

**FINAL BRIEFING DOCUMENT FOR ADVISORY COMMITTEE MEETING
Efficacy Review Of New Drug Application**

NDA (Serial Number)	21487 (000)
Sponsor:	Forest Laboratories
Drug:	Memantine
Proposed Indication:	Alzheimer's Disease
Material Submitted:	New Drug Application
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Reviewer:	Ranjit B. Mani, M.D.

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NOTE: The executive summary and main review contained in this document are intended only for briefing participants in a Peripheral and Central Nervous System Drugs (PCNS) Advisory Committee meeting that has been scheduled for September 24, 2003. It is not the final version of the efficacy review of this application.

2 Executive Summary

This summary is restricted to an evaluation of the efficacy of memantine for the proposed indication.

2.1 Recommendation

Deferred.

2.2 Proposed Indication

“The treatment of moderate-to-severe dementia of the Alzheimer’s type.”

2.3 Summary Of Clinical Findings

In support of the efficacy of memantine as a treatment for moderate-to-severe dementia of the Alzheimer’s type, the sponsor has submitted the results of 3 clinical studies.

- A randomized, double-blind, placebo-controlled, parallel-arm study (MRZ 9605) of the efficacy of memantine in comparison with placebo in patients with moderate-to-severe dementia of the Alzheimer’s type.
- A randomized, double-blind, placebo-controlled, parallel-arm study (MEM-MD-02) of the efficacy of memantine in comparison with placebo in patients with moderate-to-severe dementia of the Alzheimer’s type, already taking a stable dose of donepezil.
- A randomized, double-blind, placebo-controlled, parallel-arm study (MRZ 9403) of the efficacy of memantine compared with placebo in patients with moderate-to-severe dementia of the Alzheimer’s, vascular, or mixed type.

These studies are summarized in greater detail below.

2.3.1 MRZ 9605

This study was conducted in the United States

2.3.1.1 Design

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, and a baseline Mini-Mental Status Examination score of 3 to 14. Patients taking acetylcholinesterase inhibitors or other drugs intended for the treatment of cognitive dysfunction were excluded from the trial.

Patients enrolled in this study were randomized to treatment with one of the following regimes for the 28-week period of double-blind, parallel-arm treatment

- Memantine 10 mg b.i.d (reached by titration)
- Placebo

The primary efficacy measures for the study a measure of function, a modification of the Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) scale, and a global measure, the Clinician-Interview Based Impression of Change – Plus (CIBIC-Plus). Among the 7 secondary efficacy measures was the Severe Impairment Battery (SIB), a measure of cognition.

The primary efficacy analysis and the analysis of the secondary efficacy measures was carried out on an intent-to-treat (ITT) basis, using the last-observation-carried-forward (LOCF) method for imputing data; the statistical method used to compare the treatment groups was the Wilcoxon-Mann-Whitney test for independent samples.

2.3.1.2 Results

252 patients were enrolled in the study and randomized in exactly equal proportions to the 2 treatment groups. 97 memantine-treated patients and 84 placebo-treated patients completed the study.

Patients actually enrolled in this study had a baseline Mini-Mental Status Examination score that ranged from 1 to 14.

The primary efficacy analysis of the modified ADCS-ADL compared the mean change from baseline to endpoint between the memantine and placebo groups. While the difference between the treatment groups was small (2.00 points), it was statistically significant ($p = 0.022$) and in favor of memantine.

The primary efficacy analysis of the CIBIC-Plus compared the mean scores at endpoint between the memantine and placebo groups. Again, the difference between treatment groups was small (0.25 points) and did not quite reach pre-specified levels of statistical significance ($p = 0.064$), although the difference did favor memantine.

Analysis of the change from baseline to endpoint mean score on the SIB, using the LOCF method, yielded a nominally, but highly statistically significant p-value

of 0.0003, for a mean group difference in score of 5.91 points that favored memantine.

2.3.2 MEM-MD-02

This study was conducted in the United States.

2.3.2.1 Design

The three key criteria used for enrolling patients in this study were a diagnosis of probable Alzheimer's Disease, using the NINCDS-ADRDA criteria, a baseline Mini-Mental Status Examination score of 5 to 14, and treatment with donepezil for at least 6 months, with a stable dose for at least 3 months.

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.

- Memantine 10 mg b.i.d (reached by titration) plus donepezil
- Placebo plus donepezil

The primary efficacy measures for the study consisted of a subset of the Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) scale, as a measure of function, and the Severe Impairment Battery (SIB), as a measure of cognition. The study also had multiple secondary efficacy measures.

The primary efficacy analysis was carried out on an intent-to-treat (ITT) basis, using the last-observation-carried-forward (LOCF) method for imputing data; the statistical method used to compare the treatment groups was a two-way analysis of covariance (ANCOVA), with treatment group and center as main effects and baseline score as the covariate.

2.3.2.2 Results

404 patients were enrolled in the study. They were randomized as follows to the 2 treatment groups.

- Memantine plus donepezil: 203 patients
- Placebo plus donepezil: 201 patients

Patients actually enrolled in this study had a baseline Mini-Mental Status Examination score that ranged from 5 to 16.

322 patients completed the study. Their distribution among the treatment groups was as follows:

- Memantine plus donepezil: 172 patients
- Placebo plus donepezil: 150 patients

The primary efficacy analysis of the modified ADCS-ADL compared the mean change from baseline to endpoint between the memantine plus donepezil and placebo plus donepezil groups. Although the difference between the treatment groups was small (1.40 points), it was statistically significant ($p = 0.028$) and favored memantine.

The primary efficacy analysis of the SIB also compared the mean change from baseline to endpoint between the 2 treatment groups. While small (3.40 points), the treatment difference between the groups was statistically significant ($p < 0.001$) and favored memantine.

2.3.3 MRZ 9403

This study was conducted in Latvia.

2.3.3.1 Design

Key inclusion criteria for this study were the presence of dementia, according to DSM-III-R, a Mini-Mental Status Examination score of < 10 , and Global Deterioration Scale staging of 5 to 7; the dementia could of the Alzheimer's, vascular, or mixed variety, without any diagnostic criteria for these conditions being specified. Those enrolled in the study were then classified, after their enrollment in the study, and based on their Hachinski Ischemic Scale score, as having either vascular dementia or Alzheimer's Disease.

Patients enrolled in this study were randomized to treatment with one of the following regimes for the 12-week period of double-blind, parallel-arm treatment.

- Memantine 10 mg q.d. (reached by titration)
- Placebo

The protocol-designated primary efficacy measures were as follows

- The Behavioral Rating Scale in Geriatric Patients (BGP) Care Dependency Subscale, a measure of activities of daily living and behavior. This is in turn a subset of the BGP proper.
- The Clinician Global Impression of Change (CGI-C), a global measure. For use as a primary efficacy measure, the original 7-point scale was to be dichotomized.

A third primary efficacy measure was introduced when a second analysis plan was formulated several years after the study blind was broken, and the study results published. This measure, designated as the BGP Cognitive Subscale was an ad-hoc subset of the BGP Care Dependency Subscale, and contained 5 items (that were considered to measure cognition) out of 23 items in the BGP Care Dependency Subscale.

When the post-hoc statistical analysis plan was formulated, the original 7-point CGI-C was designated as a primary efficacy measure, instead of the dichotomized scale.

The protocol-specified primary efficacy analysis was to be done on the intent-to-treat population. As part of this analysis, the treatment groups were to be compared on the change from baseline score for the BGP Care Dependency Subscale using Wilcoxon-Mann-Whitney U tests. Analysis of the CGI-C (dichotomized) was to be carried out using Fisher's exact test. Missing data were to be imputed using the worst possible score (worst change) for each efficacy parameter.

In the statistical analysis plan formulated post-hoc, the analysis of all 3 primary efficacy measures was to be based on the Wilcoxon rank-sum test, stratified by center.

2.3.3.2 Results

166 patients were enrolled in the study and randomized as follows:

- Memantine: 82 patients
- Placebo: 84 patients

158 patients completed the study and were distributed as follows:

- Memantine: 78 patients
- Placebo: 80 patients

The results of the protocol-specified primary efficacy analysis were as follows:

- 73.2% of memantine-treated patients versus 45.2% of placebo-treated patients were considered responders at endpoint on the dichotomized CGI-C; the difference was statistically significant ($p < 0.001$).
- The difference between the 2 treatment groups on the mean change from baseline to endpoint on the BGP Care Dependency Subscale score was 1.9 in favor of memantine ($p = 0.016$).

The results of the post-hoc primary efficacy analysis were as follows:

- The difference between the treatment groups on the mean CGI-C score (7-point scale) at endpoint was 0.4 and in favor of memantine ($p < 0.001$).

- The difference between the 2 treatment groups on the mean change from baseline to endpoint on the BGP Care Dependency Subscale score was 2.0, and in favor of memantine ($p = 0.012$).
- The difference between the 2 treatment groups on the mean change from baseline to endpoint on the BGP Cognitive Subscale score was 0.8 and in favor of memantine ($p = 0.001$).

2.3.3.2.1 Subset Analysis

Patients who were enrolled in the study and randomized were classified after enrollment as having either dementia of the Alzheimer's type or vascular dementia based on their modified Hachinski Ischemic Scale at study entry (they were considered to have dementia of the Alzheimer's type if their score was ≤ 4).

79 patients subsequently diagnosed to have dementia of the Alzheimer's type entered the study. Their distribution among the treatment groups was as follows

- Memantine: 41 patients
- Placebo: 38 patients

76 patients diagnosed to have dementia of the Alzheimer's type completed the study and were distributed as follows:

- Memantine: 39 patients
- Placebo: 37 patients

The results of the analysis of the dementia of the Alzheimer's type subset, using the same methods as used for the post-hoc primary efficacy analysis, were as follows:

- The difference between the treatment groups on the mean CGI-C score (7-point scale) at endpoint was 0.4 and in favor of memantine ($p = 0.003$).
- The difference between the 2 treatment groups on the mean change from baseline to endpoint on the BGP Care Dependency Subscale score was 3.0, and in favor of memantine ($p = 0.003$).
- The difference between the 2 treatment groups on the mean change from baseline to endpoint on the BGP Cognitive Subscale score was 1.0 and in favor of memantine ($p = 0.007$).

A similar analysis performed on the vascular dementia subset, revealed statistically significant differences ($p < 0.05$) favoring memantine only for the CGI-C (7-point scale).

2.4 Conclusions

- Based on the paradigm used for demonstrating the efficacy of drugs intended for the treatment of mild-to-moderate Alzheimer's Disease, it appears appropriate that a claim for memantine in the treatment of moderate-to-severe Alzheimer's Disease should be supported by evidence of efficacy on both a cognitive efficacy measure and, separately, on a global or functional primary efficacy measure
- On the above basis, Studies MRZ 9605 and MEM-MD-02 have provided sufficient evidence to support the efficacy of memantine in moderate-to-severe dementia of the Alzheimer's type. This evidence is as follows:
 - Patients enrolled in both studies had probable Alzheimer's Disease and a baseline Mini-Mental Status Examination score that ranged from 1 to 16.
 - In Study MRZ 9605, a study evaluating memantine as monotherapy in a dose of 10 mg b.i.d, evidence for efficacy was seen on the Severe Impairment Battery, a measure of cognition, and on the modified ADCS-ADL scale, a measure of activities of daily living.
 - In Study MEM-MD-02, a study evaluating the efficacy of memantine, in a dose of 10 mg b.i.d as add-on therapy in patients already taking a stable dose of donepezil, evidence for efficacy was again seen on the Severe Impairment Battery and modified ADCS-ADL
 - The Severe Impairment Battery and modified ADCS-ADL, have at the very least, face validity as measures that can be used in patients with moderate-to-severe cognitive impairment
- Study MRZ 9403 provides less-than-convincing evidence of the efficacy of memantine in moderate-to-severe dementia of the Alzheimer's type
 - Patients enrolled in this study could have Alzheimer's Disease, vascular dementia, or mixed dementia
 - 48% of patients enrolled in this study did not undergo brain imaging of any kind.
 - This study lacked a satisfactory cognitive outcome measure, and especially one that was prospectively-designated

3 Introduction

This submission contains a New Drug Application (NDA) for memantine hydrochloride tablets, which the sponsor is seeking to market for the treatment of moderate-to-severe dementia of the Alzheimer's type.

This review also evaluates data contained in an Amendment to this NDA, which was submitted on 1/10/03.

The efficacy of memantine for the proposed indication is considered by the sponsor to be based on 3 pivotal efficacy studies contained in this application. The reports of 2 of these studies (MRZ 90001-9605 and MRZ 90001-9403) are contained in the original application. The report of a third study (MEM-MD-02) constitutes most of the Amendment submitted on 1/10/03.

This submission is confined to reviewing data that are intended to support the efficacy of memantine. Data contained in this submission that are intended to support the safety of memantine are being reviewed separately by Dr Gerald Boehm of this Division.

The statistical review of efficacy data contained in this submission is being performed by Dr Tristan Massie.

Memantine has been developed for the treatment of moderate-to-severe dementia of the Alzheimer's type under IND 33392. The previous sponsor of that application was Merz and Company, with whom this Division earlier had a number of discussions about the development of this drug.

In this review, the terms "dementia of the Alzheimer's type" and "Alzheimer's Disease" are often used interchangeably.

4 Organization Of Submission

The original submission of this NDA consists of 437 print volumes; the Amendment of 1/10/03 consists 24 print volumes. Selected components of the print application are also provided in electronic format; Case Report Forms and Case Report Tabulations (SAS transport files) are provided electronically only.

The reports of the efficacy studies that are considered pivotal are contained in the following print volumes.

Study	Volume
MRZ 9605	Volumes 117 – 141 of original application
MRZ 9403	Volumes 142 – 145 of original application
MEM-MD-02	Volumes 1 – 23 of Amendment (submitted Jan 10, 2003)

An Integrated Summary of Effectiveness is contained in Volumes 263 – 264 of the original application. In addition to summarizing the results of the 2 pivotal efficacy studies contained in that submission (MRZ 9605 and MRZ 9403), the Integrated Summary of Efficacy also summarizes data from 2 efficacy studies of memantine in mild-to-moderate probable vascular dementia (MRZ 9202 and MRZ 9408) the results of which, the sponsor believes, are pertinent to the claim that the sponsor is currently seeking.

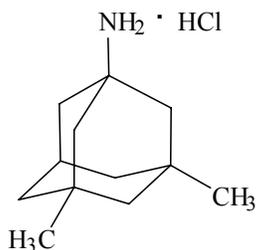
5 Outline Of Review

This review will address the 3 pivotal efficacy studies, using information contained in the respective study reports; this will be supplemented by information contained in the Integrated Summary of Effectiveness, ancillary study reports, and related electronic components. The review will consist of the following in the same order as below:

- Chemistry
- Proposed mechanism of action
- Summary of memantine pharmacokinetics
- Rating scales/outcome measures used in the key efficacy studies
- Summary of the key efficacy studies (in table form)
- Review of the key efficacy studies individually
- Summary of additional efficacy studies
- Overall comments about efficacy of memantine for the proposed indication
- Review of draft labeling
- Site inspection summary
- Financial disclosure certification
- Recommendations

6 Chemistry

The chemical name for memantine hydrochloride is 1-amino-3,5-dimethyladamantane hydrochloride. The chemical structure of memantine is in the following figure.



The sponsor has proposed that memantine be marketed for oral administration as capsule-shaped film-coated tablets, containing the equivalent of 5 mg, 10 mg, 15 mg, and 20 mg of memantine hydrochloride.

Please see the Agency Chemistry review for further details.

7 Proposed Mechanism Of Action

The sponsor has suggested that memantine exerts its effects in Alzheimer's Disease as follows:

- Memantine is a moderate-affinity, uncompetitive, N-methyl-D-aspartate (NMDA) receptor antagonist that binds preferentially to the NMDA receptor-operated cation channel.
- The NMDA receptor is activated by glutamate. Glutamate neurotoxicity may have a role in the pathogenesis of Alzheimer's Disease.
- Non-clinical evidence suggests that blockade of NMDA receptors by memantine can provide protection from the neurotoxic effects of glutamate, and improve memory and learning.

For further details, please see the Agency Pharmacology review.

8 Summary Of Memantine Pharmacokinetics And Clinical Pharmacology

The following is based on information provided by the sponsor in the Application Summary.

- Following oral administration, memantine is completely absorbed, with a t_{max} of 4 to 6 hours, and an oral bioavailability of 100%.
- Food does not affect the bioavailability of memantine administered as a tablet.
- Exposure levels, based on C_{max} and $AUC_{0-\infty}$, are dose-proportional after single doses ranging from 10 to 40 mg.
- Memantine is extensively distributed in tissues and readily crosses the blood-brain barrier.
- Memantine is about 45% protein-bound.
- The terminal half-life of memantine is 60 to 80 hours with no changes in half-life over the 5 to 40 mg single-dose range.
- Memantine undergoes little metabolism and is excreted largely (75 to 90%) unchanged in the urine (and in part by renal tubular secretion); the remainder is converted to 3 polar metabolites - the N-gludantan conjugate, 6-hydroxy memantine, and 1-nitroso-deaminated memantine - all of which have minimal or no NMDA receptor antagonist activity.
- Memantine clearance is reduced with increasing degrees of renal impairment. No dosage adjustment, based on age and gender, is felt to be needed.
- The CYP450 system is minimally involved in the metabolism of memantine. Based on in-vitro studies, memantine produces only minimal

inhibition of CYP450 isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4.

- Memantine does not have any pharmacokinetic or pharmacodynamic interaction with donepezil.

Please see the Agency Biopharmaceutics and Clinical Pharmacology review for further details.

9 Rating Scales/Outcome Measures Used In Key Efficacy Studies

In this section I will summarize instruments used as primary and secondary efficacy measures for key studies included in this application, as well as those used to evaluate patients at the time of entry into these studies

9.1 Primary Efficacy Variables

9.1.1 Severe Impairment Battery

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; 51 such tests are assessed altogether. Total scores range from 0 to 100 points with higher scores indicating better cognitive function.

The test-retest reliability, construct validity and sensitivity to change of the Severe Impairment Battery have been evaluated (*Schmitt FA et al. The severe impairment battery: concurrent validity and the assessment of longitudinal change in Alzheimer's disease. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord. 1997;11 Suppl 2:S51-6*) in a one-year study. The results may be summarized as follows

- Test-retest reliability was assessed using baseline to one-month, and baseline to two-month correlations in 90 patients. Correlations were statistically significant for the following Mini Mental Status Examination score groups at one month: 0-4, 5-9 and 10-15, but not for the 16-20 group. At 2 months correlations were seen for all groups
- Construct validity was assessed by comparison with the following: CDR, CDR "sum of boxes", FAST, GDS and Mini Mental Status Examination. Baseline scores were compared on 192 patients. Statistically significant correlations were demonstrated between the Severe Impairment Battery and each of the other measures
- Sensitivity to change was assessed using in comparison with CDR, CDR "sum of boxes", FAST, and GDS. 180 patients were evaluated over one year. Correlations were best for subjects with baseline Mini Mental Status Examination scores in the 5-9 range as indicated by the following table.

Correlations of 12-month change in SIB with change in AD severity measures

Baseline severity group	Change in CDR	Change in CDR "sum of boxes"	GDS change	FAST change
All subjects (n)	-0.25** (161)	-0.38*** (161)	-0.19** (166)	-0.25** (166)
MMSE 16-20 (n)	-0.06 ^{NS} (44)	-0.21 ^{NS} (44)	-0.06 ^{NS} (44)	-0.23 ^{NS} (44)
MMSE 10-15 (n)	-0.36* (38)	-0.63*** (38)	-0.08 ^{NS} (39)	-0.22 ^{NS} (39)
MMSE 5-9 (n)	-0.35* (41)	-0.40** (41)	-0.38* (42)	-0.40** (42)
MMSE 0-4 (n)	-0.05 ^{NS} (38)	-0.18 ^{NS} (38)	-0.30 ^{NS} (41)	-0.02 ^{NS} (41)

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$; NS, not significant.

9.1.2 *Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL): Modified*

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 the studies described below, a modified version of the ADCS-ADL was 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 was calculated by adding the scores for the individual items, and used as a primary efficacy measure. The sum score could range from 0 to 54, with higher scores indicating better function.

A second method of scoring the modified ADCS-ADL items has been used to derive a secondary efficacy measure. Each post-baseline item score has been divided into 2 categories, and each category rated as follows

Unchanged or improved score:	Rated as an improvement
Declining score:	Rated as a deterioration

The sum of the scores for those items rated as an improvement was used as the secondary efficacy measure.

9.1.3 *Clinician Interview Based Impression of Change-Plus (CIBIC-Plus)*

The format for this instrument consists of the assessment 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".

