A 5-month, randomized, placebo-controlled trial of galantamine in AD

P.N. Tariot, MD; P.R. Solomon, PhD; J.C. Morris, MD; P. Kershaw, MD; S. Lilienfeld, FCP (Neuro); C. Ding, PhD; and the Galantamine USA-10 Study Group*

Article abstract—*Objective:* To investigate the efficacy and tolerability of galantamine, using a slow dose escalation schedule of up to 8 weeks, in 978 patients with mild to moderate AD. *Methods:* A 5-month multicenter, placebo-controlled, double-blind trial. Following a 4-week placebo run-in, patients were randomized to one of four treatment arms: placebo or galantamine escalated to final maintenance doses of 8, 16, or 24 mg/day. Outcome measures included the cognitive subscale of the AD Assessment Scale (ADAS-cog), the Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-plus), the AD Cooperative Study Activities of Daily Living inventory, and the Neuropsychiatric Inventory. Standard safety evaluations and adverse event monitoring were carried out. *Results:* After 5 months, the galantamine–placebo differences on ADAS-cog were 3.3 points for the 16 mg/day group and 3.6 points for the 24 mg/day group ($p < 0.001$ versus placebo, both doses). Compared with placebo, the galantamine 16- and 24-mg/day groups also had a significantly better outcome on CIBIC-plus, activities of daily living, and behavioral symptoms. Treatment discontinuations due to adverse events were low in all galantamine groups (6 to 10%) and comparable with the discontinuation rate in the placebo group (7%). The incidence of adverse events in the galantamine groups, notably gastrointestinal symptoms, was low and most adverse events were mild. *Conclusions:* Galantamine 16 and 24 mg/day significantly benefits the cognitive, functional, and behavioral symptoms of AD as compared with placebo. Slow dose escalation appears to enhance the tolerability of galantamine, minimizing the incidence and severity of adverse events. **Key words:** AD—Galantamine—Allosteric modulation—Nicotinic receptors—Acetylcholinesterase inhibition—Randomized controlled trial—Efficacy—Dose escalation—Tolerability.

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The serious and far-reaching consequences of AD have stimulated considerable research into the development of effective treatments. For the last two decades, the primary focus of drug development has been on strategies that enhance central cholinergic function. The basis for this approach is the "cholinergic hypothesis," which proposes a link between the decline in cognitive function and the loss of cholinergic neurotransmission in the hippocampus and cortex of patients with AD.[1,2] Inhibition of acetylcholinesterase (AChE), the enzyme responsible for hydrolysis of acetylcholine (ACh) at the cholinergic synapse, is currently the most established approach to treating AD. Drugs with this mode of action improve cognitive and global function, presumably by augmenting cholinergic function.[2-4]

Galantamine enhances cholinergic function by competitively and reversibly inhibiting AChE.[5,6] Galantamine also potentiates cholinergic nicotinic neurotransmission by allosterically modulating nicotinic acetylcholine receptors (nAChR).[7,8] In vitro, galantamine binds to a site on nAChR that is different from the binding site of the natural agonist, ACh (described as allosteric, meaning "other site").[7,8] When galantamine and ACh bind simultaneously to nAChR, the response of these receptors to ACh is amplified.[7,8] Nicotinic receptors play an important role in memory and learning, and are reduced in patients with AD.[9-11] Therefore, its dual effect on the cholinergic system makes galantamine a promising treatment for AD.

The efficacy and safety of galantamine have been evaluated using daily doses of 24 and 32 mg in a 6-month placebo-controlled trial.[12] At these doses,

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*Members of the Galantamine USA-10 Study Group can be found in the Appendix on page 2275.

From the Department of Psychiatry (Dr. Tariot), University of Rochester Medical Center, NY; Department of Psychology (Dr. Solomon), Williams College, MA, and the Memory Clinic, Southwestern Vermont Medical Center, Bennington, VT; Department of Neurology (Dr. Morris), Washington University School of Medicine, St. Louis, MO; the Janssen Research Foundation (Drs. Kershaw and Ding), Titusville, NJ; and the Janssen Research Foundation (Dr. Lilienfeld), Beerse, Belgium.

