CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-487

Medical Review(s)

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
Correspondence Date:	12/19/02
Date Received / Agency:	12/24/02
Date Review Completed	10/1/03
Reviewer:	Ranjit B. Mani, M.D.

1 Table Of Contents

2 Executive Summary

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

2.1 Recommendation

The evidence for efficacy contained in this application is sufficient to justify approval of memantine for the treatment of moderate to severe dementia of the Alzheimer's type. I therefore recommend approval of memantine for that indication.

This recommendation assumes that there are no serious concerns about the safety of memantine when used for that indication; the Safety Review of this application, performed by another reviewer, indicates that there are no such concerns.

2.2 Proposed Indication

"The treatment of moderate to severe dementia of the Alzheimer's type."

2.3 Summary Of Clinical Findings

The sponsor has submitted the results of 3 clinical studies in support of the efficacy of memantine as a treatment for moderate-to-severe dementia of the Alzheimer's type. These studies are as follows:

- 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

- The following merit emphasis

    - The effect sizes seen in all 3 studies were small

    - There is no evidence that memantine has a disease-modifying effect in Alzheimer's Disease

- Only a minority of memantine-treated patients in Studies 9605 and MEM-MD-02 had a discernible improvement

APPEARS THIS WAY
ON ORIGINAL

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. The brand name NAMENDA ™ has been proposed for memantine.

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 has been reviewed separately by Dr Gerald Boehm of this Division.

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

This application was also discussed at a meeting of the Peripheral and Central Nervous System Drugs (PCNS) Advisory Committee held on September 24, 2003.

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 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.

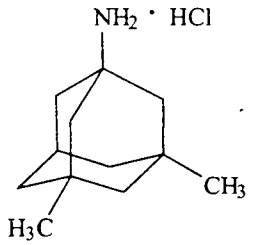
5 Outline Of Review

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
- Summary of PCNS Advisory Committee meeting
- 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	-0.25^{**}	-0.38^{***}	-0.19^{**}	-0.25^{**}
(*n*)	(161)	(161)	(166)	(166)
MMSE 16–20	-0.06^{NS}	-0.21^{NS}	-0.06^{NS}	-0.23^{NS}
(*n*)	(44)	(44)	(44)	(44)
MMSE 10–15	-0.36^{*}	-0.63^{***}	-0.08^{NS}	-0.22^{NS}
(*n*)	(38)	(38)	(39)	(39)
MMSE 5–9	-0.35^{*}	-0.40^{**}	-0.38^{*}	-0.40^{**}
(*n*)	(41)	(41)	(42)	(42)
MMSE 0–4	-0.05^{NS}	-0.18^{NS}	-0.30^{NS}	-0.02^{NS}
(*n*)	(38)	(38)	(41)	(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 was10 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	
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	-5.08	0.022	-2.49	-5.86	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

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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

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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	• 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	• Severe Impairment Battery • ADCS-ADL (modified)	
Population For Primary Efficacy Analysis	Intent-to-treat-LOCF	
Secondary Outcome Measure	• 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 (± 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 ≥ 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 B_{12}, 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

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11.1.9 Schedule

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

	Washout		*Memantine 10 mg b.i.d./Placebo*		
Time/Weeks	*-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 x [(total number of tablets dispensed) – (total number of tablets returned) – (total number of tablets reported lost)]/[(2 x 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

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

Treatment Duration (Days)	Placebo (n = 125)	Memantine (n = 123)
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

	Placebo (N=126)	*Memantine (N=126)*	*Total (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

Assessment	*Placebo N=126*	*Memantine 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

