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MEMANTINE HCl

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LIST OF ABBREVIATIONS

Aß	Beta-Amyloid
AD	Alzheimer's Disease
ADAS-cog	Alzheimer's Disease Assessment Scale-Cognitive Subscale
ADCS	Alzheimer's Disease Cooperative Study
ADCS-ADL	Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory
$ADCS\text{-}ADL_{19}$	Modified 19-item Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory
ADL	Activities of Daily Living Inventory
ADO	Adverse Event Leading to Discontinuation
AE	Adverse Event
AE CRF	Adverse Event Case Report Form
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase (also termed "SGPT")
ANCOVA	Analysis of Covariance
ACE	Angiotensin Converting Enzyme
AST	Aspartate Aminotransferase (also termed "SGOT")
AUC	Area Under the Curve
AV	Atrioventricular
BfArM	Bundesinstitut for Medicaments and Medicine Products
BGP	Behavioral Rating Scale for Geriatric Patients (also known as Beoordelingsschaal Voor Oudere Patienten [BOP])
BID	Twice a Day
CGI	Clinical Global Impression
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
ChAT	Choline Acetyl Transferase
ChE	Cholinesterase
ChEI	Cholinesterase Inhibitor
CIBIC+	Clinician's Interview-Based Impression of Change Plus Caregiver Input
Cmax	Maximum Concentration
CNS	Central Nervous System

CSF	Cerebrospinal Fluid
CT	Computerized Tomography Scan (CAT Scan)
CYP 450	Cytochrome P-450
DAD	Disability Assessment for Dementia
DAT	Dementia of the Alzheimer's Type
DSM-III-R	Diagnostic and Statistical Manual for Mental Disorders, Third Edition
DSM-IV-TR	Diagnostic and Statistical Manual for Mental Disorders, 4th Edition, Text Revision
EAAT2	Excitatory Amino Acid Transporter-2
EC50	Concentration Providing 50% Maximal Response
ECG	Electrocardiogram
ED100	Dose Providing 100 % of Maximal Effect
ED50	Dose Providing 50 % of Maximal Effect
FAST	Functional Assessment Staging
FDA	Food and Drug Administration
fEPSP	Fast Excitatory Post-Synaptic Potential
FSH	Follicle-Stimulating Hormone
G2	Modified Ferm's D-Test
G2-C	G2 Change Scale
GDS	Global Deterioration Scale
GFAP	Glial Fibrillary Acidic Protein
HAMD	Hamilton Depression Rating Scale
HCTZ/TA	Hydrochlorothiazide/Triamterene
HERG	Human Ether a-go-go-Related Gene
HIS	Hachinski Ischemia Scale
HIV-1	Human Immunodeficiency Virus Type-1
5HT	Serotonin, 5-hydroxytryptamine
HVA	Homovanillic acid
IADL	Instrumental Activities of Daily Living
IC50	Concentration Providing 50% Inhibition of Response
ISS	Integrated Summary of Safety
ITT	Intention-To-Treat
Ki	Dissociation Constant for Inhibitor Binding

Koff	Dissociation Rate Constant
LDH	Lactate Dehydrogenase
LH	Luteinizing Hormone
LOCF	Last Observation Carried Forward
LTP	Long Term Potentiation
MA	Methamphetamine
MAO	Monoamine Oxidase
MAP-2	Mitogen Activated Protein-2
MCI	Mild Cognitive Impairment
MIS	Modified Ischemic Score
MK-801	Dizocilpine
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
MRP	Multidrug-Resistance-Gene-Related Protein
N	Number of Subjects
NBM	Nucleus Basalis Magnocellularis
NFTs	Neurofibrillary Tangles
NIA	National Institute on Aging
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke- Alzheimer's Disease and Related Disorders Association
NINDS-AIREN	National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et L'Enseignement en Neurosciences
NMDA	N-Methyl-D-Aspartate
NOEL	No Observed Effect Level
NPI	Neuropsychiatric Inventory
NSAIDS	Nonsteroidal Anti-Inflammatory Drugs
NTI	Neurobiological Technologies, Inc.
OC	Observed Cases
PC/RSC	Posterior Cingulate/Retrosplenial Cortex
PCP	Phencyclidine
PCS	Potentially Clinically Significant
PDS	Progressive Deterioration Scale
PFC	Prefrontal Cortex
Pgp	P-Glycoprotein

PK	Pharmacokinetic
PR interval	Time in seconds from the beginning of the P wave to the beginning of the QRS complex
QRS interval	Ventricular Depolarization Time
QT interval	Ventricular Depolarization and Repolarization Time
QTc interval	QT Interval at Standardized Heart Rate
SAE	Serious Adverse Event
SEM	Standard Error of the Mean
SD	Standard Deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase (also termed "AST")
SGPT	Serum Glutamic Pyruvic Transaminase (also termed "ALT")
SIB	Severe Impairment Battery
TEAE	Treatment Emergent Adverse Event
TID	Three Times a Day
T1/2	Half-life
Tmax	Time to Maximum Concentration
TSH	Thyroid-Stimulating Hormone
VaD	Vascular Dementia
WHO	World Health Organization
WHO-ART	World Health Organization Adverse Reaction Terminology

1.0 EXECUTIVE SUMMARY

Alzheimer's disease (AD) is the most common form of dementia in the elderly and is the fourth leading cause of death for patients aged 65 or older. The prevalence of AD is estimated to be about 4 million people in the US alone and approximately one million elderly Americans have severe dementia.

Moderate to severe AD represents an identifiable stage of a recognized disease and can be reliably diagnosed. Progressive loss of the ability to perform activities of daily living is a hallmark of the transition to the moderate and severe stages of AD. Currently, no approved therapeutic options exist for the treatment of more advanced AD.

The current therapeutic options for AD approved by the Food and Drug Administration (FDA) are the cholinesterase inhibitors (ChEIs) which are indicated for "the treatment of mild to moderate dementia of the Alzheimer's type (DAT)." However, it is believed that seventy percent of diagnosed dementia patients exhibit disease severity in the advanced dementia stages. The time the average AD patient spends in the mild stages, where episodic memory loss is the primary clinical finding, is relatively brief. Once the disease severity reaches the moderate stage, the remaining years of the patient's life, anywhere from 3 to 12 or more years, depending upon age of onset, are spent experiencing further deterioration in cognition and activities of daily functioning (ADLs). There is no approved antidementia treatment in the US for patients with more advanced AD (MMSE <10).

During the mild to moderate stages of AD, cognitive skills show deterioration and this decline leads to impaired ADLs. Instrumental ADLs are impacted beginning in the mild to moderate stages of AD followed by more pronounced deterioration in physical or self-care ADL functions during the moderate to severe stages. As the symptoms of AD become more severe, changes in the patient's ADLs ultimately lead to nursing home placement. Decline in ADLs and cognition further impact the caregiver burden. Once AD reaches the severe stage, all intellectual functions are severely compromised, and the clinical picture is dominated by the patient's limited function and his/her disruptive behavior. As a result, the estimated annual cost for patient care rises as AD severity worsens from mild ($18,408) to severe ($36,132) stages. Thus, there is a need for therapeutic agents for moderate to severe AD patients that will slow cognitive and functional decline and, in turn, potentially reduce patient care costs and time to institutionalization.

Preclinical and post-mortem studies of AD have associated changes in glutamatergic function with deficits in memory, a hallmark of AD. Moreover, chronic glutamatergic overstimulation is thought to lead to neurodegeneration (the excitotoxicity hypothesis). Thus, the glutamatergic neurotransmitter pathway has been implicated in the pathology of AD and serves as a target for therapeutic intervention in AD.

Memantine is a novel low-moderate affinity, uncompetitive, NMDA receptor antagonist that has demonstrated efficacy and safety in AD and is approved for use in the European Union and Australia.

Memantine is a novel therapeutic agent that represents a new class of AD treatment options. Memantine has shown efficacy and safety in the symptomatic treatment of patients with moderate to severe AD. Memantine has recently been approved for the treatment of moderately severe to severe AD in the European Union and Australia. The history of the memantine clinical development program is summarized in Section 2.1. Memantine has been available since 1982 in Germany (originally approved for the treatment of organic brain syndrome) and is currently available outside the US in 42 countries. As of February 2003, there were over 600,000 patient-years of exposure to memantine.

Memantine is a low-moderate affinity, uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist with strong voltage dependency and rapid blocking/unblocking kinetics. These pharmacological features appear to allow memantine to block the sustained activation of the receptor by glutamate that may occur under pathological conditions, and to rapidly leave the NMDA receptor channel during normal physiological activation. In humans, memantine is 100% bioavailable after an oral dose, undergoes minimal metabolism, and exhibits a terminal elimination half-life of 60 to 80 hours (75% or greater of the dose is eliminated intact in the urine). It rapidly crosses the blood brain barrier with a CSF/serum ratio of 0.52. Memantine does not inhibit cytochrome P-450 (CYP 450) isoenzymes *in vitro,* and its pharmacokinetics are not affected by food, sex, or age.

The efficacy of memantine has been demonstrated in double-blind, placebo-controlled trials in a well-defined population of moderate-severe AD patients utilizing appropriate diagnostic and outcome measures.

Memantine demonstrated efficacy in the treatment of moderate to severe AD using a dose of up to 20 mg/day in two key double-blind, placebo-controlled trials (Trials 9605 and MD-02) of 6-month duration in patients with probable AD. Efficacy of 10 mg/day memantine also has been shown in an earlier key trial (Trial 9403) of 12-week duration in dementia patients (AD patients were defined as having Hachinski Ischemia Scale [HIS] scores ≤ 4; see Panel 1). In these studies, memantine was titrated from a starting dose of 5 mg/day (weekly titration by 5 mg/day increments) to a target dose of 20 mg/day administered as 10 mg twice daily in the two 6-month trials and a target dose of 10 mg/day administered as 10 mg once daily in the 12-week trial. Patients were diagnosed with probable AD using National Institute of Neurological and Communicative Disorders and Stroke- Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria in Trials 9605 and MD-02 and with dementia using the Diagnostic and Statistical Manual for Mental Disorders, 3rd revised edition (DSM–III-R), criteria in Trial 9403. AD stages were identified as moderate to severe based on scores on the Mini Mental State Examination (MMSE scores of 3-14 in Trial 9605; 5-15 in Trial MD-02; and <10 in Trial 9403), Global Deterioration Scale (GDS; overall range 5-6 in Trial 9605 and 5-7 in

Trial 9403), Functional Assessment Staging (FAST ≥ 6a in Trial 9605), and/or Clinical Global Impression of Severity (CGI-S; range 5-7 in Trial 9403).

These three key memantine clinical trials are the first to evaluate the treatment of moderate to severe AD. Outcome measures were chosen to reflect the symptomatology of the more severe dementia patient population in the memantine trials. Specifically, in Trials 9605 and MD-02, the Severe Impairment Battery (SIB) and the 19-item version of the ADCS-Activities of Daily Living Inventory (ADCS-ADL_{19}), which is modified for more advanced AD patients, were used as the indices of cognitive and functional change, respectively, and a global assessment of change was made by the clinician using the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC+).

When Trial 9403, the earliest of the three key placebo-controlled trials, was conducted, the ADCS-ADL_{19} and SIB instruments were not generally available. Trial 9403 utilized the care dependency subscale of the Behavioral Rating Scale for Geriatric Patients (BGP) as a functional assessment along with a co-primary measure of global change, the Clinical Global Impression of Change (CGI-C). The BGP-cognitive subscale which was a subset of items from the BGP-care dependency subscale was retrospectively defined and analyzed as a cognitive measure. Panel 1 summarizes efficacy of memantine as measured in cognition, function, and global status from the 3 key, randomized, double-blind, placebo-controlled trials in moderate to severe AD using both the observed cases (OC) and last observation carried forward (LOCF) analyses.

Panel 1. Efficacy Results from 3 Key, Double-Blind, Placebo-Controlled Dementia Studies

Trial *Randomized Patients N*	*Treatment Duration/ Groups/ Dosage*	*Patient Population/ Diagnostic and Inclusion Criteria*	*Efficacy Outcome Measures (Protocol Defined Primary Endpoints) P-values for 3 Key Domains*					
			Cognition		*Function*		*Global*	
9605 Total N = 252 Memantine N = 126	28-week Placebo Memantine 10 mg BID	Diagnosis: Probable AD (DSM-IV and NINCDS-ADRDA) Severity: Moderate to Severe ◆ MMSE 3-14 ◆ GDS 5-6 ◆ FAST ≥ 6a ◆ HIS ≤ 4 ◆ ≥ 50 years of age	**SIB**		**ADCS-ADL$_{19}$ (Primary)**		**CIBIC+ (Primary)**	
			LOCF	*OC*	*LOCF*	*OC*	*LOCF*	*OC*
			<0.001	0.002	0.022	0.003	0.064	0.025
MD-02 Total N = 404 Memantine N = 203	24-week Placebo Memantine 10 mg BID	Diagnosis: Probable AD (NINCDS-ADRDA) Severity: Moderate to Severe ◆ MMSE 5-14 ◆ ≥ 50 years of age ◆ Ongoing donepezil therapy ≥ 6 months at a stable dose (5-10 mg/day) for the past 3 months	**SIB (Primary)**		**ADCS-ADL$_{19}$ (Primary)**		**CIBIC+**	
			LOCF	*OC*	*LOCF*	*OC*	*LOCF*	*OC*
			<0.001	<0.001	0.028	0.020	0.027	0.028
9403 Total N = 166 Memantine N = 82	12-week Placebo Memantine 10 mg QD	Diagnosis: Dementia (DSM-III-R) Severity: Severe ◆ MMSE <10 ◆ GDS 5-7 ◆ CGI-S 5-7 ◆ HIS ≤ 4 (AD patients) ◆ 60-80 years of age	**BGP-Cognitive**		**BGP-Care Dependency (Primary)**		**CGI-C (Primary)**	
			LOCF	*OC*	*LOCF*	*OC*	*LOCF*	*OC*
			0.001	0.001	0.012	0.010	<0.001	<0.001

Memantine has been found to be safe and well tolerated in clinical trials and in clinical use for the treatment of dementia.

Memantine has exhibited an acceptable safety and tolerability profile in 2297 patients in 27 clinical trials involving a variety of neurodegenerative disorders (e.g., dementia, neuropathic pain, spasticity, and Parkinson's disease). In this overall safety database, including studies with limited safety information, as well as in the European post-marketing clinical practice experience and in other post-marketing drug experience studies, there is no evidence for any signals of rare serious safety findings. A total of 1748 patients were exposed to memantine in the core dementia (AD or VaD) and neuropathy safety studies. Adverse events (AEs), vital signs, and laboratory tests were systematically evaluated in the core safety trials, and electrocardiograms (ECGs) were assessed in two dementia (Trials MD-02 and 9605) studies and the two neuropathic pain studies.

The core double-blind, placebo-controlled dementia trials (AD or VaD patients) included 922 placebo patients and 940 memantine patients. Approximately 80% of patients in both treatment groups completed the studies. Serious adverse events (SAEs) that were reported in greater than 1% of either treatment group were confusion (memantine 1.6% vs. placebo 0.9%), inflicted injury (memantine 1.1% vs. placebo 1.7%), cerebrovascular disorder (memantine 1.0% vs. placebo 1.5%), fall (memantine 0.6% vs. placebo 1.1%), and agitation (memantine 0.5% vs. placebo 1.1%). Most of the SAEs were considered unrelated or unlikely to be related to the trial drug. The most common reason for discontinuation in both placebo and memantine patients was adverse events (11.5% in the placebo group and 10.1% in the memantine group). The most frequent adverse events (AEs) leading to discontinuation in this trial group were agitation (memantine 1.2% vs. placebo 2.0%), confusion (memantine 1.2% vs. placebo 1.1%), and cerebrovascular disorder (memantine 0.7% vs. placebo 1.1%).

Treatment emergent adverse events (TEAE) which were reported most frequently (> 5% in incidence) by memantine-treated dementia patients and at an incidence greater than placebo patients were dizziness, confusion, headache, and constipation. None of the TEAEs were reported by >7% of memantine-treated patients or at a rate two times higher than in the placebo group (Panel 2). Most TEAEs were considered mild or moderate in severity and not related to the trial drug in either the placebo- or memantine-treated patients. The percentage of AD patients reporting TEAEs was similar in placebo- and memantine-treated groups. Patients with moderate to severe dementia had an overall TEAE profile similar to that of the entire dementia group. The profile and incidence of TEAEs (as compared to placebo) reported for AD patients receiving memantine as concomitant treatment with donepezil (Trial MD-02) was not different overall than that observed in AD patients receiving memantine alone (Trial 9605).

Panel 2. TEAEs in ≥5.0% of Patients in Either Treatment Group – Core Double-Blind, Placebo-Controlled Dementia Trials

Adverse Events	***Placebo (N=922) n (%)***	***Memantine (N=940) n (%)***
Dizziness	49 (5.3)	64 (6.8)
Agitation	98 (10.6)	63 (6.7)
Confusion	42 (4.6)	58 (6.2)
Headache	31 (3.4)	54 (5.7)
Constipation	28 (3.0)	50 (5.3)
Fall	50 (5.4)	48 (5.1)
Inflicted Injury	64 (6.9)	44 (4.7)

Analyses of vital sign measurements, clinical laboratory data, and ECG results in the placebo-controlled trials revealed no clinically relevant differences between treatment groups. There was no evidence for any special safety concerns based on the preclinical safety trial results and specific assessments of possible psychotomimetic, neurologic, ophthalmologic, and cardiovascular effects from the clinical trials.

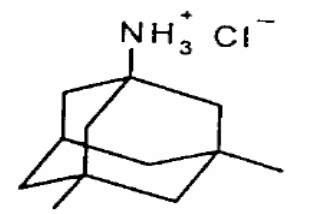
Memantine at its recommended dosage of 10 mg BID is well tolerated with a safety profile similar to that of placebo treatment and is effective in providing clinical benefit for patients with moderate to severe Alzheimer's dementia.

2.0 BACKGROUND

Memantine is a low-moderate affinity, uncompetitive NMDA receptor antagonist with strong voltage dependency and rapid blocking/unblocking kinetics.[1]

These pharmacological features appear to allow memantine to block the sustained activation of the receptor by glutamate (excitotoxicity) that may occur under pathological conditions, and to rapidly leave the NMDA receptor channel during normal physiological activation. These features also distinguish memantine from earlier NMDA receptor antagonists (e.g., dissociative anesthetics, ketamine, MK-801) and confer good safety and tolerability with a high therapeutic margin. Preclinical studies have consistently demonstrated that memantine administration can decrease the neuronal toxicity and neurodegeneration associated with excessive glutamate release.[1]

The chemical name for memantine (as the hydrochloride salt) is 1-amino-3, 5-dimethyladamantane hydrochloride, with a molecular formula of $C_{12}H_{21}N$ HCl and a



molecular weight of 215.77. The structural formula of memantine is shown below.[1] It is formulated as a tablet and a solution for oral administration.

2.1 Clinical Development History

Memantine has been marketed in Germany (as Akatinol Memantine®) since 1982 for the treatment of organic brain syndrome. Based on clinical benefits observed during the marketing experience in patients with cognitive dysfunction, a new preclinical and clinical development program investigating memantine for the treatment of AD and VaD was implemented.

The first large scale placebo-controlled trial in dementia (Trial 9403) was initiated by Merz Pharmaceuticals, GmbH, in the early 1990's. It was designed to investigate the efficacy and safety of memantine in nursing home patients with severe dementia (MMSE <10) of either the Dementia of the Alzheimer's type (DAT) or VaD type. This population was of interest as there were no therapies approved or in development for this patient group. At the time the study was initiated, the outcome measures that were of interest and could reliably be tested, were related to patient function and global performance. Hence, Trial 9403 included the BGP-care dependency and CGI-C scales as protocol defined primary outcome measures. Trial 9403 became the "proof of principle" study for the direction and design of further trials in patients with moderate to severe AD. Due to the

advanced disease status and presumed frailty of the patient population of interest, the dose for this trial was conservatively chosen as 10 mg/day.

At this same time, Merz also initiated two large clinical trials in mild-moderate VaD (Trials 9202 [MMSE 10-22] and 9408 [MMSE 12-20]), another form of dementia that was not under wide study at the time. The dosing regimen for these trials was 10 mg BID and was selected based on earlier studies in normal subjects, who demonstrated good tolerance to a total daily dose of 20 mg when delivered as a divided daily regimen (an attempt to reduce the incidence of any adverse events potentially associated with peak drug plasma concentrations).

Merz chose to pursue a centralized registration strategy in Europe. This necessitated the development of a unique claim for memantine (advanced dementia) and the creation of a new dossier to support this claim. A second trial was initiated to include a moderate to severe dementia population (Trial 9605 [MMSE 3-14]) involving AD outpatients in US centers. The dosing regimen chosen based on the previous clinical trial experience was 10 mg bid. This strategy ultimately led to the approval of memantine in the EU and Australia for the treatment of moderately severe to severe AD.

Forest Laboratories acquired the license to memantine in 1999 and initiated a series of studies in AD. These trials evaluated memantine treatment in both moderate to severe AD (building on the results of Trial 9605) and mild-moderate AD populations (based on the positive cognitive effects observed in the mild-moderate VaD patients in Trials 9202 and 9408). In each of these programs, trials were designed to investigate the efficacy of memantine either as monotherapy or as add-on treatment to stable regimens of ChEIs. The first of these trials to be completed was Trial MD-02 which investigated the safety and efficacy of memantine in patients with moderate to severe AD (MMSE 5-14) who were also receiving treatment with donepezil for a minimum of 6 months. The 10 mg BID dosing regimen chosen for this study was based on the Trial 9605 experience. The results of Trial MD-02 were added to the US NDA filing which had included reports of the results from Trials 9605 and 9403.

Memantine is currently available for use in more than 42 countries around the world. As of February 2003, there were over 600,000 patient-years of exposure to memantine.

The proposed indication for memantine in the US is for the treatment of patients with moderate to severe dementia of the Alzheimer's type.

2.2 AD Diagnosis and Assessment Tools

Moderate to severe AD represents an identifiable stage of a recognized disease and can be reliably diagnosed. Progressive loss of the ability to perform activities of daily living is a hallmark of the transition to the moderate and severe stages of AD. Currently, no approved therapeutic options exist for the treatment of moderate to severe AD. Appropriate diagnostic, staging, and outcome measures exist for the population of interest. These measures can reliably assess changes in the characteristic disease symptomatology in moderate to severe AD, particularly with respect to daily function, cognitive performance, and global status.

2.2.1 Epidemiology and Pathology of AD

AD is the most common form of dementia in the elderly and is the fourth leading cause of death for patients aged 65 or older.[2] The prevalence of AD is estimated to be about 4 million people in the US alone, and approximately one million elderly Americans have severe dementia.[3, 4] The estimated annual cost for patient care rises as the AD severity worsens from mild ($18,408) to severe ($36,132).[2] The need for therapeutic agents for the moderate to severe AD patient that can delay cognitive and functional decline, reduce caregiver burden, contain patient care costs and delay time to institutionalization is clear.

Recent studies that examined the brains of AD patients who died in earlier stages of the disease suggest that there is greater preservation of neuronal circuitry than was previously thought. These findings suggest that medications can be beneficial throughout a longer proportion of the disease's course. The pioneering neuropathological studies that led to the findings of loss of cholinergic enzymes,[5,6] and cholinergic[7] and cortical neurons and synapses[8, 9, 10] were performed for the most part on severe end-stage cases. While some functional decline of cholinergic and glutamatergic systems may occur early in the course, newer autopsy studies in earlier stages —mild cognitive impairment (MCI) and mild to moderate AD—demonstrate preservation of choline acetyl transferase (ChAT) activity,[11, 12, 13] neurons of the cholinergic basal forebrain[14] entorhinal cortex neurons,[15] and other cortical regions[16] until later in the course of the disease. Significant loss of these markers now appears to be delayed until late-stage disease. Thus there are new opportunities and rationales for treatment of cognition, especially with respect to the regulation of glutamatergic neurotransmission because many of the neurons now known to be preserved into later stages of the disease (e.g., cortical and entorhinal neurons) are glutamatergic.[17]

2.2.2 Current Therapeutic Options in AD

To date there is no approved antidementia treatment in the US for more advanced AD. The currently approved pharmacotherapeutic options for AD are the four ChEIs, tacrine, donepezil, rivastigmine, and galantamine. Each is approved for "the treatment of mild to moderate dementia of the Alzheimer's type [MMSE ≥10]."[18] The National Institute for Clinical Excellence in the UK issued guidelines in January 2001, recommending that ChEI therapy not be prescribed in more severe stages when "MMSE score falls below 12 points[19]." Unfortunately, patients will inevitably progress to more severe stages of AD, at which there is no approved treatment option.

2.2.3 Definition of Moderate to Severe AD

2.2.3.1 Clinical Diagnosis of AD

The various diagnosis standards for AD that exist today do not implicitly consider disease severity, but they do consider functional deficits. According to the NINCDS-ADRDA criteria (see below), a diagnosis of probable AD is supported by having at least one other additional cognitive domain deficit besides memory impairment *plus* an accompanying impairment in activities of daily living or behavior, which are supportive of the diagnosis.[20]

Panel 3. Summary of NINCDS-ADRDA Diagnostic Criteria for Probable Alzheimer's Disease

Diagnostic Criteria:

- Dementia established by clinical examination and neuropsychological testing
- Deficits in two or more areas of cognition
- Progressive cognitive worsening of memory and other cognitive functions
- Onset of dementia between 40-90 years of age
- Absence of systemic disorders and other brain diseases that could account for the progressive deficit in memory and cognition
- No disturbance of consciousness

Supportive Diagnostic Information:

- Progressive deterioration of specific cognitive functions (e.g., language, motor skills, and perception)
- Impaired activities of daily living and altered patterns of behavior
- Family history of similar neuropathological disorders
- Personal history of normal lumbar puncture
- Evidence of a normal or nonspecific changes in ECG patterns
- Evidence of cerebral atrophy on computerized tomography (CT) or magnetic resonance image (MRI)

The DSM-IV-TR criteria focus on the requirement for multiple cognitive deficits, one of which is memory loss and the others being aphasia, apraxia, agnosia, and/or impaired executive functioning.[20] In addition, functional impairment is a mandatory criterion for the diagnosis of probable DAT.

The positive predictive value of the NINCDS-ADRDA 'probable AD' category and that of the AD diagnosis by DSM-III-R is very high and ranges from 89 to 100% when validated against an autopsy diagnosis. This makes these tools suitable for research purposes.[21] The combination of the NINCDS-ADRDA 'possible' and 'probable dementia of the Alzheimer type' categories has a high sensitivity (91-98%), but lower specificity (40-61%).[22]

NINCDS-ADRDA and DSM criteria incorporate a differential diagnosis to exclude other conditions presenting similar clinical symptoms. Computerized tomography (CT) or Magnetic Resonance Imaging (MRI) scans are used to aid the physician in assessing presence or risk of vascular disease.[2] The HIS has been used in key dementia trials to exclude patients with dementia caused by or complicated by vascular lesions.[23] The medical history from the patient, when possible, and caregiver, laboratory assessments (chemistry, hematology, and urinalysis panels), and physical examination aid the physician in both the diagnosis and the differential diagnosis.

2.2.3.2 The Progression of AD in Severity

AD has a long and insidious course. Although the progression from stage to stage does not always occur in a discrete step-wise fashion, there are clinical features that signal these changes. Each of these phases can last for several years, depending on the individual. In general, the mild stage of AD is characterized by progressive impairment in delayed-recall memory performance, with word-finding difficulties noted when tested directly and reduction in executive abilities such as planning and problem solving. The time the average patient spends in this stage, where episodic memory loss is the primary clinical finding is brief relative to the overall length of the disease,[24] though these symptoms are often present before a diagnosis is made, with some patients having mild impairment of remote recall.[20,22, 25] Symptoms of depression may occur, and this is likely due to the patient's reaction to the disease.[26] While the course of decline is variable, most indices of memory are severely impaired by the time the patient reaches the moderate stage of the disease. Difficulties in performing activities of daily living may be present along with changes in behavior, but not to a great extent owing to the retention of many cognitive functions.

