NDA Safety Review

NDA:	**21-487**
Drug Name:	**Generic Name: Memantine** **Proposed Trade Name: Pending**
Sponsor:	**Forest Laboratories, Inc.**
Reviewer:	**Gerard Boehm, MD, MPH**

The Executive Summary-Safety Review

Memantine is an NMDA receptor antagonist that is administered orally. Memantine has been marketed in Germany as Akatinol Memantine since 1982 for the treatment of Parkinsonism, cerebral and peripheral spasticity, and organic brain syndrome. In 2002, the European Union approved memantine for the treatment of Alzheimer's disease. Forest is seeking FDA approval to market memantine for the treatment of moderate to severe dementia of the Alzheimer's type. The currently approved Alzheimer's disease treatments are acetylcholinesterase inhibitors and are approved for the treatment of mild to moderate dementia of the Alzheimer's type.

The memantine NDA development program included primary safety data from eight phase II/III double blind, placebo controlled trials in dementia (vascular and Alzheimer's type), four open label extensions of these trials, and two phase II/III double blind, placebo controlled trials in neuropathic pain. Forest also submitted safety data from thirty clinical pharmacology trials, and limited safety data from completed trials exploring other treatment indications, from ongoing trials, and from post marketing reports.

The NDA includes 487 subjects exposed to memantine in clinical pharmacology trials and 1,748 subjects exposed to memantine in dementia and neuropathic pain trials. Forest reports that over 4,000 patients have been exposed in completed trials exploring other treatment indications and in ongoing trials. Forest estimates over 400,000 person years of memantine exposure in post marketing use.

The number of patients exposed in the primary safety data trials exceeds ICH guidelines, and Forest submitted adequate safety data for the intended recommended dose. However, only a subset of those exposed in the primary data had Alzheimer's disease. In the Group 1 dementia placebo controlled trials, approximately 42% of memantine exposed subjects had diagnoses of Alzheimer's dementia with the remaining subjects having vascular dementia. There did not appear to be meaningful differences in memantine's safety profile when comparing the Alzheimer's and vascular dementia populations.

The safety testing, capture of adverse events, coding of investigator terms and analyses of safety data were generally adequate. The safety data were consistent across the submitted case report forms, electronic data sets, and summary tables.

In the dementia placebo controlled trials, the percentage of subjects who died was similar in the memantine and placebo treatment groups. The reported causes of death were those expected in an elderly population.

Memantine and placebo subjects had similar SAE risks, and there did not appear to be clusters of unexpected SAEs in memantine exposed individuals. In the primary data trials there were no SAEs of liver failure, acute renal failure, rhabdomyolysis, aplastic anemia, serious skin reactions, or pancreatitis. Three SAEs of pancreatitis were reported in ongoing studies, one associated with elevated triglycerides and two with cholelithiasis. Four cases of renal failure were reported from ongoing trials. In three of these cases, the treatment assignment remains blinded. Forest identified memantine post marketing reports of epidermal necrolysis (2), aplastic anemia (1) and liver failure (1).

Common AEs that occurred more frequently among memantine subjects and in some cases that exhibited evidence of a dose response relationship included dizziness, headache, constipation, pain, and dyspnea.

In dementia placebo controlled trials but not neuropathic pain controlled trials, memantine was associated with a mean increase in alkaline phosphatase compared to placebo. Memantine was not associated with increases in transaminases or bilirubin.

Memantine was not associated with changes in blood pressure or pulse. Memantine did not appear to be associated with orthostatic blood pressure changes, although Forest was unable to provide sufficient information about the methodology used to measure orthostatic blood pressure to allow a complete assessment of these results.

Forest's analyses of ECGs did not suggest memantine related QT prolongation compared to placebo, but the ECG data were limited and the available ECGs were not adequately examined. For one of the three studies included in the pooled analysis, ECGs were measured at a central laboratory using standardized measuring methodology. For the remaining ECGs, the intervals analyzed were either the machine read intervals or were investigator over-read intervals.

Recommendations
Forest should reanalyze the available ECG interval data after all ECGs have been read by a central laboratory using standardized measuring methodology.

I recommend removing wording about memantine's lack of effect on orthostatic blood pressure from labeling. Forest was unable to provide sufficient information about BP measurement methodology to allow adequate assessment of this claim.

Forest should be asked to submit additional eye examination result information from ongoing studies (particularly the glaucoma studies) as it becomes available.

Forest should provide additional information for the post marketing reports of epidermal necrolysis and aplastic anemia and follow up for the 15 day IND encephalopathy report.

1. Materials Used in This Review

This safety review is based on the information included in the following submissions:

- December 19, 2002; NDA Integrated Summary of Safety (ISS)-paper copy with electronic post text tables, Study reports for individual studies-paper copies, electronic data sets, electronic Case Report Forms (CRFs),
- January 10, 2003; Final Study Report for MEM-MD-02-paper copy with electronic post text tables
- April 11, 2003 submission, Safety Update-paper copy with electronic post text tables, electronic data sets, electronic Case Report Forms (CRFs)
- January 24, 2003, May 15, 2003, July 3, 2003, July 9, 2003 submissions; responses to reviewer questions-electronic/paper submissions

2. Background

2.1 Name, Drug Class, Proposed Indication

Memantine (1-amino-3, 5-dimethyladamantane hydrochloride) is an NMDA receptor antagonist that is administered orally. Pre-clinical studies suggest that memantine can decrease neuronal toxicity associated with excessive glutamate release (NDA vol. 265, p.77). The sponsor, Forest Laboratories, seeks FDA approval to market memantine for the treatment of patients with moderate to severe dementia of the Alzheimer's type.

Memantine has been marketed in Germany as Akatinol Memantine since 1982 for the treatment of Parkinsonism, cerebral and peripheral spasticity, and organic brain syndrome. In 2022, the European Union approved memantine (trade name Axura) for the treatment of Alzheimer's disease.

2.2 State of Armamentarium- Safety

Currently, there are no NMDA receptor antagonists approved in the United States for the treatment of Alzheimer's disease. The PDR includes four cholinesterase inhibitors (tacrine, donepezil, rivastigmine and galantamine) approved in the United States for the treatment of Alzheimer's disease. The cholinesterase inhibitors are associated with cardiovascular effects (bradycardia), and GI effects (nausea and vomiting). In addition to the mentioned cardiovascular and GI effects, tacrine is associated with increased risk of transaminase elevations.

2.3 Proposed Memantine Label with Respect to Safety

Forest would contraindicate memantine use in patients with known hypersensitivity to memantine. Forest has no warnings in their proposed memantine label.

Forest would include a statement in the PRECAUTIONS section of the memantine label suggesting that caregivers be instructed about administration and dose escalation for memantine. Forest would also include a precaution statement noting that memantine use has not been evaluated in patients with seizure disorder and that patients with a history of seizure disorder be carefully monitored.

Forest comments that increases in urine pH may decrease elimination of memantine, resulting in increased plasma levels. Forest does not recommend dose adjustment with

hepatic impairment or with mild or moderate renal impairment. Forest does not recommend the use of memantine in patients with severe renal impairment. Forest notes that concomitant use of memantine and donepezil does not affect the pharmacokinetics of either compound. Co-administration of memantine with other drugs that are eliminated by the same renal cationic system (ex, HCTZ) could result in altered plasma levels of both drugs. Memantine is not highly protein bound (45%) and therefore interaction with highly protein bound drugs is unlikely. Effects of L-dopa, dopaminergic agents, or anticholinergics may be enhanced with concomitant memantine use requiring dose adjustment of these other agents.

Forest notes that in dementia trials where patients received memantine 20mg/day, no AE led to discontinuation of more than 1% of memantine subjects and at a rate greater than placebo.

Forest would include the following table of AEs in their memantine label. The table includes events reported by at least 2% of memantine subjects and at a rate greater than placebo.

Table 1: Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving *TRADENAME*® and at a Higher Frequency than Placebo-treated Patients.

Body System Adverse Event	Placebo (N = 922) %	*TRADENAME*® (N = 940) %
Body as a Whole		
Fatigue	1	2
Pain	1	3
Cardiovascular System		
Hypertension	2	4
Central and Peripheral Nervous System		
Dizziness	5	7
Headache	3	6
Gastrointestinal System		
Constipation	3	5
Vomiting	2	3
Musculoskeletal System		
Back pain	2	3
Psychiatric Disorders		
Confusion	5	6
Somnolence	2	3
Hallucinations	2	3
Respiratory System		
Coughing	3	4
Dyspnea	1	2

Other adverse events occurring with an incidence of at least 2% in *TRADENAME*®-treated patients but at a greater or equal rate on placebo were agitation, fall, inflicted injury, urinary incontinence, diarrhea, bronchitis, insomnia, urinary tract infection, influenza-like symptoms, gait abnormal, depression, upper respiratory tract infection, anxiety, peripheral edema, nausea, anorexia, and arthralgia

Proposed labeling states that memantine was not associated with clinically important changes in vital signs or orthostatic changes, clinically important laboratory test changes, or clinically important ECG changes.

The proposed memantine label includes a list of all events observed during clinical trials and a list of events not seen in clinical trials but reported by more than one patient during post marketing use in other countries.

The proposed memantine label lists restlessness, psychosis, visual hallucinations, proconvulsiveness, somnolence, stupor, and loss of consciousness in a patient who took an overdose of memantine (400mg). Forest would note that elimination of memantine can be enhanced by acidification of the urine.

2.4 Animal Pharmacology and Toxicology
In section 16 of the memantine NDA ISS, Forest summarized data from their nonclinical studies. Forest reported that memantine doses of 100mg/kg produced decreased awareness, motor activity, and reflexes. Memantine doses ≥30mg/kg caused decreased cardiac output, stroke volume, and systolic left ventricular pressure. Forest reported that memantine inhibited intestinal motility in rats with an ED_{50} of 20mg/kg and produced diuresis and saluresis in rats at doses of 40mg/kg (SU vol. 1.11, p.316).

Forest reported that memantine was not carcinogenic in the 113-week mouse and 128-week rat studies, and that memantine tested negative in a battery of mutagenicity studies (SU vol. 1.11, p.317).

Forest reported that the lowest lethal dose in both mouse and rat was ≥300mg/kg. Ataxia, prone position, bradypnea, and tremor reportedly preceded death. In subchronic and chronic studies, ataxia, tremor, unsteadiness, and aggressiveness or hyperexcitability in rodents and apathy or quietness in dogs and baboons were among the most prominent clinical signs observed. Forest reported that at overtly toxic doses they observed foamy macrophages in the lungs, renal papillary mineralization, tubulointerstitial nephritis, vacuolization of defined cortical neurons, and corneal opacities. (SU vol. 1.11, p.317).

Forest further described the findings of corneal opacities and obscured retinal blood vessels in mouse, rat and dog studies. Specifically, Forest reported findings of corneal thickening, with thickening of corneal epithelium and endothelial vacuolization. The findings in dogs disappeared despite increases in dose and the findings in rodents were only present at doses associated with profound systemic toxicity and/or death. Effects seen in the 13-week rat study were reportedly not seen in the 12-month chronic feeding study. Forest feels that the eye findings reflect abnormal local drug storage due to saturated excretion mechanisms and are not clinically relevant (SU, vol. 1.11, p. 318).

Forest further described the findings of cortical neuron vacuolization. Forest stated that rodents are prone to cerebrocortical neuron injury, specifically Olney-type lesions, from NMDA receptor antagonists including (+) MK-801, PCP, and ketamine. Forest found that single oral memantine doses of 100mg/kg/day or greater produced a dose- related

increase in the frequency and severity of Olney-type lesions. Repeated daily oral doses of 40mg/kg/day administered in a dose escalation manner did not demonstrate evidence of neurotoxicity. Furthermore, Forest reports that numerous repeated dose studies were performed without any significant observations regarding neuropathology. Forest reported that histopathological examination revealed no evidence of vacuolization or necrosis in baboons (primates are considered resistant to NMDA antagonist induced Olney-type lesions). Forest concludes that the neuropathological lesions observed in high-dose rat studies are not expected to occur during therapeutic exposure in humans. They note that the lesions did not occur with slow escalation of dose and that primate brains are felt to be resistant to induction of these lesions (SU, vol. 1.11, p. 319).

2.5 Human Pharmacokinetics

Forest reports that memantine exhibited linear pharmacokinetics following single and multiple dose administration and that the terminal elimination half-life was 60 to 80 hours. Forest notes that T_{max} occurs at approximately 4 to 6 hours post dose. Memantine absorption from oral tablet formulations was complete and was not affected by food. Forest reports that memantine is primarily excreted unchanged in the urine (75-90%) and that acidic urine pH enhances memantine excretion. The major metabolites of memantine excreted in the urine were the memantine N-gludantan conjugate and 6-hydroxy memantine. Forest reports that the potential for interaction with drugs metabolized by cytochrome P450 is low. Memantine exhibits a low level of protein binding (45%).

In *in vitro* studies, memantine did not attenuate the inhibition of acetylcholinesterase caused by donepezil, galantamine and tetrahydroaminoacridine. In a study of 24 subjects, Forest found no differences in the pharmacokinetics of memantine or donepezil or in the inhibition of acetylcholinesterase by donepezil when the two drugs were administered alone and in combination. In an interaction study with hydrochlorothiazide/triamterene, memantine did not affect the bioavailablity of triamterene or its metabolite but did cause a 20% reduction in the bioavailability of hydrochlorothiazide (SU vol. 1.11, pp. 293-6).

3. Approach to Safety Review/Methods

Using the paper and electronic NDA ISS submissions, the two-month Safety Update, and responses to specific reviewer questions, I reviewed treatment emergent adverse events identified from the memantine development program. To verify the accuracy of the primary data for all deaths and serious adverse events summarized by the sponsor, I cross checked data from the sponsor's listings, case report forms (CRFs), narrative summaries, and electronic data sets. To evaluate the adverse event (AE) coding procedures, I compared investigator verbatim terms with the corresponding preferred terms assigned by the sponsor. For selected events (e.g., liver related abnormalities, rashes), I reviewed the coding in more detail by examining the CRF, electronic data sets, narrative summaries, and study report listings to determine if the coded terms accurately reflected the described events. I reviewed the death narratives for all study subjects who died and summarized the clinical details for selected deaths. In addition, I reviewed the CRFs, narrative summaries, data sets and study reports for serious adverse events (SAEs), selected AEs leading to discontinuation from a study, and any AE preferred terms suggestive of events of interest.

I reviewed the results of the sponsor's treatment emergent AE risk calculations. I reviewed the sponsor's lab and vital sign data analyses. I conducted additional analyses of extreme lab outliers, blood pressure outliers, and QTc data.