The CIBIC-Plus was also a secondary efficacy measure in a study.

9.1.4 *Clinician Global Impression of Change (CGI-C)*

This instrument was used in a single study. The format for this instrument in that study was similar to the CIBIC-Plus except that the rater had access to all information (including psychometric scores and physical examination results) at

baseline, when the severity of the disease (Clinical Global Impression of Severity [CGI-S]) was assessed. Subsequent ratings were based only on patient assessment and on information provided by the caregiver.

The CGI-C was scored using the same 7-point scale that was used for the CIBIC-Plus.

Analyses of the CGI-C used either the original 7-point scale, or a dichotomized scale; the dichotomized scale grouped patients into responders (CGI-C scores of 1 to 4) and non-responders (CGI-C score of 5 to 7)

9.1.5 Behavioral Rating Scale In Geriatric Patients (BGP)

The BGP itself is a 35-item clinician-rated measure that assesses behavior (including mood), basic cognitive functions, mobility and activities of daily living. Each item is rated from 0-2, with 2 indicating the worst level of functioning. For example the item “requires assistance with eating” is rated as follows: 0 = no assistance; 1 = limited assistance and 2 = frequently. Rating is based upon direct observation by the clinician

The BGP has 4 standard subscales

- Care Dependency Subscale
- Aggressiveness Subscale
- A composite subscale comprising physical disability, depression, and mental disability items
- Inactivity Subscale

The BGP Care Dependency Subscale comprises 23 out of the 35 items in the entire BGP. The items assessed by this subscale are representative of either activities of daily living or behavior. Each item is scored on a scale from 0 to 2. The maximum score on this sub-scale is 46, with higher scores indicating a worse level of function.

An ad-hoc (and post-hoc) subscale derived from the BGP, termed the BGP Cognitive Subscale, was used in the key efficacy study 9403. This subscale comprised 5 out of 23 items in the BGP Care Dependency Subscale. Each item was rated on a scale from 0 to 2. The maximum score for this subscale was 10 with a higher score indicating a worse level of functioning. The items that were rated as part of the BGP Cognitive Subscale were as follows:

Item	Scoring		Cognitive Domain Assessed (According To Sponsor)
The patient makes himself understood (by speaking, writing, or gestures)	Always	0	Expressive speech
	Sometimes	1	
	Rarely	2	
The patient finds his way in the nursing home (e.g., to his room, to the toilet, to his place at the table)	Generally yes	0	Spatial orientation
	Some ways yes, others no	1	
	Generally no	2	

Item	Scoring		Cognitive Domain Assessed (According To Sponsor)
The patient understands in what home or clinic he is	Always	0	Orientation for place
	Sometimes	1	
	Rarely	2	
The patient knows the names of the stuff (sic)	More than one	0	Naming
	Only one	1	
	None	2	
The patient understands what you communicate with him (by speaking, writing, or gestures)	Always	0	Receptive language function
	Sometimes	1	
	Never	2	

9.2 Secondary Efficacy Variables

9.2.1 Mini-Mental Status Examination (MMSE)

This is a multi-item instrument that examines orientation, registration, attention, calculation, recall, visuospatial abilities and language. The maximum score is 30, with higher scores indicating better cognitive function.

9.2.2 Functional Assessment Staging

This instrument is intended to assess functional decline in patients with Alzheimer’s Disease. It evaluates a patient’s ability to perform a variety of functions. The scale has seven major stages ranging from Stage I (“normal”) to Stage 7 (“severe”); Stage 6 is further divided into 5 subsets (6a to 6e); and Stage 7 is further divided into 6 subsets (7a to 7f). Staging is based on specific deficits in functional ability

9.2.3 Neuropsychiatry Inventory

This is a validated instrument that assesses the following 10 domains (subscales): delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability and aberrant motor behavior. Each item is rated according to its frequency and severity; rating is based on interviewing a caregiver. The maximum total score (the sum of the subscale scores) is 120 with a higher score indicating greater behavioral abnormality.

9.2.4 Resource Utilization In Dementia

This instrument is designed to assess caregiver burden for those caring for patients with Alzheimer’s Disease. The assessment consists of a structured interview with the caregiver and has 2 parts

Part A: This is a questionnaire administered at baseline

Part B: This is a follow-up questionnaire

The questionnaires assess basic demographic information, significant health events since the first questionnaire was administered, time spent with patient, changes in caregiver’s work status and changes in health care utilization

9.2.5 G2 Scale

This is a 16-item nurse-rated scale that assesses the following: cognition, mobility, behavior, and activities of daily living. The scale is rated in 2 ways

9.2.5.1 G2 Condition (G2)

In this method of rating, patient evaluations at specific timepoints are independent of each other. Each item is rated on a 6-point categorical scale with a higher score indicating more severe impairment

9.2.5.2 G2 Change (G2-C)

In this method of rating, the patient's condition at specific timepoints is rated in comparison with baseline on a 7-point categorical scale ranging from 1 ("very much improved") to 7 ("very much worse")

9.2.6 Instrumental Activities of Daily Living Performance Test (IADLPT)

This is a nurse-rated measure that evaluates a patient's ability to perform specific motor activities of daily living. The activities assessed are as follows: buttoning and unbuttoning 3 buttons; opening and closing 3 safety pins; making a knot and bow with a shoelace; applying a plaster (bandage); and reading and dialing a 6-digit phone number. Each activity is rated based on time taken, and on quality (1 = good; 2 = moderate; and 3 = bad)

9.2.7 Clinical Global Impression of Severity (CGI-S)

The severity of Alzheimer's Disease was graded according to the following scale in an efficacy study included in this application.

Score	Severity of disease
1	Normal, not at all ill
2	Borderline mentally ill
3	Mildly ill
4	Moderately ill
5	Markedly ill
6	Severely ill
7	Among the most extremely ill

9.2.8 Clinician Global Impression of Change (CGI-C) Benefit/Risk Index

This measure was the ratio of the CGI-C Efficacy (Benefit) Index to the CGI-C Risk Index

The CGI-C Efficacy Index was rated based on a 4-point scale that ranged from 1 to 4 (1 to 3 for good to minimal improvement; 4 for unchanged or worse)

For the CGI-C Risk Index, adverse events were rated according to the following 4-point scale:

No adverse events:	1
No significant interference with function:	2
Significant interference with function:	3
Adverse events outweigh therapeutic benefits:	4

9.3 Rating Scales Not Used As Efficacy Variables

9.3.1 Hamilton Depression Scale (HDS)

This is an observer-rated measure that is used to assess the severity of depression based on an interview of the patient and caregiver. 21 symptoms (e.g., anxiety, feelings of guilt, depressed mood) are each rated based on a

structured categorical scale with a higher score indicative of a greater severity of symptoms. Nine of the items are rated on a 5-point scale (0 to 4), 11 items are rated on a 3-point scale (0 to 2), and a single item on a 4-point scale (0 to 3)

9.3.2 Global Deterioration Scale (GDS)

This is an instrument intended to assess the magnitude of cognitive, functional and behavioral decline. A clinician provides an overall rating for the patient on a scale from 1, indicating “no cognitive decline”, to 7, indicating “very severe cognitive decline” as in the table below. Guidelines for rating the individual for each integral value on the scale from 1 through 7 are specified.

Stage	Stage
1	No cognitive decline
2	Very mild cognitive decline
3	Mild cognitive decline
4	Moderate cognitive decline
5	Moderately severe cognitive decline
6	Severe cognitive decline
7	Very severe cognitive decline

9.3.3 Hachinski Ischemic Scale (Rosen Modification)

This is a nine-item instrument that is intended to help distinguish between vascular dementia and Alzheimer’s Disease. The items assessed consist of the following: abrupt onset; stepwise deterioration; fluctuating course; somatic complaints; emotional incontinence; history of hypertension; history of stroke; focal neurological symptoms; and focal neurological signs. Each of the items is assigned a pre-specified score of either “1” or “2” if present; items rating a score of “2” are abrupt onset, fluctuating course, history of stroke, focal neurological symptoms and focal neurological signs. The maximum score is 14 with higher scores being considered more indicative of vascular dementia.

10 Tabular Summary Of Key Efficacy Studies

The sponsor has submitted the reports of 3 studies that are intended to support the claim for memantine in the treatment of moderate-to-severe Alzheimer’s Disease. These studies are outlined below. For full details about each of these studies, please see the individual study summaries later in the review.

10.1 Study MRZ 9605

This study was performed in the United States under IND 33392, and is outlined in the table below.

Design	Randomized, double-blind, placebo-controlled, parallel-group	
Duration	28 weeks of double-blind, parallel-arm treatment	
Key Inclusion Criteria	Probable Alzheimer’s Disease Mini-Mental Status Examination: 3-14 GDS: Stages 5-6 FAST ≥ 6a	
Primary Outcome Measures	ADCS-ADL, CIBIC-Plus	
Population For Primary Efficacy Analysis	Intent-to-treat-LOCF	
Secondary Outcome Measure	SIB, NPI, Global Deterioration Scale, Categorical ADCS-ADL, Functional Assessment Scale, Resource Utilization in Dementia	
Dose Arms	Memantine 10 mg b.i.d	Placebo
Number randomized	126	126
Number completing	97	84

Note that the mean Mini-Mental Status Examination at study entry was 7.9

The results of this study are summarized in the table below

	LOCF Analysis			OC Analysis		
	Memantine (n = 126)	Placebo (n = 126)	p-value*	Memantine (n = 97)	Placebo (n = 84)	p-value*
CIBIC-Plus	4.48	4.73	0.064	4.38	4.74	0.025
ADCS-ADL	-3.02	-5.02	0.022	-2.49	-5.48	0.003
SIB	-3.93	-9.84	< 0.001	-4.46	-10.16	0.002

*p-values are based on Wilcoxon-Mann-Whitney test for between treatment comparisons

10.2 Study MRZ 9403

This ex-IND study was conducted in Latvia

Design	Randomized, double-blind, placebo-controlled, parallel-group	
Duration	12 weeks of double-blind, parallel-arm treatment	
Key Inclusion Criteria	Alzheimer's Disease, vascular dementia, or mixed dementia* Mini-Mental Status Examination: 0-9 GDS: Stages 5-7	
Primary Efficacy Measures	BGP Care Dependency Subscale CGI-C	
Secondary Efficacy Measures	G2, G2-C, IADL	
Post-Hoc Primary Efficacy Measure	BGP Cognitive Subscale	
Dose Arms	Memantine 10 mg daily	Placebo
Number randomized	82	84
Number completing	78	80

*Randomization was not stratified by dementia type. Using the Hachinski Ischemic Scale, all patients enrolled in the study were grouped **post-hoc** into 2 categories: Alzheimer's Disease and vascular dementia

Only a total of 86 patients (40 placebo and 46 memantine) had brain imaging studies (CT scan only) done

The results of the post-hoc primary efficacy analysis for this study are summarized in the table below

	LOCF Analysis			OC Analysis		
	Memantine (n = 82)	Placebo (n = 84)	p-value*	Memantine (n = 78)	Placebo (n = 80)	p-value*
CGI-C	3.09	3.52	0.001	3.01	3.48	0.001
BGP Care Dependency	-5.29	-3.27	0.012	-5.56	-3.50	0.010
BGP Cognitive	-1.85	-1.12	0.001	-1.95	-1.19	0.001

*p-values are based on Cochran-Mantel-Haenszel test for row means (using modified ridit score) controlling for center

10.3 Study MEM-MD-02

This study was conducted in the United States under IND 33392, and is outlined in the table below

Design	Randomized, double-blind, placebo-controlled, parallel-group	
Duration	24 weeks of double-blind, parallel-arm treatment	
Key Inclusion Criteria	<ul style="list-style-type: none"> • Probable Alzheimer's Disease • Mini-Mental Status Examination: 5-14 • Treatment with donepezil for at least 6 months, and on a stable dose for 3 months 	
Primary Outcome Measures	<ul style="list-style-type: none"> • Severe Impairment Battery • ADCS-ADL (modified) 	
Population For Primary Efficacy Analysis	Intent-to-treat-LOCF	
Secondary Outcome Measure	<ul style="list-style-type: none"> • CIBIC-Plus • Neuropsychiatry Inventory • Functional Assessment Staging • Resource Utilization In Dementia • Behavioral Rating Scale For Geriatric Patients 	
Dose Arms	Memantine 10 mg b.i.d + donepezil	Placebo + donepezil
Number randomized	203	201
Number completing	172	150

Note that the mean Mini-Mental Status Examination (\pm standard deviation) at study entry was 9.9 (3.13) in the memantine plus donepezil group and 10.2 (2.98) in the placebo plus donepezil group

The results of the primary efficacy analysis for this study are summarized in the tables below

10.3.1 Least Square Mean Change From Baseline In Severe Impairment Battery

	Placebo/Donepezil		Memantine/Donepezil		p-value
	N	Mean	N	Mean	
Week 24 (LOCF)	196	-2.5	198	0.9	< 0.001
Week 24 (OC)	153	-2.4	171	1.0	< 0.001

10.3.2 Least Square Mean Change From Baseline In ADCS-ADL

	Placebo/Donepezil		Memantine/Donepezil		p-value
	N	Mean	N	Mean	
Week 24 (LOCF)	197	-3.4	198	-2.0	0.028
Week 24 (OC)	152	-3.3	172	-1.7	0.020

11 Study MRZ 9605

This study was conducted at 32 centers in the United States

11.1 Study Protocol

The version of the protocol summarized below is the final one, and does not appear to have been amended further before the study blind was broken.

11.1.1 Objective

To demonstrate that memantine is superior to placebo, as assessed by global and functional measures, in treating patients with moderately severe Alzheimer's Disease.

11.1.2 Design

Randomized, double-blind, placebo-controlled, parallel-arm trial of 28 weeks duration.

The proposed study was to be followed by an optional 24-week open-label period during which all patients were to receive the active drug

11.1.3 Sample Size

250 patients randomized equally to the 2 treatment groups

11.1.4 Key Inclusion Criteria

- Men or post-menopausal/surgically sterile women > 50 years old
- Probable Alzheimer's Disease, according to DSM-IV and NINCDS-ADRDA criteria
- Clinical and psychometric rating scores as follows:
 - Mini-Mental Status Examination range of 3-14
 - Global Deterioration Scale 5 or 6
 - Functional Assessment Scale Score $\geq 6a$
 - Hachinski Ischemic Scale score (as modified by Rosen) ≤ 4
- CT or MRI of brain, within 12 months prior to randomization, compatible with Alzheimer's Disease
- Ability to walk, at least with an assistive device
- Vision and hearing sufficient to comply with testing
- Normal cognitive and social functioning prior to onset of dementia
- Consistent caregiver to accompany patient to assessment visits as far as possible
- Sufficient basic education to be testable
- Living outside an institution
- Informed consent from patient, caregiver, legal guardian (if applicable) and a witness

11.1.5 Key Exclusion Criteria

- Dementia to any condition other than Alzheimer's Disease, including vascular dementia (modified Hachinski Ischemic Scale ≥ 5 ; positive NINDS-AIREN criteria)

- Significant neurological disease other than Alzheimer's Disease, including cerebral tumor, Huntington's Disease, Parkinson's Disease, normal pressure hydrocephalus, and other entities
- Major depression according to DSM-IV
- Psychotic episodes requiring hospitalization or antipsychotic therapy for more than 2 weeks within the past 10 years, not linked to Alzheimer's Disease
- Agitation sufficient to preclude participation in this trial
- Alcohol or drug dependence diagnosed within the past 10 years
- Epilepsy or anti-epileptic drug therapy
- Abnormal laboratory tests that might point to another etiology for dementia: serum B₁₂, folate, thyroid functions, electrolytes, syphilis serology
- Musculoskeletal diseases that could interfere with assessment
- Acute or poorly controlled medical illness: blood pressure > 180 mmHg systolic or 100 mmHg diastolic; myocardial infarction within 6 months; uncompensated congestive heart failure (NYHA Class III or IV), severe renal, hepatic or gastrointestinal disease that could alter drug pharmacokinetics; blood glucose > 180 mg/dl on repeated testing at entry into study or need for insulin therapy
- Previous randomization in this trial or participation in another investigational trial < 2 months prior to randomization
- Likelihood, according to clinical judgement, of being transferred to a nursing home within 6 months

11.1.6 Concomitant Medications

11.1.6.1 Prohibited Medications:

Investigational drugs, anticonvulsants, anti-Parkinsonian drugs, benzodiazepines, barbiturates, other hypnotics, neuroleptics, initiation of antidepressant and anxiolytic medication, cholinesterase inhibitors (the last of these may be used after a 30 day washout period), other drugs intended for the treatment of cognitive dysfunction

11.1.6.2 Permitted medications:

Chloral hydrate as a hypnotic (not within 24 hours of an assessment; maximum dose 2000 mg/day), xanthine derivatives (if dose remains stable throughout trial), beta-blockers and estrogens (if dose remains stable for 3 months prior to or during trial), "anti-inflammatory" drugs (if dose is constant for at least 1 month before trial, unless drug is used on an acute basis in which case the drug should not be used except for 3 days prior to each assessment), Ginkgo (if not investigational), Vitamin E and coenzyme Q (if dose is constant for at least 1 month before trial), all other medications (without restrictions)

11.1.7 Dosage

The dosing regime for the double-blind phase study is summarized in the following table

Groups	Time	weeks			
		1	2	3	4 to 28
Memantine	breakfast	5 mg	10 mg	10 mg	10 mg
	lunch	P	P	5 mg	10 mg
Placebo (P)	breakfast	P	P	P	P
	lunch	P	P	P	P

Matching placebo was to be used as indicated above, during the double-blind phase.

11.1.8 Duration

28 weeks of double-blind treatment

11.1.9 Schedule

The study schedule is summarized in the following table which I have copied from the submission

Time/Weeks	Washout		Memantine 10 mg b.i.d./Placebo		
	-4 to -2	0	4	12	28*
Visit No.	1	2	3	4	5
Informed Consent	x				
Demographics	x				
Medical History/AD History	x				
Physical Examination	x				x
Vital Signs	x	x	x	x	x
Neurological Examination	x				x
ECG	x				x
CT or MRI Brain Scan	x				
DSM-IV: Dementia	x				
NINCDS-ADRDA	x				
HIS (Mod. Rosen)	x				
DSM-IV: Depression	x				
In-/Exclusion Criteria	x	x			
Clinical Chemistry/ Hematology/Urinalysis	x			x	x
Plasma Sample (Drug)				x	x
CIBIC-Plus		x		x	x
Modified ADCS-ADL		x	x	x	x
SIB		x	x	x	x
MMSE	x	x	x	x	x
FAST	x	x		x	x
GDS	x	x		x	x
NPI		x		x	x
RUD		x		x	x
Adverse Event Inquiry		x	x	x	x
Concomitant Medication	x	x	x	x	x
Compliance Check			x	x	x
Dispense Medication		x	x	x	
ApoE		x			

Note: Additionally, phone contacts at Weeks 2, 6, 8, 10, 18, and 24 were scheduled.

* In case of premature termination before Week 28, an unscheduled visit (all procedures scheduled for Visit 5) was to be performed as soon as possible.

11.1.10 Outcome Measures

11.1.10.1 Primary Efficacy Measures

- Clinician Interview Based Impression of Change-Plus
- Alzheimer's Disease Cooperative Study-Activities of Daily Living (modified inventory)

11.1.10.2 Secondary Efficacy Measures

- Functional Assessment Scale
- Mini-Mental Status Examination
- Severe Impairment Battery
- Global Deterioration Scale
- Modified ADCS-ADL: Sum Scores of Responses
- Neuropsychiatry Inventory: Total Score (based on frequency and severity of each behavior) and NPI Caregiver Distress Scale
- Resource Utilization in Dementia

11.1.10.3 Safety Variables

Adverse events, vital signs, laboratory tests, electrocardiograms

11.1.10.4 Pharmacokinetic Measures

Plasma level of memantine

11.2 Analysis Plan

The analysis plan, finalized 11/29/99 after discussions with the Division, will be reviewed only as it pertains to the assessment of efficacy

11.2.1 General Considerations

- All statistical tests on the primary and secondary efficacy variables were to be 2-sided and a p-value of < 0.05 was to be considered statistically significant

11.2.2 Study Populations

- The intention-to-treat population was to consist of every patient randomized regardless of whether the patient received any treatment at all or the correct treatment.
- The treated-per-protocol population was to consist of the intention-to-treat population excluding patients with any of the following: no measurement of primary efficacy variables after 28 weeks of treatment; intake of less than 75 % of the prescribed individual daily dose in the course of the trial; major deviations from the protocol; violation of inclusion or exclusion criteria and change in caregiver status without adequate substitution or supervision.
- The evaluable-for-safety population was to consist of all those randomized who received at least one dose of study medication
- Retrieved dropout analyses were also planned for those patients missing Week 28 data

11.2.3 Demographic And Baseline Characteristics

The analysis plan does not specifically state how these parameters were to be analyzed

11.2.4 Drug Compliance

Overall compliance for the study was to be computed as follows: $100 \times \frac{[(\text{total number of tablets dispensed}) - (\text{total number of tablets returned}) - (\text{total number of tablets reported lost})]}{[(2 \times \text{number of days for which 2 tablets were prescribed per day plus number of days for which 1 tablet was prescribed per day})]}$

11.2.5 Primary Efficacy Parameters

- The primary efficacy parameters were as follows
 - CIBIC-Plus score at endpoint
 - Change from baseline in ADCS-ADL score at endpoint
- The primary efficacy analysis was to be performed using the intent-to-treat population and the last-observation-carried-forward (LOCF) method of imputation (unless data from a retrieved dropout visit was available, in which case that was to be used)
- The 2 treatment groups were to be compared using the Wilcoxon-Mann-Whitney test for independent samples; p-values and 95% confidence intervals were to be presented for treatment differences (the confidence intervals will be calculated based on normality assumptions)
- Treatment-by-center interactions were to be evaluated in an exploratory manner, only.