During the moderate to severe stages, the cognitive clinical symptoms that develop include visuospatial deficits such as spatial disorientation and poor construction ability, language deficits such as expressive and receptive aphasia, and other deficits such as dyscalculia and ideomotor dyspraxia. Memory performance continues to worsen, with losses in recognition memory occurring. These deficits lead to difficulties in instrumental activities of daily living such as operating office or home appliances, financial capacity, and decision-making. As AD continues to progress, basic activities of

daily living such as grooming, control of continence, and eating are progressively compromised.[2] Some aspects of memory, such as the ability to perform overlearned tasks (procedural memory), function during this phase.

Accompanying these cognitive and functional deficits are changes in the patient's personality; behavioral symptoms such as hallucinations and delusions appear, and motor functioning is gradually lost. Decline in these areas progressively impacts on the caregiver's daily functioning as well as mental, physical, and emotional well being. As caregiver stress increases, changes in the patient's daily living skills (more so than changes in memory) ultimately may lead to placement in a nursing home. Indifference and irritability, the presence of delusions and accusatory behavior, restlessness, wandering, and pacing are common at this stage, making care for the patient more taxing.[27] The time required for care is often more than 12 or 18 hours per day, as many of the behavioral problems also occur when the patient and caregiver would normally be sleeping. As patients move into the severe stage, all intellectual functions are generally substantially compromised, and the clinical picture is dominated by the patient's limited function and his/her behavioral symptoms.

2.2.3.3 Diagnostic Criteria for Staging Patients with Moderate to Severe AD Suitable for Use in Clinical Trials

There are three key double-blind, placebo-controlled trials of memantine in patients with moderate-severe AD (Trials 9605, MD-02, and 9403). The standard criteria for establishing the diagnosis of AD used in the memantine clinical trial program included NINCDS-ADRDA, DSM-IV, DSM-III-R, and HIS. In general, a review of the medical history, CT/MRI scans, physical examination results, and interviews with the caregiver confirmed the AD diagnosis. In addition, other validated assessments were used to identify and stage patients with moderate to severe AD. The MMSE was used to assess dementia severity in all three trials. An MMSE score of 10-14 is generally considered to reflect moderate illness; MMSE scores below 10 reflect severe illness. In addition to the MMSE, the CGI-S, GDS and FAST (as described in Panel 4) were utilized to identify and characterize moderate to severe AD patients. Individual instruments are described in greater detail in Appendix 8.3.1.

Panel 4. Summary of Dementia Severity Staging Tools

Trial	*Dementia Severity*	*MMSE*	*Other Assessment Tools* *Examples of Clinical Characteristics*
9605	Moderate to Severe	Score 3-14	Global Deterioration Scale 5-6 and Functional Assessment Staging Tool ≥6a ◆ Difficulties in choosing proper clothing, bathing and toileting ◆ Reduced personal hygiene ◆ Urinary and fecal incontinence ◆ Inability to speak, walk, sit, smile or hold head up independently
MD-02	Moderate to Severe	Score 5-14	None
9403	Severe	Score <10	Global Deterioration Scale 5-7 ◆ Difficulties in choosing proper clothing, bathing and toileting ◆ Reduced personal hygiene ◆ Loss of psychomotor and verbal function Clinical Global Impression of Severity 5-7 ◆ 5=Markedly ill ◆ 6=Severely ill ◆ 7=Most extremely ill

2.2.4 Outcome Assessment in the Memantine Moderate-Severe AD Trials

The outcome measures in the key memantine trials reflect the population's symptomatology. Each trial evaluated three common domains (See Panel 5):

- Activities of daily living
- Cognition
- Global status

Panel 5. Summary of Key Efficacy Measures

Trial	*Functional*	*Cognitive*	*Global*
9605	ADCS-ADL_{19} (primary)	SIB	CIBIC+ (primary)
MD-02	ADCS-ADL_{19} (primary)	SIB (primary)	CIBIC+
9403	BGP-Care Dependency (primary)	BGP-Cognitive	CGI-C (primary)

The use of the individual instruments in the key memantine trials is described in additional detail in Section 5.1.2.

2.2.4.1 Assessment of Function

Functional assessment is a crucial aspect of assessing efficacy in patients with moderate-severe AD because it is in this domain that AD shows its most obvious effects. This approach was used successfully by the ADCS to demonstrate benefit from antioxidants in moderate to severe AD[28] and in studies of dementia progression in untreated individuals.[29] Thus, functional scales were included as primary outcome measures in the key memantine trials. In discussions with the sponsor, the FDA Division of Neuropharmacological Drug Products indicated that a suitable ADL outcome measure could be used as an alternative to a global status outcome measure as a second primary outcome measure in addition to an acceptable cognitive outcome measure. A common method for assessing daily function in AD regulatory trials is with a structured interview of an informant, often a spouse, using an ADL scale such as the Progressive Deterioration Scale (PDS), the Disability Assessment for Dementia (DAD), and the IADL.[30] However, these scales primarily tap complex activities which are often lost in the moderate to severe stages.

The key memantine US AD trials (Trials 9605 and MD-02) used a modified version of the ADCS-ADL scale (see Appendix 8.1.1). The original ADCS-ADL scale has 45 items that cover a wide range of ADLs, but it was not intended to be used with all items included.[31] Patients who had an MMSE score in the moderate to severe range (5 to 15) showed the greatest amount of change. The ADCS-ADL$_{19}$, a 19-item subset of the ADCS-ADL, was created to better reflect change in the moderate to severe population.[32] The 19 items were chosen based on an item analysis in the ADCS instrument protocol. Items were discarded if they: (1) were not attempted by at least 50% of the patients, (2) had low reliability based on Kappa statistics less than 0.4, (3) were redundant as determined by high intercorrelation statistics with other items, as well as loading on to the same factor (in this case, the item with the greater reliability was retained), and (4) did not show a mean change score over 6 months of at least 0.20. Items that were determined to be clinically relevant and attempted by most patients, but were not expected to show a high rate of decline, such as turning lights on and off, were retained.

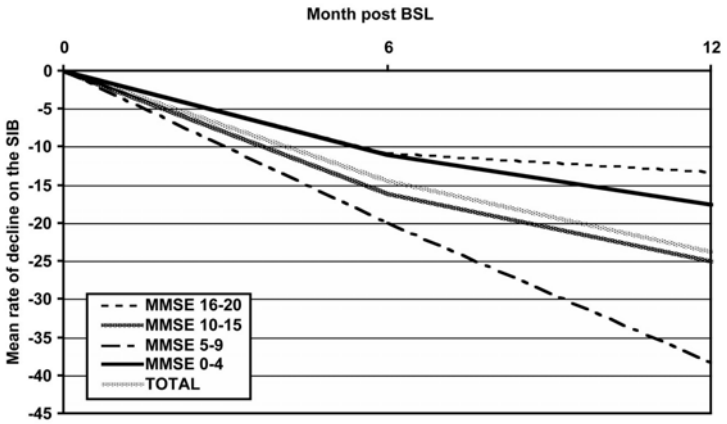
Trial 9403 was conducted in 1994 prior to the validation of the ADCS-ADL. In this trial, assessment of patient function was performed utilizing the BGP-care dependency subscale (shown in Appendix 8.1.3). The BGP was adapted from the Stockton Geriatric Rating scale, an investigator-rated scale that provides an objective behavioral assessment of geriatric patients. The BGP-care dependency subscale included items that are loaded onto the first factor of a factor analysis of the scale's items. The BGP had been used in Europe since 1971 and has good inter-rater and test-retest reliability.[33,34,35] The clinical utility of the BGP in measuring and interpreting longitudinal change in dementia has been established, and its usefulness as an outcome measure for the assessment of treatment response in dementia has been demonstrated.[36,37,38,39] See Section 5.1.2.1 for further descriptions of these scales.

2.2.4.2 Assessment of Cognition

The classical approach to the evaluation of the effectiveness of antidementia pharmacological treatment in mild to moderate AD patients requires the primary outcomes to include a measure of cognition (to date, the ADAS-cog) with an interview-based measure of global clinical status (to date, a CIBIC+). The ADAS-cog is a valid objective measure of cognitive performance in patients with mild to moderate AD. It was used extensively in the ChEI clinical trials for mild to moderate AD patients in the 1990s. However, ADAS-cog items include multiple-step instructions, is dependent on verbal response ability, and requires enough executive abilities to be willing to tolerate the test. It was not designed to comprehensively sample the lowest range of function. Specifically, patients who score in the moderate range show significant decline on the ADAS-cog over time due to the disease's course, but patients in the more advanced stages show little change over time.[40]

The two key US memantine trials used the Severe Impairment Battery (SIB)[41] designed to assess cognitive function in patients who are unable to complete a standard neuropsychological test such as the ADAS-cog (see Section 5.1.2.1, Appendix 8.1.2 for further information). The reliability and validity of the SIB has been demonstrated in AD patients with MMSE scores 0-20 by the NIA-funded ADCS as well as in peer-reviewed research. [41,42,43] Figure 1 demonstrates, in untreated AD patients who were followed for 12 months, that the SIB has adequate range to detect change in moderate to severe AD patients.

Figure 1. Change in SIB Scores Over 6- and 12-Month Periods



The domains assessed with the SIB are similar to those in the ADAS-cog: language, memory, praxis, orientation, and attention. However the emphasis on each domain is different, and individual items are simpler and tend to be one-step commands. Several of the approved ChEIs that were evaluated using the ADAS-cog in the mild to moderate dementia patients, are presently being evaluated using the SIB[44] as a cognitive measure in moderate to severe patients.

Trial 9403 did not use the SIB as an outcome measure because it had yet to be validated by the ADCS. To assess cognition in patients from Trial 9403, the BGP-cognitive subscale, which consists of 5 items from the BGP-care dependency subscale that have face validity for assessing cognitive function, was retrospectively defined. The BGP-cognitive subscale rated patient activities that are clearly dependent upon memory, language, and orientation. The BGP-cognitive subscale is further described in Section 5.1.2.2 and Appendix 8.1.3.

2.2.4.3 Global Patient Status

A global rating of change is typically included as a primary outcome measure in dementia trials of ChEIs as well as in the memantine program. In the key US memantine trials, the two versions of the CIBIC+ used were the NYU (Trial 9605)[45] and the ADCS[46] (Trial MD-02) versions. Trial 9403 used a CGI-C to assess global status. All the global ratings used a 7-point scale rated by an independent clinician using the impression at baseline as a reference point. The primary difference is that the CGI-C is based on an interview with the patient whereas the CIBIC+ is based on separate interviews with the patients and the caregivers and uses a worksheet for collecting information.[45,47] Panel 6 provides a comparison of the tools used to assess global status in the memantine trials.

Panel 6. Comparison of the CIBIC+ and the CGI-C Used in Memantine Trials

Parameter	*CIBIC+*	*CGI-C*
Scale	7 points	7 points
Rater	Experienced clinician	Experienced clinician
Interviews	Patient Informant	Patient
Reference	Severity at baseline	Severity at baseline
Trial	MD-02 (ADCS version) 9605 (NYU version)	9403

2.3 Summary

Due to the increasing prevalence of AD and the inevitable progression to more severe stages of disease, there remains a need to identify safe and effective treatments for these individuals. Currently no therapies have been approved for use in this population. Within the overall AD population, patients with moderate to severe AD can be diagnosed and staged using currently available assessment tools.

Outcome measures assessing daily function, cognitive performance and global status are available that can reliably assess symptomatic change in patients with more severe AD. The key memantine efficacy and safety trials, using such functional and cognitive assessment tools along with global ratings of change, were performed to measure the clinical benefit resulting from memantine treatment in patients with moderate to severe dementia.

3.0 NON-CLINICAL PHARMACOLOGY

There is evidence for enhanced glutamatergic tone and excitotoxicity in neurodegenerative disorders such as AD. Memantine is a low-moderate affinity, uncompetitive NMDA receptor antagonist that appears to selectively block pathological activation of the receptor while preserving physiological neurotransmission by glutamate. Memantine exhibits a distinct in vitro and in vivo profile which differentiates it from the dissociative anesthetic NMDA receptor antagonists.

3.1 Glutamate and NMDA Receptors in Physiological and Pathological Conditions

Glutamate is the major excitatory neurotransmitter in the mammalian brain. About 70% of all synapses in the central nervous system (CNS) utilize glutamate as a transmitter. Glutamate is essential for various physiological processes such as learning and memory, perception and execution of motor acts. However, enhanced levels of glutamate, as observed in several CNS disorders, are associated with neurotoxicity.

Glutamate activates several classes of ionotropic and metabotropic glutamate receptors. One ionotropic glutamate receptor subtype is the NMDA receptor, which regulates glutamate-operated ion channels that are highly permeable to Ca^{2+}. Under resting conditions, NMDA receptor channels do not allow Ca^{2+} influx since they are blocked by Mg^{2+}. Membrane depolarization relieves the Mg^{2+}-blockade of the NMDA receptor channel, permitting Ca^{2+} influx.[48]

Under physiological conditions, the concentration of glutamate in the synaptic cleft is about 1 μM and rises transiently (for 1-2 milliseconds) to millimolar levels during various forms of neural activity, including processes involved in learning and memory.[49,50]

In contrast to the synaptic levels of glutamate achieved during learning and memory, chronic activation of NMDA receptors by relatively lower concentrations of glutamate is believed to be pathologic and to underlie mechanisms of excitotoxicity/neurotoxicity. For example, the persistent elevated synaptic glutamate levels during hypoxia and ischemia can cause cell death due to excessive influx of calcium via NMDA receptors.[51]

Recent studies indicate that persistent activation of glutamate receptors may play an important role in the pathophysiology of several neurodegenerative diseases such as AD, Parkinson's disease, Acquired Immunodeficiency Syndrome (AIDS)-dementia and amyotrophic lateral sclerosis.[52,53,54] Preclinical and post-mortem studies have associated the loss of glutamatergic function resulting from decreased glutamate neurotransmission or excitotoxic neurodegeneration with progressive deterioration in memory.[1,17]

3.1.1 Evidence for Enhanced Glutamatergic Tone and NMDA Receptor Overactivity in AD

According to the glutamatergic hypothesis of dementia as proposed by Greenamyre, enhanced sensitivity of postsynaptic NMDA receptors to elevated or normal levels of synaptic glutamate contributes to excitotoxicity leading to neuronal loss and cognitive impairment seen in AD patients.[55,56] The following evidence supports the hypothesis that abnormal glutamatergic activity plays a role in the pathogenesis of AD:

i. The brains of AD patients exhibit decreased expression of the excitatory amino acid transporter-2 (EAAT2) subtype of glutamate transporter. Deficient functioning of EAAT2 is likely to increase synaptic glutamate levels, which in turn, can cause neuronal damage.[52]

ii. Mice lacking the EAAT2 gene have high synaptic glutamate levels and exhibit impaired long term potentiation (LTP), the cellular correlate of learning and memory. NMDA receptor antagonists partially restore LTP in EAAT2 null mutants.[53]

iii. Overactivation of NMDA receptors by NMDA (both *in vivo* and *in vitro*) or by decreasing the concentration of Mg^{2+}(*in vitro*) produces deficits in synaptic plasticity (e.g., learning or LTP). Low-moderate affinity NMDA receptor antagonists, in contrast to MK-801, can restore synaptic plasticity.[57,58]

iv. Beta-amyloid (Aβ) has been shown to produce NMDA receptor-dependent hippocampal excitotoxicity and reduce the uptake of glutamate. NMDA receptor antagonists are known to block Aβ-induced neurotoxicity.[59,60,61,62]

v. A subset of familial AD is caused by mutations in the presenilin-1 (PS1) gene. Hippocampal neurons from mice with PS1 mutations exhibit increased vulnerability to glutamate-mediated toxicity.[63]

vi. Phosphorylated *tau* protein is a major component of the paired helical filaments that form the neurotoxic neurofibrillary tangles (NFTs) observed in AD brains. Glutamate-toxicity enhances *tau* gene expression in neuronal cultures.[64]

3.2 NMDA Receptor Antagonists

Simultaneous binding by glutamate and glycine is required for the NMDA receptor ion channel to be activated (i.e., for the channel to be opened). In addition to the binding sites for glutamate and glycine, the NMDA receptor contains other distinct modulatory sites to which Mg^{2+}, Zn^{2+}, polyamines, and exogenous ligands bind. The binding sites for Mg^{2+} and exogenous ligands such as phenylcyclidine (PCP), MK-801, and ketamine are located within the channel and are accessible for pharmacologic modulation only when the channel is activated or in the "open state". Therefore, PCP and MK-801 are often referred to as "open channel" or "uncompetitive" or "use-dependent" NMDA receptor antagonists.

It is now well known that some uncompetitive NMDA receptor antagonists (e.g., PCP and ketamine; also referred to as dissociative anesthetic like agents) cause neurobehavioral side effects. However, other uncompetitive antagonists such as memantine, amantadine and dextromethorphan are free of such side effects. The NMDA receptor antagonists are thus often subdivided into two broad categories: drugs which possess dissociative anesthetic-like/hallucinogenic properties (e.g., PCP, MK-801 and ketamine) and drugs that lack dissociative anesthetic-like properties (e.g., amantadine, memantine and dextromethorphan).

3.3 Pharmacological Properties of Memantine

Dissociative anesthetic-like NMDA receptor antagonists typically exhibit high affinity for NMDA receptors, whereas better-tolerated NMDA receptor channel blockers such as memantine, possess lower affinity for NMDA receptors. However, lower binding affinity for the receptor is not the sole determinant for improved drug tolerability. Other pharmacological properties such as the voltage dependency of channel blockade and channel kinetics also clearly distinguish memantine from dissociative anesthetic-like NMDA receptor antagonists. Overall, it is likely the combined effects of a relatively low affinity, high voltage dependency and fast channel unblocking kinetics that provide memantine with an acceptable tolerability profile compared to the dissociative anesthetics. The following data provide evidence that differentiates memantine from NMDA receptor antagonists with dissociative anesthetic-like properties.

- **Memantine has low to moderate affinity for the NMDA receptor:**
  Memantine inhibits [^{3}H]MK-801 binding in rat and human cortical membranes with Ki of 0.5-0.7 μM. By comparison, (+) MK-801 inhibits [^{3}H]MK-801 binding with higher affinity [Ki =2.5-9.4 nM] .[65,66] For reference, serum memantine concentrations in patients reach up to 0.5 μM after daily oral doses of between 5 and 30 mg of memantine.[67]

- **Memantine exhibits strong voltage-dependent channel blocking characteristics:**
  Memantine blocks NMDA-induced currents in cultured rat hippocampal neurons (IC_{50}= ~ 3 μM) in a voltage-dependent manner. For example, memantine (10 μM) produced ~ 77% inhibition of NMDA-induced currents at -70mV, but did not affect NMDA-currents at +70 mV. In contrast, (+) MK-801-mediated inhibition of NMDA-induced currents was voltage-independent.[68,69]

- **Memantine exhibits rapid channel unblocking kinetics (off-rate or K_{off}):**
  At equieffective concentrations, lower affinity NMDA receptor channel antagonists exhibit faster rates of channel unblock than the high affinity antagonists, implying that the faster channel unblocking rates could contribute to improved tolerability of lower affinity NMDA receptor antagonists. Memantine's channel unblocking kinetics (K_{off}=0.2 sec^{-1}) is 40 times faster than that of MK-801 (K_{off} = 0.005sec^{-1}).[69]

- **Memantine does not impair LTP or spatial learning:**
  Memantine, at doses producing therapeutic plasma levels, does not impair the induction of LTP (a cellular correlate of learning and memory) in rat hippocampal slices or disrupt performance in the rat water maze test for spatial learning. By comparison, neuroprotective doses of MK-801 significantly attenuate LTP and impair spatial learning.[70]

- **Memantine does not increase dopamine output in the prefrontal cortex:**
  PCP (10 mg/kg), (+)-MK-801 (0.2-2 mg/kg, i.p.) and ketamine (10-30 mg/kg, i.p.) all increase dopamine output in the rat prefrontal cortex (PFC) by 140-1000% of basal values.[71,72,73] By comparison, neither acute (20 mg/kg, i.p.) nor chronic administration of memantine (20 mg/kg/day, s.c., for 14 days followed by a single challenge dose of 20 mg/kg, i.p.) affects the extracellular levels of dopamine in the prefrontal cortex of freely moving rats. The lack of dopamine release by memantine may contribute to a better tolerability profile of memantine observed at therapeutically relevant doses, as dopamine is thought to contribute to the psychotomimetic effects observed with the dissociative anesthetics.

- **Memantine has a high therapeutic index:**
  Memantine inhibits NMDA receptor-mediated currents with an IC_{50} of ~ 3 μM whereas it tends to inhibit the induction of LTP at a much higher concentration (IC_{50}=11.6 μM). In contrast, MK-801 inhibits both LTP and NMDA receptor-mediated currents with an IC_{50} of 0.14 μM.[74]

  Similarly, while memantine attenuates NMDA-induced decrease in rat cortical ChAT activity with an ED_{50} of 2.81 mg/kg, it induces ataxia at a higher dose (ED_{50} of 24.1 mg/kg) in rats. By comparison, (+) MK-801 protects cholinergic neurons and induces ataxia within a similar dose range (0.077-0.091 mg/kg).[75]

The above pharmacological properties may allow memantine to selectively block sustained activation of NMDA receptors under pathological conditions (such as are likely to occur in AD) and rapidly leave the NMDA receptor channel during normal activation of the receptor (e.g., during learning). This selective sparing of "physiological" NMDA receptor function by memantine is also thought to play a significant role in its reduced risk of neurobehavioral side effects, as compared to NMDA receptor antagonists of the dissociative anesthetic class.

3.4 Efficacy in Cognition and AD-Like Models

Memantine improves learning and memory in several *in vitro* and *in vivo* assays.

- **Memantine improves LTP in aged, memory-impaired rats:**
  Twelve month-old Fisher 344 rats exhibit impairment in LTP and spatial learning. Memantine (30 mg/kg/day, p.o. for 8 weeks equivalent to a steady state plasma level of ~ 1 μM) strengthens hippocampal LTP *in vivo*.[76]

- **Memantine reverses NMDA-induced impairment in learning and LTP:**
  Direct tonic activation of NMDA receptors by NMDA leads to increased synaptic "noise," which in turn results in the loss of association detection (i.e., learning).[57,58] Memantine (2.5 and 5 mg/kg) attenuates NMDA-induced deficits in passive avoidance learning.[57]

  Incubation of rat hippocampal slices with NMDA (10 μM) decreases the magnitude of LTP. Co-incubation of memantine (1μM) with NMDA (10 μM) significantly preserves the induction of LTP.[57]

- **Memantine improves learning in rats with entorhinal cortex lesions:**
  The entorhinal cortex is known to be affected early in the development of AD.[77,78] The effects of memantine on reference and working memory-based learning were determined in the radial maze test in quinolinic acid-induced entorhinal cortex-lesioned rats which exhibit increased reference memory errors on testing. In control (non-lesioned) rats, subcutaneous infusion of memantine (20 mg/kg/day for 12 days) had no effect on either reference or working memory-dependent learning, whereas memantine significantly improved reference memory-based learning in the lesioned rats.[79]

3.5 Neuroprotective Effects

Memantine has demonstrated neuroprotective effects in both *in vitro* and *in vivo* models:

- **Memantine protects neurons from excitotoxic insults:**
  Memantine protects rat cortical and hippocampal neurons from glutamate-induced toxicity with an EC_{50} of between 1.1 and 1.4 μM.[80,81]

  Memantine prevents cell death of rat retinal ganglion cells caused by high Ca^{2+} and low Mg^{2+} in the incubation medium with an ED_{100} of ~ 6 μM.[82] Administration of memantine (12 μM) to the retinal ganglion cells (up to 4 hr after the initiation of the insult) also produced a significant neuroprotective effect.[83]

  Injection of NMDA into the rat nucleus basalis magnocellularis (NBM) destroys cholinergic cells and decreases cortical ChAT activity. Memantine prevents the NMDA-induced decrease in ChAT activity in rat cortex with an ED_{50} of 2.81 mg/kg.[75]

- **Memantine protects rat hippocampal cells from ß-amyloid-toxicity:**
  Memantine (15 mg/kg/day, subcutaneous), produced a steady-state plasma level ranging from between 1.4 and 3.6 μM and significantly reduced Aβ-induced neurotoxicity (apoptotic cell loss and neuroinflammation) in the hippocampus.[62]

- **Memantine exhibits anti-apoptotic effects:**
  Rat cortical cell cultures exposed to human immunodeficiency virus type 1 (HIV-1) coat protein gp120 for 12 hr exhibit DNA fragmentation and decreased cell viability. Memantine (10 μM) significantly reduced gp120–induced DNA-fragmentation (a characteristic feature of apoptosis) and increased cell viability.[84]

- **Memantine protects transgenic mice overexpressing HIV-1 gp120 protein from neurotoxicity:**
  Overexpression of gp120 protein resulted in changes in the morphology and number of dendrites (detected with MAP-2 immunostaining) and presynaptic terminals (immunolabeled with synaptophysin) in gp120 overexpressing mice.

  Memantine treated (20 mg/kg, s.c., as the loading dose, followed by a 1 mg/kg, s.c., maintenance dose every 12 hr for 6 weeks) transgenic mice had significantly decreased gp120-induced neuropathology compared to untreated mice.[85]

3.6 Interactions with Other Receptors and Channels

- **Memantine Interacts with $5HT_3$ and Nicotinic Acetylcholine Receptors**
  Memantine inhibits $5HT_3$ receptor-mediated currents in HEK-293 cells (expressing recombinant $5HT_3$ receptors) as well as in the N1E-115 cell line (containing native $5HT_3$ receptors) in a noncompetitive manner with an IC_{50} of ~ 2 μM.[86] Memantine exhibited affinity for nicotinic acetylcholine receptors, inhibiting end plate current with an IC_{50} of ~ 10 μM in the frog neuromuscular junction.[87] Memantine has also been shown to block human neuronal $\alpha_4\beta_2$ nicotinic receptors with an IC_{50} of 6.6 μM.[88]

- **Memantine Lacks Interaction with Other Receptors and Channels**
  Memantine (10 μM) lacks affinity for serotonin receptor subtypes (with the exception of $5HT_3$ receptors), muscarinic acetylcholine receptors, α and β adrenergic receptors, dopamine receptors, histamine receptors, glycine receptors, sigma receptors and metabotropic glutamate receptors (mGluR1 and mGluR5). Memantine also does not affect voltage-dependent Ca^{2+}, Na^+, K^+ or Human Ether-a-go-go-Related Gene (HERG) K^+ channel function. Memantine does not affect the release of dopamine or serotonin, nor does it alter monoamine oxidase (MAO-A or B) or adenylate cyclase activity.[89,90]

3.7 Non-Clinical Pharmacology Summary

- Memantine binds to the NMDA receptor channel with low to moderate affinity and exhibits strong voltage-dependent channel blocking characteristics and fast channel unblocking kinetics that differentiate it from the dissociative anesthetic NMDA receptor antagonists.

- Memantine does not impair LTP or spatial learning in rats at therapeutically relevant doses.

- Memantine improves LTP and learning in aged and memory-deficient rats and protects neurons from Aβ and other excitotoxic insults.