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Address correspondence and reprint requests to Dr. Pierre N. Tariot, Department of Psychiatry, Monroe Community Hospital, 435 East Henrietta Road, Rochester, NY 14620.

galantamine was effective and, in the majority of patients, well tolerated. There did not appear to be any difference in efficacy between the 24- and 32-mg doses. The majority of treatment-emergent adverse effects occurred during the 4-week dose escalation period. In clinical practice, slow dose escalation is advocated as a means of improving the tolerability of cholinergic agents.[13] The current 5-month, placebo-controlled study was undertaken in patients with mild to moderate AD to evaluate the efficacy and tolerability of galantamine 16 and 24 mg/day, using a slow dose escalation schedule of up to 8 weeks. A lower dose of galantamine, 8 mg/day, was also studied to test for a dose–response effect.

Methods. *Patients.* Patients were included in the study if they met each of the following criteria: history of cognitive decline that was gradual in onset and progressive over a period of at least 6 months; diagnosis of probable AD according to the criteria of the National Institute of Neurologic and Communicative Disorders and Stroke and AD and Related Disorders Association (NINCDS-ADRDA)[14]; Mini-Mental State Examination score (MMSE)[15] of 10 to 22; *and* score of ≥18 on the standard, 11-item cognitive subscale of the AD Assessment Scale (ADAS-cog).[16]

Patients with concomitant diseases such as hypertension, heart failure (New York Heart Association class I to II), type II diabetes mellitus, or hypothyroidism were included in the study if their illness was controlled. Patients were excluded from the study if they had evidence of any other neurodegenerative disorders; any cardiovascular disease thought likely to prevent completion of the study; clinically significant psychiatric, hepatic, renal, pulmonary, metabolic, or endocrine conditions, or urinary outflow obstruction; an active peptic ulcer; or any history of epilepsy or significant drug or alcohol abuse. At inclusion, a CT or MRI scan not older than 12 months had to be available that showed no signs of clinically significant multi-infarct dementia or active cerebrovascular disease.

Patients who had been treated for AD with a cholinomimetic agent in the preceding 60 days were also excluded. Any other antidementia medication (e.g., chronic use of nonsteroidal anti-inflammatory drugs, selegiline, or estrogens taken without medical need) had to be discontinued before entry to the study, if licensed, and at least 30 days before entry, if unlicensed. The use of drugs for concomitant conditions was permitted during the study, with the exception of sedative–hypnotics and sedating cough and cold remedies, which were discontinued, if possible, 48 hours before cognitive evaluation. Any other drugs with anticholinergic or cholinomimetic effects were avoided.

Eligible patients had a responsible caregiver who, together with the patient (or appropriate representative), provided written informed consent to participate in the study. The study was conducted according to the Declaration of Helsinki and subsequent revisions, and approved by institutional review boards at each center or centrally.

Design. The study was a multicenter, parallel-group, placebo-controlled, double-blind trial undertaken in the United States. Following a 4-week single-blind, placebo run-in period, patients were randomized to one of four treatment arms for 5 months, using a computer-generated code (weeks 1 to 21): placebo for 5 months; galantamine 8 mg/day for 5 months; galantamine 8 mg/day for 4 weeks followed by galantamine 16 mg/day for 17 weeks; galantamine 8 mg/day for 4 weeks, then galantamine 16 mg/day for 4 weeks, and then a maintenance dose of galantamine 24 mg/day from weeks 9 to 21. The galantamine 8 mg/day group was not powered to detect efficacy, but rather to contribute to the test for a dose–response effect. Therefore, according to the randomization ratio, half as many patients were randomly assigned to the galantamine 8 mg/day group as compared with the other three groups. Galantamine and placebo were administered as identical single tablets taken orally twice daily.

Outcome measures. Efficacy. The primary efficacy measures were the standard 11-item ADAS-cog subscale, with a score range of 0 to 70,[16] and the Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-plus).[17] This instrument provides a global impression of the patient's deterioration or improvement over the course of the trial. The CIBIC-plus was scored by a trained clinician, based on separate interviews with the patient and the caregiver. The protocol recommended that the interview order should be standardized. Scores ranged from 1 to 7 (1 = markedly improved compared with baseline; 7 = markedly worse).