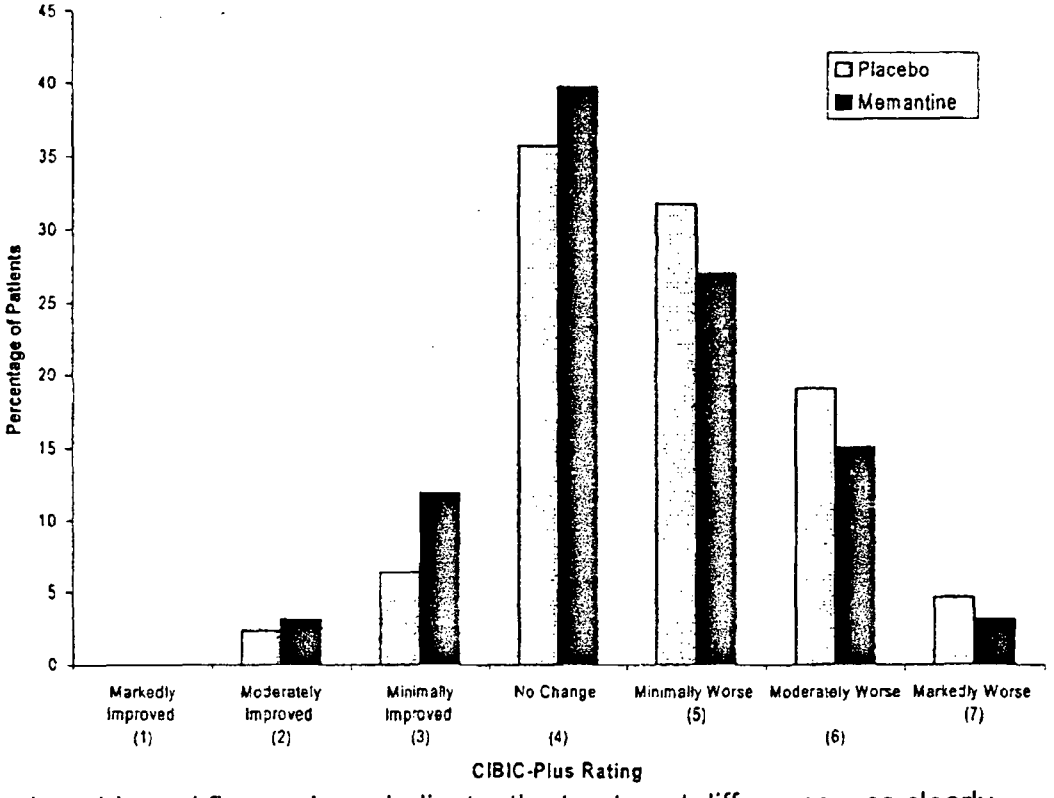
Mean CIBIC-Plus ratings at endpoint for the primary LOCF dataset and for Observed Cases (OC) are summarized in the following table, taken from the submission

Mean CIBIC-Plus Rating

	Placebo		*Memantine*		*p-value*
	N	*Mean*	*N*	*Mean*	
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

	Placebo		*Memantine*		*p-value*
	N	*Mean*	*N*	*Mean*	
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

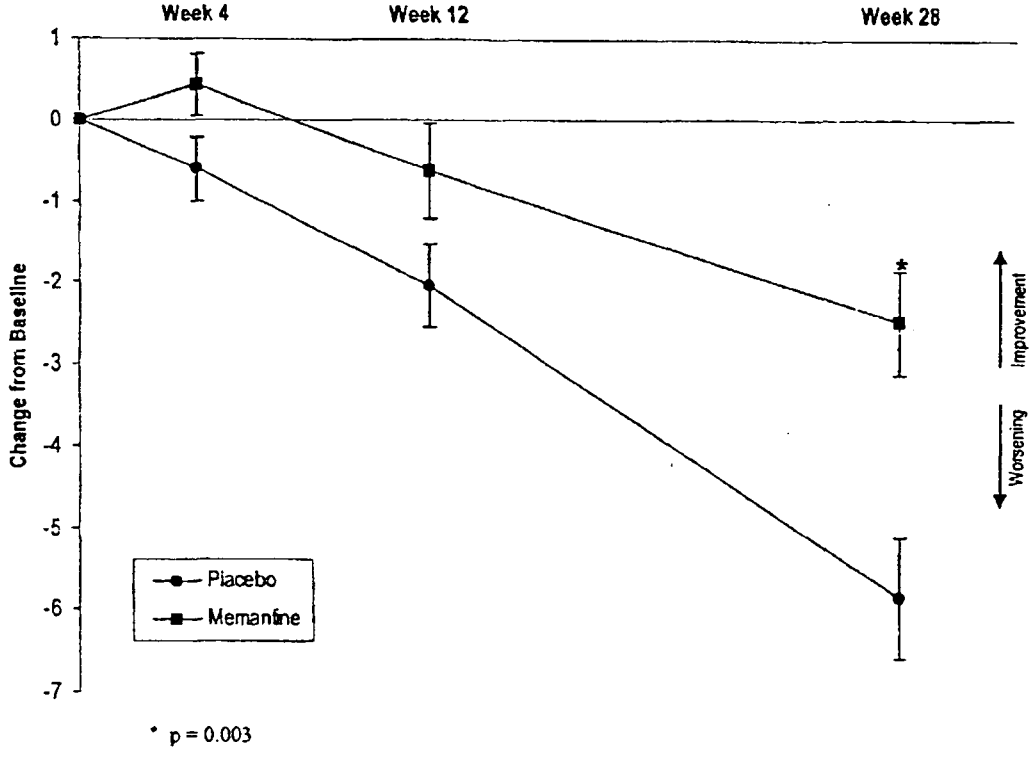
Mean change from baseline in the modified ADCS-ADL at endpoint for the primary LOCF dataset and for Observed Cases (OC) are summarized in the following table, taken from the submission