4.0 CLINICAL PHARMACOLOGY

Memantine is essentially 100% bioavailable after oral administration and exhibits a linear pharmacokinetic profile that is not affected by food, age, or sex. It undergoes minimal metabolism and is eliminated largely by renal mechanisms with a terminal half-life of 60-80 hours. Memantine does not significantly inhibit CYP 450 isoenzymes in vitro and does not interact with donepezil in vivo.

A total of 30 clinical pharmacology trials were conducted with memantine in 487 subjects.

4.1 Clinical Pharmacology Overview

Panel 7 provides a summary of memantine's clinical pharmacology profile.

Panel 7. Summary of Memantine's Clinical Pharmacology Profile

Bioavailability and Dose Proportionality	◆ 100% bioavailable ◆ Linear PK over 5-40 mg single doses
T_{max}	◆ 4-6 hours
$T_{1/2}$	◆ 60 to 80 hours
Protein Binding	◆ 42-45%
CSF/Serum Ratio	◆ 0.52
Distribution	◆ Volume of distribution of 9 to 11 L/kg ◆ Rapidly crosses the blood-brain barrier
Metabolism and Elimination	◆ Undergoes little metabolism ◆ largely (75-90%) excreted unchanged in urine ◆ remainder (10-25%) converted to polar metabolites with minimal pharmacological activity ◆ Dose-independent elimination
Drug-Drug/ Food Interaction	◆ Minimal inhibition of CYP 450 enzymes *in vitro* ◆ Minimal interaction with drugs that are substrates of CYP450 enzymes. ◆ No adverse interaction between memantine and donepezil *in vivo*. ◆ No significant food interaction
Special Populations	◆ No age or sex pharmacokinetic differences ◆ No differences in steady-state plasma levels between healthy subjects and dementia patients.
CNS Effects	◆ Minimal effects on memory function and information processing in healthy subjects.

4.2 Human Pharmacokinetics

Following oral administration in humans, memantine is rapidly and completely absorbed (T_{max} values of approximately 4 to 6 hours post-dose).[91,92,93,94,95,96,97,98]

Dose proportionality was observed following single oral doses of 5 to 40 mg memantine and multiple doses of 10 to 40 mg.[91,98,99]

The volume of distribution of memantine following intravenous doses of 20, 30, and 40 mg memantine was approximately 9 to 11 L/kg suggesting extensive distribution of memantine into tissues.[98,99] Memantine exhibits a low level of plasma protein binding (approximately 45%).[100]

Memantine rapidly crosses the blood-brain barrier. Following a 20 mg infusion, memantine was detected in cerebrospinal fluid (CSF) within 30 minutes.[101] After intravenous administration of 5 to 30 mg/day over 6 to 12 days in patients with dementia, the mean CSF/serum ratio was 0.52.[67]

The majority of the administered memantine dose was excreted unchanged in urine (75-90%), with the remainder converted primarily to polar metabolites.[100,102,103] The major metabolites excreted in urine are memantine N-gludantan conjugate and 6-hydroxy memantine.[104,105,106] The human metabolites do not have NMDA receptor antagonistic activity.[107]

Memantine is eliminated with a terminal half-life of approximately 60 to 80 hours[92,93,97] and exhibits dose-independent elimination after single or multiple dose administration.[91,99, 108]

Renal clearance accounted for 90% of total memantine clearance under physiological conditions, 92% under acidic conditions, and 60 – 67% under alkaline conditions.[102,109,110,111] Total clearance and renal clearance under physiological urinary conditions averaged 182 mL/min and 164 mL/min, respectively.[102] Memantine renal clearance substantially exceeded renal filtration rates, indicating the presence of renal secretion.[103]

4.2.1 Drug-Drug Interactions

4.2.1.1 In Vitro Trials

The potential for interaction of memantine with drugs metabolized by the CYP 450 isozymes is low based on *in vitro* experiments. A moderate degree of inhibition of flavin containing monooxygenase (21, 23, and 41% at memantine concentrations of 0.1, 1, and 10 μM, respectively) was observed (by reference, steady-state therapeutic plasma concentrations of memantine are within the range of 0.37 - 0.5 μM).[112]

The active transport of memantine does not appear to be mediated via p-glycoprotein (Pgp) or the multidrug-resistance-gene-related protein (MRP).[113,114]

In vitro investigation of the potential interaction between memantine and the ChEIs donepezil, galantamine and tetrahydroaminoacridine showed that memantine did not attenuate the inhibition of ChE by these drugs.[115]

4.2.1.2 In Vivo Trials

In 24 subjects following a single dose of 10 mg memantine and multiple daily doses of 10 mg donepezil, there were no clinically significant differences in the pharmacokinetics of memantine and donepezil or in the inhibition of ChE by donepezil when the two drugs were administered alone and in combination.[97]

Because memantine is excreted in part by tubular section, the interaction between memantine and hydrochlorothiazide/triamterene (HCTZ/TA) was investigated in 20 adult subjects who received multiple oral doses of 20 mg memantine and 25 mg/50 mg HCTZ/TA. HCTZ/TA did not alter the bioavailability of memantine at steady-state. Memantine did not affect the bioavailability of triamterene and its metabolite hydroxytriamterene but caused a reduction of about 20% in the bioavailability of HCTZ.[116]

4.2.2 Special Populations

4.2.2.1 Age, Disease, and Gender Effects

The effects of age and gender on memantine pharmacokinetics were evaluated using pooled data from various PK trials that had similar PK sampling times. In the pooled data set of 3 single dose trials, the age of the subjects ranged from 19 – 69 years and included 32 male and 19 female subjects. In the pooled data set of 2 multiple dose trials, the age of the subjects ranged from 50 – 71 years and included 30 male and 18 female subjects. No statistically significant differences were found in C_{max} and AUC parameters of memantine between male and female subjects and between elderly and young subjects when adjusting for differences in weight.[117]

Memantine plasma concentrations in patients with dementia were determined in four clinical trials (Trials 9605, 9403, 9408, and 9202). No differences were observed in memantine steady-state plasma concentrations between healthy subjects and patients with dementia.[118]

4.2.2.2 Renal Impairment

When a single 20 mg oral dose of memantine HCl was administered to geriatric subjects with different levels of renal function (40 to >80 mL/min/1.73 m^2), memantine total clearance was decreased and AUC was increased with increasing degrees of renal impairment. No significant relationships were observed for $T_{1/2}$ and C_{max} values versus creatinine clearance.[95]

4.2.2.3 Hepatic Impairment

Memantine undergoes little hepatic metabolism, so the elimination of memantine is unlikely to be affected in patients with hepatic impairment.[100,102,103]

4.3 Human Pharmacodynamics

4.3.1 Effects on Central Nervous System

Twenty-four healthy subjects (age range 20 to 35 years) received a single dose of 30 mg memantine or placebo and were tested for choice reaction time, visual flicker fusion frequency, subjective well-being (including 10-point verbal scales for agitated, alert, mood, tired, relaxed, focused, energetic), sleep quality, and long-term, short-term and everyday memory.[119] Memantine had no effect on temporal information processing or on short-term and long-term memory functions in these healthy subjects. Based on the well-being scale, subjects in the memantine group had an increase in perceived tiredness and a decrease in subjective alertness relative to placebo treatment.

In a double-blind, placebo-controlled, cross-over study in 40 healthy male subjects (age range 20 – 35 years) who received a single 30 mg oral memantine dose or placebo, no effect was observed on perceptual and psychomotor tasks (temporal discrimination, reaction time, critical flicker fusion frequency, and signal detection). In terms of long-term memory functions, recognition performance for objects was impaired under memantine treatment as compared to placebo but performance on face recognition was not affected by memantine.[120]

Another double-blind, placebo-controlled study was conducted in 16 healthy male subjects who also received a single dose of 30 mg memantine or placebo. Memantine did not affect a range of cognitive functions such as attention and concentration, verbal fluency, and short-term and long-term memory functions. However, memantine delayed the acquisition of a classically conditioned eyeblink response and reduced the frequency of conditioned responses without affecting reflex or spontaneous eyeblinks.[121]

The relative absence of effects of memantine on memory functions and information processing in healthy subjects are in agreement with the mode of action of the drug as a low-moderate affinity, uncompetitive, voltage-dependent NMDA receptor antagonist, blocking the pathological stimulation of neurotransmission but allowing physiological

neurotransmission, thus exerting an effect only when glutamate transmission is abnormal.[1,68]

4.3.2 Other Findings

The effect of memantine on the endocrine system was investigated in two trials.[122,123] One study evaluated the effects of memantine (0.16 mg/kg infused over 60 minutes) and another NMDA receptor antagonist, ketamine (0.5 mg/kg), relative to placebo treatment in 15 healthy male subjects. Memantine had no effect on serum cortisol or prolactin levels relative to placebo treatment while ketamine increased the levels of both of these hormones ($p < 0.001$).[122] In another study, the effect of memantine on pituitary function was evaluated in healthy elderly subjects who received multiple daily doses of 20 mg memantine as immediate release tablets or sustained release tablets.[123] Memantine had no effect on pituitary function as measured by Thyroid-Stimulating Hormone (TSH), Luteinizing Hormone (LH), Follicle-Stimulating Hormone (FSH), prolactin, and vasopressin levels.

Hemodynamic evaluations were performed in 6 healthy male subjects who received intravenous doses of memantine at 15-60 mg in a single-dose, placebo controlled, dose-escalating crossover study with a 14-day washout period between treatments.[124] Hemodynamic measurements were performed pre-dose and repeatedly post-dose for 6 hours. No clinically relevant effects on cardiohemodynamics or electrophysiological parameters were observed.

In another study in 3 healthy male subjects, memantine was administered as a cumulative intravenous dose starting at 15 mg (0 hours), 30 mg at 1 hour and 60 mg at 2 hours.[125] There was a slight vasoconstriction followed by a decrease in heart rate and a mild increase in blood pressure compared to baseline values.

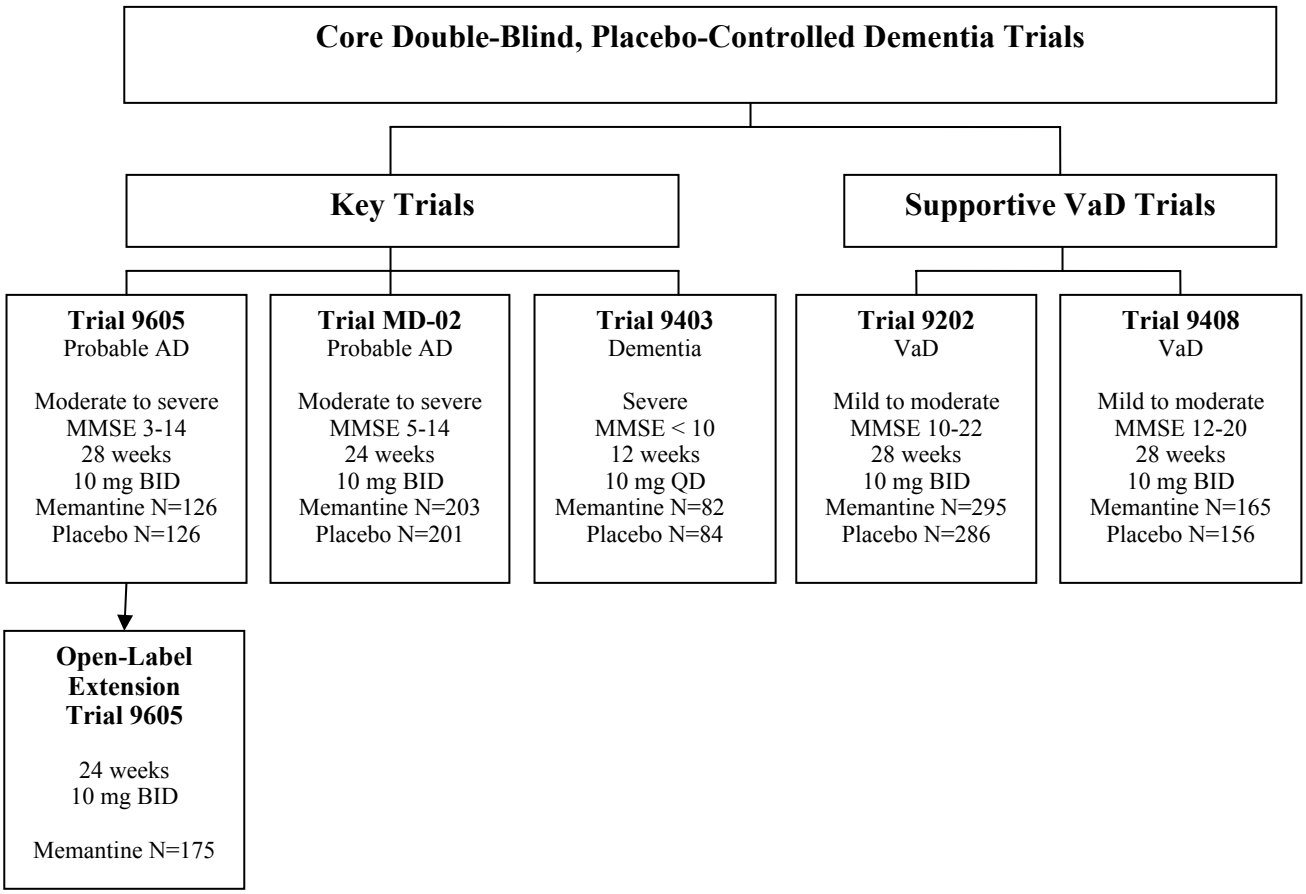
5.0 CLINICAL EFFICACY

Three key double-blind, placebo-controlled trials have utilized appropriate diagnostic and outcome measures to demonstrate that memantine in the dose range of up to 20 mg/day provides clinical benefit in the domains of cognition, function, and global status for patients with advanced AD.

5.1 Efficacy Overview

The clinical development history of memantine is described in Section 2.1. The results from two key double-blind, placebo-controlled dementia trials (Trials 9605 and MD-02 in AD patients and one earlier key trial in patients with dementia (Trial 9403) clearly establish the efficacy of memantine as a treatment for moderate to severe AD. These trials showed that memantine produces a clinically and statistically significant therapeutic benefit relative to placebo in day-to-day function, cognitive abilities, and global clinical status in patients with moderate to severe AD. Additionally, in two supportive randomized, double-blind, placebo-controlled, multicenter clinical trials (Trials 9202 and 9408) in patients with mild to moderate VaD, memantine demonstrated significant beneficial effects on cognition in comparison to placebo as measured by the ADAS-cog.

Figure 2. Patient Populations in the Core Double-Blind, Placebo-Controlled, Dementia Trials



5.1.1 Summary of Key Efficacy Results

Trial 9605 was a randomized, double-blind, placebo-controlled, parallel group multicenter trial. Patients had MMSE scores of 3 to 14 and diagnoses of dementia of the Alzheimer's type (DSM-IV) and probable AD (NINCDS-ADRDA criteria). A total of 252 patients were randomized to 28 weeks of double-blind treatment with 20 mg/day (10 mg BID) memantine or placebo. The functional, cognitive, and global outcome measures used to assess efficacy were, respectively, the ADCS-ADL_{19}, the SIB, and the CIBIC+ (NYU version). The ADCS-ADL_{19} and CIBIC+ were the protocol-specified primary efficacy measures.

A significantly greater therapeutic effect was observed in the memantine group relative to the placebo group on the ADCS-ADL_{19} and SIB by LOCF analyses (Panel 8). There was a numerical difference in favor of memantine on the CIBIC+ using the LOCF approach. Analyses using the OC approach revealed significant effects for memantine relative to placebo on the ADCS-ADL_{19}, the SIB, and the CIBIC+.

Panel 8. Summary of Efficacy: Mean Change from Baseline – Trial 9605

	Domain	***Scale***	***Placebo***		***Memantine***		***Between Treatment Differences***	***p-value***
			N	*Δ*	*N*	*Δ*		
Endpoint (LOCF) (N=126)	Function	ADCS-ADL_{19}	126	-5.1	126	-3.0	2.1	0.022
	Cognition	SIB	126	-9.8	126	-3.9	5.9	< 0.001
	Global Status	CIBIC+*	126	4.73	126	4.48	0.25	0.064
Week 28 (OC)	Function	ADCS-ADL_{19}	84	-5.9	97	-2.5	3.4	0.003
	Cognition	SIB	83	-10.2	96	-4.5	5.7	0.002
	Global Status	CIBIC+*	84	4.74	97	4.38	0.36	0.025

*Δ = mean change from baseline; *Values shown are mean CIBIC+ scores*

Trial MD-02 was a randomized, double-blind, placebo-controlled, parallel group multicenter trial in patients maintained on stable donepezil therapy. Patients had a MMSE score of 5 to 14 and a diagnosis of probable AD according to NINCDS-ADRDA criteria. A total of 404 patients were randomized to 24 weeks of double-blind treatment with 20 mg/day (10 mg BID) memantine or placebo. There was a 1-2 week placebo lead in solely used to assess compliance. The functional, cognitive, and global outcome measures used to assess efficacy were, respectively, the ADCS-ADL_{19}, the SIB, and the CIBIC+ (ADCS-CGIC version). The ADCS-ADL_{19} and SIB were the protocol-specified primary efficacy parameters.

A significantly greater therapeutic effect was observed in the memantine group relative to the placebo group on the SIB, ADCS-ADL_{19}, and CIBIC+, using both the LOCF and the OC approaches (Panel 9).

Panel 9. Summary of Efficacy: Mean Change from Baseline – Trial MD-02

	Domain	***Scale***	***Placebo***		***Memantine***		***Between Treatment Differences***	***p-value***
			N	*Δ*	*N*	*Δ*		
Endpoint (LOCF)	Function	ADCS-ADL$_{19}$	197	-3.2	198	-1.8	1.4	0.028
	Cognition	SIB	196	-2.3	198	1.1	3.4	< 0.001
	Global Status	CIBIC+*	196	4.66	198	4.41	0.25	0.027
Week 24 (OC)	Function	ADCS-ADL$_{19}$	152	-3.0	172	-1.5	1.5	0.020
	Cognition	SIB	153	-2.1	171	1.2	3.3	< 0.001
	Global Status	CIBIC+*	152	4.64	172	4.38	0.26	0.028

*Δ = mean change from baseline; *Values shown are mean CIBIC+ scores*

Trial 9403 was a randomized, double-blind, placebo-controlled, parallel group multicenter trial. Patients had MMSE scores below 10, and the study population included patients with a diagnosis (DSM-III-R) of dementia: either AD VaD. A total of 166 inpatients (79 AD and 87 VaD) were randomized to 12 weeks of double-blind treatment with 10 mg/day memantine or placebo. The functional, cognitive, and global measures used to assess efficacy were, respectively, the BGP-care dependency subscale, the BGP-cognitive subscale (defined and analyzed retrospectively), and the CGI-C. The BGP-care dependency and CGI-C were the protocol-specified primary efficacy parameters.

Significantly greater improvement was observed in the memantine dementia group relative to the placebo dementia group on the BGP-care dependency subscale, the BGP-cognitive subscale, and the CGI-C by the LOCF approach (Panel 10). Analyses using the OC approach yielded similar results. Separate analyses of the AD population alone also yielded statistically significant results in favor of memantine-treated patients, by either the LOCF or the OC approach on all three outcome measures.

Panel 10. Summary of Efficacy: Mean Change from Baseline – Trial 9403 (All Patients)

	Domain	***Scale***	***Placebo***		***Memantine***		***Between Treatment Differences***	***p-value***
			N	*Δ*	*N*	*Δ*		
Endpoint (LOCF)	Function	BGP-care dependency	84	-3.3	82	-5.3	2.0	0.012
	Cognition	BGP-cognitive	84	-1.1	82	-1.9	0.8	0.001
	Global Status	CGI-C*	84	3.5	82	3.1	0.4	<0.001
Week 12 (OC)	Function	BGP-care dependency	80	-3.5	78	-5.6	2.1	0.010
	Cognition	BGP-cognitive	80	-1.2	78	-1.9	0.7	0.001
	Global Status	CGI-C*	80	3.5	78	3.0	0.5	<0.001

**Values are mean CGI-C scores*

5.1.2 Outcome Measures

5.1.2.1 Assessment of Function

The following assessment tools were used to measure changes in functional impairment in patients participating in the three key studies. The choice of the prospective outcome measures for each trial reflected the appropriate domains of interest and the scales which were considered valid and/or accepted by the investigator community at the time the trials were initiated.

ADCS-ADL$_{19}$
The ADCS-ADL$_{19}$ [32,126] utilized in Trials 9605 and MD-02 is a subset of 19 items from the original item pool. This subset has been demonstrated to be appropriate for the assessment of patients with moderate to severe dementia. [32] ADL functioning is evaluated by interviewing a person who is in close contact with the patient and covers the most usual and consistent performance of the patient over the preceding four weeks. A total of 54 points signifies optimal performance.

BGP-Care Dependency Subscale
The BGP scale utilized in Trial 9403 consists of 35 items assessing observable behaviors, rated by nursing staff, with higher scores reflecting greater disability.[33,34,35] In Trial 9403, the BGP ratings are made after a real time, direct observation of concrete patient activities by trained clinic staff, taking full advantage of the extended sampling period provided by the inpatient setting. The BGP-care dependency subscale consisted of 23 items, scored as 0-2 points, including dressing, eating, toileting, conversation, and travel (range 0-46).

5.1.2.2 Assessment of Cognition

SIB
The SIB[42,43] instrument used in Trials 9605 and MD-02 was developed to assess the severity of cognitive dysfunction in more advanced AD patients. The SIB consisted of 51 items that assess the following domains: social interaction, memory, language, attention, orientation, praxis, visuospatial ability, construction, and orientating to name. The items were developed as simple, one-step commands, presented with gestural cues and repeated if necessary. Further, the SIB scoring system allows for partial responses given that expressive language impairments are common in advanced AD. The range of possible scores is 0 to 100 (with 100 being the best result).

BGP-Cognitive Subscale
Cognitive performance was measured by the BGP-cognitive subscale, a retrospectively identified efficacy parameter in Trial 9403. In Trial MD-02, the BGP- cognitive subscale was a prospectively defined secondary cognitive outcome measure. The BGP-cognitive score consisted of 5 items from the BGP scale and could range from 0 to 10, with higher values denoting greater impairment.

5.1.2.3 Assessment of Global Status

CIBIC+

A CIBIC+ was used in Trials 9605 (NYU version)[45] and MD-02 (ADCS version)[46] as the measure of global change.

CIBIC+ evaluations were performed by an independent, experienced clinician who was not responsible for the care or management of the patient. At the baseline visit, the rater was encouraged to assimilate all available information relative to the current clinical status of the patient. The relevant information could be obtained from the patient, family members, clinic staff, baseline psychometric test scores, and ADL assessments. A patient worksheet was provided for each patient to assist the rater in forming his/her baseline impression. Specific target domains included (but were not limited to) concentration, orientation, memory, language, behavior, initiative, and ADLs.

The same rater conducted subsequent CIBIC+ interviews, and the ratings were based exclusively upon the patient assessment and caregiver information, independent of the results from psychometric tests or other clinical or safety assessments. The caregiver and the patient were interviewed separately, if possible. The CIBIC+ rater had access to the forms from the baseline interview, but to no other patient information.

After completion of each interview, the clinician rated the patient's global clinical status relative to the baseline interview. The patient was rated on a standardized 7-point ordinal scale (1 = markedly improved, 4 = unchanged, and 7 = markedly worse).

CGI-C

The CGI-C[47] was used in Trial 9403 as the measure of global change. Similar to the CIBIC+, the CGI-C rating was a direct evaluation of the patient independently performed by a clinician, but unlike the CIBIC+, the CGI-C rating did not incorporate caregiver input or worksheets. At the baseline evaluation, the rater had access to all information (psychometric scores, physical examination, caregiver information, etc.) to perform a severity assessment. After baseline, the CGI-C rating was based on a general interview/assessment with the patient. This scale uses the same 7-point scale as the CIBIC+.

5.1.2.4 Other Assessments

Several secondary assessments were utilized in the clinical program (Panel 11). These measures either supported the diagnosis or staging of the disease, or were identified as secondary efficacy outcome evaluations. Descriptions of these scales can be found in Appendix 8.2.

5.2 Placebo-Controlled Dementia Trials

A brief overview of the trial design, patient population, treatment schedule and duration, inclusion criteria, and outcome measures for the three key trials and the two supportive dementia studies is presented in Panel 11.

Panel 11. Summary of Trial Design and Efficacy Assessments

Trial Randomized (N)	*Design/ Treatment Groups*	*Patient Population/ Diagnosis and Inclusion Criteria*	*Efficacy Outcome Measures and Assessment Schedule*
CORE DOUBLE-BLIND, PLACEBO-CONTROLLED DEMENTIA TRIALS - KEY TRIALS			
9605 Total N = 252 Memantine N = 12 _____ Memantine N=80 (new exposure)	28-week double-blind trial Placebo Memantine 10 mg BID _____ 24-week optional open-label extension Memantine 10 mg BID	Diagnosis: Probable AD (DSM-IV and NINCDS-ADRDA) Severity: Moderate to Severe ◆ MMSE 3-14 ◆ GDS 5-6 ◆ FAST ≥ 6a ◆ HIS ≤ 4 ◆ ≥ 50 years of age	◆ Cognition: SIB ◆ **Function: ADCS-ADL*19* (primary)** ◆ **Global: CIBIC+ (primary)** ◆ Others: MMSE, FAST, NPI, and GDS Assessed at baseline, Week 4, 12, and 28 for the double-blind period; CIBIC+ was assessed at baseline, Week 12 and Week 28 (ADCS-ADL*19*, SIB, and CIBIC+ were assessed at weeks 32, 40, and 52 in the open-label extension)
MD-02 Total N = 404 Memantine N = 203	24-week Placebo Memantine 10 mg BID	Diagnosis: Probable AD (NINCDS-ADRDA) Severity: Moderate to Severe ◆ MMSE 5-14 ◆ ≥ 50 years of age ◆ Ongoing donepezil therapy ≥ 6 months at a stable dose (5-10 mg/day) for the past 3 months	◆ **Cognition: SIB (primary)** ◆ **Function: ADCS-ADL*19* (primary)** ◆ Global: CIBIC+ ◆ Others: BGP, FAST, and NPI Assessed at Weeks 4, 8, 12, 18, and 24
9403 Total N = 166 Memantine N = 82	12-week, Placebo Memantine 10 mg QD	Diagnosis: Dementia (DSM-III-R) Severity: Severe ◆ MMSE <10 ◆ GDS 5-7 ◆ CGI-S 5-7 ◆ HIS ≤ 4 (AD patients) ◆ 60-80 years of age	◆ Cognition: BGP-cognitive ◆ **Function: BGP-care dependency (primary)** ◆ **Global: CGI-C (primary)** ◆ Others: G2, G2-C, CGI-S, CGI-Benefit/Risk Index, and IADL Assessed at Weeks 1, 4, 8 and 12; CGI-C assessed at Weeks 4 and 12.

Panel 11. Summary of Trial Design and Efficacy Assessments

Trial Randomized (N)	*Design/ Treatment Groups*	*Patient Population/ Diagnosis and Inclusion Criteria*	*Efficacy Outcome Measures and Assessment Schedule*
CORE DOUBLE-BLIND, PLACEBO-CONTROLLED DEMENTIA TRIALS - SUPPORTIVE TRIALS			
9202 Total N = 581 Memantine N =295	28-week, Placebo Memantine 10 mg BID	Diagnosis: VaD (NINDS-AIREN) Severity: Mild to moderate ◆ MMSE 10-22 ◆ HIS > 4 ◆ HAMD ≤ 17 ◆ ≥ 50 years of age	◆ **Cognitive: ADAS-cog (primary)** ◆ **Global: CGI-C (primary)** ◆ Others: GBS, NOSGER, and MMSE
9408 Total N = 321 Memantine N=165	28-week, Placebo Memantine 10 mg BID	Diagnosis: VaD (NINDS-AIREN) Severity: Mild to moderate ◆ MMSE 12-20 ◆ MIS > 4 ◆ HAMD ≤ 14 ≥ 60 years of age	◆ **Cognitive: ADAS-cog (primary)** ◆ **Global: CIBIC+ (primary)** ◆ Others: GBS, CGI-C (physician), CGI-C (caregiver), CGI-S, MMSE and NOSGER II,

Titration schedule: All patients assigned to memantine treatment received a starting dose of 5 mg once daily and were titrated over a 3-week period to a maintenance dose of 20 mg/day (10 mg twice a day) by Week 4 except for Trial 9403 in which the target dose of 10 mg/day was reached at Week 2 and maintained until Week 12.

