≥ 7%	11/233 (4.7)	6/228 (2.6)	2/49 (4.1)	0/48	1/40 (2.5)	1/44 (2.3)
	Decrease ≥ 7%	7/233 (3.0)	8/228 (3.5)	0/49	0/48	1/40 (2.5)	0/44

DBP = diastolic blood pressure; IR = immediate release; Mem = memantine; N = number of patients in treatment group; N_1 = number of patients with a non-PCS baseline value and at least one postbaseline value during double-blind treatment; n = subgroup of N_1 with at least one PCS postbaseline value during double-blind treatment; PCS = potentially clinically significant; SBP = systolic blood pressure.

7.9.2.2 Open-Label Uncontrolled Clinical Studies In Patients

Changes from baseline to endpoint in these studies in vital sign parameters were small as was the incidence of recordings deemed potentially clinically significant.

7.9.2.3 Placebo-Controlled Drug-Drug Interaction Study In Healthy Subjects

No clinically significant changes in vital signs appear to have been observed in this study.

7.9.3 Group 3

There were no noteworthy alterations in vital signs in the clinical pharmacology studies of memantine ER.

7.10 Electrocardiograms

7.10.1 Group 1

7.10.1.1 Placebo-Controlled Clinical Study

See Section 6.2.4.5.

7.10.1.2 Open-Label Uncontrolled Clinical Studies

Changes from baseline to endpoint in these studies in electrocardiographic parameters were small and the incidence of recordings deemed potentially clinically significant very low.

7.10.2 Group 2

7.10.2.1 Placebo-Controlled Clinical Studies In Patients

No clinically significant differences were seen between the memantine and placebo groups in these studies in regard to the changes from baseline to endpoint in individual electrocardiogram parameters.

The incidence of potentially clinically significant electrocardiographic abnormalities was quite low and without striking differences between the treatment groups in these studies as indicated in the following sponsor table.

Parameter	***PCS Criterion***	***MEM-MD-06A***		***MEM-MD-19***		***MEM-MD-20***	
		Placebo (N = 266)	*Mem (N = 259)*	*Placebo (N = 52)*	*Mem (N = 51)*	*Placebo (N = 46)*	*Mem (N = 51)*
		n/N_1 (%)	**n/N_1 (%)**	**n/N_1 (%)**	**n/N_1 (%)**	**n/N_1 (%)**	**n/N_1 (%)**
PR interval, msec	≥ 250	0/231	1/215 (0.5)	0/46	1/44 (2.3)	0/39	0/44
QRS Interval, msec	≥ 150	2/230 (0.9)	5/220 (2.3)	0/46	1/45 (2.2)	0/39	0/45
QTc Bazett, msec	≥ 500	7/232 (3.0)	5/220 (2.3)	0/48	0/46	0/41	0/45
QTc Fridericia, msec	≥ 500	—	—	0/48	0/46	0/41	0/45

IR = immediate release; Mem = memantine; N = number of patients in treatment group; N_1 = number of patients with a non-PCS baseline value and at least one postbaseline value during double-blind treatment; n = subgroup of N_1 with at least one PCS postbaseline value during double-blind treatment; PCS = potentially clinically significant.

7.10.2.2 Open-Label Uncontrolled Clinical Studies In Patients

Changes from baseline to endpoint in these studies in electrocardiographic parameters were again small and the incidence of recordings classified as potentially clinically significant based on pre-specified criteria very low.

7.10.2.3 Placebo-Controlled Drug-Drug Interaction Study In Healthy Subjects

No electrocardiogram changes of significance appear to have seen in this study.

7.10.3 Group 3

No electrocardiographic findings of clinical significance were noted in the clinical pharmacology studies of memantine ER.

7.11 Electrocardiograms: QT Interval

The sponsor has performed an analysis based on centrally-read electrocardiographic intervals derived from randomized, double-blind, placebo-controlled studies of memantine IR at doses up to 80 mg/day. In these studies, 1994 patients out of 3679 patients with either Alzheimer's Disease or neuropathic pain were treated with memantine. No signal for an increase in QT/QT_c interval was seen either at the therapeutic dose of 20 mg/day or at higher doses.

The sponsor has supplemented that analysis with an in-depth assessment of post-marketing data (these reports include instances of overdose up to 2000 mg), and with data from open-label studies conducted during the clinical development program for memantine. Note that data in the "post-marketing category" extends to that obtained since memantine was first approved in Germany in 1982.

This analysis has been described fully in the submission and does not a more detailed description in this review.

After review of the sponsor's report of the above analyses, I concur that there is no indication so far suggesting that the clinical administration of memantine is associated with a prolongation of the QT interval.

7.12 Post-Marketing Experience

The sponsor states that since memantine ER is currently not marketed anywhere in the world, the safety data for that product that is included in this submission is based entirely on the Group 1 and Group 3 studies described in this Integrated Summary of Safety.

The sponsor has however reviewed the Forest Drug Safety Surveillance database for all serious spontaneous adverse reactions involving memantine IR use worldwide from October 16, 2003 through September 30, 2008. The objective of the review was to update the current approved package insert for memantine IR. Based on that review, the sponsor has proposed the addition of the following adverse reactions to the current approved label based on one or more of the following factors: seriousness, frequency of reporting, and potential causal connection to memantine. The adverse reactions to be described and the number of patients affected by each are in the following table, which I have copied from the submission.

Adverse Event	Number of Patients
Agranulocytosis	2
Pancytopenia	3
Thrombotic thrombocytopenic purpura	1
Torsades de pointes	2
Syndrome of inappropriate anti-diuretic hormone secretion	3

I have read each of the brief narratives for the above events that have been provided by the sponsor. All are compromised by either multiple confounding factors or a lack of detail to the extent that any relationship between those events and memantine use is hard to discern.

