Week 12	194.2 (67)	194.4 (141)	193.7 (119)
Creatinine (mg/dL)			
Baseline	0.9 (77)	0.9 (159)	0.9 (153)
Week 8	0.9 (69)	0.9 (145)	1.0 (128)
Week 12	0.9 (67)	0.9 (141)	0.9 (119)
Glucose (mg/dL)			
Baseline	203.1 (77)	215.8 (158)	198.6 (153)
Week 8	203.3 (69)	230.5 (145)	202.4 (128)
Week 12	216.5 (67)	230.8 (141)	209.9 (119)
AST (IU/L)			
Baseline	24.3 (77)	24.8 (159)	23.7 (153)
Week 8	23.1 (69)	23.8 (145)	22.6 (128)
Week 12	22.5 (67)	23.6 (141)	21.8 (119)
ALT (IU/L)			
Baseline	28.1 (77)	28.4 (159)	27.1 (153)
Week 8	25.2 (69)	26.6 (145)	25.5 (128)
Week 12	24.2 (67)	26.4 (141)	24.2 (119)
Hemoglobin (g/dL)			
Baseline	14.1 (76)	14.0 (159)	14.0 (153)
Week 8	13.9 (67)	13.9 (140)	13.9 (127)
Week 12	13.8 (66)	13.7 (140)	13.8 (118)
WBC count (x10E3/UL)			
Baseline	7.5 (76)	7.3 (159)	7.4 (153)
Week 8	7.1 (67)	7.0 (140)	7.1 (127)
Week 12	7.2 (66)	6.8 (140)	7.0 (118)
Platelets (x10E3/UL)			
Baseline	224.8 (75)	223.1 (156)	230.5 (153)
Week 8	228.1 (65)	224.3 (136)	224.0 (123)
Week 12	235.2 (65)	221.4 (136)	227.8 (114)

From Tables 25 and 26, NDA vol. 236, pp. 304-7.

Lab Outliers

Group 1 Dementia Placebo Controlled Trials

Forest provided a comparison of the treatment emergent PCS lab results from the Group 1 Dementia Placebo Controlled Trials. There did not appear to be meaningful risk differences between the treatment groups. I provide those results in the table below.

FDA TABLE 15 Subjects with Lab PCS results Group 1 Dementia Placebo Controlled Trials

		Potentially Clinically Significant Results	
Parameter	Criteria	Memantine (n)	Placebo (n)
Hemoglobin (g/dL)	≤.9 x LNL	2.3% (19/836)	2.5% (20/816)
Hematocrit (%)	≤.9 x LNL	1% (8/830)	1.1% (9/806)
WBC count (G/L)	≥16	0.1% (1/855)	0.4% (3/835)
	≤2.8	0/855	0.2% (2/835)
Eosinophils (%)	≥10	1.3% (9/712)	1.4% (10/696)
AST (U/L)	≥3 x ULN	0.1% (1/863)	0.6% (5/840)
ALT (U/L)	≥3 x ULN	0.3% (3/862)	0.7% (6/839)
ALP (U/L)	≥3 x ULN	0.2% (2/861)	0/839
Total Bilirubin (mg/dL)	≥2.0	0.4% (3/810)	0.1% (1/789)
BUN (mg/dL)	≥30	4.2% (27/647)	2.7% (17/627)
Uric Acid (mmol/L)	≥0.6246 male	1.8% (14/800)	1.2% (9/782

	≥0.5056 female		
Creatinine (mg/dL)	≥2	0.7% (6/856)	0.6% (5/833)
Cholesterol (mg/dL)	≥301	3.4% (26/765)	3.6% (27/742)
Sodium (mmol/L)	≥155	0.4 (3/813)	0.5 (4/789)
	≤125	0.2 (2/813)	0/789
Potassium (mmol/L)	≥5.5	6.1% (47/773)	5.5% (41/742)
	≤3.0	0/773	0.3% (2/742)

From SU vol. 1.11, Panel 39, p. 276.

Forest provided a listing of all patients with PCS lab results (SU Table 8.3.1). This listing included the actual result that met the outlier criteria. I reviewed this listing to identify memantine treated subjects with extreme lab result outliers. The lowest recorded hemoglobin in these studies was 8.2 g/dL and followed a GI bleed that was an SAE (Subject 9202/00649, summarized above). The highest ALT in these studies was 213 U/L in a 76-year-old female hospitalized for biliary pain. The event resolved and this patient continued into the subsequent extension trial. Three memantine subjects (9605/00096, 9202/000773, and 9403/00072) had total bilirubin results ≥2.0 mg/dL (2, 2.1, and 2.2mg/dL, respectively) and none of these subjects had associated increases in transaminases. A 73-year-old male memantine subject (9403/00035) had a sodium result of 189.9mmol/l. This subject had baseline sodium of 148.2 mmol/l that decreased to 142.5mmol/l and then increased to the high abnormal result at last visit. This result occurred in the setting of normal BUN, and creatinine but the subject also had an elevated potassium level of 6.25 mmol/l on the day of the high abnormal sodium. This subject completed the study and had no recorded AEs for the study.

Group 1 Open Label Dementia Studies

Forest identified the percentage of patients in open label dementia studies with treatment emergent lab results that met their PCS outlier criteria (SU vol. 1.11, Panel 41, pp.281-2). In the table below, I summarize the lab outliers that occurred in at least 1% of memantine subjects in open label dementia trials.

FDA TABLE 16 Subjects with Lab PCS Results where risk was present in ≥1% of Treated Population, Open Label Dementia Trials, by Treatment Assignment in Previous RCT

Lab (outlier criteria)	**Placebo-Memantine** N=417	**Memantine-Memantine** N=439	**Total** N=856
Hemoglobin (≤ 0.9 x LLN)	1.6% (6/376)	2.3% (9/390)	2% (15/766)
BUN (≥30mg/dL)	6.8% (19/279)	6.3% (19/301)	6.6% (38/580)
Uric Acid (≥0.6246 male ≥0.5056 female)	0.6% (2/360)	2.4% (9/368)	1.5% (11/728)
Creatinine (≥2.0mg/dL)	0.8% (3/382)	2.3% (9/392)	1.6% (12/774)
Cholesterol (≥301mg/dL)	5.3% (18/341)	5.1% (18/356)	5.2% (36/697)
Potassium (≥5.5 mmol/L)	5.2% (18/346)	4.5% (16/357)	4.8% (34/703)

For creatinine, the group randomized to placebo in the preceding controlled trials had a creatinine PCS outlier risk similar to the risk observed in the controlled trials. The group randomized to memantine in the controlled trials and that continued on memantine in the extension had the highest risk for a creatinine PCS outlier. I examined the listings for the

nine memantine-memantine subjects that had creatinine PCS values. For eight of these cases, the outlier creatinine value was ≤2.2mg/dL. The largest creatinine increase among these eight subjects was 0.9mg/dL (Subject 9202/00220 had a baseline Cr 1.2mg/dL, highest 2.1mg/dL, returned to 1.8mg/dL at end of study). This subject had no recorded concomitant medications and experienced no related AEs during the study. For the remaining seven subjects, most had some degree of renal insufficiency at baseline and experienced a transient increase in creatinine that improved by study end. I summarize the clinical details for subject 9202-00138, the ninth subject with a creatinine PCS value from these studies.

9202-00138 This 78 year old male with a history of prostate cancer, cerebrovascular disease, and esophagitis, had two pre-study BUN/creatinine results of 21.6/1.2mg/dL and 22.1/1.3mg/dL. He was randomized to memantine in the double blind phase and his first memantine dose was on 4/6/94. He had the following BUN and creatinine results during the double blind study: 22.1/1.8 mg/dL (6/28/94) and 48.7/3.5 mg/dL (10/19/94). He entered the open label extension phase and had the following BUN and creatinine results: 61.1/3.3 mg/dL (12/20/94) and 89.4/4.1 mg/dL (1/3/95). He stopped memantine for an adverse event (diagnosis: chest infection) and one day after stopping memantine he had a BUN/creatinine of 75.9/3.4 mg/dL. Shortly after stopping memantine he was hospitalized for decompensated congestive heart failure, hypotension, and hypothermia, and died. Neither the CRF nor the AE dataset noted worsening renal insufficiency or renal failure as adverse events. This subject had two UTIs during the studies (both treated with amoxicillin/clavulanate).

4.6.6 Vital Signs

Forest analyzed vital sign data by identifying subjects with outlier results and by examining mean changes at end of study compared to baseline. Forest's outlier analyses calculated the percentage of subjects who had treatment emergent potentially clinically significant results (PCS). The following table summarizes the criteria that Forest used to identify PCS vital sign results. Forest noted that in order to meet the outlier criteria, the vital sign result had to meet both the observed value and the change from baseline criteria.

FDA TABLE 17 Criteria for Potentially Clinically Significant Vital Signs

Vital Sign Parameter	Observed Value	Change Relative to Baseline
Systolic Blood Pressure	≥180mmHg	Increase of ≥20mmHg
	≤90mmHg	Decrease of ≥20mmHg
Diastolic Blood Pressure	≥105mmHg	Increase of ≥15mmHg
	≤50mmHg	Decrease of ≥15mmHg
Pulse	≥120bpm	Increase of ≥15bpm
	≤50bpm	Decrease of ≥15bpm
Weight	NA	Increase of ≥7%
	NA	Decrease of ≥7%

From Forest Panel 13, SU vol. 1.11, p.185.

Group 1 studies

Investigators collected vital signs at baseline, every two to four weeks, and at the end of study in Group 1 placebo controlled studies (except study 9202, which did not collect vital sign data for 278 memantine subjects). In the Group 1 open label extensions, investigators collected vital signs data at intervals ranging from every 12 weeks to as long as once yearly (Safety Update vol. 1.11, p.135).

Mean change analyses
Group 1 Dementia Placebo Controlled Trials
In the pooled analyses of Group 1 vital sign data from placebo controlled dementia trials, there did not appear to be meaningful differences between the treatment groups in the mean changes at end of study compared to baseline. The mean change results from these studies are presented in the following table.

FDA TABLE 18 Vital Sign Mean Change at End of Study Compared to Baseline Group 1 Dementia Placebo Controlled Trials

	Mean Change from Baseline	
Parameter	Memantine (n)	Placebo (n)
Systolic Blood Pressure	-1.0mm Hg (606)	-0.8 mm Hg (604)
Diastolic Blood Pressure	-0.4mm Hg (606)	-0.7 mm Hg (604)
Pulse	0.7 bpm (606)	0.4 bpm (602)
Weight*	0.9 kg (211)	0.4 kg (211)

*Data predominantly from study MEM-MD-02
From SU vol. 1.11, Panel 38, pp. 270-1.

I used the data sets provided by Forest to depict the distribution of end study vital sign changes from baseline by treatment group. There did not appear differences in the distribution of the vital sign changes from baseline by treatment. Those results are provided as an attachment to this review.

The above analyses use the last on-study drug vital sign results to calculate the mean change from baseline and therefore are last observation carried forward analyses. For study MEM-MD-02, Forest provided the mean change for study weeks four, eight, twelve, eighteen and twenty-four compared to baseline, a survivor analysis for each visit (1/10/03 submission, Table 8.1). I reviewed the mean vital sign changes from baseline by study week in MEM-MD-02 and there did not appear to be meaningful differences between the memantine and placebo treated groups at the different study visits (data not shown).

Double Blind Placebo Controlled Neuropathic Pain Studies
Forest collected but did not summarize the vital sign data from study NTI 9702. However, for study NTI 9801, Forest summarized the mean vital sign changes from baseline by study week and by treatment group in table 24 (NDA vol.236, pp.300-303). This study included two memantine dose groups (20mg, 40mg) and therefore allowed a dose-response analysis. There did not appear to be meaningful differences among the treatment groups. I provide the results of that analysis in the table below.

FDA TABLE 19 Mean Vital Sign Change by Study Week and Treatment Group, Study NTI 9801

		Treatment Group	
Parameter	Placebo (n)	Memantine 20mg (n)	Memantine 40mg (n)
Systolic BP			
Week 2	-2.4 (77)	-2.4 (161)	-1.8 (150)
Week 4	-2.9 (74)	-0.9 (154)	-0.2 (144)
Week 8	-0.1 (68)	-0.8 (145)	-1.7 (124)

Week 12	-0.6 (69)	-1.8 (143)	-4.4 (119)
Diastolic BP			
Week 2	-0.1 (77)	0.2 (161)	0.3 (150)
Week 4	0.1 (74)	-0.1 (154)	0.1 (144)
Week 8	0.1 (68)	0.3 (145)	0 (124)
Week 12	-0.1 (69)	-0.4 (143)	-0.9 (119)
Pulse			
Week 2	-0.4 (76)	-1.3 (161)	0.3 (150)
Week 4	-1.1 (74)	-1.1 (154)	0.5 (144)
Week 8	-1.4 (68)	-1.0 (145)	-1.2 (124)
Week 12	-2.5 (69)	-1.2 (143)	-0.6 (119)

Outlier PCS Analysis

Group 1 Dementia Placebo Controlled Trials

There did not appear to be meaningful differences by treatment group in the vital sign results meeting Forest's outlier criteria in the Group 1 placebo controlled dementia trials. I provide the outlier results in the following table.

FDA TABLE 20 Vital Sign Outliers Group 1 Dementia Placebo Controlled Trials

	Potentially Clinically Significant Results	
Parameter	Memantine (n)	Placebo (n)
Systolic Blood Pressure Low	0.5% (3/628)	0.6% (4/629)
Systolic Blood Pressure High	2.1% (13/628)	1.9% (12/629)
Diastolic Blood Pressure Low	0.5% (3/628)	0.5% (3/629)
Diastolic Blood Pressure High	0.8% (5/628)	0.5% (3/629)
Pulse Low	0.3% (2/627)	0.5% (3/626)
Pulse High	0/627	0.2% (1/626)
Weight Low	2.4% (5/211)	5.2% (11/211)
Weight High	10.4% (22/211)	10.4% (22/211)

From SU vol. 1.11, Panel 37, p. 269.