4. Review Findings

4.1 Description of Data Sources

Forest submitted safety data from fifty-three completed trials, and additional safety data from twenty-one ongoing studies through 4/30/02 in their NDA. In a supplement submitted 1/10/03, Forest submitted safety data from a recently completed placebo controlled trial MEM-MD-02. The safety update, submitted 4/11/03, integrated the data from MEM-MD-02 with the NDA analyses and updated deaths and SAEs through 9/30/02 for the twenty-one ongoing studies. The safety update also included data from three newly completed clinical pharmacology trials.

The fifty-seven completed trials submitted in the NDA and safety update include studies exploring a number of treatment indications including dementia, neuropathic pain, Parkinson's disease, organic brain syndrome, and spasticity. A list of the completed studies is provided as an appendix to this review.

Forest presented the memantine safety data using 4 major groupings. Group 1 data includes eight Phase II/III double blind, placebo-controlled studies in dementia, four open-label extensions of these trials and two phase II/III double-blind, placebo-controlled trials in neuropathic pain. Group 1 data constitute the primary safety data for the memantine NDA. Group 2 data includes thirteen studies in patients with dementia, organic brain syndrome, Parkinsonism, multiple sclerosis, and spasticity. In these studies, only AEs considered drug-related were reported and therefore these data are not complete with regard to safety data captured. Group 3A data includes eight completed clinical pharmacology studies in healthy subjects. Group 3B data includes twenty-two clinical pharmacology studies for which limited safety data are available. The safety data from group 3B studies could not be incorporated into the electronic ISS safety database and Forest summarized these data separately. Forest summarized separately limited safety data from 51 other completed memantine trials (3,750 subjects).

In their presentation of safety data, Forest provided analyses for various sub-groups of the Group 1 safety data. The subgroups are listed below.

FDA TABLE 1 Group 1 Safety data sub-groups

Subgroup	**Trials**
All Placebo Controlled Trials	9605, 9403, 9202, 9408, 9104, 9105, 9206, NTI 9702, NTI 9801, MEM-MD-02
Placebo Controlled Dementia Trials	9605, 9403, 9202, 9408, 9104, 9105, 9206, MEM-MD-02
Open Label Extension Dementia Trials	9605 OLEX, 9202 OLEX, 9408 OLEX, 9206 OLEX
Long-term dementia patients (≥12 months exposure to memantine)	9605+9605 OLEX, 9202+9202 OLEX, 9408+ 9408 OLEX, 9206+9206 OLEX
All memantine dementia patients	9605, 9403, 9202, 9408, 9104, 9105, 9206, MEM-MD-02, 9605 OLEX, 9202 OLEX, 9408

	OLEX, 9206 OLEX
Placebo controlled studies, dementia diagnosis (vascular vs. Alzheimer's)	9605, 9403, 9202, 9408, 9104, 9105, 9206, MEM-MD-02
Moderate to severe dementia	9605, 9403, 9202, 9408, 9104, 9105, 9206, MEM-MD-02

(From SU vol. 1.11, pp. 131-132)

4.1.1 Primary Safety Data

Group 1 studies

Group 1 double blind placebo-controlled dementia studies

Forest submitted data from eight double blind placebo-controlled dementia studies in the memantine NDA and safety update. The following table summarizes features of these studies.

FDA TABLE 2: Summary of Group 1 double blind placebo controlled dementia studies

Trial Number	Location	Dementia type	N	Duration	Dose
9605	USA	Alzheimer's	Memantine 126 Placebo 126	28 weeks	20mg
9403	Latvia	Alzheimer's or Vascular	Memantine 82 Placebo 84	12 weeks	10mg
9202	UK	Vascular	Memantine 295 Placebo 286	28 weeks	20mg
9408	France	Vascular	Memantine 165 Placebo 156	28 weeks	20mg
9104	France	Alzheimer's	Memantine 27 Placebo 29	13 weeks	20mg
9105	Portugal	Vascular	Memantine 15 Placebo 12	12 weeks	20mg
9206	Sweden	Vascular	Memantine 28 Placebo 28	14 weeks	20mg
MEM-MD-02	USA	Alzheimer's	Memantine 202 Placebo 201	24 weeks	20mg

Information from Forest Panel 1, SU vol. 1.11, pp. 95-100

Subjects randomized to memantine in the Group 1 placebo-controlled dementia trials were started at 5mg/day and were titrated to the study target dose by weekly increases of 5mg/day. Generally, these studies did not allow down-titration of dose. All subjects in MEM-MD-02 were also taking donepezil (patients had to have been taking donepezil for 3 months at a stable dose prior to randomization).

Group 1 open label dementia studies

Forest provided safety data from four open label extension trials. Studies 9605OLEX, 9202OLEX, 9408OLEX, and 9206OLEX enrolled subjects who completed the preceding placebo controlled trials. Studies 9605OLEX, 9202OLEX, 9408OLEX were 24 weeks long, while study 9206OLEX was up to 104 weeks long (NDA vol. 265, pp. 37-38).

Group 1 Placebo Controlled Neuropathic Pain Studies
Forest provided safety data from two neuropathic pain trials. Trial NTI9702 was an 8-week double blind placebo-controlled trial that randomized subjects with diabetic neuropathy or post herpetic neuralgia to memantine 40mg/day (n=58) or placebo (n=64). Trial NTI9801 was an 8-week double blind placebo-controlled trial that randomized subjects with diabetic neuropathy to placebo (n=85) or memantine (n=333) 20mg/day or 40mg/day (NDA vol. 265, p.113).

4.2 Exposure
4.2.1 Number of subjects
Forest reports memantine exposure that exceeds ICH guidelines with respect to total number of subjects exposed to the proposed effective dose and for 6 months and 1 year. Forest reported that they have safety information for 2,504 patients exposed to memantine and 1,288 exposed to placebo in group 1, 2 and 3A studies (SU vol. 1.11, p.93). Group 1 studies, which constitute the Primary safety data, include 1,748 memantine subjects and 1,071 placebo subjects.

Group 1 studies
The following table summarizes the number of subjects exposed by treatment in the Group 1 studies (Adapted from Forest Fig 2, SU vol. 1.11, p.124 and Panel 2, SU vol. 1.11, p.125).

FDA TABLE 3 Group 1 studies- Number of Subjects Exposed

Trial Number	**Indication**	**Memantine**	**Placebo**
9605	Alzheimer's dementia	126	126
9403	Vascular /Alzheimer's dementia mix	82	84
9202	Vascular dementia	295	286
9408	Vascular dementia	165	156
9104	Alzheimer's dementia	27	29
9105	Vascular /Alzheimer's dementia mix	15	12
9206	Vascular dementia	28	28
MEM-MD-02	Alzheimer's dementia	202	201
Dementia Placebo Controlled Trial Subtotal		*940*	*922*
NTI 9702	Peripheral Neuropathy	58	64
NTI 9801	Peripheral Neuropathy	333	85
Peripheral Neuropathy Placebo Controlled Trial Subtotal		*391*	*149*
Group 1 Placebo Controlled Trial Subtotal		*1,331*	*1,071*
9605 OLEX	Alzheimer's dementia	80/175*	
9202 OLEX	Vascular dementia	226/464*	
9408 OLEX	Vascular dementia	88/171*	
9206 OLEX	Vascular dementia	23/46*	
Dementia Open Label Trial Subtotal		*417/856**	
Dementia Subtotal (PC+OL first exposures)		*1,357*	
Group I Studies Total		**1,748**	**1,071**

*Number with first exposure to memantine/total number exposed to memantine during trial

Within the Group 1 studies, 476 of the 1,748 subjects (27%) exposed to memantine had Alzheimer's disease (Controlled trials N=194, NDA vol. 265, p. 116; MEM-MD-02 N=202, SU vol. 1.11, p.126, First exposure in open label extensions N=80, see above). For Group 1 dementia placebo controlled trials, 42% (396/940) had Alzheimer's dementia and 58% (544/940) had vascular dementia.

Exposure Group 2 studies
Forest reported that 549 subjects were exposed to memantine and 173 to placebo in Group 2 studies (NDA vol. 265, p.189).

Exposure Group 3 studies
Forest reported that 207 subjects were exposed to memantine in Group 3A studies, which include primarily pharmacokinetic study results (NDA vol. 265, p.190). Forest reported that 280 subjects were exposed in Group 3B studies, for which little safety data is available (SU vol. 1.11, p.122).

Additional exposure
Forest reported that 3,750 patients were exposed to memantine in clinical trials not included in the NDA safety and safety update databases (SU vol. 1.11, p.149). In addition, they state that there have been more than 400,000 person years of memantine use in Germany since approval in 1982.

4.2.2 Exposure by duration
Group 1 studies
Forest summarized exposure by duration for the Group 1 dementia studies (SU vol. 1.11, p.208, NDA vol. 265, p.184). I provide exposure by selected periods of duration in the following table.

FDA TABLE 4 Exposure by duration, Group 1 dementia studies

	Double Blind		***Open Label***	***Total***
	Placebo N=922	*Memantine N=939**	*Memantine N=856*	*Memantine N=1,357*
Treatment Duration (Days)				
Mean	150.7	151.2	173.8	214.4
SD	58.6	59.2	105.5	135.7
Median	171	172	168	169
Range	1 to 241	1 to 232	1 to 796	1 to 884
Treatment Duration n (%)				
≥4 weeks	884 (95.9%)	896 (95.4%)	835 (97.5%)	1,306 (96.3%)
≥24 weeks	553 (60%)	584 (62.2%)	506 (59.1%)	862 (63.6%)
≥52 weeks	0	0	32 (3.7%)	277 (20.4%)
≥78 weeks	0	0	23 (2.7%)	25 (1.8%)

*Missing exposure data for subject 9408-0162

Forest stratified exposure data for the Group 1 dementia trial subjects by dementia diagnosis type (Alzheimer's v. vascular). For all Group 1 dementia trials (placebo

controlled and open label) of the 862-dementia subjects exposed for ≥24 weeks, 276 (32%) had Alzheimer's dementia and 586 (68%) had vascular dementia (SU vol. 1.11, p.205). Of the 277-dementia subjects exposed for ≥52 weeks, 46 (17%) had Alzheimer's dementia and 231 (83%) had vascular dementia (Forest 1/24/03 submission, response to reviewer questions).

In table 3.1.4, Forest reported 796 person-years exposure to memantine for Group 1 dementia subjects. In the Group 1 dementia placebo-controlled trials, Forest reported 389 person-years exposure to memantine and 381 person-years exposure to placebo (SU Table 3.1.1). Forest reported 407 person-years exposure to memantine in Group 1 open-label dementia studies.

Group 1 Neuropathic pain studies
The neuropathic pain subjects had short-term exposures to memantine and Forest reported that only 1 memantine subject was exposed for 12 or more weeks in these studies (SU Table 3.1.5).

Group 2 Studies
Forest reported that 221 subjects received memantine for at least 24 weeks and 104 subjects received memantine for at least 48 weeks in Group 2 studies (SU Table 3.1.6). Forest reported 217 person years exposure to memantine and 19 person years exposure to placebo in Group 2 studies (SU Table 3.1.6).

Group 3 Studies
Forest reported that 207 subjects were exposed to memantine in Group 3A studies, with a mean exposure of 21 days (SU vol. 1.11, p.305). Forest reported that 280 subjects were exposed to memantine in Group 3B studies.

4.2.3 Exposure by Dose and Duration
Group 1 Exposure by Dose and Duration
In their summary of exposure dose by duration, Forest reported that most of the memantine exposures occurred at the proposed effective dose specified in labeling, 10-20mg/day. In their summary of duration by dose, Forest classified subjects by maximal daily dose and HFD-120 requested an additional table classifying exposure by modal dose. The results for 24 and 52 weeks were the same regardless of whether patients were classified by maximal or modal dose. For Group 1 subjects with at least 24 weeks exposure, 862 had a maximal/modal daily dose of 20mg. For Group 1 subjects with at least 52 weeks exposure, 277 had a maximal/modal daily dose of 20mg (SU Tables 3.1.9, 3.1.9A).

4.2.4 Exposure by Age
Group 1 Dementia Placebo Controlled Trials
The mean age of memantine subjects enrolled in Group 1 dementia placebo controlled trials was 75.7 years (median 76 years, range 50 to 97 years) compared to 76 years (median 76 years, range 50 to 96 years) in the placebo group (SU vol. 1.11, p.194).

Forest provided summary statistics for age stratified by dementia diagnosis for the Group 1 dementia placebo controlled trials. The mean age for memantine subjects with an Alzheimer's disease diagnosis was 75.3 years (median 76 years, range 50 to 92 years) compared to 75.7 years (median 76 years, range 50 to 93 years) for placebo subjects with and Alzheimer's disease diagnosis. For subjects with a vascular dementia diagnosis, the mean age of memantine subjects was 76.1 years (median 76 years, range 54 to 97 years) compared to 76.2 years (median 76 years, range 54 to 96 years) for placebo subjects with a vascular dementia diagnosis (SU table 12.1.1A).

4.2.5 Exposure by Sex

Group 1 Dementia Placebo Controlled Trials

Fifty-seven percent of memantine subjects in the Group 1 dementia trials were female compared to 55% of placebo subjects (SU vol. 1.11, p.194).

When stratified by dementia diagnosis, there was a predominance of females among subjects with an Alzheimer's disease diagnosis while the percentage of males and females was similar for subjects with a vascular dementia diagnosis. In these trials, 67.2% of memantine subjects with an Alzheimer's disease diagnosis were female compared to 65% of placebo subjects. Fifty percent of memantine subjects with a vascular dementia diagnosis were female compared to 47% of placebo subjects with a vascular dementia diagnosis (SU table 12.1.1A).

4.3 Review of AE Surveillance, Coding of AEs, and Approach to Evaluating Safety

Adverse events were captured by investigators using open ended questions. Forest summarized the SAEs, AEs leading to discontinuation and treatment emergent AEs from the memantine development program. SAEs were defined as "any untoward medical occurrence that resulted in death; was life-threatening; required inpatient hospitalization or prolonged an existing hospitalization; resulted in persistent or significant disability/incapacity; or was a congenital anomaly/birth defect" (SU vol. 1.11., p.181). Forest also considered other "medically important events that required intervention in order to prevent one of the above outcomes" as serious. Forest defined treatment emergent adverse events (AEs) as adverse events which started after the start date of dosing with study medication and occurred within 30 days following the last dose of study medication (SU vol. 1.11., p.181). Forest defined adverse events leading to discontinuation as those adverse events where the action taken with regard to study drug was associated with discontinuation and the AE onset date was on or before the last dose date of study medication (SU vol. 1.11, p.182).