7.13 Sponsor's Conclusions

The sponsor has concluded from the Integrated Summary of Safety that memantine ER administered in a dose of 28 mg QD was well-tolerated and had a safety profile similar to that of placebo.

7.14 Reviewer's Summary And Conclusions

Studies included in the Integrated Summary of Safety were in 3 groups, as listed below.

- Group 1, comprising studies of memantine ER in patients with Alzheimer's Disease and including
  - The randomized, double-blind, placebo-controlled study MEM-MD-50
  - The following open-label uncontrolled studies
    - MEM-MD-51, a 52-week free-standing (i.e., non-extension) study
    - MEM-MD-54, a 28-week extension to MEM-MD-50
    - MEM-MD-82, a still-ongoing extension to MEM-MD-51 and MEM-MD-82
- Group 2, consisting of studies of the immediate-release formulation of memantine at doses > 20 mg/day (and as high as 80 mg/day). These included controlled and uncontrolled studies in neuropathic pain and bipolar disorder and a drug-drug interaction study with bupropion
- Group 3, consisting of clinical pharmacology studies of memantine ER.

A total of 775 patients with Alzheimer's Disease and 114 healthy subjects were exposed to memantine ER in the Group 1 and Group 3 studies.

Safety outcome measures in the majority of these studies included adverse events, vital signs, safety laboratory tests, and electrocardiograms.

Information from the above studies was supplemented in the Integrated Summary of Safety by a summary of post-marketing safety data for the immediate-release formulation of memantine and a review of the medical literature by the sponsor.

The cut-off date for data included in the Integrated Summary of Safety was September 30, 2008.

The data in the Integrated Summary of Safety indicated that the safety profile of the extended-release formulation of memantine, administered in a dose up to 20 mg QD, was broadly similar to that of the immediate-release formulation administered in a dose up to 10 mg BID and did not raise any new safety concerns.

8. 120-Day Safety Update

The 120-Day Safety Update was submitted on December 17, 2009, and was based on a proposal submitted on October 30, 2009 (i.e., after the original submission of this application), and agreed to by the Agency.

The cut-off date for data included in the Update was June 30, 2009; thus, the 120-Day Safety Update provides additional data accrued between September 30, 2008, the cut-off date for safety data included in the Integrated Summary of Safety and June 30, 2009.

The contents of the Update include information from the following sources:

- A clinical pharmacology study (MEM-PK-24) completed after the original submission of this application
- The ongoing open-label extension study MEM-MD-82
- A literature search
- Post-marketing experience.

Note that no safety data from the clinical pharmacology study MEM-PK-21 in which a dose of 3 mg was used in children aged 6 to 16 years with autistic spectrum disorder, which reported in the original submission of this NDA as being ongoing, has been included in either that original submission or in the 120-Day Safety Update.

8.1 Safety Data From Study MEM-PK-24 (Completed)

The design and safety data for this study are summarized below.

8.1.1 Design

This was an open-label, randomized, single-dose, two-way crossover study assessing the bioequivalence of a memantine ER capsule after administration as an intact capsule and after the capsule's contents were sprinkled on soft food (applesauce) in healthy subjects.

Healthy men and women, aged 18 to 45 years were each administered Treatments A and B (see below) in random order. The two treatments were separated by a washout period of 21 days.

Treatment A: Single oral dose of memantine ER capsule (28 mg) administered intact under fasted conditions

Treatment B: Single oral dose of memantine ER capsule (28 mg) administered after the capsule contents were sprinkled on 1 teaspoon of applesauce under fasted conditions.

8.1.2 Exposure

29 patients completed the study, receiving both treatments; 1 patient received only Treatment B.

Those enrolled in the study consisted of 6 men and 24 women between the ages of 20 and 44 years.

8.1.3 Adverse Events

There were no deaths, serious adverse events, or discontinuations due to adverse events in this study. All adverse events were mild to moderate in severity and are listed in the next sponsor table.

AE Preferred Term	No. of TEAEs (No. of Subjects)
Total	31 (10)
Headache	9 (7)
Abdominal pain	3 (2)
Insomnia	3 (1)
Constipation	2 (2)
Diarrhea	2 (2)
Nausea	2 (2)
Cough	1 (1)
Dermatitis contact	1 (1)
Dizziness	1 (1)
Muscle spasm	1 (1)
Muscle twitching	1 (1)
Pain in extremity	1 (1)
Presyncope	1 (1)
Somnolence	1 (1)
Vessel puncture site pain	1 (1)
Vomiting	1 (1)

AE - adverse event; TEAE = treatment-emergent adverse event.

8.1.4 Laboratory Data, Vital Signs, And Electrocardiograms

There were no findings of note in these data.

8.2 Safety Data From Ongoing Study MEM-MD-82

The limited safety data included in this submission are summarized below.

8.2.1 Deaths

Deaths that have occurred during this study are listed below; these include one death that occurred over 30 days after the last dose of study drug.

Patient Number	*Age, y*	*Sex*	*Day of Onset of Fatal SAE*[a]	*Day of Death*	*Days Off Study Drug*[b]	*SAE Preferred Term*	*Relationship*
1875104	71	F	223	237	0	Dementia Alzheimer's type	Not related
1525006	78	F	296	296	11	Cardiac arrest	Not related
1595004	70	F	195	205	44	Subarachnoid hemorrhage	Not related

a Day of onset is in relationship to date of first dose of open-label memantine ER (Day 1).
b At the time of death

It is improbable that any of the above deaths was causally related to memantine use.