11.2.6 Null And Alternative Hypotheses

The null and alternative hypotheses for each primary efficacy variable were to be tested independently. The outcome of the study was to be considered statistically significant only if **both** null hypotheses are rejected.

H_0^C :	Average CIBIC-Plus scores of memantine and placebo groups after 28 weeks of treatment are equal
H_1^C :	Average CIBIC-Plus scores of memantine and placebo groups after 28 weeks of treatment are unequal
H_0^A :	Average ADCS-ADL sum scores of memantine and placebo groups after 28 weeks of treatment are equal
H_1^A :	Average ADCS-ADL sum scores of memantine and placebo groups after 28 weeks of treatment are unequal

11.2.7 Additional Analyses On Primary Efficacy Parameters

Exploratory analyses were to be performed on the primary efficacy parameters, using the same statistical method as for the primary efficacy analysis, using the treated-per-protocol dataset at each timepoint (Weeks 4, 12, and 28) and the intent-to-treat dataset at Weeks 4 and 12.

11.2.8 Pooling Of Centers

The analysis plan stated that it might become necessary to pool study sites with small numbers of patients (e.g., those with ≤ 5 randomized patients) in order to

analyze center effects (center effects on the efficacy analysis were to be analyzed on an exploratory basis only)

11.2.9 Secondary Efficacy Parameters

- The secondary efficacy parameters were the change from baseline to each study timepoint in secondary efficacy measure scores
- Analyses were to be performed on both the intent-to-treat and treated-per-protocol populations at each timepoint
- The treatment groups were to be compared on the secondary efficacy parameters using the same statistical methods applied to the primary efficacy parameter

11.2.10 Responder Analyses

- Patients were to be classified as responders or non-responders based on their status on global, functional, and cognitive outcome measures after 28 weeks of treatment
- Two responder definitions were to be used, based on the following criteria (all of which implied improvement or no change)
 - CIBIC-Plus score ≤ 4
 - Change from baseline in the modified ADCS-ADL sum score is ≥ 0
 - Change from baseline in the Severe Impairment Battery score is ≥ 0
- One definition of responder satisfied all 3 criteria; the other definition of responder satisfied only the CIBIC-Plus criterion, and the ADCS-ADL or Severe Impairment Battery criterion
- Analyses using both responder definitions were to be performed on the intent-to-treat and treated-per-protocol populations
- Responder frequencies in the 2 treatment groups were to be compared using Fisher's exact test

11.2.11 Subgroup Analyses

Additional exploratory analyses of the primary efficacy parameters were to be performed for subgroups defined by age (< 75 vs > 75), sex, ApoE genotype, severity of Alzheimer's Disease at baseline (Mini-Mental Status Examination score < 10; Mini-Mental Status Examination score ≥ 10); and memantine plasma levels at endpoint

11.2.12 Handling Of Missing Items

The methods of replacing missing items for the Severe Impairment Battery and ADCS-ADL are summarized below

11.2.12.1 Severe Impairment Battery

There are 51 separate items in this scale, with a total score ranging from 0 to 100; higher scores indicate better functioning. Single missing items were to be replaced with a "0" before calculating the total score. If more than 11 items were missing, then the total score was to be set to missing

11.2.12.2 *ADCS-ADL*

There are 19 separate items in this scale, with a total score ranging from 0 to 54; higher scores indicate better functioning. Single missing items were to be replaced with a "0" before calculating the total score. If more than 4 items were missing, then the total score was to be set to missing

11.2.13 *Sample Size Rationale*

- The sample size estimate was based on the CIBIC-Plus change in another memantine clinical trial, using the standard 7-point scale
- Assumptions
 - Mean memantine-placebo difference of 0.4 points on the CIBIC-Plus at study end, with a standard deviation of 0.85 points
 - Type I error of 0.05 (2-sided)
 - Type II error of 0.05 (i.e., 95% power)
- Based on the above assumptions, it was estimated that 107 patients would need to be randomized to each treatment group

11.3 *Protocol Amendments*

These have been incorporated into the outline above

11.4 *Actual Analyses Performed*

A supplemental statistical analysis plan is included in an appendix to the study report. It does not appear as if this plan was finalized prior to the breaking of the study blind. The key changes made to the analysis plan already described above are as follows

11.4.1 *Alternative Imputation Schemes For Analysis Of CIBIC-Plus*

- In the pre-specified efficacy analysis, patients with no post-baseline CIBIC-Plus ratings were assigned a score of 4 ("unchanged") as their endpoint rating in the LOCF dataset
- To examine the effect of this imputation rule on the analysis results, additional endpoint analyses, using several alternate imputation schemes were conducted. These analyses were conducted after patients with missing Week 28 CIBIC-Plus scores were assigned each of the following as their endpoint assessment
 - Group mean score
 - Group median score
 - Worst case score (i.e., 7)
 - Worst group score
- Each of the modified datasets was analyzed using a Wilcoxon-Mann-Whitney test of the difference in group means

11.4.2 *Additional Analyses Of The Severe Impairment Battery*

Additional analyses of the Severe Impairment Battery were conducted using the same methods as specified for the modified ADCS-ADL. These included

- Analyses of subgroups, based on sex, age, ApoE genotype, and Alzheimer's Disease severity at baseline
- Analyses of treatment-by-center interactions

11.4.3 Elimination Of The Resource Utilization In Dementia Analyses From The Main Study Report

These analyses were reported separately

11.4.4 Elimination Of The Treated-Per-Protocol Analyses

Analyses using this dataset were eliminated altogether

11.4.5 Elimination Of Subgroup Efficacy Analyses Based On Plasma Levels

These analyses were eliminated altogether

11.4.6 Determination Of The Primary Reason For Discontinuation

One primary reason for treatment discontinuation was to be identified for each patient prematurely terminating the study

11.5 Efficacy Results

11.5.1 Patient Disposition

Patient disposition in this study is summarized in the following table which I have copied from the submission

	<i>Placebo</i>		<i>Memantine</i>		<i>Total</i>	
	<i>N</i>	<i>(%)</i>	<i>N</i>	<i>(%)</i>	<i>N</i>	<i>(%)</i>
<i>Number of Patients Randomized</i>	126		126		252	
<i>Patients Who Completed the Study</i>	84	(67)	97	(77)	181	(72)
<i>Patients Who Discontinued</i>	42	(33)	29	(23)	71	(28)
REASONS FOR DISCONTINUATION						
<i>Adverse Event</i>	24	(19)	14	(11)	38	(15)
<i>Insufficient Therapeutic Response</i>	0	(0)	1	(0.8)	1	(0.4)
<i>Withdrawal of Consent</i>	10	(8)	8	(6)	18	(7)
<i>Protocol Violation</i>	6	(5)	4	(3)	10	(4)
<i>Lost to Follow-up</i>	1	(0.8)	2	(2)	3	(1)
<i>Other reasons</i>	1	(0.8)	0	(0)	1	(0.4)

As the study results indicate, discontinuations were more frequent in the placebo group than in the memantine group, with the majority being attributable to adverse events

11.5.2 Treatment Duration

The duration of treatment in the placebo and memantine groups is as displayed in the following 2 tables, which I have derived from tables contained in the submission. The data are based on the intent-to-treat population

	Placebo (n = 125)	Memantine (n = 123)
Treatment Duration (Days)		
Mean	166.1	169.58
Median	193.0	195.0
Standard Deviation	56.42	56.03
Range	3 to 218	2 to 229

Treatment Duration	Placebo (n = 126)	Memantine (n = 126)
1 to 30 days	9 (7%)	7 (6%)
31 to 60 days	3 (2%)	5 (4%)
61 to 90 days	7 (6%)	7 (6%)
91 to 120 days	3 (2%)	3 (2%)
121 to 150 days	5 (4%)	1 (1%)
151 to 180	20 (16%)	11 (9%)
181 to 210	71 (56%)	84 (67%)
211 to 240	7 (6%)	6 (5%)
Missing	1 (1%)	3 (2%)

The tables indicate that the majority of patients in both treatment groups received more than 180 days of study drug.

11.5.3 Demographic And Other Baseline Characteristics

Demographic characteristics are summarized in the following table which I have copied from the submission

Demographic Characteristics

	<i>Placebo</i> (N=126)	<i>Memantine</i> (N=126)	<i>Total</i> (N=252)
MEAN AGE, years (SD)	76.3 (7.8)	75.9 (8.4)	76.1 (8.1)
< 65 n (%)	10 (8)	12 (10)	22 (9)
≥ 65 and < 75 n (%)	41 (33)	38 (30)	79 (31)
≥ 75 and < 85 n (%)	60 (48)	60 (48)	120 (48)
≥ 85 n (%)	15 (12)	16 (13)	31 (12)
SEX			
Male n (%)	47 (37)	35 (28)	82 (33)
Female n (%)	79 (63)	91 (72)	170 (67)
ETHNICITY			
Non-Caucasian n (%)	11 (9)	14 (11)	25 (10)
Caucasian n (%)	115 (91)	112 (89)	227 (90)
WEIGHT (KG) mean (SD)	66.1 (14.1)	64.5 (12.4)	65.3 (13.2)

Summary statistics for baseline efficacy measures are in the following table, which I have copied from the submission

Summary of Mean Baseline Efficacy Assessments

<i>Assessment</i>	<i>Placebo</i> N=126	<i>Memantine</i> N=126
ADCS-ADL Mean (SD)	27.4 (10.9)	26.8 (9.2)
SIB Mean (SD)	68.3 (20.8)	65.9 (22.5)
MMSE Mean (SD)	8.05 (3.6)	7.72 (3.7)

The tables above indicate that the treatment groups were broadly comparable in regard to mean age and baseline cognitive and functional status.

The distribution of baseline Mini-Mental Status Examination scores in the entire population enrolled in the study is in the following table:

Mini-Mental Status Examination Score	N	%
1	1	0.4
2	2	0.79
3	27	10.7
4	35	13.9
5	26	10.3
6	19	7.5
7	11	4.4
8	16	6.3
9	18	7.1
10	23	9.1
11	19	7.5
12	24	9.5
13	11	4.4
14	20	7.9

As the table above indicates, 38.4% of those enrolled in the study had a baseline Mini-Mental Status Examination score ≥ 10 .

11.5.4 Primary Efficacy Analysis

11.5.4.1 CIBIC-Plus

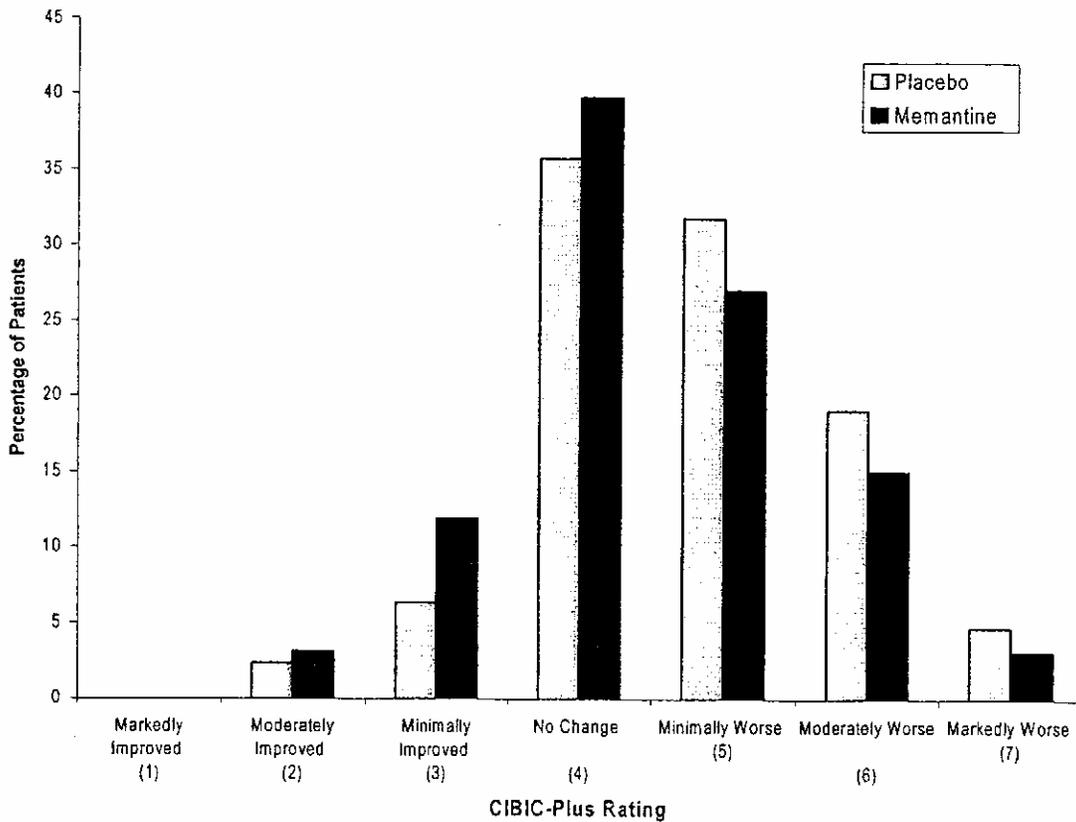
Mean CIBIC-Plus ratings at endpoint for the primary LOCF dataset and for Observed Cases (OC) are summarized in the following table, taken from the submission

Mean CIBIC-Plus Rating

	<i>Placebo</i>		<i>Memantine</i>		<i>p-value</i>
	<i>N</i>	<i>Mean</i>	<i>N</i>	<i>Mean</i>	
Endpoint (LOCF)	126	4.73	126	4.48	0.064
Week 28 (OC)	84	4.74	97	4.38	0.025

The distribution of CIBIC-Plus ratings at endpoint for the LOCF dataset is in the following figure, which I have taken from the submission

Distribution of CIBIC-Plus Ratings at Endpoint (LOCF)



As the table and figure above indicate, the treatment difference was clearly statistically significant only for the Observed Cases dataset; for the primary LOCF dataset, the results were borderline ($p = 0.064$) as regards statistical significance. For both datasets, memantine was superior to placebo.

Analyses of the CIBIC-Plus were also conducted using alternative imputation rules, i.e., rules that were different from those used for the LOCF analysis (these schemes are described in Section 11.4.1.). The results, which indicate a statistically significant superiority of memantine over placebo regardless of which alternative imputation scheme was used are summarized in the next table, which I have copied from the submission.

Mean CIBIC-Plus Ratings at Endpoint Using Alternative Imputation Rules

	<i>Placebo</i>		<i>Memantine</i>		<i>p-value</i>
	<i>N</i>	<i>Mean</i>	<i>N</i>	<i>Mean</i>	
Worst Case (WC)	126	5.49	126	4.98	0.005
Group Mean (GM)	126	4.74	126	4.38	<0.001
Group Median (GMN)	126	4.83	126	4.29	<0.001

ITT population

11.5.4.2 Modified ADCS-ADL

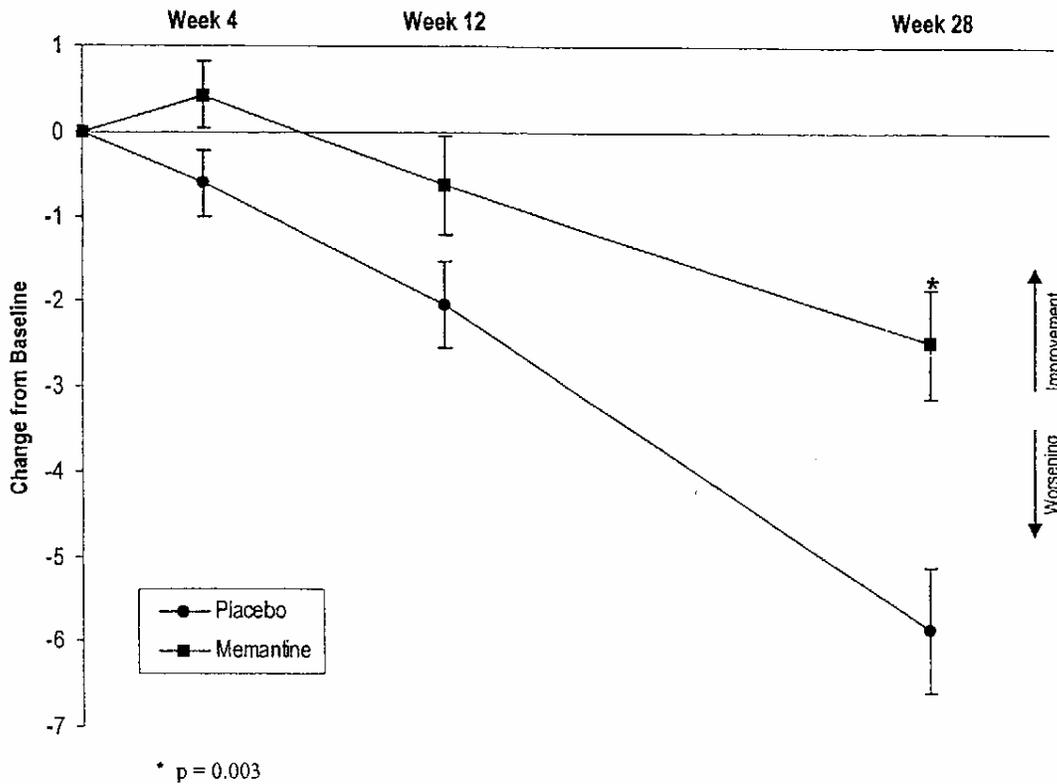
Mean change from baseline in the modified ADCS-ADL at endpoint for the primary LOCF dataset and for Observed Cases (OC) are summarized in the following table, taken from the submission

Change from Baseline in ADCS-ADL

	Placebo		Memantine		p-value
	N	Mean	N	Mean	
Endpoint (LOCF)	126	-5.08	126	-3.02	0.022
Week 28 (OC)	84	-5.86	97	-2.49	0.003

Changes from baseline in the ADCS-ADL (Observed Cases dataset) at each study timepoint are in the following figure taken from the submission

Change from Baseline in the ADCS-ADL by Visit (Observed Cases)



As the table and figure above indicate, there were statistically significant differences between the treatment groups on this measure for both datasets, with the memantine group being superior to the placebo group.