AE investigator verbatim terms for AEs were mapped to World Health Organization Adverse Reaction Terminology (WHOART) Dictionary, version 1997/Q3 (SU vol. 1.11, p.179). Forest calculated AE risks by dividing the number of subjects in the treatment group with an AE by the total number of subjects in that treatment group for the particular safety database analysis group.

In addition to AE data, investigators collected vital sign data, laboratory data and ECGs during memantine studies. Orthostatic blood pressure measurements were not performed in phase II/III trials. In group 1 placebo controlled studies subjects had screening and end

study labs in two studies (MEM-MD-02, and 9206) and in the remaining studies, at least three and as many as five laboratory test evaluations (SU vol. 1.11, p.135). For group 1 placebo controlled studies, subjects had only screening ECGs in four studies (9202, 9104, 9105, and 9206). In studies 9605, MEM-MD-02, 9403, 9408, NTI-9702, and NTI-9801, ECGs were collected at screening or week 0 and at end of study (SU vol. 1.11, p.135).

4.4 Audit Findings and Evaluation of the AE Coding

I reviewed the investigator actual/verbatim terms listed in the CRFs of selected memantine subjects with serious AEs or who discontinued for AEs and the terms were accurately summarized in the narrative summaries, and the electronic data sets. I repeated these comparisons for lab and vital sign data across the available data sources. I found agreement between sources.

Using the electronic adverse event data sets, I reviewed the results of the coding process that the sponsor used to group the investigator terms for adverse event analyses. I compared investigator verbatim terms for adverse events to the coded terms (WHOART).

The coding of investigator verbatim adverse event terms to preferred terms was generally acceptable. Although I found infrequent inconsistencies that resulted from the coding process, none would markedly impact the safety assessment of the memantine NDA. There were occasional occurrences of splitting similar investigator terms to different preferred terms. One example of apparent splitting was for the preferred terms oedema, oedema dependent, and oedema peripheral. I found investigator terms of “swollen ankle”, “swelling of feet”, and “leg swelling” coded to oedema. The investigator terms “ankle oedema” and “bilateral ankle edema” were coded to the preferred term oedema dependent. The preferred term oedema peripheral included investigator verbatim terms of “bilateral ankle edema, edema (legs)”, “leg oedema”, and “swollen right ankle”. In addition, I found the investigator term of apractic gait coded to the preferred term of ataxia while the investigator term of ataxic gait was coded to the preferred term gait abnormal. I also discovered an instance where the investigator term “moderate renal failure” was coded to the preferred term uremia, under the Metabolic and nutritional body system, even though there were preferred terms of renal function abnormal and renal failure acute under the Urinary system disorders body system. I did not find evidence of lumping of dissimilar investigator terms under single preferred terms. I rarely identified instances of incorrect coding (ex. investigator term T4 increased coded to TSH increased).

4.5 Clinical Pharmacology Studies, Safety

Forest presented safety data from their Clinical Pharmacology Studies as the Group 3 studies in the NDA and safety update. Forest identified thirty memantine Group 3 studies. Forest further divided the Group 3 studies into Group 3A and Group 3B studies on the basis of the adequacy of the data. Group 3A studies included safety data from eight studies that had adequate documentation to allow inclusion into the electronic ISS database. The group 3B studies include the safety data from the remaining twenty-two clinical pharmacology studies, where limited safety data were collected and the data could not be included in the electronic safety database (SU vol. 1.11, p.142).

4.5.1 Clinical Pharmacology, Exposure
Forest reported that 207 subjects were exposed to memantine in Group 3A studies, with a mean exposure of twenty-one days a median exposure of twenty-six days and a range of one to fifty days (SU vol. 1.11, p.305). Forest reported that 280 subjects were exposed to memantine in Group 3B studies.

The group 3A studies exposed healthy volunteers and used an immediate release memantine tablet dosage form that was used in the phase II-IV studies, as well as memantine drops, and a slow release tablet form of memantine. The group 3B studies exposed various subpopulations of users to various dosage forms of memantine and used various routes of administration.

4.5.2 Clinical Pharmacology Mortality
Forest reported no deaths from Group 3A studies (0/207) and one death from a Group 3B study (0.4%, 1/280). This Group 3B death occurred in an elderly subject with renal failure who experienced a myocardial infarction (NDA vol. 265, p.275).

4.5.3 Clinical Pharmacology Serious Adverse Events
Forest reported no SAEs from Group 3A studies (0/207) and three SAEs from Group 3B studies (1.1%, 3/280). The Group 3B SAEs were MI in a subject with renal insufficiency, respiratory failure in a subject with pronounced emphysema and renal insufficiency, and adenocarcinoma diagnosed in an AIDS patient (NDA vol. 265, p.276-7, Response to Reviewer questions 5/15/03).

4.5.4 Clinical Pharmacology Discontinuations for Adverse Events
Forest reported that 4.8% (10/207) of Group 3A subjects and 2.9% (8/280) of Group B subjects discontinued for AEs; aside from ataxia, there did not appear to be clusters of similar events leading to discontinuation from these trials. Five group 3A subjects (11, 16, 33, 34, 36) discontinued for ataxia, all from one study, 9704 (NDA vol. 104, pp. 68-70). Some of these subjects also reported other AEs such as impaired concentration, and dizziness. Study 9704 assessed the food interaction of the test formulation, a new film tablet, and compared the bioavailability of the new film tablet to a reference formulation in healthy elderly males and females. The subjects were divided into two groups. The first group received a single dose of test formulation (20mg) while fasting, followed by multiple doses of the test formulation (10mg, 20mg). The second group received a single dose of the test formulation (20mg) following a standard meal, followed by multiple doses of the reference formulation (10mg, 20mg). Two dropouts were from the first treatment group and three from the second treatment group. Three dropouts were males and two were females. These events resolved in all cases, in one case on the day of withdrawal and in the other cases within 2 to 5 days (one did not note the time to improvement). There was little other information provided about these events.

4.5.5 Clinical Pharmacology Treatment Emergent Adverse Events
Forest reported that 71% (34/48) of memantine exposed subjects in single dose Group 3A studies reported one or more AEs (SU vol. 1.11, p.306). Dizziness (35%, 17/48), headache (23%, 11/48), fatigue (17%, 8/48), somnolence (10%, 5/48), concentration

impaired (8%, 4/48) and ataxia (6%, 3/48) were the AEs reported by at least 5% of subjects from these trials (SU Panel 50, vol. 1.11, p.307).

Forest reported that 65% (103/159) of memantine exposed subjects in multiple dose Group 3A studies reported one or more AEs (SU vol. 1.11, p.307). Fatigue (32%, 51/159), headache (27%, 43/159), dizziness (18%, 29/159), somnolence (16%, 25/159), mouth dry (7%, 11/159), agitation (6.3%, 10/159), nausea (6%, 9/159) and concentration impaired (6%, 9/159) were the AEs reported by at least 5% of subjects from these trials (SU table 12.2.2b).

I read through SU Table 12.2.2, which summarized all AEs from Group 3A studies and there were no events suggestive of renal failure, hepatic failure, rhabdomyolysis, pancreatitis, or serious skin reactions. Below I summarize selected AEs from the Group 3A studies.

Face edema

9402-1-8 This 66 year old female had an AE of face edema and the AE data set included the verbatim term "eyelid edema" for this event. This AE resolved the same day, was not serious, did not lead to discontinuation, and required no treatment. This subject did not report any AEs related to allergy or breathing difficulty.

Hepatic Enzymes increased

9704-1-37 This 59 year old female had an AE of hepatic enzymes increased. The lab data set noted a baseline SGPT of 5 that increased to 39 (ULN=30) and returned to 9. There were no associated increases in SGOT, GGT, ALP, or bilirubin.

Anemia

9702-1-12 This 59 year old male had a baseline Hgb of 14.3g/dL and HCT of 45% that decreased to 10.7g/dL and 34%, respectively. WBC count was 5.1 at baseline and increased to 5.2 while the platelet count was 135 at baseline and increased to 316. There were no abnormally increased bilirubin or LDH results. This event was reported as resolved, was not considered serious, and did not lead to discontinuation.

9702-1-18 This 55 year old female had a baseline Hgb of 13.4g/dL and HCT of 39% that decreased to 10.6g/dL and 31%, respectively. The comment section of the AE data set noted that the drop was due to blood loss but did not explain and no bleeding AEs were reported. WBC was 4.8 at baseline and decreased to 3.8 while baseline platelet count was 212 and it increased to 230. The comment section reported that the values were clearly increased 3 weeks later but the data set did not include these results. There were no abnormally increased bilirubin or LDH results. This event was reported as resolved, was not considered serious, and did not lead to discontinuation.

Leucopenia

9201-1-2 This 23 year old male had an AE of leucopenia. The comment section of the data set noted a relative lymphocytosis. Baseline WBC count was 4, which was followed by WBC counts of 3.8, and 4.1. There were no remarkable changes in Hgb, HCT, or platelet count. The data set had no outcome recorded for this event, it was considered non-serious, and did not lead to discontinuation.

Forest did not provide a complete list of AEs from Group 3B studies. They commented that some Group 3B studies did not capture AE data. For the studies that included AE data, Forest summarized the most commonly reported AEs (at least 10%). The commonly reported AEs were similar to AEs reported in other studies.

4.5.6 Clinical Pharmacology, Lab Data
Aside from a mean increase in platelets (15.1), there were no remarkable laboratory mean changes for the single dose Group 3A studies. No memantine subjects in Group 3A single dose studies met laboratory potentially clinically significant outlier criteria.

Aside from a mean increase in platelets (7.1), there were no remarkable laboratory mean changes for the multiple dose Group 3A studies. Two memantine subjects in multiple dose group 3A studies met potentially clinically significant criteria for low hemoglobin (10.6g/dl, and 10.7g/dL), two for low hematocrit (0.28, and 0.31) and two for high potassium (5.5mmol/L and 6.0mmol/L). One memantine subject had a low platelet count of 8,000 that appeared to be a lab error since the platelet count the next day was 310,000 (SU tables 12.4.2b and 12.4.1).

Forest did not provide a lab data summary for Group 3B studies.

4.5.7 Clinical Pharmacology, Vital Sign Data
Forest reported a mean decrease in systolic BP (-9.9mmHg) and diastolic BP (-0.9 mmHg) and a slight increase in pulse (0.9 bpm) in the single dose Group 3A studies. One subject in these studies had a decrease in systolic BP from 140mm Hg to 88mmHg that returned to 107mmHg at the next measurement, five and a half hours later. A second subject had an increase in systolic BP from 148mmHg at baseline to 221mmHg. Forest reported that the systolic blood pressure for this subject returned to normal at follow up (SU vol. 1.11, p.308).

Forest reported mean decreases in systolic BP (-4.2mm Hg), diastolic BP (-2.8mm Hg) and pulse (-0.2bpm) in the group 3A multiple dose studies (SU table 12.3.2b). No blood pressure outliers were identified but Forest reported that three subjects had met potentially clinically significant criteria for decreases in pulse (all three decreased to 48bpm).

When asked for data supporting the proposed labeling claim that memantine does not cause orthostatic blood pressure changes, Forest referenced two clinical pharmacology trials, IE1801 and HUK-610/5P. Both studies were Group 3B studies. Forest noted that supine and standing blood pressures were captured during both studies. Forest was unable to describe the methodology used to collect blood pressures in these trials, specifically the duration of time subjects were supine and the time between capture of supine and standing blood pressure. In study IE1801, at 4 hours post dose, the measurement closest to T_{max}, for each dose studied there appeared to be mean increases in systolic and diastolic blood pressure and pulse when comparing standing to supine measurements. In study HUK-610/5P, an iv study, there did not appear to be consistent differences between supine and standing blood pressures, but mean standing pulse was increased compared to mean supine pulse for all time points and in both the placebo and memantine phases. Forest reported that four subjects (one placebo, one 30mg, and two 40mg) experienced dizziness on standing between three and five hours of the start of infusion, lasting 1 to 2 minutes, and not associated with blood pressure changes (July 3, 2003 submission, Response to reviewer questions).

Forest did not provide a summary analysis of vital sign data for the Group 3B studies.

4.5.8 Clinical Pharmacology, ECG data
Forest submitted no clinical pharmacology studies specifically designed to evaluate the effect of memantine on cardiac repolarization. Forest summarized the ECG data for the 88 memantine subjects in Group 3A studies that had baseline and end of study ECGs. The mean change from baseline for QTcB was -6.5msec and no subjects had a QTcB≥500msec (SU tables 12.5.1, 12.5.3).

4.6 Phase II/III Studies, Other Studies Safety
4.6.1 Deaths
Forest reports that 75 memantine-treated subjects (3.3%, 75/2,297) from Group 1 and 2 trials died (SU, vol. 1.11, p.212). I include a complete listing of all reported Group 1 and 2 trials memantine deaths as an appendix to this review. Forest presented the number of patients who died within 30 days of last dose by treatment for Group 1 studies. Forest did not specify the period of time since last dose for the deaths from Group 2 trials.

Deaths Group 1 trials
Forest reports 51 deaths (2.9%, 51/1,748) within 30 days of last exposure in memantine subjects enrolled in Group 1 studies.

Deaths Group 1 Dementia Placebo Controlled Trials
Mortality risk was similar in the memantine and placebo treatment groups from Group 1 dementia placebo controlled trials. Eighteen memantine subjects (1.9%, 18/940) and 21 placebo subjects (2.3%, 21/922) enrolled in Group 1 dementia placebo controlled trials died within 30 days of last exposure. The mortality rate was slightly higher among placebo subjects (5.5/100 patient-years, 21/381) compared to memantine subjects (4.6/100 patient-years, 18/389) in these studies (SU, vol. 1.11, p.212).

The following table lists the causes of death by body system and preferred term and stratified by dementia type. The cause specific mortality risks were similar for the memantine and placebo treated groups. I provide clinical descriptions for selected memantine deaths in a section below.