8.2.2 Serious Adverse Events

17 patients have had serious adverse events either while receiving study drug or within 30 days of completing treatment. They are listed in the following table. None appear likely to be caused by memantine.

Patient ID	*Age (yrs)*	*Sex*	*SAE Start Day*[a]	*Preferred Term*
1515015	76	F	283	Gout
1525006	78	F	101	Metabolic encephalopathy
			286	Acute myocardial infarction[b]
				Thyrotoxic crisis[b]
			287	Dementia Alzheimer's type[b]
			296	Cardiac arrest[b,c]
1565105	55	F	277	Dementia Alzheimer's type
1575003	75	M	100	Gastric ulcer hemorrhage
1615009	73	M	190	Decubitus ulcer
				Wound infection bacterial
			217	Cardiac failure congestive
				Pneumonia
				Respiratory failure
1735011	62	M	241	Respiratory failure[b]
1745118	64	F	166	B-cell lymphoma
1755008	69	F	182	Bronchitis viral
1795111	79	M	342	Aggression
				Confusional state
1815101	82	F	74	Cholecystitis
1815104	76	F	232	Convulsion
1845112	75	M	26	Balance disorder
				Dysarthria
				Nausea
				Transient ischemic attack
				Vomiting
1845124	81	M	24	Mental status changes
1855004	82	F	361	Pneumonia
1875103	72	F	135	Aggression
				Agitation
				Anger
				Anxiety
				Depression
1875104	71	F	223	Dementia Alzheimer's type[b,c]
1875106	79	F	66	Escherichia urinary tract infection

a SAE Start Day = SAE Start Date - Date of First Dose + 1.
b Patient prematurely discontinued due to this SAE.
c Patient died due to this SAE.
SAE = serious adverse event

8.2.3 Drug Overdose

An 83-year-old woman who received memantine ER for 8 days in Study MEM-MD-82 developed confusion and lethargy; on evaluation, it was discovered that she had received four 28 mg capsules of memantine ER (instead of one 28 mg

capsule) daily for all 6 days. Memantine ER was withheld for 3 days and then resumed at an unspecified dose (presumably ≤ 28 mg/day). Her confusion and lethargy resolved.

8.3 Literature Search

The sponsor conducted a literature search for memantine citations using methods that are identical to those used for the Integrated Summary of Safety, but with a reporting period extending from October 1, 2008 through June 30, 2009.

Articles identified are listed in the submission.

A single article has warranted further description by the sponsor. The citation for the article is below.

Villoslada P, Arrondo G, Sepulcre J. et al. Memantine induces reversible neurologic impairment in patients with MS. Neurology 2009;72:1630-3.

The abstract for that article, which is self-explanatory, is copied verbatim from PubMed below.

BACKGROUND: Cognitive dysfunction is very common in multiple sclerosis (MS) and it severely impairs patients' quality of life. Thus, we explored whether memantine might improve cognitive performance in patients with MS.

METHODS: We conducted a pilot trial with memantine (30 mg/day) in patients with MS with cognitive impairment. The trial was designed as a 1-year, randomized, double-blind, crossover study comparing memantine against a placebo in 60 patients with MS and cognitive impairment. Cognitive impairment was defined as the performance 1.5 standard deviations below the normative data in at least two tests of two cognitive domains in the Brief Repeatable Battery-Neuropsychology. The primary endpoint was improvement of verbal memory and the secondary endpoints were safety and improvements in the other cognitive domains, disability and quality of life. The trial was registered at www.clinicaltrials.org: NCT00638833.

RESULTS: Although 19 patients had been included, the trial was halted after nine patients reported a worsening of their neurologic symptoms that deteriorated their quality of life. Seven of the nine patients in the memantine arm had blurred vision, fatigue, severe headache, increased muscle weakness, walking difficulties, or unstable gait. Only two patients in the placebo group reported neurologic symptoms and in both cases they were related with changes in their disease-modifying therapy. The adverse events only occurred on reaching the maximum dose (30 mg/day). After stopping medication, the patients reverted to their baseline disability within a few days.

CONCLUSIONS: Memantine at a dose of 30 mg/day may induce transient worsening of neurologic symptoms of multiple sclerosis.

The sponsor's summary of the article is similar to what is stated in the PubMed abstract.

8.4 Post-Marketing Experience For Memantine IR

8.4.1 Extent Of Memantine IR Use

The sponsor states the following:

- In addition to being approved for marketing in the United States since October 16, 2003, memantine IR is available in over 70 countries

- As of September 15, 2008, the exposure to memantine IR exceeded 3.3 million patient-years worldwide; as of September 15, 2009, that exposure had increased to more than 4.3 million patient-years worldwide

- Since memantine ER is not marketed anywhere in the world, there has been no exposure to that product, except during clinical studies.

8.4.2 Spontaneous Adverse Event Reports

The sponsor has reviewed the Forest Drug Safety Surveillance database for all spontaneous adverse reactions involving memantine from October 1, 2008 (the cut-off date for safety data included in the Integrated Summary of Safety) through June 30, 2009.

245 individuals were reported to have experienced adverse events during that period; 151 individuals experienced serious adverse events. Further information regarding the total number of patients with adverse events and the total number of adverse events is in the following table, which I have copied from the submission.

Seriousness	*Number of Cases*	*Number of Events*
Serious	151	381
Nonserious	94	178
Total	245	559

Only one event was considered by the sponsor to be of possible clinical significance and is further described below.

A woman of unknown age who was prescribed memantine developed angioedema a few weeks later. This patient was concomitantly taking aspirin (for an unspecified period) but other details of her medical history were not provided. She was treated with a steroid in an outpatient setting, but her further clinical course and the status of her memantine treatment were not provided.