Group 1 Open Label Dementia Trials

Forest provided results of an outlier analysis, but did not provide mean change results for their open label dementia study vital sign data. Few subjects met PCS criteria for vital sign results in the open label dementia trials. The following table summarizes the vital sign PCS results from these studies.

FDA TABLE 21 Vital Sign PCS Results Group 1 Dementia Open Label Trials

	Potentially Clinically Significant Results	
Parameter	Placebo*/Memantine (n)	Memantine*/ Memantine (n)
Systolic Blood Pressure Low	0.3% (1/295)	0.9% (3/329)
Systolic Blood Pressure High	1% (3/295)	1.8% (6/329)
Diastolic Blood Pressure Low	1.4% (4/295)	0.3% (1/329)
Diastolic Blood Pressure High	0.7% (2/295)	0.9% (3/329)
Pulse Low	0.3% (1/295)	0.6% (2/329)
Pulse High	0/295	0/329

*Treatment assignment in the preceding placebo controlled trial

From SU Table 7.1.2.

4.6.7 ECG data

Group 1 Studies

The ECG data collected during the Group 1 studies were limited, and interval measurement methodology varied across studies. Forest collected baseline and end of study ECGs for dementia studies 9605, MEM-MD-02, 9403, 9408, and neuropathic pain studies NTI 9702 and NTI 9801 (SU vol. 1.11, p.135). The remaining Group 1 studies had only screening/pre-treatment ECGs. The intervals on ECGs from studies NTI9801 and NTI 9702 were evaluated on the printouts from the ECG recording machine and signed by the attending physician. Any over-reads were performed at the discretion of the attending physician. The intervals on ECGs from study MEM-MD-02 were evaluated by individual investigators or qualified consultants. Each site had the option to use the machine recorded interval or a manual reading by the investigator and no standard methodology was applied across sites. The intervals on ECGs from studies 9605 were read by a central lab, eReseach Technology. eResearch measured intervals using a digitizing pad, and used lead II, lead V, or a lead specified by the sponsor (7/3/03 Submission, Response to reviewer questions).

For the studies with baseline and end of study ECGs, Forest identified the percentage of patients with a normal ECG at baseline and then an abnormal ECG at end of study. This analysis did not specify the type of abnormality and therefore provides little useful information.

Forest provided mean change from baseline analyses using the ECG data from Group 1 dementia studies 9605 and MEM-MD-02, and Group 1 neuropathic pain studies NTI 9702 and NTI 9801. The ECG data presentation also included an outlier analyses. Forest's PCS criteria for QTcB was ≥500msec. They did not explore outliers for changes from baseline. The following table summarizes Forest's mean change from baseline analyses of Group 1 ECG data.

FDA TABLE 22 Mean Changes from baseline for ECG parameters, for dementia studies 9605 and MEM-MD-02 and neuropathic pain studies NTI 9702 and NTI 9801

	Mean Change from Baseline		
	Memantine 20mg		Placebo
Dementia Studies			
Ventricular rate	2.6 (n=284)		2.0 (n=269)
QRS	0.3 (n=285)		-0.2 (n=269)
PR	-1.2 (n=275)		-1.6 (n=259)
QT	-4.7 (n=285)		-2.5 (n=269)
QTcB	2.8 (n=284)		3.4 (n=269)
Neuropathic pain studies	Memantine 20mg	Memantine 40mg	Placebo
Ventricular rate	0.2 (n=154)	0.9 (n=174)	0.5 (n=119)
QRS	0.2 (n=153)	-1.1 (n=173)	-1.7 (n=119)
PR	1.2 (n=146)	-3.4 (n=167)	1.3 (n=120)
QT	-0.3 (n=152)	-1.0 (n=174)	6.5 (n=120)
QTcB	0.1 (n=152)	2.1 (n=174)	8.0 (n=119)

From Forest Panels 44 and 45, SU pp.288-9.

Forest reported that for the Group 1 dementia studies 9605 and MEM-MD-02, the risk for a QTcB≥500msec was 0.3% (1/293) for the memantine group and 1.1% (3/269) for the placebo group. For the neuropathic pain trials, the risk for a QTcB≥500msec was 0.7%

(1/151) for the memantine 20mg group, 0 (0/174) for the memantine 40mg group, and 0.8% (1/119) for the placebo group (SU vol. 1.11, Panel 46, p.290).

FDA Analysis of Group 1 dementia QTcB data
Using the ECG datasets, I performed an outlier analysis by identifying the percentage of subjects that had QTcB ≥30msec increase from baseline and QTcB ≥60msec in dementia trials 9605 and MEM-MD-02. The placebo group had a slightly increased risk for these change outliers. I present those results in the following table.

FDA TABLE 23 Percentage of subjects with QTcB increase of ≥30msec and ≥60msec in dementia studies 9605 and MEM-MD-02

Change Outlier Criteria	Memantine	Placebo
QTcB ≥30msec	9.5% (27/284)	11.5% (31/269)
QTcB ≥60msec	0.7% (2/284)	2.9% (8/269)

Since the ECGs from study 9605 were measured by eResearch using a standardized approach, I used the submitted ECG electronic data sets to analyze these data separately. I summarize those results below.

FDA TABLE 24 Mean change from baseline for selected ECG parameters for study 9605

	Mean Change from Baseline	
	Memantine 20mg	Placebo
Ventricular rate	4.0 (n=99)	3.2 (n=87)
QT	-7.8 (n=99)	-8.0 (n=87)
QTcB	3.1 (n=99)	0.5 (n=87)

In the following table, I provide an outlier analysis examining percentage of subjects that had QTcB ≥30msec increase from baseline and QTcB ≥60msec using the data from study 9605. No subjects had a QTc ≥500msec in this study.

FDA TABLE 25 Percentage of subjects with QTcB increase of ≥30msec and ≥60msec in dementia studies 9605

Change Outlier Criteria	Memantine	Placebo
QTcB ≥30msec	14.1% (14/99)	5.7% (5/87)
QTcB ≥60msec	(0/99)	2.3% (2/87)

4.7 Special Safety Issues
Ophthalmologic Effects
To further evaluate the significance of the animal findings of corneal opacities, the memantine development program included ophthalmologic exams in the 28 week randomized controlled trial 9001-9202 and its open label extension (SU vol. 1.11, p. 341). I reviewed the results from these exams as presented in the study report for 9001-9202 (NDA vol. 150, p.93).

Methods
Ophthalmologic testing included visual acuity, and slit lamp examination. For cornea and lens examination, subjects were classified as clear or unclear. A subject was classified as

clear if one or both eyes were clear, and unclear if both eyes were unclear. In a separate analysis, those subjects with at least one unclear side were examined and classified as worsening or not worsening after 28 weeks. Worsening for cornea unclear was defined as worsening of corneal clouding, superficial punctuate keratitis, striate keratopathy, edema, or other. For lens, worsening was defined as worsening cataract or other.

Findings
Four hundred and forty-eight subjects in this study underwent an ophthalmologic exam and were included in the final analysis. At baseline, 77% of placebo and 84% of memantine subjects were classified as cornea clear. At week 28, 78% of placebo and 81% of memantine subjects were classified as cornea clear. The lens was classified as clear for 27% of placebo subjects and 31% of memantine subjects at both baseline and week 28.

For subjects with one or both corneas unclear at baseline, examiners classified 10% of placebo subjects as worsening during the 28 weeks compared to 5% of the memantine unclear cornea subjects. For subjects with one or both lenses unclear at baseline, 7% of both placebo and memantine subjects were classified as worsening after 28 weeks.

4.8 Drug Demographic Interactions
Forest further explored memantine's adverse event profile data in the Group 1 double blind placebo controlled dementia trials by stratifying on the demographic variables of sex, age, and race. Forest reported that information on race was not captured for all subjects in these studies (16% of subjects in did not have race recorded) and for those with race identified, 80% were Caucasian (SU vol. 1.11, p.194) limiting the usefulness of these race-stratified analyses. I will restrict my review to the sex and age stratified analyses.

4.8.1 Sex
Double Blind Placebo Controlled Dementia Trials, Deaths by Sex
When stratified by sex, males had a higher risk of death (memantine 2.7%, 11/402, placebo 2.9%, 12/418) than females (memantine 1.3%, 7/538, placebo 1.8%, 9/504) but the relative risks when comparing memantine to placebo male (RR 0.9) and female (RR 0.7) treated subjects were similar. There were too few deaths in these studies to allow reliable sex-stratified analyses of cause specific mortality risks (SU table 4.2.1C).

Double Blind Placebo Controlled Dementia Trials, SAEs by Sex
The SAE risks were slightly higher among females (placebo 15.1%, 76/504, memantine 14.1%, 76/538) compared to males (placebo 14.1%, 59/418, memantine 12.7%, 51/402) in these studies. The relative risks when comparing memantine to placebo male (RR 0.9) and female (RR 0.9) treated subjects were similar. I did not find strong evidence of differences in relative risks for specific SAEs when stratified by sex (SU table 4.5.1C).

Double Blind Placebo Controlled Dementia Trials, AEs leading to Discontinuation by Sex
The risk for discontinuation due to AE was similar for memantine and placebo treated males (11.7%, 47/402, 11.5%, 48/418, respectively) and placebo treated females (11.5%,

58/504) and was slightly lower for memantine treated females (8.9%, 48/538). I did not find strong evidence of differences in relative risks for specific AEs leading to discontinuation when stratified on sex (SU table 5.2.1C).

Double Blind Placebo Controlled Dementia Trials, Treatment Emergent AEs by Sex
A slightly higher percentage of male memantine treated subjects had one or more treatment emergent AE (72.4%, 291/402) than placebo treated males (65.6%, 274/418) while the percentage of female memantine (69%, 371/538) and placebo (69.4%, 350/504) treated subjects with one or more AE were similar. When examining specific treatment emergent adverse events, there were several AEs where the relative risk varied by sex but these differences were generally based on small numbers of subjects in each group. I provide a list of those events in the following table.

FDA TABLE 26 AEs from Double Blind Placebo Controlled Dementia Trials where the relative risk was >2 in at least one of the sex stratified groups and there was at least a two fold difference when comparing the relative risks between groups

Event	Risk in Females		RR_F	Risk in Males		RR_M
	Memantine (n=538)	PBO (n=504)		Memantine (n=402)	PBO (n=418)	
Rash	1.3% (7)	0.2% (1)	6.5	1.5% (6)	1.4% (6)	1.1
Leg Pain	1.1% (6)	0.2% (1)	5.5	0.5% (2)	1.0% (4)	0.5
Asthenia	2.4% (13)	1.0% (5)	2.4	0.5% (2)	1.2% (5)	0.4
Fever	1.3% (7)	0.6% (3)	2.2	1.0% (4)	1.9% (8)	0.5
Hallucination	3.0% (16)	1.4% (7)	2.1	2.0% (8)	1.9% (8)	1.0
Eye abn.‡	0.2% (1)	0.4% (2)	0.5	1.2% (5)	0.2% (1)	6.0
Hyperuricemia	0.2% (1)	0.2% (1)	1.0	1.2% (5)	0.2% (1)	6.0
Basal Cell Carc.	0.2% (1)	0.2% (1)	1.0	1.0% (4)	0.2% (1)	5.0
Fatigue	1.9% (10)	1.8% (9)	1.1	3.2% (12)	0.7% (3)	4.6
Cataract	1.3% (7)	2.0% (10)	0.7	2.5% (10)	0.7% (3)	3.6
Dyspepsia	0.9% (5)	1.2% (6)	0.8	2.2% (9)	0.7% (3)	3.1
Speech disorder*	0.2% (1)	0.6% (3)	0.3	1.5% (6)	0.5% (2)	3.0

From SU Table 6.1.1C.
*Includes investigator terms such as slurred speech, incoherent speech, dysarthria, logorrhea, fabrication, and echolalia
‡Includes investigator terms such as funny eye, macular degeneration, arcus senilis, band keratopathy, iris atrophy, microcyst, and worsened nuclear sclerosis

4.8.2 Age
For their age stratified analyses, Forest used the following age groupings: <65 years, 65-74 years, 75-84 years, and ≥85 years.

Double Blind Placebo Controlled Dementia Trials, Deaths by Age
The mortality risks varied slightly in the different age groups, although the risks were based on small numbers of events in each group. In the table below, I provide the mortality risks by age groups and treatment.

FDA TABLE 27 Mortality risks by age groups and treatment, Double Blind Placebo Controlled Dementia Trials

<65years		65-74 years		75-84 years		≥85 years	
Memantine (n=76)	PBO (n=80)	Memantine (n=316)	PBO (n=273)	Memantine (n=438)	PBO (n=460)	Memantine (n=110)	PBO (n=109)
2.6% (2)	1.3% (1)	2.5% (8)	1.5% (4)	1.4% (6)	2.2% (10)	1.8% (2)	5.5% (6)

From SU Table 4.2.1D

There were too few deaths to allow for meaningful analysis of cause specific mortality stratified by age.

Double Blind Placebo Controlled Dementia Trials, SAEs by Age

The SAE risk for placebo treated subjects was greater than or equal to the SAE risk for memantine subjects for all age categories except for the ≥85 years age group, where the SAE risk among memantine subjects (23.6%, 26/110) was slightly higher than the placebo group (21.1%, 23/109). There were generally too few SAEs to allow for meaningful analysis of specific SAEs stratified by age (SU Table 4.5.1D).

Double Blind Placebo Controlled Dementia Trials, AEs leading to Discontinuation by Age

The discontinuation for AE risk for placebo treated subjects was greater than the discontinuation for AE risk for memantine subjects for all age categories except for the ≥85 years age group, where the risk for the memantine group (18.2%, 20/110) was slightly higher than the placebo group (16.5%, 18/109). There were generally too few AEs leading to discontinuation to allow for meaningful analysis of the specific event risks stratified by age (SU Table 5.2.1D).