FDA TABLE 5 Group 1 dementia placebo controlled study deaths by body system and preferred term and stratified by dementia type

Body System Preferred Term	**Alzheimer's Dementia**		**Vascular Dementia**	
	Memantine	Placebo	Memantine	Placebo
	N=396	N=394	N=544	N=528
Body as a Whole	**0**	**0**	**1 (0.2%)**	**0**
Sudden Death	0	0	1 (0.2%)	0
Cardiovascular Disorders	**2 (0.5%)**	**0**	**0**	**0**
Cardiac Failure	2 (0.5%)	0	0	0
Centr and Periph Nerv Sys	**0**	**1 (0.3%)**	**4 (0.7%)**	**5 (0.9%)**
Cerebral Hemorrhage	0	0	1 (0.2%)	1 (0.2%)
Cerebrovascular disorder	0	1 (0.3%)	1 (0.2%)	3 (0.6%)
Coma	0	0	2 (0.4%)	2 (0.4%)
Quadraplegia	0	0	0	1 (0.2%)
GI System Disorders	**0**	**0**	**2 (0.4%)**	**1 (0.2%)**
Diarrhea	0	0	1 (0.2%)	0
GI disorder NOS	0	0	1 (0.2%)	0
Hematemesis	0	0	0	1 (0.2%)
Heart Rate/Rhythm disorder	**0**	**0**	**3 (0.6%)**	**2 (0.4%)**
Cardiac Arrest	0	0	3 (0.6%)	2 (0.4%)
Myo Endo Pericardial & Valve Disorders	**3 (0.8%)**	**2 (0.5%)**	**0**	**0**
Myocardial infarction	3 (0.8%)	2 (0.5%)	0	0
Neoplasm	**0**	**2 (0.5%)**	**1 (0.2%)**	**1 (0.2%)**
Carcinoma	0	0	0	1 (0.2%)
Metastasis NOS	0	0	1 (0.2%)	0
Thyroid neoplasm malignant	0	1 (0.3%)	0	0
Pulmonary Carcinoma	0	1 (0.3%)	0	0
Psychiatric disorder	**0**	**2 (1.0%)**	**0**	**0**
Alzheimer's disease	0	2 (1.0%)	0	0
Respiratory system disorder	**1 (0.5%)**	**1 (0.5%)**	**5 (0.9%)**	**5 (0.9%)**
Apnea	0	0	2 (0.4%)	2 (0.4%)
Bronchitis	0	0	1 (0.2%)	1 (0.2%)
Pneumonia	1 (0.5%)	1 (0.5%)	2 (0.4%)	2 (0.4%)
Vascular disorders	**0**	**0**	**0**	**2 (0.4%)**
Aneurysm ruptured	0	0	0	1 (0.2%)
Embolism Pulmonary	0	0	0	1 (0.2%)

Adapted from SU table 4.2.1A. * 3 placebo and 2 memantine patients had 2 causes of death each and 1 placebo and 1 memantine patient had 3 causes of death each.

Deaths Group 1 Dementia Open Label Extension Trials
Forest reported thirty-two deaths (3.7%, 32/856) within 30 days of last exposure to memantine in dementia open-label extension studies. The mortality rate in the dementia open-label extensions (7.9/100 person-years, 32/407 person years) was similar to the mortality rate observed in the placebo (5.5/100 patient-years, 21/381) and memantine subjects (4.6/100 patient-years, 18/389) during the Group 1 dementia placebo controlled trials (see above). The mortality risk for the subgroup that received memantine for the first time during an extension trial was 3.8% (16/417) compared to 3.6% (16/439) for those who received memantine in the previous controlled trial.

The following table lists the causes of death by body system and preferred term and stratified by treatment for Group 1 dementia open label extension trials. I provide clinical descriptions for selected memantine deaths in a section below.

FDA TABLE 6 Group 1 dementia open-label study deaths by body system and preferred term and stratified by treatment

Body System Preferred Term	**Placebo- Memantine** N=417	**Memantine-Memantine** N=439
Body as a Whole	**3 (0.7%)**	**1 (0.2%)**
Condition Aggravated	1 (0.2%)	0
Inflicted Injury	1 (0.2%)	0
Sepsis	1 (0.2%)	0
Sudden death	0	1 (0.2%)
Cardiovascular disorders	**1 (0.2%)**	**3 (0.7%)**
Cardiac failure	1 (0.2%)	2 (0.5%)
Hypertension	0	1 (0.2%)
Centr and Periph Nerv Sys	**3 (0.7%)**	**4 (0.9%)**
Cerebral Hemorrhage	1 (0.2%)	1 (0.2%)
Cerebrovascular disorder	2 (0.5%)	3 (0.7%)
Heart rate/rhythm disorders	**1 (0.2%)**	**0**
Cardiac arrest	1 (0.2%)	0
Metabolic/Nutrition disorders	**0**	**1 (0.2%)**
Dehydration	0	1 (0.2%)
Myo Endo Pericardial & Valve Disorders	**1 (0.2%)**	**3 (0.7%)**
Myocardial Infarction	1 (0.2%)	3 (0.7%)
Neoplasm	**1 (0.2%)**	**0**
Carcinoma	1 (0.2%)	0
Psychiatric disorder	**0**	**1 (0.2%)**
Anorexia	0	1 (0.2%)
Somnolence	0	1 (0.2%)
Respiratory system disorder	**7 (1.7%)**	**5 (1.1%)**
Pneumonia	6 (1.4%)	3 (0.7%)
Bronchitis	0	1 (0.2%)
Respiratory disorder	1 (0.2%)	0
Respiratory insufficiency	0	1 (0.2%)
Urinary System disorder	**1 (0.2%)**	**0**
Urinary tract infection	1 (0.2%)	0
Vascular disorder	**0**	**1 (0.2%)**
Aneurysm ruptured	0	1 (0.2%)

Adapted from SU table 4.2.2. Three subjects had 2 causes of death each and one subject had 3 causes of death.

Deaths Group 1 Neuropathic Pain Trials
Forest reported one memantine death (0.3%, 1/391) from a neuropathic pain study.

Deaths Group 1 Dementia Trials, Clinical Descriptions
I found no clusters of unexpected causes of death in the Group 1 safety information provide by Forest. Forest reported no deaths attributable to hepatic failure, renal failure, serious skin reactions, hematologic dyscrasias, pancreatitis, or rhabdomyolysis.

I used narrative summaries, electronic data sets, CRFs and information provided in the NDA to summarize selected Group 1 memantine deaths below. I selected the most common causes of death for memantine subjects.

Pneumonia
Respiratory system disorders were listed as a cause of death for 18 memantine treated subjects in Group 1 dementia studies and the most common respiratory cause of death was pneumonia (n=12). In the placebo controlled trials the risk for dying from pneumonia was similar for the memantine (0.3%, 3/939) and placebo (0.3%, 3/922) treated groups. I read the narrative summaries for the twelve-memantine subjects who died and had pneumonia listed as the cause of death. Ten subjects who died of pneumonia were males and two were females and the age range was 71-90 years. The narratives and CRFs generally included little information about these events. Forest reported that the patients died from pneumonia but did not provide supportive data such as physical exam, laboratory, and X-ray results. Using the submitted electronic lab data sets, I determined that none of these subjects had a low leukocyte counts prior to these events.

Cerebrovascular disorder
Central and Peripheral Nervous system disorders were listed as the cause of death for 11 memantine subjects in Group 1 dementia trials and cerebrovascular disorder was the most common cause of death from this body system group (n=6). In the Group 1 dementia placebo controlled trials, the risk dying from cerebrovascular disorder was higher among the placebo subjects (0.4%, 4/922) than among memantine subjects (0.1%, 1/939). I read the narratives and CRFs for the six-memantine subjects who died and had cerebrovascular disorder listed as the cause of death. Five of these events occurred in males and one in a female and the age range was 62 to 83 years. The narratives generally used verbatim terms such as stroke and cerebrovascular accident to describe the events and did not provide additional details. One narrative (9202-00658) did provide the results from a CT scan that documented a fresh basal ganglia infarction.

Myocardial Infarction
Seven memantine treated subjects from Group 1 dementia studies died and had myocardial infarction listed as the cause of death. In the dementia placebo controlled trials, 3 memantine (0.3%, 3/939) and 2 placebo subjects (0.2%, 2/922) died and had myocardial infarction listed as the cause of death. I read the narratives and CRFs for the seven memantine subjects that died of MIs and found that none of the narratives included information (ECGs, cardiac enzymes, etc.) to support the diagnoses. Four of the deaths occurred following hospitalization, and in that setting the diagnosis is presumably

accurate. In the remaining three cases, the patient either died suddenly (9202-00843) or Forest provided no details about the events leading to death (9408-00388, MEM-MD-02-9206) to allow an assessment of the cause of death.

Cardiac Failure
Five memantine treated subjects from Group 1 dementia studies died and had cardiac failure listed as a cause of death. In the dementia placebo controlled trials, 2 memantine (0.2%, 2/939) and 0 placebo subjects (0/922) died and had cardiac failure listed as a cause of death. I read the narratives and CRFs for the five memantine subjects that died of cardiac failure and found that in four cases the subjects had preexisting histories of cardiac insufficiency or CHF. In the remaining case (9202-00153), the subject had cardiac failure and unspecified carcinomatosis listed as causes of death. This subject also experienced increases in liver enzymes and total bilirubin prior to death but the sponsor noted that these lab abnormalities initially arose during the double blind period when this subject was treated with placebo.

Death Group 1 Neuropathic Pain Trials, Clinical Description
One memantine treated subject from a peripheral neuropathy study died within 30 days of last exposure. Subject 100094, a 78-year-old female with a history of coronary artery disease, had myocardial infarction reported as the cause of death.

Deaths Group 2 Studies
Forest reported that the mortality risk among memantine subjects in Group 2 studies was 4.4% (24/549). This mortality risk is greater than the risk observed in Group 1 studies. Forest felt the difference in risk was likely due to underlying differences in the studied populations. Forest explained that all of these deaths were from two studies (MRZ90001-9406, MRZ9001-8801). MRZ9001-9406 was a 14-month trial in subjects with spasticity, and MRZ9001-8801 was a 6-month trial in hospitalized subjects with organic brain syndrome (average age 79 years). Forest commented that these populations were "extremely ill" (NDA vol. 265, p.197).

The data from the Group 2 studies do not allow for accurate exploration of cause specific mortality due to missing data. Four subjects had missing causes of death and 3 subjects had "death" listed as the cause of death. The most common listed causes of death in this group were cardiac failure (n=10), and pneumonia (n=4). No other cause was listed for more than 2 patients. Forest did not report any Group 2 deaths due to hepatic failure, renal failure, serious skin reactions, rhabdomyolysis, pancreatitis, or hematologic dyscrasias.

Deaths Ongoing Studies
Forest reported in the SU that 35 subjects (0.77%, 35/4,537) from ongoing studies died through 9/2002 (SU vol. 1.11, p.220). Forest did not report any deaths from ongoing studies due to hepatic failure, renal failure, serious skin reactions, rhabdomyolysis, pancreatitis, or hematologic dyscrasias. I include a list of deaths from ongoing studies as an appendix to this review.

Deaths Post Marketing Reports
In their SU submission, Forest reported one death identified from a post marketing report: An 81 year old female with Alzheimer's disease experienced cachexia, hyperthyroidism, shock, and ulcerative colitis on day 639 of treatment. The outcome was death (SU vol. 1.11, p.339).

In a separately submitted line listing of post marketing reports, Forest identified another post marketing report with an outcome of death: a 63 year old female who died with a diagnosis of epidermal necrolysis (July 9, 2003 submission).

During the review of the memantine NDA, Forest submitted a post marketing report of hepatic failure that resulted in death. This case is from France (initial report 4/21/03, follow-up 4/30/03). An 83 year old male treated with prazepam, piracetam, zopiclone, ginkgo, irbesartan, tamulosin, and memantine (approximately 25 days) was admitted to a hospital for a fall and worsening state, and was diagnosed with fulminant hepatitis. Galantamine was discontinued about one month before this event. A CT scan and liver serologies (hepatitis A, B, and C) were reportedly normal. CPK was 879, ALT 106. During hospitalization the patient fell and developed rhabdomyolysis. The hospitalization was further complicated by development of disseminated intravascular coagulation, coma, and left foot ischemia and the patient subsequently died. A post mortem liver biopsy revealed "a large injury of sinusoidal dilation in the centrovascular area with congestive intracellular cholestasis and intracanular and macrovesicular steatosis." The reporter noted that "some drugs could induce this type of injury, but most of the time, it is due to cardiac insufficiency." This patient apparently did not have recognized cardiac insufficiency at the time of the event.

4.6.2 Serious Adverse Events
I include a listing of all SAEs reported during Group 1 dementia trials as an attachment to this review.

Group 1 Dementia Placebo Controlled Trials
Forest reported that the SAE risk was higher in the placebo treated group (14.6%, 135/922) than in the memantine treated group (13.5%, 127/940) in the Group 1 placebo controlled dementia trials. The SAE rate in the memantine group was 32.7/100PY (127/389PY) compared to 35.5/100PY (135/381PY) in the placebo group (SU vol. 1.11, p.224).

No memantine treated subjects had a SAE due to hepatic failure, renal failure, rhabdomyolysis, or pancreatitis. Memantine subject 00181, an 83-year-old female, had a SAE that was listed as skin ulceration. The narrative for this event described a decubitus ulcer of the left leg that subsequently resolved without interruption of memantine. Memantine subject 9202-0649 had an SAE of anemia with a positive test for occult blood in her stool. She was treated with iron, the anemia resolved, and she continued in the study.

The following table provides the SAEs occurring in at least 3 memantine subjects and at least twice as frequently compared to placebo.

FDA TABLE 7: SAEs occurring in at least 3 memantine subjects and twice as frequently when compared to placebo, Group 1 placebo controlled dementia trials

Preferred Term	**Memantine (n=940)**	**Placebo (n=922)**
Cardiac Failure	0.7% (7)	0.2% (2)
Thrombophlebitis deep	0.6% (6)	0
Dyspnea	0.5% (5)	0.2% (2)
Transient Ischemic Attack	0.5% (5)	0.1% (1)
Constipation	0.4% (4)	0.1% (1)
Dehydration	0.4% (4)	0.1% (1)
Malaise	0.4% (4)	0.2% (2)
Breast neoplasm malignant	0.3% (3)	0.1% (1)
Chest pain	0.3% (3)	0
Heart disorder	0.3% (3)	0
Hemiplegia	0.3% (3)	0
Sepsis	0.3% (3)	0

From Forest Panel 27, SU vol. 1.11, p. 225.

I reviewed the heart disorder events to determine the nature of the AEs that this preferred term subsumed. All three memantine patients with heart disorder SAEs (9202-00591, 9408-00506, and 9048-00012) had pacemaker insertions (two described as replacement and one as planned insertion). None of the three patients had AEs suggestive of new onset or worsening arrhythmia, bradycardia, or syncope during the trials.

Group 1 Dementia Open label Extension Trials
Forest reported that 17.4% (149/856) of subjects in the dementia open label extension trials experienced an SAE. The SAE rate in the dementia open label extension trials, 36.6/100PY, was similar to the rate observed in the memantine group during the placebo controlled trials (32.7/100PY). The SAE risk observed during the open label trials for subjects who received placebo in the controlled trials and then received memantine during the extension (16.8%, 79/417) was similar to the SAE risk for patients who previously received memantine in the controlled trials (18%, 79/439).

