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 ≤ 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; SL	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; MP	The 4th and 3rd 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; MS	The 4th and 3rd 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

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.

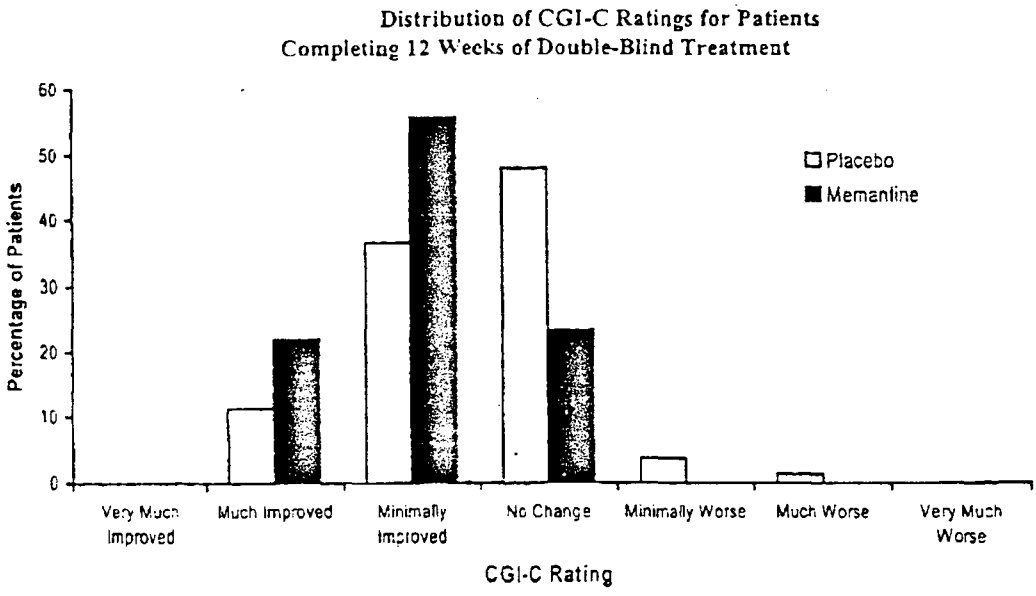
Dataset	Placebo		Memantine		p-value
	N	Mean (± SEM)	N	Mean (± SEM)	Memantine vs placebo
LOCF	84	3.5 ± 0.1	82	3.1 ± 0.1	< 0.001
WC	84	3.6 ± 0.1	82	3.2 ± 0.1	< 0.001
OC	80	3.5 ± 0.1	78	3.0 ± 0.1	< 0.001

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.



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
	N	Mean	N	Mean	Memantine vs placebo
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
	N	Mean (± SEM)	N	Mean (± SEM)	Memantine vs placebo

Dataset	Placebo		Memantine		p-value Memantine vs placebo
	N	Mean (± SEM)	N	Mean (± SEM)	
LOCF	38	3.5 ± 0.1	41	3.1 ± 0.1	0.003
WC	38	3.6 ± 0.1	41	3.3 ± 0.2	0.004
OC	37	3.5 ± 0.1	39	3.1 ± 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 ≥ 75 years) and baseline BGP Care Dependency Subscale scores (< 20 vs ≥ 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 antidementia 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

Dr Tristan Massie noted the following, among other comments

- The differences between the memantine and placebo group on both protocol-specified primary efficacy measures were statistically significant and favored memantine; this was true for the entire study population as well as for the subset designated as having Alzheimer's Disease
- The study did not have a cognitive efficacy measure

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 form 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) B_{12} 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 cetrizine 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 B_{12} 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 ≥ 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

	Placebo/Donepezil N=201	*Memantine/Donepezil N=202*	*Total N=403*
	n (%)	*n (%)*	*n (%)*
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

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

Treatment Duration	Placebo (n = 201)	Memantine (n = 202)
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 ≥ 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

	Placebo/Donepezil N=201	*Memantine/Donepezil N=202*	*Total 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 ± SD)

Assessment	*Placebo/Donepezil N=201*	*Memantine/Donepezil 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)

Assessment	*Placebo/Donepezil N=197*	*Memantine/Donepezil N=198*
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