Double Blind Placebo Controlled Dementia Trials, Treatment Emergent AEs by Age

In each of the age strata, a slightly higher percentage of memantine subjects reported one or more AE than placebo subjects. In the following table, I list AEs where the relative risk comparing memantine to placebo exceeded two and was at least two-fold greater than the relative risk in the other age strata. In selected cases where there were no events in the placebo group I counted one event to allow for a relative risk calculation. The result is an underestimation of the relative risk for memantine in such cases. These cases are identified by an asterisk in the table.

FDA TABLE 28 AE risks by age groups and treatment, Double Blind Placebo Controlled Dementia Trials

	<65 years			65-74 years			75-84 years			≥85 years		
AE	M (76)	P (80)	R R	M (316)	P (273)	R R	M (438)	P (460)	R R	M (110)	P (109)	R R
Hypo-aesthesia	0	1.3% (1)	0	1.3% (4)	0.4% (1)	3.3	0	0.2% (1)	0	0	0	0
Hypokinesia	0	0	-	0.6% (2)	0.4% (1)	1.5	1.1% (5)	0.2% (1)	5.5	2.7% (3)	1.8% (2)	1.5
Constipation	1.3% (1)	0	-	4.4% (14)	3.3% (9)	1.3	6.2% (27)	3.7% (17)	1.7	7.3% (8)	1.8% (2)	4.1

Dyspepsia	0	0	-	1.6% (5)	1.1% (3)	1.5	1.1% (5)	1.3% (6)	0.8	3.6% (4)	0.9% (1*)	4
Weight dec	1.3% (1)	0	-	1.3% (4)	0.4% (1)	3.3	0.9% (4)	1.1% (5)	0.8	1.8% (2)	1.8% (2)	1.0
Arthritis	0	0	-	0.9% (3)	0.4% (1)	3.3	0.7% (3)	0.7% (3)	1.0	0.9% (1)	0.9% (1)	1.0
Arthrosis	1.3% (1)	2.5% (2)	0.5	0.6% (2)	0.7% (2)	0.9	0.9% (4)	0.2% (1)	4.5	1.8% (2)	0.9% (1)	2.0
Back pain	6.6% (5)	1.3% (1*)	5.1	2.5% (8)	2.9% (8)	0.9	2.1% (9)	2.4% (11)	0.9	1.8% (2)	1.8% (2)	1.0
Asthenia	1.3% (1)	1.3% (1)	1.0	2.5% (8)	0.7% (2)	3.6	0.9% (4)	1.1% (5)	0.8	1.8% (2)	1.8% (2)	1.0
Fatigue	1.3% (1)	0	-	3.2% (10)	0.7% (2)	4.6	2.3% (10)	1.7% (8)	1.4	1.8% (2)	1.8% (2)	1.0
Malaise	0	0	-	0.3% (1)	0.7% (2)	0.4	0.9% (4)	1.1% (5)	0.8	1.8% (2)	0.9% (1)	2.0
Edema	0	0	-	1.3% (4)	0.4% (1)	3.3	0.9% (4)	1.7% (8)	0.5	2.7% (3)	1.8% (2)	1.5
Edema Peripheral	0	1.3% (1)	0	2.2% (7)	1.5% (4)	1.5	2.3% (10)	1.7% (8)	1.4	5.5% (6)	1.8% (2)	3.1
Cardiac failure	0	0	-	0.9% (3)	0.4% (1)	2.3	2.1% (9)	0.2% (1)	11	0.9% (1)	0.9% (1)	1.0
Ataxia	0	0	-	0.3% (1)	1.1% (3)	0.3	0.9% (4)	0.2% (1)	4.5	1.8% (2)	0.9% (1)	2.0
Myalgia	0	0	-	1.3% (4)	0.4% (1)	3.3	0.7% (3)	1.1% (5)	0.6	0.9% (1)	0.9% (1)	1.0
Clotting d/o	0	0	-	0.6% (2)	0.7% (2)	0.9	1.6% (7)	1.5% (7)	1.0	2.7% (3)	0.9% (1*)	3.0
Confusion	6.6% (5)	1.3% (1*)	5.1	4.7% (15)	5.5% (15)	0.9	7.1% (31)	5.2% (24)	1.4	6.4% (7)	2.8% (3)	2.3
Delusion	1.3% (1)	0	-	1.9% (6)	0.4% (1)	4.8	0.9% (4)	2.0% (9)	0.5	0.9% (1)	3.7% (4)	0.2
Hallucinat.	6.6% (5)	1.3% (1)	5.1	3.8% (12)	2.2% (6)	1.7	1.1% (5)	1.3% (6)	0.8	1.8% (2)	1.8% (2)	1.0
Coughing	3.9% (3)	5.0% (4)	0.8	4.4% (14)	4.8% (13)	0.9	3.0% (13)	2.8% (13)	1.1	6.4% (7)	0.9% (1)	7.1
Eye Abnormality	0	0	-	0	0	-	1.4% (6)	0.2% (1)	7.0	0	1.8% (2)	0

From SU Table 6.1.1D

In most of the cells in the above table, there are relatively few events and therefore these data do not necessarily provide strong evidence of effect modification by age.

4.9 Drug-Drug Interaction

Forest reported that they found no meaningful differences in adverse event frequencies when they compared memantine subjects taking concomitant medications to memantine subjects not taking those medications (SU vol. 1.11, p.300). Forest provided tables depicting the AE risks from the double blind placebo controlled dementia trials, stratified by the use of a medication from a category of concomitant medications. Forest's comparisons used the following groupings of concomitant medications:

antihypertensives, neuroleptics, antidepressants, sedatives, analgesics/NSAIDs, antacids, estrogens, diuretics, antiepileptics, anti-parkinsonian agents, blood glucose lowering drugs, antiarrhythmic agents, vasodilators used in cardiac disease, peripheral vasodilators, beta blockers, calcium channel blockers, ACE inhibitors and AII antagonists, cholesterol and triglyceride reducers, urinary antispasmodics, thyroid hormones, antibacterials, psychostimulants and nootropics, systemic antihistamines, gingko biloba, vitamin E, and donepezil.

In the following table I identify AEs occurring in at least 5% of memantine subjects taking a medication included in a specific concomitant medication category and where the relative risk compared to placebo subjects taking that medication is ≥2 and the relative risk is at least two-fold greater than the relative risk for subjects not taking a medication in that category. I exclude the following medication categories from consideration because there were less than 50 memantine subjects taking a medication from the category: antihypertensives, estrogens, antiepileptics, anti-parkinsonian, antispasmodics, psychostimulants, antihistamines, and gingko biloba.

FDA TABLE 29 AEs from Double Blind Placebo Controlled Dementia Trials where the relative risk was ≥2 among memantine subjects compared to placebo subjects in the concomitant medication group and the relative risk was at least a two fold greater when compared to the relative risk in the non-concomitant medication group

Event	Risk in Concomitant medication group		RR_C	Risk in Non Concomitant Medication Group		RR_{NC}
	Memantine	PBO		Memantine	PBO	
	Antacids			No Antacids		
	(n=117)	(n=107)		(n=823)	(n=815)	
Chest pain	5.1% (6)	0	-	0.9% (7)	0.9% (7)	1.0
Constipation	14.5% (17)	4.7% (5)	3.1	4.0% (33)	2.8% (23)	1.4
	Diuretics			No Diuretics		
	(n=187)	(n=168)		(n=753)	(n=754)	
Fall	8.6% (16)	4.2% (7)	2.0	4.2% (32)	5.7% (43)	0.7
Edema periph.	8.6% (16)	2.4% (4)	3.6	0.9% (7)	1.5% (11)	0.6
Dizziness	9.6% (18)	4.2% (7)	2.3	6.1% (46)	5.6% (42)	1.1
	ACEI/AII antagonist			No ACEI/AII antagonist		
	(n=141)	(n=132)		(n=799)	(n=790)	
Influenza sympt.	5.0% (7)	0.8% (1)	6.3	3.0% (24)	3.4% (27)	0.9
Headache	7.1% (10)	0	-	5.5% (44)	3.9% (31)	1.4
Constipation	8.5% (12)	2.3% (3)	3.7	4.1% (33)	4.8% (38)	0.9
Somnolence	5.7% (8)	2.3% (3)	2.5	2.5% (20)	2.5% (20)	1.0
	Cholesterol lowering			No Cholesterol lowering		
	(n=106)	(n=97)		(n=834)	(n=825)	
Fall	5.7% (6)	2.1% (2)	2.7	5.0% (42)	5.8% (48)	0.9
	Thyroid hormone			No Thyroid hormone		
	(n=76)	(n=59)		(n=864)	(n=863)	
Influenza sympt.	5.3% (4)	0	-	3.1% (27)	3.2% (28)	1.0
Edema periph.	5.3% (4)	1.7% (1)	3.1	2.2% (19)	1.6% (14)	1.4
Somnolence	5.3% (4)	1.7% (1)	3.1	2.8% (24)	2.5% (22)	1.1

	Antibacterials			No Antibacterials		
	(n=151)	(n=156)		(n=789)	(n=766)	
Dyspnea	7.9% (12)	2.6% (4)	3.0	0.9% (7)	0.7% (5)	1.3
	Donepezil			No Donepezil		
	(n=202)	(n=201)		(n=738)	(n=721)	
Confusion	7.9% (16)	2.0% (4)	4.0	5.7% (42)	5.3% (38)	1.1

From SU tables 10.2.1-10.29.1

4.10 Overdose

Forest reported that no cases of human overdose were identified during the memantine development program (SU vol. 1.11, p. 320). Forest provided a summary of a post marketing case of overdose from Germany. In the cited case, a 19 year old female attempted suicide by ingesting 70 to 80 tablets of memantine (up to 400mg) along with wine, two to three aspirin tablets, and two to three benproperine embonate tablets. Reported symptoms included ataxia, vertigo, nystagmus, restlessness approaching psychosis, and leg cramps. She was admitted to an ICU and discharged two days later (no information about hospital course). All symptoms were reported as resolved at 18 days after discharge.

4.11 Withdrawal

Forest submitted no studies designed specifically to evaluate withdrawal symptoms associated with discontinuation of memantine. In the group 1 dementia placebo controlled trials, two subjects had AEs of withdrawal syndrome and both events were reported in subjects following discontinuation of placebo. In the Group 1 open label dementia trials, one subject had an AE of withdrawal syndrome (investigator term "resistive to care"). No subjects in the neuropathic pain group 1 studies had an AE of withdrawal syndrome.

4.12 Drug Disease Interaction

Using data from Group 1 placebo controlled dementia studies, Forest explored AE risks in patients with the following conditions at baseline: hypertension, cerebrovascular disorder, and heart failure (SU tables 11.1-3). In general the relative risks comparing memantine and placebo treated subjects were similar for those with and without the diseases under consideration. There did not appear to be strong evidence of drug disease interaction for the considered diseases.

5. Review of Systems

In the following sections, I review the safety data by body system. Forest's presentations grouped their coded adverse event terms by body systems and I generally used the same groupings used by Forest. In some cases I grouped one or more related body system to facilitate the review and I noted when I used such groupings in the headings of those sections.

5.1 Cardiovascular

(CV, includes CV disorders, general, heart rate and rhythm disorders, and myo, endo, and pericardial disorders)

The dementia placebo controlled trials data did not suggest differences in risk for specific CV causes of death for memantine and placebo treated subjects, based on small numbers of events. The CV causes of death in memantine treated subjects were events that commonly occur in elderly patients and included cardiac failure, myocardial infarction, and cardiac arrest.

No CV SAEs occurred in ≥ 1% of subjects during the dementia placebo controlled or open label trials, and the CV SAEs reported in the open label dementia trials were similar to the CV SAEs reported in the dementia placebo controlled trials. Cardiac failure was the most frequently occurring CV SAE in the dementia placebo controlled trials with 0.7% (n=7) memantine subjects and 0.2% (n=2) placebo subjects reported with this SAE.

CV events did not commonly lead to discontinuation from the memantine trials and the dementia placebo controlled trials did not suggest differences in risk for discontinuation due to specific CV events.

With the exception of cardiac failure, the risks for specific treatment emergent CV AEs was similar for memantine and placebo treated subjects in the dementia placebo controlled trials. Memantine subjects more frequently experienced cardiac failure (1.4%, n=13) compared to the placebo subjects (0.3%, n=3) in the dementia placebo controlled trials. Hypertension was the only CV AE reported by more than 1% of subjects (2.5%, n=21) in the open label dementia trials.

Vital sign data did not support memantine related effects on either blood pressure or pulse. In the dementia placebo controlled trials, the mean changes for systolic BP, diastolic blood pressure, and risk for outliers for these parameters were similar for the memantine and placebo treated subjects (see above).

Forest's analyses of ECG data did not suggest memantine related effects on heart rate or cardiac repolarization.

5.2 Gastrointestinal
(GI, includes GI system disorders and liver and biliary system disorders)
In the placebo controlled and open label dementia trials there were two memantine subjects who died from GI related causes (ischemic colitis, diarrhea and dehydration).

GI SAEs were infrequently reported in the dementia placebo controlled trials. Constipation (memantine 0.4%, n=4, placebo 0.1%, n=1) was the most frequently reported GI SAE in these trials. None of the four constipation SAEs in memantine subjects resulted in megacolon or required surgical intervention. In the open label dementia trials, vomiting (0.5%, n=4) and abdominal pain (0.4%, n=3) were the only GI SAEs reported more than once.

GI AEs infrequently led to discontinuation from dementia placebo controlled or open label trials. Diarrhea and nausea (0.3%, n=3, each) were the only GI AEs leading to discontinuation of more than one memantine subject in the dementia placebo controlled

trials. Abdominal pain (0.2%, n=2) was the only GI AE leading to discontinuation of more than one memantine subject in the open label dementia trials.