The SAEs occurring in more than one percent of patients in the dementia open label extension trials were cerebrovascular disorder (1.8%), pneumonia (1.6%), TIA (1.3%), fall (1.2%), bronchitis (1.1%) and inflicted injury (1.1%).

Since Inflicted injury SAEs were common in the dementia placebo controlled trials (reported by 1.7% (16/922) of placebo subjects and 1.1% (10/940) of memantine subjects) and open label extensions (reported by 1.1% of open label subjects) I reviewed the inflicted injury SAEs to determine the nature of the AEs that this preferred term subsumed. I found that nine subjects from dementia open label trials had SAEs coded to the term inflicted injury. In eight cases, inflicted injury was the term used to subsume the injury following a fall. In three of these eight cases, the patients also had AEs of fall recorded while in the other five cases, only inflicted injury was captured as an AE and the fall event, while present in the CRF, was not reported as a separate AE. The inflicted

injury event not obviously associated with a fall occurred in an 81 year old female (9202-00134) who developed dizziness, somnolence, nausea and agitation, which was treated with thioridazine, and subsequently suffered a head injury, mechanism not described. This subject's condition deteriorated and she died seven days later.

I reviewed the listing of all SAEs occurring in dementia open label trials and there were no events suggestive of acute liver failure, rhabdomyolysis, or pancreatitis. There was one reported for each of the following events: jaundice, anemia, rash, blindness, creatinine increased, and hepatitis. I reviewed the narratives, CRFs, and data sets for these events and summarize the cases below.

Jaundice

9202-00257 This 67-year-old male developed an SAE described as obstructive jaundice. Lab results included GGT 646, ALP 492, Bilirubin 3.7, SGOT 346, and SGPT 731. The patient's CRF noted that he had an ultrasound that demonstrated gallstones and was awaiting an ERCP. The CRF subsequently noted that the gallstones were removed and that he recovered.

Anemia

9202-00089 This 84 year old male was hospitalized for transfusion with a hemoglobin of 7.9g/dL. I reviewed the lab data sets and found that this event was isolated to the red blood cell line (WBC and platelet counts remained normal). The CRF reported colon cancer but there was no other information provided about this diagnosis. Forest reported that the colon cancer and long term aspirin and naproxen use likely contributed to this event (Response to reviewer questions, 5/15/03).

Rash

9202-00764 This 76-year-old female had an SAE of rash and the narrative described the occurrence of herpes zoster.

Blindness

9202-00078 A 64 year old male developed blindness, headache, and abnormal gait after 199 days on drug. The subject was scheduled for a head CT but no other information was provided. Forest noted that the subject had an abnormal baseline ophthalmologic exam (bilateral decreased visual acuity, pseudophakia OS, cataract OD) and they were seeking additional information about this event (Response to reviewer questions, 5/15/03).

Creatinine Increased

9206-00047 An 84 year old male who received memantine in a controlled trial and its extension developed increased creatinine after 147 days of memantine. The subject was discontinued from the trial for confusion (SAE) and increased creatinine (not considered serious). The lab data set demonstrated a baseline creatinine of 1.9mg/dL and a creatinine of 2.2mg/dL at the time of discontinuation.

Hepatitis

9408-00185 A 72 year old male discontinued from an open label trial for hepatitis. The event was identified after 257 days of memantine treatment. This diagnosis was made by the investigator, apparently based on labs that were not included in the CRF. Memantine and other concomitant medications (acetylsalicylate lysine, trimetazidine, piretanide, pentoxifylline, bisoprolol, amlodipine, ramipril, and alprazolam) were discontinued. Follow-up liver related lab tests drawn one week later were normal.

Group 1 Neuropathic Pain Trial SAEs

In the placebo controlled neuropathic pain trials, the SAE risk for the memantine group was 4.1% (16/391) compared to 3.4% (5/149) in the placebo group. The SAE risk for the

memantine 20mg/day group was 2.9% (5/171) compared to 5% (11/220) in the memantine 40mg/day group (NDA table 4.4.5).

I reviewed the SAE narratives for the memantine subjects in the neuropathic pain trials. There were no events suggestive of renal failure, hepatic failure, hematologic dyscrasias, rhabdomyolysis, pancreatitis, or serious skin reactions. Abdominal pain was the only SAE reported by more than one memantine subject (n=2) in these studies.

Group 2 SAEs

Forest reported that 4.9% (27/549) of subjects in group 2 studies had SAEs. Forest acknowledged the low frequency of SAEs compared to the group 1 studies and attributed the lower frequency to the less stringent reporting requirements with group 2 studies. I read through the listing of SAEs from group 2 studies (NDA table 4.6.6). There were no events suggestive of renal failure, hepatic failure, hematologic dyscrasias, rhabdomyolysis, pancreatitis, or serious skin reactions.

Ongoing Studies

Forest reported that there were 345 patients with SAEs from ongoing studies being conducted by Forest, Merz, Suntory, and Allergan through 9/02 (SU vol. 1.11, p.229). Some of the SAEs are from double blind placebo controlled trials where the treatment blind has not yet been broken.

Forest provided narratives from their ongoing studies for patients who experienced SAEs. While they listed patients and SAEs from studies being conducted by Merz, Suntory and Allergan, they did not provide narratives for these patients. I reviewed the narratives for SAEs from the ongoing Forest studies. Forest did not report any events suggestive of serious skin reactions or rhabdomyolysis from their ongoing studies. Forest identified four patients with SAEs of renal failure, one with kidney dysfunction, one with anemia, three with pancreatitis and two with hepatic-related SAEs. I summarize those events below.

Renal SAEs

MEM-MD-01 179112 An 83 year old male, with blinded treatment assignment had an SAE of kidney dysfunction. The narrative summarized an event of obstructive uropathy secondary to benign prostatic hyperplasia.

MEM-MD-01 319101 An 85 year old female, with blinded treatment assignment, had an SAE of renal failure. The narrative described an episode of pre-renal azotemia that occurred in a patient with pseudomembranous colitis and pneumonia.

MEM-MD-06-A 099002 A 60 year old female with blinded treatment assignment and a history of diabetes mellitus, chronic renal insufficiency, hypertension, and nephrosclerosis had an SAE of renal failure. This patient experienced an increase in blood pressure (253/213 mmHg) that was associated with labs indicating acute renal failure (not further described). She was treated with IV medications (not specified) and hydration and improved.

MEM-MD-06-B 259001 A 73-year-old male with a history of diabetes, hypertension and cerebrovascular disease, received memantine during an open label trial and developed acute renal failure. This patient was admitted for atrial fibrillation and had a creatinine of 2.2mg/dL. His renal function worsened with his creatinine increasing to 4.4 mg/dL. His condition deteriorated and he died with the cause of death listed as cardiac arrest secondary to myocardial infarction, pericarditis, and acute renal failure. Forest felt that the subject's underlying medical conditions and concomitant medications (lisinopril, triamterene

hydrochlorthiazide) were the most likely etiology of this subject's acute renal failure (Response to Reviewer Questions 5/15/03).
MEM-MD-10 189021 An 88 year old female with a history of hypertension, elevated cholesterol, and renal failure was receiving blinded therapy and developed pneumonia and renal failure and died. The cause of death was pneumonia and ARDS and there were no additional details about the renal failure.

Anemia SAE

MEM-MD-01 319119 An 88 year old female with blinded treatment assignment had a hemoglobin of 7.5g/dL. This subject, who was taking warfarin, fell and sustained a large hematoma. Warfarin treatment was stopped and the patient was transfused.

Pancreatitis SAEs

MEM-MD-06-A 029015 This 40-year-old male with blinded treatment assignment and a history of diabetes mellitus and elevated triglycerides developed acute pancreatitis. He was treated with gemfibrozil, glipizide, pantoprazole and an increased dosage of atorvastatin and improved.
MEM-MD-06-B 099006 This 76 year old male with a history of pancreatitis, cholelithiasis, diabetes, diabetic neuropathy, duodenal ulcer, and anemia had an SAE of pancreatitis. This patient received blinded therapy in MD-06A and open label memantine in MD-06B. He was hospitalized for epigastric pain and was diagnosed with pancreatitis (lipase 7,561, amylase 1,577). An ultrasound showed a thickened gall bladder and multiple stones. A cholecystectomy was planned pending resolution of the pancreatitis. This patient had an EGD demonstrated two duodenal ulcers one with adherent clot. He underwent surgery (unspecified) and electrocautery. The pancreatitis resolved and the patient continued in the study.
ME-MD-06B 209005 This 55 year old female with diabetes mellitus and diabetic neuropathy was receiving open label memantine and was hospitalized for abdominal pain, nausea, and vomiting. She was diagnosed with cholecystitis and biliary pancreatitis resulting from cholelithiasis. She underwent a laparoscopic cholecystectomy and the event was considered resolved. She discontinued from the study.

Hepatic SAEs

MEM-MD-06-B 049016 This 64 year old male with a history of diabetes mellitus, diabetic neuropathy, cryptogenic cirrhosis and portal hypertension had an SAE of cirrhosis biliary. This condition was present prior to initiation of memantine treatment.
MEM-MD-10 119009 This 79 year old male received blinded medication for 31 days and was seen by his primary care physician for cough, poor oral intake, and two episodes of syncope. He was subsequently found to have an AST of 103, an ALT of 177, and an ALP of 336 with a PSA of 10. The impression was possible prostate cancer with liver metastases. The subject was discontinued. The primary care physician did not provide additional information but the sponsor documented that after stopping memantine the subject had an AST of 15, an ALT of 11 and an ALP of 138.

Post Marketing Reports Serious Adverse Events

Forest included the following five post marketing reports in their SU that appeared to meet the regulatory criteria for SAEs: hypotension during anesthesia; vertigo and nausea; psychosis; agitation, hallucinations and CVA (SU vol. 1.11, p.339).

In a separate line listing, Forest identified 24 serious post marketing reports and a listing of 13 additional reports where the seriousness was not specified. The line listing included two reports of epidermal necrolysis and a single report for each of the following events: aplastic anemia, vasculitis allergic, and hepatic enzymes increased (July 9, 2003 submission).

During the review cycle, Forest forwarded a report of a SAE from a Japanese clinical trial with the terms encephalopathy, EEG abnormal, cognitive disorder, and convulsions NOS. I summarize that report below.

An 82 year old male with Alzheimer's disease, hypertension, diabetes, diabetic retinopathy, cardiac hypertrophy, prostatic hyperplasia and herpes zoster completed four weeks of placebo treatment in a controlled memantine study. The narrative states that he first experienced a convulsion while receiving placebo (lasting 5-6 seconds). During the open label phase, he developed acute encephalopathy with symptoms of bilateral convulsions, abnormal EEG, and abnormal cognitive function. While taking memantine 20mg each morning, he experienced a seizure described as "trembling of the whole body from morning until 3:00 pm". Four days later he had a similar event that lasted from 7:30am to 9:30am. On the next day he had a similar event from 7:20 am to 9:00am. He was hospitalized and was noted to provide poor responses to questions and had head CT and MRI scans that indicated diffuse encephalopathy, bilateral atrophy of the hippocampus and ischemic changes to the parenchyma. No comparison was made to previous scan results. During an EEG, seizures (21 times during 12 minutes) with tremors were recorded. Additional reported EEG findings included a basal rhythm of alpha rhythm of 30μv, 10Hz predominantly observed in C-P-O, sporadic delta waves in Fp-F-C-P-O and a theta waves frequently in all leads. The tremors were described as right hand grasping and right forearm rhythmic movements at 7Hz. The narrative noted that sometimes similar tremors were noted on the left side. The hospitalization was complicated by pneumonia. The investigator described the events observed during hospitalization as acute encephalitis, with paroxysmal bilateral convulsions (or myoclonus). Memantine was stopped. An EEG one day after memantine discontinuation showed increased delta waves, which was improved by the following day. After hospital discharge, the narrative noted that the tremors and abnormal cognitive function were resolved and the EEG was improved. At this time, the investigator noted that the EEG and clinical course did not indicate epileptic seizure but instead, possible temporal worsening of extrapyramidal symptoms.

4.6.3 Discontinuations for Adverse Events

Group 1 Dementia Placebo Controlled Trials

Forest reported that the discontinuation due to AE risk was similar for the placebo treated group (11.5%, 106/922) and the memantine treated group (10.1%, 95/940) in the Group 1 placebo controlled dementia trials (SU vol. 1.11, p.251). The discontinuation due to AE rate in the memantine group was 24.4/100PY (95/389PY) compared to 27.8/100PY (106/381PY) in the placebo group.

The following table includes the AEs leading to discontinuation that occurred in at least three memantine subjects and at least twice as frequently compared to placebo.

FDA TABLE 8. AEs Leading to Discontinuation That Occurred in at Least Three Memantine Subjects and at Least Twice as Frequently Compared to Placebo, Group 1 Dementia Placebo Controlled Trials

AE leading to Discontinuation	Memantine (n=940)	Placebo (n=922)
Dehydration	0.4% (4)	0
Nausea	0.3% (3)	0
Diarrhea	0.3% (3)	0.1% (1)
Personality disorder	0.3% (3)	0.1% (1)
Asthenia	0.3% (3)	0.1% (1)
Urinary Tract Infection	0.3% (3)	0.1% (1)

From Forest Panel 31, SU vol. 1.11, p.252

I reviewed the narratives for the four memantine subjects who discontinued for dehydration (9605-028-0214, MEM-MD-02-2096, MEM-MD-02 2383, MEM-MD-02 2473). At the time of discontinuation, dehydration was diagnosed along with infections in three of the subjects and with dysphagia and poor intake resulting in a feeding tube placement in the fourth subject.

No memantine treated subjects discontinued from Group 1 dementia placebo controlled trials for events suggestive of hepatic failure, renal failure, rhabdomyolysis, pancreatitis, or serious rash. One subject discontinued for anemia, one for increasing BUN and creatinine. Those cases are summarized below.

Anemia

MEM-MD-02 037 2383 This 79-year-old female had only baseline lab values and her baseline hemoglobin was 11.3g/dL with a hematocrit of 33%. Baseline WBC count was 6.6 with a platelet count of 207. She was hospitalized for sepsis, arthralgia, anemia (extent not described) and atelectasis. She subsequently developed dehydration, a urinary tract infection, increased confusion and asthenia. She discontinued from the study for all of these events and was transferred to a nursing home. The anemia was reported as resolved.