11.5.5 Analysis Of Secondary Efficacy Measures

11.5.5.1 Severe Impairment Battery

Mean changes from baseline in the Severe Impairment Battery at endpoint for the primary LOCF dataset and for Observed Cases (OC) are summarized in the following table, taken from the submission

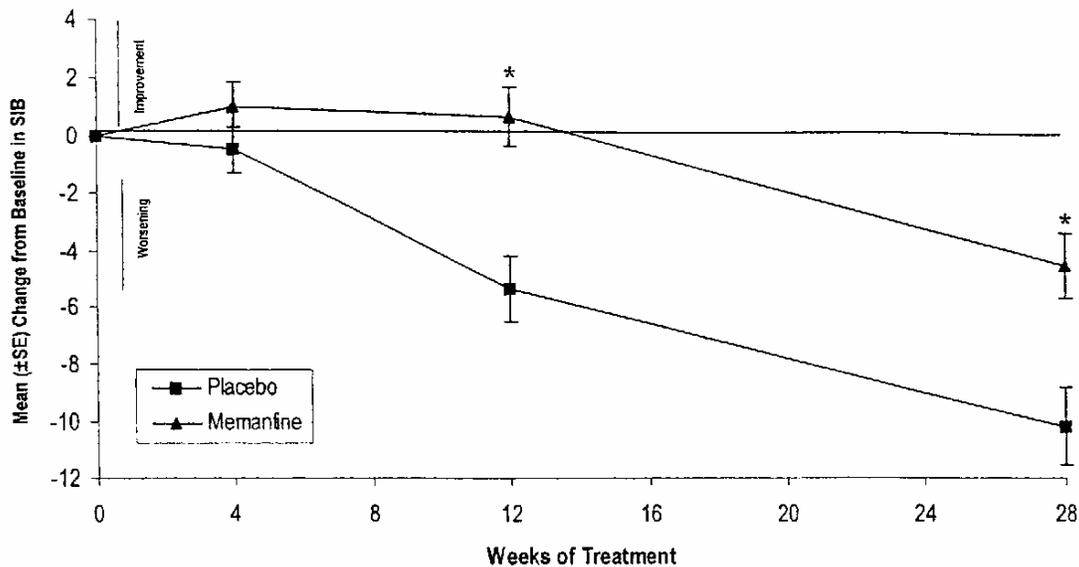
Change from Baseline in SIB

	Placebo		Memantine		p-value
	N	Mean	N	Mean	
Endpoint (LOCF)	126	-9.84	126	-3.93	<0.001
Week 28 (OC)	83	-10.16	96	-4.46	0.002

Note that the exact p-value for the endpoint LOCF comparison was 0.0003

Changes from baseline in the Severe Impairment Battery (Observed Cases dataset) at each study timepoint are in the following figure taken from the submission

Change from Baseline in the SIB Score by Visit (Observed Cases)



*p < 0.01

As the table and figure above indicate, there were at least nominally statistically significant differences between the treatment groups on this measure for both datasets, with the memantine group being superior to the placebo group. Although many analyses were performed in this study, apart from the primary efficacy analysis, the p-value (p = 0.0003) for the treatment group comparison on this measure on the LOCF dataset was robust enough to remain statistically significant (i.e., p < 0.05) even after adjustment for multiple comparisons.

11.5.5.2 Other Secondary Efficacy Measures

Changes from baseline to endpoint for the other secondary efficacy parameters are in the following table which I have copied from the submission. A nominally statistically significant difference ($p < 0.05$) between treatment groups was seen only for Functional Assessment Staging

Change from Baseline to Endpoint (LOCF) in Other Secondary Efficacy Parameters

	<i>Placebo</i>	<i>Memantine</i>	<i>p value</i>
NPI, mean (SD)	3.63 (15.62)	0.44 (15.38)	0.371
FAST, mean (SD)	0.52 (1.35)	0.20 (1.22)	0.020
GDS, mean (SD)	0.19 (0.47)	0.10 (0.46)	0.124
MMSE, mean (SD)	-1.14 (3.00)	-0.52 (2.38)	0.192

11.5.6 Additional Sponsor Analyses

The results of these analyses have been summarized by the sponsor as follows

11.5.6.1 Subscale Analyses

Analyses of individual domains/items for the CIBIC-Plus, ADCS-ADL, and Neuropsychiatry Inventory generally showed numerical trends in agreement with observations for the complete scales

11.5.6.2 Responder Analyses

Responder analyses were based on the two definitions already outlined in Section 11.2.10.

For the first definition, 6% of placebo patients and 11% of memantine patients were classified as responders ($p = 0.170$).

For the second definition, 10% of placebo patients and 29% of memantine patients were classified as responders ($p < 0.001$).

11.5.6.3 Consistency Of Treatment Effect Across Centers

In the statistical models used for analysis of the CIBIC-Plus, ADCS-ADL, and Neuropsychiatry Inventory, there was a lack of significant center effects or treatment-by-center interactions for all 3 scales ($p > 0.1$); the observed memantine-placebo differences at each center supported the consistency of the treatment effect across centers.

11.5.6.4 Efficacy In Subgroups

Additional exploratory analyses for subgroups defined by sex, age, severity of dementia at baseline, and presence or absence of ApoE4 allele, showed an advantage for memantine over placebo on both the LOCF and Observed Cases datasets at Week 28

11.5.6.5 Relationship Of Efficacy To Memantine Plasma Level

Plasma concentrations of memantine were determined in samples obtained from 108 memantine-treated patients at their final visit; they do not appear to have been determined in placebo-treated patients.

Based on their plasma levels, patients treated with memantine were grouped into 4 categories: ≤ 70 ng/mL; 71 – 100 ng/mL; 101 – 130 ng/mL; > 130 ng/mL.

The mean change from baseline in Severe Impairment Battery score in each of these categories is in the following table for both the LOCF and Observed Cases datasets.

Dataset	Memantine Plasma Level Category			
	≤ 70 ng/mL (n = 7)	71 – 100 ng/mL (n = 28)	101 – 130 ng/mL (n = 32)	> 130 ng/mL (n = 41)
LOCF at endpoint	- 4.0	- 4.25	- 4.44	- 4.66
Observed Cases at Week 28	- 5.20	- 3.92	- 4.96	- 4.35

As the above table indicates, there was no suggestion of a correlation between memantine plasma levels and change from baseline in Severe Impairment Battery scores.

11.5.7 Agency Subgroup Analysis

Dr Tristan Massie, Agency Biometrics Reviewer of this submission, has, at my request, compared the effects of the two treatment groups on the primary efficacy parameters, after dividing those enrolled into 2 subgroups: those with a Mini-Mental Status Examination (MMSE) score ≥ 10 , and those with a Mini-Mental Status Examination score < 10 .

The purpose of this additional analysis was to help determine if any effect on memantine in Alzheimer’s Disease was actually determined by patients with more severe dementia, for the following reasons

- 4 drugs have currently been approved for the treatment of mild-to-moderate dementia of the Alzheimer’s type, whereas the sponsor is currently seeking a claim for memantine in the treatment of moderate-to-severe dementia of the Alzheimer’s type. Baseline Mini-Mental Status Examination scores used to include patients in clinical trials for mild-to-moderate Alzheimer’s Disease range from 10-26; that range overlaps with the range used to select patients for MEM-MD-02
- Patients enrolled in this study had a baseline Mini-Mental Status Examination score that ranged from 1 to 14 (with the vast majority having Mini-Mental Status Examination scores that ranged from 3 to 14, as specified by the inclusion criteria for this study). The majority of those enrolled had a Mini-Mental Status Examination score < 10 .

The results of the analysis are summarized in the following table

Study 9605: ITT-LOCF MMSE Subgroup Analyses							
Variable	MMSE Group	Treatment Group	n	Baseline Mean (SD)	Mean Change From Baseline To Endpoint Mean (SD)	p-value for treatment group comparison	Interaction p value
Primary							
ADL Total	<10	Placebo	73	25.5 (11.9)	-5.6 (6.5)	0.2668	0.0951
	<10	Memantine	79	24.3 (9.0)	-4.5 (6.7)		
	≥ 10	Placebo	50	30.7 (8.4)	-4.6 (6.1)	0.0095	
	≥ 10	Memantine	45	31.0 (7.8)	-0.6 (6.4)		
Secondary							
CIBIC-Plus	<10	Placebo	70	N/A	4.80 (1.06)	0.5364	
	<10	Memantine	75	N/A	4.68 (1.10)		
	≥ 10	Placebo	48	N/A	4.75 (1.14)	0.0231	
	≥ 10	Memantine	43	N/A	4.23 (1.09)		
Secondary							
SIB Total	<10	Placebo	73	58.0 (19.4)	-11.8 (14.0)	0.0091	0.8136
	<10	Memantine	79	55.0 (20.4)	-5.8 (12.6)		
	≥ 10	Placebo	50	83.7 (8.8)	-7.6 (12.5)	0.0087	
	≥ 10	Memantine	45	84.8 (11.3)	-0.8 (7.9)		

As the table above indicates, differences between treatment groups (effect sizes) appeared to be greater for those with a baseline Mini-Mental Status Examination ≥ 10, for both primary measures (and to a lesser extent for the Severe Impairment Battery)

11.6 Sponsor’s Conclusions Regarding Efficacy

- A statistically significant superiority of memantine over placebo was observed for the ADCS-ADL and Severe Impairment Battery on the LOCF analysis at endpoint, and for the Observed Cases analysis at the same timepoint
- A marginally significant superiority of memantine over placebo was observed for the CIBIC-Plus on the LOCF analysis at endpoint. However, a clearly statistically significant advantage was observed for the Observed Cases analysis at Week 28. The robustness of the analysis of the CIBIC-Plus was further supported by analyses using alternative imputation rules

11.7 Agency Statistical Reviewer’s Comments

Final comments from the Agency statistical reviewer are pending.

11.8 Reviewer’s Comments

- This study was intended to evaluate the efficacy of memantine compared with placebo in moderate-to-severe Alzheimer’s Disease. The study had 2 primary efficacy measures, the CIBIC-Plus (a global measure) and the modified ADCS-ADL (a measure of activities of daily living). The prospectively-finalized analysis plan indicated, that for the study to be declared positive, a statistically significant difference ($p < 0.05$) between memantine and placebo needed to be seen on both primary efficacy measures, using the prospectively-specified dataset and analytical method.
- The protocol-specified primary analysis, on the LOCF dataset, provided a borderline level of statistical significance for the CIBIC-Plus ($p = 0.064$) and

clear statistical significance for the modified ADCS-ADL (0.022), when the 2 treatment groups were compared. More clearly statistically significant results were seen for both parameters when the Observed Cases (at Week 28) dataset was analyzed.

- Thus far, the regulatory standard for determining the efficacy of drugs intended for the treatment of Alzheimer's Disease/dementia of the Alzheimer's type has been the demonstration of a statistically significant ($p < 0.05$) advantage for the drug in comparison with placebo on 2 types of primary efficacy measure: a cognitive measure, since cognitive dysfunction is the core manifestation of dementia; and a global or functional measure, so as to confirm that any effect on the cognitive measure is clinically meaningful
- This study lacks a cognitive primary efficacy measure; in designing this protocol, the original sponsor took the view that demonstrating efficacy on global and functional measures was more practical and meaningful than demonstrating efficacy on a cognitive measure, in a population with severely impaired cognition
- The study does however have a secondary efficacy measure (one of seven), the Severe Impairment Battery, that is specifically intended to measure change in cognition in patients with severe dementia. An at least nominally statistically significant difference ($p = 0.0003$) between memantine and placebo was seen on this measure for the LOCF dataset at study endpoint; this p-value appeared robust enough to remain statistically significant ($p < 0.05$) when adjusted for multiple comparisons.
- Thus this study could be considered to have shown evidence of a statistically significant superiority for memantine over placebo on both a cognitive and a global primary efficacy measure, and to be consistent with the regulatory standard for determining the efficacy of drugs in Alzheimer's Disease/dementia of the Alzheimer's type.
- The following are also noteworthy, however
 - In both the memantine and placebo groups there was a mean deterioration in cognitive function over the 28-week course of the study
 - The effect size on the Severe Impairment Battery remained relatively small (5.91 point mean difference between treatment groups on the Severe Impairment Battery for the LOCF dataset at study end)
 - Based on the response patterns seen on the CIBIC-Plus, only a small minority of patients treated with memantine showed even a minimal or moderate improvement, with no patients showing a marked improvement, and the most common response being "no change"

12 Study MRZ 9403

This study was conducted at 7 centers in Latvia.

12.1 Title

Efficacy And Tolerability Of Akatinol Memantine In Care-Dependent Patients With Moderate To Severe Primary Dementia

12.2 Objective

To evaluate the clinical efficacy and tolerability of memantine in care-dependent patients with moderate-to-severe dementia

12.3 Design

Randomized, double-blind, placebo-controlled, parallel-arm study

12.4 Duration

12 weeks of double-blind treatment

12.5 Dosage

The dosing regime for this study was as follows

Study Days	Dosage
1 to 7	Memantine 5 mg or matching placebo once daily in the morning
8 to 84	Memantine 10 mg or matching placebo once daily in the morning

12.6 Sample Size

150 patients were to be enrolled in the study and randomized equally to the two treatment groups

12.7 Main Inclusion Criteria

- Male or female
- Age: 60 to 80 years
- Resident in a nursing home
- Education up to at least the elementary school level
- Moderate-to-severe dementia based on the DSM-III-R and the following criteria
 - Global Deterioration Scale: 5 to 7 points
 - Clinical Global Impression of Severity score of 5 to 7
 - Mini-Mental Status Examination score < 10

Note that the original study protocol states that patients targeted for enrollment in this study were to include those with Alzheimer’s Disease, vascular dementia, and mixed dementia (combining Alzheimer’s Disease with vascular dementia); criteria for making these diagnoses at study entry are not specified. The original study protocol further states the following: “As patients with both (*sic*) types of dementia are to be included in the trial, the results of a CT examination and a Hachinski Ischemic Scale test done at the beginning of the trial will NOT (emphasis mine) be utilized to differentiate between primary degenerative dementia and vascular dementia.”

- Duration of dementia or symptoms > 12 months
- No “clinically relevant pathological changes” in the following laboratory data (taking into consideration age-related alterations): CBC, electrolytes, BUN, serum creatinine, GGT, ALT, total protein, and urinalysis
- No clinically relevant reductions in serum vitamin B₁₂ or in thyroid functions
- No central nervous system active drugs taken within 14 days before the trial
- Informed consent

12.8 Main Exclusion Criteria

- Severe hypothyroidism and other relevant endocrine diseases
- Unstable diabetes mellitus
- Severe chronic or terminal diseases
- Cardiac failure (NYHA Class III or IV)
- Severe fixed hypertension (WHO Class III) or labile hypertension while under treatment
- Myocardial infarction, endocarditis, or myocarditis during the last 3 months
- Severe arrhythmias requiring treatment
- Severe orthostatic “dysregulation”
- Severe chronic obstructive pulmonary disease
- Chronic liver disease (transaminases > 2 x upper limit of normal); hepatic encephalopathy
- Severe renal disease or dysfunction (serum creatinine > 2 mg/dL)
- Brain tumor
- Schizophrenia
- Major depression (Hamilton Depression Scale [21-item version] score > 18)
- “Oligophrenia”
- Epilepsy
- Parkinson’s Disease
- Secondary dementia
- Alcoholism, drug addiction
- Participation in a clinical trial within the preceding 30 days
- Blood loss of > 500 mL within the preceding 2 months
- The following concomitant medications
 - Medications with could interact with the study drug or influence the results of efficacy testing (these were to be withdrawn 14 days before the start of the trial, and were not to be administered during the trial)
 - Anticonvulsants
 - Monoamine oxidase inhibitors, neuroleptics, tricyclic antidepressants
 - Nootropics or agents stated to promote cerebral circulation
 - Hypnotics, except for chloral hydrate or benzodiazepines with short half-lives

12.9 Concomitant Medications

12.9.1 Prohibited Medications

The following concomitant medications are prohibited (as already noted)

- Medications with could interact with the study drug or influence the results of efficacy testing (these were to be withdrawn 14 days before the start of the trial, and were not to be administered during the trial)
- Anticonvulsants
- Monoamine oxidase inhibitors, neuroleptics, tricyclic antidepressants
- Nootropics or agents stated to promote cerebral circulation
- Hypnotics, except for chloral hydrate or benzodiazepines with short half-lives

12.9.2 Permitted Medications

Long-term treatment with drugs such as cardiac glycosides, antihypertensives and oral anti-diabetic agents is permitted as long as dosage is kept constant before and during the clinical trial phase

12.10 Schedule

Study visits were to be at screening/baseline (no clear distinction is made in the protocol between the screening and baseline visits) and Days 7, 28, 56, and 84.

The study schedule is summarized in the following table

Day	0	7	28	56	84
History	X				
Physical examination	X				X
Risk factor data	X				X
Neurological examination	X				
Memantine plasma concentration	X		X		X
Safety laboratory tests	X		X		X
Hachinski	X				
CT scan of brain (optional)	X				
DSM-III-R	X				
GDS	X				
MMSE	X				
CGI-C	X		X		X
CGI-S	X				X
CGI Benefit/Risk Index	X				X
G2	X				X
G2-C		X	X	X	X
BGP	X	X	X	X	X
IADLPT	X				X
Medication compliance		X	X	X	X
Medication dispensation	X	X	X	X	
Adverse events		X	X	X	X
Blood pressure, heart rate	X	X	X	X	X

12.11 Outcome Measures (Per-Protocol)

12.11.1 Primary Efficacy Measures

BGP Care Dependency Subscale

CGI-C (dichotomized): responder rate

(note that a responder is not clearly defined in the protocol)

12.11.2 Secondary Efficacy Measures

IADLPT (timing and quality)

G2 (single item scores and total score)

G2-C (single item scores and total score)

12.11.3 Safety Measures

(The analysis of these measures will be not be further addressed here, as this is an efficacy review)

Adverse events

Safety laboratory tests (hematology, clinical chemistry and urinalysis)

12.11.4 Pharmacokinetic Measures

Plasma levels of memantine

12.12 Analysis Plan (Per-Protocol)

12.12.1 General Considerations

- A Type I error of 0.025 (2-sided) was to be used
- Results were to be presented using descriptive statistics

12.12.2 Demographic And Baseline Characteristics

No details are supplied

12.12.3 Study Hypotheses

$H_0(1)$: There are no differences at the end of treatment between memantine and placebo with regard to the responder rate on the basis of the dichotomized CGI-C

$H_1(1)$: There are differences at the end of treatment between memantine and placebo with regard to the responder rate on the basis of the dichotomized CGI-C

$H_0(2)$: There are no differences at the end of treatment between memantine and placebo with regard to the BGP Care Dependency Subscale change from baseline score

$H_1(2)$: There are differences at the end of treatment between memantine and placebo with regard to the BGP Care Dependency Subscale change from baseline score

12.12.4 Primary Efficacy Parameters

- The primary efficacy parameters were to be as follows
 - Change from baseline to endpoint in the BGP Care Dependency Subscale
 - CGI-C (dichotomized) responder rate at study endpoint
- The population for the primary efficacy was “intent-to-treat,” defined as all those who received study medication and had Day 28 measurements while taking study medication
- Differences between the 2 treatment groups on the BGP Care Dependency Subscale were to be analyzed using Wilcoxon-Mann-Whitney U tests
- Differences between treatment groups on the CGI-C were to be analyzed using Fisher’s exact test
- Missing data were to be replaced using “worst ranks”

12.12.5 Secondary Efficacy Parameters And Other Analyses

- Secondary efficacy variables, and the residual results of the CGI-C and BGP, were to be checked for medication and time effects, as well as for interactions using suitable non-parametric methods
- Subgroup analyses, based on age and severity of disease, were to be done using the relevant frequency distributions.
- If the sample was big enough, descriptive analyses for center effects were also intended

12.12.6 *Sample Size Calculation*

12.12.6.1 *For CGI-C*

- Assumptions
 - Type I error: 0.025
 - Power: 90%
 - 30% difference in responder rate on the CGI-C between the treatment and placebo groups; responder rate 30% in placebo group (on dichotomized scale).
- Based on the above assumptions a sample size of 68 patients per treatment group was estimated

12.12.6.2 *For BGP Care Dependency Subscale*

- Assumptions
 - Type I error: 0.025
 - Power: 90%
 - 7.8 point difference in the change from baseline on the BGP care dependency subscale.
- Based on the above assumptions a sample size of 23 patients per treatment group was estimated

12.12.6.3 *Overall*

Based on the above sample size calculation, a total enrollment of 136 patients was estimated

12.12.7 *Interim Analysis*

None planned.

12.13 *Protocol Amendments*

The following key amendments were made to the protocol prior to the study blind being broken

- Introduction of 6 additional study centers
- An increase in total number of patients randomized to 168

12.14 *Post-Hoc Analysis Plan (Forest Laboratories)*

The study was completed by Merz in 1995, and the results published in 1999 as follows.