5.2.1 Trial 9605 (Reisberg et al., 2003)[127]

Efficacy and Long-Term Tolerability of Memantine in Patients with Moderately Severe to Severe AD

This was a 28-week, multicenter, randomized, double-blind, placebo-controlled trial conducted in the US. The study design, inclusion criteria, efficacy assessments and titration schedule are provided in Panel 11. The primary efficacy measures were the ADCS-ADL_{19} and the CIBIC+. The secondary efficacy measures included the SIB, MMSE, Neuropsychiatric Inventory (NPI),[128] FAST, and GDS. Patients who completed double-blind treatment were given the opportunity to enter a 24-week open-label memantine treatment extension.

A total of 252 patients were randomized, 126 to each of the treatment groups. A total of 181 (72%) patients completed the trial (Panel 12). The discontinuation rate was 33% in the placebo group and 23% in the memantine group. The average memantine-treated patient was about 76 years old and weighed about 65 kg. Eighty nine percent of memantine-treated patients were Caucasian, 72% were female, and the mean MMSE score at baseline was 7.7 points (range 2 to 14). No patient had a HIS score greater than 4. The demographic profile for placebo patients was very similar to that of memantine. The baseline disease severity assessment scores (including FAST staging, GDS and MMSE) and the baseline values for functional (ADCS-ADL_{19}) and cognitive (SIB) outcome measures showed that the two treatment groups were well matched at the start of the trial.

Panel 12. Patient Demographics and Baseline Assessments – Trial 9605

Demographics and Baseline Assessments	*Placebo (N = 126)*	*Memantine (N = 126)*
AGE (YEARS) Mean ± SD	76.3 ± 7.8	75.9 ± 8.4
FEMALE, N (%)	79 (63)	91 (72)
CAUCASIAN N (%)	115 (91)	112 (89)
WEIGHT (KG) Mean ± SD	66.1 ± 14.1	64.5 ± 12.4
MMSE* Mean ± SD	8.1 ± 3.6	7.7 ± 3.7
FAST** Mean ± SD	2.8 ± 1.4	2.8 ± 1.2
GDS Mean ± SD	5.6 ± 0.5	5.5 ± 0.5
SIB Mean ± SD	68.3 ± 20.8	65.9 ± 21.7
ADCS-ADL_{19} Mean ± SD	27.4 ± 10.9	26.8 ± 9.2

*Range from 1 to 14 (one placebo patient with a score of 1; one placebo and one memantine patient each with a score of 2)
**Mean baseline value corresponds to the FAST stage of 6c

5.2.1.1 Assessment of Function

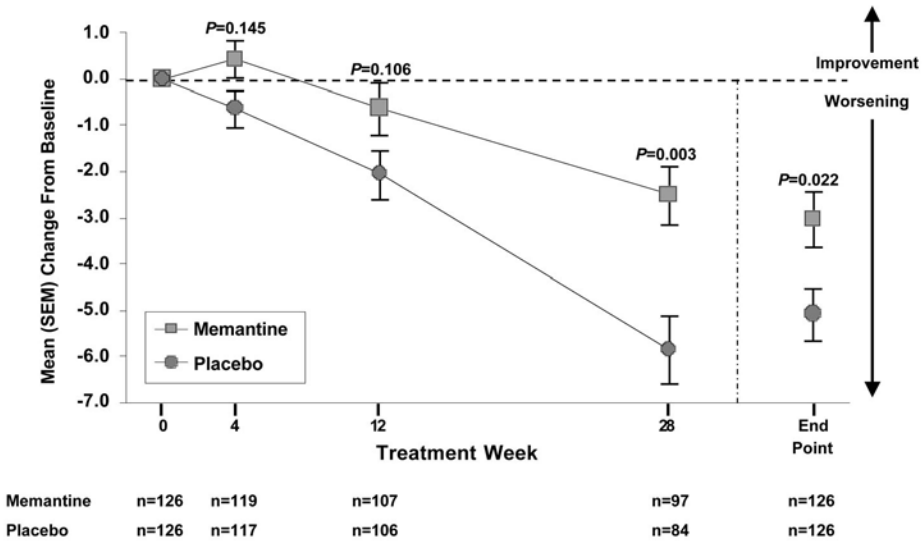
Using the ADCS-ADL$_{19}$, memantine treatment resulted in significantly less deterioration over time compared with placebo (Panel 13). In the LOCF analysis, the mean change from baseline to endpoint was –3.0 for memantine compared with –5.1 for placebo (p= 0.022). In the OC analysis, the mean change from baseline to endpoint was –2.5 for memantine compared with –5.9 for placebo (p = 0.003).

Panel 13. Mean Change from Baseline in ADCS-ADL$_{19}$ – Trial 9605

	Placebo		***Memantine***		***p-value***
	N	*Mean*	*N*	*Mean*	
Endpoint (LOCF)	126	-5.1	126	-3.0	0.022
Week 28 (OC)	84	-5.9	97	-2.5	0.003

The mean change scores for placebo treatment reflected continuous deterioration in functionality during the trial (Figure 3). In contrast, there was evidence of a slight improvement in functionality at Week 4 with memantine treatment, as judged by the positive mean change score at this visit. At subsequent visits (Weeks 12 and 28) the mean change score deteriorated under memantine treatment but to a lesser extent than under placebo treatment.

Figure 3. Mean Change from Baseline in the ADCS-ADL$_{19}$ by Visit (OC) and at Endpoint (LOCF) – Trial 9605



5.2.1.2 Assessment of Cognition

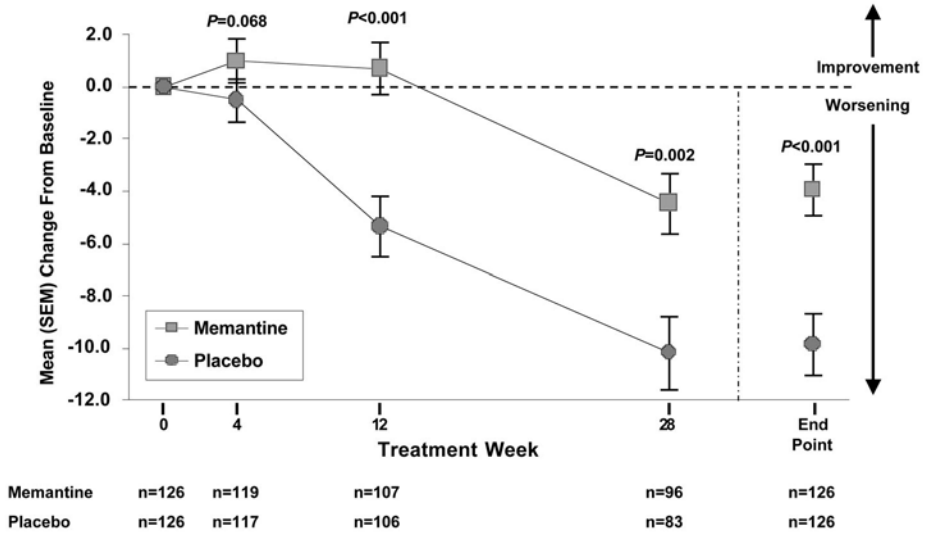
In the LOCF analysis, the SIB showed significantly less decline with memantine treatment compared to placebo (p <0.001;Panel 14). With memantine treatment, the mean SIB scores fell 3.9 points compared with a decline of 9.8 points with placebo. In the OC analysis, the mean score fell 4.5 points in the memantine group and 10.2 points in the placebo group (p = 0.002).

Panel 14. Mean Change from Baseline in SIB – Trial 9605

	Placebo		***Memantine***		***p-value***
	N	*Mean*	*N*	*Mean*	
Endpoint (LOCF)	126	-9.8	126	-3.9	< 0.001
Week 28 (OC)	83	-10.2	96	-4.5	0.002

Figure 4 illustrates the time course of the change from baseline in SIB score at each visit during the trial. The mean change scores under placebo treatment provided evidence of continuous deterioration of cognitive performance during the trial. Mean change scores in the memantine group provide evidence of maintenance of cognitive abilities over the first 12 weeks of treatment. Mean cognitive test performance deteriorated after 12 weeks of treatment with memantine, but to a lesser extent than with placebo treatment.

Figure 4. Mean Change from Baseline in the SIB Score by Visit (OC) and at Endpoint (LOCF) – Trial 9605



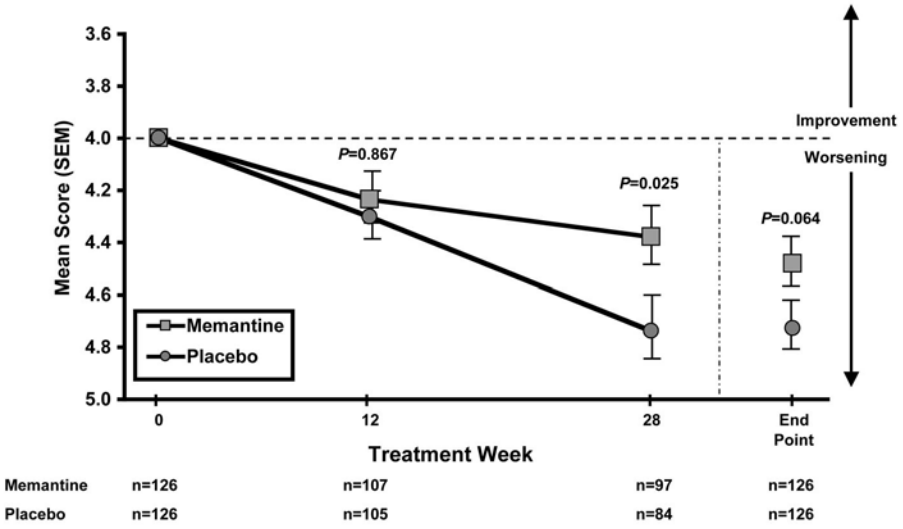
5.2.1.3 Assessment of Global Status

For the CIBIC+, a mean difference of 0.25 points was observed in favor of memantine in the LOCF analysis, with memantine showing superiority over placebo by 0.36 points in the OC analysis (Panel 15 and Figure 5). The p-value for the treatment difference in the LOCF analysis was 0.064 and the treatment difference was statistically significant (p = 0.025) in the OC analysis.

Panel 15. Mean CIBIC+ Score – Trial 9605

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

Figure 5. Mean CIBIC+ Score by Visit (OC) and at Endpoint (LOCF) – Trial 9605



5.2.1.4 Open-Label Extension

Patients who completed the 28-week double-blind phase of Trial 9605 were invited to enter the optional 24-week open-label memantine treatment extension. Of the 252 patients who were randomized to double-blind treatment in Trial 9605, 175 (69%) entered the open-label extension. Of the 175 patients who entered the extension phase, 80 had previously been treated with placebo in the lead-in double-blind trial (the placebo-memantine group) and 95 had previously been treated with memantine (the memantine-memantine group). A total of 137 patients (78%) completed the 6-month extension. The mean baseline MMSE score at the beginning of open-label treatment (Week 28 of the double-blind phase) was 7.

Patients switched from placebo to memantine treatment exhibited a decreased rate of decline on the SIB, ADCS-ADL_{19}, and CIBIC+ relative to the projected rate of the previous 6 months of observation. This finding provides additional support for the efficacy of memantine in the treatment of moderate to severe AD. Patients remaining on memantine treatment showed an unchanged rate of decline on the SIB, ADCS-ADL_{19}, and CIBIC+, which was slower than the extrapolated rate of decline for patients who had previously received placebo during the double-blind phase. This finding suggests that memantine treatment beyond 6 months for up to at least one year provides a therapeutic benefit for moderate to severe AD patients.

5.2.2 Trial MD-02 (Tariot et al., 2003)[129]

A Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Memantine in Patients with Moderate to Severe Dementia of the Alzheimer's Type

This was a 24-week, multicenter, randomized, double-blind, placebo-controlled trial conducted in the US. The study design, inclusion criteria, efficacy assessments, and titration schedule are listed in Panel 11. All patients must have received ChEI therapy, specifically, donepezil, for at least 6 months, and at a stable dose (5-10 mg/day) for the last 3 months prior to randomization. Patients were required to continue donepezil for the duration of the trial. The primary efficacy measures were the SIB and ADCS-ADL_{19}. The secondary efficacy measures included the CIBIC+ (ADCS-CGIC), BGP, FAST, and NPI. Patients who completed double-blind treatment and fulfilled other criteria were eligible to enter a 28-week open-label memantine treatment extension.

A total of 404 patients who had maintained ongoing donepezil therapy for approximately 2 years were randomized: 203 in the memantine group and 201 in the placebo group. A total of 322 (80%) patients completed the trial. The discontinuation rate was 25% in the placebo group and 15% in the memantine group. All randomized patients received their assigned treatment (except 1 randomized memantine patient who discontinued prior to receiving trial medication).

The average memantine patient was approximately 76 years old and weighed about 70.9 kgs (Panel 16). Ninety percent of memantine patients were Caucasian, 63% were female and the mean MMSE score at baseline was 9.9 points (range 5 to 14- one patient had MMSE score of 16). No patient had a HIS score greater than 4. All patients had received ChEI therapy for at least 6 months prior to enrollment in this trial. No statistically significant differences in any of the baseline demographic characteristics were observed between treatment groups with the exception of mean body weight (p=0.003). Additional analyses have shown no evidence that the difference in weight between the treatment groups had an impact on the efficacy results. Baseline scores for the MMSE and the functional (ADCS-ADL_{19}) and cognitive (SIB) outcome measures showed that the two treatment groups were well matched at the start of the trial.

Panel 16. Patient Demographics and Baseline Assessments – Trial MD-02

Demographics and Baseline Assessments	*Placebo (N = 197)*	*Memantine (N = 198)*
AGE (YEARS) Mean ± SD	75.5 ± 8.76	75.5 ± 8.48
FEMALE N (%)	134 (68)	124 (63)
CAUCASIAN N (%)	183 (93)	179 (90)
WEIGHT (Kg) Mean ± SD	66.2 ± 14.2	70.6 ± 14.4
MMSE* Mean ± SD	10.3 ± 3.0	10.0 ± 3.1
SIB Mean ± SD	79.8 ± 14.2	77.8 ± 15.5
ADCS-ADL_{19} Mean ± SD	36.2 ± 9.3	35.9 ± 9.8

*All patients had MMSE scores 5-14 at screening (at baseline, one memantine patient had a score of 16); values shown are for the safety population (N=201 placebo and N=202 memantine).

5.2.2.1 Assessment of Function

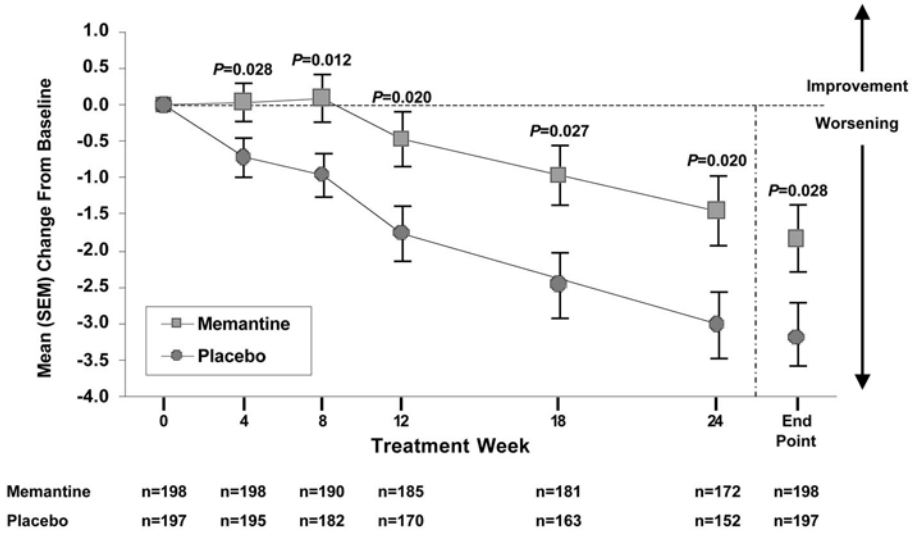
When daily functioning was evaluated using the ADCS-ADL$_{19}$, memantine treatment resulted in significantly less deterioration over time compared with placebo (Panel 17). In the LOCF analysis, the mean change from baseline to endpoint was –1.8 for memantine compared with –3.2 for placebo (p = 0.028). In the OC analysis, the mean change from baseline to endpoint was –1.4 for memantine compared with –3.0 for placebo (p = 0.020).

Panel 17. Mean Change from Baseline in ADCS-ADL$_{19}$ – Trial MD-02

	Placebo		***Memantine***		***p-value***
	N	*Mean*	*N*	*Mean*	
Endpoint (LOCF)	197	-3.2	198	-1.8	0.028
Week 24 (OC)	152	-3.0	172	-1.5	0.020

Figure 6 illustrates the mean change from baseline ± SEM on the ADCS-ADL$_{19}$ by visit for the memantine and placebo treatment groups. The memantine patients showed a favorable response to treatment, as noted by the stabilization of function in the first 8 weeks, followed by a gradual decline over the duration of the trial thereafter. The placebo patients demonstrated a decline in function through the entire course of the trial. There was a statistically significant difference ($p<0.05$) in favor of the memantine group at all visits in the OC analysis.

Figure 6. Mean Change from Baseline in the ADCS-ADL$_{19}$ by Visit (OC) and at Endpoint (LOCF) – Trial MD-02



5.2.2.2 Assessment of Cognition

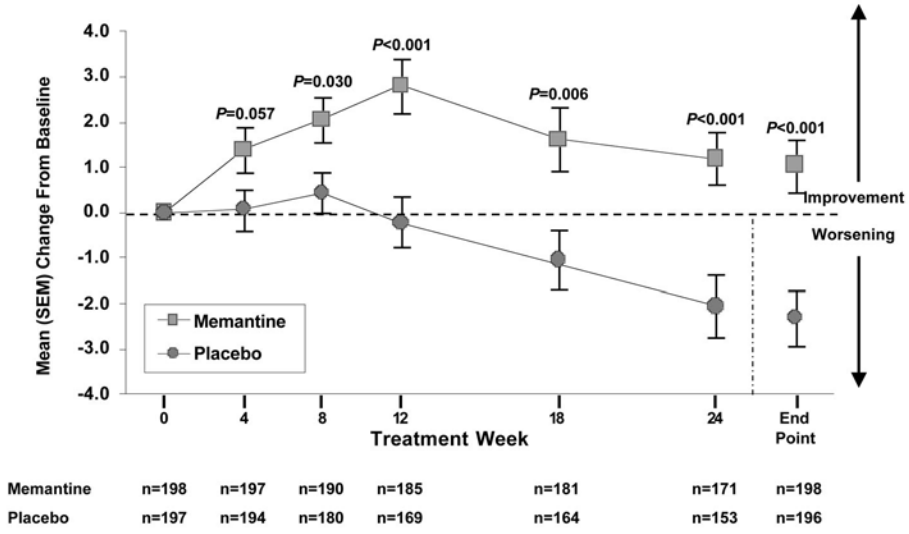
In the LOCF and OC analyses of the SIB, patients treated with memantine showed improvement compared to placebo-treated patients, who declined in cognition ($p < 0.001$; Panel 18). The treatment group difference of 3.4 points favored memantine (increase of 1.1 points with memantine treatment compared with a decline of 2.3 points with placebo). In the OC analysis, the mean score increased 1.2 points in the memantine group and decreased 2.1 points in the placebo group.

Panel 18. Mean Change from Baseline in SIB – Trial MD-02

	Placebo		***Memantine***		***p-value***
	N	*Mean*	*N*	*Mean*	
Endpoint (LOCF)	196	-2.3	198	1.1	<0.001
Week 24 (OC)	153	-2.1	171	1.2	<0.001

Figure 7 illustrates the mean change from baseline ± SEM on the SIB by visit for the memantine and placebo treatment groups. The memantine patients showed an improvement from baseline in cognitive function for all visits from Week 4 to 24. In comparison, the placebo patients showed an overall decline from baseline in cognitive function over the course of the trial, as noted by the negative change from baseline from Week 12, onwards. The difference between treatment groups was statistically significant ($p<0.05$) in favor of the memantine group at all post-baseline evaluations after Week 4.

Figure 7. Mean Change from Baseline in the SIB Score by Visit (OC) and at Endpoint (LOCF) – Trial MD-02



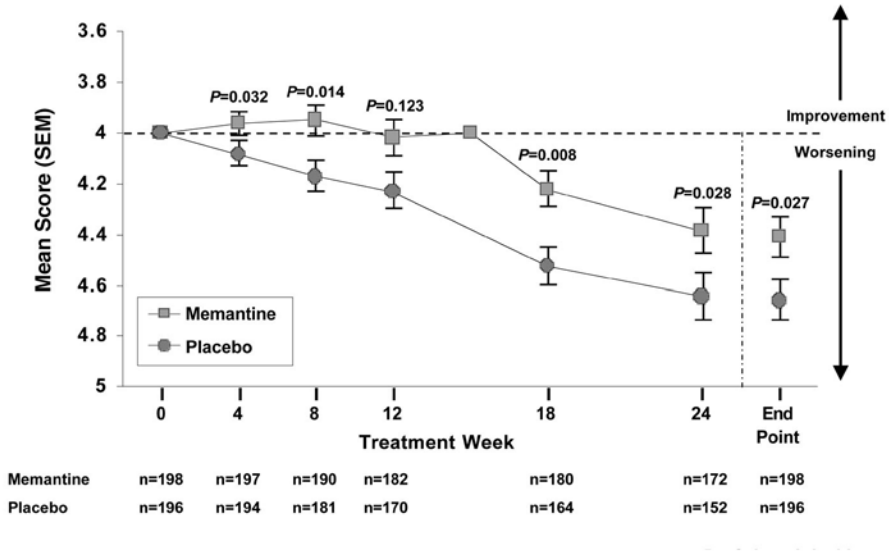
5.2.2.3 Assessment of Global Status

The mean CIBIC+ rating for memantine patients was 4.41 at Week 24 (LOCF analysis) compared to 4.66 for patients treated with placebo (Panel 19 and Figure 8). The difference between treatment groups was statistically significant in favor of memantine (p=0.027). A similar change in favor of memantine compared to placebo treatment was shown on OC analyses (p=0.028).

Panel 19. Mean CIBIC+ Score– Trial MD-02

	Placebo		***Memantine***		***p-value***
	N	*Mean*	*N*	*Mean*	
Endpoint (LOCF)	196	4.66	198	4.41	0.027
Week 24 (OC)	152	4.64	172	4.38	0.028

Figure 8. Mean CIBIC+ Score by Visit (OC) and at Endpoint (LOCF) – Trial MD-02



5.2.3 Trial 9403 (Winblad and Poritis, 1999)[130]

Efficacy and Tolerability of Memantine in Care-Dependent Patients with Moderate to Severe Primary Dementia

Trial 9403 was the first large, randomized, placebo-controlled trial of memantine in severe dementia. It was conducted in 7 inpatient care facilities (6 nursing homes and 1 psychiatric hospital) in Latvia and was 12 weeks in duration. The study design, main inclusion criteria, efficacy assessments, and titration schedule are provided in Panel 11. Both AD and VaD patients were enrolled (DSM-III-R criteria for Dementia), and patients with other causes of dementia were excluded.

A total of 167 patients were randomized, one patient dropped out before receiving study medication and was not included in the ITT population, which consisted of 82 patients in the memantine group and 84 in the placebo group. A total of 158 patients (95%) completed the trial. The dropout rate was 5% in both treatment groups. A total of 79 AD patients (defined as a HIS score ≤4) were included in this trial; 38 were treated with placebo and 41 were treated with memantine. Of these 79 patients, 76 (96%) completed the trial. No statistically significant differences in any of the demographic characteristics were found. The baseline disease severity assessment scores (including MMSE, GDS, and CGI-S) and the baseline values for the functional (BGP-care dependency) and cognitive (BGP-cognitive) outcome measures showed that the two treatment groups were well matched at the start of the trial (Panel 20).

Panel 20. Patient Demographics and Baseline Assessments – Trial 9403

Demographics and Baseline Assessments	*Placebo (N=84)*	*Memantine (N=82)*
AGE (YEARS) Mean ± SD	71.9 ± 6.1	71.2 ± 6.2
FEMALE, N (%)	47 (56%)	49 (60%)
DEMENTIA DIAGNOSIS, N (%)		
Alzheimer's Disease (HIS ≤4)	38 (45.2)	41 (50.0)
Vascular Dementia (HIS >4)	46 (54.8)	41 (50.0)
WEIGHT (KG) Mean ± SD	67.4 ± 11.4	67.9 ± 13.6
MMSE Mean ± SD	6.1 ± 2.8	6.5 ± 2.6
GDS Mean ± SD	6.0 ± 0.3	6.0 ± 0.3
CGI-S Mean ± SD	5.7 ± 0.7	5.5 ± 0.6
BGP-CARE DEPENDENCY Mean ± SD	21.8 ± 7.7	21.3 ± 7.6
BGP-COGNITIVE Mean ± SD	5.4 ± 2.5	5.5 ± 2.6

5.2.3.1 Assessment of Function

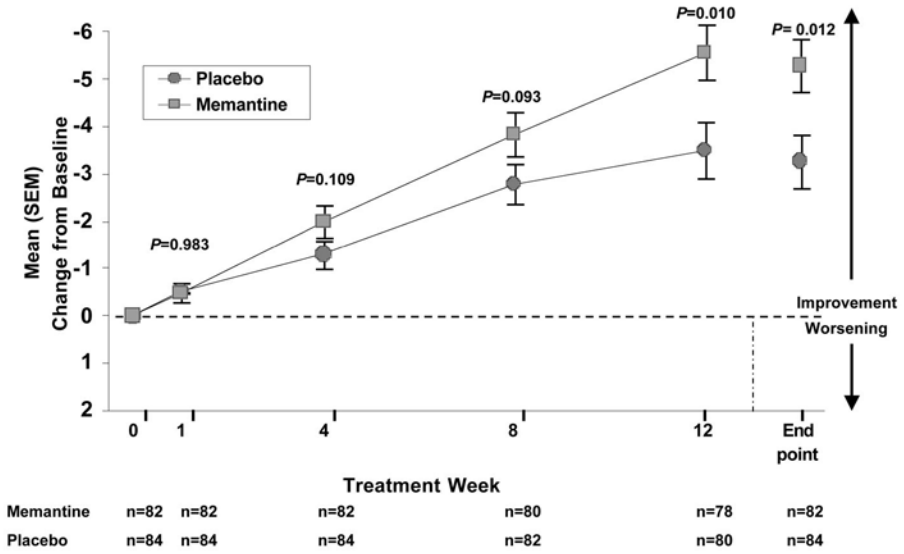
5.2.3.1.1 All Patients

When daily functioning was evaluated using the BGP-care dependency subscale, memantine was significantly superior to placebo (p = 0.012) at endpoint (LOCF), as represented in Panel 21. In the memantine group, the mean score decreased by 5.3 points from baseline (decrease denotes improvement). In the placebo group, the corresponding values decreased by 3.3 points from baseline. A similar statistically significant difference (p = 0.010) favoring memantine was observed at Week 12 (OC).