8.5 Reviewer's Summary And Conclusions

The contents of the Update include information from the following sources:

- A clinical pharmacology study (MEM-PK-24) completed after the original submission of this application
- The ongoing open-label extension study MEM-MD-82
- A literature search
- Post-marketing experience with the immediate-release formulation of memantine.

While safety data from Study MEM-PK-24 included information about adverse events, vital signs, safety laboratory tests and electrocardiograms, those from Study MEM-MD-82 included only a listing of deaths and other serious adverse events, as well as a description of a single patient who experienced a drug overdose.

The cut-off date for data included in the Update was June 30, 2009.

The contents of the 120-Day Safety Update did not raise any concerns pertinent to the safety and tolerability of memantine ER administered in a dose of 28 mg QD to patients with moderate to severe Alzheimer's Disease.

9. Sponsor's Summary Of Clinical Pharmacokinetics Of Namenda® XR

The sponsor's summary of the clinical pharmacokinetics of the proposed extended-release formulation of memantine is based primarily on the results of Study MEM-PK-18, supplemented by the results of Studies MEM-PK-13, MEM-PK-17, and MEM-PK-23.

The designs of all 4 studies have already been summarized in Section 7.1.3.

Since Study MEM-PK-18 is considered to be the key pharmacokinetic study of memantine ER by the sponsor, its design will again be presented below, along with its pharmacokinetic results. Other data included in the sponsor's clinical pharmacokinetic summary will also be presented

9.1 Study MEM-PK-18

9.1.1 Design

This was an open-label multiple-dose study intended to evaluate the pharmacokinetics of the to-be-marketed memantine ER capsule (28 mg) at steady-state.

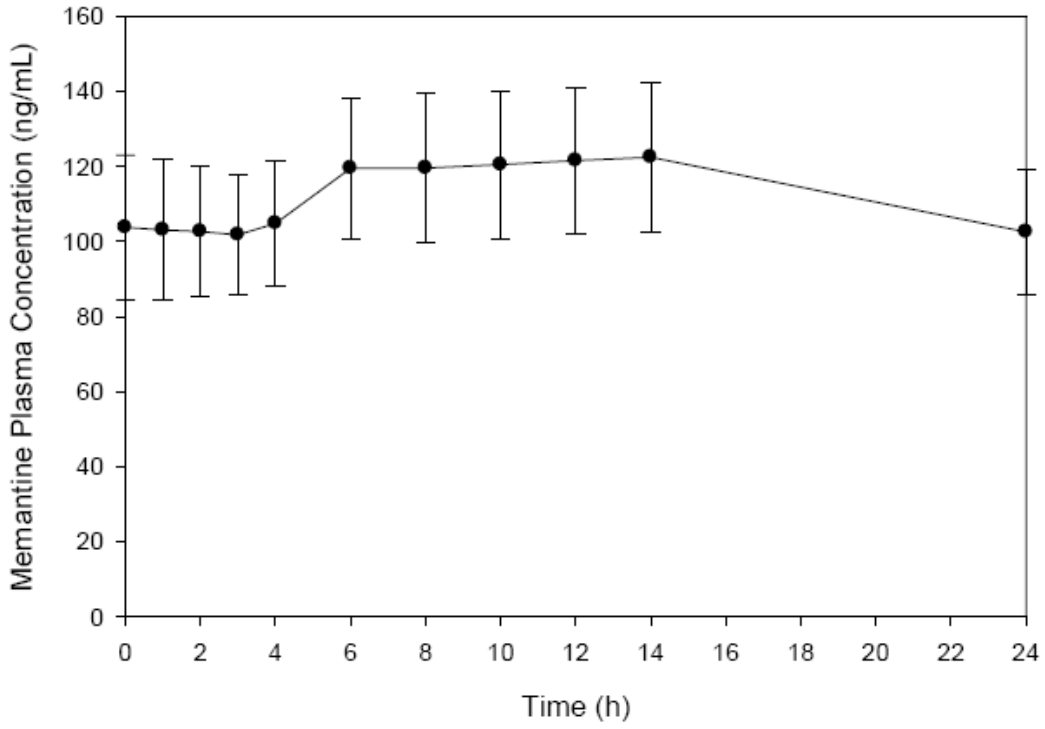
Healthy men and women, aged 18 to 45 years, were enrolled in the study.

The memantine ER dosing regime used in this study was as follows:

Study Days	Memantine ER Dose
1 through 3	7 mg QD
4 through 9	14 mg QD
10 through 15	21 mg QD
16 through 29	28 mg QD

9.1.2 Pharmacokinetic Results

Mean (± standard deviation) plasma concentrations versus time data at steady-state (Day 29) for the memantine ER 28 mg QD dose are displayed in the following figure, which I have copied from the submission.



Steady-state (Day 29) pharmacokinetic parameters for the memantine ER 28 mg QD dose are displayed in the following table, also taken from the submission.

PK Parameter	*Mean ± SD (N = 18)*[a]
C_{max}, ng/mL	127.08 ± 21.09
T_{max}, h	11.1 ± 2.8 12.0 (6.0-14.0)[b]
$AUC_{0-\tau}$, ng•h/mL	2726 ± 430
C_{min}, ng/mL	102.52 ± 16.53
C_{av}, ng/mL	113.58 ± 17.92
$T_{½}$, h	55.7 ± 9.5
Swing	0.24 ± 0.07
Fluctuation	0.21 ± 0.05

a Subjects who completed the study without vomiting on PK Day 29.

b Median (range).