Winblad B, Poritis N. Memantine in severe dementia: results of the 9M-Best Study (Benefit and efficacy in severely demented patients during treatment with memantine). *Int J Geriatr Psychiatry* 1999;14:135-46

A new analysis plan was finalized by Forest Laboratories on May 24, 2002. This analysis plan is further described below. The analysis described in the study report is based on this post-hoc analysis plan

12.14.1 Objectives

12.14.1.1 Primary

To evaluate the efficacy, safety, and tolerability of memantine as compared with placebo in patients with moderate-to-severe dementia of Alzheimer's and vascular type

12.14.1.2 Secondary

- To further compare the efficacy of memantine relative to placebo using several secondary efficacy parameters
- To assess the safety and tolerability of memantine (this appears to be a primary as well as secondary objective)

12.14.2 Efficacy Outcome Measures

12.14.2.1.1 Primary

- CGI-C (7-point scale);
Data for the dichotomized CGI-C responder analysis were also to be presented, but the analysis of the 7-point scale was to be primary
- BGP Care Dependency Subscale
- BGP Cognitive Subscale

12.14.2.1.2 Secondary

- BGP Total Score and all other BGP sub-scales
- CGI Efficacy Index and CGI Risk Index
- CGI-S
- G2; G2-C
- IADLPT (timing and quality)

12.14.3 Study Populations

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

12.14.3.1 Randomized Population

This population was to consist of all patients randomized into the study

12.14.3.2 Safety Population

This population was to consist of all randomized patients who received at least one dose of double-blind study medication

12.14.3.3 Intent-To-Treat Population

This population was to consist of all those in the safety population who completed at least one post-baseline efficacy evaluation of the CGI-C or BGP. Missing data were to be imputed when an analysis was performed on this population

12.14.4 *Patient Disposition And Study Completion*

- The number of patients in each study population (i.e., randomized, safety, intent-to-treat) were to be summarized by treatment group and center
- The number of patients with Alzheimer's Disease and the number of patients with vascular dementia in each study population were to be presented by treatment group and center
- The number and percentage of the total population, as well in each dementia subtype population (i.e., Alzheimer's Disease and vascular dementia) completing and discontinuing during the double-blind treatment period were to be presented by treatment group. Reasons for discontinuation were to be presented by treatment group

12.14.5 *Demographic And Other Baseline Characteristics*

- Demographic parameters and other baseline characteristics were to be summarized by treatment group
- The treatment groups were to be compared as follows
 - Continuous variables were to be analyzed using a 2-way ANOVA model with treatment and study center as the factors
 - Categorical variables were to be analyzed using a Cochran-Mantel-Haenszel test controlling for study center

12.14.6 *Efficacy Analyses*

12.14.6.1 *General*

- All efficacy analyses were to be based on the intent-to-treat population
 - Primary analyses were to be performed using the LOCF approach: the change score from baseline to Week 24 will be used
 - Supportive analyses were to use the Observed Cases and Worst Case approaches
 - Descriptive statistics were to be calculated for each visit using both approaches
- All statistical tests were to be 2-sided and a p-value of < 0.05 was to be considered statistically significant for main effects, and 10% for interaction terms

12.14.6.2 *Primary Efficacy Parameters*

- The two primary efficacy parameters were to be the following
 - CGI-C score at endpoint (based on original 7-point scale) [data for the responder analysis of the dichotomized CGI-C scale was also to be presented]
 - Change from baseline to endpoint in BGP Care Dependency Subscale
- Another "key" parameter of efficacy (also considered a primary efficacy parameter) was to be the BGP Cognitive Subscale
- The primary efficacy analysis was to use the intent-to-treat population with the last-observation-carried-forward (LOCF) method of imputing missing data.
- The original 7-point CGI-C scale was to be analyzed using the stratified (by center) Wilcoxon rank-sum test. The dichotomized CGI-C was to be analyzed using Fisher's exact test and the stratified (by center) Wilcoxon rank-sum test.
- The BGP Care Dependency Subscale and the BGP Cognitive Subscale were to be analyzed using the stratified (by center) Wilcoxon rank-sum test.

- Since treatment superiority needed to be shown on all 3 primary efficacy parameters ($p < 0.05$), no multiplicity adjustment was felt to be necessary.

12.14.6.3 Sub-Population Analyses

Those with a modified Hachinski Ischemic Scale score of ≤ 4 were identified as having dementia of the Alzheimer's type. The primary efficacy analyses on the total population were to be repeated on this subset.

12.14.6.4 Secondary Efficacy Parameters

- Analyses of the secondary efficacy parameters were to use the same statistical methods that were used for the primary efficacy analyses
- Analyses were to use the intent-to-treat-LOCF population, with supportive analyses using the Observed Cases and Worst Case datasets

12.14.6.5 Additional Analyses

- By-center descriptive analyses for the 3 key efficacy parameters were to be provided to assess center consistency
- Descriptive analyses of three key efficacy variables were to be provided based on gender, age group (< 75 , ≥ 75), and baseline BGP Care Dependency Subscale score (< 20 or ≥ 20)
- A correlation analysis was to be conducted to assess the extent to which changes in the BGP Care Dependency Subscale score were attributable to changes in the BGP Cognitive Subscale score.

12.14.6.6 Handling Of Missing Data

- Missing values for efficacy variables were to be imputed using the following methods
 - Last-observation-carried-forward (LOCF): The last observed value prior to the missing value was to be used
 - Worst case: Imputation was to be based on the worst rank for each efficacy parameter, as depicted in the following table

Efficacy Parameter	Worst Rank
CGI-C (7-point scale)	7
CGI-C (Dichotomized)	Non-responder
BGP Care Dependency Subscale	46
BGP Cognitive Subscale	10
BGP Total	70
BGP Aggressiveness	10
BGP Depression	6
BGP Mental Disability	8
BGP Inactivity	12
G2 Total	102
G2 Item	6 per item
G2-C Total	112
G2-C Item	7 per item
CGI-S	7

12.14.7 Exposure And Dosing Compliance

- The safety population will be used for both exposure and study medication compliance.

- Double-blind medication exposure will be calculated as the difference between the date when double-blind medication was first taken, and the date when the last dose was taken (i.e., total days dosed) plus 1.
- Study medication compliance is calculated as the total number of tablets taken by a patient during the patient's participation in the double-blind medication phase divided by the number of tablets expected to be taken during that period, multiplied by 100. Overall, compliance rates $\leq 75\%$ of double-blind medication are considered compliant.
- Descriptive statistics for study medication compliance rate and frequency distribution for the number of compliant patients will be presented by treatment group for the double-blind study period.

12.14.8 *Sample Size Estimate*

12.14.8.1 *For CGI-C*

- Assumptions
 - Type I error: 0.025
 - Power: 90%
 - 30% difference in responder rate on the CGI-C between the treatment and placebo groups; responder rate 30% in placebo group (on dichotomized scale).
- Based on the above assumptions a sample size of 68 patients per treatment group was estimated

12.14.8.2 *For BGP Care Dependency Subscale*

- Assumptions
 - Type I error: 0.025
 - Power: 90%
 - 7.8 point difference in the change from baseline on the BGP care dependency subscale.
- Based on the above assumptions a sample size of 23 patients per treatment group was estimated

12.14.8.3 *Overall*

Based on the above sample size calculation, a total of 136 patients completing the study was estimated. Assuming a 10% dropout rate, 150 patients per treatment group were estimated to be needed

12.15 Key Changes Contained In Post-Hoc Analysis Plan

The following were the key changes contained in the post-hoc analysis plan, as drawn up in 2002, as compared with the original protocol and analysis plan that was drawn up prior to the study blind being broken

- The primary efficacy analysis was to use the LOCF approach for imputing missing data, rather than the Worst Case approach
- The 7-point CGI-C scale was to be used for the primary efficacy analysis, rather than the responder analysis of the dichotomized scale
- The BGP Cognitive Subscale, a subset of the BGP Care Dependency Subscale, was to be included as a "key" (i.e., primary) efficacy measure.

- The primary efficacy analysis was also to be performed on the dementia of the Alzheimer’s type subset as defined by a modified Hachinski Ischemic Scale score ≤ 4
- The per-protocol dataset was eliminated from the efficacy analysis
- The method for imputing the worst possible change from baseline on the BGP Care Dependency Subscale was altered as follows
 - Scores on this scale range from 0 (best) to 46 (worst)
 - In the original statistical analysis plan, when the post-baseline measurement was missing, a change score of 46 was imputed, implying that the baseline value was considered to be zero; i.e., the true baseline value was not used
 - In the post-hoc analysis plan, the missing value was set to 46, but the observed baseline value was not replaced
 - The same method was used for imputing all data related to the BGP

12.16 Efficacy Results

12.16.1 Patient Disposition

166 patients were randomized; their disposition, according to dementia subgroup was as follows (as noted earlier, those with a modified Hachinski Ischemic Scale ≤ 4 were considered to have dementia of the Alzheimer’s type, where those with a score > 4 were considered to have vascular dementia). Randomization was NOT stratified by dementia subgroup

	PLACEBO			MEMANTINE		
	DAT n	VAD n	Total n	DAT n	VAD n	Total n
Randomized	38	46	84	41	41	82
Completed	37	43	80	39	39	78
Discontinued	1	3	4	2	2	4

DAT: Dementia of the Alzheimer’s type; VAD: vascular dementia

All discontinuations were due to adverse events.

12.16.2 Protocol Deviations

2 patients in each treatment group entered the study despite not satisfying eligibility criteria based on age, laboratory abnormalities or age; these included one patient in the placebo group with cirrhosis.

12.16.3 Demographic And Other Baseline Characteristics

These are summarized in the following table

Variable	Placebo (n = 84)	Memantine (n = 82)
Males (%)	44.0	40.2
Mean Age (years)	71.9	71.2
Mean Weight (kg)	67.4	67.9
Mean MMSE Score	6.1	6.5
Mean GDS Score	6.0	6.0
Mean CGI-S Score	5.7	5.5
Mean Hachinski Ischemic Scale Score	5.7	5.2
Mean Hamilton Depression Scale Score	8.9	8.5
Mean BGP Care Dependency Subscale Score	21.8	21.3
Mean BGP Cognitive Subscale Score	5.4	5.5

As the table above indicates, the treatment groups were largely comparable at baseline.

Note, that the mean modified Hachinski Ischemic Scale score at baseline was above 4 in both treatment groups; further data regarding the distribution of this measure among the 2 treatment groups was as follows.

Variable	Placebo (n=84)	Memantine (n = 82)
Mean Hachinski Ischemic Scale Score	5.7	5.2
Median Hachinski Ischemic Scale Score	5.0	4.5
Standard Deviation	3.2	2.9
Range	1 to 12	1 to 12

12.16.4 Brain Imaging At Study Entry

Only a total of 86 patients enrolled in this study had brain imaging at study entry. Their CT scan reports (translated into English) were provided to this Division on request.

I have read these reports in detail and have attempted to find patients whose radiological findings suggested a possible cause for dementia other than Alzheimer’s Disease, vascular dementia, or mixed dementia.

Note that patients were grouped post-hoc into 2 categories based on their modified Hachinski Ischemic Scale score rather than based on their CT scan reports.

All CT scans were done without contrast.

CT scan reports which suggested a possible etiology for dementia separate from, or in addition to, a primary degenerative dementia and/or vascular dementia are as follows

Patient #; Initials	CT scan report
011	Quite remarkably enlarged ventricular system. Osteoplasty of the right temporal-parietal bone after craniotomy; metallic blood vessel clips on the dura mater. There is large area of encephalomalacia in the left temporal lobe – sequelae of previous cranial trauma Heavily calcified syphon parts of both carotid arteries Conclusion; Atrophic changes in the brain due to cranial trauma and atherosclerosis
064	The 4 th and 3 rd ventricles are localized in the midline. The enlarged lateral ventricles are symmetrically localized. The anterior horn of the left lateral ventricle is retracted anteriorly The subarachnoid spaces are enlarged There is a liquor density space (approx 5 x 5 cm in the axial plane) in the left parietal lobe, localized against the medial part of the lateral ventricle The bone fragment in the place of surgical operation is mildly pressed out Conclusion: Moderate to marked atrophic changes in the brain. Porencephalic cavity in the left parietal lobe communicates with the lateral ventricle.
124	The 4 th and 3 rd ventricles are positioned in the midline and enlarged, more so the third ventricle. The lateral ventricles are symmetrically localized. There is hypodense (liquor isodense) area (approx 2 x 2 cm in size) in the right parietal lobe towards the

	occipital horn and communicates with it. There is hyperdense area in the region of calvarium Conclusion: Atrophic changes of the brain. The cystic lesion towards the right occipital horn with greater possibility could be sequelae of head trauma
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12.16.5 Extent Of Exposure And Compliance

The mean treatment duration was 82.3 days (standard deviation 9.1 days) and 81.9 days (standard deviation 9.6 days) in the placebo and memantine treatment groups, respectively.

All patients in both treatment groups were considered compliant, based on pre-specified criteria

12.16.6 Primary Efficacy Analysis

The analysis of the original two primary efficacy parameters, as well as an additional efficacy measure designated post-hoc as key and primary, are described in this section

12.16.6.1 CGI-C

Mean CGI-C scores, on the 7-point scale, at Week 12 in each treatment group are in the following table, which depicts the results for each dataset.

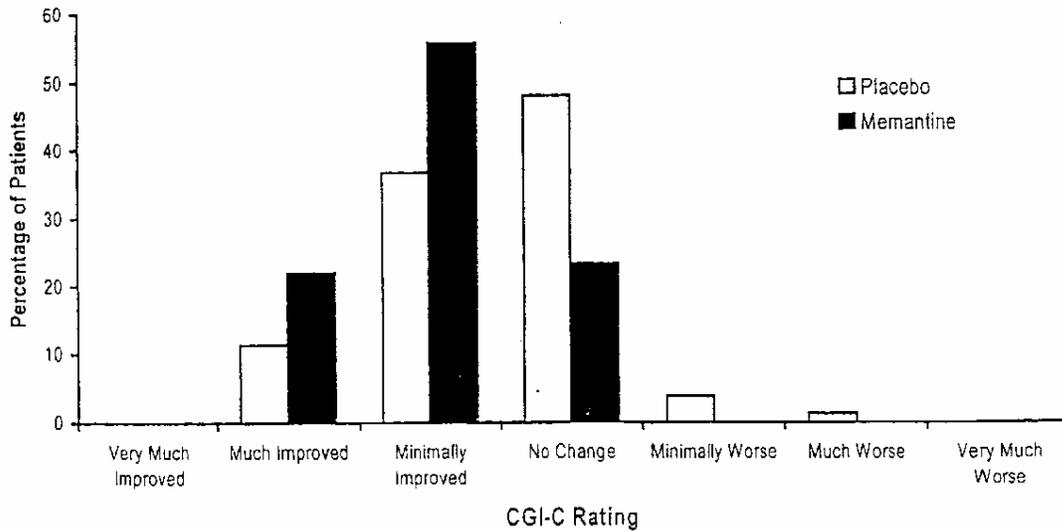
Dataset	Placebo		Memantine		p-value Memantine vs placebo
	N	Mean (± SEM)	N	Mean (± SEM)	
LOCF	84	3.5 ± 0.1	82	3.1 ± 0.1	< 0.001
WC	84	3.6 ± 0.1	82	3.2 ± 0.1	< 0.001
OC	80	3.5 ± 0.1	78	3.0 ± 0.1	< 0.001

LOCF: Last-Observation-Carried-Forward
 WC: Worst Case
 OC: Observed Cases
 SEM: Standard error of mean

For each dataset, the treatment differences favored memantine and were statistically significant. A nominally statistically significant difference (p =0.006) favoring memantine was seen on the Observed Cases dataset at Week 4

The distribution of 7-point CGI-C ratings for the Observed Cases dataset at Week 12 is in the following figure, which I have copied from the submission. As the figure indicates, the majority of patients were in the “minimally improved” or “no change” category.

**Distribution of CGI-C Ratings for Patients
 Completing 12 Weeks of Double-Blind Treatment**



Using the dichotomized CGI-C, the response rate in each treatment group for each dataset is in the following table. Again, the differences between treatment groups for each dataset were statistically significant

Dataset	Placebo		Memantine		p-value Memantine vs placebo
	N	Response rate %	N	Response rate %	
LOCF	84	46.4	82	73.2	< 0.001
WC	84	45.2	82	73.2	< 0.001
OC	80	47.5	78	76.9	< 0.001

LOCF: Last-Observation-Carried-Forward
 WC: Worst Case
 OC: Observed Cases

12.16.6.2 BGP Care Dependency Subscale

The changes from baseline to Week 12 in BGP Care Dependency Subscale scores are in the following table, which depicts the results for each dataset

Dataset	Placebo		Memantine		p-value Memantine vs placebo
	N	Mean	N	Mean	
LOCF	84	-3.3	82	-5.3	0.012
WC	84	-2.3	82	-4.2	0.016
OC	80	-3.5	78	-5.6	0.010

LOCF: Last-Observation-Carried-Forward
 WC: Worst Case
 OC: Observed Cases

As the table indicates, both treatment groups improved over the course of this study on this parameter; the differences between treatment groups for each dataset were statistically significant and favored memantine. Trends toward improvement were seen in the memantine group relative to the placebo group were seen beginning at Week 1; these trends increased gradually towards Week 12

12.16.6.3 BGP Cognitive Subscale

The changes from baseline to Week 12 in BGP Cognitive Subscale scores are in the following table, which depicts the results for each dataset

Dataset	Placebo		Memantine		p-value Memantine vs placebo
	N	Mean	N	Mean	
LOCF	84	-1.1	82	-1.9	0.001
WC	84	-0.9	82	-1.6	0.002
OC	80	-1.2	78	-1.9	0.001

LOCF: Last-Observation-Carried-Forward

WC: Worst Case

OC: Observed Cases

As the table indicates, both treatment groups improved over the course of the study on this parameter; the differences between treatment groups for each dataset were statistically significant and favored memantine. Trends toward improvement were seen in the memantine group relative to the placebo group beginning at Week 1; these trends increased gradually towards Week 12

12.16.7 “Primary Efficacy Analysis” On Dementia Of The Alzheimer’s Type Subset

A post-hoc analysis of the Alzheimer’s Disease subset, was performed in a manner similar to the primary efficacy analysis of the entire study population. This subset was defined solely on the basis of having a modified Hachinski Ischemic Scale score ≤ 4 . Details are below

12.16.7.1 Demographic And Other Baseline Characteristics

These are presented in the following table

Variable	Placebo (n = 38)	Memantine (n = 41)
Males (%)	36.8	29.3
Mean Age (years)	74.9	73.4
Mean Weight (kg)	66.2	68.1
Mean MMSE Score	6.8	6.7
Mean GDS Score	6.0	6.0
Mean CGI-S Score	5.3	5.3
Mean Hachinski Ischemic Scale Score	2.7	2.9
Mean Hamilton Depression Scale Score	9.0	8.7

As the table indicates, the treatment groups were largely comparable for this subset

12.16.7.2 Results Of “Primary Efficacy Analysis”

The analysis of the original two primary efficacy parameters, as well as an additional efficacy measure designated post-hoc as key and primary, are described in this section

12.16.7.2.1 CGI-C

Mean CGI-C scores, on the 7-point scale, at Week 12 in each treatment group are in the following table, which depicts the results for each dataset.

Dataset	Placebo		Memantine		p-value Memantine vs placebo
	N	Mean (\pm SEM)	N	Mean (\pm SEM)	
LOCF	38	3.5 \pm 0.1	41	3.1 \pm 0.1	0.003
WC	38	3.6 \pm 0.1	41	3.3 \pm 0.2	0.004
OC	37	3.5 \pm 0.1	39	3.1 \pm 0.1	0.001

LOCF: Last-Observation-Carried-Forward
 WC: Worst Case
 OC: Observed Cases
 SEM: Standard error of mean

As the table indicates, in all 3 datasets the treatment differences favored memantine and were statistically significant.

12.16.7.2.2 BGP Care Dependency Subscale

The changes from baseline to Week 12 in BGP Care Dependency Subscale scores are in the following table, which depicts the results for each dataset

Dataset	Placebo		Memantine		p-value Memantine vs placebo
	N	Mean	N	Mean	
LOCF	38	-2.8	41	-5.8	0.003
WC	38	-2.3	41	-4.6	0.005
OC	37	-2.9	39	-6.1	0.002

LOCF: Last-Observation-Carried-Forward
 WC: Worst Case
 OC: Observed Cases

As the table indicates, both treatment groups improved over the course of this study on this parameter; the differences between treatment groups for each dataset were statistically significant and favored memantine.

12.16.7.2.3 BGP Cognitive Subscale

The changes from baseline to Week 12 in BGP Care Dependency Subscale scores are in the following table, which depicts the results for each dataset

Dataset	Placebo		Memantine		p-value Memantine vs placebo
	N	Mean	N	Mean	
LOCF	38	-1.0	41	-2.0	0.007
WC	38	-1.0	41	-1.7	0.013
OC	37	-1.1	39	-2.1	0.004

LOCF: Last-Observation-Carried-Forward
 WC: Worst Case
 OC: Observed Cases

As the table indicates, both treatment groups improved over the course of this study on this parameter; the differences between treatment groups for each dataset were statistically significant and favored memantine.