Panel 21. Mean Change from Baseline in BGP-Care Dependency Subscale – Trial 9403

	Placebo		***Memantine***		***p-value***
	N	*Mean*	*N*	*Mean*	
Endpoint (LOCF)	84	-3.3	82	-5.3	0.012
Week 12 (OC)	80	-3.5	78	-5.6	0.010

Figure 9. Mean Change from Baseline in the BGP-Care Dependency Score by Visit (OC) and at Endpoint (LOCF) – Trial 9403



5.2.3.1.2 AD Patients

Analysis of the subset of patients with AD showed there were significant differences in the mean change from baseline for the BGP-care dependency subscale score at endpoint (LOCF; p=0.003) and Week 12 (OC; p=0.002) favoring memantine over placebo (Panel 22). These differences in favor of memantine were of the same magnitude as those observed in the total population.

Panel 22. Change from Baseline in BGP-Care Dependency Subscale – Trial 9403 AD Patients

	Placebo		***Memantine***		***p-value***
	N	*Mean*	*N*	*Mean*	
Endpoint (LOCF)	38	-2.8	41	-5.8	0.003
Week 12 (OC)	37	-2.9	39	-6.1	0.002

As with the total population, improvement in the mean BGP-care dependency score was observed in both treatment groups over the course of the trial. Significantly greater mean improvement in the memantine group relative to the placebo group was also observed at Week 4 (p=0.050, OC analysis).

5.2.3.2 Assessment of Cognition

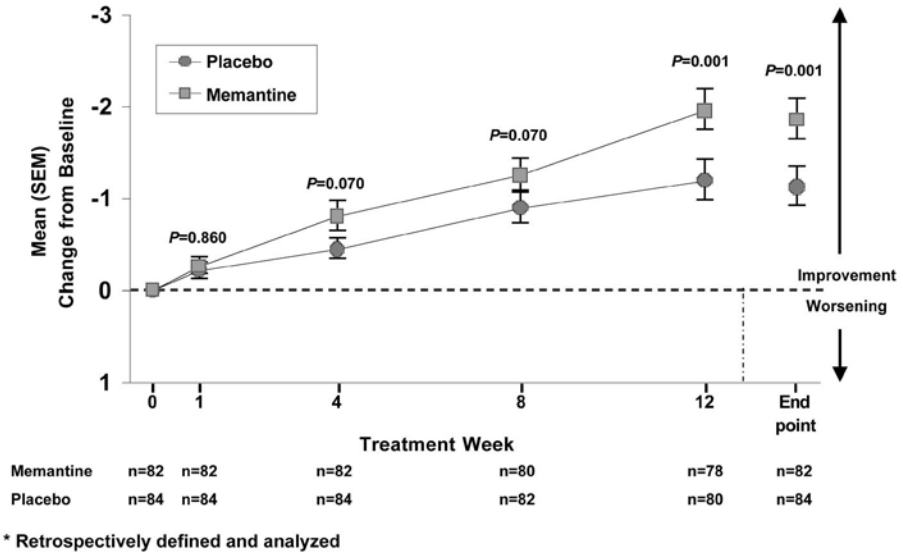
5.2.3.2.1 All Patients

When cognition was assessed using the BGP-cognitive subscale, there was significantly greater improvement (decrease denotes improvement) in the memantine group as compared to the placebo group (p=0.001) at endpoint (LOCF) and Week 12 (p=0.001, OC analysis; Panel 23).

Panel 23. Mean Change from Baseline in BGP-Cognitive Subscale – Trial 9403 All Patients

	Placebo		*Memantine*		*p-value*
	N	*Mean*	*N*	*Mean*	
Endpoint (LOCF)	84	-1.1	82	-1.9	0.001
Week 12 (OC)	80	-1.2	78	-1.9	0.001

Figure 10. Change from Baseline in the BGP-Cognitive Score* by Visit (OC) and at Endpoint (LOCF) – Trial 9403



* Retrospectively defined and analyzed

5.2.3.2.2 AD Patients

The mean change from baseline in the BGP-cognitive subscale in the subset of patients with AD is presented in Panel 24. As with the total population, there was a significant difference favoring memantine over placebo both at endpoint (p=0.007, LOCF analysis) and at Week 12 (p=0.004, OC analysis). The mean changes in each treatment group were similar to those observed in the total population.

Panel 24. Mean Change from Baseline in BGP-Cognitive Subscale: AD Patients – Trial 9403 AD Patients

	Placebo		***Memantine***		***p-value***
	N	*Mean*	*N*	*Mean*	
Endpoint (LOCF)	38	-1.0	41	-2.0	0.007
Week 12 (OC)	37	-1.1	39	-2.1	0.004

5.2.3.3 Assessment of Global Status

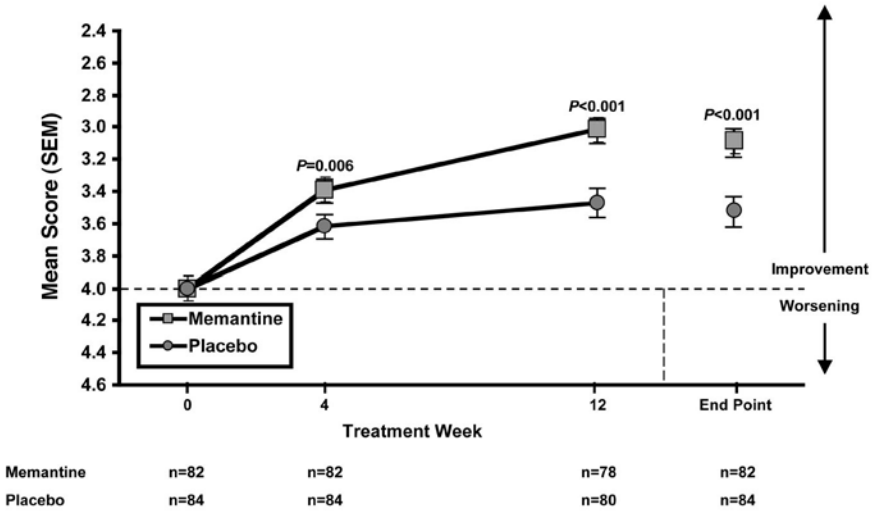
5.2.3.3.1 All Patients

Panel 25 presents the mean rating for the CGI-C at endpoint (LOCF) and Week 12 (OC). Memantine-treated patients exhibited significantly greater improvement than placebo-treated patients at endpoint (p<0.001, LOCF analysis) and Week 12 (p<0.001, OC analysis).

Panel 25. Mean CGI-C Score – Trial 9403 All Patients

	Placebo		***Memantine***		***p-value***
	n	*Mean*	*n*	*Mean*	
Endpoint (LOCF)	84	3.5	82	3.1	<0.001
Week 12 (OC)	80	3.5	78	3.0	<0.001

Figure 11. Mean CGI-C Score by Visit (OC) and at Endpoint (LOCF)— Trial 9403



5.2.3.3.2 AD Patients

Panel 26 shows the mean CGI-C scores in the subset of AD patients. Memantine-treated patients exhibited significantly greater improvement than placebo-treated patients at endpoint ($p<0.01$, LOCF analysis) and Week 12 ($p<0.01$, OC analysis). Mean CGI-C ratings were also significantly improved ($p=0.035$) in the memantine group relative to the placebo group at Week 4 of double-blind treatment.

Panel 26. Mean CGI-C Score– Trial 9403 AD Patients

	Placebo		***Memantine***		***p-value***
	n	*Mean*	*n*	*Mean*	
Endpoint (LOCF)	38	3.5	41	3.1	0.003
Week 12 (OC)	37	3.5	39	3.1	0.001

5.2.4 Supportive VaD Trials[131,132]

Trials 9202 and 9408 were each randomized, double-blind, placebo-controlled, parallel group multicenter trials in mild to moderate vascular dementia. The study design, inclusion criteria, and efficacy assessments are described in Panel 11. A total of 581 patients in Trial 9202 and 321 patients in Trial 9408 were randomized to 28 weeks of double-blind treatment with memantine or placebo. In both studies, the ADAS-cog (LOCF and OC analyses) showed significantly greater therapeutic benefit of memantine treatment relative to placebo treatment (Panel 27). Assessment of global status using the CGI-C in Trial 9202 and CIBIC+ in Trial 9408 did not demonstrate significant differences between treatment groups.

Panel 27. Summary of Efficacy: Mean Change from Baseline to Week 28 in ADAS-Cog –Trial 9202 and Trial 9408

	Parameter	*Placebo*	*Memantine*	*p-value*
TRIAL 9202				
LOCF	ADAS-cog	2.28	0.53	0.007
OC	ADAS-cog	1.78	0.15	0.029
TRIAL 9408				
LOCF	ADAS-cog	1.64	-0.41	0.013
OC	ADAS-cog	1.58	-1.25	< 0.001

5.3 Efficacy Summary

Trial 9605 demonstrated a clinically relevant therapeutic benefit of memantine treatment relative to placebo treatment on the day-to-day function, cognitive abilities, and overall clinical status of patients with moderate to severe AD. In the LOCF analyses at endpoint, a statistically significant therapeutic benefit for memantine treatment relative to placebo treatment was observed for the ADCS-ADL_{19} and SIB. The p-value for the treatment difference in the LOCF analysis of the CIBIC+ was 0.064. In the OC analyses at Week 28, a statistically significant advantage for memantine treatment relative to placebo treatment also was observed for both of these efficacy variables, as well as for the CIBIC+.

Trial MD-02 also demonstrated a clinically relevant benefit of memantine treatment relative to placebo treatment on the day-to-day function, cognitive abilities, and overall clinical status of patients with moderate to severe AD receiving ongoing donepezil therapy. In the LOCF analyses at endpoint, a statistically significant therapeutic benefit for memantine treatment relative to placebo treatment for patients maintained on stable donepezil therapy was observed for the ADCS-ADL_{19}, SIB, and CIBIC+. In the OC analyses at Week 24, a statistically significant advantage for memantine treatment relative to placebo treatment also was observed for all three key efficacy variables. It is of particular note that patients treated with memantine demonstrated improved cognitive performance relative to baseline over the 24-week course of the trial, whereas patients receiving placebo exhibited progressive cognitive decline over the same duration.

Trial 9403, conducted earlier than the two US AD trials, demonstrated that memantine produces clinically relevant improvement relative to placebo on functional, cognitive, and clinical (global) measures of dementia (both AD and VaD patients studied). In the LOCF analyses at endpoint, a statistically significant therapeutic benefit for memantine treatment relative to placebo treatment was observed for the BGP-care dependency, CGI-C, and the BGP-cognitive scales. In the OC analysis at Week 12, a statistically significant advantage for memantine treatment relative to placebo treatment also was observed for all three efficacy variables. The subset of patients with AD (defined as patients with HIS ≤ 4) similarly showed statistically significant and clinically relevant advantages for the memantine-treated patients relative to the placebo-treated group on all three efficacy variables using both the LOCF and OC analyses.

Trials 9408 and 9202 conducted in patients with mild to moderate VaD provide additional evidence that memantine treatment produces an amelioration of the decline in cognitive performance, a core symptom of dementia. In both VaD trials, the results from the ADAS-cog scale support the efficacy of memantine.

The results from these trials demonstrate that memantine is efficacious in the treatment of moderate to severe AD patients based on functional, cognitive and global outcome assessments.

6.0 CLINICAL SAFETY

Based on information from 2297 memantine-treated patients in 27 clinical trials and over 600,000 patient years of exposure, memantine exhibits a safety profile similar to that of placebo and has been found to be well-tolerated in the treatment of dementia.

6.1 Overview of Safety

6.1.1 Patient Population for the Evaluation of Safety

The safety information summarized is derived from relevant clinical trials and an approximate 20 years of post-marketing experience in Europe (primarily Germany). Included are 27 completed clinical trials with memantine in patients with dementia, neuropathic pain, Parkinson's disease, organic brain syndrome, and spasticity, as well as 30 completed clinical pharmacology studies in normal volunteers. The overall completed clinical safety experience from the 27 clinical trials comprises a total of 2297 patients who received memantine, and 1244 patients who received placebo.

For purposes of the safety analyses, completed clinical trials with memantine have been organized into groups based on the population studied, quality of data, and availability of data for incorporation into an electronic database. The four trial groupings for completed studies are as follows (Figure 12):

- *Core Safety Trials:* Eight Core Phase II/III double-blind, placebo-controlled trials in dementia, four open-label extensions of these trials, and two Core Phase II/III double-blind, placebo-controlled trials in neuropathic pain are included in this group. The Core double-blind, placebo-controlled dementia safety database includes 940 patients treated with memantine and 922 patients treated with placebo. With the addition of the placebo-controlled neuropathic pain trials and the open-label extension dementia trials, a total of 1748 patients were exposed to memantine in the core safety trials.

- *Additional Clinical Trials:* Thirteen completed trials in patients with various neurological conditions (including dementia, organic brain syndrome, Parkinsonism, multiple sclerosis, and spasticity) in which only adverse events considered to be drug related were reported. A total of 549 patients were exposed to memantine in these trials.

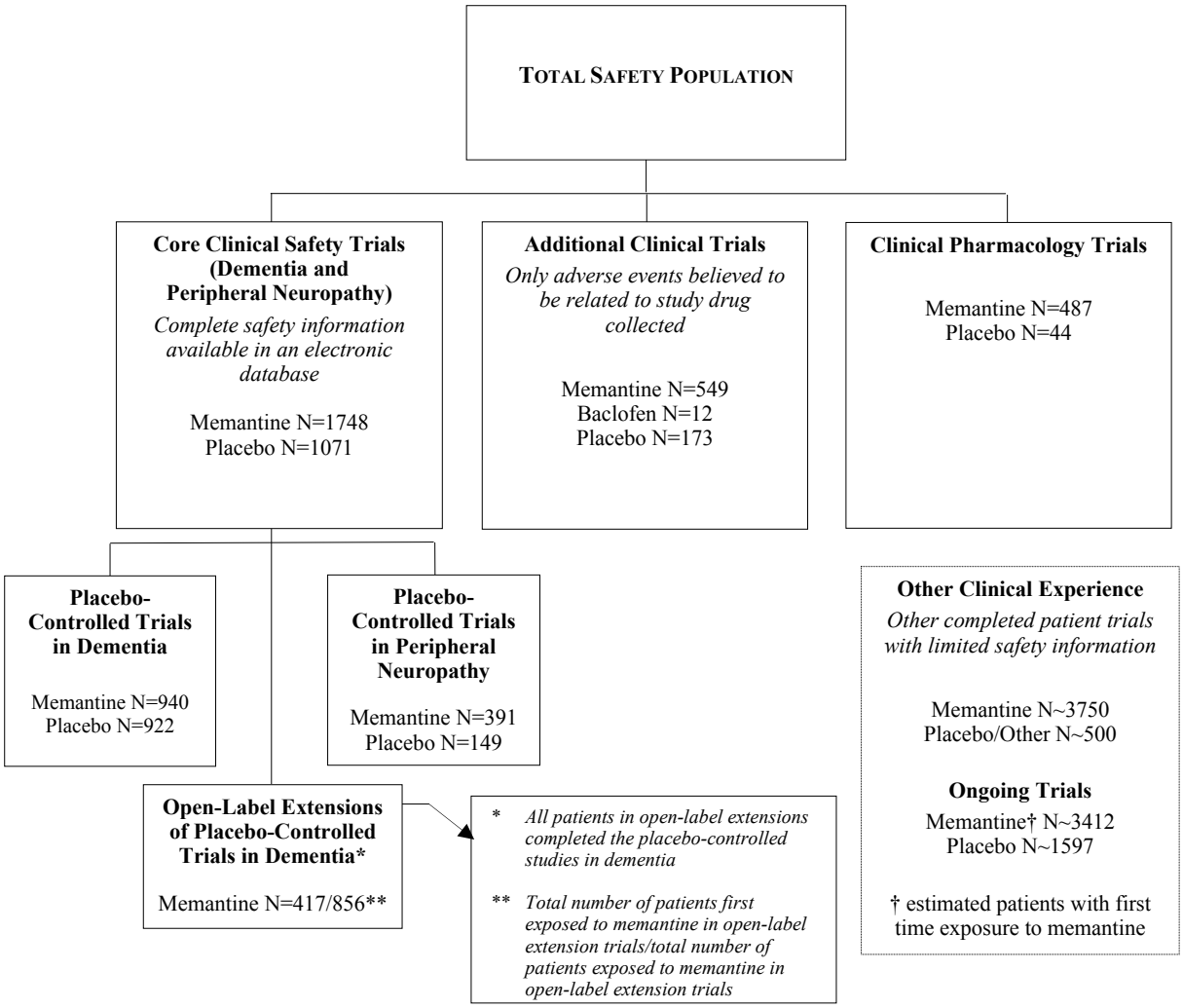
- *Clinical Pharmacology Trials:* A total of 487 subjects were exposed to memantine in 30 completed clinical pharmacology trials. A brief summary of the safety data for these trials is presented in Section 6.8.1.

- *Other Clinical Experiences:* In addition, other completed memantine investigations with limited safety information (primarily post-marketing or drug experience trials) involved approximately 3750 patients exposed to memantine.

This information is summarized briefly in this document due to the paucity of data. As of September 30, 2002, there were 21 ongoing trials in the US, Europe, and Asia involving an estimated total of 4537 subjects (of which an estimated 3412 subjects have been exposed to memantine for the first time in these trials). These trials consist of double-blind, placebo-controlled, and open-label trials including patients with AD, VaD, neuropathy, and glaucoma as well as healthy subjects.

A schematic representation of the studies and sources of safety information on memantine can be found in Figure 12 and Panel 28.

Figure 12. Patient Populations in the Development Program for Memantine – Total Safety Population



Panel 28. Core Safety Trials

Trial	*Placebo (N)*	*Memantine (N)*
CORE DOUBLE-BLIND, PLACEBO-CONTROLLED DEMENTIA TRIALS		
Key Trials		
9605 — AD (US)	*126*	*126*
MD-02 — AD (US)	*201*	*202*
9403 — AD/VaD (EU)	*84*	*82*
Supportive Trials		
9202 — VaD (EU)	*286*	*295*
9408 — VaD (EU)	*156*	*165*
Other Dementia Trials	*69*	*70*
Subtotal Placebo-Controlled Trials in Dementia	922	940
CORE DOUBLE-BLIND, PLACEBO-CONTROLLED NEUROPATHY TRIALS		
Subtotal Placebo-Controlled Trials in Neuropathy	149	391
Subtotal Placebo-Controlled Trials	1071	1331
CORE OPEN-LABEL EXTENSION (OLEX) DEMENTIA TRIALS		
Subtotal Core Open-Label Extension Dementia Trials	*0*	417/856*
GRAND TOTAL	**1071**	**1748 ****

* Number of patients first exposed to memantine in open-label trial/ total number of patients exposed to memantine in open-label trial.
** Unique patients exposed to memantine in Core trials.

Safety analyses in addition to analyses by dementia diagnosis (HIS ≤ 4 for AD patients) and dementia severity (MMSE ≤ 14 for moderate to severe patients) were performed in the following patient subgroups in the placebo-controlled dementia trials:

- *Age:* Analyses of four subgroups: less than 65 years, 65-74 years, 75-84 years, and 85 years and older.
- *Sex*
- *Race: S*ubgroup analyses based on Caucasian versus non-Caucasian.

6.1.2 Trial Plans and Safety Assessments

A brief description of safety assessments in each of the Core double-blind, placebo-controlled dementia trials (described in Section 5.2), open label extensions and neuropathy trials is presented in Panel 29.

Panel 29. Summary of the Trial Design and Safety Assessments

Trial	*Design/ Treatment Groups*	*Population/Inclusion Criteria*	*Safety Assessments*
CORE DOUBLE-BLIND, PLACEBO-CONTROLLED DEMENTIA TRIALS — KEY TRIALS			
9605 Total N = 252 Memantine N = 126	28-week Placebo Memantine 10 mg BID	Diagnosis: Probable AD (DSM-IV and NINCDS-ADRDA) Severity: Moderate to Severe ◆ MMSE 3-14 ◆ GDS 5-6 ◆ FAST ≥ 6a ◆ HIS ≤ 4 ◆ ≥ 50 years of age	◆ AEs ◆ Vital signs ◆ Clinical Laboratory Tests ◆ ECGs ◆ Physical and Neurological Examinations
MD-02 Total N = 404 Memantine N = 203	24-week Placebo Memantine 10 mg BID	Diagnosis: Probable AD (NINCDS-ADRDA) Severity: Moderate to Severe ◆ MMSE 5-14 ◆ ≥ 50 years of age ◆ Ongoing donepezil therapy ≥ 6 months at a stable dose (5-10 mg/day) for the past 3 months	◆ AEs ◆ Vital signs ◆ Clinical Laboratory Tests ◆ ECGs ◆ Physical Examinations
9403 Total N = 166 Memantine N = 82	12-week Placebo Memantine 10 mg QD	Diagnosis: Dementia (DSM-III-R) Severity: Severe ◆ MMSE <10 ◆ GDS 5-7 ◆ CGI-S 5-7 ◆ HIS ≤ 4 (AD patients) ◆ 60-80 years of age	◆ AEs ◆ Vital signs ◆ Clinical Laboratory Tests ◆ Global Tolerability Assessments

Panel 29. Summary of the Trial Design and Safety Assessments

Trial	*Design/ Treatment Groups*	*Population/Inclusion Criteria*	*Safety Assessments*
CORE DOUBLE-BLIND, PLACEBO-CONTROLLED DEMENTIA TRIALS — SUPPORTIVE TRIALS			
9202 Total N = 581 Memantine N = 295	28-week Placebo Memantine 10 mg BID	Diagnosis: VaD (NINDS-AIREN) Severity: Mild to moderate ◆ MMSE 10-22 ◆ HIS > 4 ◆ HAMD ≤ 17 ◆ ≥ 50 years of age	◆ AEs ◆ Vital signs ◆ Clinical Laboratory Tests ◆ Ophthalmologic Assessments
9408 Total N = 321 Memantine N = 165	28-week Placebo Memantine 10 mg BID	Diagnosis: VaD (NINDS-AIREN) Severity: Mild to moderate ◆ MMSE 12-20 ◆ MIS > 4 ◆ HAMD ≤ 14 ◆ ≥ 60 years of age	◆ AEs ◆ Vital signs ◆ Clinical Laboratory Tests ◆ ECGs ◆ Physical and Neurological Examinations
CORE OPEN LABEL EXTENSION DEMENTIA TRIALS			
9605 OLEX Total N= 175 Memantine (new exposure)=80	24-week open-label extension of Trial 9605 (28-wk double-blind trial) Memantine 10 mg BID	Diagnosis: Probable AD (DSM-IV and NINCDS-ADRDA) Severity: Moderate to Severe ◆ Same criteria as in the double-blind trial above	◆ AEs ◆ Vital signs ◆ Clinical Laboratory Tests
9202 OLEX Total N= 464 Memantine (new exposure)=226	24-week open-label extension of Trial 9202 (28-wk double-blind trial) Memantine 10 mg BID	Diagnosis: VaD (NINDS-AIREN) Severity: Mild to moderate ◆ Same criteria as in the double-blind trial above	◆ AEs ◆ Clinical Laboratory Tests ◆ Physical Examination ◆ Ophthalmologic Assessments
9408 OLEX Total N= 171 Memantine (new exposure)=88	24-week open-label extension of Trial 9408 (28-week double-blind trial) Memantine 10 mg BID	Diagnosis: VaD (NINDS-AIREN) Severity: Mild to moderate ◆ Same criteria as in the double-blind trial above	◆ AEs ◆ Clinical Laboratory Tests

Panel 29. Summary of the Trial Design and Safety Assessments

Trial	*Design/ Treatment Groups*	*Population/Inclusion Criteria*	*Safety Assessments*
9206 OLEX Total N= 46 Memantine (new exposure)=23	104-week open-label extension of Trial 9206 (14-week double-blind trial) Memantine 10 mg bid Following one year of open-label treatment, all patients were withdrawn from memantine. In patients who showed signs of deterioration during this three month washout, memantine therapy could be reinstituted for an additional 12 months.	Diagnosis: VaD (DSM III-R) Severity: Moderately Severe ◆ MMSE 10-20 ◆ 50-90 years of age	◆ AEs ◆ Clinical Laboratory Tests ◆ Physical and Neurological Examination
NEUROPATHY TRIALS			
NTI 9702 Total N= 122 Memantine N=58	◆ 8-week Placebo Memantine 40 mg/day	Diagnosis: Neuropathic Pain (Diabetes mellitus or Post-herpetic neuralgia) ◆ 18-80 years of age	◆ AEs ◆ Vital Signs ◆ Clinical Laboratory Tests ◆ ECGs
NTI 9801 Total N= 418 Memantine N= 333	◆ 8-week Placebo Memantine 20 mg/day Memantine 40 mg/day	Diagnosis: Painful Peripheral Neuropathy (Diabetes mellitus) ◆ 18-80 years of age	◆ AEs ◆ Vital Signs ◆ Clinical Laboratory Tests ◆ ECGs

6.2 Demographic and Exposure Data

The overall completed clinical trial safety experience (core trials and additional clinical trials) comprises a total of 2297 patients who received memantine, and 1244 patients who received placebo. In addition, 487 subjects were exposed to memantine in the clinical pharmacology trials. A total of 1748 patients were exposed to memantine in the Core dementia and neuropathy trials.

6.2.1 Core Double-Blind, Placebo-Controlled Dementia Trials

A total of 1357 patients were treated with memantine in the Core double-blind, placebo-controlled and open-label extension dementia trials.

The demographic characteristics of the memantine and placebo treatment groups were similar in the Core double-blind, placebo-controlled dementia trials (see Panel 30) and similarly, there were no clinically important differences in any demographic parameters between placebo- and memantine-treated patients with AD or VaD.

Panel 30. Demographic Profile – Core Double-Blind, Placebo-Controlled Dementia Trials

Demographic Parameters	*Placebo (N=922)*	*Memantine (N=940)*
AGE (YEARS) Mean ± SD	76.0 ± 7.5	75.7 ± 7.5
FEMALE n (%)	504 (54.7)	538 (57.2)
CAUCASIAN n/N (%)	741/769 (96.4)	751/788 (95.3)
WEIGHT (KG) Mean± SD (N)	66.07±13.14 (898)	66.98±13.04 (924)
HEIGHT (CM) Mean± SD (N)	163.70 ± 9.77 (896)	163.47 ± 9.91(922)
MMSE Mean± SD (N)	13.7 ± 5.5 (904)	13.6 ± 5.4 (925)
MMSE ≤14 % (N)	54.4 (502)	53.1 (499)

Across the double-blind and open-label extension dementia trials, the memantine-treated patients experienced the equivalent of a total of 796 patient-years of drug exposure. Patients were treated with memantine for a mean of 214 days of combined double-blind and open-label trial exposure (Panel 31). A total of 862 (63.6%) patients received memantine for at least 24 weeks, of whom 584 were patients in double-blind, placebo-controlled studies, and 387 patients (28.5%) were exposed to memantine for at least 48 weeks. Patients in the Core double-blind, placebo-controlled dementia studies were treated with memantine or placebo for a mean of 151 days.

Among the 790 total patients with AD, the mean durations of double-blind treatment were 141.0 and 146.3 days in the placebo and memantine treatment groups, respectively. Approximately half of the AD patients received trial medication for at least 24 weeks.