Increased BUN/Creatinine

9202/00273 This 88 year old male with a history of hypertension and angina had a screening BUN/Cr of 27.5mg/dL/1.5mg/dL. Prior to his first memantine dose his BUN/Cr had increased to 31.7mg/dL/1.8mg/dL. After 90 days of memantine treatment his BUN/Cr was 36.4mg/dL/2mg/dL, despite increased oral fluid intake. The subject was discontinued from the study and the narrative and data sets did not include additional lab results.

The discontinuation due to AE risks for Alzheimer's disease subjects did not appear to be meaningfully different when compared to the discontinuation due to AE risks for vascular dementia subjects (SU vol. 1.11, Panel 32, p.253).

Open Label Dementia Trials

Forest reported that 10.7% (92/856) of subjects enrolled in open label dementia trials discontinued for adverse events. The discontinuation for adverse event rate in open label dementia trials (22.6/100PY; 92/407PY) was similar to the discontinuation due to AE -rates observed in the memantine (24.4/100PY) and placebo (27.8/100PY) groups in the group 1 placebo controlled dementia trials. The discontinuation due to AE risk for subjects who received placebo during the preceding placebo controlled trial (9.8%, 41/417) was similar to the risk in those who received memantine in the preceding controlled trial (11.6%, 51/439).

Cerebrovascular disorder (1.2%, 10/856) and pneumonia (1.2%, 10/856) were the only AEs leading discontinuation reported for more than 1% of dementia open label study subjects.

I reviewed the table of discontinuations due to AEs for the open label dementia trials (NDA Table 5.2.2) to look for infrequent events of particular significance. No subjects discontinued for events suggestive for liver failure, serious rash rhabdomyolysis, or pancreatitis. One subject discontinued for hepatitis (9408-00185, also an SAE, see above) and one for hepatic function abnormal (9202-00657). One subject discontinued for anemia (9408-00075), one for renal function abnormal (9202-00375) and one for creatinine increased (9206-00047, also an SAE, see above). I summarize the non-serious discontinuations for these AEs of interest below.

Abnormal Liver Function Tests

9202-00657 An 83 year old male discontinued from a trial for abnormal liver function tests. The CRF documented that the subject was consuming alcohol at the time of the abnormal test results. The subject was instructed to abstain from alcohol and the CRF commented that the subject subsequently improved. The subject had a normal bilirubin (0.6), SGOT (29) and SGPT (36) at visit 1. The last on-drug bilirubin was 1.5, (1.9, one week later) with an SGOT 88 (74, one week later), and SGPT 67 (58 one week later).

Anemia

9408-00075 A 79-year-old female discontinued from a trial after developing anemia due to GI bleed that was attributed to NSAID (piroxicam) use. Her hemoglobin was low (11.3g/dL) at the first visit and did not substantially change throughout the study. The CRF commented that the anemia was beginning to resolve following discontinuation from the study.

Renal Function Abnormal

9202- 00375 A 90-year-old male with a history of hypertension developed abnormal renal function and discontinued from the study. The CRF commented that the patient had abnormal blood tests throughout the study showing gradual age-related renal deterioration. The subject's baseline creatinine was 2.1mg/dL and increased to 2.9mg/dL (last on drug) and was 2.6mg/dL approximately one month later. BUN at baseline was 37mg/dL and increased to 55mg/dL (last on drug) and was 47mg/dL approximately one month later.

Group 1 Neuropathic Pain Trials

In the placebo controlled neuropathic pain trials, the discontinuation due to AE risk for memantine group was 12.5% (49/391) compared to 12.1% (18/149) in the placebo group. The discontinuation due to AE risk for the memantine 20mg/day group was 7% (12/171) compared to 16.8% (37/220) in the memantine 40mg/day group (NDA table 5.2.5).

I reviewed Forest's listing to look for AEs leading to discontinuation more frequently among memantine subjects and with evidence of dose response. Dizziness led to discontinuation of 5.9% (32/391) of memantine subjects and 1.3% (2/149) of placebo subjects. Most of the dizziness leading to discontinuation occurred in the 40mg memantine group (10%, 20/220) with one 20mg subject (0.6%, 1/171) discontinuing for dizziness (NDA table 5.2.5). There was also some suggestion of dose response for discontinuations due to nausea with 2.3% (5/220) of the memantine 40mg group, 1.2% (2/171) of the memantine 20mg group, and 1.3% (2/149) of the placebo group discontinuing for nausea.

I reviewed the discontinuations due to AEs listing for the memantine subjects in the neuropathic pain trials to look for infrequent events of particular importance. There were no discontinuations for events suggestive of renal failure, hepatic failure, hematological dyscrasias, rhabdomyolysis, pancreatitis, or serious skin reactions. One memantine subject discontinued for bilirubinemia (NTI 9801-00074) and one for photosensitivity reaction (NTI 9801-00320). I summarize those cases below.

Bilirubinemia

NTI 9801-00074 A 53 year old male who received treatment with memantine for 56 days, developed elevated bilirubin. This subject had an elevated alkaline phosphatase at screening (179) with normal bilirubin (0.6), AST (23), and ALT (24). At week 2, the alkaline phosphatase increased (207) while the bilirubin (0.6), AST (22), and ALT (20) remained normal. At week 4, the alkaline phosphatase (216) and bilirubin (2.1, repeat 2.4) were elevated while the AST was 29 and ALT was 25. The subject discontinued

from the trial and follow up labs approximately 1 month later found alkaline phosphatase 160, bilirubin 0.6, AST 22, and ALT 19. (Study report NTI 9801, Appendix 111.2, NDA vol. 239).

Photosensitivity

NTI 9801-00329 A 33 year old male developed sweating, parasthesias of the lips, photosensitivity of the eyes, tremors, slurred speech, dizziness and nausea with all events resolving the same day except dizziness and nausea (resolved 2 days later).

Group 2 Studies

Forest reported that 10.9% (60/549) of memantine subjects and 1.7% (3/173) of placebo subjects discontinued from Group 2 studies (NDA table 5.1.6). Cardiac failure (memantine 1.5%, 8/549, placebo 0/173), dizziness (memantine 3.6%, 20/549; placebo 1.2%, 2/173) and agitation (memantine 1.1%, 6/549; placebo 0/173) were the only AEs leading to discontinuation in at least 1% of memantine subjects and at least twice as frequently compared to placebo. No memantine treated subjects in these studies discontinued for AEs suggestive of renal failure, hepatic failure, hematological dyscrasias, rhabdomyolysis, pancreatitis, or serious skin reactions.

Ongoing Studies

Forest did not summarize the discontinuations for AEs from ongoing studies.

4.6.4 Treatment Emergent AEs

Group 1 Dementia Placebo Controlled Trials

In Group 1 dementia trials, the proportion of memantine treated subjects with at least one AE (70.4%, 662/940) was similar to the proportion of placebo subjects with at least one AE (67.7%, 624/922). The rate of subjects with one or more AEs in the memantine group (170/100PY, 662/389PY) was similar to the rate in the placebo treated group (164/100PY, 624/381PY).

Forest presented a table summarizing AEs reported for at least 2% of memantine subjects and greater than placebo (NDA Panel 35, p.233) and I summarized those data below. I highlighted events that were reported in at least double the percentage of memantine subjects compared to placebo subjects.

FDA TABLE 9 Treatment Emergent AEs in ≥2% of Memantine Patients and at a Higher Rate than Placebo Patients- Double Blind Placebo Controlled Dementia Studies

Preferred Term	Memantine (n=940)	Placebo (n=922)
Dizziness	6.8% (64)	5.3% (49)
Confusion	6.2% (58)	4.6% (42)
Headache	5.7% (54)	3.4% (31)
Constipation	5.3% (50)	3% (28)
Urinary Incontinence	4.4% (41)	3.9% (36)
Coughing	3.9% (37)	3.4% (31)
Hypertension	3.5% (33)	2.2% (20)
Gait abnormal	3% (28)	2.7% (25)
Somnolence	3% (28)	2.5% (23)
Vomiting	3% (28)	2.3% (21)
Back pain	2.6% (24)	2.3% (21)
Hallucination	2.6% (24)	1.6% (15)
Pain	2.6% (24)	0.9% (8)

Anxiety	2.4% (23)	1.6% (15)
Edema Peripheral	2.4% (23)	1.6% (15)
Fatigue	2.4% (23)	1.3% (5)
Anorexia	2.2% (21)	1.8% (17)
Dyspnea	2% (19)	1% (9)

From Forest Panel 35, NDA vol. 265, p.233.

I reviewed the investigator terms subsumed by the preferred term pain for the memantine treated subjects. The preferred term pain subsumed a variety of investigator terms including pain in an extremity, sore mouth due to dentures, and generalized aches. There did not appear to be a cluster of distinct or related events among the AEs coded to the preferred term pain.

Since there was an excess risk of dyspnea in the memantine treated subjects and since this term refers to a symptom rather than a diagnosis, I examined these AEs further to look for a unique event responsible for this AE. I identified the 19 memantine treated subjects who experienced dyspnea. I then used the AE data set to identify associated AEs occurring around the same time as the dyspnea AE (within 1 week). In seven cases the subjects with dyspnea also had an AE of cough or fever and in some of these cases the subject was diagnosed with bronchitis, pneumonia, or influenza symptoms. Malaise, confusion, worsening allergies, chest pain and fatigue were reported on the same day as dyspnea in six cases. For the remaining six cases, dyspnea was reported without other AEs and in most of these cases the events were non-serious, did not lead to discontinuation and resolved within a matter of days. I saw a similar distribution of concomitant AEs among the placebo subjects with dyspnea AEs.

When considering only the Alzheimer's dementia trials, the following events occurred in at least 2% of memantine subjects and more often than compared to placebo (highlighted events were reported in at least double the percentage of memantine subjects compared to placebo subjects).

FDA TABLE 10 Treatment Emergent AEs in ≥2% of Memantine Patients and at a Higher Rate than Placebo Patients- Double Blind Placebo Controlled Alzheimer Dementia Studies

Preferred Term	**Memantine (n=396)**	**Placebo (n=394)**
Urinary Incontinence	6.3% (25)	5.6% (22)
Fall	6.1% (24)	5.8% (23)
Dizziness	5.8% (23)	5.3% (21)
Headache	5.6% (22)	2% (8)
Confusion	5.3% (21)	3% (12)
Insomnia	4.8% (19)	4.1% (16)
Anorexia	4% (16)	2.8% (11)
Hallucination	4% (16)	2.5% (10)
Prostatic disorder*	3.8% (5)	0
Vomiting	3.8% (15)	2.5% (10)
Constipation	3.5% (14)	3.3% (13)
Depression	3.5% (14)	3% (12)
Edema peripheral	3.5% (14)	2.5% (10)
Hypertension	3.5% (14)	2.3% (9)
Somnolence	3.5% (14)	3.3% (13)

Coughing	3.3% (13)	3% (12)
Gait abnormal	3% (12)	1.5% (6)
Fatigue	2.8% (11)	2% (8)
Back pain	2.5% (10)	2% (8)
Pain	2.3% (9)	0.3% (1)
Abdominal Pain	2% (8)	1.5% (6)
Arthralgia	2% (8)	1.5% (6)
Cardiac Failure	2% (8)	0
Micturition frequency	2% (8)	1% (4)
Rash	2% (8)	1.3% (5)

From Forest SU Table 6.1.1A
*Uses the number of males in the denominator of the risk calculation

I read through the entire list of AEs from Group 1 Dementia Placebo Controlled Trials and found no events in memantine treated subjects suggestive of hepatic failure, renal failure, rhabdomyolysis, pancreatitis, or serious skin reactions.

There were several liver-related lab abnormalities identified as AEs in Group 1 Dementia Placebo Controlled Trials. I identified the memantine treated subjects with these events and then summarized the events using the lab data sets, AE data sets, concomitant medication data sets, and narratives and CRFs (for SAEs and events leading to discontinuation).

Four memantine-treated subjects (9202-00049, 9202-00147, 9403-00072, 9605-00100) had AEs of bilirubinemia, with or without other liver-related lab AEs, compared to one placebo subject. Those events are summarized below.

Subject 9202-00049 (AE bilirubinemia) had a bilirubin of 1.5mg/dL that exceeded the lab ULN (1.2mg/dL) but that was not associated with increases in transaminases.

Subject 9202-00147 (AEs bilirubinemia increased GGT, increased ALP) had a treatment emergent bilirubin of 2.1mg/dL along with an increased GGT of 466 and an ALP of 1,247 with normal SGOT and SGPT. These abnormal lab values occurred in a setting of worsening CHF, which led to discontinuation from the trial. The subject died nine days after discontinuation and the cause of death was CHF.

Subject 9403-00072 (AEs bilirubinemia, increased ALP) had a treatment emergent bilirubin of 2.2mg/dL and ALP of 363 that was not associated with increases in GGT, SGOT or SGPT.

Subject 9605-00100 (AEs bilirubinemia, increased ALP, increased GGT, increased SGOT and SGPT) had a bilirubin of 1.3mg/dL that exceeded the ULN (1.2mg/dL) along with increased GGT of 77, increased SGOT of 172, increased SGPT of 169 and an ALP of 174. The subject fractured her pelvis just prior to these lab results and subsequently withdrew consent. There were no follow-up lab results.

Two memantine-treated subjects (9202-00654, 9408-00229) had AEs of hepatic enzymes increased compared to none with placebo. Those events are summarized below.

Subject 9202-00654 (AEs hepatic enzymes increased, hepatic function abnormal) had an elevated ALP (406) and GGT (174) at baseline. Approximately one month later, while taking memantine, the ALP and GGT were decreasing while the SGOT (79) and SGPT (101) were elevated. The SGOT and SGPT declined while the ALP and GGT increased again. Throughout the study, the bilirubin was normal (highest recorded 0.5mg/dL).

Subject 9408-00229 (AEs hepatic enzymes increased, GGT increased) had an increased ALP (291) at baseline with no other liver related abnormalities. During the study, the subject had increases in GGT (54), SGOT (76) and SGPT (52). At the last visit these labs were normal. This subject's highest recorded bilirubin was at baseline (0.9mg/dL).

Eight memantine-treated subjects (9202-00147, 9202-00573, 9403-00082, 9408-00229, 9408-00257, 9605-00027, 9605-00100, 9605-00298) had AEs of increased GGT, with or without other liver-related lab AEs, compared to six placebo subjects. Below I summarize the GGT increased AEs not previously discussed.

Subject 9202-00573 (AE increased GGT) had an elevated GGT of 143 that was not associated with increases in transaminases or bilirubin.

Subject 9403-00082 (AEs increased GGT, increased SGOT, increased SGPT, and increased ALP) had an increased GGT (99) and ALP (266) at baseline. One month later, GGT was 76 with ALP 256, SGOT 27, and SGPT 29. At the last visit, GGT was 113, ALP was 449, SGOT was 43 and SGPT was 71. The subject completed the trial. Bilirubin was normal throughout the study and there were no concomitant medications recorded.