$AUC_{0-\tau}$ = area under the plasma concentration versus time curve during the dosing interval, τ, at steady state; C_{av} = average steady-state plasma drug concentration; C_{max} = maximum plasma drug concentration; C_{min} = minimum plasma drug concentration at steady state; PK = pharmacokinetic; $T_{½}$ = terminal elimination half-life; T_{max} = time of maximum plasma drug concentration.

The sponsor draws attention to the following.

- The rate of absorption of memantine from the Namenda® XR capsule was slow with a median T_{max} of 12 hours
- The elimination half-life of memantine following administration of the extended-release capsule was similar to that following administration of the immediate-release tablet
- At steady-state following administration of memantine ER in a dose of 28 mg QD, the C_{max} of memantine was only 24% higher than the C_{min}, indicating a low variability in memantine plasma concentrations.

9.2 Comparison Of Pharmacokinetics Of Memantine ER Across Studies

The sponsor has compared pharmacokinetic data across the 4 clinical pharmacology studies of memantine ER. The following have been noted, in particular, by the sponsor:

- Steady-state exposure data – mean C_{min}, $AUC_{0-\tau}$, C_{max} and C_{av} - following the administration of memantine ER were lower in Study MEM-PK-18 than in MEM-PK-23. C_{max} itself was about 22% lower in Study MEM-PK-18 than in MEM-PK-23 (the other parameters were about 10% lower), with the difference being contributed to largely by 2 subjects.
- There was no difference in the elimination half-life of memantine comparing single- or multiple-dose administration (as might be expected from the long half-life of memantine).

- Single-dose $AUC_{0-\infty}$ was similar to steady-state $AUC_{0-\tau}$, confirming the linear and time-independent pharmacokinetics of memantine.

9.3 Comparison Of Steady-State Pharmacokinetics Of Extended-Release Memantine Capsules With Those Of Immediate-Release Memantine Tablets

Study MEM-PK-23 compared the steady-state pharmacokinetics of Namenda® XR capsules in a dose of 28 mg QD with those of Namenda® tablets in a dose of 10 mg BID. The comparison is summarized in the following sponsor table, which I have copied from the submission.

Mean Steady-State Pharmacokinetic Parameters of Memantine on Day 29 Following Administration of either 28-mg ER Memantine HCl Capsule or 10-mg IR Memantine HCl Tablet

PK Parameters	28-mg ER Capsule, QD Mean ± SD (N = 20)	10-mg IR Tablet, BID Mean ± SD (N = 20)	Ratio of Geometric Means (%), ER/IR	90% CI or p-Value
$C_{max,ss}$, ng/mL	163.1 ± 68.2	109.2 ± 36.6	147.9	134.5-162.7
$C_{min,ss}$, ng/mL	113.5 ± 35.2	95.9 ± 27.2	116.4	104.2-130.0
C_{ave}, ng/mL	127.4 ± 34.7	93.5 ± 25.5	-	-
$AUC_{0-\tau}$, ng•h/mL	3057.9 ± 833.4	1121.5 ± 306.1	-	-
AUC_{0-24}, ng•h/mL	3057.9 ± 833.4	2324.6 ± 652.7	132.7	123.18-143.1
$T_{½}$, h	56.7 ± 8.4	58.5 ± 10.9	-	-
$T_{max,ss}$, h	9.5 ± 3.8 9.0 (6.0-16.0)[a]	6.6 ± 3.7 7.0 (2.0-11.95)[a]	-	p = 0.100
Swing	0.48 ± 0.50	0.15 ± 0.12[b]	-	-
Fluctuation	0.37 ± 0.29	0.15 ± 0.11[b]	-	-
AI	4.62 ± 1.34	7.27 ± 1.42	-	-
CL/F, L/h	8.20 ± 2.38	7.87 ± 1.83	-	-

[a] Median (range). [b] N = 17. AI = accumulation index; $AUC_{0-\tau}$ = area under the plasma concentration versus time during the dosing interval τ at steady state; C_{av} = average steady-state plasma drug concentration; CL/F = oral plasma clearance; $C_{max,ss}$ = maximum plasma drug concentration at steady state; $C_{min,ss}$ = minimum plasma drug concentration at steady state; PK = pharmacokinetic; $T_{½}$ = terminal elimination half-life; $T_{max,ss}$ = time of maximum plasma drug concentration following administration at steady state.

As the above table indicates, and as might have been expected:

- Exposure, based on C_{max} and AUC was higher with the extended-release formulation than with the immediate-release formulation.

- Terminal half-life was similar for both formulations

- The T_{max} was greater for the extended-release formulation than for the immediate-release formulation.

9.4 Population Pharmacokinetic Analysis Using Studies Of High-Dose Immediate-Release Memantine

The sponsor has performed a population pharmacokinetic analysis using data from the randomized, double-blind, placebo-controlled studies MEM-MD-19 and MEM-MD-20, conducted in painful diabetic neuropathy and post-herpetic neuralgia respectively. Doses of immediate-release memantine ranging from 40 to 60 mg/day were used in these studies.

A report of that analysis has concluded that inter-subject variability in pharmacokinetic parameters was high in those studies, and that to improve efficacy and tolerability at high doses of memantine, weight- and age-based dosing should be considered.

10. Description Of Namenda® XR Drug Product

The Namenda® XR drug product is a gelatin capsule filled with polymer-coated beads. The beads are sugar spheres coated with an aqueous dispersion of the drug substance, talc, (b) (4)

The Namenda® XR drug product is to be available in 7 mg, 14 mg, 21 mg, and 28 mg strengths.

11. Summary Of Additional Agency Reviews Of Current Application

11.1 Chemistry, Manufacturing, And Controls Review

The Chemistry review of this submission was completed by Sherita McLamore, PhD, on May 19, 2010.