Panel 31. Summary of Treatment Duration by Memantine Dose – Core Dementia Trials

	Double-Blind		***Open-Label Memantine (N=856)***	***Total Memantine** (N=1357)***
	Placebo (N=922)	*Memantine (N=940)*		
TREATMENT DURATION (DAYS)				
Mean ± SD (N)	150.7± 58.6 (922)	151.2 ± 59.2 (939)*	173.8 ± 105.5 (856)	**214.4 ±135.7 (1356*)**
TREATMENT DURATION, n (%)				
≥ 4 weeks (28 days)	884 (95.9)	896 (95.4)	835 (97.5)	**1306 (96.3)**
≥ 12 weeks (84 days)	802 (87.0)	818 (87.1)	778 (90.9)	**1202 (88.6)**
≥ 24 weeks (168 days)	553 (60.0)	584 (62.2)	506 (59.1)	**862 (63.6)**
≥ 36 weeks (252 days)	0	0	42 (4.9)	**429 (31.6)**
≥ 48 weeks (336 days)	0	0	37 (4.3)	**387 (28.5)**
≥ 52 weeks (364 days)	0	0	32 (3.7)	**277 (20.4)**

SD = Standard deviation.
*Data on treatment duration for one patient (#162) in Trial 9408 was not available and not included.
**Total memantine exposure is the total treatment duration on memantine for each patient (treatment in double-blind + treatment duration in open-label phases).

6.2.1.1 Core Open-label Extension Dementia Trials

The demographic profile of the patients in the Core open-label extensions was similar to that of all patients in the Core double-blind, placebo-controlled dementia trials.

A total of 856 patients received memantine in the Core open-label extension dementia trials of which 417 (48.7%) patients were newly exposed to memantine. Their mean duration of open-label treatment was 174 days. Of the 856 patients, 506 (59.1%) received open-label memantine treatment for at least 24 weeks.

6.2.1.2 Core Double-Blind, Placebo-Controlled Neuropathy Studies

A total of 391 patients were treated with memantine in the Core Neuropathy studies. Of these patients, 171 received memantine 20 mg/day and 220 received memantine 40 mg/day. A total of 149 patients received placebo.

The demographic characteristics of the placebo- and memantine-treated patients were similar. The mean age in the placebo group was 61.5 years (range 30 to 80 years). In the memantine group the mean age was 62.2 years (range 30 to 81 years). The majority of both placebo- (55.0%) and memantine-treated (57.0%) patients were <65 years of age. There were more males (59.7% placebo, 57.8% memantine) than females in both treatment groups. The majority of both placebo- (84.6%) and memantine-treated (83.6%) patients were Caucasian. Mean weight was 91.4 kg in placebo-treated patients and 92.6 kg in memantine-treated patients.

Patients were treated with memantine for a mean of 49.5 days and with placebo for a mean of 49.2 days (both trials were eight weeks in duration).

6.3 Disposition

6.3.1 Core Double-Blind, Placebo-Controlled Dementia Trials

A total of 1862 patients (922 placebo, 940 memantine) were enrolled in the double-blind, placebo-controlled dementia trials. There was no meaningful difference between the placebo and memantine groups in the percentage of patients who discontinued or the reason for discontinuation. The most common reason for discontinuation was adverse events (11.5% placebo, 10.1% memantine). The number of patients who discontinued from a trial prematurely, along with the reasons for discontinuation, are summarized in Panel 32. The most common reason for discontinuation in patients with AD was adverse events (13.2% of placebo patients and 7.8% of memantine patients).

Panel 32. Number (%) of Patients Discontinued and Reasons for Discontinuation – Core Double-Blind, Placebo-Controlled Dementia Trials

	Placebo (N=922) n (%)	*Memantine (N=940) n (%)*
Completed	721 (78.2)	764 (81.3)
Discontinued	201 (21.8)	176 (18.7)
REASONS FOR DISCONTINUATION		
Adverse Event	106 (11.5)	95 (10.1)
Insufficient Therapeutic Response	5 (0.5)	4 (0.4)
Protocol Violation	43 (4.7)	38 (4.0)
Withdrawal of Consent	37 (4.0)	30 (3.2)
Lost to Follow-up	2 (0.2)	4 (0.4)
Other reasons	8 (0.9)	5 (0.5)

6.3.2 Core Open-Label Extension Dementia Trials

Overall, the percentage of patients who prematurely discontinued from the open-label extension dementia trials was 17.9% (the most common reason for discontinuation was adverse events, 10.7% of all patients).

6.3.3 Core Double-Blind, Placebo-Controlled Neuropathy Trials

Overall, the percentage of patients who prematurely discontinued from the double-blind, placebo-controlled neuropathy studies was similar in the placebo (24.2%) and memantine groups (23.5%); and the most common reason for discontinuation in both groups was adverse events (12.1% and 12.5% in the placebo and memantine groups, respectively). A greater number of memantine-treated patients discontinued due to AEs in the 40 mg/day group (16.8%) than in the 20 mg/day group (7.0%).

6.4 Mortality and Serious Adverse Events

An SAE was 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. In addition, other medically important events that required intervention in order to prevent one of the outcomes listed above were also considered serious.

6.4.1 Core Double-Blind, Placebo-Controlled Dementia Trials

Of the 1862 patients in the double-blind, placebo-controlled dementia trials, a total of 262 (14.1%) experienced a serious adverse event; 127 (13.5%) in the memantine group and 135 (14.6%) in the placebo group. The overall exposure-adjusted rates for SAEs in the double-blind period were 32.7 and 35.5 SAEs per 100 patient-years in the memantine and placebo treatment groups, respectively. SAEs reported by >1% of patients in either treatment group are listed in Panel 33.

Panel 33. Number (%) of Patients With SAEs Occurring in >1% of Patients in Either Treatment Group – Core Double-Blind, Placebo-Controlled Dementia Trials

Serious Adverse Event	***Placebo (N=922) n(%)***	***Memantine (N=940) n(%)***
Inflicted Injury	16 (1.7)	10 (1.1)
Confusion	8 (0.9)	15 (1.6)
Cerebrovascular Disorder	14 (1.5)	9 (1.0)
Fall	10 (1.1)	6 (0.6)
Agitation	10 (1.1)	5 (0.5)

Eighteen (1.9%) memantine patients and 21 (2.3%) placebo patients died during the Core double-blind, placebo-controlled dementia trials. Exposure-adjusted rates for these studies were 5.5 and 4.6 deaths per 100 patient-years for the placebo and memantine groups, respectively. The causes of death appeared most likely related to underlying medical conditions expected in the patient population under trial. There were no clinically important differences in the causes of death between the two treatment groups. Adverse events with an outcome of death which occurred in more than two patients in any treatment group included: cerebrovascular disorder (4 placebo, 1 memantine), cardiac arrest (2 placebo, 3 memantine), myocardial infarction (2 placebo, 3 memantine), and pneumonia (3 placebo, 3 memantine). No death in either treatment group was considered (by the investigators) as related to the trial medication.

There were no clinically important differences in the number of SAEs or causes of deaths in patient subgroups, including the subgroups by dementia diagnosis or by dementia severity. The profiles of SAEs were generally similar in males and females, and between-sex differences in the incidence of individual SAEs were similar in the memantine and placebo groups. For males (11 deaths) in the memantine group, the number of deaths per 100 patient years was 6.6 compared to 3.2 for memantine-treated females (7 deaths). A similar trend was seen in the placebo group.

6.4.2 Core Open-Label Extension Dementia Trials

A total of 149 patients (17.4%) experienced a SAE during the open-label extension dementia trials (36.6 SAEs per 100 patient-years). Most of the SAEs in the open-label extensions were considered not to be related or unlikely to be related to the trial drug. There did not appear to be any important differences between the SAE profile in the open-label extensions and the SAE profile in the double-blind, placebo controlled dementia trials.

Thirty-two patients died during the open-label extension dementia trials (7.9 deaths per 100 patient years). Adverse events with an outcome of death that occurred in more than

two patients included pneumonia (9 patients), cerebrovascular disorder (5 patients), myocardial infarction (4 patients), and cardiac failure (3 patients). The causes of death in the open-label dementia trials were similar to those observed in the double-blind, placebo-controlled dementia trials and were most likely related to the underlying medical conditions of the patients. All but one of the deaths (a head injury in an 81-year-old female who died seven days after discontinuing treatment) were considered (by the investigators) as unrelated to study medication.

6.4.3 Core Double-Blind, Placebo-Controlled Neuropathy Studies

A total of 21 patients reported SAEs during the double-blind, placebo-controlled neuropathy studies, 5 (3.4%) in the placebo group, 5 (2.9%) in the memantine 20 mg/day group, and 11 (5.0%) in the memantine 40 mg/day group. Only two specific SAEs were reported in more than one patient in the overall memantine group. Abdominal pain and gangrene were each reported in one patient in the memantine 20 mg/day group and one patient in the memantine 40 mg/day group. Most of the SAEs were considered not related to trial drug; they were thought to be due to either a concurrent illness or a pre-existing condition. One 78-year-old memantine-treated patient with a history of coronary artery disease and prior myocardial infarction died due to a myocardial infarction.

6.4.4 Additional Clinical Studies and Other Clinical Experience

The overall profile of SAEs reported in the additional clinical studies did not differ from that in the core dementia trials. A total of 24 (4.4%) memantine patients died during the additional clinical studies. All of the deaths occurred in two uncontrolled studies: a 14-month trial conducted in patients with various forms of spasticity in 1988 and a 6-month trial conducted in 1984 in hospitalized organic brain syndrome patients with a mean age of 79 years. The patient populations in both trials were extremely ill and, in one of the studies, two patients died during the 2-week lead-in period. Similar to the core safety studies, the deaths recorded were more likely a result of the patients' underlying medical condition rather than the use of trial drug. A total of 27 (4.9%) memantine patients (including the 24 deaths) experienced a serious adverse event during these studies.

In the other clinical experience, seventeen of approximately 3750 patients died (0.5%); the majority of cases due to pneumonia, cardiovascular disease, or stroke. In all cases, the investigators assessed the deaths as not related to memantine.

Sixteen patients died during ongoing blinded studies and nineteen patients treated with memantine died in the ongoing open-label extension studies. Based on an estimated 4537 subjects in the ongoing studies as of September 30, 2002, the crude incidence rate of death was 0.77%. Overall the AEs resulting in death for the ongoing studies were not different from the core safety double-blind, placebo-controlled dementia trials and typically were attributed to cerebrovascular disorder, cardiovascular disorders, respiratory disorders (pneumonia), or cancer-related.

Likewise, the profile of SAEs reported in the ongoing studies was not different from those reported in the core safety studies.

6.5 Discontinuations Due to Adverse Events

If action taken with regard to trial drug was associated with discontinuation and the adverse event onset date was on or before the last dose date of trial medication in the double-blind or open-label extension phase, as applicable, then this event was classified as a discontinuation due to an adverse event.

6.5.1 Core Double-Blind, Placebo-Controlled Dementia Trials

Of the 1862 patients in the double-blind, placebo-controlled dementia trials, a total of 201 (10.8%) discontinued due to an adverse event; 95 (10.1%) in the memantine group and 106 (11.5%) in the placebo group. The only adverse events associated with discontinuation in greater than 1.0% of memantine patients (Panel 34) were agitation (1.2% in the memantine group versus 2.0% in the placebo group) and confusion (1.2% in the memantine group versus 1.1% in the placebo group). In the AD group, 52 (13.2%) of 394 placebo patients in contrast to 31 (7.8%) of 396 memantine patients had an AE associated with discontinuation. The profile of AEs associated with discontinuations was similar across dementia patient subgroups categorized by dementia diagnosis, severity, or sex.

Panel 34. Number (%) of Patients With AEs Associated with Trial Discontinuation Occurring in >1.0% of Patients in Either Treatment Group – Core Double-Blind, Placebo-Controlled Dementia Trials

Adverse Event	***Placebo (N=922) n (%)***	***Memantine (N=940) n (%)***
Patients with at least one adverse event resulting in discontinuation	*106 (11.5)*	*95 (10.1)*
Agitation	18 (2.0)	11 (1.2)
Confusion	10 (1.1)	11 (1.2)
Cerebrovascular Disorder	10 (1.1)	7 (0.7)

N = total number of patients in the treatment group.

6.5.2 Core Open-Label Extension Dementia Trials

A total of 92 (10.7%) of 856 patients had an AE associated with trial discontinuation during the Core open-label extension dementia trials. The most common AEs associated with discontinuation reported in patients in the open-label extension trials (those reported in ≥ 1% of memantine-treated patients) were pneumonia (1.2%) and cerebrovascular disorder (1.2%).

6.5.3 Core Double-Blind, Placebo-Controlled Neuropathy Studies

A total of 49 (12.5%) memantine patients (12 [7%] memantine 20 mg/day, 37 [16.8%] memantine 40 mg/day) and 18 (12.1%) placebo patients discontinued due to an AE in the double-blind, placebo-controlled neuropathy studies. Overall, there was no clinically relevant difference in AEs leading to premature discontinuation between the placebo group and the 20 mg/day memantine group. Dizziness was the only AE leading to discontinuation that was notably greater in the 40 mg/day memantine group (10%) compared to the placebo group (1.3%).

6.6 Adverse Events

A TEAE is defined as an adverse event that started on or after the start date of dosing with trial medication and occurred within thirty days following the last dose of trial medication. In the core double-blind, placebo-controlled dementia studies, if an AE occurred prior to dosing, and was also observed after the start of dosing with a higher severity, this adverse event was recorded as a TEAE.

6.6.1 Core Double-Blind, Placebo-Controlled Dementia Trials

Of the 1862 patients in the double-blind, placebo-controlled dementia trials TEAEs were reported by 1286 patients; 624 (67.7%) placebo patients and 662 (70.4%) memantine patients. The profile of TEAEs was similar in the memantine and placebo treatment groups. Dizziness, confusion, headache, and constipation were reported in greater than 5% of memantine patients and at an incidence greater than in placebo patients. None of these TEAEs was reported by ≥7% of memantine patients or at a rate two times greater than in the placebo group. For TEAEs reported in a greater percentage of memantine-treated versus placebo-treated patients, the difference between the memantine and placebo groups was less than 2.4% for any individual AE term reported. Most TEAEs were considered mild or moderate in severity and not related to the trial drug in both placebo and memantine patients. TEAEs occurring in ≥3% of patients in either treatment group are shown in Panel 35.

Panel 35. TEAEs Occurring in ≥ 3.0% of Patients in Either Treatment Group – Core Double-Blind, Placebo-Controlled Dementia Trials

Adverse Event	***Placebo (N=922) n (%)***	***Memantine (N=940) n (%)***
Dizziness	49 (5.3)	64 (6.8)
Agitation	98 (10.6)	63 (6.7)
Confusion	42 (4.6)	58 (6.2)
Headache	31 (3.4)	54 (5.7)
Constipation	28 (3.0)	50 (5.3)
Fall	50 (5.4)	48 (5.1)
Inflicted Injury	64 (6.9)	44 (4.7)
Urinary Incontinence	36 (3.9)	41 (4.4)
Diarrhea	42 (4.6)	40 (4.3)
Bronchitis	39 (4.2)	37 (3.9)
Coughing	31 (3.4)	37 (3.9)
Hypertension	20 (2.2)	33 (3.5)
Urinary Tract Infection	43 (4.7)	32 (3.4)
Insomnia	42 (4.6)	32 (3.4)
Influenza-like Symptoms	28 (3.0)	31 (3.3)
Gait Abnormal	25 (2.7)	28 (3.0)
Somnolence	23 (2.5)	28 (3.0)
Vomiting	21 (2.3)	28 (3.0)

The overall profiles of TEAEs in patients were not affected by dementia diagnosis or severity. The profile of TEAEs observed in AD patients was similar for the placebo and memantine groups. Headache was the only event that was reported at an incidence rate of >5% in memantine-treated AD patients and which occurred at greater than twice the placebo incidence rate (5.6% vs. 2.0%, respectively). The profile and incidence of TEAEs relative to placebo treatment reported for AD patients (Panel 36) receiving memantine as concomitant treatment with donepezil (Trial MD-02) was not substantially different than that observed in AD patients receiving memantine alone (Trial 9605).

For the specific AEs where there were apparent differences in incidence rates between the memantine groups in the two trials, similar trends were generally observed for the placebo groups. Rates of hallucination, anorexia, and vomiting were higher by 4% to 6% for memantine-treated patients compared to placebo-treated patients in the monotherapy study but were higher in placebo-treated patients or were similar (≤5% difference) between groups in the add-on trial to donepezil. Confusion was reported in more memantine-treated patients (7.9%) compared to placebo-treated patients (2.0%) in the add-on trial to donepezil but was reported in fewer memantine-treated patients than placebo-treated patients in the monotherapy trial (3.2% and 4.8%, respectively).

Panel 36. TEAEs Occurring in ≥ 5.0% of Either Treatment Group – Trials 9605 and MD-02

Adverse Event	***Trial 9605***		***Trial MD-02***	
	Placebo (N=126) n (%)	*Memantine (N=126) n (%)*	*Placebo (N=201) n (%)*	*Memantine (N=202) n (%)*
Agitation	41 (32.5)	21 (16.7)	24 (11.9)	19 (9.4)
Urinary Incontinence	14 (11.1)	14 (11.1)	6 (3.0)	11 (5.4)
Insomnia	10 (7.9)	13 (10.3)	6 (3.0)	4 (2.0)
Diarrhea	10 (7.9)	12 (9.5)	17 (8.5)	9 (4.5)
Hallucination	4 (3.2)	11 (8.7)	6 (3.0)	5 (2.5)
Inflicted Injury	11 (8.7)	10 (7.9)	16 (8.0)	10 (5.0)
Anorexia	3 (2.4)	10 (7.9)	8 (4.0)	5 (2.5)
Fall	9 (7.1)	9 (7.1)	14 (7.0)	15 (7.4)
Vomiting	4 (3.2)	9 (7.1)	6 (3.0)	7 (3.5)
Headache	3 (2.4)	8 (6.3)	5 (2.5)	13 (6.4)
Dizziness	3 (2.4)	7 (5.6)	16 (8.0)	14 (6.9)
Urinary Tract Infection	17 (13.5)	7 (5.6)	10 (5.0)	12 (5.9)
Somnolence	6 (4.8)	7 (5.6)	7 (3.5)	7 (3.5)
Constipation	10 (7.9)	7 (5.6)	3 (1.5)	6 (3.0)
Coughing	10 (7.9)	7 (5.6)	2 (1.0)	6 (3.0)
Fecal Incontinence	7 (5.6)	7 (5.6)	10 (5.0)	4 (2.0)
Upper Respiratory Tract Infection	6 (4.8)	6 (4.8)	13 (6.5)	10 (5.0)
Confusion	6 (4.8)	4 (3.2)	4 (2.0)	16 (7.9)
Influenza-like Symptoms	6 (4.8)	3 (2.4)	13 (6.5)	15 (7.4)

For the core double-blind, placebo-controlled dementia studies overall, while there were some differences in the TEAE profile between males and females these differences generally appeared to be similar in both placebo- and memantine-treated patients. Headache and constipation were the only TEAEs reported in ≥ 5% of males in the memantine group which occurred at a rate two times greater than in the placebo group (5.0% versus 2.2% for headache; 6.5% versus 3.1% for constipation, respectively). No TEAEs that were reported in ≥ 5% of females in the memantine group occurred at a rate two times or greater than in the placebo group.

The percentage of patients with TEAEs tended to increase with age in both placebo- and memantine-treated patients. The profile of TEAEs observed in non-Caucasians appeared to be similar to that in Caucasians.

6.6.2 Core Open-Label Extension Dementia Trials

A total of 604 patients (70.6%) experienced a TEAE during the open-label extension dementia trials. The overall profile of TEAEs reported in the open-label dementia trials was similar to that reported in the double-blind, placebo-controlled dementia trials. The most frequently reported TEAEs in the open-label studies were agitation (6.9%), urinary tract infection (5.6%), fall (5.4%), inflicted injury (5.3%), and dizziness (5.1%). The majority of TEAEs were considered mild or moderate in severity and not related to the trial drug. No TEAE, by preferred term, was reported by more than one patient after 12 months of memantine treatment that had not been reported prior to 12 months.

6.6.3 Core Double-Blind, Placebo-Controlled, Neuropathy Studies

In the double-blind, placebo-controlled neuropathy studies, of 171 patients receiving memantine 20 mg/day, 116 (67.8%) reported TEAEs; and of 220 patients receiving memantine 40 mg/day, 181 (82.3%) reported TEAEs. Of 149 patients who received placebo, 111 (74.5%) reported TEAEs. TEAEs reported by greater than 5% of memantine patients in the 20 mg/day dose group were: dizziness (9.9%), nausea (8.2%), headache (6.4%), hypertension (5.3%), and upper respiratory tract infection (5.3%). Of these TEAEs, only hypertension occurred at a rate at least twice that of placebo-treated patients (2.0%, placebo vs. 5.3%, memantine patients).

TEAEs reported by ≥ 5% of memantine-treated patients in the 40 mg/day treatment group were: dizziness (32.7%), headache (11.4%), diarrhea (10%), fatigue (7.3%), paresthesia (6.8%), upper respiratory tract infection (6.4%), nausea (5.9%), back pain (5.9%), and somnolence (5.0%). Of these TEAEs, only two occurred at a rate at least twice that of placebo: dizziness (11.4% placebo vs. 32.7% memantine) and paresthesia (1.3% placebo vs. 6.8% memantine).

6.7 Vital Signs, Laboratory Values, and ECGs

Hematology and clinical chemistry laboratory parameters, vital signs values (systolic and diastolic blood pressure, pulse rate, and weight) and ECG parameters (PR interval, QRS interval, QT interval, and QTc interval) were recorded for each patient per protocol specifications. All parameters were deemed potentially clinically significant (PCS) if the values exceeded the standard criteria (see Appendix 8.3.2.8).

6.7.1 Vital Signs and Laboratory Values

6.7.1.1 Core Double-Blind, Placebo-Controlled Dementia Trials

There were no clinically important mean changes in vital sign values from baseline to end of trial in either memantine or placebo patients in the double-blind, placebo-controlled dementia trials (Panel 37).

Panel 37. Change from Baseline for Vital Sign Measures – Core Double-Blind, Placebo-Controlled Dementia Trials

	Placebo (N=922)	*Memantine (N=940)*
DIASTOLIC BLOOD PRESSURE (MM HG)		
BASELINE Mean±SD (N)	78.0±9.9 (604)	78.1±10.2 (606)
CHANGE FROM BASELINE Mean	-0.7	-0.4
SYSTOLIC BLOOD PRESSURE (MM HG)		
BASELINE Mean±SD (N)	136.6±16.6 (604)	138.0±16.5 (606)
CHANGE FROM BASELINE Mean	-0.8	-1.0
PULSE (BPM)		
BASELINE Mean±SD (N)	71.2±9.7 (602)	70.8±9.8 (606)
CHANGE FROM BASELINE Mean	0.4	0.7
WEIGHT (KG)		
BASELINE Mean±SD (N)	66.0±14.2 (211)	69.6±14.1 (211)
CHANGE FROM BASELINE Mean	0.4	0.9

The overall incidence of PCS vital signs (blood pressure, pulse; definition of criteria in Appendix 8.3.2.8, Panel 45) was low and was almost identical between memantine and placebo treatment groups (approximately 630 placebo-treated and 630 memantine-treated patients had baseline and post-baseline vital sign measures). The most frequent PCS vital sign was for high systolic blood pressure observed in 12 (1.9%) placebo-treated patients and 13 (2.1%) memantine-treated patients. PCS high diastolic blood pressure values were observed in 0.8% memantine-treated and 0.5% placebo-treated patients. PCS low systolic blood pressure values were observed in 0.5% of memantine-treated and 0.6% of placebo-treated patients. The incidence of PCS values for all other vital sign measures was less than or equal to 0.5% for the memantine group.

PCS increases in body weight were reported in 22 of 211 (10.4%) placebo and 22 of 211 (10.4%) memantine patients. PCS decreases in body weight were observed in 11 (5.2%) placebo patients and 5 (2.4%) memantine patients.

There were no clinically important mean changes in laboratory values from baseline to end of trial in either memantine or placebo patients in the double-blind, placebo-controlled dementia trials.

The most frequent PCS laboratory values (Panel 38; PCS criteria defined in Appendix 8.3.2.8, Panel 47) were high serum potassium (placebo, 5.5%; memantine, 6.1%), high urea nitrogen (placebo, 2.7%; memantine, 4.2%), high cholesterol (placebo, 3.6%; memantine, 3.4%), and low hemoglobin (placebo, 2.5%; memantine, 2.3%). The apparent high incidence of elevated potassium levels in both groups is considered most likely to have been related to cell hemolysis in the collected blood specimens. These incidence rates were not different between the two treatment groups.

Panel 38. Number (%) of Memantine Patients with Potentially Clinically Significant Laboratory Parameters at an Incidence of ≥ 0.5% in Either Treatment Group: Core Double-Blind, Placebo-Controlled Dementia Trials

Laboratory Parameter (Unit) *PCS Criterion*		*Placebo* *n/N (%)*	*Memantine* *n/N (%)*
Total Number of Patients		922	940
HEMATOLOGY			
Hemoglobin (g/dL)	≤0.9*LNL	20/816 (2.5)	19/836 (2.3)
Hematocrit (l / l)	≤0.9*LNL	9/806 (1.1)	8/830 (1.0)
CHEMISTRY			
Blood Urea Nitrogen (mmol/L)	≥10.7	17/627 (2.7)	27/647 (4.2)
Uric Acid (mmol/L)	≥0.6246 (male) ≥0.5056 (female)	9/782 (1.2)	14/800 (1.8)
Creatinine (umol/l)	≥175	5/833 (0.6)	6/856 (0.7)
Cholesterol, Total (mmol/L)	≥7.8	27/742 (3.6)	26/765 (3.4)
Potassium (mmol/L)	≥5.5	41/742 (5.5)	47/773 (6.1)

6.7.1.2 Core Double-Blind, Placebo-Controlled Neuropathy Studies

In the double-blind, placebo-controlled neuropathy studies, there were no clinically important differences in the mean change for vital sign measures or laboratory values from baseline to end of trial between treatment groups.

6.7.2 ECGs

A total of 602 placebo and 816 memantine patients in the double-blind, placebo-controlled dementia and neuropathy studies had ECG recordings obtained at baseline and at end of trial; approximately 63% of these patients had an abnormal ECG diagnosis at baseline (Panel 39). A total of 231 placebo patients had a normal ECG diagnosis at baseline and of these patients, 53 (23%) had an abnormal diagnosis at end of trial. A total of 295 memantine patients had a normal ECG diagnosis at baseline and of these patients, 74 (25%) had an abnormal diagnosis at end of trial.

ECG interval data is available from the two placebo-controlled AD (Trials 9605 and MD-02) and two neuropathy trials (Trials NTI 9702 and 9801). There were no clinically important mean changes in ECG parameters from baseline to end of trial in either memantine- or placebo-treated patients (Panel 40 and Panel 41). A total of 7 placebo and 6 memantine-treated dementia patients with a non-PCS ECG interval value at baseline had a post-baseline PCS ECG interval value. Three patients in each treatment group had a PR interval of ≥250 milliseconds. Three placebo and one memantine patients had a QTc interval of > 500 milliseconds. One placebo and two memantine patients had a QRS interval of ≥150 milliseconds. In the double-blind, placebo-controlled neuropathy studies, post-baseline PCS ECG interval values were reported in 2 placebo and 2 memantine-treated patients who had non-PCS ECG interval values at baseline. One placebo and one memantine 20 mg/day patient had a PR interval of ≥ 250 milliseconds. One placebo and one memantine 20 mg/day patient had a QTc interval of > 500 milliseconds.