Subject 9408-00257 (AE GGT increased) experienced increases in GGT (566) and ALP (407) and a single increased SGPT of 71 (ULN30) and SGOT of 36 (ULN 30). Bilirubin was normal throughout the study and the transaminases were normal at end of study.

Subject 9605-00027 (AEs GGT increased, ALP increased) This subject had normal labs at baseline and the only other labs 3 months later included GGT 89, ALP 132, SGOT 34, and SGPT 35. Bilirubin was normal during the study. This subject discontinued from the trial after experiencing a fall and myoclonic jerks.

Subject 9605-00298 (AEs GGT increased, ALP increased) This subject had normal labs while treated with memantine and had an elevated ALP (195) and GGT (128) twenty-four days after stopping memantine, and after starting phenytoin.

Three memantine-treated subjects (9202-00465, 9202-00005, 9202-00654) had AEs of hepatic function abnormal compared to six placebo subjects. Below I summarize the hepatic function abnormal AEs not previously discussed.

Subject 9202-00465 (AE hepatic function abnormal) had an elevated ALP (316) during the trial without associated increases in GGT, SGOT, SGPT, or bilirubin.

Subject 9202-00005 (AE hepatic function abnormal) had normal liver related labs at baseline and after approximately seven months of memantine treatment developed increased ALP (748), GGT (261), SGOT (58) and SGPT (114). Bilirubin was normal (0.6mg/dL). Approximately one week prior to these lab results, the subject was diagnosed with a UTI and began treatment with amoxicillin/clavulanate and acetaminophen. These lab abnormalities resolved without interruption of memantine.

Four memantine-treated subjects (9403-00082, 9403-00133, 9605-00100, 9605-00324) had SGOT increased AEs compared to five placebo subjects. Below I summarize the SGOT increased AEs not previously discussed.

Subject 9403-00133 (AEs SGOT increased, SGPT increased) had normal liver related lab results at baseline. After approximately two and a half months of treatment and at end of study, this subject had elevated SGOT (83) and SGPT (84) results, while GGT, ALP, and bilirubin were normal. Follow up SGOT (19) and SGPT (12) approximately two weeks after stopping memantine were normal.

Subject 9605-00324 (AE SGOT increased) a single elevated SGOT of 48 (ULN 36) and SGPT of 42 (ULN 37) during the study and these abnormalities resolved by the end of the study.

Four memantine-treated subjects (9403-00082, 9403-00133, 9408-00205, 9605-00100) had SGPT increased AEs compared to six placebo subjects. Below I summarize the SGPT increased AEs not previously discussed.

Subject 9408-00205 (AE SGPT increased) had a SGPT of 41 (ULN 39) and a SGOT of 37 (ULN 39) at baseline. This subject experienced increased SGPT (highest 52) and SGOT (highest 41). ALP, GGT, and bilirubin were normal throughout the study.

Nine memantine-treated subjects (9202-00147, 9202-00463, 9403-00072, 9403-00082, 9408-00330, 9408-00506, 9605-00027, 9605-00100, 9605-00298) had ALP increased

AEs compared to 5 placebo subjects. Below I summarize the ALP increased AEs not previously discussed.

Subjects 9202-00463, 9408-00330, and 9408-00506 all had on treatment increases in ALP (subject 9408-00330 also had an elevated ALP at baseline) and none were associated with increased GGT, suggesting non-liver related increases in ALP.

Seven memantine subjects had AEs of anemia compared to nine placebo subjects. I summarize the anemia events in memantine treated subjects below.

9202-00120 This 71 year old female had a Hgb at baseline of 10.9g/dL that decreased to 10.3g/dL on the day of her first memantine dose. After two weeks of memantine, her Hgb was 9.9g/dL. This anemia was not associated with thrombocytopenia or leucopenia. She was treated with iron sulfate and her Hgb increased to 14.5g/dL with continued memantine treatment. She completed the study.

9202-00649 SAE, summarized above.

9605-00028 This 88 year old female had an AE of anemia that did not lead to discontinuation. The lab data set included only results from this subject's last study visit and at that time the hemoglobin was 12.6g/dL. Forest noted that the subject's other study lab values were hemolyzed. Labs drawn during the study period but not part of the safety database included a hemoglobin of 12.5mg/dL, and two months later a hemoglobin of 11.4mg/dL.Following recognition of the anemia AE, this subject had a hemoglobin of 12.6mg/dL (Addition data from response to reviewer question dated 7/3/03).

MEM-MD-02 29216 This 77 year old female 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. The investigator also noted anemia as an AE during this admission but provided no laboratory results to support the diagnosis. Physical exam noted a right breast mass suspicious for cancer, but no surgery was performed. She was discharged to a long term care facility.

MEM-MD-02 209215 This 89 year old female with a history of anemia treated with ferrous sulfate, had AEs of anemia and leucopenia . This subject had a baseline hemoglobin of 11.2g/dL, HCT 35%, WBC 4.2, PLT 222. She was hospitalized for right sided congestive heart failure and had a hemoglobin of 11.7g/dL, HCT 34.9%, and a WBC count of 4.5. The subject's caregiver stopped giving the study medication and two days later, the subject was admitted after being found unconscious on the floor. Hospital records noted anemia and leucopenia but Forest could find no lab values to corroborate these findings. Three days after hospitalization, the subject's WBC count was 9.5. (Addition data from response to reviewer question dated 7/3/03).

MEM-MD-02 379222 This 83 year old male had an AE of anemia that was not serious, did not lead to discontinuation, and required no action. This subject had a baseline hemoglobin of 14g/dL, HCT 43%, WBC count 6.8, PLT 196; On 4/5/02, the date of the anemia AE, this subject had a hemoglobin of 12.5g/dL, HCT 38%, WBC count 5.2, and PLT 202.

MEM-MD-02 379236 This 79 year old female, had a baseline hemoglobin of 11.3mg/dL, HCT 33%, WBC count 6.6, PLT 207. This subject had a recorded AE of anemia; however, the anemia was not quantified and occurred in the setting of sepsis and UTI. This subject discontinued from the study and the anemia was reported as resolved two weeks after discontinuation.

Group 1 Dementia Open Label Trials

Forest reported that 71% (604/856) of subjects enrolled in open label dementia trials experienced one or more adverse events (NDA vol. 265, p.236). The rate of subjects experiencing one or more AEs in open label dementia trials (148/100PY; 604/407PY) was similar to the AE rates observed in the memantine (170/100PY) and placebo (164/100PY) groups in the group 1 placebo controlled dementia trials. The AE risk for subjects who received placebo during the preceding placebo controlled trial (72%, 301/417) was similar to the risk in those who received memantine in the preceding controlled trial (69%, 303/439).

Using Forest's table 6.1.2, I summarized the AEs occurring in at least 2% of patients from open label dementia trials. I present the risks stratified by those who received memantine and those who received placebo in the preceding double blind clinical trial.

FDA TABLE 11 Treatment Emergent AEs Reported by ≥2% of Treated Population, Open Label Dementia Trials, by Previous Treatment

Adverse Event	**Placebo-Memantine** N=417	**Memantine-Memantine** N=439	**Total** N=856
Agitation	7.2% (30)	6.6% (29)	6.9% (59)
Urinary tract infection	5.5% (23)	5.7% (25)	5.6% (48)
Fall	5.5% (23)	5.2% (23)	5.4% (46)
Inflicted Injury	4.3% (18)	6.2% (27)	5.3% (45)
Dizziness	7.2% (30)	3.2% (14)	5.1% (44)
Bronchitis	3.8% (16)	5.7% (25)	4.8% (41)
Confusion	5% (21)	4.3% (19)	4.7% (40)
Headache	4.8% (20)	3.2% (14)	4.0% (34)
Cataract	2.4% (10)	5.2% (23)	3.9% (33)
TIA	3.8% (16)	3.6% (16)	3.7% (32)
Influenza symptoms	3.8% (16)	3.4% (15)	3.6% (31)
Urinary incontinence	3.4% (14)	3.6% (16)	3.5% (30)
Insomnia	3.1% (13)	3.9% (17)	3.5% (30)
Depression	3.1% (13)	2.7% (12)	2.9% (25)
Coughing	2.6% (11)	3.2% (14)	2.9% (25)
Vomiting	3.1% (13)	2.7% (12)	2.9% (25)
Diarrhea	3.8% (16)	1.8% (8)	2.8% (24)
Somnolence	3.1% (13)	2.5% (11)	2.8% (24)
Vision abnormal*	2.9% (12)	2.7% (12)	2.8% (24)
Cerebrovascular disorder	1.9% (8)	3.4% (15)	2.7% (23)
Gait abnormal	3.8% (16)	1.4% (6)	2.6% (22)
Constipation	2.6% (11)	2.3% (10)	2.5% (21)
Hypertension	2.4% (10)	2.5% (11)	2.5% (21)
Arthralgia	2.6% (11)	1.8% (8)	2.2% (19)
Dyspnea	2.2% (9)	2.3% (10)	2.2% (19)
Aggressive reaction	1.4% (6)	2.5% (11)	2.0% (17)

*Included a number of verbatim terms but most commonly blurred vision and decreased visual acuity.

I read through the entire list of AEs from these trials and found no events in memantine treated subjects suggestive of hepatic failure, renal failure, rhabdomyolysis, pancreatitis, or serious skin reactions. Below I summarize selected AEs from the Open label dementia studies.

GGT increased

9605-00345- 65-year-old female who got memantine during the double blind trial had normal bilirubin, GGT, AST, ALT and ALP throughout. During the open label extension, the subject experienced increased GGT to 159, ALP 127 (up from 95), SGOT 30 (up from 15) and SGPT 76 (up from 22). The only other AE listed for this subject was urinary frequency. This subject withdrew from the study at the time of the abnormal results and the reason listed was consent withdrawn.

9408-00148- 79-year-old male treated with memantine during the double blind study had normal bilirubin, GGT, TA and ALP throughout. On the last visit of extension this subject had an elevated GGT (92). The highest recorded bilirubin for this subject was 0.7mg/dL and the highest ALP was 218 (ULN 277). SGOT and SGPT were normal throughout this subject's treatment with memantine.

Hepatic enzymes increased

9408-00221 This 75 year old female subject who received placebo during the double blind study experienced an increased ALP (highest 387) and GGT (highest 92) that were most abnormal on the last visit of the double blind study/start of the extension. These abnormalities gradually returned toward normal during the extension and while the subject received memantine. This subject had a slightly elevated SGPT at the last visit of the extension (34, ULN 30). Bilirubin and SGOT were normal throughout the double blind and extension phases. This subject experienced no other liver-related AEs and no other AEs within one month of this event.

Hepatic Function Abnormal

9408-00251 This 81-year-old male subject had elevated GGT (147), SGOT (72) and SGPT (113) at the baseline visit of the double blind trial and was randomized to placebo. He experienced increases in GGT (highest 171), SGOT (highest 107) and SGPT (highest 138) with the highest increases at the last visit of the double blind study/start of the extension. These abnormalities improved while the subject was treated with memantine and on the last visit of the extension trial/date of last memantine dose, the GGT was 130, SGOT was 27 and SGPT was 33. This subject had normal bilirubin results throughout the double blind and extension trials.

9605-00024 This 71 year old female subject had normal liver related lab tests throughout the double blind and extension phases and on the last day of the extension phase had elevated ALP (127), GGT (139), SGOT (44), SGPT (40). Bilirubin at the time of these other abnormalities was 0.4mg/dL. This subject had no other liver related abnormalities and follow up was to be with the subject's primary care physician.

Jaundice

9202-00257 This subject had an SAE of jaundice due to cholelithiasis and the event was summarized above.

SGOT increased

9408-00324 This 76 year old female subject had an abnormal GGT at baseline (59) and received placebo during the double blind phase. The GGT increased during the study period and was highest at the second to last visit of the extension phase (153). This subject had normal SGOT throughout and SGPT was slightly increased during the double blind phase (31, ULN 30) and the highest value (51) was at the last visit approximately ten days after stopping memantine. These abnormalities were not associated with increases in ALP or bilirubin. This subject had no other liver related AEs. (Note the investigator term for the event was abnormal transaminase, which was coded to SGOT increased even though the SGOT was normal and it was the SGPT that was increased).

Thrombocytopenia

9202-00319 This 66 year old male subject had a platelet count of 111,000 at baseline. At the completion of the extension phase the platelet count was 78,000. This was repeated 16 days later, off memantine, and was 68,000. Two weeks later, it was 83,000. This abnormality was not associated with a low WBC count or hemoglobin. This subject had no bleeding related AEs reported around the time of the thrombocytopenia AE. This subject was taking multiple medications including quinine.

Leucopenia

9605-00031 This 71 year old female subject had a baseline WBC count of 6.5. She was randomized to placebo and during the double blind phase had a WBC was 6. Three days after starting the extension, her WBC count was 2.8 (66% neutrophils). Ten days later the WBC count was 3.6. Three months later (last available lab) her WBC count was 2.8 (70% neutrophils). The subject discontinued from the trial at this time and the reason given was patient request. These findings were not associated with decreases in hemoglobin or platelets. This subject was treated with multiple concomitant medications including fluoxetine, donepezil, trazodone, haloperidol, chloral hydrate, and aspirin.

Pulmonary Fibrosis

9202-00247 This 70-year-old male subject had an AE coded to the preferred term of pulmonary fibrosis. This subject received placebo during the controlled trial phase. During the extension phase, the subject developed consolidation in the right lung base (event coded to pulmonary fibrosis) and associated tachypnea. Thirteen days after the onset of this AE, the patient died suddenly and the CRF noted ischemic heart disease as the cause of death.

Group 1 Neuropathic Pain Trials

Forest reported that 76% (297/391) of memantine treated subjects and 75% (111/149) of placebo subjects in Group 1 neuropathic pain trials experienced one or more AE (NDA vol. 265, p.237). In the memantine group, 68% (116/171) of subjects randomized to 20mg/day experienced one or more AEs compared to 82% (181/220) of subjects randomized to 40mg/day. In the table below, I summarize AEs from Group 1 neuropathic pain trials. The table includes events occurring in at least 1% of memantine subjects, ≥1.5 times more frequently compared to placebo, and with evidence of dose response, that is a higher risk in the 40mg/day group compared to the 20mg/day group (Source: NDA Table 6.1.5).