In the dementia placebo controlled trials, constipation (memantine 5.3%, n=50 placebo 3%, n=28) and dyspepsia (memantine 1.5%, n=14 placebo 1% n=9) were the only GI AEs occurring in at least 1% of memantine subjects and at least 1.5 times as frequently compared to placebo. In the open label dementia trials, vomiting (2.9%, n=25), diarrhea (2.8%, n=24), constipation (2.5%, n=21), abdominal pain (1.9%, n=16), nausea (1.6%, n=14) and tooth disorder (1.1%, n=9) were the GI AEs reported for at least 1% of subjects.

The mean change and outlier analyses did not suggest memantine related changes in AST, ALT, or total bilirubin. Memantine subjects in the dementia placebo controlled trials did demonstrate an increase in mean ALP compared to placebo subjects but the ALP isoenzyme (i.e., liver vs. bone) is not known.

Forest reported no cases of acute hepatic failure in their ISS and safety update. Forest submitted one post marketing case of hepatic failure that resulted in death (described above).

While there were no cases of pancreatitis in the Group 1 studies, Forest reported three cases from ongoing studies (two memantine, one treatment blinded, described above). In one of the cases, the subject had elevated triglycerides at the time of the event and in the other two cases the events were attributed to cholelithiasis (cases described above).

5.3 Central and peripheral nervous system
(CPNS)

In the dementia placebo controlled trials, four memantine (0.4%) and six placebo subjects (0.7%) died and had a CPNS event listed as the cause of death. In the open label dementia trials, the CPNS events leading to death were cerebral hemorrhage (0.2%, n=2) and cerebrovascular disorder (investigator term CVA, 0.6%, n=5).

CPNS SAEs were infrequently reported in the dementia placebo controlled trials. The most frequent CPNS SAE in these trials was cerebrovascular disorder (memantine 1.0%, n=9, placebo 1.5%, n=14). In the open label dementia trials, cerebrovascular disorder (1.8%, n=15) and TIA (1.3%, n=11) were the CPNS SAEs reported for at least 1% of subjects.

CPNS AEs led to discontinuation of 3% (n=28) of memantine subjects and 3.5% (n=32) of placebo subjects in dementia placebo controlled trials. The most frequently reported CPNS AE leading to discontinuation among memantine subjects was cerebrovascular disorder (memantine 0.7%, n=7, placebo 1.1%, n=10). In the open label trials, cerebrovascular disorder was the only CPNS AE leading to discontinuation of more than 1% of subjects (1.2%, n=10).

In the dementia placebo controlled trials, headache (memantine 5.7%, n=54, placebo 3.4%, n=31) and hypokinesia (memantine 1.1%, n=10, placebo 0.4%, n=4) were the CPNS AEs that occurred in at least 1% of memantine subjects and at least twice as frequently compared to placebo. In the dementia open label trials, dizziness (5.1%, n=44), headache (4%, n=34), TIA (3.7%, n=32), cerebrovascular disorder (2.7%, n=23), gait abnormal (2.6%, n=22), and speech disorder (1.2%, n=10) were the CPNS AEs reported for more than 1% of subjects.

Forest reported a CPNS SAE from a Japanese clinical trial (described above). A clear diagnosis was not offered but the differential included encephalopathy, encephalitis, and seizures.

5.4 Respiratory System
(RS)
In the dementia placebo controlled trials, the percentage of memantine subjects who died from a RS event (0.6%, 6/940) was similar to the percentage of placebo subjects who died from a RS event (0.7%, 6/922). The RS causes of death in these studies were apnea, bronchitis, and pneumonia. In the dementia open label studies, pneumonia (1.1%, n=9) was the only RS cause of death reported for more than one subject.

In the dementia placebo controlled trials, the risk for overall RS SAEs (memantine 2%, n=19, placebo 2.1%, n=19) and specific RS SAEs was similar in the two treatment groups. Pneumonia was the only RS SAE occurring in more than two memantine subjects in these studies (memantine 0.9%, n=8, placebo 1%, n=9). In the open label dementia studies, pneumonia (1.6%, n=14), bronchitis (1.1%, n=9), and dyspnea (0.7%, n=6) were the RS SAEs reported by more than one subject.

RS AEs infrequently led to discontinuation from the dementia placebo controlled trials and pneumonia was the only RS AE leading to discontinuation of more than one memantine subject (memantine 0.5%, n=5, placebo 0.3%, n=3). In the open label dementia trials, pneumonia was the only RS AE leading to discontinuation of at least 1% of subjects (1.2%, n=10).

In the dementia placebo controlled trials, the risk for overall RS AEs (memantine 14%, n=132, placebo 13.2%, n=122) was similar in the treatment groups. Dyspnea was the only RS AE occurring in at least 1% of memantine subjects and at least twice as frequently compared to placebo subjects (memantine 2%, n=19, placebo 1%, n=9). In the dementia open label studies, bronchitis (4.8%, n=41), coughing (2.9%, n=25), dyspnea (2.2%, n=19), pneumonia (1.9%, n=16), and upper respiratory tract infection (1.3%, n=11) were the RS AEs reported by at least 1% of subjects. The open label studies included an AE coded to the term pulmonary fibrosis (described above) but this event appeared to be a physical exam finding of focal lung consolidation in the right base.

5.5 Psychiatric
In the dementia placebo controlled trials, no memantine subjects died and had a psychiatric cause listed as the cause of death. Anorexia and somnolence (n=1, each) were the psychiatric causes of death reported in the dementia open label studies. Both of these

events occurred in the same subject, who also had respiratory insufficiency listed as the cause of death.

Psychiatric SAEs were reported for 2.9% (n=27) of memantine subjects and 3.4% (n=31) of placebo subjects in the dementia placebo controlled trials. Confusion (memantine 1.6%, n=15, placebo 0.9%, n=8) was the only psychiatric AE reported for more than 1% of memantine subjects in these trials. No specific psychiatric SAEs were reported for at least 1% of subjects in the dementia open label trials.

Psychiatric AEs more commonly led to discontinuation of placebo subjects (5.3%, n=49) than memantine subjects (3.8%, n=36) in the dementia placebo controlled trials. Agitation (memantine 1.2%, n=11, placebo 2%, n=18) and confusion (memantine 1.2%, n=11, placebo 1.1%, n=11) were the only psychiatric AEs leading to discontinuation of more than 1% of memantine subjects in these studies. In the open label dementia studies, no psychiatric AEs led to discontinuation of more than 1% of subjects.

Psychiatric AEs were reported for 26.4% (n=248) of memantine subjects and 27.1% (n=250) of placebo subjects in the dementia placebo controlled trials. No psychiatric AE occurred in at least 1% of memantine subjects and at least twice as frequently compared to placebo subjects. In the open label dementia trials, agitation (6.9%, n=59), confusion (4.7%, n=40), insomnia (3.5%, n=30), depression (2.9%, n=25), somnolence (2.8%, n=24), aggressive reaction (2%, n=17), anorexia (1.6%, n=14), anxiety (1.4%, n=12) and hallucination 1.3% (n=11) were the psychiatric AEs reported by more than 1% of subjects.

5.6 Musculoskeletal
(MS)
No subjects in dementia placebo controlled trials or dementia open label trials died and had a MS cause listed as the cause of death.

In the dementia placebo controlled trials, arthralgia and back pain (n=1, each) were the only MS SAEs in memantine subjects. In the open label dementia trials, no MS SAE was reported for more than one subject.

In the dementia placebo controlled trials, arthralgia and back pain (n=1, each) were the MS AEs leading to discontinuation of memantine subjects. No MS AEs led to discontinuation of subjects in the open label dementia trials.

MS AEs were reported by 8% (n=75) memantine subjects and 6.7% (n=62) placebo subjects in the dementia placebo controlled trials. No MS AEs were reported by at least 1% of memantine subjects and twice as frequently compared to placebo subjects in these trials. In the open label dementia trials, arthralgia (2.2%, n=19), back pain (1.5%, n=13), and myalgia (1.3%, n=11) were the MS AEs reported by at least 1% of subjects.

There were no cases of rhabdomyolysis reported in the NDA safety database.

5.7 Metabolic and Nutritional
(MN)
No subjects in dementia placebo controlled trials died and had a MN cause listed as the cause of death. In the open label dementia trials one subject died and had a MN cause (dehydration) listed as the cause of death.

In the dementia placebo controlled trials, 0.6% (n=6) of memantine subjects and 0.3% (n=3) placebo subjects had a MN SAE. Dehydration (memantine 0.4%, n=4, placebo 0.1%, n=1) was the only MN SAE reported for more than 1 memantine subject in these trials. In the open label dementia trials, dehydration (0.4%, n=3) was the only MN SAE reported for more than 1 memantine subject.

Six memantine (0.6%) and 1 placebo (0.1%) subjects discontinued from dementia placebo controlled trials for MN AEs. Dehydration was the only MN AE leading to the discontinuation of more than one memantine subject from these trials (memantine 0.4%, n=4, placebo n=0). In the open label trials, no MN AE led to the discontinuation of more than one subject.

ALP increased (memantine 1%, n=9 placebo 0.5%, n=2) was the only MN AE occurring in at least 1% of memantine subjects and at least twice as frequently compared to placebo subjects in dementia placebo controlled trials. No MN AEs were reported for more than 1% of subjects in open label dementia trials.

5.8 Urological Reproductive
(UR, includes Urinary System, Reproductive Male, Female)
In the dementia double blind studies and open label studies, no subjects died and had a UR cause listed as the cause of death.

Urinary tract infection (memantine 0.5%, n=5, placebo 0.5%, n=5) and urinary retention (memantine 0.3%, n=3 placebo 0.2%, n=2) were the UR SAEs reported for more than one memantine subject in the dementia placebo controlled trials. In open label dementia trials, urinary tract infection (0.7%, n=6), urinary retention (0.5%, n=2) and prostatic disorder (0.5%, n=2, investigator terms "prostata hypertrophy and resection", "acute prostatis") were the UR SAEs reported for more than one subject.

In the dementia placebo controlled trials, no UR events led to discontinuation of at least 1% of memantine subjects. In the open label dementia trials, no UR events led to discontinuation of more than one subject. One subject discontinued from a dementia open label trial for renal function abnormal (case described above).

In the dementia placebo controlled trials, prostatic disorder was the only AE reported by at least 1% of memantine subjects and at least twice as frequently compared to placebo subjects (memantine 1.2%, n=5, placebo 0). In these studies, three memantine subjects had AEs of renal function abnormal (memantine 0.3%, n=3, placebo 0.3%, n=3) and no memantine subjects had an AE of acute renal failure. In open label dementia trials, urinary tract infection (5.6%, n=48), moniliasis (1.2%, n=5), micturition frequency

(1.1%, n=9), and prostatic disorder (1%, n=4) were the UR events reported for more than 1% of subjects. No subjects in the open label dementia studies experienced acute renal failure and 3 subjects (0.4%) had an AE of renal function abnormal.

Analysis of the creatinine and BUN mean change from baseline and outliers did not suggest meaningful differences for these parameters when comparing the memantine and placebo treated subjects in the group 1 trials.

5.9 Skin and Appendages
In the dementia double blind studies and open label studies, no subjects died and had a skin related cause listed as the cause of death.

Skin ulceration (n=1, described above, decubitus ulcer) was the only skin related SAE reported for a memantine subject in the dementia placebo controlled trials. In the dementia open label trials there were two skin related SAEs, one subject had a cellulitis SAE and one had a rash SAE (described above, herpes zoster).

No skin related AEs led to discontinuation of more than one memantine subject in the dementia placebo controlled trials. One subject from the dementia open label studies discontinued for a skin related AE (cellulitis).

In the dementia placebo controlled trials, rash (memantine 1.4%, n=13, placebo 0.8%, n=7) was the only skin related AE reported for at least 1% of memantine subjects. In the open label dementia studies, rash (1.2%, n=12) was the only skin related AE reported for at least 1% of subjects. There were no AEs suggestive of TEN, Stevens Johnson Syndrome, or Erythema multiforme in the dementia studies.

Forest identified two post marketing reports coded as epidermal necrolysis, but provided no additional information about these cases.

5.10 Vascular
No memantine subjects in the dementia placebo controlled trials died and had a vascular related cause listed as the cause of death. In the open label dementia studies, one subject died and had aneurysm ruptured listed as the cause of death.

Thrombophlebitis deep (memantine 0.6%, n=6, placebo 0) and embolism pulmonary (memantine 0.2%, n=2, placebo 0) were vascular SAEs reported by more than one memantine subject in the dementia placebo controlled trials (one of the subjects with an SAE of thrombophlebitis deep also had an SAE of pulmonary embolism). In addition one memantine subject each had SAEs of phlebitis, and thrombophlebitis (the subject with the SAE of phlebitis also had an SAE of pulmonary embolism). In the open label dementia trials, there were two thrombophlebitis deep SAEs (0.2%), one pulmonary embolism SAEs (0.1%) and one thrombophlebitis SAE.

In the dementia placebo controlled trials, two memantine subjects discontinued for thrombophlebitis deep (memantine 0.2%, n=2, placebo 0), and one for phlebitis

(memantine 0.1%, n=1, placebo 0). In the dementia open label trials, one subject discontinued for aneurysm ruptured and one for thrombophlebitis deep (0.1%, n=12, each).

In the dementia placebo controlled trials, thrombophlebitis deep (memantine 0.7%, n=7, placebo 0), phlebitis (memantine 0.4%, n=4, placebo 0.1%, n=1), embolism pulmonary (memantine 0.2%, n=2, placebo 0.1%, n=1) were the AEs reported for more than one memantine subject. In addition, one memantine (0.1%) and no placebo subjects had a thrombophlebitis AE. In the dementia open label trials, thrombophlebitis deep (0.2%, n=2) thrombophlebitis (0.2%, n=2) and aneurysm (0.2%, n=2) were the vascular AEs reported for more than one subject. In addition, one subject had an AE of pulmonary embolism in these trials.