12.16.7.3 Reviewer’s Conclusions

The results of the “primary efficacy analysis” of the Alzheimer’s Disease subset tended to be similar to those of the entire study cohort

12.16.8 “Primary Efficacy Analysis” On Vascular Dementia Subset

A post-hoc analysis of the vascular dementia subset, was performed, although not specified in any version of the analysis plan, in a manner similar to the primary efficacy analysis of the entire study population. This analysis is not described in the study report either, but is displayed in after-text tables. This subset was defined by having a modified Hachinski Ischemic Scale score > 4. Details are below

12.16.8.1 Demographic And Other Baseline Characteristics

These are presented in the following table

Variable	Placebo (n = 46)	Memantine (n = 41)
Males (%)	50.0	51.2
Mean Age (years)	69.5	69.1
Mean Weight (kg)	68.5	67.7
Mean MMSE Score	5.5	6.4
Mean GDS Score	6.1	6.1
Mean CGI-S Score	5.9	5.6
Mean Hachinski Ischemic Scale Score	8.1	7.6
Mean Hamilton Depression Scale Score	8.8	8.3

As the table indicates, the treatment groups were largely comparable for this subset

12.16.8.2 Results Of “Primary Efficacy Analysis”

The analysis of the original two primary efficacy parameters, as well as an additional efficacy measure designated post-hoc as key and primary, are described in this section

12.16.8.2.1 CGI-C

Mean CGI-C scores, on the 7-point scale, at Week 12 in each treatment group are in the following table, which depicts the results for each dataset.

Dataset	Placebo		Memantine		p-value Memantine vs placebo
	N	Mean (± SD)	N	Mean (± SD)	
LOCF	46	3.6 ± 0.96	41	3.0 ± 0.79	0.016
WC	46	3.7 ± 1.19	41	3.1 ± 1.13	0.010
OC	43	3.5 ± 0.83	39	2.9 ± 0.72	0.006

LOCF: Last-Observation-Carried-Forward
 WC: Worst Case
 OC: Observed Cases
 SEM: Standard error of mean

As the table indicates, in all 3 datasets the treatment differences favored memantine and were nominally statistically significant.

12.16.8.2.2 BGP Care Dependency Subscale

The changes from baseline to Week 12 in BGP Care Dependency Subscale scores are in the following table, which depicts the results for each dataset

Dataset	Placebo		Memantine		p-value Memantine vs placebo
	N	Mean	N	Mean	
LOCF	46	-3.7	41	-4.8	0.365
WC	46	-2.3	41	-3.9	0.337
OC	43	-4.0	39	-5.1	0.334

LOCF: Last-Observation-Carried-Forward
 WC: Worst Case
 OC: Observed Cases

As the table indicates, both treatment groups improved over the course of this study on this parameter; the differences between treatment groups for each dataset favored memantine, but they were not statistically significant.

12.16.8.2.3 BGP Cognitive Subscale

The changes from baseline to Week 12 in BGP Care Dependency Subscale scores are in the following table, which depicts the results for each dataset

Dataset	Placebo		Memantine		p-value Memantine vs placebo
	N	Mean	N	Mean	
LOCF	46	-1.2	41	-1.7	0.064
WC	46	-0.9	41	-1.6	0.072
OC	43	-1.3	39	-1.8	0.086

LOCF: Last-Observation-Carried-Forward

WC: Worst Case

OC: Observed Cases

As the table indicates, both treatment groups improved over the course of this study on this parameter; the differences between treatment groups for each dataset favored memantine, but they were not statistically significant.

12.16.8.3 Reviewer's Conclusions

The results of the "primary efficacy analysis" of the vascular dementia subset showed trends similar to those of the entire study cohort, and the Alzheimer's Disease subset, but the effect sizes were smaller.

12.16.9 Analysis Of Secondary Efficacy Measures

The results for selected secondary efficacy parameters, for the LOCF dataset, are summarized in the following table, which I have taken from the submission

Parameter	Placebo (n = 84)	Memantine (n = 82)	p-value
BGP Total Score Mean change from baseline	-4.6	-7.1	0.015
G2 Total Score Mean change from baseline	-6.5	-8.9	0.028
G2-C Total Score Mean	57.1	53.0	0.041
CGI-S Mean	5.3	5.1	0.849
CGI Efficacy Index % improved	55%	80%	< 0.001

For the IADLPT

- Mean performance time was reported to be better in the memantine group than in the placebo group for 8/12 tasks
- A higher percentage of memantine patients than placebo patients exhibited good quality performance on 10/12 tasks.

12.16.10 Additional Analyses

The following additional analyses are described in the study report

12.16.10.1 Correlation Between Change From Baseline In BGP Care Dependency Subscale And Change From Baseline In BGP Cognitive Subscale

Analyses were conducted comparing the change from baseline in these 2 measures, for all patients and for each treatment group, at each study timepoint. For all 16 correlations performed, the correlation coefficient was ≥ 0.8 , and statistically significant ($p < 0.001$ in each instance). The sponsor further believes

that much of the variance in the BGP Care Dependency Subscale is explained by BGP cognitive subscale.

(Dr Tristan Massie, Agency Biometrics Reviewer, has, however, questioned the true significance of the above correlation; he has found a further subset of 5 items in the BGP Care Dependency subscale, which are distinct from the BGP Cognitive Subscale, that have an even better correlation with the BGP Care Dependency Subscale total score)

12.16.10.2 Consistency Across Centers

The sponsor has presented a summary of by-center results at Week 12 (LOCF dataset) for the CGI-C, the change from baseline in BGP Care Dependency Subscale, and BGP Cognitive Subscale. These are presented in the form of tables and graphically

For all 3 measures, the majority of centers showed a greater mean benefit for the memantine group, as follows

Measure	Proportion of centers showing a mean memantine benefit
CGI-C	6/7
BGP Care Dependency Subscale	5/7
BGP Cognitive Subscale	6/7

There were no centers that were prominent outliers, based on the graphical display provided.

12.16.10.3 Sub-Group Analyses

These have been performed based on sex, age (< 75 years vs \geq 75 years) and baseline BGP Care Dependency Subscale scores (< 20 vs \geq 20). A superior effect of memantine relative to placebo, albeit small, was maintained across these subgroups, based on the descriptive statistics provided by the sponsor.

12.17 Sponsor's Conclusions Regarding Efficacy

- The analysis of the 2 primary efficacy parameters, the CGI-C and BGP Care Dependency Subscale, showed a statistically significant treatment effect in the memantine group relative to the placebo group at Week 12, on the Last-Observation-Carried-Forward, Observed Cases, and Worst Case datasets. A similar statistically significant treatment effect was seen on the BGP Cognitive Subscale, a specific measure of cognitive function
- Similar effects were also seen in separate analyses of the sub-population with dementia of the Alzheimer's type, on all 3 parameters (CGI-C, BGP Care Dependency Subscale, and BGP Cognitive Subscale)
- Analysis of the secondary efficacy parameters provided further confirmation of the consistently greater antedementia effect of memantine in comparison to placebo
- A significantly greater effect was observed in the memantine group relative to the placebo group by Week 4 of double-blind treatment.
- The therapeutic effects of memantine were consistently superior to placebo without regard to sex, age, or baseline disease severity

12.18 Agency Statistical Review

Final comments from the Agency statistical reviewer are pending.

12.19 Reviewer's Comments

- The study enrolled nursing home residents with moderate-to-severe dementia; such a population was to include those with Alzheimer's Disease, vascular dementia, and mixed dementia, and was therefore not to be confined to those with Alzheimer's Disease.
- The study report indicates that of the 166 patients randomized to treatment, 79 were diagnosed to have Alzheimer's Disease and 87 were diagnosed to have vascular dementia; randomization was not stratified based on diagnosis, and the study protocol does, in fact, indicate that a distinction between these entities was not to be made at the time of enrollment. The study report indicates that the distinction between these 2 entities was made based solely on the Hachinski Ischemic Scale score (without using information from CT scans, which, in any case, were done only for 86 out of 186 patients enrolled in the study); this is no longer a widely-accepted method for making a diagnosis of either Alzheimer's Disease or vascular dementia. Moreover, it was not prospectively specified that patients would be assigned to the Alzheimer's Disease and vascular dementia subgroups as part of the analysis, let alone what method would be used to make that distinction; it also remains unclear whether the assignment of patients to the Alzheimer's Disease and vascular dementia categories was done before the study blind was broken. Further, there was no provision for assigning patients to the "mixed dementia" category, i.e., a category that is considered to subsume features of both Alzheimer's Disease and vascular dementia; the medical literature suggests that this is a not-uncommon condition in a population such as that enrolled in this study, and the inclusion criteria for this study also indicated that patients with "mixed dementia" were to be enrolled.
- The study did not have a prospectively designated cognitive outcome measure. A subset of five items from the BGP Care Dependency Subscale, a measure of activities of daily living, was used as a post-hoc cognitive measure with a statistically significant benefit in favor of memantine. It is questionable whether these 5 items really assess cognitive function; this subset of items has clearly not been validated as a measure of cognition, which, in any case, is assessed very crudely at best with this measure. It is also worth noting that this subset was introduced as a cognitive outcome measure in a post-hoc analysis plan 7 years after the study was completed and 3 years after the study results were published.
- The evidence for efficacy on the primary global and activities of daily living measures on the Alzheimer's Disease subset was based on a small sample: a total of 79 patients, 38 of whom received memantine and 41 placebo. The subset analysis was not prospectively specified.
- The response in the vascular dementia and Alzheimer's Disease subsets was similar based on at least one of the primary efficacy measures (CGI-C) suggesting that the response may not have been strongly specific for

dementia type (effect sizes were however larger in the Alzheimer's Disease subset than in the vascular dementia subset for the BCP Care Dependency Subscale and the BGP Cognitive Subscale; trends favored memantine on all 3 measures in both subsets)

- Only a total of 86 patients (40 placebo and 46 memantine) had brain imaging studies (CT scan only) done; these scans were done without contrast. Although it is likely, by chance alone, that the majority of patients enrolled in this study would have had Alzheimer's Disease, vascular dementia, primary degenerative dementia other than Alzheimer's Disease, or mixed forms of dementia, a proportion may have had etiologies for their dementia, such as slow-growing brain tumors, that would have been detected by imaging only, and even better delineated by imaging after a contrast medium was administered. In clinical efficacy trials in Alzheimer's Disease, it is customary for brain imaging (CT scan or MRI) to be performed at, or within a period of 6 to 12 months prior to, enrollment, although not usually with contrast.

13 Study MEM-MD-02

This study was conducted at 38 centers in the United States.

13.1 Study Protocol

The following consists of the full study protocol with amendments already included, and a later-submitted statistical analysis plan

13.1.1 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

13.1.2 Objective

To evaluate the safety and efficacy of memantine versus placebo in the treatment of moderate to severe dementia of the Alzheimer's type

13.1.3 Design

Randomized, double-blind, placebo-controlled, parallel-arm study

13.1.4 Duration

24 weeks of double-blind treatment preceded by 1-2 weeks of single-blind placebo treatment

13.1.5 Sample Size

340 patients at 35 centers, randomized equally to the 2 treatment groups

13.1.6 Selection

13.1.6.1 Key Inclusion Criteria

- Male or female outpatients > 50 years
- If female, must be at least 2 years post-menopausal or surgically sterile
- Probable Alzheimer's Disease, according to NINCDS-ADRDA criteria
- Mini-Mental Status Examination of 5-14

- CT or MRI of brain, within 12 months prior to randomization, compatible with Alzheimer's Disease
- Physical examination, laboratory data and electrocardiogram results from screening visit must be normal, or abnormal findings must be judged not 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 donepezil for at least the preceding 6 months with a stable dose for 3 months**

13.1.6.2 Key Exclusion Criteria

- Lack of a reliable caregiver
- Recent (≤ 2 years) B₁₂ or folate deficiency that is considered clinically significant
- Thyroid disease, unless euthyroid on treatment
- Clinically significant and active pulmonary, gastrointestinal, renal, hepatic, endocrine or cardiovascular system disease
- Other neurological/psychiatric disorders, including but not limited to stroke, Parkinson's disease, seizure disorder, head injury with loss of consciousness within the past 5 years, any psychotic disorder, bipolar or unipolar depression
- 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 or DSM-IV-defined dementia of the Alzheimer's type with delusions or delirium
- 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 of the screening visit
- Treatment with a depot neuroleptic within 6 months of the screening visit
- Positive test for a prohibited medication on the urine drug screen
- Previous treatment with memantine or participation in an investigational study of memantine

- 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 before baseline

13.1.6.3 Concomitant Medications

13.1.6.3.1 Prohibited Medications

These include

- Opioid containing analgesics
- Local and general anesthetics
- Anti-anginal agents
- Anorexic drugs
- Anti-arrhythmic agents
- Anticholinergics
- Anticonvulsants
- Antidepressants
- Antidiarrheal agents
- Anti-emetics
- Systemic antifungal agents
- Antihistamines
- Anti-neoplastic agents, except tamoxifen which is allowed if the dose has been stable for 3 months prior to screening
- Anti-Parkinsonian agents
- Anxiolytics
- Cholinesterase inhibitors other than donepezil
- Lipid-lowering agents
- Muscle relaxants
- Sedatives and hypnotics
- Systemic steroids
- Stimulants
- Cisapride
- No anti-platelet agent other than aspirin and clopidrogel

13.1.6.3.2 Exceptions And Qualifications Regarding Prohibited And Permitted Medications

The following are the key items

- Opioid-containing analgesics may be used on an as-needed basis
- The only anti-arrhythmic agent permitted is digoxin, whose dose must be stable for 3 months prior to screening.
- Selective serotonin re-uptake inhibitors and venlafaxine are permitted but the medications and dose should be stable for 3 months prior to screening throughout the study
- Kaolin, Imodium® and Pepto-Bismol® are permitted for diarrhea
- Phosphoric acid preparations, Pepto-Bismol® and cola syrup are permitted for vomiting
- Fexofenadine, loratadine and cetirizine are permitted
- The only anti-obesity drug permitted is orlistat

- The only anti-psychotic drugs permitted are risperidone (daily dose ≤ 6 mg), olanzapine (daily dose ≤ 5 mg) and quetiapine (daily dose ≤ 200 mg/day); the dose of both drugs should have been stable for at least one month prior to screening and kept stable during the study
- Patients taking Ginkgo biloba and Vitamin E should have been on a stable dose for at least 1 month prior to screening
- The only hypnotics permitted are zolpidem (maximum 10 mg/day), zaleplon (maximum 10 mg/day) and trazodone (maximum 100 mg/day) which is allowed PRN for sleep in doses not exceeding 10 mg/day used a maximum of 3 times per week.
- Patients taking rivastigmine and galantamine must have stopped these drugs for at least 30 days prior to screening

13.1.7 Dosage

Memantine doses were to be titrated as follows

Week Of Double-Treatment	Memantine Dose		Total Daily Dose
	AM	PM	
Week 1	5 mg	0	5 mg
Week 2	5 mg	5 mg	10 mg
Week 3	10 mg	5 mg	15 mg
Weeks 4 - 24	10 mg	10 mg	20 mg

Matching placebo was to be used

13.1.8 Schedule

- Visits were to be at screening, baseline, and the end of Weeks 4, 8, 12, 18 and 24
- The following were to be checked exclusively at the screening visit: informed consent, selection criteria (this will be confirmed at the baseline visit), urine drug screen, thyroid functions, serum B₁₂ and folate, and medical history
- The Mini-Mental Status Examination were to be checked at screening and baseline
- CT scan/MRI were to be performed at screening if not done during the previous 12 months
- The Hachinski Ischemic Scale was to be checked at screening
- The Severe Impairment Battery, ADCS-ADL and CIBIC-Plus were to be checked at baseline and every subsequent visit
- The Neuropsychiatry Inventory and Resource Utilization in Dementia were to be checked at baseline and Weeks 12 and 24
- The Functional Assessment Staging and Behavioral Rating in Geriatric Patients were to be checked at baseline and Week 24
- Physical examinations, safety laboratory tests and electrocardiograms were to be checked at screening and Week 24
- Vital signs and concomitant medications were to be checked at every visit
- Medication compliance and adverse events were to be checked at baseline and every subsequent visit

13.1.9 Outcome Measures

13.1.9.1 Primary Efficacy Measures

Severe Impairment Battery
ADCS-ADL

13.1.9.2 Secondary Efficacy Measures

CIBIC-Plus
Neuropsychiatry Inventory
Functional Assessment Staging
Resource Utilization In Dementia
Behavioral Rating Scale For Geriatric Patients

13.1.9.3 Safety Measures

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

13.1.10 Safety Monitoring

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

13.1.11 Statistical Analysis Plan

The statistical analysis plan summarized below is that contained in submission #143, dated 7/29/02. In the cover letter, the sponsor stated that the study blind had not been broken at the time of the submission.

Only those aspects of the analysis plan that pertain to the assessment of efficacy will be outlined below.

13.1.11.1 Patient Populations

The sponsor had defined the following patient populations for purposes of analysis as follows

13.1.11.1.1 Randomized Population

This population was to consist of all patients randomized into the study

13.1.11.1.2 Safety Population

This population was to consist of all randomized patients who received at least one dose of double-blind study medication

13.1.11.1.3 Intent-To-Treat Population

This population was to consist of all those in the safety population who completed at least one post-baseline efficacy evaluation of the Severe Impairment Battery or ADCS-ADL

13.1.11.2 Patient Disposition And Study Completion

- The number of patients in each study population (i.e., randomized, safety, intent-to-treat) was to be summarized by treatment group and center

- The number and percentage of patients in the safety population who completed the study was to be presented by treatment group
- Reasons for discontinuation were to be summarized by treatment group using number and percentage.
- Treatment differences in the proportion of patients completing the study were to be evaluated using a Cochran-Mantel-Haenszel test, controlling for center, sample size permitting; otherwise, a Fisher's exact test was to be used.

13.1.11.3 *Demographic And Baseline Characteristics*

- Demographic parameters and other baseline characteristics were to be summarized by treatment group
- The treatment groups were to be compared as follows
 - Continuous variables were to be analyzed using a 2-way ANOVA model with treatment and study center as the factors
 - Categorical variables were to be analyzed using a Cochran-Mantel-Haenszel test controlling for study center

13.1.11.4 *Extent Of Exposure And Dosing Compliance*

- The safety population was to be used for both exposure and study medication compliance.
- Data regarding medication exposure and compliance were to be presented by treatment group using descriptive statistics
 - For categorical variables, frequency distributions and percentages were to be used
 - For continuous variables, the number of patients, mean, standard deviation, median and range were to be used
- Double-blind medication exposure was to be calculated as the difference between the date when double-blind medication was first taken, and the date when the last dose was taken (i.e., total days dosed) plus 1.
- Study medication compliance was to be calculated as the total number of tablets taken by a patient during the patient's participation in the double-blind medication phase divided by the number of tablets expected to be taken during that period, multiplied by 100. Overall, compliance rates $\leq 75\%$ of double-blind medication were to be considered compliant.

13.1.11.5 *Prior And Concomitant Medications*

- Prior and concomitant medications were to be summarized by drug class, category, and treatment group.
- Multiple instances of drug usage by a patient were to be counted once only per drug class and category for a treatment group
- Medications for the treatment of dementia taken within 5 years prior to the screening visit were to be summarized separately. In addition,
 - The duration of donepezil treatment at baseline was to be summarized by treatment group.
 - The distribution of donepezil doses at the baseline visit, the final visit and the end of Week 24 was to be summarized by treatment group

13.1.11.6 *Efficacy Analyses*

13.1.11.6.1 General

- All efficacy analyses were to be based on the intent-to-treat population
 - Primary analyses were to be performed using the LOCF approach: the change score from baseline to Week 24 was to be used
 - Supportive analyses were to use the Observed Cases approach at each visit
 - Descriptive statistics were to be calculated for each visit using both approaches
- All statistical tests were to be 2-sided and a p-value of < 0.05 was to be considered statistically significant

13.1.11.6.2 Primary Efficacy Parameters

- The primary efficacy parameters were to be the change from baseline in the total ADCS-ADL and Severe Impairment Battery scores at Week 24
- As noted earlier, the primary efficacy analysis was to be performed on the LOCF dataset at Week 24
- The comparison between the 2 treatment groups was to be made using 2-way ANCOVA with treatment group and center as main effects and baseline score as the covariate
- The results of the ANCOVA were to be summarized using the treatment groups' least square means, the difference between the treatment groups' least square means, the 95% confidence interval for the treatment group difference and the p-value
- Descriptive statistics were to be calculated by visit

13.1.11.6.3 Secondary Efficacy Parameters

- The secondary efficacy parameters were as follows
 - CIBIC-Plus rating
 - Change from baseline in total score on the Neuropsychiatry Inventory
 - Change from baseline in Functional Assessment Staging
 - Change from baseline in Behavioral Rating Scale In Geriatric Patients (total, care-dependency and cognitive sub-scores)
 - Change from baseline in Resource Utilization In Dementia scale (this is to be presented in a separate analysis plan)
- The CIBIC-Plus rating was to be analyzed using the Cochran-Mantel-Haenszel test using modified ridit scores, controlling for study center.
- For other secondary efficacy parameters
 - Descriptive statistics were to be calculated by study visit
 - The treatment groups were to be compared using the same approach as for the primary efficacy parameters
- Results from the CIBIC-Plus were to be included in labeling if memantine demonstrated a statistically significant superiority to placebo ($p < 0.05$) on the Severe Impairment Battery, ADCS-ADL, and the CIBIC-Plus.
- Results from the caregiver time parameter of the Resource Utilization in Dementia were to be included if memantine demonstrated a statistically significant superiority to placebo on the Severe Impairment Battery, ADCS-

ADL, CIBIC-Plus, and the caregiver time parameter of the Resource Utilization in Dementia

13.1.11.6.4 Additional Efficacy Analyses

The following plots were to be prepared for the LOCF and Observed Cases sets using the intent-to-treat population

- Plots of the cumulative percentage of patients with differing degrees of change at Week 24 in Severe Impairment Battery and ADCS-ADL
- Plot of the time-course of the mean changes from baseline in the Severe Impairment Battery and ADCS-ADL
- Histogram of the frequency distribution of the CIBIC-Plus score at Week 24

13.1.11.6.5 Treatment-By-Center Interaction

An exploration of the homogeneity of treatment effects across centers were to be conducted graphically. The difference of mean changes between treatment groups in Severe Impairment Battery and ADCS-ADL were to be plotted versus study center

13.1.11.6.6 Sub-Group Analyses

- Analyses may be performed for subgroups based on demographic and other baseline characteristics. These subgroups were to include, but not be limited to, the following
 - Age: < 75 years versus \geq 75 years
 - Race: White versus non-white
 - Gender

13.1.11.7 Data Handling Conventions

13.1.11.7.1 Visit Time Windows

These are summarized in the following table which I have copied from the submission

Visit Time Windows		
Visit	Scheduled Day	Window
Visit 3 (Week 4)	Day 28	Days [1, 42]
Visit 4 (Week 8)	Day 56	Days [43, 70]
Visit 5 (Week 12)*	Day 84	Days [71, 105]
Visit 6 (Week 18)	Day 126	Days [106, 147]
Visit 7 (Week 24)*	Day 168	Days [148, 190]
Endpoint	Final or termination visit during the double-blind study period	

Day = visit date – first date on study medication + 1

*For NPI, the Week 12 window is Days 63-105 and the Week 24 window is Days 148-190. For the FAST and BGP, the Week 24 window is Days 148-190.