Panel 39. Shift from Baseline in ECG Results – Core Double-Blind, Placebo-Controlled Trials

Screening/ Baseline	***End of Trial***	***Placebo***			***Memantine***		
		Dementia Trials (n)[a]	*NP Trials (n)[b]*	*Total (%) (N=602)*	*Dementia Trials (n)[a]*	*NP Trials (n)[b]*	*Total (N=816)*
Normal	Normal	134	44	178 (29.6)	133	88	221 (27.1)
Normal	Abnormal	45	8	53 (8.8)	48	26	74 (9.1)
Abnormal	Abnormal	260	59	319 (53.0)	263	171	434 (53.2)
Abnormal	Normal	42	10	52 (8.6)	44	43	87 (10.7)

[a] Core double-blind, placebo-controlled dementia trials
[b] Core double-blind, placebo-controlled neuropathy trials
N = Number of patients with non-missing ECG results.
n = Number of patients in the shift category.

Panel 40. Mean Change in ECG Parameters – Trials 9605 and MD-02

		Placebo (N=327)	*Memantine (N=328)*
Ventricular heart rate (bpm)	Baseline	65.3	63.2
	N	269	284
	Change	2.0	2.6
QRS Interval (msec)	Baseline	90.7	89.6
	N	269	285
	Change	-0.2	0.3
PR Interval (msec)	Baseline	159.8	164.2
	N	259	275
	Change	-1.6	-1.2
QT Interval (msec)	Baseline	406.3	408.8
	N	269	285
	Change	-2.5	-4.7
QTc Interval (msec)[a]	Baseline	420.3	415.8
	N	269	284
	Change	3.4	2.8

Change = Change from baseline to end of trial.
[a] $QT_c = QT * (HR/60)^{1/2}$ (Bazett's Correction)

Panel 41. Mean Change in ECG Parameters – Core Double-Blind, Placebo-Controlled, Neuropathy Trials

		Placebo	***Memantine Dose Group***	
			20 mg/day	*40 mg/day*
Ventricular heart rate (bpm)	Baseline	74.4	74.9	73.6
	N	119	154	174
	Change	0.5	0.2	0.9
QRS Interval (msec)	Baseline	92.3	93.1	90.6
	N	119	153	173
	Change	-1.7	0.2	-1.1
PR Interval (msec)	Baseline	162.7	165.2	166.1
	N	114	146	167
	Change	1.3	1.2	-3.4
QT Interval (msec)	Baseline	366.0	380.1	373.2
	N	120	152	174
	Change	6.5	-0.3	-1.0
QTc Interval (msec)	Baseline	404.6	420.3	408.7
	N	119	152	174
	Change	8.0	0.1	2.1

Change = Change from baseline to end of trial.
$QTc=QT*(HR/60)^{1/2}$ (Bazett's correction)

6.8 Summary of Clinical Pharmacology and Non-Clinical Safety Information

6.8.1 Clinical Pharmacology

In 8 of the 30 clinical pharmacology studies in which a total of 207 subjects received memantine and where AEs were recorded in a consistent manner, 60% of memantine subjects reported AEs (most frequent AEs were were fatigue, headache, and dizziness). Additional pharmacodynamic information from these trials is summarized in Section 4.3.

6.8.2 Toxicology

A comprehensive program of preclinical studies was conducted with memantine. These studies included acute, subchronic and chronic (both by dietary and gavage dosing), carcinogenicity, reproduction, developmental and genetic toxicity and ADME studies.

Acute oral and intravenous toxicity studies in rats and mice demonstrated that memantine is moderately toxic.[133] The lowest lethal oral dose is ≥300 mg/kg in both species. Ataxia, prone position, bradypnea and tremor preceded death. In subchronic and chronic studies the most prominent clinical signs in all species were related to the central nervous system and included ataxia, tremor, and/or unsteadiness and aggressiveness or hyperexcitability in rodents[134,135,136,137,138,139] and apathy or quietness in dogs[140,141,142] and baboons.[143,144] Reduced body weight, which was sometimes accompanied by a change in food consumption, was noted in all studies. The central nervous system was identified as the primary target organ. At overtly toxic doses, foamy macrophages in the lung, renal papillary mineralization, tubulointerstitial nephritis, vacuolization of defined cortical neurons, and corneal opacities were also observed. The no observed effect level (NOEL) for overt toxicity in subchronic and chronic studies is 7 to 44 times the maximum therapeutic dose of 20 mg/day on a mg/m^2 basis, indicating that an adequate margin of safety exists for human exposure.

Memantine was not carcinogenic in the 113-week mouse[145,146,147,148] and 128-week rat studies.[149,150,151,152] Memantine tested negative in a battery of mutagenicity studies.[153,154,155,156,157,158]

Placental transfer of memantine was demonstrated in the rabbit[159]; however, memantine was not teratogenic in rats[160] and rabbits[161], even at maternally toxic doses. No adverse effects of memantine were noted on fertility[162] or reproductive capacity.[163]

In mouse,[164,165] rat[134] and dog[140] studies, ophthalmological exams revealed opacities of cornea and/or obscured retinal blood vessels. Corneal edema, thickening of the layers of corneal epithelium and endothelial vacuolization observed during the histopathologic exam confirmed these (in-life) observations. The findings in the dog are questionable because the symptoms disappeared even though doses were increased. Ophthalmologic changes in rodents were only observed at doses that produced profound systemic toxicity and/or death. Ophthalmological effects noted in the 13-week rat study were not observed

during the 12 month chronic feeding study up to the highest doses tested (70 and 50 mg/kg/day in males and females, respectively).[166,167,168,169] A further evaluation of the eye tissues in the control and high-dose groups at the end of the treatment and recovery periods by electron microscopy confirmed the absence of structural damage.[169] The NOEL for ocular lesions in these studies is 8 to 44 times the maximum therapeutic dose of 20 mg/day on a mg/m^2 basis, indicating that an adequate margin of safety exists for human exposure.

Cerebrocortical neurons in adult rodent brain are prone to injury (vacuolization and/or necrosis) by systemic administration of high affinity uncompetitive (or open channel blocking) NMDA receptor antagonists, such as (+) MK-801, PCP, and ketamine.[170] Olney first reported this particular type of lesion occurring as neuronal vacuoles in the rat posterior cingulate/retrosplenial cortex (PC/RSC).[170] Although NMDA antagonists were initially thought to produce reversible lesions (vacuolization) limited to specific neurons in the PC/RSC, there is evidence that a subpopulation of these neurons do not recover, thus resulting in cell necrosis.[171,172]

To determine the potential of memantine to induce Olney–type lesions, studies were conducted in rats that indicated single intraperitoneal doses of 20 mg/kg/day or greater produced a dose-related increase in the frequency and severity of Olney-type lesions.[173,174] Experiments comparing the effect of dosing duration (acute vs. subchronic) and administration route (dietary vs. gavage) of memantine on the development of Olney-type lesions demonstrated that regardless of duration or route of administration, ataxia occurred at doses 2 to 4 times lower than Olney-type lesions.[175]

Numerous repeated dose toxicology studies with memantine were performed without any significant observations regarding neuropathology. While vacuolization can only be detected in a brain that is aldehyde-perfusion fixed, neuronal necrosis can be identified in the brain tissue prepared by immersion fixation as is done in standard toxicology studies.[176] Re-examination of the existing brain tissue slides and examination of the newly prepared slides from the 52-week rat study (doses up to 70 and 50 mg/kg/day in males and females, respectively) revealed no neurodegenerative changes in the PC/RSC.[167,168]

The ability of memantine to produce Olney-type lesions in baboons was also examined in the 52-week study. While ptosis was observed in all treated animals, histopathological examination revealed no evidence of vacuolization or necrosis.[183] These results are consistent with findings for both MK-801 and CGS 19755 (selfotel) which were ineffective in inducing Olney-type lesions in primates.[177,178] Similarly in humans subjected to high doses of a low-moderate affinity uncompetitive NMDA receptor antagonist, amantadine, no necrosis in posterior cingulate/retrosplenial cortex or elsewhere in the brain was found at autopsy.[179]

In rodents, NMDA receptor antagonist-induced vacuolization and necrosis may occur as a result of hypermetabolic neuropathology. In rats, (+) MK-801 induces focal hypermetabolism of the cingulate cortex whereas co-administration of halothane prevents the hypermetabolism[180] as well as Olney-type lesions.[181] Due to lower neuronal density

and metabolic rate per brain region, primates may be less likely to develop Olney-type lesions after administration of uncompetitive NMDA receptor antagonists.[177,182,183]

In summary, memantine at high doses in rats causes neurotoxicity, consisting of an increased incidence of vacuolization and/or necrosis of specific cortical neurons (i.e., Olney-type lesions). Clear signs of CNS involvement, principally ataxia, occur at doses lower than those associated with these neuronal toxicity findings. Escalation of the dose over time in rats and dogs eliminated signs of CNS toxicity; this procedure of upward titration to the final maintenance dose is characteristic of the proposed therapeutic use. The NOEL for memantine-induced Olney-type lesions in rats is greater than or equal to 6 times the maximum therapeutic dose of 20 mg/day on a mg/m^2 basis, indicating that an adequate margin of safety exists for human exposure. Based on the evidence that signs of intolerance precede the neuronal lesions, that these lesions occur only under conditions of overt toxicity; and that an adequate safety margin exists in man, this apparently unique rodent toxicity finding is not expected to occur during therapeutic exposure in humans.

6.9 Overdose

No cases of overdose were reported during clinical studies with memantine. One reported case of overdose occurred with the marketed product in Germany.

A 19-year-old female with reactive depression attempted suicide by consuming approximately 500 to 750 ml of wine with 2 to 3 tablets of aspirin 500 mg, 2 to 3 tablets of benproperine embonate, and 70 to 80 tablets (up to 400 mg) of memantine over a period of about one hour. On the following morning, she could not stand up and had ataxic gait even when supported. Other symptoms included pronounced vertigo, nystagmus, restlessness approaching a psychosis, and leg cramps. The patient was discharged two days after being admitted to the hospital. Eighteen days after discharge, all symptoms had disappeared.

6.10 Abuse Liability

The NMDA receptor antagonists ketamine and PCP are known to possess abuse liability. Therefore, studies were conducted in rats, mice and monkeys to evaluate the abuse potential of memantine. In both rat and monkey drug-discrimination paradigms, memantine partially substituted for PCP, but with a significant decrease in the rates of responding.[184,185] In monkeys trained to self-administer PCP, memantine did not produce PCP-like self-administration rates, and exhibited weak reinforcing potential only at high doses. In this paradigm, memantine was 50 times less potent than PCP.[185] Mice did not self-administer memantine.[186] Therefore, based on these data, it is unlikely that memantine has significant potential for abuse.

In clinical trials with memantine, there was no evidence of drug-seeking behavior, tolerance or withdrawal symptoms upon drug discontinuation. In surveillance reports spanning thirteen years, memantine was not cited as an abused substance among patients receiving treatment at a representative sample of addiction centers throughout Germany. A review of two decades of German post-marketing adverse event data did not reveal any clear signals suggestive of drug likeability or the potentiation of drug seeking behavior associated with memantine use.

6.11 Dose Response Effects

Panel 42 presents the TEAEs that occurred in greater than 5% of memantine-treated patients in the double-blind, placebo-controlled dementia and neuropathic pain studies, and at a rate two times higher than placebo patients, by dose. Across the placebo-controlled dementia trials, patients received memantine 10 mg BID (except for Trial 9403 where the dose regimen was 10 mg QD). In the neuropathy trials, patients received memantine dosing regimens of either 10 mg BID or 20 mg BID. The highest incidence of dizziness occurred at the 40 mg/day dose of memantine (32.7%). Other TEAEs with an incidence ≥5% in the 40 mg/day memantine dose group and which occurred at a rate greater than twice that of placebo patients were headache (11.4%), fatigue (7.3%), paresthesia (6.8%), upper respiratory tract infection (6.4%), and back pain (5.9%). For each TEAE presented in Panel 42, the incidence at the 40 mg/day dose was also approximately two-fold or more higher than that in the ≤20 mg/day dose group. Overall, the incidence of each TEAE was similar between the ≤20 mg/day memantine-treated patients and placebo-treated patients.

Panel 42. TEAEs Occurring in ≥ 5% of Memantine Patients (Any Dose Group) and At a Rate ≥ 2x that of Placebo Patients – Core Double-Blind, Placebo-Controlled Dementia and Neuropathy Studies

Preferred Term	*Placebo N = 1071 n (%)*	*Memantine ≤ 20 mg/day N = 1111 n (%)*	*Memantine 40 mg/day N = 220 n (%)*
Dizziness	66(6.2)	81(7.3)	72(32.7)
Headache	51(4.8)	65(5.9)	25(11.4)
Fatigue	19(1.8)	30(2.7)	16(7.3)
Paresthesia	6(0.6)	14(1.3)	15(6.8)
Upper respiratory tract infection	30(2.8)	33(3.0)	14(6.4)
Back pain	28(2.6)	27(2.4)	13(5.9)

No dose-related trends were observed for vital sign measures, laboratory values, or ECG assessments in the double-blind, placebo-controlled neuropathy studies.

6.12 Drug-Drug Interactions — Clinical Trial Experience

Concomitant medication was used by approximately 89% of the patients in each treatment group in the Core double-blind, placebo-controlled dementia trials. The most frequently used concomitant medications (≥ 10%) in all treatment groups were donepezil, tocopherol, multivitamins, acetylsalicylic acid and acetaminophen. The overall profile and incidence of the use of any concomitant medication was similar in both the placebo and memantine treatment groups.

The incidence of TEAEs was examined for those classes of medication received by at least 5% of the patients in the memantine group which included antihypertensives, neuroleptics, antidepressants, sedatives, analgesics/nonsteroidal anti-inflammatory drugs (NSAIDS), antacids, estrogens, diuretics, antiepileptics, anti-parkinsonian agents, blood glucose lowering drugs, antithrombotic agents, cardiac glycosides, antiarrhythmic agents, vasodilators, peripheral vasodilators, beta-blocking agents, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors and angiotensin II antagonists, cholesterol and triglyceride reducers, urinary antispasmodics, thyroid hormones, antibacterials, psychostimulants and nootropics, systemic antihistamines, Ginkgo biloba, vitamin E, and donepezil.

When the frequency of individual TEAEs was compared between memantine patients taking concomitant medications and memantine patients not taking concomitant medications, no clinically meaningful differences were observed. Adverse events occurring with a higher incidence in memantine patients receiving concomitant medications were typically related to the indication for that medication or were known adverse events associated with the use of the concomitant medication examined.

6.13 Other Sources of Information

A total of six post-marketing spontaneous adverse event reports (five foreign and one domestic) were received by Forest from September 2000 through September 30, 2002. Additional post-marketing adverse event reports have been obtained, covering the period from 1982 through September 2000 for serious adverse events, and from 1982 through September 2002 for non-serious events and include the following:

- 42 non-serious reports obtained from Merz;
- 19 serious reports obtained from Merz;
- 9 reports from the Bundesinstitut for medicaments and medicine products (BfArM) and four (4) reports from the World Health Organization (WHO) International Center for Drug Monitoring-Uppsala. Seriousness of these reports is unknown as neither the BfArM nor WHO provided that data.

The profile of adverse events reported were similar to that observed in the Core dementia trials.

6.14 Special Safety Concerns

6.14.1 Psychotomimetic Effects

High-affinity, non-voltage dependent NMDA antagonists are known to cause hallucinations, agitation, transient psychotic symptoms, and other psychotomimetic effects in humans. In the placebo-controlled dementia trials, hallucinations (2.6% vs. 1.6%) and confusion (6.2% vs. 4.6%) were reported slightly more frequently in memantine-treated patients than in placebo-treated patients, respectively. However, memantine-treated patients had a lower frequency of agitation (6.7% vs. 10.6%). Reports of delirium (0.1% vs. 0.2%), paranoid reaction (0.1% vs. 0.8%), and psychosis (0.3% vs. 0.4%) were similar in frequency in the memantine and placebo treatment groups, respectively. Considering the fact that these symptoms can also be caused by worsening of the dementia itself, memantine treatment does not appear to be associated with psychotomimetic effects.

6.14.2 Dizziness

Dizziness, which occurred in <10% of patients in the double-blind, placebo-controlled dementia trials, was the most common adverse event observed with memantine treatment. It was reported slightly more frequently in memantine-treated patients (6.8 % vs. 5.3%) than placebo-treated patients in the placebo-controlled dementia trials. Dizziness also appears to be dose-dependent: in the dose-ranging diabetic neuropathy trial, dizziness was reported more frequently in patients receiving 40 mg/day than in those receiving 20 mg/day. In most cases, dizziness was reported as mild in severity, and there was no increase in the incidence of serious AEs or discontinuations related to dizziness in the memantine group compared to placebo-treated patients.

Also, there were no apparent increases in memantine-treated patients compared to the placebo group for the following potentially related TEAEs in the double-blind, placebo-controlled dementia trials: hypotension, postural hypotension, syncope, falls, or inflicted injury.

6.14.3 Ophthalmologic Effects

Ophthalmologic examinations, which included slit-lamp examination, were performed in elderly demented patients in the placebo-controlled Trial 9202 (both double-blind and open-label phases) at weeks 0, 28, and 52. Overall, there were no differences in the incidence of abnormalities involving the cornea, lens or other ocular diagnoses or conditions between the placebo and memantine groups during the double-blind period.

6.14.4 Cardiovascular Effects

In two small pilot studies, the effects of memantine on the cardiovascular system were evaluated in healthy male subjects who received intravenous doses of memantine at 15

mg, 30 mg, and 60 mg in a dose-escalating crossover design and as a cumulative dose over 2 hours, respectively. Memantine appeared to have only minimal hemodynamic effects (see Section 4.3.2). No effects on conduction were observed.

In the double-blind, placebo-controlled, dementia and neuropathy trials, the effects of memantine on the cardiovascular system were assessed by the recording of vital signs, adverse events and ECGs.

In the double-blind, placebo-controlled studies that recorded ECGs, the percentage of patients whose ECGs shifted from normal at baseline to abnormal at trial endpoint were similar between memantine- (8.8%) and placebo-treated patients (9.1%). There were no clinically important mean changes in ECG parameters from baseline to the end of trial in either memantine- or placebo-treated patients.

There were no clinically important mean changes in vital signs from baseline to the end of trial in either treatment group in the double-blind, placebo-controlled and open-label dementia trials, and the overall incidence of PCS vital sign values was similar for placebo- and memantine-treated patients.

Across the double-blind, placebo-controlled dementia trials, the only cardiovascular system TEAE reported in ≥ 2% of memantine-treated patients was hypertension (3.5% in memantine-treated patients and 2.2% in placebo patients). In the open-label dementia trials, hypertension occurred in 2.5% of memantine-treated patients.

Deaths related to cardiovascular events in the double-blind, placebo-controlled dementia trials were cardiac failure [2 (0.2%) memantine and 0 placebo patients], cardiac arrest [3 (0.3%) memantine and 2 (0.2%) placebo patients] and myocardial infarction [3 (0.3%) memantine and 2 (0.2%) placebo patients]. In the open-label extension studies, 3 deaths occurred due to cardiac failure, and cardiac arrest and hypertension were each reported for a patient that died. There was one memantine-treated patient who died in the double-blind neuropathy studies due to a myocardial infarction.

In the double-blind, placebo-controlled dementia trials, cardiac failure (which includes the AEs leading to death listed above) was reported as an SAE by 7 (0.8%) memantine- and 2 (0.2%) placebo-treated patients and by 5 (0.6%) memantine-treated patients in the open-label extension studies. Other cardiovascular-related SAEs in the double-blind, placebo-controlled dementia trials (all reported by ≤0.4% of each treatment group) included myocardial infarction and heart disorder. In the open-label extension studies, cardiovascular related SAEs (all reported by ≤0.4% of each treatment group) included hypertension, atrial fibrillation, and bradycardia.

In summary, serious cardiovascular-related events were infrequently observed in memantine-treated patients within the core safety trails. Analyses of cardiovascular related AEs, vital signs, and ECGs did not reveal any clinically important effects on the cardiovascular system associated with memantine treatment.

6.15 Safety Summary

This safety review of memantine is derived from a number of sources. The overall completed clinical trial safety experience comprises a total of 2297 subjects who received memantine, and 1244 subjects who received placebo. A total of 1748 patients were exposed to memantine in the core dementia and neuropathy studies. In the post-marketing experience in Europe, there has been an estimated memantine exposure of 600,000 patient-years as of February 2003.

Across the double-blind, placebo-controlled dementia trials, the memantine and placebo groups were well matched in terms of demographic profiles. Overall, the percentage of patients who prematurely discontinued from the Core double-blind, placebo-controlled dementia trials was similar in placebo and memantine patients. The most common reason for discontinuation in both placebo and memantine patients was adverse events.

When adjusted for exposure, the rates for deaths in the Core double-blind, placebo-controlled dementia trials were 4.6 and 5.5 deaths per 100 patient years for the memantine and placebo groups, respectively. The most frequent causes of death in both treatment groups were cerebrovascular and cardiac disorders and pneumonia, which were considered most likely related to the underlying illnesses and age (mean age ~76 years) of the population under trial. The causes of death during long-term memantine treatment for periods of up to 884 days were similar to those occurring in the double-blind, placebo-controlled studies.

In the double-blind, placebo-controlled studies, 13.5% (32.7 per 100 patient years of exposure) of memantine patients and 14.6% (35.5 per 100 patient years of exposure) of placebo patients experienced one or more SAEs. SAEs reported in greater than 1% of memantine patients were confusion (memantine 1.6% vs. placebo 0.9%) and inflicted injury (memantine 1.1% vs. placebo 1.7%). Most of the SAEs were considered not to be related or unlikely to be related to the trial drug. A similar SAE rate and profile was observed in the open-label extension trials.

The percentage of patients with adverse events associated with trial discontinuation in the Core double-blind, placebo-controlled dementia trials was similar in placebo and memantine patients (11.5% vs. 10.1%, respectively). The most frequent AEs leading to discontinuation were agitation (1.2% in the memantine group vs. 2.0% in the placebo group) and confusion (1.2% in the memantine group vs. 1.1% in the placebo group). A total of 92 (10.7%) patients had an adverse event associated with trial discontinuation during the open-label extension dementia trials and the overall profile of AEs leading to premature discontinuation was similar to that observed in the placebo-controlled studies.

In the double-blind, placebo-controlled dementia trials, TEAEs were reported by 67.7% of placebo and 70.4% of memantine patients. The profile of TEAEs was similar in the memantine and placebo treatment groups. No individual treatment emergent adverse events by preferred term were reported by ≥5% of memantine patients and at a rate two times or greater than in the placebo group. Most TEAEs were considered mild or moderate in severity and not related to the trial drug in either the placebo or memantine-treated patients.

The percentage of patients with AD reporting TEAEs was similar in placebo- and memantine-treated groups. While there are some differences in the TEAE profile between males and females, these differences appeared to be similar in both placebo- and memantine-treated patients. Overall, the percentage of patients with TEAEs increased with age in both placebo- and memantine-treated patients. There did not appear to be an effect of race on the profile of TEAEs observed.

Analysis of vital sign measurements, clinical laboratory data, and ECG results in the placebo-controlled studies revealed a low incidence of PCS values. Mean changes from baseline in the memantine group for each of these safety measures were small in magnitude and similar to those observed in the placebo group.

There was also no evidence for any special safety concerns based on the preclinical safety trial results or from specific assessments of possible psychotomimetic, neurologic, ophthalmologic, and cardiovascular effects. Analysis of TEAEs in patients receiving various classes of concomitant medications did not reveal any evidence of drug-drug interactions with memantine.

Overall, memantine at its recommend target dosage of 10 mg BID was found to be well tolerated, with a safety profile similar to that of placebo treatment, and is judged safe for use in the treatment of AD patients.

7.0 OVERALL SUMMARY

Moderate to severe AD represents an identifiable stage of a recognized disease and can be reliably diagnosed. Currently, no approved therapeutic options exist for the treatment of more advanced AD (MMSE <10). A clinical trial program was completed with memantine, an uncompetitive NMDA receptor antagonist, to evaluate its efficacy and safety in the treatment of moderate to severe AD. This program included studies in nursing home patients with severe dementia and in outpatients with moderate to severe AD as monotherapy and as add-on treatment to a stable regimen of donepezil.

Three key double-blind, placebo-controlled trials have utilized appropriate diagnostic and outcome measures to demonstrate the efficacy and safety of memantine. Memantine in the dose range of up to 20 mg/day provides clinical benefit in the domains of cognition, function, and global status for patients with moderate to severe AD.

The efficacy of memantine was demonstrated in two key double-blind, placebo-controlled trials (Trials 9605 and MD-02) of 6 months duration in patients with probable AD and in an earlier key trial (Trial 9403) of 12 weeks duration in dementia patients. In these studies, memantine was titrated from a starting dose of 5 mg/day to a target dose of 20 mg/day administered as 10 mg twice daily in the two 6-month trials and a target dose of 10 mg/day administered as 10 mg once daily in the 12-week trial. Outcome measures were chosen to reflect the symptomatology of the more severe dementia patient population in the memantine trials, and to assess changes in the domains of cognitive performance, ADLs, and global status as the disease progresses.

For these three clinical trials, changes from baseline in the cognition, function, and global measures were analyzed using both the LOCF and OC approaches. In total, 18 separate analyses representing the outcome measures of interest were performed across the key memantine clinical trials. The robust response to memantine was demonstrated by the finding that 17 of the 18 analyses were statistically significant in favor of memantine treatment. This is summarized in Panel 43.

Panel 43. Summary of Efficacy in Key Domains of Cognition, Function, and Global Status

Trial Randomized (N)	*Efficacy Outcome Measure – P-Values for 3 Key Domains*					
	Cognition		*Function*		*Global*	
9605 N = 252	**SIB**		***ADCS-ADL$_{19}$**		***CIBIC+**	
	LOCF	*OC*	*LOCF*	*OC*	*LOCF*	*OC*
	<0.001	0.002	0.022	0.003	0.064	0.025
MD-02 N = 404	***SIB**		***ADCS-ADL$_{19}$**		**CIBIC+**	
	LOCF	*OC*	*LOCF*	*OC*	*LOCF*	*OC*
	<0.001	<0.001	0.028	0.020	0.027	0.028
9403 N = 166	**BGP-Cognitive**		***BGP-Care Dependency**		***CGI-C**	
	LOCF	*OC*	*LOCF*	*OC*	*LOCF*	*OC*
	0.001	0.001	0.012	0.010	<0.001	<0.001
*Protocol-defined primary endpoints						

Based on information from 27 clinical trials and over 600,000 patient years of exposure, memantine has been found to be safe and well-tolerated in the treatment of dementia.

Based on results from the overall memantine clinical development program, and the global post-marketing clinical study and clinical use experience (estimated 600,000 patient years of exposure), there is no evidence for any signals of rare serious safety findings due to memantine treatment. Moreover, memantine exhibited an acceptable safety and tolerability profile in 2297 patients in 27 clinical trials involving a variety of neurodegenerative disorders (e.g., dementia, neuropathic pain, spasticity, and Parkinson's disease). Specifically, a total of 1748 patients were exposed to memantine in the dementia (AD or VaD) and neuropathy clinical trials, and the core double-blind, placebo controlled dementia trials included 922 placebo patients and 940 memantine patients.

In the core dementia trials, approximately 80% of patients in both treatment groups completed the studies. SAEs that were reported in greater than 1% of either treatment group were confusion, inflicted injury, cerebrovascular disorder, fall, and agitation and were not different in incidence between the memantine and placebo treatment groups. Most of the SAEs were considered not to be related to the study drug. The incidence of discontinuation due to AEs was also similar in the placebo and memantine groups. TEAEs which were reported most frequently (> 5% in incidence) by memantine-treated dementia patients and at an incidence greater than placebo patients were dizziness, confusion, headache, and constipation. None of these TEAEs were reported by >7% of memantine-treated patients or at a rate two times higher than in the placebo group. The percentage of AD patients reporting TEAEs was similar in the placebo- and memantine-treated groups. The profile and incidence of TEAEs, as compared to placebo treatment, reported for AD patients receiving memantine as concomitant treatment with donepezil was not different than that observed in AD patients receiving memantine alone.