I reviewed and summarized all of the memantine treated group 1 dementia trial cases of phlebitis, thrombophlebitis, thrombophlebitis deep and pulmonary embolism. I include those summaries as an attachment to this review. In some cases, patients had predisposing conditions (immobility, cancer or suspected cancer, recent fractures) and in other cases there were no identified predisposing conditions other than age. There were no events of phlebitis, thrombophlebitis, thrombophlebitis deep and pulmonary embolism in the neuropathic pain trials (n=391 memantine treated patients).

5.11 Hematological
(Includes platelet, bleeding, and clotting disorders, RBC disorders, and White cell and RES disorders)
No subjects in dementia placebo controlled or open label studies died and had a hematological related cause listed as a cause of death.

In the dementia placebo controlled trials one memantine subject had a hematological related SAE (anemia, due to an occult GI bleed, see above). In the dementia open label trials no specific hematological SAEs occurred more than once.

One memantine treated subject discontinued for a hematological AE (anemia, described above) during the dementia placebo controlled trials. In the dementia open label trials, one subject discontinued for hematoma and one for anemia.

In the dementia placebo controlled trials there were no hematological AEs that occurred in at least one percent of memantine treated subjects. In the dementia open label trials, anemia was the only hematological AE reported for at least 1% of subjects (1.2%, n=10). There were no hematological AEs suggestive of aplastic anemia or agranulocytosis in the submitted database. Forest noted one post marketing report of aplastic anemia in a line listing that did not provide details about the event.

5.12 Special Senses disorders
(includes Hearing and vestibular disorders, Special senses other, and vision disorders)
No subjects in dementia placebo controlled or open label studies died and had a Special senses related cause listed as a cause of death.

In the dementia placebo controlled studies, one memantine subject had an eye pain SAE (suspected conjunctivitis) and one had a cataract SAE (planned surgery). Cataract (0.4%, n=3) was the only Special senses SAE reported more than once in the open label dementia studies. One subject in the open label dementia studies had an SAE of blindness (noted above).

Two memantine subjects discontinued from dementia placebo controlled trials for Special senses AEs (both tinnitus). Two subjects discontinued from open label dementia studies for Special senses AEs (blindness, same subject noted above, and conjunctival hemorrhage).

Cataract (memantine 1.8%, n=17, placebo 1.4%, n=13) and vision abnormal (subsumed a variety of terms including decreased visual acuity, eye strain, and blurred vision, memantine 1.2%, n=11, placebo 1.0%, n=9) were the Special senses AEs occurring in at least 1% of memantine treated subjects in the dementia placebo controlled trials. Cataract (3.9%, n=33), vision abnormal (2.8%, n=24), eye abnormality (1.9%, n=16), macula lutea degeneration (1.4%, n=12) were the Special senses AEs reported for at least 1% of subjects in dementia open label trials.

There did not appear to be differences in risk for cataract or lens abnormalities between memantine and placebo treated subjects in study 9202, which included ophthalmologic examinations.

5.13 Endocrine

No subjects in dementia placebo controlled or open label studies died and had an Endocrine related cause listed as a cause of death.

In the dementia placebo controlled trials there two Endocrine SAEs in the memantine treated subjects (hyperthyroidism and hypothyroidism). There were no reported Endocrine SAEs in the dementia open label trials.

In the dementia placebo controlled trials, one memantine subject discontinued with an Endocrine AE (TSH increased). No subjects discontinued from dementia open label trials for Endocrine AEs.

No Endocrine AEs were reported more than once for memantine treated subjects in dementia placebo controlled trials. No Endocrine AEs were reported during dementia open label studies.

5.14 Body as a Whole

Forest reported one Body as a whole category death (sudden death) in memantine treated subjects from the dementia placebo controlled trials. In the dementia open label trials Forest reported the following Body as a whole category deaths: condition aggravated, inflicted injury*, sepsis, and sudden death (n=1 each).

*Preferred term that subsumes injuries, some resulting from falls.

Inflicted injury (memantine 1.1%, n=10, placebo 1.7%, n=16) was the only Body as a whole SAE reported by at least 1% of memantine treated subjects. In the dementia open label trials, fall (1.2%, n=10) was the only Body as a whole SAE reported for at least 1% of subjects.

No Body as a whole category AEs led to discontinuation of at least 1% of memantine subjects in the dementia placebo controlled or open label trials.

In the dementia placebo controlled trials, fall (memantine 5.1%, n=48, placebo 5.4%, n=50), fatigue (memantine 2.4%, n=23, placebo 1.3%, n=12), asthenia (memantine 1.6%, n=15, placebo 1.1%, n=10), chest pain (memantine 1.4%, n=13, placebo 0.8%, n=7), and fever (memantine 1.2%, n=11, placebo 1.2%, n=11) were the body as a whole category AEs reported for at least 1% of memantine subjects. In the dementia open label trials the following body as a whole category AEs were reported for more than 1% of subjects: fall (5.4%, n=46), inflicted injury (5.3%, n=45), influenza like symptoms (3.6%, n=31), malaise (1.9%, n=16), fatigue (1.8%, n=15), pain (1.5%, n=13), chest pain (1.4%, n=12), edema (1.3%, n=11), and edema peripheral (1.1%, n=9).

6. Discussion

Forest adequately captured and described safety data during the memantine development program Group 1 studies. The Group 1 memantine studies appear to have been appropriately designed to capture treatment emergent adverse events and other safety data. The coding of adverse events generally appeared acceptable, with few instances of splitting similar adverse events to different terms and rare instances of incorrect coding. The results of the coding process should have allowed an accurate depiction of memantine's adverse event profile.

Forest appears to have adequate numbers of subjects exposed, and in their Group 1 studies, subjects were exposed to the memantine dose intended for use. The overall number of individuals exposed to memantine exceeds ICH guidelines. The Group 1 studies generally used a memantine dose of 20mg/day, the dosage that Forest intends to recommend for treatment of Alzheimer's disease. As with most NDA safety databases, based on the number of subjects exposed in Group 1 studies, there was limited power to detect infrequent drug related adverse events.

While most of the Group 1 safety data included subjects with dementia, only a subset of these dementia subjects had Alzheimer's disease diagnoses, the intended indication for memantine. For all Group 1 studies, 27.2% (476/1,748) of memantine exposed subjects had Alzheimer's disease while the remainder had vascular dementia. For dementia trial subjects exposed for at least 24 weeks, 32% (276/862) had Alzheimer's disease and for those exposed for at least one year, 17% (46/277) had Alzheimer's disease.

The age distribution was similar for subjects with different dementia diagnoses but there were differences in the percentages of males and females when stratified by dementia diagnosis. The age mean, median, and range for the Alzheimer's disease and vascular dementia subjects were similar. Approximately two-thirds of subjects with an

Alzheimer's disease diagnosis were female while there was an equal distribution of males and females with a vascular dementia diagnoses.

Despite the sex distribution differences for the Alzheimer's and vascular dementia groups in the dementia Group 1 placebo controlled studies, Forest's analyses of safety data that stratified by dementia diagnoses showed similar results, suggesting that pooling of the safety data was appropriate. When adverse event risks and other safety data were stratified by dementia diagnosis, there did not appear to be meaningful differences by dementia diagnosis.

The primary safety data AE analyses predominately come from a population of patients with moderate to severe dementia, a group that likely has difficulty verbalizing complaints. The impact of difficulties in verbalizing complaints on the observed AE risks is not completely clear. Decreased reporting would likely only affect the observed risks for AEs, and not likely impact risk estimates for cause specific deaths, SAEs and discontinuation risks, since these events require verification and diagnosis by the investigator. For the observed AE risks, one might expect that dementia may result in reduced reporting of adverse events, and therefore in decreased capture of events. One might also speculate that if memantine is effective, those subjects treated with active drug in the controlled trials might improve and therefore be more able to report complaints compared to placebo treated subjects. In this case, observed differences in risk might reflect patients' improved ability to communicate complaints rather than a drug related adverse effect. AE risks from the neuropathic pain trials provide additional information in a population not expected to have difficulty communicating complaints. The overall AE risks were slightly higher in the neuropathic pain trials (memantine 76%, placebo 75%) compared to the dementia trials (memantine 70%, placebo 68%). The AEs identified as occurring commonly among memantine subjects and more frequently compared to placebo subjects were generally similar for the dementia and neuropathic pain study populations providing some assurance about the validity of the observed AE risks in the dementia trials.

In the Group 1 dementia placebo controlled trials, memantine was not associated with increased mortality risk compared to placebo. The causes of death reported during dementia trials were causes expected in an elderly population. Forest did not report any clusters of unusual causes of death. The database included none of the following causes of death: acute hepatic failure, acute renal failure, serious skin reactions, rhabdomyolysis, pancreatitis, or hematological dyscrasias.

Memantine was not associated with an overall increased risk of SAEs in the Group 1 placebo controlled dementia trials. For a few specific SAEs (ex. cardiac failure, thrombophlebitis deep) there were numerically higher risks for memantine subjects compared to placebo subjects, but these observations are based on a small number of events and therefore do not provide strong evidence of a drug related effect. No specific SAEs were reported by at least 2% of subjects in group 1 open label trials, and the SAEs reported by at least 1% of subjects were cerebrovascular disorder, pneumonia, TIA, fall, bronchitis, and inflicted injury. The Group 1 studies safety database did not include SAEs

of acute hepatic failure, acute renal failure, serious skin reactions, rhabdomyolysis, pancreatitis, or hematological dyscrasias.

Forest reported three pancreatitis SAEs in ongoing studies (two memantine, one blinded treatment), two cases associated with cholelithiasis and one case associated with elevated triglycerides. Forest reported four cases of acute renal failure SAEs from ongoing studies, and for three cases, the treatment assignment remains blinded.

Memantine was not associated with an overall increased risk of discontinuing from Group 1 placebo controlled dementia trials for AEs. Based on a small number of events, there did not appear to be strong evidence of an increased risk for discontinuing for specific AEs in the memantine group compared to the placebo group in the Group 1 dementia placebo controlled trials. Cerebrovascular disorder and pneumonia (1.2%, 10/856 each) were the only AEs leading discontinuation reported for more than 1% of dementia open label study subjects. No memantine treated subjects discontinued from Group 1 dementia trials for events suggestive of hepatic failure, renal failure, rhabdomyolysis, pancreatitis, or serious rash.

Several common treatment emergent adverse events occurred more frequently among memantine subjects compared to placebo in Group 1 dementia placebo controlled trials, but only pain and dyspnea occurred in at least 1% of memantine subjects and at least twice as commonly compared to placebo. The neuropathic pain trials, which used two doses of memantine (20mg, 40mg/day) provided evidence of a potential dose response for the following AEs that also occurred more commonly among memantine subjects in the dementia trials: dizziness, confusion, constipation, and pain.

The Group 1 dementia controlled trials database included a numerical imbalance for selected, potentially related, vascular AEs but there does not appear to be strong evidence that these events were related to memantine at this time. Specifically, there were seven AEs coded as thrombophlebitis deep among memantine subjects and none for placebo subjects. Additionally, there was one thrombophlebitis event and four phlebitis events among memantine subjects and no thrombophlebitis and two phlebitis events among placebo subjects. There were two events coded to pulmonary embolism for memantine subjects and one for placebo subjects. The patient data for the memantine subjects with these events noted that some subjects had predisposing factors such as cancer or immobility while others had no identified predisposing factors. There did not appear to be strong evidence of increased risk among memantine subjects for other AEs related to thrombosis such as myocardial infarction, cerebrovascular disorder (subsumed CVAs or TIAs). In the neuropathic pain trials there were no thrombophlebitis deep, thrombophlebitis, phlebitis, or pulmonary embolism AEs listed in either treatment group. While there is a slight imbalance in the risk for thrombotic/phlebitic AEs, this observation is based on a small number of events, is not supported by observations in other body systems (cardiovascular, CNS) and is not supported by randomized controlled trial data in other populations (neuropathic pain).

Eye examination results from study 9202 and adverse event data from the Group 1 studies did not support increased risk of eye toxicity with memantine. Investigators performed eye examinations during study 9202 to explore the relationship between memantine and eye toxicity, particularly corneal and lens changes, that were signaled by animal studies findings (corneal epithelium thickening and endothelial vacuolization). Forest felt that the animal eye findings reflected abnormal local drug storage due to saturated excretion mechanisms and were not clinically relevant. In study 9202, eye exams, which included slit lamp examinations, were performed on over 400 patients. There did not appear to be differences by treatment in the percentage of patients who had clear corneas or lenses at baseline and then at end study. There did not appear to be differences by treatment in the percentage of subjects with abnormal results at baseline that worsened during treatment. In the open label phase, there did not appear to be large increases in the number of patients with abnormalities at the end of study. The eye exam results from study 9202 suggest that memantine exposure is not associated with large increases in risk for lens or cornea abnormalities in a large proportion of users. The Group 1 dementia and neuropathic pain studies adverse event data did not support differences in risk by treatment for reported eye-related adverse events. Additional eye exam results will become available in the future since memantine use is currently being studied in patients with glaucoma. Forest should forward any new information collected from these studies as it becomes available.

Forest submitted no special analyses or neurological testing results to evaluate the potential for neurological toxicity with memantine as signaled by the animal findings of Olney-type lesions with NMDA antagonists and memantine. Aside from dizziness (memantine 6.8%, placebo 5.3%) and headache (memantine 5.7%, placebo 3.4%), the AE data did not suggest remarkable differences in risk by treatment for specific neurological findings by treatment in Group 1 dementia placebo controlled trials. The trials did not include specific neurological examinations or imaging studies to look for evidence of neurological toxicities and no brain section autopsy data were identified or summarized. Forest reported a nervous system SAE from an ongoing study that included encephalopathy, tremors, and possible seizures. The diagnosis was not clearly stated in the narrative provided by Forest. There did not appear to be similar cases in the NDA or safety update submissions. Forest should provide additional information for this case as it becomes available.