Secondary efficacy variables were the following: the proportion of responders, as defined by the Food and Drug Administration (improvement in ADAS-cog of ≥4 points relative to baseline),[18] and the proportion of patients who improved by ≥7 points on ADAS-cog; a 23-item version of the AD Cooperative Study Activities of Daily Living inventory (ADCS/ADL), with a score range of 0 to 78,[19] which was developed to assess daily activities in patients with AD, such as using household appliances, choosing clothes to wear, bathing, and toileting; and the Neuropsychiatric Inventory (NPI), which assesses the frequency and severity of symptoms in 10 behavioral domains (delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, and aberrant motor behavior), with a score range of 0 to 120.[20] These assessments were performed at baseline, at weeks 4 and 13, and at 5 months.

Safety. Safety evaluations throughout the study were comprised of physical examinations, electrocardiography, vital signs, standard laboratory tests, and monitoring for adverse events (classified according to World Health Organization Preferred Terms).

Statistical analysis. Data from an earlier 6-month trial of galantamine[12] indicated that 208 patients were needed in each treatment group to detect a mean difference of three points in the change from baseline in ADAS-cog score between patients in the placebo group and either of the two higher dose galantamine groups with >95% power ($\alpha = 0.05$).

All randomized patients who received at least one dose of trial medication were included in the analyses of baseline characteristics and safety data. The primary statistical analysis of efficacy was of observed cases (OC analysis). This included data from patients who were randomized and were available for evaluation at the designated assessment times. Furthermore, to confirm the robustness of the efficacy results, more conservative intention-to-treat (ITT) analyses were performed using the last observation carried

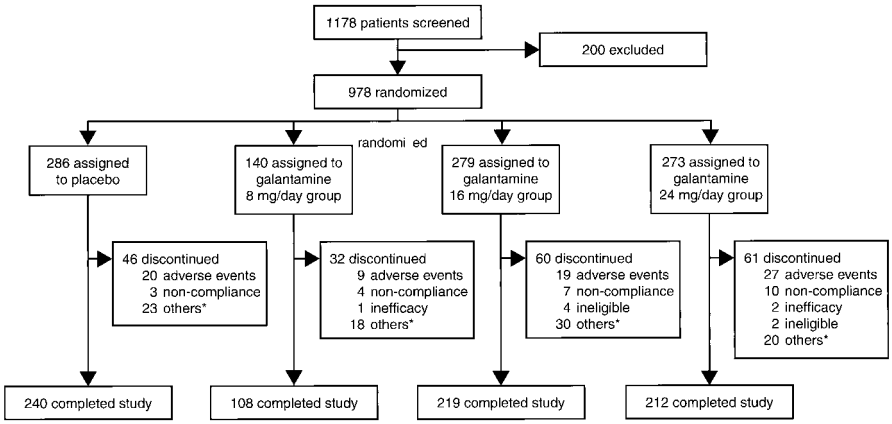

*Figure 1. Trial profile. *The majority of discontinuations due to "other" reasons were for withdrawal of consent.*

forward method (the last postbaseline observation available for each patient who received treatment).

Baseline characteristics of the different treatment groups were compared using two-way analyses of variance (ANOVA) for continuous variables, and the generalized Cochran–Mantel–Haenszel test for categorical variables. Changes in efficacy variables, vital signs, and body weight from baseline were assessed using two-tailed, paired *t*-tests. Comparisons of variables between each galantamine group and the placebo group were made with ANOVA for changes from baseline in ADAS-cog, ADCS/ADL, and NPI scores, including treatment and investigator as factors. An analysis of covariance (ANCOVA) model was also carried out in the analysis of change score, with baseline ADAS-cog value as covariate. The ANCOVA and ANOVA models produced similar conclusions, and therefore the results based on the ANOVA model are reported here. Treatment by investigator interaction was tested and removed from the model as it was not significant at the 5% level. Generalized Cochran–Mantel–Haenszel tests were used to compare ADAS-cog response rates and Van Elteren tests[21] for CIBIC-plus.