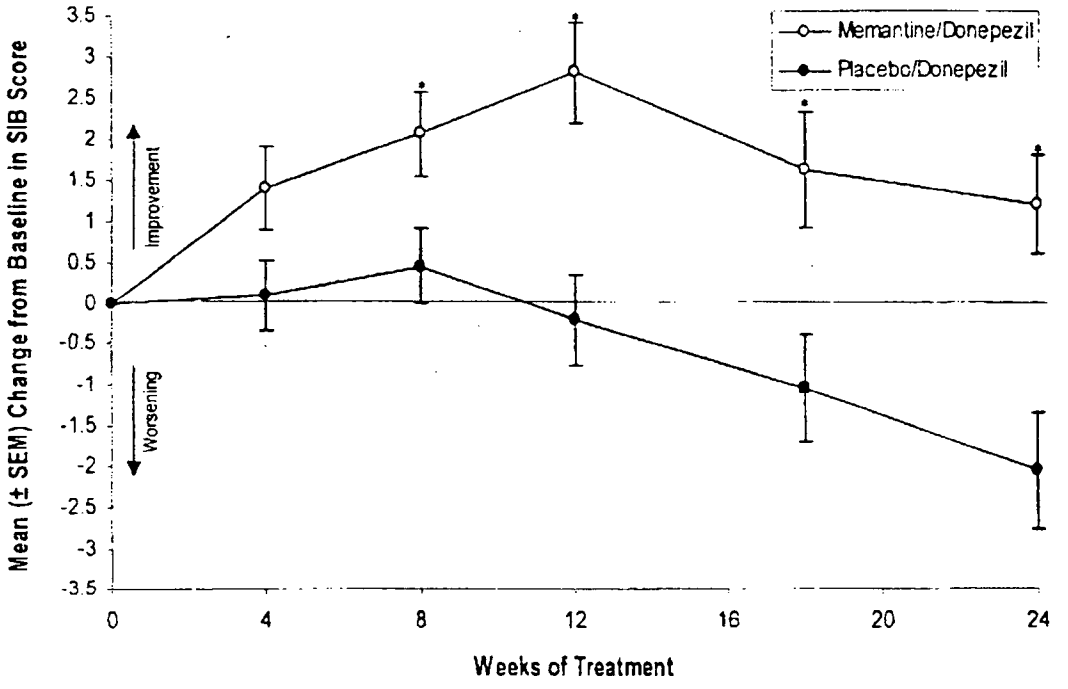
Change from baseline scores for this measure on the primary LOCF dataset, and on the Observed Cases dataset, are in the following table, which I have copied from the submission

Least Square Mean Change from Baseline in SIB

	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

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

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



*p < 0.05.

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

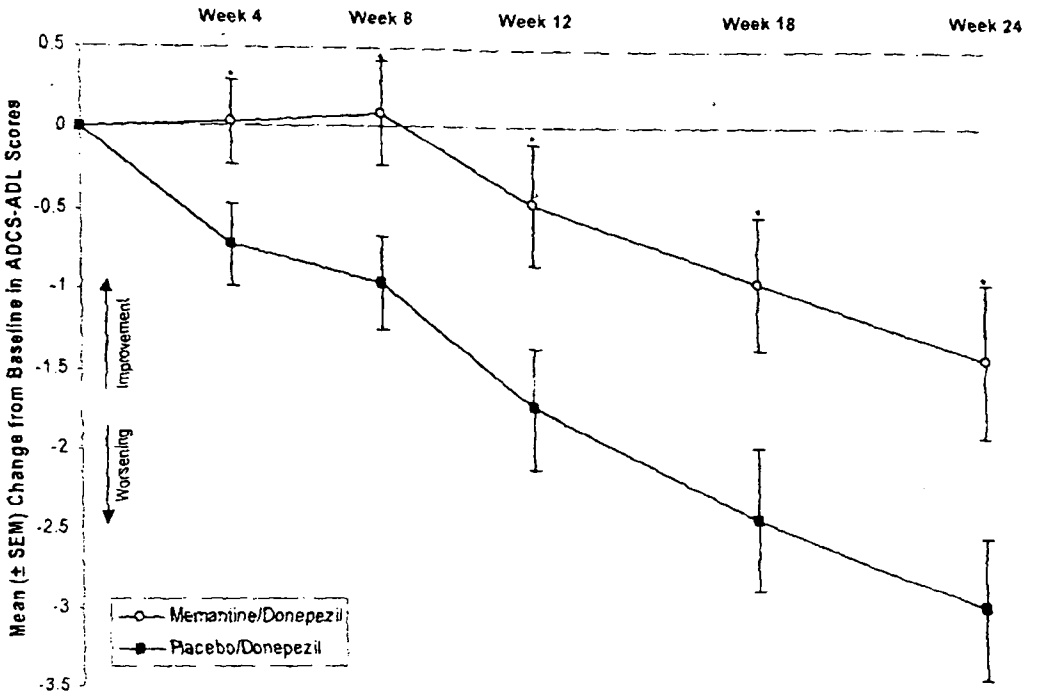
Change from baseline scores for this measure on the primary LOCF dataset and on the Observed Cases dataset are in the following table, which I have copied from the submission