While the development program database did not suggest an association between memantine and serious skin AEs, Forest identified two post marketing AE reports of epidermal necrolysis. Forest provided no additional information about these cases. The reporting rate for epidermal necrolysis of 5/1,000,000 person years (2/400,000 person years) exceeds an estimate of the background rate of toxic epidermal necrolysis of 0.4 to 1.2/1,000,000 person years[1].

Forest should attempt to collect additional information about these cases of epidermal necrolysis including confirmation of the diagnosis, and the use of other suspect medications.

[1]Roujeau JC, Kelly P, et al, Medication Use and the Risk of Stevens-Johnson Syndrome or Toxic Epidermal Necrolyis, N Engl J Med, 1995;333:1600-7.

Neither the lab data nor the AE data supported an association between memantine and hematological toxicity but Forest did note one post marketing report of aplastic anemia. Forest should attempt to obtain details about this case.

Forest lab data analyses demonstrated a mean ALP increase for memantine and not placebo subjects, but no indication of notable differences by treatment for other studied laboratory parameters. In the Group1 dementia placebo controlled trials, the memantine treated subjects experienced a mean increase in ALP of 7.4 compared to a mean decrease of -0.12 in the placebo group. Two memantine and no placebo subjects in these trials had PCS outliers for ALP. A large part of the difference in ALP mean change seemed to be driven by five memantine subjects. A review of the safety data for these subjects did not suggest a single specific explanation for the ALP increases as one subject had Paget's disease, one cholelithiasis and another a hepatic neoplasm. A review of the mean ALP by study week in study NTI 9801 (neuropathic pain) did not suggest differences in ALP by treatment.

There did not appear to be a signal of memantine related hepatic toxicity based on analyses of transaminase and total bilirubin lab data. There were no cases of acute liver failure in the NDA database. Forest reported one post marketing case of liver failure resulting in death in 400,000 person years of use. Forest should continue to monitor post marketing reports for additional cases of liver failure in patients treated with memantine.

The vital sign data did not support that memantine is associated with changes in heart rate or blood pressure. The observed vital sign mean changes were relatively small and similar for the memantine and placebo subjects in the Group 1 placebo controlled trials. There were no remarkable differences in PCS outliers by treatment in these studies. Two clinical pharmacology trials that measured supine and standing blood pressures did not suggest orthostatic blood pressure changes with memantine; however, there was no description of the blood pressure measurement methodology, and therefore we cannot fully evaluate these results.

Analyses of ECG data did not suggest memantine related effects on cardiac reporlarization, although the submitted analyses were based on a review of ECGs from a subset of the placebo controlled trials, and not all interval measurements were made using acceptable methodology. Forest did not perform clinical pharmacology studies in humans to evaluate the effect of memantine on cardiac repolarization. The human ECG data come from a subset of the Group 1 placebo controlled trials. These trials included a single baseline and a single end study ECG. By today's standards, this approach would not be considered optimal for evaluating repolarization effects given the inherent variability of the QT interval. For the ECGs used in Forest's analysis, only those from one study were measured using methodology considered acceptable. For the remaining ECGs the interval measurements were taken from the machine or re-read when the investigator felt it necessary (no indication of the number of ECGs that were re-read). I re-analyzed the data from the study that used acceptable measurement methodology and did not find strong evidence of a memantine related effect on cardiac repolarization, although this

observation is based on a relatively small number of ECGs. I would recommend that all ECGs used in the analysis be re-read using optimal methodology.

7. Attachments

List of Completed Studies in the Memantine NDA

Completed Studies (Cutoff 9/30/02)			
Study Number	Study Title	Number treated (per group)	Treatment length
Group 1			
Controlled US Clinical Studies in Dementia			
MRZ 90001-9605	Efficacy and long term tolerability of memantine in patients with moderately severe Alzheimer's disease	252 (126/126)	28 weeks
MEM-MD-02	A randomized, double blind, placebo controlled evaluation of memantine in patients with moderate to severe dementia of the Alzheimer's type	403 (202/201)	24 weeks
Controlled Non-US Clinical Studies in Dementia			
MRZ 90001-9403	Efficacy and tolerability of memantine in care-dependent patients with moderate to severe primary dementia	166 (84/82)	12 weeks
MRZ 90001-9202	Multi center, randomized, double blind, comparative study of long term efficacy and tolerability of memantine versus placebo in patients suffering from probable vascular dementia	581 (286/295)	28 weeks
MRZ 90001-9408	Multi center, randomized, double blind, comparative study of long term efficacy and tolerability of memantine versus placebo in patients suffering from probable vascular dementia	321 (156/165)	28 weeks
MRZ 90001-9104	Multi center, randomized, double blind, comparative study of the efficacy and tolerability of Akatinol Memantine and placebo in patients suffering from dementia of Alzheimer type	56 (29/27)	13 weeks
MRZ 90001-9105	Efficacy and tolerability of memantine in mild to moderate severe stages of primary dementia	27 (12/15)	12 weeks
MRZ 90001-9206	Efficacy and tolerability of memantine in moderately severe vascular dementia	56 (28/28)	14 weeks
Uncontrolled US Clinical Studies in Dementia			

MRZ 90001-9605 OLEX	Efficacy and long term tolerability of memantine in patients with moderately severe Alzheimer's disease (AD) (Open memantine treatment period)	175	24 weeks
Uncontrolled Non-US Clinical Studies in Dementia			
MRZ 90001-9202 OLEX	Multi center, randomized, double blind, comparative study of long term efficacy and tolerability of memantine versus placebo in patients suffering from probable vascular dementia (Open memantine treatment period)	464	24 weeks
MRZ 90001-9408 OLEX	Multi center, randomized, double blind, comparative study of long term efficacy and tolerability of memantine versus placebo in patients suffering from probable vascular dementia (Open memantine treatment period)	171	24 weeks
MRZ 90001-9206	Efficacy and tolerability of memantine in moderately severe vascular dementia	46	104 weeks
Controlled US Clinical Studies in Other Populations			
NTI 9702	A phase II randomized placebo controlled trials of NEU 3004 in patients with neuropathic pain	122 (64/58)	8 weeks
NTI 9801	A phase II randomized placebo controlled trials of NEU 3004 in patients with painful peripheral neuropathy	418 (85/171/162)	8 weeks
Group 2			
Uncontrolled Non-US Clinical Studies in Dementia			
MRZ 90001-9802	Akatinol Memantine pharmacological effect on care dependency of patients with moderate dementia	20	12 weeks
Controlled Non-US Clinical Studies in Other Populations			
MRZ 90001-8603	Pilot study on Akatinol Memantine in geriatric patients with organic brain syndrome	63 (33/30)	9 weeks
MRZ 9001-8608	Effect of Akatinol memantine in the treatment of spasticity in advanced multiple sclerosis	20 (9/11)	4 weeks
MRZ 90001-8803	Akatinol memantine compared	11 (4/7)	3 weeks

	to baclofen in the therapy of patients with spastic syndromes		
MRZ 90001-8806	Efficacy and tolerability of Akatinol memantine tablets in the treatment of de novo parkinsonian patients	141 (70/71)	6 weeks
MRZ 90001-8807	Clinical study on efficacy and safety of Akatinol memantine in elderly patients with organic brain syndrome, particularly focusing on vigilance and fine motor response	46 (24/22)	8 weeks
MRZ 90001-8810	Efficacy of Akatinol memantine tablets in the treatment of de novo parkinsonian patients	50 (25/25)	6 weeks
MRZ 90001-8902	Efficacy of Akatinol memantine in the spasticity of patients with multiple sclerosis	30 (15/15)	4 weeks
MRZ 90001-8903	Efficacy and tolerability of Akatinol memantine in patients from old people's home suffering from moderate to severe dementia syndrome	60 (30/30)	4 weeks
MRZ 90001-8904	Efficacy and tolerability of Akatinol memantine tablets compared to baclofen in patients with spasticity syndrome and neurogenic bladder dysfunction	16 (8/8)	3 weeks
MRZ 90001-9406	Akatinol memantine tolerability study	140 (46/46/48)	26 weeks
Uncontrolled Non-US Clinical Studies in Other Populations			
MRZ 90001-8602	Akatinol memantine in the therapy of patients in the end stage of Parkinson's disease with on-off phenomenon	14	4 weeks
MRZ 90001-8801	Efficacy and tolerability of memantine in the long term treatment of patients with spastic syndrome	123	14 months
Group 3A			
Non-US Clinical Pharmacological Studies			
MRZ 90001-9601	PK and relative bioavailablity of three pharmaceutical formulations of Akatinol memantine in a crossiver study	12 (12/12/12)	3 days
MRZ 90001-9601	PK study to investigate the influence of urinary pH and	13	43 days

	urine flow on renal clearance of memantine		
MRZ 90001-9604	PK and relative bioavailability of memantine tablets and memantine slow release tablets in a crossover design in healthy subjects	12/12	2 days
MRZ 90001-9702	Study of the PK interaction between memantine and HCTZ 25mg/triamterene 50mg under steady state conditions	21	32 days
MRZ 90001-9704	Study on the influence of food on the bioavailability of memantine from a new memantine SR formulation and on the relative bioavailability of this formulation versus IR formulation following repeated peroral doses	56	26 days
MRZ 90001-9402	Study of the bioequivalence of the new slow release tablet of memantine and a reference tablet formulation, determination of TSH, LH, FSH, prolactin and vasopressin in human plasma	49 (24/25)	27 days
MRZ 90001-9405	Influences of Akatinol memantine on information processing and memory functions taking into account interindividual differences	24 (24/24)	2 days
MRZ 90001-9502	Effect of Akatinol memantine in perception of experimental pain stimuli and primary and secondary hyperalgesia	40 (20/20)	19 days
Group 3B			
Non-US Pharmacokinetic Studies			
MRZ 90001-8610	Open pilot study to assess the penetration of Akatinol memantine into the liquor (CSF)	10	1 day
MRZ 90001-8610	Study on tolerability and kinetic effects of Akatinol memantine in healthy subjects under mental stress in the Pharmaco-EEG	16 (9/7)	1 day
MRZ 90001-9100	Determination of memantine in lacrimal fluid of patients under long-term treatment	10	47.9 month (mean)

	with Akatinol memantine		
PAZ 1983	Orienting PK studies on 14C-memantine in healthy subjects	2 (1/1)	1 day
HUK 610/5	Memantine: safety, tolerance and PK after single i.v. infusions of 30 and 40mg given at a rate of 10mg/h to healthy male volunteers	12 (4/4/4)	1 day
MRZ 90001-8201	Human PK studies with memantine	6 (4/3/6/3)	1-4 days
HUK 610/4	Memantine PK, dose relationships and absolute bioavailability for single oral doses of 10, 20, and 40mg in comparison with a single i.v. infusion	12 (12/12/12/12)	4 days
HUK 610/6	Memantine: PK study with repeat oral doses of 5, 10, and 20mg every 8 hours for 12 days	20 (8/8/8)	12 days
MRZ 90001-9506	Comparative bioavailability of two galenical formulations of memantine in elder subjects	24 (24/24)	2 days
HUK 610/13	14C memantine: Astudy of the absorption, metabolism, and excretion following oral administration to healthy human volunteers	6	19 days
PAZ 3049	Memantine: Single oral application (20mg) in 12 geriatric volunteers with reduced renal function and to 6 volunteers of the same age group with normal renal function: determination of plasma levels, total clearance, and terminal half-lives	18	1 day
IE 1801	Study on the safety and pharmacokinetics of a single oral SUN Y7017 dose in healthy adult males	32 (8/6/6/6/6)	1 day
MRZ 90001-9203	Pilot study of the excretion of memantine in sweat	4	1 day
MRZ 90001-Z035	Preliminary report on the Akatinol trial in patients suffering from renal insufficiency	8	12 weeks
MRZ 90001-8704	Investigation of the dizziness symptomatology and testing of an influence on the vestibular	16 (8/8)	10 days

	system of Akatinol memantine		
MRZ 90001-8909	Topographical analysis (EEG Mapping) of a pharmaco-EEG .study with memantine	18 (18/18)	2 days
MRZ 90001-Z040	Dose response study of Akatinol memantine on the cardiovascular system of 6 healthy male subjects	6 (6/6/6/6)	4 days
MRZ 9001-Z041	Efficacy of Akatinol Memantine on the cardiovascular system in healthy male volunteers	3	1 day
US Pharmacokinetic Studies			
NTI-0015	A study of the safety and single-dose and steady state PK of NEU 3004 in healthy volunteers and AIDS patients	16	44 days
MEM-PK-01	A single dose, open label, three way crossover bioequivalence and food effect study comparing 10 mg memantine tablets manufactured by Forest and Merz in human subjects	23 (23/23/23)	3 days
MEM-PK-04	An open label, randomized, three-way crossover, bioavailablility study comparing memantine modified release to immediate release tablets in human subjects	23 (22/23/21)	3 days
MEM-PK-07	A study of the PK interaction of memantine and aricept in healthy young subjects	24 (24/19/19)	2 days