FDA TABLE 12 Treatment Emergent AEs Reported by ≥1% of Memantine Treated Population, Group 1 Neuropathic Pain Trials, AEs occurring ≥1.5 times more Frequently among Memantine Subjects and with Evidence of Dose Response

AE	Memantine 20mg (n=171)	Memantine 40mg (n=220)	Memantine total (n=391)	Placebo (n=149)
Dizziness	9.9% (17)	32.7% (72)	22.8% (89)	11.4% (17)
URI	5.3% (9)	6.4% (14)	5.9% (23)	4% (6)
Parasthesia	4.1% (7)	6.8% (15)	5.6% (22)	1.3% (2)
Inflicted Injury	2.9% (5)	4.1% (9)	3.6% (14)	1.3% (2)
Constipation	2.9% (5)	3.6% (8)	3.3% (13)	1.3% (2)
Pain	1.8% (3)	4.1% (9)	3.1% (12)	1.3% (2)
Confusion	1.2% (2)	3.2% (7)	2.3% (9)	0.7% (1)
Concentration imp	1.8% (3)	2.3% (5)	2% (8)	0.7% (1)
Depression	0.6% (1)	3.2% (7)	2% (8)	0.7% (1)
Skin ulceration	0.6% (1)	2.3% (5)	1.5% (6)	0.7% (1)
Fever	1.2% (2)	1.4% (3)	1.3% (5)	0.7% (1)
Sweating increased	0	2.3% (5)	1.3% (5)	0.7% (1)
Syncope	0.6% (1)	1.4% (3)	1% (4)	0.7% (1)

I read through the entire list of AEs from the neuropathic pain trials and found no events in memantine treated subjects suggestive of hepatic failure, renal failure, rhabdomyolysis, pancreatitis, or serious skin reactions. Below I summarize selected AEs in memantine subjects not discussed in previous sections of this review.

Transaminase elevations

Subjects 9801-087, 9801-088, 9801-101, and 9801-156 had AEs of SGOT elevation, SGPT elevation, or both. None of these events were associated with increases in bilirubin. The highest increase in this group was approximately 3 times upper limit of normal (subject 9801-156 had an ALT of 128) and three of these subjects had mild elevations at baseline.

Renal AEs
Subjects 9801-094 and 9801-561 had AEs of NPN (creatinine) increased and subject 9801-022 had an AE of renal function abnormal. Subject 9801-094 developed elevated creatinine (lab result not reported) while hospitalized for treatment on myocardial infarction and cardiogenic shock (treatment included diuretics). This subject died during the hospitalization. Subject 9801-561 had a baseline creatinine of 1.8mg/dL and BUN of 31mg/dL that increased to 2.9mg/dL and 80mg/dL, respectively (week 8, last on drug). One month later the creatinine was 2.1mg/dL and the BUN was 39mg/dL. Subject 9801-022 had a baseline creatinine of 1.4mg/dL and BUN of 35mg/dL and the highest on drug creatinine was 1.8mg/dL (last on drug) and BUN was 41mg/dL (last on drug). Five days after stopping memantine this subject's creatinine was 1.5mg/dL and BUN was 33mg/dL.

Group 2 AEs
Forest reported that 23% (127/549) of memantine subjects in Group 2 studies had AEs compared to 13% (22/173) of placebo patients. Forest acknowledged that Group 2 studies had less stringent reporting requirements (included only events believed possibly or definitely due to study drug), which could impact the validity of these comparisons. I read through the listing of AEs from Group 2 studies (NDA table 6.1.6). Dizziness (memantine 8.2%, 45/549, placebo 3.5%, 6/173), and headache (memantine 2.6%, 14/549, placebo 0.6%, 1/173) were the only AEs occurring in at least 2% of memantine subjects and at least twice as frequently compared to placebo subjects. There were no events suggestive of renal failure, hepatic failure, hematologic dyscrasias, rhabdomyolysis, pancreatitis, or serious skin reactions.

4.6.5 Laboratory Data
Forest analyzed lab data by identifying subjects with outlier results and by examining mean changes at end of study compared to baseline. Forest's outlier analyses looked at the percentage of subjects who had treatment emergent potentially clinically significant (PCS) results. I include Forest's PCS criteria for lab results as an attachment to this review.

Lab Mean Changes
Group 1 Dementia Placebo Controlled Trials
The most notable difference between treatment groups from Forest's analysis of the mean changes from baseline for lab results was an increase in ALP among memantine subjects (7.37) compared to a slight decrease for placebo treated subjects (-0.12). For the remainder of the lab analytes, the mean changes were generally small and similar in both groups. I summarize the lab mean change from baseline results in the table below.

FDA TABLE 13 Lab Mean Change at End of Study Compared to Baseline, Group 1 Dementia Placebo Controlled Trials

	Mean Change from Baseline	
Parameter	Memantine (n)	Placebo (n)
Hemoglobin (g/dL)	-0.01 (833)	-0.04 (819)
Hematocrit (%)	0 (811)	0 (797)
RBC count (10**12/L)	0.02 (829)	-0.01 (816)
WBC count (G/L)	0.02 (833)	0 (818)

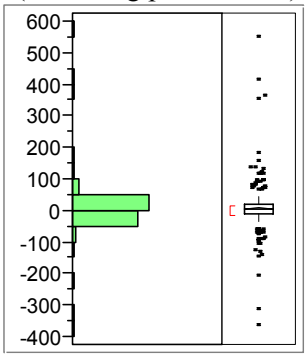
Platelet count (G/L)	0.02 (742)	4.46 (730)
Neutrophils (%)	-0.2 (701)	0.23 (684)
Eosinophils (%)	0.07 (701)	0.1 (684)
Chloride (mmol/L)	-0.6 (188)	-0.3 (183)
LDH (U/L)	2.2 (186)	-5.4 (182)
AST (U/L)	0.11 (836)	0.71 (822)
ALT (U/L)	0.65 (836)	1.58 (822)
GGT (IU/L)	2.72 (649)	1.41 (638)
ALP (U/L)	7.37 (837)	-0.12 (823)
Total Bilirubin (umol/L)	-0.19 (786)	-0.07 (771)
Blood Urea Nitrogen (mmol/L)	0.16 (650)	0.19 (638)
Creatinine (umol/L)	2.38 (838)	1.61 (823)
Uric Acid (mmol/L)	0.01 (788)	0 (772)
Total Protein (g/L)	-0.14 (650)	-0.49 (638)
Albumin (g/L)	-0.54 (650)	-0.56 (638)
Glucose (mmol/L)	0.05 (839)	0.2 (819)
Total Cholesterol (mmol/L)	-0.07 (788)	-0.1 (772)
Sodium (mmol/L)	-0.02 (788)	-0.22 (771)
Potassium (mmol/L)	-0.02 (785)	-0.03 (768)
Calcium (mmol/L)	-0.02 (301)	-0.02 (298)

From SU Table 8.4.1

Using the SU lab data sets, I examined the changes from baseline for ALP to characterize the nature of the difference between treatment groups. I plotted the distributions of changes from baseline and found one memantine subject with a very large ALP increase (1,796). After excluding this subject (to allow more comparable graphs), I plotted the distributions of the ALP changes from baseline and they are included below.

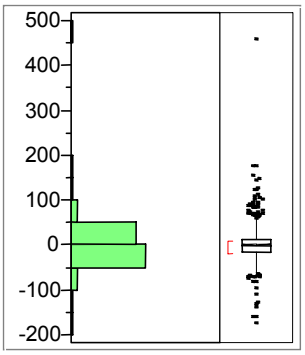
Distribution of ALP changes from baseline, Group 1 Placebo Controlled Dementia Trials

Memantine (excluding pt 9408/342)



Mean	5.2
Median	2.0
N	836

Placebo



Mean	-0.12
Median	-2.0
N	823

It appeared that five memantine outliers (four in the above graph and one excluded) were responsible for a large part of the difference in mean ALP changes from baseline between the treatment groups. In fact, when I excluded the five extreme memantine outliers and the one extreme placebo outlier, the mean ALP change from baseline in the memantine group was 3.2 compared to -0.7 in the placebo.

I reviewed available data for the five memantine subjects with extreme ALP outliers. There did not appear to be a cluster of similar events. I summarize that information below.

Subject 9408-00342 This 84 year old female had normal total bilirubin, AST and ALT at baseline and an elevated ALP of 326 (ULN 277). ALP increased to 1,035 and 2,122 during the study and the subject was diagnosed with a hepatic neoplasm and subsequently died.

Subject 9202-00005 had normal liver related labs at baseline (ALP 188) and after approximately seven months of memantine treatment developed increased ALP (748), GGT (261), SGOT (58) and SGPT (114). Bilirubin was normal (0.6mg/dL). Approximately one week prior to these lab results, the subject was diagnosed with a UTI and began treatment with amoxicillin/clavulanate and acetaminophen. These lab abnormalities resolved without interruption of memantine.

Subject 9202-00147 had a treatment emergent ALP of 1,247 along with an increased GGT of 466 and a bilirubin of 2.1mg/dL with normal SGOT and SGPT. These abnormal lab values occurred in a setting of worsening CHF, which led to discontinuation from the trial. The subject died nine days after discontinuation and the cause of death was CHF.

Subject 9202-00147 This 76 year old female had an ALP of 234 at baseline. Her ALT increased to 648 and she was hospitalized for gall bladder pain. She was diagnosed with cholelithiaisis and the CRF mentioned that surgery was planned but it was not clear if this subject underwent a cholecystectomy. She continued on memantine and at end of study, her ALP was 246.

Subject 9202-00147 This 86 year old female with a history of Paget's disease had a baseline ALP of 943 that increased to a high of 1,452 and was 1,308 at end of study.

Group 1 Double Blind Placebo Controlled Neuropathic Pain Studies

Forest summarized the mean lab results by study week and by treatment group for study NTI 9801 in tables 25 and 26 (NDA vol.236, pp.304-307). This study in diabetics with peripheral neuropathy included two memantine dose groups (20mg, 40mg) and therefore allows a dose-response analysis. There did not appear to be meaningful differences among the treatment groups. I provide selected results of that analysis in the table below.

FDA TABLE 14 Mean Lab Results by Study Week and Treatment Group, Study NTI 9801

		Treatment Group	
Parameter	Placebo (n)	Memantine 20mg (n)	Memantine 40mg (n)
ALP (IU/L)			
Baseline	93.8 (77)	99.2 (159)	95.5 (153)
Week 8	93.6 (69)	100.5 (145)	97.2 (128)
Week 12	95.6 (67)	97.4 (141)	93.1 (119)
Total Bilirubin (mg/dL)			
Baseline	0.6 (77)	0.6 (159)	0.5 (153)
Week 8	0.5 (69)	0.5 (145)	0.5 (128)
Week 12	0.5 (67)	0.5 (141)	0.5 (119)
BUN (mg/dL)			
Baseline	17.6 (77)	17.7 (159)	17.5 (153)
Week 8	17.6 (69)	18.5 (145)	18.1 (128)
Week 12	17.5 (67)	18.8 (141)	18.3 (119)
Calcium (mg/dL)			
Baseline	9.3 (76)	9.3 (159)	9.3 (153)
Week 8	9.3 (69)	9.3 (145)	9.3 (128)
Week 12	9.3 (67)	9.3 (141)	9.3 (119)
Cholesterol (mg/dL)			
Baseline	198.5 (77)	205.2 (159)	197.7 (153)
Week 8	196.2 (69)	198.7 (145)	196.1 (128)

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)	RR	M (316)	P (273)	RR	M (438)	P (460)	RR	M (110)	P (109)	RR
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

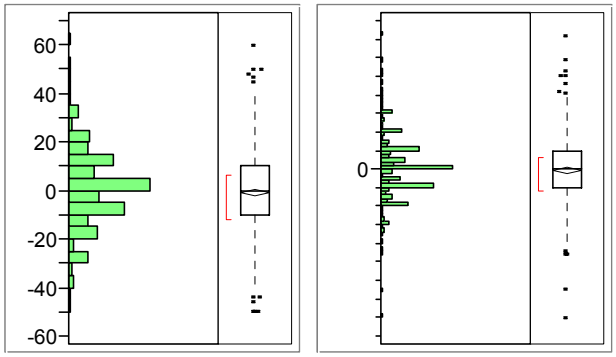
Panel 12. PCS Criteria for Laboratory Parameters

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	1/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/1	60.0000	U/L		
LDH*	U/L	1	U/L	---	≥3*ULN
Alkaline Phosphatase	IU/L	1.0000	U/L	---	≥3*ULN
	ukat/1	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

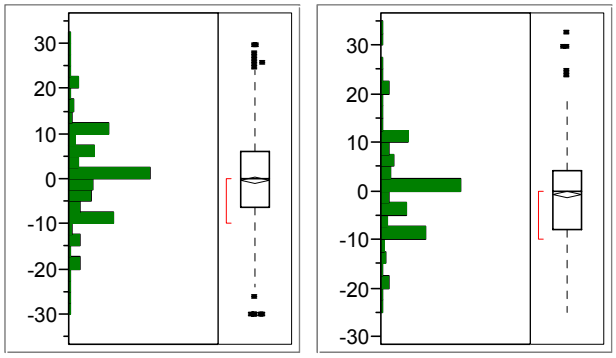
Memantine Placebo



	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

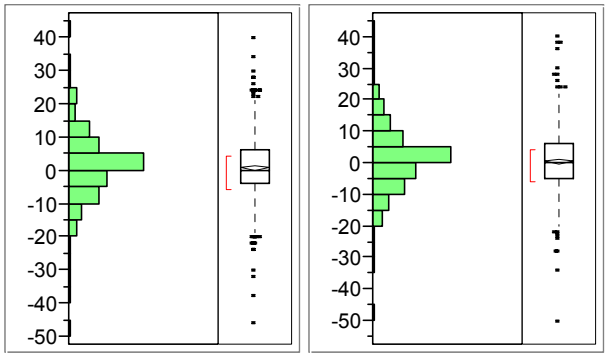
Memantine Placebo



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

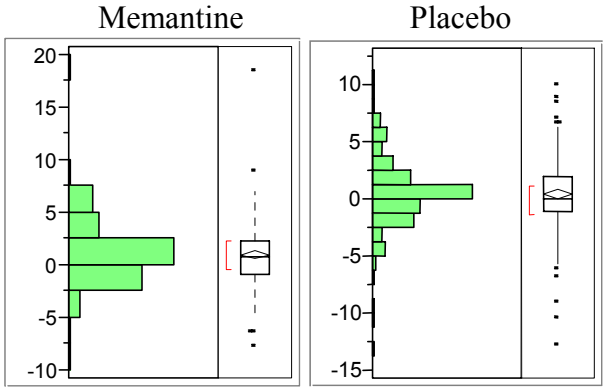
Distribution for Pulse Changes from Baseline

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.

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/s/

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

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