For the primary efficacy measures, an *a priori* sequential, step-down, closed testing procedure was used to allow multiple statistical comparisons between each galantamine group (starting with the 24-mg/day group) and the placebo group, while maintaining the Type I error rate (α) at 0.05.[22] In this method, the first hypothesis in the sequence to be tested was the difference between the highest galantamine dose (24 mg/day) and placebo. If the null hypothesis was rejected at the 0.05 level (i.e., galantamine was significantly more effective than placebo), then the sequence continued by testing the second highest dose (16 mg/day) against placebo, and so on. The procedure is stopped if a lack of significance is found at the first or second step. As it is a closed testing procedure, the step-down approach preserves the experiment-wise error rate at 0.05. The same method was used for exploratory comparisons between the two higher dose galantamine groups and the 8-mg/day group for the primary efficacy measures. Analyses were performed using standard statistical software (SAS Institute, Cary, NC).

Results. Figure 1 illustrates the trial profile. Of the 1178 patients screened, 978 were randomized to trial medication, of whom 80% completed the study. The baseline demographic and medical characteristics of the treatment groups were comparable (table 1). Almost all patients (97%) had active comorbid illnesses (mainly cardiovascular, musculoskeletal, and ocular conditions). During the double-blind treatment phase, most patients received concomitant medication (97% in placebo group, 96 to 98% in the galantamine treatment groups). About 27% of the placebo group received antidepressants during the study compared with 26 to 34% in the galantamine groups. The proportions of patients who received other psychotropic medication, such as anxiolytics, hypnotics, and neuroleptics, was also comparable across treatment groups (23% in the placebo group compared with 24 to 27% for the galantamine groups). The proportions of protocol deviations were low (12 to 17%) and similar across treatment groups. Data from one site were excluded from the efficacy analyses (but not the safety analyses) before the database was analyzed, because the investigator failed to adhere to the principles of Good Clinical Practice. Of the 40 patients screened at this site, 32 patients were randomly assigned to the three galantamine groups and 6 patients were randomly assigned to placebo.

Primary efficacy variables. At 5 months, an improvement in cognitive function in galantamine-treated patients compared with placebo-treated patients was observed, with treatment effects in favor of galantamine of 1.7 points (8-mg/day group; $p < 0.05$ versus placebo), 3.3 points (16-mg/day group; $p < 0.001$), and 3.6 points (24-mg/day group; $p < 0.001$), as measured by the ADAS-cog scale (table 2). The superiority of galantamine over placebo was confirmed on ITT analysis for the 16-mg/day and 24-mg/day groups ($p < 0.001$, both comparisons), but not for the 8-mg/day group.

Improvements in ADAS-cog score over baseline with galantamine at the two higher doses were statistically significant at 5 months, reaching a mean improvement from baseline of 1.5 points in the galantamine 16-mg/day group and of 1.8 points in the galantamine 24-mg/day group ($p < 0.001$ for both doses) compared with a deterioration in the placebo group of 1.8 points ($p < 0.001$) (figure 2, table 2). Furthermore, the change in ADAS-cog score from baseline was significantly greater in the two higher dose galantamine groups than the lower dose group at 5 months ($p < 0.05$, 16 mg versus 8 mg; $p < 0.01$, 24 mg versus 8 mg). There was no significant difference between the galantamine 16-mg/day and galantamine 24-mg/day groups in the mean change from baseline in ADAS-cog at 5 months. All of these results were confirmed using the ITT analysis.