Least Square Mean Change from Baseline in ADCS-ADL

	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

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

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



*$p < 0.05$

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

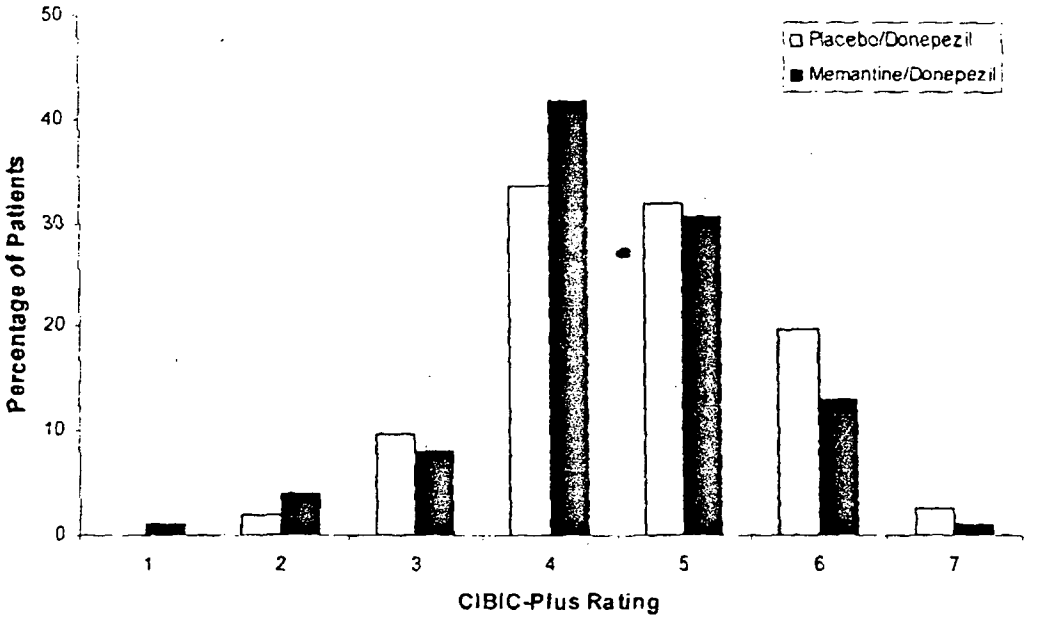
Mean CIBIC-Plus ratings at endpoint for the primary LOCF dataset and for Observed Cases (OC) are summarized in the following table, taken from the submission

Mean CIBIC-Plus Rating

	Placebo/Donepezil		*Memantine/Donepezil*		*p-value*
	N	*Mean*	*N*	*Mean*	
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)



1=Marked Improvement; 2=Moderate Improvement; 3=Minimal Improvement; 4=No Change; 5=Minimal Worsening, 6=Moderate Worsening; 7=Marked Worsening

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

	Placebo/Donepezil	*Memantine/Donepezil*	*p value*
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

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 ≥ 50 years Probable Vascular Dementia (NINDS-AIREN criteria) Mini-Mental Status Examination: 10-22 Modified Hachinski Ischemic Scale ≥ 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 ≥ 50 years Probable Vascular Dementia (NINDS-AIREN criteria) Mini-Mental Status Examination: 12-20 Modified Hachinski Ischemic Scale ≥ 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 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	• CIBIC-Plus • ADCS-ADL (modified)	• CGI-C • BGP Care Dependency subscale • BGP Cognitive Subscale	• 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.