Analyses of vital sign measurements, clinical laboratory data, and ECG results in the placebo-controlled trials revealed no clinically relevant differences between treatment groups. There was no evidence for any special safety concerns based on the preclinical safety study results or from specific assessments of possible psychotomimetic, neurologic, ophthalmologic, and cardiovascular effects.

Memantine demonstrates linear pharmacokinetic characteristics, is essentially 100% bioavailable by the oral route, is not highly protein bound, does not inhibit CYP 450 isoenzymes, *in vitro*, and is eliminated largely intact in the urine. Given these characteristics, clinically important pharmacokinetic drug-drug interactions with memantine are unlikely. Memantine pharmacokinetics are unaffected by food, age, or sex. No adjustment of dosage is recommended for patients with mild or moderate renal impairment or in hepatically impaired patients.

Memantine at its recommended target dosage of 10 mg BID is well tolerated with a safety profile similar to that of placebo treatment and is effective in providing clinical benefit for patients with moderate to severe Alzheimer's dementia.

8.0 APPENDICES

8.1 Outcome Instruments of Function and Cognition in Key Trials

The actual functional and cognitive assessment tools performed in the three key memantine trials (SIB and ADCS-ADL$_{19}$, Trials 9605 and MD-02; BGP-care dependency subscale, Trial 9403) are included below as representative case report forms from these studies.

8.1.1 Assessment of Function: ADCS-ADL$_{19}$

ACTIVITIES OF DAILY LIVING INVENTORY (ADCS-ADL) - (Page 1 of 4)

Rater's Initials: ☐☐☐

Instructions: For each question, use the patient's name where {S} appears. Before beginning, read the questionnaire guidelines located on the opposite page.

1. Regarding eating:
Which best describes {S} usual performance during the past 4 weeks?
   - ☐ 3 = ate without physical help, and used a knife
   - ☐ 2 = used a fork or spoon, but not a knife, to eat
   - ☐ 1 = used fingers to eat
   - ☐ 0 = usually or always was fed by someone else

2. Regarding walking (or getting around in a wheelchair) in the past 4 weeks, which best describes {S} optimal performance?
   - ☐ 3 = mobile outside of home without physical help
   - ☐ 2 = mobile across room without physical help
   - ☐ 1 = transferred from bed or chair without help
   - ☐ 0 = required physical help to walk or transfer

3. Regarding bowel and bladder function at the toilet, which best describes {S} usual performance during the past 4 weeks?
   - ☐ 3 = did everything necessary without supervision or help
   - ☐ 2 = needed supervision, but no physical help
   - ☐ 1 = needed physical help, and was usually continent
   - ☐ 0 = needed physical help, and was usually incontinent

4. Regarding bathing, in the past 4 weeks, which best describes {S} usual performance?
   - ☐ 3 = bathed without reminding or physical help
   - ☐ 2 = no physical help, but needed supervision/reminders to bathe completely
   - ☐ 1 = needed minor physical help (e.g., washing hair) to bathe completely
   - ☐ 0 = needed to be bathed completely

5. Regarding grooming, in the past 4 weeks, which best describes {S} optimal performance?
   - ☐ 3 = cleaned and cut fingernails without physical help
   - ☐ 2 = brushed and combed hair without physical help
   - ☐ 1 = kept face and hands clean without physical help
   - ☐ 0 = needed help for grooming of hair, face, hands, and fingernails

6. Regarding physically getting dressed, which best describes {S} usual performance in the past 4 weeks?
   - ☐ 4 = dressed completely without supervision or physical help
   - ☐ 3 = dressed completely with supervision, but without help
   - ☐ 2 = needed physical help only for buttons, clasps, or shoelaces
   - ☐ 1 = dressed without help if clothes needed no fastening or buttoning
   - ☐ 0 = always needed help, regardless of clothing type

ACTIVITIES OF DAILY LIVING INVENTORY (ADCS-ADL) - (Page 2 of 4)

7. In the past 4 weeks, did {S} use a telephone?

☐ 0 = No
☐ 0 = Don't know

If Yes; which *best* describes {S} highest level of performance:

☐ 5 = made calls after looking up numbers in white or yellow pages
☐ 4 = made calls only to well-known numbers without referring to a directory or list
☐ 3 = made calls only to well-known numbers, by using a directory or list
☐ 2 = answered the phone; did not make calls
☐ 1 = did not answer the phone, but spoke when put on the line

8. In the past 4 weeks, did {S} watch television?

☐ 0 = No
☐ 0 = Don't know

If Yes; ask all questions;

a. Usually select or ask for different programs or {S} favorite show?
☐ 2 = Yes
☐ 0 = No

b. Usually talk about the content of a program while watching it?
☐ 1 = Yes
☐ 0 = No

c. Talk about the content of a program within a day (24 hours) after watching it?
☐ 1 = Yes
☐ 0 = No

8. In the past 4 weeks, did {S} watch television?

☐ 0 = No
☐ 0 = Don't know

If Yes; ask all questions;

a. Usually select or ask for different programs or {S} favorite show?
☐ 2 = Yes
☐ 0 = No

b. Usually talk about the content of a program while watching it?
☐ 1 = Yes
☐ 0 = No

c. Talk about the content of a program within a day (24 hours) after watching it?
☐ 1 = Yes
☐ 0 = No

9. In the past 4 weeks, did {S} ever appear to pay attention to conversation or small talk for at least 5 minutes?
Note: {S} did not need to initiate the conversation.

☐ 0 = No
☐ 0 = Don't know

If Yes; which *best* describes {S} usual degree of participation:

☐ 3 = usually said things that were related to the topic
☐ 2 = usually said things that were not related to the topic
☐ 1 = rarely or never spoke

ACTIVITIES OF DAILY LIVING INVENTORY (ADCS-ADL) - (Page 3 of 4)

10. Did {S} clear the dishes from the table after a meal or snack?

☐ 0 = No
☐ 0 = Don't know

If Yes; which *best* describes how {S} usually performed:

☐ 3 = without supervision or help
☐ 2 = with supervision
☐ 1 = with physical help

11. In the past 4 weeks, did {S} usually manage to find his/her personal belongings at home?

☐ 0 = No
☐ 0 = Don't know

If Yes; which *best* describes how {S} usually performed:

☐ 3 = without supervision or help
☐ 2 = with supervision
☐ 1 = with physical help

12. In the past 4 weeks, did {S} obtain a hot or cold beverage for him/herself? *(A cold beverage includes a glass of water.)*

☐ 0 = No
☐ 0 = Don't know

If Yes; which *best* describes {S} highest level of performance:

☐ 3 = made hot beverage, usually without physical help
☐ 2 = made a hot beverage, usually if someone else heated the water
☐ 1 = obtained a cold beverage, usually without physical help

13. In the past 4 weeks, did {S} dispose of garbage or litter in an appropriate place or container at home?

☐ 0 = No
☐ 0 = Don't know

If Yes; which *best* describes how {S} usually performed:

☐ 3 = without supervision or help
☐ 2 = with supervision
☐ 1 = with physical help

ACTIVITIES OF DAILY LIVING INVENTORY (ADCS-ADL) - (Page 4 of 4)

14. In the past 4 weeks, did {S} get around (or travel) outside of his/her home?

☐ 0 = No
☐ 0 = Don't know

If Yes; which *best* describes {S} optimal performance:

☐ 4 = alone, went at least 1 mile away from home
☐ 3 = alone, but remained within 1 mile of home
☐ 2 = only when we accompanied and supervised, regardless of the trip
☐ 1 = only with physical help, regardless of the trip

15. In the past 4 weeks, was {S} ever left on his/her own?

☐ 0 = No
☐ 0 = Don't know

If Yes; ask all questions;

Was {S} left:

a. Away from home for 15 minutes or longer during the day?
☐ 1 = Yes
☐ 0 = No

b. At home for an hour or longer during the day?
☐ 1 = Yes
☐ 0 = No

c. At home for less than 1 hour during the day?
☐ 1 = Yes
☐ 0 = No

16. In the past 4 weeks, did {S} usually run water from a faucet to wash {S} hands or face without help?

☐ 1 = Yes
☐ 0 = No

17. In the past 4 weeks, did {S} usually turn off the faucet after finishing running water without help?

☐ 1 = Yes
☐ 0 = No

18. In the past 4 weeks, did {S} usually turn on a light without help when entering a dark room or area?

☐ 1 = Yes
☐ 0 = No

19. In the past 4 weeks, did {S} usually turn off lights without help when leaving a room or going to sleep?

☐ 1 = Yes
☐ 0 = No

8.1.2 Assessment of Cognition: SIB

SEVERE IMPAIRMENT BATTERY (SIB) (Page 1 of 3)			
Rater's Initials: ☐☐☐ **Instructions:** Please circle the appropriate scores from the SIB scoring sheet to the boxes provided.			
1a. Shakes hands	2	1	0
1b. Follows directions	2	1	0
1c. Sit/move to table	2	1	0
2. Examiner's name – immediate	2	1	0
3. Subject's name	2	1	0
4a. Write name	2	1	0
4b. Copy name	2	1	0
5. Month	2	1	0
6. Months of year	2	1	0
7. City	2	1	0
8a. Responsive naming – cup	2	1	0
8b. Responsive naming – spoon	2	1	0
9a. Reading comprehension	2	1	0
9b. Verbal comprehension	2	1	0
9c. Reading	2	1	0
10. Sentence	2	1	0

SEVERE IMPAIRMENT BATTERY (SIB) (Page 2 of 3)			
Instructions: Please circle the appropriate scores from the SIB scoring sheet to the boxes provided.			
11a. Repetition – people spend money	2	1	0
11b. Repetition – baby	2	1	0
12. Digit span	2	1	0
13. Fluency	2	1	0
14. Examiner's name – delayed	2	1	0
15. Confrontational naming – cup	2	1	0
16. Using cup – photograph	2	1	0
17. Object naming – cup	2	1	0
18. Using cup – cup	2	1	0
19. Forced-choice naming – cup	2	1	0
20. Confrontational naming – spoon	2	1	0
21. Using spoon – photograph	2	1	0
22. Object naming – spoon	2	1	0
23. Using spoon – spoon	2	1	0
24. Forced-choice naming – spoon	2	1	0
25. Object - immediate	2	1	0
26. Color naming – blue	2	1	0

SEVERE IMPAIRMENT BATTERY (SIB) (Page 3 of 3)			
Instructions: Please circle the appropriate scores from the SIB scoring sheet to the boxes provided.			
27. Color matching	2	1	0
28. Colored block	2	1	0
29. Color discrimination	2	1	0
30a. Color naming – red	2	1	0
30b. Color naming – green	2	1	0
30c. Shape identification – square	2	1	0
31. Shape matching	2	1	0
32. Shape	2	1	0
33. Shape discrimination	2	1	0
34a. Shape identification – circle	2	1	0
34b. Shape identification – triangle	2	1	0
35a. Drawing – circle	2	1	0
35b. Drawing - square	2	1	0
36. Auditory span	2	1	0
37. Visual span	2	1	0
38. Object – delayed	2	1	0
39. Orienting to name	2	1	0
40. Free disclosure	2	1	0

8.1.3 Assessment of Function: BGP-Care Dependency

The BGP-care dependency subscale of the BGP (Trial 9403) was utilized to assess the patient's capacity to function independently in a broad array of cognitive tasks and daily activities. The BGP-care dependency subscale included the following 23 items of the BGP scale (below): 3, 4, 10, 11, 12, 13, 14, 17, 18, 20, 21, 22, 23, 25, 26, 27, 28, 30, 31, 32, 33, 34, and 35.

The BGP-cognitive subscale was retrospectively identified and analyzed by the sponsor as a measure of cognition in this study. It included five items (#10, 11, 12, 13 and 14) from the BGP scale.

BGP
Rating Scale for Geriatric Patients

Directions
Evaluate the patient's behavior within the last week.
Please mark the appropriate digit and rate all 35 items, even in complicated cases

1. The patient threatens to harm others either verbally (e.g. I get you) or by gestures (e.g. making a fist).
   never |0|
   sometimes |1|
   frequently |2|

2. The patient blames others for doing him harm (e.g. beating, stealing), though that's not true.
   never |0|
   sometimes |1|
   frequently |2|

3. Requires assistance with eating.
   no assistance |0|
   limited assistance |1|
   feeding |2|

4. The patient is urinary or faeces incontinent at daytime.
   never |0|
   sometimes (1-2x/week) |1|
   frequently (more than 1-2x/week or has catheter) |2|

5. The patient beats or kicks others.
   never |0|
   sometimes |1|
   frequently |2|

6. A special support (e.g. soft ties) is required to prevent the patient from falling from chair.
   never |0|
   sometimes |1|
   frequently |2|

7.	The patient disturbs other residents at daytime (e.g. by talking loudly and permanently, by taking objects from others, interfering in affairs of others	never sometimes frequently	|0| |1| |2|
8.	The patient is dejected or has sorrow.	never sometimes frequently	|0| |1| |2|
9.	The patient can walk.	easily slowly without help or using a stick not at all	|0| |1| |2|
10.	The patient makes himself understood (by speaking, writing or gestures).	always sometimes rarely	|0| |1| |2|
11.	The patient finds his way in the nursing home (e.g. to his room, to the toilet, to his/her place at the table).	generally yes some ways yes, others no generally no	|0| |1| |2|
12.	The patient understands in what home or clinic he is.	always sometimes never	|0| |1| |2|
13.	The patient knows the names of the stuff.	more than one only one none	|0| |1| |2|

14.	The patient understands what you communicate to him (by speaking, writing or gestures).	always sometimes never	|0| |1| |2|
15.	The patient helps in the department (e.g. washing dishes, caring for flowers, dusting) or elsewhere (e.g. in the garden, in the laundry, sewing room).	frequently sometimes never	|0| |1| |2|
16.	The patient complains of physical discomfort.	never sometimes frequently	|0| |1| |2|
17.	The patient reacts when being called by his name.	always sometimes never	|0| |1| |2|
18.	The patient keeps self occupied in useful activities out of therapeutic activities (e.g. working, reading, playing games, hobbies, talking to others).	always sometimes never	|0| |1| |2|
19.	The patient starts crying at the slightest reason.	never sometimes frequently	|0| |1| |2|
20.	The patient socializes to one or several other patients.	frequently sometimes never	|0| |1| |2|
21.	The patient urinates or defecates at inappropriate places.	never sometimes frequently	|0| |1| |2|

22.	The patient helps other residents on his own initiative. (e.g. moving the wheel-chair, passing items).	frequently sometimes never	|0| |1| |2|
23.	The patient is cooperative to do what is asked.	frequently sometimes never	|0| |1| |2|
24.	The patient goes for a walk voluntarily.	frequently sometimes never	|0| |1| |2|
25.	The patient always repeats the same movements of no use (e.g. walking to an fro, toddling back and forth, wringing hands, arranging dress).	never sometimes frequently	|0| |1| |2|
26.	The patient makes sounds which are directed to no one. (e.g. screaming, groaning, moaning).	never sometimes frequently	|0| |1| |2|
27.	The patient enters into a conversation on his own initiative.	frequently sometimes never	|0| |1| |2|
28.	The patient is allowed to go out.	unsupervised only together with others not at all	|0| |1| |2|
29.	The patient is angry very quickly.	never sometimes frequently	|0| |1| |2|
30.	The patient drowses during daytime.	never sometimes frequently	|0| |1| |2|

31.	The patient requires assistance with dressing.	none minimal needs being dressed completely	|0| |1| |2|
32.	The patient is urinary or faeces incontinent at night.	never sometimes (1-2x/week frequently (more than 2x/week) or has catheter)	|0| |1| |2|
33.	A special support is required to prevent the patient from falling out of bed (e.g. side rails).	never sometimes frequently	|0| |1| |2|
34.	The patient disturbs other residents at night (e.g. by loud or permanent talking, wandering around, climbing into the bed of another patient).	never sometimes frequently	|0| |1| |2|
35.	The patient is restless at night.	never sometimes frequently	|0| |1| |2|

8.2 Other Efficacy Outcome and Staging Assessments

Global Deterioration Scale (GDS). The GDS[187] is a seven-stage rating scale in which each stage represents a clinical phase ranging from normal to pronounced dementia and for each stage a brief description of clinical characteristics is given. Stage 1 reflects no impairment, Stage 2 reflects very mild impairment, and stages 3 to 7 are defined, respectively, as mild, moderate, moderately severe, severe, and very severe impairment.

Mini Mental State Examination (MMSE). The MMSE[188] is a brief status exam consisting of verbal and performance subtests. Four verbal subtests have a maximum score of 21 points and evaluated orientation in time, memory and attention. Two performance subtests have a maximum score of 9 points and involve naming of objects, execution of written or spoken orders, writing, and copying overlapping pentagons. The total score has a maximum of 30 points.

Functional Assessment Staging (FAST). The FAST[189] scale is specifically designed to assess progressive functional deterioration in AD patients. It evaluates a patient's ability to perform daily and necessary life activities. The FAST is divided into seven major stages, from normality (FAST Stage 1) to severe dementia (FAST Stage 7) scaled to coincide with the seven stages of the GDS in otherwise healthy AD patients. Stages 6 and 7 are further divided into 11 substages (6a to 6e and 7a to 7f). Each stage is based on specific deficits in functional ability.

Clinical Global Impression of Severity (CGI-S). The CGI-S[47] scale assesses the global severity of the patient's current state of mental illness through a descriptive rating based on the clinical opinion of the physician rater. Patients are rated on a 7-point scale with 1 being considered normal and 7 being considered the most extremely ill.

Clinical Global Impression of Benefit/Risk (CGI Benefit/Risk Index). The CGI Benefit/Risk Index[47] is a global impression rating which used a 4-point scale to evaluate the therapeutic efficacy (Efficacy Index) and safety (Risk Index) of the trial medication. For the Efficacy Index, ratings are assigned as follows: 1-3 for very good to minimal improvement and 4 for unchanged or worsened. For the Risk Index, ratings were assigned as: 1 for no side effects, 2 for no significant interference with function, 3 for significant interference, and 4 for side effects that outweighed any therapeutic benefits.

G2 Scale. The G2-Scale is a modified version of the Ferm's D-test[190,191] that was designed to evaluate day-to-day function in geriatric patients. On this 16-item scale, the patient is rated with respect to their motor and cognitive abilities, social behavior, and other activities important in daily life. The degree of care dependency is measured by the G2-condition scale (G2) that was rated on a 6-point scale with higher numbers indicating more severe impairment. The change of each item of the G2 tests relative to baseline at subsequent evaluations was assessed on the 7-point G2 change scale (G2-C) with scores ranging from 1 = very much improved to 7 = very much worsened).

Instrumental Activities of Daily Living (IADL). The IADL[30] is used to assess the ability of patients to perform motor activities of daily living. Five simple subtests are administered: button and unbutton three buttons; open and close three safety pins; make a knot and a bow with a shoelace; apply a plaster (bandage); read and dial a six-digit telephone number. After a practice run (not rated) of each test, the time required to perform each test as well as the quality of performance of each test are rated twice. Quality is assessed on a 3-point scale (1=good, 2=moderate, 3=bad).

Neuropsychiatric Inventory (NPI). The NPI[128] is designed to assess behavioral disturbances occurring in dementia patients, and provides scores for 12 subscales (delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, and aberrant motor activity, night-time behavior, and appetite/eating changes). The NPI was based on responses from an informed caregiver. For each subscale, both the frequency, on a scale of 0 (absent) to 4, and severity, on a scale of 1 to 3 of each behavior was determined. A total subscale score was calculated by multiplying frequency and severity for a patient behavior total score ranging from 0 to 144. A separate subscale of the NPI rated subjective caregiver burden: for each symptom/ subscale, the caregiver's distress was rated on an ordinal scale ranging from 1 to 5 for a total score ranging from 0 to 60. For each domain and for the total score, higher scores reflect greater disability.

8.3 Statistical Methodology

8.3.1 Efficacy Analyses

Efficacy results were presented for three key double-blind, placebo-controlled, dementia trials (Trials 9605, 9403, and MD-02) and supportive trials (Trials 9202 and 9408, and 9605 open label extension). Descriptions of the studies can be found in Section 5.2 of the Briefing Book.

All statistical tests were two-sided with a 5% significance level. The analyses were performed using the LOCF and OC approaches for missing data imputation. A brief overview of the analysis population, key efficacy parameter, and statistical testing employed for these trials is presented in Panel 44.

Panel 44. Summary of the Statistical Methods

Trial	*Definition of the ITT Population Analyzed*	*Efficacy Variables*	*Statistical Test(s)*
CORE DOUBLE-BLIND, PLACEBO-CONTROLLED DEMENTIA TRIALS			
9605	All randomized patients	*CIBIC+ at Week 28	Wilcoxon-Mann-Whitney test
		*ADCS-ADL_{19} change from baseline at Week 28	Wilcoxon-Mann-Whitney test
		SIB change from baseline at Week 28	Wilcoxon-Mann-Whitney test
MD-02	All treated patients with at least one post-baseline SIB or ADL measurement	CIBIC+ at Week 24	Van ElterenTest (stratified by study center)
		*ADCS-ADL_{19} change from baseline at Week 24	Additive ANCOVA model with treatment group and study center as factors and baseline value as covariate
		*SIB change from baseline at Week 24	Additive ANCOVA model with treatment group and study center as factors and baseline value as covariate
9403	All treated patients with one post-baseline measurement of CGI-C or BGP	*CGI-C at Week 12	Van Elteren Test (stratified by study center)
		*BGP-care dependency subscale change from baseline at Week 12	Van Elteren Test (stratified by study center)
		BGP-cognitive subscale change from baseline at Week 12	Van Elteren Test (stratified by study center)
SUPPORTIVE TRIALS			
9202	All treated patients with one post-baseline primary efficacy measurement	*ADAS-cog change from baseline at Week 28	Additive ANCOVA model with treatment group as factor and baseline value as covariate
9408	All treated patients with one post-baseline primary efficacy measurement	*ADAS-cog change from baseline at Week 28	Additive ANCOVA model with treatment group and pooled study center as factors and baseline value as covariate
9605 Long-Term Extension	All entered patients	CIBIC+, ADCS-ADL_{19}, SIB	Descriptive statistics only

* indicates the pre-specified primary efficacy parameters

8.3.2 Safety Analyses

8.3.2.1 Grouping of Studies

Analyses of safety data were performed separately for the Core Clinical Safety Trials, Clinical Pharmacology Trials, and Additional Clinical Trials (see Section 6.0 for a description of the groups of studies).

8.3.2.2 Safety Population

All safety analyses were performed on the Safety Population in the Core Clinical Safety Trials, Clinical Pharmacology Trials, and Additional Clinical Trials (see Section 6.0 for a description of the groups of trials). The Safety Population is defined as all randomized patients who received at least one dose of trial medication.

8.3.2.3 Patient Disposition

The number of patients who discontinued the trial prematurely and the associated reason for discontinuation are presented. The study design for each of these trials, excluding Trial MD-02, allowed for selection of more than one reason for discontinuation. For the purpose of summarizing the reasons for discontinuation, patients with multiple reasons for discontinuation were recoded to one primary reason based on a hierarchy of reasons (Adverse Event, Insufficient Therapeutic Response, Protocol Violation, Withdrawal of Consent, Lost to Follow-up, Other).

8.3.2.4 Demographics and Other Baseline Characteristics

A summary of key demographics and baseline characteristics is presented. Race is summarized as Caucasian and non-Caucasian (Black, Asian, Hispanic, and other), where available. HIS scores and MMSE scores are presented as recorded at Screening for the Core dementia trials.

8.3.2.5 Extent of Exposure

Duration of exposure to trial medication is summarized for the Core Clinical Safety Trials.

Duration of exposure (days) is calculated as the last dose date of double-blind trial medication minus the first dose date of double-blind trial medication plus 1 (for the Core Safety Double-Blind, Placebo-Controlled Trials), and as the last dose date of open-label trial medication minus the first dose date of open-label trial medication plus 1 (for Core Open-Label Extension Dementia Trials).

For Core Safety Trials, patient-years exposure is calculated as the sum of the duration of treatment, divided by 365.25.

8.3.2.6 Concomitant Medication

All medications in the ISS database, with the exception of those in Trial MD-02, were coded using the World Health Organization (WHO) Drug Dictionary, version 1997/Q2. Medications in Trial MD-02 were coded using the WHO Drug Dictionary version Q1/1998.

Medication use at baseline and concomitant medications are presented for Core Clinical Safety Dementia Trials. Medication use at baseline is defined as any medication with start date prior to the first dose date of the double-blind treatment period and continuing during the double-blind period. Concomitant medications are medications started after the first dose of double-blind trial medication or medications at baseline continuing into the double-blind treatment period.

8.3.2.7 Adverse Events

AEs were coded using the World Health Organization Adverse Reaction Terminology (WHO-ART) Dictionary, version 1997/Q3.

TEAEs are defined as AEs which occurred on or after the start date of dosing with double-blind trial medication and within thirty days following the last dose of double-blind trial medication. Additionally, in the Core Double-Blind, Placebo-Controlled Dementia Trials, if an AE occurred prior to dosing, and was also observed after the start of dosing with a higher severity, this AE is also considered a TEAE.

TEAEs are presented by severity (mild, moderate, severe), with missing severity categorizations imputed as 'mild' or 'severe' based on whether the start date for the AE was before or after the date of the first dose of double-blind medication, respectively. TEAEs are also presented by relationship to trial medication, recoded into two categories: not related (including not related, unlikely) and related (including possible, probable, definite, highly probable). For TEAEs with missing relationship to trial medication, a relationship of 'not related' or 'related' was imputed based on whether the start date for the AE was before or after the date of the first dose of double-blind medication, respectively.

An SAE was 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. Other medically important events that required intervention in order to prevent one of the outcomes listed above were also considered serious. For the Trial NTI 9702, SAEs were identified as those AEs requiring inpatient hospitalization or prolonged an existing hospitalization. SAEs and deaths included all events with a start date on or after the date of first dose of double-blind or open-label trial medication and within 30 days of the last dose of double-blind or open-label trial medication.

If the action taken for an AE with regard to trial drug was associated with discontinuation and the AE onset date was on or before the last dose date of trial medication in the double-blind or open-label extension phase, as applicable, then this AE was classified as an adverse

event leading to discontinuation (ADO). Presentation of ADOs includes all AEs which occurred during the trial (including placebo run-in or double blind trial periods).

8.3.2.8 Other Safety Assessments

Hematology and clinical chemistry laboratory parameters, vital signs values (systolic and diastolic blood pressure, pulse rate, and weight), and ECG parameters (PR interval, QRS interval, QT interval, and QTc interval) are presented as descriptive statistics for the Core Clinical Safety Trials. Vital sign, ECG and laboratory parameters are also evaluated for PCS criteria as shown in Panel 45, Panel 46, and Panel 47, respectively.

Panel 45. PCS Criteria for Vital Signs

Vital Sign Parameter	*Observed Value*	*Change Relative to Baseline*
Systolic Blood Pressure	≥180 mm Hg	Increase of ≥20
	≤90 mm Hg	Decrease of ≥20
Diastolic Blood Pressure	≥105 mm Hg	Increase of ≥15
	≤50 mm Hg	Decrease of ≥15
Pulse	≥120 bpm	Increase of ≥15
	≤50 bpm	Decrease of ≥15
Weight	Not Applicable	Increase of ≥7%
	Not Applicable	Decrease of ≥7%

Panel 46. PCS Criteria for ECG Values

Parameter	*PCS Low Criteria*	*PCS High Criteria*
QRS interval (msec)	--	≥ 150
PR interval (msec)	--	≥ 250
QTc interval (msec)	--	*> 500*

Panel 47. 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.
* Trial MD-02 only.

9.0 REFERENCES

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