She has concluded that the Chemistry, Manufacturing, and Controls section of NDA 22525 is approvable, but that its approval from a Chemistry perspective is contingent on an acceptable recommendation from the Office of Compliance. The Office of Compliance later issued an “Acceptable” recommendation for this application, dated May 27, 2010. Dr Martha Heimann, Chemistry Team Leader, then issued a memorandum, dated June 14, 2010, which stated the following: “Based on Dr. McLamore's review, and the Compliance recommendation, the Office of New Drug Quality Assessment recommends approval of NDA 22525.”

She has no recommendations regarding Phase 4 commitments, agreements, and/or risk management steps.

An Office of New Drugs Quality Assessment (ONDQA) Biopharmaceutics review was performed in consultation by Sandra Suarez Sharp, PhD. While that consultation recommended the granting of a sponsor-requested waiver from *in vivo* bioequivalence requirements and found the sponsor's proposed *in vivo in vitro* correlation model acceptable, the sponsor's dissolution specifications were not found to be acceptable. ONDQA recommended that the sponsor adopt new dissolution acceptance criteria, which were conveyed to the sponsor in a letter dated April 6, 2010. The sponsor agreed to the Agency-recommended dissolution specifications in an Amendment submitted on April 16, 2010.

Please see the full text of the above reviews and related communication to the sponsor for further details.

11.2 Office Of Clinical Pharmacology Review

The Office of Clinical Pharmacology review of this submission has been completed by Huixia Zhang, PhD.

Dr Zhang recommends the approval of Namenda® XR 7 mg, 14 mg, 21 mg, and 28 mg capsules, and that the product be taken once daily.

Dr Zhang does not recommend any Phase IV commitments.

Her review notes that at steady state, the average plasma concentration of memantine was 36.5% higher for the extended-release formulation at a dose of 28 mg QD as compared with the immediate-release formulation at a dose of 10 mg BID, consistent with the overall increase in dose with the extended-release formulation. She further notes that the extended-release formulation of memantine is bioequivalent when administered under both fed and fasted conditions.

Her review also concludes that both actual and simulation pharmacokinetic data support switching directly from a dose of 10 mg BID of Namenda® directly to 28 mg QD of Namenda® the following day.

Dr Zhang's review has the following comments about the dose-dumping effect of alcohol on the memantine ER capsule, based on an *in vitro* study.

"Moderate dose-dumping effect of ethanol on memantine ER capsule was observed in 20% v/v alcohol, and pronounced effect was observed in 40% v/v ethanol, for all dose strengths.

The extreme situation of dose dumping with 40% alcohol means that the entire capsule dose of 28 mg would be released in 30-45 minutes, i.e., ER is behaving as an IR. Based on simulation, 28 mg XR QD and 28 mg IR QD have comparable concentration at steady state. Single 40 mg doses of memantine were safe and well tolerated. In order to understand the impact of a patient receiving a bolus of memantine 28 mg, the sponsor has

looked at the adverse events for memantine in worldwide post marketing and clinical trials experience for doses up to 100 mg. The majority of the events included dizziness, somnolence, confusion, vertigo, weakness and vomiting. There were no deaths in overdoses up to 100 mg. Further, data from clinical trials for other indications where the daily dose was over 20 mg, reaching up to 100 mg, revealed the same events as mentioned above, and were mild in intensity and reversible. Overall, the events were mild and reversible. Efficacy will not be decreased with one incidence or infrequent consumption of alcohol. Thus, there is no concern about alcohol consumption from a clinical pharmacology standpoint."

[I have discussed the above at length with the Clinical Pharmacology team and agree with the Clinical Pharmacology comments].

Dr Zhang's review also incorporates a pharmacometrics review completed by Hao Zhu, PhD, who has no additional recommendations.

Attached to her review is a report of an audit conducted by the Division of Scientific Investigations of the clinical and analytical sites for Study MEM-PK-17. While the inspection of the clinical site (Elite Research Institute, Miami, FL) was satisfactory, the inspection of the analytical site (Forest Research Institute, Farmingdale, NY) resulted in the issuance of a Form 483 on account of failure to document calibration standards in several analytical runs, and several other errors. The sponsor's response to that deficiency has been reviewed by the Office of Clinical Pharmacology which has considered the response to be acceptable.

The Office of Clinical Pharmacology review did recommend several modifications to the sponsor's proposed labeling text. These changes were in the DOSAGE AND ADMINISTRATION (Recommended Dosing subsection), DRUG INTERACTIONS and CLINICAL PHARMACOLOGY (Pharmacokinetics - Absorption subsection) sections

Please see the full text of the Office of Clinical Pharmacology review and related communications for further details.

11.3 Proprietary Name Review

A review of the proposed Namenda® XR proprietary name was completed by Irene Chan, PharmD, of the Division of Medical Error Prevention and Analysis (DMEPA) on April 23, 2010.

Dr Chan has concluded that "Namenda® XR" is neither vulnerable to name confusion nor considered proprietary, and that at the time of completion of her review, DMEPA had no objection to the proprietary name "Namenda® XR" for this product.

Please see the contents of her review for further details.

11.4 Label And Labeling Review

A label and labeling review of this application was also completed by Irene Chan, PharmD, of the Division of Medical Error Prevention and Analysis (DMEPA) on March 30, 2010.

Dr Chan had comments for both the Division and applicant

11.4.1 Comments For The Division

Her comments pertained only to the Dosage and Administration subsection, and are copied below.

> In order to help minimize the risk of administration errors, we recommend including the statement "Namenda XR should be swallowed whole and should not be divided, chewed, or crushed."