- **The following merit emphasis**
  - **The effect sizes seen in all 3 studies were small**
  - **Studies 9605, 9403 and MEM-MD-02 were not designed to detect a disease-modifying effect of memantine, i.e., an effect of memantine on the pathology of Alzheimer's Disease. Thus it cannot be inferred from the results of these studies that memantine is disease-modifying**
  - **Responder analyses, based on the CIBIC-Plus, for Studies 9605 and MEM-MD-02, confirm that only a minority of memantine-treated patients showed a discernible overall improvement over the course of these studies.**

16 Advisory Committee Meeting

A meeting of the Peripheral and Central Nervous System Drugs Advisory Committee was held on September 24, 2003 to discuss this application. The sponsor was asked to vote on 4 questions. These questions are listed below

1. Has the population for which the use of memantine is proposed been adequately identified in the studies included in this application?

2. Are the designs of the key studies in this application adequate for evaluating the efficacy of memantine for the proposed indication? In particular, are the instruments used to evaluate efficacy in these studies appropriate for patients with moderate-to-severe Alzheimer's Disease?

3. Has substantial evidence of the effectiveness of memantine for the proposed indication been demonstrated by the studies included in this application?

4. Has substantial evidence of the safety of memantine for the proposed indication been demonstrated by the studies included in this application?

The Committee voted "YES" unanimously on each of the above questions

Concerns expressed by one of more members of the Committee while addressing the above questions included, but were not limited to, the following

- The deficiencies in design of Study 9403 for assessing the efficacy of memantine in patients with Alzheimer's Disease (as opposed to a more generic dementia), as well as the lack of an adequate and prospectively-defined cognitive outcome measure for that study. Several Committee members felt that Studies 9605 and MEM-MD-02, and not Study 9403, were the key efficacy studies.

- The lack of a clearly statistically significant (i.e., $p < 0.05$) superiority of placebo over memantine in Study 9605; however, it was also felt that this deficiency was partly offset by the evidence for efficacy on a global measure in Study 9403

- The smallness of the effect size seen with memantine in comparison with placebo

- The long-term safety of memantine and its potential for drug-interactions. Attention was also drawn to a letter to the Committee from Dr John Olney, an expert on excitotoxic injury to the central nervous system, regarding the potential for memantine to cause such injury especially with concurrent acetylcholinesterase inhibitor administration

- Whether patients with truly severe Alzheimer's Disease were evaluated in any study other than 9403.

- Future drug studies for the same indication should use both cognitive and global/functional primary efficacy measures

Please refer to the transcript of the Committee's deliberations for full details.

17 Review Of Draft Labeling

My review of the sponsor's draft labeling (the version submitted 9/19/03) is confined to the Clinical Trials, Indications And Usage, and Dosage And Administration sections of the labeling

This section lists changes made by to the labeling, and my reasons for making those changes.

The actual draft labeling combined with the changes made by me are in a separate document.

Comments

CLINICAL TRIALS section

- Given its serious deficiencies which have already been outlined in this review, Study 9403 cannot be considered a key efficacy study, although it

may be argued that the results of this study may provide supportive evidence of the efficacy of memantine in patients with severe dementia. I have, therefore, provided only an abbreviated description of this study in the label.

- I have eliminated the description of the CIBIC-Plus analysis from the account of Study MEM-MD-02, as this was a secondary efficacy measure, and as evidence for efficacy had been clearly demonstrated on both primary efficacy measures
- Note that the sponsor's descriptions of the clinical trials included in labeling have been based on Observed Cases data, as has traditionally been the case with such descriptions in labeling for other drugs approved for the treatment of dementia of the Alzheimer's type.

INDICATIONS AND USAGE section

This section has not been altered

DOSAGE AND ADMINISTRATION section

Based on Studies 9605 and MEM-MD-02, the only effective dose of memantine appears to be 20 mg/day. A reference to the 10 mg/day dose as being effective has therefore been deleted; although that dose was the only one used in Study 9403, that study lacked a convincing cognitive efficacy measure.