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

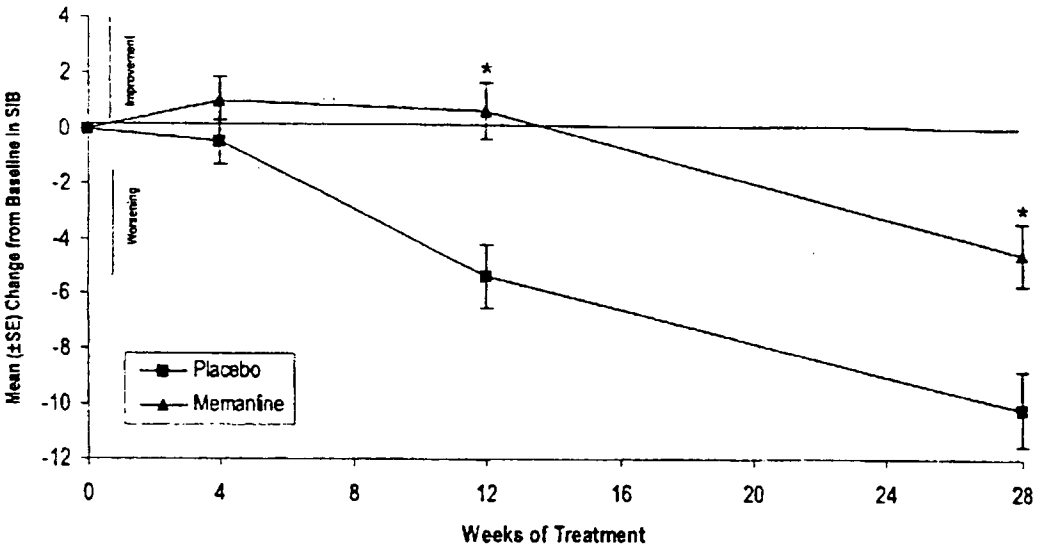
Change from Baseline in SIB

	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

	Placebo	*Memantine*	*p value*
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)		
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

Key comments made by Dr Tristan Massie about this study may be summarized as follows

- A statistically significant difference favoring memantine over placebo was seen on the Severe Impairment Battery and ADCS-ADL
- However, only a marginally statistically significant difference favoring memantine was seen on the CIBIC-Plus, a co-primary efficacy measure, using the protocol-specified primary efficacy analysis. While a statistically significant difference favoring memantine was seen on the observed cases population using this measure, dropouts fared worse on this measure than completers in the memantine group and the results on this dataset (i.e., observed cases) may therefore have been biased in favor of memantine.

- This study did not, therefore, technically meet the protocol-specified criteria for a "win."

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. These data will be required for later interpretations and investigations."

- 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 B_{12} 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