11.4.2 Comments For The Applicant

In addition to general comments pertaining to labels and labeling, she also had comments pertaining to retail container labels, retail unit dose carton labels, retail unit dose blister labels, retail titration pack, and professional sample unit dose carton labels. Please see her review for further details

11.5 Biometrics Review

Please see Section 6.4

11.6 Pharmacology-Toxicology Review

The Pharmacology-Toxicology review of this submission was completed by David Hawver, PhD, on June 13, 2010.

Dr Hawver has noted that no non-clinical study reports have been included in the current application. However, he has also observed that the sponsor's proposed labeling includes a description of an oral toxicity study of memantine in juvenile rats that is not included in the current approved labeling for memantine. He has, therefore, reviewed the results of preliminary and definitive juvenile animal toxicology studies submitted to IND 73705 (for memantine in the treatment of autism; Division of Psychiatry Products). He has also summarized the results of an oral neurotoxicity study conducted in female adult rats using memantine and donepezil, alone and in combination. Please see Dr Hawver's review for a description of the afore-mentioned animal toxicology studies.

The finding of primary concern in the above animal toxicology studies was the occurrence of neurodegeneration in multiple locations in both juvenile and adult rats administered memantine, with the incidence and severity of neurodegeneration worsened in adult rats by the co-administration of donepezil.

Structures affected included the ventral anterior nucleus of the thalamus; mammillary bodies; olfactory nucleus; and the temporal, perirhinal, entorhinal, insular, piriform, and frontal cortices.

Dr Hawver considers the current application approvable.

Dr Hawver has also recommended the following:

- That the sponsor conduct a single-dose neurotoxicity study of the combination of memantine and donepezil in female adult rats; this study is intended to further characterize the neurotoxicity of that combination and a letter asking the sponsor to perform that study has already been sent on May 20, 2010; this study should be conducted as a Post-Marketing Requirement or Commitment instituted at the time of approval of the current application.

- That if memantine is developed for a pediatric indication, consideration should be given to requiring the conduct of an additional study to clearly establish the no-observed-effect level for neurodegeneration in male and female rat pups.

- That the proposed product label be revised so as to include a full description of the exacerbation of memantine-induced neurotoxicity observed in adult rats in the presence of donepezil and the associated safety margins in regard to the maximum recommended clinical dose of memantine; and that the currently-proposed description of a toxicology study in juvenile rats be deleted since the study did not include a sufficient number of animals per group to permit a definitive assessment of the no-effect level for treatment-related neurodegeneration.

12. Review Of Labeling

My review of the sponsor's annotated draft labeling (the version submitted with the 120-Day Safety Update on December 17, 2009) is below.

My review is confined to listing changes that I have made to the sponsor's proposed labeling and my reasons for making those changes. The actual label, as edited by me, is in a separate document.

The draft labeling submitted by the sponsor is in Physician's Labeling Rule format. The sub-headings in this section of my review are the same as in the label itself.

Note that the language used in many sections of the proposed draft labeling is identical to that used in the current approved labeling for the immediate-release Namenda® tablet formulation, last revised in April 2007.

12.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

I have not made any edits to the sponsor's proposed labeling for this section.

12.2 FULL PRESCRIBING INFORMATION: CONTENTS

12.2.1 INDICATIONS AND USAGE

I have not made any changes to the sponsor's proposed labeling for this section except for correcting a grammatical error.

12.2.2 DOSAGE AND ADMINISTRATION

I have made several changes to the sponsor's proposed labeling for this section, which are listed below.

- The proposed starting dose of Namenda® XR has been stipulated to be 7 mg once daily rather than 7 mg/day as specified by the sponsor.

- The sponsor's statement that a memantine capsule may be opened and the contents sprinkled on soft foods, has been changed to stipulate that the contents of the memantine capsule may be sprinkled on apple sauce. This change is in accordance with recommendations made by the Clinical Pharmacology reviewer, since the only soft food that this approach has been evaluated with is apple sauce.

- In response to a consultation from the Division of Medical Error Prevention and Analysis, a statement has been included in labeling that except when opened and sprinkled on applesauce, Namenda® XR capsules should be swallowed whole and not be crushed, divided or chewed.

- A few additional minor modifications have been made to the sponsor's text for purposes of clarification.

12.2.3 DOSAGE FORMS AND STRENGTHS

No changes have been made by me to this section of the sponsor's proposed labeling.

12.2.4 CONTRAINDICATIONS

No changes have been made by me to this section of the sponsor's proposed labeling.

12.2.5 WARNINGS AND PRECAUTIONS

No changes have been made by me to this section of the sponsor's proposed labeling.

12.2.6 ADVERSE REACTIONS

Several relatively minor changes have been made by me to this section of the sponsor's product labeling to clarify text and to correct typographical errors.

12.2.7 DRUG INTERACTIONS

The following statement has been added by me to the subsection headed "Effect of Other Drugs on Memantine" (Section 7.3 of the label) based on a recommendation from the Office of Clinical Pharmacology: *"A clinical drug-drug interaction study indicated that bupropion did not affect the pharmacokinetics of memantine."*

I have deleted the following statement from the subsection headed "Effect of Memantine on the Metabolism of Other Drugs" (Section 7.2 of the label); while the sponsor states that that statement has been taken from the current approved labeling for Namenda®, that statement is incorrect, and no additional data has been submitted to support that statement: (b) (4)

I have also deleted the following statement from the subsection headed "Use with Cholinesterase Inhibitors" (Section 7 of the label): (b) (4) No data has been provided to support to support that statement contrary to what has been stated by the sponsor; in fact, the adverse event profiles in the two treatment groups in Study MEM-MD-50 are different.