18 Site Inspections

18.1 Site Inspection Report

The Clinical Inspection Summary for study sites has been completed by Ni A. Khin, MD, of the Division of Scientific Investigations.

The sites inspected and their classification following inspection are in the following table, which I have copied from Dr Khin's report

NAME	Protocol	Location	ASSIGNED DATE	DATE EIR RECEIVED	CLASSIFICATION
Dr L. Eisner	MEM-MD-02 and MRZ 90001-9605	Fort Lauderdale, FL	03-03-2003	06-02-2003	VAI
Dr. M. Usman	MEM-MD-02 and MRZ 90001-9605	Pittsburgh, PA	03-03-2003	05-21-2003	VAI-RR
Dr S. Flitman	MRZ 90001-9605	Phoenix, AZ	04-03-2003	06-13-2003	NAI
Dr. J. Heiser	MEM-MD-02	Newport Beach, CA	04-03-2003	07-29-2003	NAI
Dr V. Sevele	MRZ 90001-9403	Riga, Latvia	04-16-2003	08-07-2003	VAI
Dr J. Sarkane	MRZ 90001-9403	Riga, Latvia	04-16-2003	09-04-2003	VAI
Sponsor: Forest Laboratories Inc	MEM-MD-02	Jersey City, NJ	06-05-2003	09-15-2003	VAI

VAI: Voluntary action indicated, data acceptable
NAI: No action indicated
VAI-RR: Voluntary action indicated, data acceptable; response from Principal Investigator received and reviewed

Dr Khin has pointed out that at several of the sites inspected, a few patients did not meet study eligibility criteria. Efficacy analyses have been repeated by Dr Tristan Massie, excluding data from these patients, with no change in the conclusions that could be derived from these studies. Please refer to Dr Khin's review for further details about these patients and about other deficiencies detected by the inspections.

Dr Khin has concluded that, overall, data from the centers inspected appear acceptable for use in support of this application

18.2 Reviewer's Comments

The deficiencies that Dr Khin has described as being found during site inspections are minor and do not preclude the use of the 3 main efficacy studies, to support this application.

19 Financial Disclosure Certification

Financial disclosure information has been collected only for the efficacy trials that are considered pivotal: 90001-9605, 90001-9403, and MEM-MD-02.

19.1 Components Of Certification

This certification provided by the sponsor has 3 components

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

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

- Certified that it has not entered into any financial agreement with the clinical investigators listed in the application, whereby the compensation to the investigator could be affected by the outcome of the study in which the investigator was a participant, as defined by 21 CFR 54.2 (a)
- Certified that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2 (b) did not disclose any such arrangements
- Certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f)

This certification has been provided on FDA Form 3454

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

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

This certification has been provided on FDA Form 3454

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

The sponsor has provided a list of investigators and sub-investigators who were involved in these studies (specifically, Study MEM-MD-02 only) who had a significant equity interest [as defined in 21 CFR 54.2 (b)] held by the clinical investigator in the sponsor. The specific disclosable financial interests that these investigators and sub-investigators had in the sponsor have also been stated.

This certification has been provided on FDA Form 3455.

19.2 Reviewer's Comments

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

20 Recommendation

The studies contained in this application provide sufficient evidence of the effectiveness of memantine in treating moderate-to-severe dementia of the Alzheimer's type to justify approval of this drug for the proposed indication. I therefore recommend approval of memantine for the treatment of moderate-to-severe dementia of the Alzheimer's type

This recommendation is based on the assumption that there are no serious concerns about the safety of use of memantine for the proposed indication. The

Safety Review of this application does not indicate that there are any such safety concerns.

Ranjit B. Mani, M.D.
Medical Reviewer

A. Oliva, M.D. _____

rbm 10/1/03
cc:
HFD-120
NDA 21487 (000)

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

/s/

Ranjit Mani
10/2/03 03:06:07 PM
MEDICAL OFFICER

Armando Oliva
10/2/03 04:03:47 PM
MEDICAL OFFICER

26 pages redacted from this section of the approval package consisted of draft labeling