13.1.11.7.2 Missing Efficacy Data

Missing visit assessments were to be replaced using the LOCF approach

The method of replacing missing items from the scales for the 2 primary efficacy parameters is below

13.1.11.7.2.1 Severe Impairment Battery

There are 51 separate items in this scale, with a total score ranging from 0 to 100; higher scores indicate better functioning. Single missing items were to be replaced with a "0" before calculating the total score. If more than 11 items were missing, then the total score was to be set to missing

13.1.11.7.2.2 ADCS-ADL

There are 19 separate items in this scale, with a total score ranging from 0 to 54; higher scores indicate better functioning. Single missing items were to be replaced with a "0" before calculating the total score. If more than 4 items were missing, then the total score was to be set to missing

13.1.11.8 Sample Size Rationale

- The sample size calculation was based on the change from baseline in the Severe Impairment Battery and ADCS-ADL
- Assumptions
 - Effect size (treatment group difference relative to pooled standard deviation) of 0.35 for each parameter
 - 90% power
 - Alpha of 0.05 (2-sided)
- Based on the above assumptions, and a 2-sample t-test, 170 patients were estimated to be needed per treatment group

13.1.11.9 Criteria For Declaring Study "Positive"

The study was to be declared "positive" if memantine demonstrated a statistically significant superiority to placebo ($p < 0.05$) on both primary outcome measures, the Severe Impairment Battery and the Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory.

13.2 Efficacy Results

13.2.1 Patient Disposition

Patient disposition, including reasons for discontinuation, is summarized in the following table which I have copied from the submission. Discontinuations were more frequent in the placebo-donepezil group than in the memantine-donepezil group, with the most common reason for discontinuation being adverse events.

Reasons for Discontinuation

	<i>Placebo/Donepezil</i>	<i>Memantine/Donepezil</i>	<i>Total</i>
	<i>N=201</i>	<i>N=202</i>	<i>N=403</i>
	<i>n (%)</i>	<i>n (%)</i>	<i>n (%)</i>
Patients Who Completed the Study	150 (74.6)	172 (85.1)	322 (79.9)
Patients Who Discontinued*	51 (25.4)	30 (14.9)	81 (20.1)
REASONS FOR DISCONTINUATION			
Adverse Event	25 (12.4)	15 (7.4)	40 (9.9)
Insufficient Therapeutic Response	3 (1.5)	1 (0.5)	4 (1.0)
Protocol Violation	5 (2.5)	1 (0.5)	6 (1.5)
Consent Withdrawn	16 (8.0)	8 (4.0)	24 (6.0)
Lost to Follow-up	0	1 (0.5)	1 (0.2)
Other reasons	2 (1.0)	4 (2.0)	6 (1.5)

* Patient may have had one or more reason for discontinuation.

13.2.2 Treatment Duration

The duration of treatment in the placebo and memantine groups is as displayed in the following 2 tables, which I have derived from tables contained in the submission. The data are based on the safety population

	Placebo (n = 201)	Memantine (n = 202)
Treatment Duration (Days)		
Mean	144.2	154.5
Median	168	168
Standard Deviation	46.37	38.41
Range	3 to 183	12 to 182

	Placebo (n = 201)	Memantine (n = 202)
Treatment Duration		
1 to 28 days	8 (4.0%)	6 (3.0%)
29 to 56 days	12 (6.0%)	10 (5.0%)
57 to 84 days	11 (5.5%)	2 (1.0%)
85 to 126 days	13 (6.5%)	6 (3.0%)
≥ 127 days	157 (78.1%)	178 (88.1%)

As the tables above indicate, the majority of patients in both treatment groups received ≥ 127 days of treatment with study drug.

13.2.3 Dosing Compliance

The extent of dosing compliance is summarized in the following table which I have derived from one contained in the submission. It is based on the safety population

	Placebo (n = 201)	Memantine (n = 202)
≥ 75% compliance	191 (95.0%)	195 (96.5%)
< 75% compliance	2 (1.0%)	1 (0.5%)
Missing	8 (4.0%)	6 (3.0%)

As the table indicates, the vast majority of patients in both treatment groups were $\geq 75\%$ compliant.

13.2.4 Demographic And Other Baseline Characteristics

Baseline demographic characteristics are summarized in the following table, which I have copied from the submission

Demographic Characteristics

	<i>Placebo/Donepezil</i> N=201	<i>Memantine/Donepezil</i> N=202	<i>Total</i> N=403
MEAN AGE, years (SD)	75.5 (8.73)	75.5 (8.45)	75.5 (8.58)
≤ 64 n (%)	28 (13.9)	26 (12.9)	54 (13.4)
65-74 n (%)	49 (24.4)	54 (26.7)	103 (25.6)
75-84 n (%)	96 (47.8)	98 (48.5)	194 (48.1)
≥ 85 n (%)	28 (13.9)	24 (11.9)	52 (12.9)
SEX			
Male n (%)	67 (33.3)	74 (36.6)	141 (35.0)
Female n (%)	134 (66.7)	128 (63.4)	262 (65.0)
ETHNICITY			
Caucasian n (%)	186 (92.5)	182 (90.1)	368 (91.3)
Non-Caucasian n (%)	15 (7.5)	20 (9.9)	35 (8.7)
WEIGHT (LB) mean (SD)	146.0 (31.07)	155.5 (31.49)	150.8 (31.60)

Baseline dementia assessments are in the following sponsor table

Summary of Mean Baseline Assessments of Dementia (Mean \pm SD)

<i>Assessment</i>	<i>Placebo/Donepezil</i> N=201	<i>Memantine/Donepezil</i> N=202
Hachinski	0.6 (0.71)	0.7 (0.87)
MMSE	10.2 (2.98)	9.9 (3.13)

Baseline efficacy parameters are in the following table, copied from the submission

Summary of Mean Baseline Efficacy Assessments (Mean ± SD)

<i>Assessment</i>	<i>Placebo/Donepezil N=197</i>	<i>Memantine/Donepezil N=198</i>
SIB	79.8 (14.18)	77.8 (15.46)
ADCS-ADL	36.2 (9.32)	35.9 (9.75)
NPI	13.8 (12.83)	13.7 (14.11)
BGP Total	13.5 (7.66)	13.3 (7.78)
BGP Care Dependency	9.2 (5.99)	8.9 (5.83)
BGP Cognitive	1.4 (1.51)	1.3 (1.51)

As the tables above indicate, mean age and baseline dementia severity were comparable across treatment groups.

The distribution of baseline Mini-Mental Status Examination in the entire population enrolled in the study is as shown in the following table:

Baseline Mini-Mental Status Examination Score	N	%
5	31	7.85
6	41	10.38
7	35	8.86
8	29	7.34
9	25	6.33
10	36	9.11
11	39	9.87
12	36	9.11
13	58	14.68
14	59	14.94
15	5	1.27
16	1	0.25
All	395	100.00

As the table above indicates, a majority of patients (59.23%) enrolled in this study had an Mini-Mental Status Examination score at baseline that was ≥ 10 .

13.2.5 Primary Efficacy Analysis

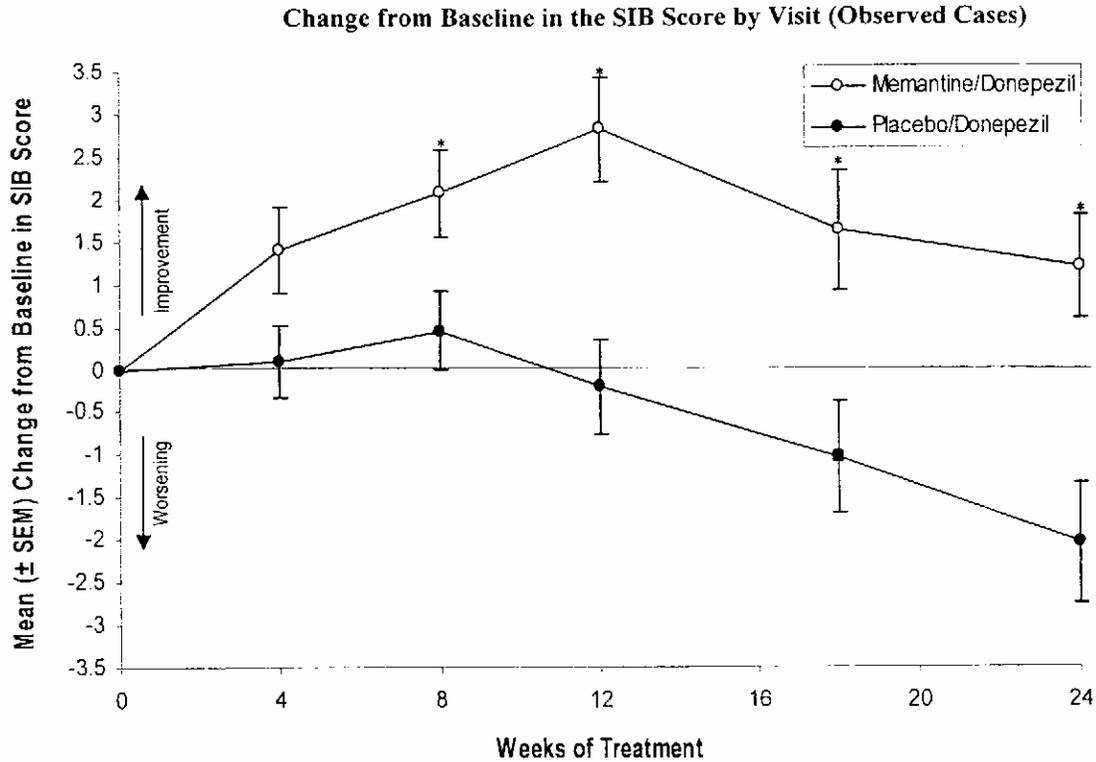
13.2.5.1 Severe Impairment Battery

Change from baseline scores for this measure on the primary LOCF dataset, and on the Observed Cases dataset, are in the following table, which I have copied from the submission

Least Square Mean Change from Baseline in SIB

	<i>Placebo/Donepezil</i>		<i>Memantine/Donepezil</i>		<i>p-value</i>
	<i>N</i>	<i>Mean</i>	<i>N</i>	<i>Mean</i>	
Week 24 (LOCF)	196	-2.5	198	0.9	<0.001
Week 24 (OC)	153	-2.4	171	1.0	<0.001

The change from baseline in Severe Impairment Battery score for the Observed Cases dataset at each visit is summarized in the following figure which I have also copied from the submission



As the table and figure above indicate, there were statistically significant differences between the treatment groups on this measure for both datasets, with the memantine-donepezil group being superior to the memantine-placebo group. It also noteworthy, however, that the effect size was very small.

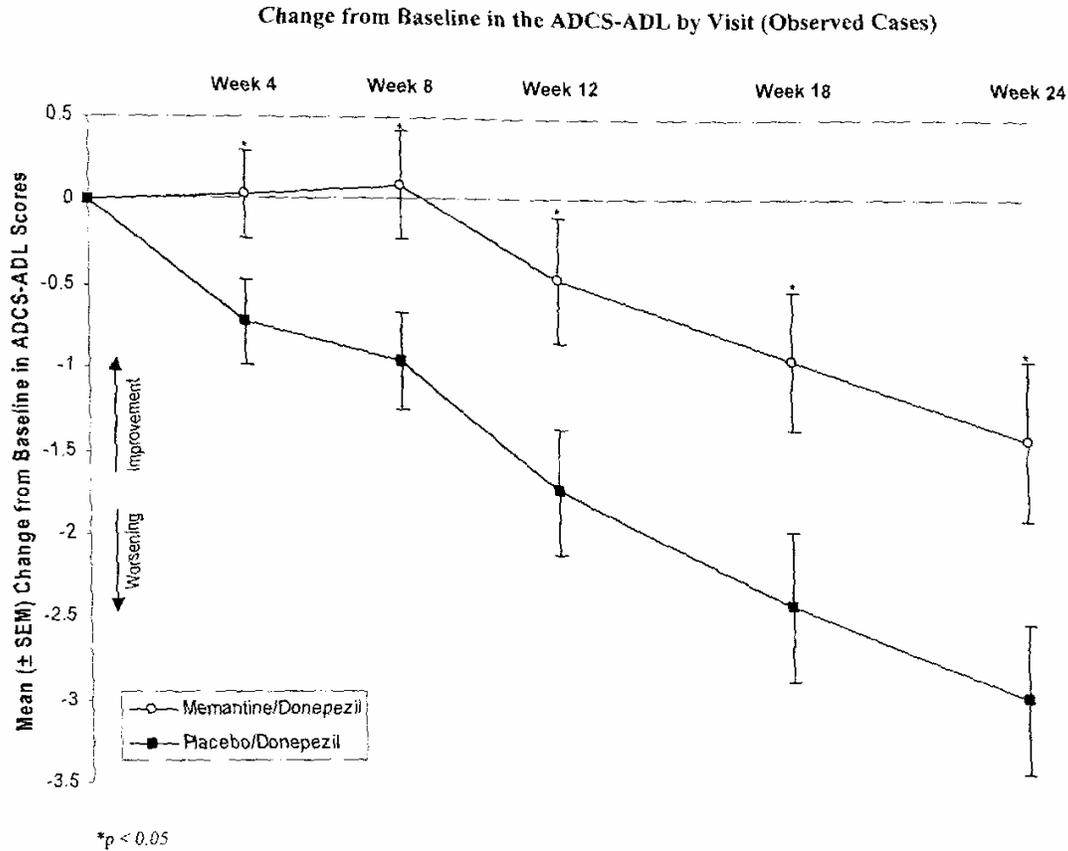
13.2.5.2 Modified ADCS-ADL

Change from baseline scores for this measure on the primary LOCF dataset and on the Observed Cases dataset are in the following table, which I have copied from the submission

Least Square Mean Change from Baseline in ADCS-ADL

	<i>Placebo/Donepezil</i>		<i>Memantine/Donepezil</i>		<i>p-value</i>
	<i>N</i>	<i>Mean</i>	<i>N</i>	<i>Mean</i>	
Week 24 (LOCF)	197	-3.4	198	-2.0	0.028
Week 24 (OC)	152	-3.3	172	-1.7	0.020

The change from baseline in modified ADCS-ADL score for the Observed Cases dataset at each visit is summarized in the following figure which I have copied from the submission



As the table and figure above indicate, there were statistically significant differences between the treatment groups on this measure for both datasets, with the memantine-donepezil group being superior to the memantine-placebo group. It again noteworthy that the effect size was small.

13.2.6 Analysis Of Secondary Efficacy Measures

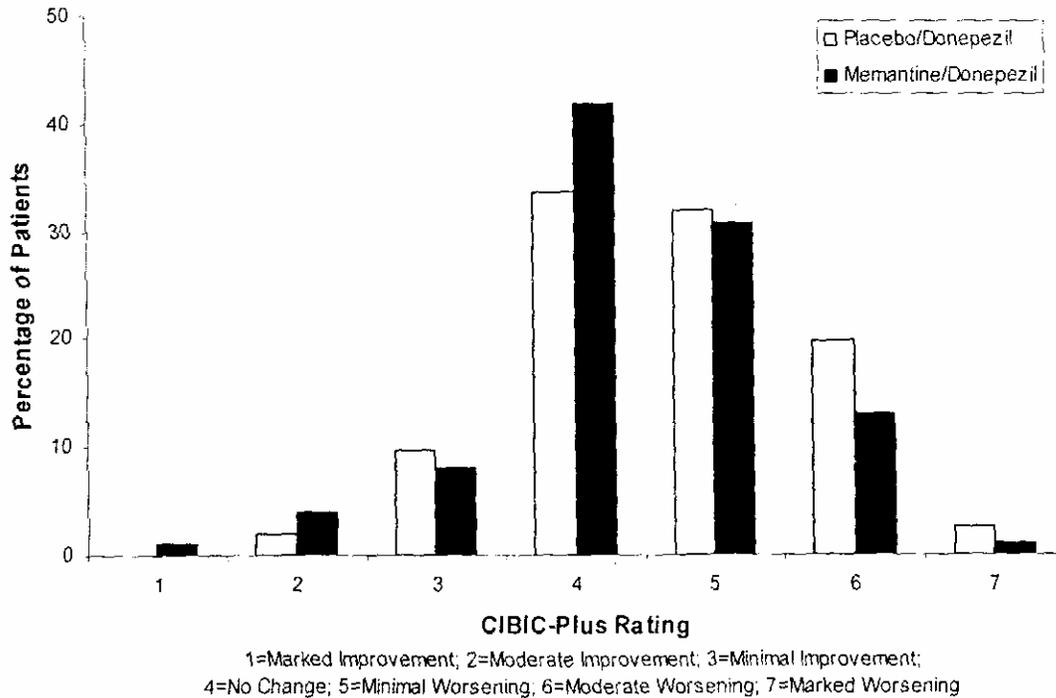
13.2.6.1 CIBIC-Plus

Mean CIBIC-Plus ratings at endpoint for the primary LOCF dataset and for Observed Cases (OC) are summarized in the following table, taken from the submission

	Mean CIBIC-Plus Rating				<i>p-value</i>
	<i>Placebo/Donepezil</i>		<i>Memantine/Donepezil</i>		
	<i>N</i>	<i>Mean</i>	<i>N</i>	<i>Mean</i>	
Week 24 (LOCF)	196	4.66	198	4.41	0.027
Week 24 (OC)	152	4.64	172	4.38	0.028

The distribution of CIBIC-Plus ratings at endpoint for the LOCF dataset is in the following figure, which I have taken from the submission

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



As the table and figure above indicate, there were nominally statistically significant differences between the treatment groups on this measure for both datasets, with the memantine-donepezil group being superior to the memantine-placebo group. It also noteworthy, however, that the effect size was very small.

13.2.6.2 Other Secondary Efficacy Measures

Changes from baseline to endpoint for the other secondary efficacy parameters are in the following table which I have copied from the submission

LS Mean Change from Baseline to Week 24 (LOCF) in Other Secondary Efficacy Parameters

	<i>Placebo/Donepezil</i>	<i>Memantine/Donepezil</i>	<i>p value</i>
NPI	3.7	-0.1	0.002
FAST	0.4	0.4	0.990
BGP (Total)	3.3	1.1	<0.001
BGP (Care Dependency)	2.3	0.8	0.001
BGP (Cognitive)	0.5	0.2	0.035

As the table above indicates, nominally statistically significant treatment differences between the treatment groups, and favoring the donepezil-memantine combination, were seen for the Neuropsychiatry Inventory, and BGP (total), BGP Care Dependency and BGP Cognitive subscales

13.2.7 Additional Sponsor Analyses

The sponsor has pointed out that

- Analyses based on individual items of the ADCS-ADL, NPI, and SIB showed numerical trends consistent with the findings for the complete scales
- The treatment effect was consistent across centers

13.2.8 Agency Subgroup Analysis

Dr Tristan Massie, Agency Biometrics Reviewer of this submission, has, at my request, compared the effects of the two treatment groups on the primary efficacy parameters, after dividing those enrolled into 2 subgroups: those with a Mini-Mental Status Examination score ≥ 10 , and those with a Mini-Mental Status Examination score < 10 .