12.2.8 USE IN SPECIFIC POPULATIONS

No changes have been made by me to this section of the sponsor's proposed labeling. Changes recommended by the Pharmacology-Toxicology reviewer to the Pregnancy and Nursing Mothers subsections have been incorporated into the labeling text.

12.2.9 DRUG DEPENDENCE

No changes have been made by me to this section of the sponsor's proposed labeling.

12.2.10 OVERDOSAGE

I have altered the text of this section of the product label to make it more clear.

12.2.11 DESCRIPTION

I have not changed the text of this section of the product label.

12.2.12 CLINICAL PHARMACOLOGY

In the Pharmacokinetics (Section 12.3 of the product label) subsection entitled Absorption (Section 12.3.1 of the product label), I have made 2 changes:

- I have changed the sponsor's statement that there is no difference in the absorption of Namenda® XR whether the capsule is taken intact or sprinkled on (b) (4) so as to substitute the more specific term "applesauce" for (b) (4) This change has been in accordance with the recommendations of the Clinical Pharmacology reviewer

- I have included a paragraph describing memantine pharmacokinetics when Namenda® XR is administered with and without food.

In the Pharmacokinetics in Special Populations (Section 12.4 of the product label) subsection entitled Hepatic Impairment (Section 12.4.1 of the product label), I have made a minor addition to the text for purposes of clarification.

12.2.13 NON-CLINICAL TOXICOLOGY

Changes recommended by the Pharmacology-Toxicology reviewer have been incorporated into the Animal Toxicology subsection.

12.2.14 CLINICAL STUDIES

I have altered the text of this section so as to indicate that at 24 weeks of treatment during Study MEM-MD-50, the mean difference in CIBIC-Plus scores between the two treatment groups was 0.3 units and no (b) (4) units as stated by the sponsor.

I have deleted a description (b) (4)

12.2.15 HOW SUPPLIED/STORAGE AND HANDLING

I have made no changes to this section.

12.2.16 PATIENT COUNSELING INFORMATION

I have made a number of changes have been made to this section label directed at making the text more clear as well as consistent with the rest of the product label. I have also corrected several typographical errors.

13. Financial Disclosure Certification

Financial disclosure information has been collected only for the single clinical efficacy trial, MEM-MD-50, included in this submission.

13.1 Components Of Certification

This certification provided by the sponsor has 3 components.

13.1.1 Certification Pertinent To Investigators/Sub-Investigators Who Declared That They Did Not Have Any Relevant Financial Interests

The sponsor has supplied a list of all such investigators and sub-investigators who were involved in these studies. In regard to this list the sponsor has

- Certified that it has not entered into any financial agreement with the clinical investigators listed in the application, whereby the compensation to the investigator could be affected by the outcome of the study in which the investigator was a participant, as defined by 21 CFR 54.2 (a)

- Certified that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2 (b) did not disclose any such arrangements

- Certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f)

This certification has been provided on FDA Form 3454.

13.1.2 Certification Pertinent To Investigators/Sub-Investigators From Whom Financial Information Could Not Be Obtained

The sponsor has listed a number of investigators and sub-investigators who were involved in these studies for whom financial information could not be obtained. For these, the sponsor states that it acted with due diligence to obtain the requisite information, but was unsuccessful after repeated attempts.

This certification has been provided on FDA Form 3454.

13.1.3 Certification Pertinent To Investigators/Sub-Investigators With Disclosable Financial Interests

The sponsor has provided a list of investigators who were involved in these studies (specifically, Study MEM-MD-50 only) who had a significant equity interest [as defined in 21 CFR 54.2 (b)] held by the clinical investigator in the sponsor. The specific disclosable financial interests that these investigators had in the sponsor have also been stated.

This certification has been provided on FDA Form 3455.

13.2 Reviewer's Comments

It appears unlikely that the financial arrangements disclosed above introduced significant bias into the results of the 3 pivotal efficacy trials conducted with memantine, and submitted with this NDA.

14. MEM-MD-50 Study Site Inspection Report

Two large sites (#s 106 and 107) for Study MEM-MD-50, both located in Buenos Aires, Argentina, were inspected by the Agency.

These sites are listed in the table below.

Site #, Name of Investigator, and Address	Number of Subjects Enrolled
Site #106 Stella M Diamanti Hospital Espanol Belgrano 2975 (C1209AAB) Ciudad Autonoma de Buenos Aires Argentina	32
Site # 107 Raul Dominguez Hospital Sirio Libanes Campana 4658 (C1419AHN) Ciudad Autonoma de Buenos Aires Argentina	35

A Clinical Inspection Summary, dated May 5, 2010, for the above sites has been provided by Antoine El-Hage, PhD, of the Division of Scientific Investigations, Office of Compliance, Center for Drug Evaluation and Research. The summary indicates that based on a preliminary e-mail communication from the inspectors, no deviations were detected at either sites. These preliminary findings were later confirmed in letters (dated May 26, 2010) to both investigators from the Division of Scientific Investigations. Please refer to both communications for further details.

15. Overall Conclusions

The efficacy, safety and pharmacokinetic data for Namenda® XR submitted with the current application support its approval for the treatment of moderate to severe dementia of the Alzheimer's type (moderate to severe Alzheimer's Disease).

16. Recommendation

I recommend the approval of Namenda® XR (7 mg, 14 mg, 21 mg, and 28 mg) for the treatment for moderate to severe dementia of the Alzheimer's type, under the conditions of use described in the product labeling.

Ranjit B. Mani, M.D.
Medical Reviewer

rbm 6/15/10
cc:
HFD-120
NDA 22525

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/

RANJIT B MANI
06/15/2010