Group 1 and 2 Trials Deaths, Memantine Subjects

Patient Number	Age/Sex	SAE start day	Preferred Term	Dose (mg/day)
Group 1 Dementia Placebo Controlled Trials				
Study 9605				
00243	83/F	197	Myocardial Infarction	20
00029	79/F	107	Myocardial Infarction	20
Study 9403				
00015	75/F	42	Cardiac Failure	10
		27	Pneumonia	
00060	66/M	48	Cardiac Arrest	10
		48	Coma	
		48	Apnea	
00118	61/M	71	Cardiac Arrest	10
		71	Apnea	
00101	69/F	57	Cardiac Failure	10
Study MEM-MD-02				
02235	67/M	170	Myocardial Infarction	20
Study 9202				
00232	71/M	47	Cerebral Hemorrhage	15
00580	75/F	48	Coma	20
00242	85/M	74	Pneumonia	20
00455	73/M	158	Pneumonia	20
00094	71/M	196	Cardiac Arrest	20
00658	62/M	30	Cerebrovascular Disorder	20
00714	72/M	100	Sudden Death	20
Study 9408				
00263	72/M	N/A	Gastro-Intestinal Disorder	20
00342	84/F	40	Metastases NOS	20
00008	87/F	4	Diarrhea	20
00135	75/M	132	Bronchitis	20
Group 1 Open Label Dementia Trials				
Study 9605 OLEX Placebo-Memantine				
00111	73/M	63	Pneumonia	20
00152	81/M	154	Pneumonia	20
Study 9202 OLEX Placebo-Memantine				
00381	86/M	72	Pneumonia	20
00227	76/M	124	Pneumonia	20
00400	71/M	34	Pneumonia	20
00134	81/F	62	Inflicted Injury	20
00843	83/M	148	Myocardial Infarction	20
00247	70/M	97	Cardiac Arrest	20
00899	88/M	21	Sepsis	10
			Urinary Tract Infection	
00327	73/M	35	Cerebrovascular Disorder	20
00035	90/F	30	Pneumonia	20
00153	68/F	-7	Cardiac Failure	20
		36	Carcinoma	

00828	86/F	105	Cerebral Hemorrhage	20
Study 9408 OLEX Placebo-Memantine				
00327	80/M	148	Respiratory Disorder	20
00147	82/M	191	Condition Aggravated	20
00361	71/M	140	Cerebrovascular disorder	20
Study 9605 OLEX Memantine-Memantine				
00063	58/M	152	Respiratory Insufficiency	20
		138	Anorexia	
		137	Somnolence	
Study 9202 OLEX Memantine-Memantine				
00282	74/M	147	Myocardial Infarction	20
00625	77/M	98	Pneumonia	20
			Dehydration	
00387	69/M	125	Cerebrovascular disorder	20
00138	78/M	80	Cardiac Failure	20
00142	73/M	49	Pneumonia	20
00280	86/M	165	Pneumonia	20
00631	80/F	165	Bronchitis	20
00394	86/F	145	Myocardial Infarction	20
00132	83/F	166	Cerebrovascular Disorder	20
00147	73/M	77	Cardiac Failure	20
00830	73/M	152	Cerebrovascular disorder	20
			Hypertension	
00561	83/M	60	Aneurysm Ruptured	20
Study 9408 OLEX Memantine-Memantine				
00425	79/M	4	Sudden Death	20
00388	74/M	77	Myocardial Infarction	20
Study 9206 OLEX Memantine-Memantine				
00039	72/F	290	Cerebral Hemorrhage	20
Group 1 Neuropathic Pain Placebo Controlled Trials				
Study NTI 9801				
100094	78/F		Myocardial Infarction	40
Group 2 Studies				
Study 8801				
00043	73/M	NA	NA	30
00050	73/M	NA	NA	30
00051	54/M	NA	NA	30
00054	73/M	NA	Cerebrovascular Disorder	30
00055	NA/M	NA	Cerebrovascular Disorder	30
09142	52/M	NA	NA	NA
09143	67/F	NA	Death	NA
Study 9406				
00038	84/M	NA	Death	30
00048	82/M	NA	Sudden Death	30
00049	85/M	NA	Death	60
00052	84/F	NA	Cardiac Failure	60
			Pneumonia	
00056	80/F	NA	Pneumonia	60

00057	74/F	NA	Cardiac Failure	15
00092	87/F	NA	Cardiac Failure	30
00100	87/F	NA	Embolism Pulmonary	30
			Sudden Death	
00101	83/M	NA	Cardiac Failure	15
			Pneumonia	
00107	84/F	NA	Cardiac Failure	30
00112	93/F	NA	Cardiac Failure	60
00139	85/M	NA	Hypertension	30
			Cardiac Failure Left	
00141	87/M	NA	Cardiac Failure	30
00147	87/F	NA	Cardiac Failure Left	60
00148	81/F	NA	Myocardial Infarction	30
00300	93/M	NA	Pneumonia	30
			Inflicted Injury	
00312	87/F	NA	Cardiac Failure	60
			Asthenia	

Deaths from Ongoing Memantine Studies

Patient Number	Age	Sex	Cause of death
MEM-MD-01* (Moderate to severe Alzheimer's)			
029102	80	M	Pneumonia
039117	88	M	Cardiac Failure
129106	80	F	Sepsis
159104	84	F	Cardiac Arrest
219110	77	M	Dehydration
319101	85	F	Sudden death
319107	84	M	Sudden death
MEM-MD-03 (Moderate to severe Alzheimer's)			
029207	81	M	Pulmonary Infarct, Neoplasia Malignant
069207	86	F	Inflicted Injury
079112	84	M	Sudden death
279201	83	F	Alzheimer's disease
289202	75	F	Myocardial Infarction
289232	89	F	Myocardial Infarction
319201	80	M	Myocardial Infarction, Apnea
369101	82	F	Arteritis (temporal), Sudden death
379206	80	M	Inflicted Injury
MEM-MD-06B (Painful diabetic neuropathy)			
089003	71	M	Sudden death
259001	73	M	Cardiac arrest
MEM-MD-10 (Mild to moderate Alzheimer's)			
129008	73	M	Sudden death, pneumonia
189021	88	F	Adult Respiratory Distress Syndrome
MEM-MD-12 (Mild to moderate Alzheimer's)			
779320	83	F	Myocardial Infarction
MRZ90001-9408/3 (Vascular dementia)			
59	94	M	Pneumonia
212	68	M	Pneumonia
224	83	M	Carcinoma, bile duct
260	88	F	Cerebral ischemia
310	77	F	Pneumonia
321	79	M	Heart failure
355	69	F	Cachexia
NA	69	F	Cachexia
192944-004* (Chronic open angle glaucoma)			
1298	56	M	Carcinoma
1253	76	F	Accidental injury
1038	74	M	Lymphoma-like reaction
99679 (Mild to moderate Alzheimer's)			
NA	66	F	Cardiac Failure, Pneumonia
NA	82	F	Cardiac Failure, Pneumonia Atrial Arrhythmia
NA	76	M	Myocardial Infarction

From Forest Panel 26, SU vol. 1.11, pp.221-2, Panel 8, SU vol. 1.11, pp.150-156.

* Double blind placebo controlled trials, treatment blinded at the time of NDA submission.

All SAEs reported for memantine treated subjects during Group 1 dementia trials (placebo controlled and open label)

Table 4.5.4

Number (%) of Patients with Serious Adverse Events By Body System and By Preferred Term All Memantine Dementia Patients 120-Day Safety Update Safety Population

Body System Memantine Preferred Term (N=1357) n(%)
PATIENTS WITH AT LEAST ONE SAE 260 (19.2)
AUTONOMIC NERVOUS SYSTEM DISORDERS 1 (0.1)
SWEATING INCREASED 1 (0.1)
BODY AS A WHOLE - GENERAL DISORDERS 75 (5.5)
ASTHENIA 2 (0.1)
CHEST PAIN 8 (0.6)
CHEST PAIN PRECORDIAL 2 (0.1)
CONDITION AGGRAVATED 5 (0.4)
DIAGNOSTIC PROCEDURE 2 (0.1)
FALL 16 (1.2)
FEVER 2 (0.1)
HERNIA INGUINAL 1 (0.1)
HERNIA NOS 1 (0.1)
HOT FLUSHES 1 (0.1)
HYPOTHERMIA 1 (0.1)
HYPOVOLAEMIA 1 (0.1)
INFLICTED INJURY 19 (1.4)
MALAISE 6 (0.4)
MEDICATION ERROR 1 (0.1)
OEDEMA 2 (0.1)
PAIN 1 (0.1)
SEPSIS 5 (0.4)
SUDDEN DEATH 2 (0.1)
SURGICAL INTERVENTION 6 (0.4)
SYNCOPE 7 (0.5)
CARDIOVASCULAR DISORDERS, GENERAL 21 (1.5)
BLOOD PRESSURE FLUCTUATION 1 (0.1)
CARDIAC FAILURE 12 (0.9)
CARDIAC FAILURE LEFT 1 (0.1)
HEART DISORDER 3 (0.2)
HYPERTENSION 4 (0.3)
HYPOTENSION 1 (0.1)
OEDEMA DEPENDENT 1 (0.1)
CENTR & PERIPH NERVOUS SYSTEM DISORDERS 75 (5.5)
APHASIA 2 (0.1)
ATAXIA 2 (0.1)
CEREBELLAR INFARCTION 1 (0.1)
CEREBRAL HAEMORRHAGE 3 (0.2)
CEREBROVASCULAR DISORDER 24 (1.8)
COMA 4 (0.3)
CONVULSIONS 3 (0.2)
DIZZINESS 4 (0.3)
DYSKINESIA 1 (0.1)
ENCEPHALOPATHY 1 (0.1)
EXTRAPYRAMIDAL DISORDER 1 (0.1)
GAIT ABNORMAL 7 (0.5)
HAEMORRHAGE INTRACRANIAL 1 (0.1)
HEADACHE 2 (0.1)
HEMIPLEGIA 5 (0.4)
HYPOKINESIA 4 (0.3)
MUSCLE CONTRACTIONS INVOLUNTARY 1 (0.1)
NYSTAGMUS 1 (0.1)
OCULOMOTOR NERVE PARALYSIS 1 (0.1)
PARALYSIS 2 (0.1)

SPEECH DISORDER 3 (0.2)
STUPOR 2 (0.1)
TRANSIENT ISCHAEMIC ATTACK 15 (1.1)
VERTIGO 1 (0.1)
ENDOCRINE DISORDERS 2 (0.1)
HYPERTHYROIDISM 1 (0.1)
HYPOTHYROIDISM 1 (0.1)
GASTRO-INTESTINAL SYSTEM DISORDERS 31 (2.3)
ABDOMINAL PAIN 5 (0.4)
ASCITES 1 (0.1)
CONSTIPATION 5 (0.4)
DIARRHOEA 3 (0.2)
DIVERTICULITIS 1 (0.1)
DYSPHAGIA 1 (0.1)
GASTRO-INTESTINAL DISORDER NOS 2 (0.1)
GASTROENTERITIS 2 (0.1)
GI HAEMORRHAGE 2 (0.1)
HAEMORRHAGE RECTUM 2 (0.1)
HAEMORRHOIDS 1 (0.1)
ILEUS 1 (0.1)
INTESTINAL OBSTRUCTION 1 (0.1)
NAUSEA 1 (0.1)
OESOPHAGITIS 1 (0.1)
VOMITING 5 (0.4)
HEART RATE AND RHYTHM DISORDERS 10 (0.7)
BRADYCARDIA 3 (0.2)
CARDIAC ARREST 4 (0.3)
FIBRILLATION ATRIAL 3 (0.2)
HEART BLOCK 1 (0.1)
LIVER AND BILIARY SYSTEM DISORDERS 3 (0.2)
BILIARY PAIN 1 (0.1)
CHOLECYSTITIS 1 (0.1)
JAUNDICE 1 (0.1)
METABOLIC AND NUTRITIONAL DISORDERS 10 (0.7)
DEHYDRATION 7 (0.5)
HYPERGLYCAEMIA 2 (0.1)
HYPERNATRAEMIA 1 (0.1)
PHOSPHATASE ALKALINE INCREASED 1 (0.1)
MUSCULO-SKELETAL SYSTEM DISORDERS 5 (0.4)
ARTHRALGIA 2 (0.1)
ARTHROSIS 1 (0.1)
BACK PAIN 1 (0.1)
MUSCLE WEAKNESS 1 (0.1)
MYO ENDO PERICARDIAL & VALVE DISORDERS 12 (0.9)
ANGINA PECTORIS 2 (0.1)
MYOCARDIAL INFARCTION 10 (0.7)
NEOPLASM 11 (0.8)
BREAST NEOPLASM MALIGNANT FEMALE 3 (0.2)
CARCINOMA 2 (0.1)
HEPATIC NEOPLASM 1 (0.1)
HEPATIC NEOPLASM MALIGNANT 1 (0.1)
LEUKAEMIA 1 (0.1)
LYMPHOMA MALIGNANT 1 (0.1)
METASTASES NOS 1 (0.1)
NEOPLASM NOS 2 (0.1)
PLATELET,BLEEDING & CLOTTING DISORDERS 3 (0.2)
EPISTAXIS 1 (0.1)
HAEMATOMA 1 (0.1)
THROMBOCYTOPENIA 1 (0.1)
PSYCHIATRIC DISORDERS 48 (3.5)
AGGRESSIVE REACTION 2 (0.1)
AGITATION 11 (0.8)
ALZHEIMER'S DISEASE 2 (0.1)
ANOREXIA 4 (0.3)
COGNITIVE DISORDERS 1 (0.1)
CONCENTRATION IMPAIRED 1 (0.1)