The purpose of this additional analysis was to help determine if any effect on memantine in Alzheimer’s Disease was actually determined by patients with more severe dementia, for the following reasons

- 4 drugs have currently been approved for the treatment of mild-to-moderate dementia of the Alzheimer’s type, whereas the sponsor is currently seeking a claim for memantine in the treatment of moderate-to-severe dementia of the Alzheimer’s type. Baseline Mini-Mental Status Examination scores used to include patients in clinical trials for mild-to-moderate Alzheimer’s Disease range from 10-26; that range overlaps with the range used to select patients for MEM-MD-02
- Patients enrolled in this study had a baseline Mini-Mental Status Examination score that ranged from 5 to 16 (with greater than 95% having Mini-Mental Status Examination scores that ranged from 5 to 14, as specified by the inclusion criteria for this study). The majority had an Mini-Mental Status Examination score ≥ 10 .

The results of the analysis are summarized in the following table

MEM-MD-02: ITT-LOCF MMSE Subgroup Analyses							
Variable	MMSE Sub-Group	Treatment Group	n	Baseline Mean (SD)	Mean Change From Baseline To Endpoint Mean (SD)	p-value for treatment group comparison	Interaction p value
ADL Total	<10	Placebo plus donepezil	72	32.4 (9.3)	-4.6 (6.1)	0.1682	0.7563
	<10	Memantine plus donepezil	89	33.0 (10.7)	-2.8 (7.6)		
	≥ 10	Placebo plus donepezil	125	38.5 (8.5)	-2.4 (5.9)	0.0821	
	≥ 10	Memantine plus donepezil	109	37.9 (8.4)	-1.1 (5.3)		
SIB Total	<10	Placebo plus donepezil	72	69.1 (14.5)	-6.2 (9.9)	0.0023	0.0374
	<10	Memantine plus donepezil	89	67.4 (15.4)	0.1 (9.8)		
	≥ 10	Placebo plus donepezil	124	86.0 (9.3)	0.0 (7.6)	0.0450	
	≥ 10	Memantine plus donepezil	109	86.0 (9.7)	1.8 (6.0)		

As the table above indicates, differences between treatment groups (effect sizes) appeared to be greater for those with a baseline Mini-Mental Status Examination < 10, for both measures (especially for the Severe Impairment Battery)

13.3 Sponsor's Conclusions Regarding Efficacy

In patients with moderate-to-severe Alzheimer's Disease, statistically significant and clinically relevant beneficial effects were seen when memantine was added to a stable dose of donepezil, on measures of cognition, daily functioning, and global status, as compared with a donepezil-placebo combination.

13.4 Agency Statistical Reviewer's Comments

Final comments from the Agency statistical reviewer are pending.

13.5 Reviewer's Comments

This study does appear to demonstrate that memantine is more effective than placebo, in patients already taking a stable dose of donepezil, on both a cognitive and a functional primary efficacy measure

14 Additional Efficacy Studies

The results of 2 additional efficacy studies that the sponsor considers indirectly pertinent to the proposed claim have been presented in the application, mainly as abbreviated study reports and abbreviated descriptions in the Integrated Summary of Effectiveness. These are Studies MRZ 9202 and MRZ 9408; both studies evaluated the efficacy of memantine in treating mild-to-moderate vascular dementia. I have briefly outlined the designs of both studies and summarized their results.

Note that the analyses presented in the abbreviated study reports are based on a re-analysis of the study data by Forest Laboratories; the methods of re-analysis have been made consistent with analyses performed for other studies in this submission

14.1 Brief Outline Of Study Design

14.1.1 MRZ 9202

This study was conducted at 57 centers in the United Kingdom and its design is summarized below

Design:	Randomized, double-blind, placebo-controlled, parallel-group study
Duration:	28 weeks
Key Inclusion Criteria:	Male or female; age \geq 50 years Probable Vascular Dementia (NINDS-AIREN criteria) Mini-Mental Status Examination: 10-22 Modified Hachinski Ischemic Scale \geq 4
Primary Efficacy Measures:	ADAS-Cog CGI-C

Secondary Efficacy Measures:	Gottfries, Brane and Steen Scale, Nurse's Observation Scale for Geriatric Patients, Mini-Mental Status Examination
Dose Arms:	Memantine 10 mg b.i.d Placebo
Primary Efficacy Analysis	Intent-to-treat population: : LOCF and Observed Cases ANCOVA for ADAS-Cog Cochran-Mantel-Haenszel test for CGI-C

The intent-to-treat population for this study was defined as all patients who were randomized, received at least one dose of dose of double-blind study medication, and had at least one post-baseline assessment of one of the primary efficacy parameters

14.1.2 MRZ 9408

This study was conducted at 50 centers in France, Belgium, and Switzerland, and its design is summarized below

Design:	Randomized, double-blind, placebo-controlled, parallel-group study
Duration:	28 weeks
Key Inclusion Criteria:	Male or female; age \geq 50 years Probable Vascular Dementia (NINDS-AIREN criteria) Mini-Mental Status Examination: 12-20 Modified Hachinski Ischemic Scale \geq 4
Primary Efficacy Measures:	ADAS-Cog CIBIC-Plus
Secondary Efficacy Measures:	ADAS-NonCog, Gottfries, Brane and Steen Scale, CGI-C-Physician, CGI-C-Caregiver, Nurse's Observation Scale for Geriatric Patients II
Dose Arms:	Memantine 10 mg b.i.d Placebo
Primary Efficacy Analysis	Intent-to-treat population: LOCF and Observed Cases ANCOVA for ADAS-Cog Cochran-Mantel-Haenszel for CIBIC-Plus

The intent-to-treat population for this study was defined as all patients who were randomized, received at least one dose of dose of double-blind study medication, and had at least one post-baseline assessment of one of the primary efficacy

14.2 Efficacy Results

The efficacy results of both studies are presented together

14.2.1 Patient Disposition

Patient disposition is presented in the following table, which I have derived from the submission. As the table indicates, the majority of those randomized in both studies, completed them.

	Study 9202		Study 9408	
	Placebo N	Memantine N	Placebo N	Memantine N
Randomized	286	295	156	165
Intent-to-treat	271	277	141	147
Completed	227	238	118	116
Discontinued	44	39	23	31

14.2.2 Demographic And Other Baseline Characteristics

These are summarized in the following table, which I have copied from the submission. The table is based on the intent-to-treat population

Patient Demographics — Studies 9202 and 9408

Demographic Parameter	Study 9202		Study 9408	
	Placebo (N=271)	Memantine (N=277)	Placebo (N=141)	Memantine (N=147)
AGE (YEARS)				
Mean ± SD	77.6 ± 7.0	77.3 ± 6.9	76.1 ± 6.9	76.6 ± 6.5
Range	57, 94	54, 97	59, 96	60, 92
SEX N (%)				
Male	138 (51%)	143 (52%)	80 (57%)	72 (49%)
Female	133 (49%)	134 (48%)	61 (43%)	75 (51%)
WEIGHT (KG)				
Mean ± SD	65.7 ± 13.2	66.4 ± 12.7	64.7 ± 11.96	66.3 ± 12.08
Range	34, 120	36, 106	39, 99	35, 96
MMSE				
Mean ± SD	17.6 ± 3.2	17.5 ± 3.3	16.9 ± 2.5	16.8 ± 2.4
Range	10, 23	10, 25	12, 20	12, 20
BASELINE ADAS-COG				
Mean ± SD	25.7 ± 10.4	25.8 ± 10.1	21.5 ± 8.7	20.6 ± 9.6

ITT population.

As the table indicates, the treatment groups in each study were comparable at baseline in regard to their cognitive status and age. The mean baseline Mini-Mental Status Examination score in each treatment group in each study ranged from 16 to 18

14.2.3 Results Of Analysis Of Primary Efficacy Parameters

The results of the analysis of these parameters at study endpoint is summarized in the following table, which combines the results of both studies and shows mean change from baseline scores for the ADAS-Cog and mean actual scores for the CGI-C and CIBIC-Plus

	LOCF Analysis			OC Analysis		
	Memantine	Placebo	p-value	Memantine	Placebo	p-value
Study 9202						
ADAS-Cog	0.53 (n=266)	2.28 (n=261)	0.007	0.15 (n=177)	1.78 (n=167)	0.029
CGI-C	4.07 (n=277)	4.04 (n=270)	0.790	4.02 (n=238)	3.94 (n=255)	0.443
Study 9408						
ADAS-Cog	-0.41 (n=147)	1.64 (n=141)	0.013	-1.25 (n=111)	1.58 (n=114)	< 0.001
CIBIC-Plus	3.98 (n=147)	4.18 (n=141)	0.235	3.98 (n=134)	4.19 (n=130)	0.244

LOCF: Last-observation-carried forward
 OC: Observed Cases
 p-values are for the memantine-placebo group comparison

14.2.4 Subgroup Analysis Of ADAS-Cog

The sponsor has performed an analysis of the ADAS-Cog data of those participating in each study who had a baseline Mini-Mental Status Examination score ≤ 14 . The results are in the following table which I have copied from the submission

Change from Baseline in ADAS-cog:
 Moderate to Severe Patients (MMSE ≤ 14) — Studies 9202 and 9408

Study/Visit	Placebo		Memantine		p-value*
	N	Mean	N	Mean	
STUDY 9202					
Endpoint (LOCF)	53	3.93	50	-0.46	< 0.01
Week 28 (OC)	29	3.44	34	-0.84	0.02
STUDY 9408					
Endpoint (LOCF)	27	4.82	25	1.83	0.10
Week 28 (OC)	20	4.76	19	-0.08	0.03

ITT population.

The sponsor draws attention to the difference between treatment groups (effect size) being larger for this subgroup than for the entire population in each study

However, these changes may not have been clinically meaningful as reflected in the analysis of the CGI-C and CIBIC-Plus outlined in the next table

Study/Visit	Placebo		Memantine		p-value
	N	Mean Score	N	Mean Score	
Study 9202					
Endpoint (LOCF)	56	4.32	53	4.32	0.998
Week 28 (OC)	41	4.20	47	4.21	0.944

Study/Visit	Placebo		Memantine		p-value
	N	Mean Score	N	Mean Score	
Study 9408					
Endpoint (LOCF)	27	4.56	25	4.40	0.459
Week 28 (OC)	25	4.6	22	4.45	0.486

14.3 Sponsor's Conclusions

The sponsor's conclusions about the results of these 2 studies, as they pertain to the current application, are as follows

- Both studies clearly demonstrated the beneficial effects of memantine on cognition, using the ADAS-Cog, an objective and accepted scale
- The beneficial effects of memantine on cognitive performance were most apparent in those with more advanced dementia at baseline (Mini-Mental Status Examination score ≤ 14)
- The 2 studies therefore contributed supportive evidence of the beneficial effects of memantine on cognition, to this application

14.4 Reviewer's Comments

- I have not performed an in-depth review of Studies 9202 and 9408, since, in the context of the claim that the sponsor is currently seeking ("treatment of moderate-to-severe dementia of the Alzheimer's type")
 - The population enrolled in these studies consisted of patients with probable vascular dementia (by the NINDS-AIREN criteria), a population that may be clinically distinct from Alzheimer's Disease/dementia of the Alzheimer's type
 - Those enrolled in these studies had mild-to-moderate, rather than moderate-to-severe, dementia
 - Although both studies did appear to show that memantine had a beneficial effect on cognition, relative to placebo, it is less clear that the effect was clinically meaningful, give the lack of benefit seen on the global primary efficacy measure in each instance.

15 Overall Comments About Key Efficacy Studies

- The sponsor is seeking a claim for memantine in the treatment of moderate-to-severe dementia of the Alzheimer's type. This is the first claim that has been sought for that indication.
- So far, 4 drugs have been approved by this Agency for the treatment of mild-to-moderate dementia of the Alzheimer's type. The efficacy of each of these drugs has been established by demonstrating a statistically significant superiority of the active drug to placebo on each of 2 primary efficacy measures: a cognitive instrument, and a global rating scale. A cognitive measure has been used on the basis that the core symptoms of dementia of the Alzheimer's type are cognitive; the global measure has been used as a means of confirming that any effect on the cognitive measure is clinically meaningful.

Since the core symptoms of moderate-to-severe dementia of the Alzheimer's type must also be considered to be cognitive, there is no reason why a similar paradigm for demonstrating efficacy should not be applicable to the entity of moderate-to-severe dementia of the Alzheimer's type. At the same time, it would also not be unreasonable for a measure of functional abilities (i.e., activities of daily living) to substitute for a global measure in helping to determine whether any effect on a cognitive measure was clinically meaningful. In earlier discussions with the previous sponsor of this drug product (Merz and Co.), it was suggested to this Division that, in severely impaired patients, the assessment of global function or activities of daily living might be a better reflection of the patient's "true" condition than an assessment of cognition (which, in any case, might be difficult to conduct in such a population), and that demonstrating efficacy on a cognitive measure might therefore be of lesser importance. However, in the absence of an effect on cognition, it could be difficult to determine if any beneficial effect was specific to the dementia itself. For example, a drug which improved alertness alone in patients with Alzheimer's Disease, might also produce improvements in global function or activities of daily living without improving cognition, but it would not be appropriate for such a drug to be approved for the treatment of dementia of the Alzheimer's type, if, as appears to be widely accepted, the core symptoms of that entity are cognitive.

- Of the 4 drugs currently approved for the treatment of mild-to-moderate Alzheimer's Disease, 3 drugs were approved using efficacy trials in which patients were enrolled if they had a Mini-Mental Status Examination score at baseline that ranged from 10 to 26. For the fourth drug, the Mini-Mental Status Examination score at baseline for the key efficacy trials was required to be in the 10 to 24 range.
- In the current application, support for the efficacy of memantine in the treatment of moderate-to-severe dementia of the Alzheimer's type has been based on 3 randomized, double-blind, placebo-controlled, parallel- and two-arm trials; each trial compared a single memantine dose with placebo (Study MEM-MD-02 was an "add-on" trial with all patients taking a stable dose of donepezil at entry and continuing with that dose during the trial). Key aspects of the design of each of these trials are summarized in the following table

Study	MRZ 9605	MRZ 9403	MEM-MD-02
Population enrolled	Probable Alzheimer's Disease	Alzheimer's Disease, vascular dementia, or mixed dementia	Probable Alzheimer's Disease
Mini-Mental Status Examination score at baseline (by protocol)	3 to 14	0 to 9	5 to 14
Duration of double-blind treatment	28 weeks	12 weeks	24 weeks

Study	MRZ 9605	MRZ 9403	MEM-MD-02
Memantine dose	10 mg b.i.d	10 mg q.d.	10 mg b.i.d
Primary Outcome Measures	<ul style="list-style-type: none"> • CIBIC-Plus • ADCS-ADL (modified) 	<ul style="list-style-type: none"> • CGI-C • BGP Care Dependency subscale • BGP Cognitive Subscale 	<ul style="list-style-type: none"> • Severe Impairment Battery • ADCS-ADL (modified)

- ❖ Study MEM-MD-02 was an “add-on” trial; all enrolled patients were on a stable dose of donepezil at entry, which was continued for the duration of the study
- ❖ In Study MRZ 9403, the BGP Cognitive Subscale was a post-hoc and ad-hoc measure, ostensibly intended to evaluate cognition
- ❖ In Study MRZ 9605, the Severe Impairment Battery was a secondary efficacy measure

- What evidence there was for the efficacy of memantine in comparison with placebo on cognitive, global, and functional measures, in each of these trials, is summarized in the following table which shows each measure and the respective p-value for the memantine-placebo comparison (according to the primary efficacy analysis)

Study	Cognitive Measure	Global Measure	Functional Measure
MRZ 9605	Severe Impairment Battery p = 0.0003	CIBIC-Plus p = 0.064	ADCS-ADL p = 0.022
MRZ 9403	BGP Cognitive Subscale p = 0.001	BGP Care Dependency Subscale p = 0.001	BGP Care Dependency Subscale p = 0.012
MEM-MD-02	Severe Impairment Battery p < 0.001	CIBIC-Plus P = 0.027	ADCS-ADL P = 0.028

- ❖ Efficacy measures that were designated as secondary are highlighted in blue
- ❖ The Severe Impairment Battery was one of 7 secondary efficacy measures for the MRZ 9605 trial
- ❖ The BGP Cognitive Subscale was a post-hoc instrument in the MRZ 9403 whose ability to evaluate cognition was questionable
- ❖ The CIBIC-Plus was one of 5 secondary efficacy measures in the MEM-MD-02 trial

- Assuming that in order to support a claim for memantine in the treatment of moderate-to-severe dementia of the Alzheimer’s type, the efficacy of memantine should have been demonstrated, in relation to placebo, on both a cognitive and a global/functional efficacy measure, the following trials may be considered to support that claim
 - Study MRZ 9605 in which reasonably clear evidence of efficacy was demonstrable on a primary efficacy measure of activities of daily living (a modified version of the ADCS-ADL), and on a cognitive measure, the Severe Impairment Battery. Although the Severe Impairment Battery was one of 7 secondary efficacy measures, and although many secondary analyses were performed, the p-value for the memantine-placebo comparison on this measure remained statistically significant (p < 0.05) even after correction for multiple comparisons. Evidence for efficacy was somewhat less robust on the global primary efficacy measure, on which the p-value approached statistical significance. This trial does appear to support the efficacy of memantine as monotherapy.

- Study MEM-MD-02 in which clear evidence of efficacy was demonstrable on both protocol-specified primary efficacy measures: the Severe Impairment Battery, a measure of cognition, and the modified ADCS-ADL (a measure of activities of daily living). This study would support the efficacy of memantine in combination with donepezil (i.e., as an “add-on” treatment in patients already taking donepezil)
- In both clinical trials, the effective dose of memantine was 10 mg b.i.d. This may, therefore, be considered to be the only dose of memantine established as being effective for moderate-to-severe dementia of the Alzheimer’s type.
- The results of Study MRZ 9403 provide less convincing support for the efficacy of memantine in moderate-to-severe dementia of the Alzheimer’s type for the following reasons
 - The study enrolled patients with Alzheimer’s Disease, vascular dementia, and mixed dementia, rather than Alzheimer’s Disease per se. Following enrollment, patients were later grouped as having Alzheimer’s Disease or vascular dementia based on their modified Hachinski Ischemic Scale score alone. Thus, those patients designated as having Alzheimer’s Disease in this trial did not have that diagnosis made using currently standard criteria.
 - The study lacked a prospectively-designated cognitive outcome measure. A subset of ad-hoc items (termed the BGP Cognitive Subscale), itself derived from a subset of a global instrument (the BGP Care Dependency Subscale), was designated post-hoc as a cognitive outcome measure; although a statistically significant superiority of memantine to placebo was seen on this measure, it is very doubtful if the BGP Cognitive Subscale adequately measures cognition.
 - Only 52% of patients enrolled in this study underwent brain imaging (in the form of CT scanning). Brain imaging is a standard screening procedure for clinical drug trials in Alzheimer’s Disease and is important in excluding conditions other than a primary degenerative dementia
- The measures used to assess cognition, global function, and activities of daily in Studies MRZ 9605 and MEM-MD-02, namely the Severe Impairment Battery, CIBIC-Plus, and modified ADCS-ADL, have at least face validity for evaluating patients with moderate to severe dementia
- The population enrolled in Studies MRZ 9605 and MEM-MD-02, appears to partly overlap, in baseline dementia severity, those enrolled in clinical efficacy trials for mild-to-moderate dementia of the Alzheimer’s type upon which the approval of those drugs has been based. In pre-approval efficacy trials in mild-to-moderate Alzheimer’s Disease the baseline Mini-Mental Status Examination score has ranged from 10 to 26. In Studies MRZ 9605 and MEM-MD-02, the baseline Mini-Mental Status Examination

score ranged from 1 to 14, and 5 to 16, respectively. Although 38.4% and 59.3% of patients in MRZ 9605 and MEM-MD-02, respectively, had a baseline Mini-Mental Status Examination score ≥ 10 , the population enrolled in these studies does support a claim directed at moderate-to-severe dementia of the Alzheimer's type.

16 Recommendation

Deferred.

Ranjit B. Mani, M.D.
Medical Reviewer

A. Oliva, M.D. _____

rbm 8/19/03

cc:

HFD-120

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