CONFUSION 20 (1.5)
DELIRIUM 1 (0.1)
DELUSION 1 (0.1)
DEMENTIA 1 (0.1)
DEPRESSION 1 (0.1)
HALLUCINATION 2 (0.1)
INSOMNIA 1 (0.1)
PERSONALITY DISORDER 2 (0.1)
PSYCHOSIS 2 (0.1)
SLEEP DISORDER 1 (0.1)
SOMNOLENCE 4 (0.3)
SUICIDE ATTEMPT 1 (0.1)
RED BLOOD CELL DISORDERS 2 (0.1)
ANAEMIA 2 (0.1)
REPRODUCTIVE DISORDERS, MALE 2 (0.3)
PROSTATIC DISORDER 2 (0.3)
RESPIRATORY SYSTEM DISORDERS 48 (3.5)
APNOEA 2 (0.1)
BRONCHITIS 11 (0.8)
COUGHING 1 (0.1)
DYSPNOEA 11 (0.8)
PNEUMONIA 22 (1.6)
PULMONARY OEDEMA 1 (0.1)
RESPIRATORY DISORDER 2 (0.1)
RESPIRATORY INSUFFICIENCY 1 (0.1)
UPPER RESP TRACT INFECTION 1 (0.1)
SKIN AND APPENDAGES DISORDERS 3 (0.2)
CELLULITIS 1 (0.1)
RASH 1 (0.1)
SKIN ULCERATION 1 (0.1)
URINARY SYSTEM DISORDERS 19 (1.4)
RENAL FUNCTION ABNORMAL 1 (0.1)
RENAL PAIN 1 (0.1)
URINARY INCONTINENCE 1 (0.1)
URINARY RETENTION 5 (0.4)
URINARY TRACT INFECTION 11 (0.8)
VASCULAR (EXTRACARDIAC) DISORDERS 16 (1.2)
ANEURYSM 1 (0.1)
ANEURYSM RUPTURED 1 (0.1)
EMBOLISM PULMONARY 3 (0.2)
PHLEBITIS 1 (0.1)
THROMBOPHLEBITIS 2 (0.1)
THROMBOPHLEBITIS DEEP 8 (0.6)
VISION DISORDERS 6 (0.4)
BLINDNESS 1 (0.1)
CATARACT 4 (0.3)
EYE PAIN 1 (0.1)
GLAUCOMA 1 (0.1)

Based on the Group 1 double blind placebo controlled dementia studies 9605, 9403, 9202, 9408, 9104, 9105, 9206, and MEM-MD-02,
and on open label extension phase of dementia studies 9605, 9202, 9408, and 9206
N = number of patients with at least 1 day exposure to memantine
SAE = Serious Adverse Event
Patients are counted only once within each body system and preferred term
Report generated by program: /sasprog/mem/memdemnda/safetyupdate/programs/tables/tae454.sas FINAL 03/12/2003 15:32

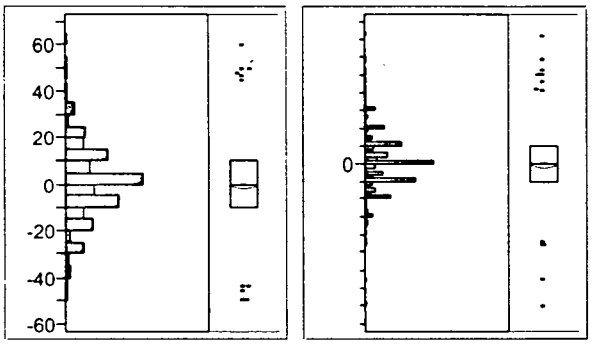
Panel 12. PCS Criteria for Laboratory Parameters

Laboratory Parameter	*Conventional (CV) Units*	*Conversion Factor*	*SI Units*	*PCS Criteria [2] Low Values*	*PCS Criteria [2] High Values*
HEMATOLOGY					
Hemoglobin[1]	g/L	0.1000	g/dL	≤0.9*LLN	
	g/dL	1.0000	g/dL		
	mmol/L	1.6113	g/dL		
Hematocrit	%	0.0100	l/l	≤0.9*LLN	
White Blood Cell Count	thou/mcl	1	G/L	≤2.8	≥16
	10**9/L	1.0000	G/L		
Eosinophils	%	1	%		≥10
Neutrophils	%	1	%	≤15	
Platelet Count	per cumm	1.0000	G/L	≤75	≥700
	10**9/L	1.0000	G/L		
CHEMISTRY					
AST (SGOT)	IU/L	1.0000	U/L	---	≥3*ULN
	ukat/l	60.0000	U/L		
ALT (SGPT)	IU/L	1.0000	U/L	---	≥3*ULN
	ukat/l	60.0000	U/L		
LDH*	U/L	1	U/L	---	≥3*ULN
Alkaline Phosphatase	IU/L	1.0000	U/L	---	≥3*ULN
	ukat/l	60.000	U/L		
Blood Urea Nitrogen (BUN)	mg/dL	0.3570	Mmol/L	---	≥10.7
	mmol/L	1.000	Mmol/L		
Calcium	mg/dL	0.2495	Mmol/L	≤1.75	≥3.0
Cholesterol	mg/dL	0.0259	Mmol/L	--	≥7.8
	mmol/L	1.0000	Mmol/L		
Creatinine	umol/L	1.0000	µmol/L	--	≥175
	mg/dl	88.4000	µmol/L		
Potassium	Meq/L	1.0000	Mmol/L	≤3.0	≥5.5
	mmol/L	1.0000	Mmol/L		
Sodium	Meq/L	1.0000	Mmol/L	≤125	≥155
	mmol/L	1.0000	mmol/L		
Total Bilirubin	umol/L	1.000	µmol/L	---	≥34.2
	mg/dL	17.1000	µmol/L		
Uric Acid (Male)	µmol/L	0.0010	mmol/L	---	≥ 0.6246
	mg/dL	0.0595	mmol/L		
	mmol/L	1.000	mmol/L		
Uric Acid (Female)	umol/L	0.0010	mmol/L	---	≥ 0.5056
	mg/dL	0.0595	mmol/L		
	mmol/L	1.000	mmol/L		

[1] Hemoglobin presented in g/dL.
[2] PCS criteria refers to the SI units.
[3] LLN = lower limit of normal value of laboratory reference range.
[4] ULN = upper limit of normal value of laboratory reference range.
* Study MEM-MD-02 only.

Distribution for Systolic Blood Pressure Changes from Baseline

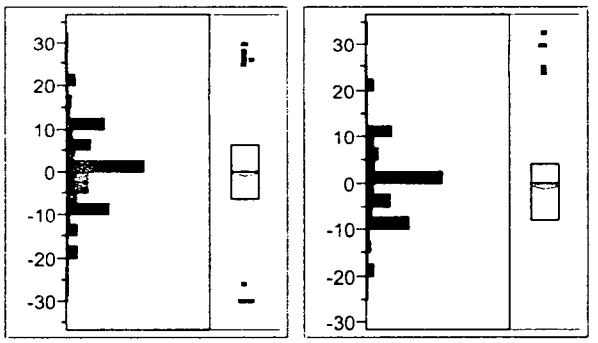
Memantine Placebo



	Memantine (606)	Placebo (604)
Mean	-0.990099	-0.764901
Std Dev	16.581177	16.950255
Std Err Mean	0.6735643	0.6896961

Distribution for Diastolic Blood Pressure Changes from Baseline

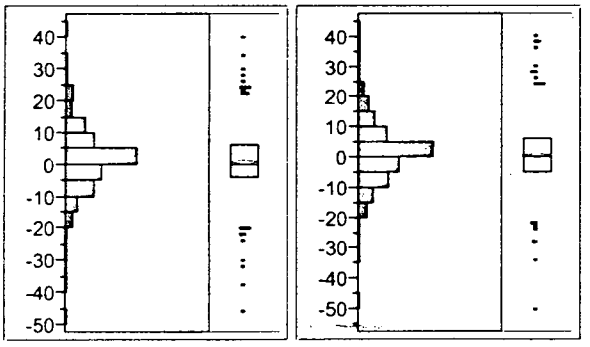
Memantine Placebo



	Memantine (606)	Placebo (604)
Mean	-0.410891	-0.69702
Std Dev	10.184796	9.1595001
Std Err Mean	0.413729	0.3726948

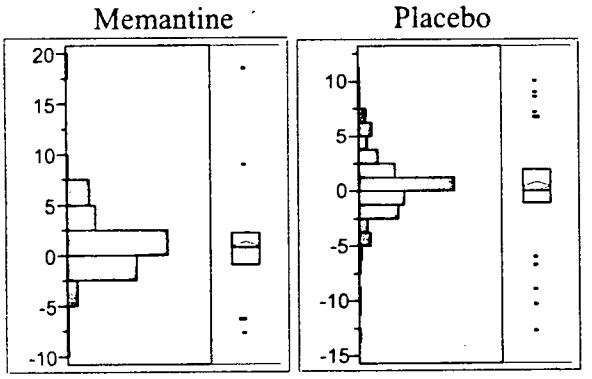
Distribution for Pulse Changes from Baseline

Memantine Placebo



	Memantine (606)	Placebo (602)
Mean	0.6534653	0.4385382
Std Dev	9.8621262	10.110885
Std Err Mean	0.4006215	0.4120889

Distribution for Weight Changes from Baseline



	Memantine (211)	Placebo (211)
Mean	0.9327014	0.3668246
Std Dev	2.9075963	3.0864742
Std Err Mean	0.2001672	0.2124816

Thrombophlebitis deep /Thrombophlebitis/Phlebitis/Pulmonary Embolism
DBPC and OLEX Dementia Trials

DBPC-Memantine treated

Thrombophlebitis deep
9202/00387 69YO male history of CVAs, HTN, varicose veins, and ankle edema. During the double blind phase he developed left calf swelling that was diagnosed as a DVT (after 160 days of memantine). He was treated with heparin, furosemide, and cephradine. He was hospitalized 41 days later for "deteriorating DVT". Three months later he discontinued from the study due to decreased mobility and he died 8 days after discontinuing from a cerebrovascular accident.

9202/00171 73YO male, history of hypothyroidism. He developed deep thrombophlebitis (after 21 days of memantine) and was hospitalized and treated with heparin, warfarin, and amoxicillin. He discontinued from the study and was lost to follow up.

9202/00119 85YO female with a history of CVA, HTN, atrial fibrillation, developed severe deep thrombophlebitis verified by angiography and was hospitalized (after 113 days of memantine). She was treated with heparin and warfarin and was discontinued from the study. The event was considered resolved on follow up.

9605/00013 84 YO male with a history of arthritis, fecal and urinary incontinence, who developed deep venous thrombosis of the right leg and was hospitalized and treated with heparin and then warfarin (after 173 days of memantine). He continued in the study for another 3 months and then discontinued at that time following a TIA.

9605/00317 83YO female with a history of MI, was hospitalized (after 80 days of memantine) for pulmonary embolism, left thrombophlebitis deep, and congestive heart failure secondary to ischemic cardiomyopathy. She was treated with heparin and furosemide and following hospitalization with lisinopril, atenolol and warfarin. She completed the double blind phase and the subsequent open label phase of the study.

9605/00138 84 YO female with a history of adenocarcinoma of the stomach, osteoarthritis, and hearing loss was hospitalized for right leg deep thrombophlebitis (after 195 days of memantine) and was prescribed warfarin. Approximately 2 months prior to this event she fell and fractured her right hip and underwent an unspecified surgical repair. She completed the double blind and open label phases of the study.

MEM-MD-02-0029216 77 YO female with a history of L breast cancer. She developed difficulty walking which led to discontinuation from the study (after 33 days of memantine). Fifteen days after discontinuation she was hospitalized for dehydration renal insufficiency, sepsis, and hypernatremia. One month after discontinuing she was hospitalized due to overall deconditioning, suspected UTI, and deep venous thrombosis. Physical exam noted a right breast mass suspicious for cancer, but no surgery was performed. She was discharged to a long term care facility.

Thrombophlebitis
MEM-MD-02-0259206 84YO female with PVD, arthritis, edema, and hypothyroidism taking celecoxib and megestrol was hospitalized for a blood clot in the right lower extremity (after 171 days of memantine). She was initially treated with warfarin, which was stopped due to a low clotting factor, and then a Greenfield filter was placed.

Phlebitis
9408/00056 83YO female with a history of hypertension and phlebitis developed phlebitis (after 99 days of memantine) and the event was considered serious, and led to discontinuation. The concomitant medication data set noted treatment with heparin. The narrative reported that the subject received a filter. The event was considered resolved.

9408/00294 76 YO female with a history of hypertension, atrial fibrillation, stroke, and left hemiplegia was hospitalized for fever, cough, dyspnea and was diagnosed with a pulmonary embolism. The phlebitis was noted on the first day of memantine treatment and the pulmonary embolism was noted on the eighth day of memantine treatment. The AE and Concomitant medications data sets noted treatment with fraxiparine (a fractionated heparin). The subject continued in the study and the event was considered resolved.

9408/00506 73YO female was diagnosed with phlebitis (investigator term periphlebitis of the left leg) after 47 days of memantine. The event was not considered serious and did not lead to discontinuation and was considered resolved after 16 days. The subject was treated with a fractionated heparin and an NSAID (niflumic acid).

9605/00243 83 YO female was diagnosed with phlebitis of the left lower extremity after 78 days of memantine treatment. The patient was treated with ciprofloxacin and the event was reported resolved after fourteen days and did not meet the regulatory definition for serious. The severity was described as mild.

OLEX
Pulmonary embolism
9202/00012 67 YO male with probable vascular dementia and hypertension was diagnosed with a pulmonary embolism (means of diagnosis not provided) after 113 days of memantine treatment. The AE data set noted that the subject was admitted for observation. The narrative reported that the pulmonary embolism was considered resolved on the same day. He continued in the study.

Thrombophlebitis/thrombophlebitis deep
9605/00257 74 YO male with Alzheimer's disease, mitral valve prolapse, hypertension, and intermittent sinus bradycardia, was hospitalized for phlebitis of the left leg and diagnosed with acute deep vein thrombosis (US) after 205 days of memantine treatment. He was treated with heparin and warfarin. The event was considered resolved on follow up and the subject completed the trial.

Thrombophlebitis
9605/00083 78 YO male with Alzheimer's disease was hospitalized with a distal venous thrombosis of the right leg. He was treated with enoxaparin and warfarin. The event was considered resolved on follow up and the subject completed the trial.

Thrombophlebitis deep
9605/00052 83 YO female with Alzheimer's disease and bilateral lower extremity edema was hospitalized and diagnosed with occlusive thrombosis of the right popliteal vein after 247 days of memantine treatment. She was treated with warfarin and lorazepam and the event was considered resolved and she completed the trial.

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

/s/

Jerry Boehm
8/20/03 12:48:32 PM
MEDICAL OFFICER

Judith Racoosin
8/20/03 05:30:22 PM
MEDICAL OFFICER