Table 1 *Baseline characteristics of the study population by treatment group*

Characteristics	Placebo (n = 286)	Galantamine 8 mg/day (n = 140)	Galantamine 16 mg/day (n = 279)	Galantamine 24 mg/day (n = 273)
Men/women	108/178	50/90	105/174	90/183
Age, y*	77.1 ± 0.5	76.0 ± 0.6	76.3 ± 0.5	77.7 ± 0.4
Weight, kg*	68 ± 0.8	70 ± 1.4	68 ± 0.9	67 ± 0.8
White race, n (%)	267 (93)	132 (94)	260 (93)	249 (91)
Other active medical conditions, n (%)	274 (96)	137 (98)	274 (98)	264 (97)
≥1 *APOE* ϵ4 allele, n (%)	165 (64.7)	80 (62.0)	142 (55.9)	160 (64.5)
Time since cognitive problem diagnosed, y*	4.33 ± 0.15	4.14 ± 0.21	4.22 ± 0.16	3.92 ± 0.16
Time since probable AD diagnosed, y*	1.42 ± 0.10	1.26 ± 0.12	1.42 ± 0.11	1.32 ± 0.11
Total MMSE score*	17.7 ± 0.2	18.0 ± 0.3	17.8 ± 0.2	17.7 ± 0.2
ADAS-cog score*	29.4 ± 0.6	27.8 ± 0.9	29.4 ± 0.7	29.0 ± 0.7
ADCS/ADL score*	52.3 ± 0.9	54.2 ± 1.2	51.6 ± 0.9	51.9 ± 1.0
NPI score*	11.0 ± 0.7	12.9 ± 1.2	12.4 ± 0.8	11.9 ± 0.8

* Values are means ± SEM.

MMSE = Mini-Mental State Examination; ADAS-cog = Alzheimer's Disease Assessment Scale—11-item cognitive subscale; ADCS/ADL = Alzheimer's Disease Cooperative Study Activities of Daily Living inventory; NPI = Neuropsychiatric Inventory.

Using the CIBIC-plus as a measure of overall clinical response to therapy, 64 to 68% of patients in the galantamine 16- and 24-mg/day groups remained stable or improved after 5 months, compared with 47% of those in the placebo group (table 2). At 5 months, the effects of these galantamine dose regimens on CIBIC-plus ratings were significantly better than both placebo ($p < 0.001$, both comparisons) and galantamine 8 mg/day ($p < 0.05$, 16 mg versus 8 mg; $p < 0.01$, 24 mg versus 8 mg). On the ITT analyses, galantamine 16 and 24 mg/day were also superior to both placebo ($p < 0.001$, both comparisons) and galantamine 8 mg/day ($p < 0.05$, both comparisons).

Secondary efficacy variables. The proportions of responders (improvement of ≥4 on ADAS-cog) in the galantamine 16-mg/day (35.6%) and 24-mg/day (37.0%) groups were higher than in the placebo group (19.6%; $p < 0.001$ for both comparisons). Similarly, more patients in these two galantamine groups (22.3% in the 24-mg group and 15.9% in the 16-mg group) than the placebo group (7.6%) improved by ≥7 points on ADAS-cog ($p < 0.01$ for both comparisons), confirmed on ITT analysis. The difference in the proportion of responders (≥7 points) between the 24-mg/day and 16-mg/day groups approached significance on OC analysis ($p < 0.1$).

Table 2 *Efficacy outcomes after 5 months*

	Placebo group		Galantamine 8 mg/day		Galantamine 16 mg/day		Galantamine 24 mg/day	
Assessment	ITT	OC	ITT	OC	ITT	OC	ITT	OC
ADAS-cog: mean (SEM) change from baseline	+1.7 (0.39) (n = 255)	+1.8 (0.43) (n = 225)	+0.4 (0.52) (n = 126)	+0.1 (0.58)* (n = 101)	−1.4 (0.35)‡¶ (n = 253)	−1.5 (0.40)‡§ (n = 208)	−1.4 (0.39)‡¶ (n = 253)	−1.8 (0.44)‡¶ (n = 211)
CIBIC-plus: patients improved/no change, n (%)	128 (49)	112 (47)	68 (53)	54 (51)	169 (66)‡§	143 (68)‡§	162 (64)‡¶	136 (64)‡¶
ADCS/ADL: mean (SEM) change from baseline	−3.8 (0.6) (n = 262)	−4.0 (0.6) (n = 235)	−3.2 (0.8) (n = 129)	−3.1 (0.9) (n = 106)	−0.7 (0.5)‡¶ (n = 255)	−0.5 (0.6)‡§ (n = 212)	−1.5 (0.6)† (n = 253)	−1.6 (0.6) † (n = 212)
NPI: mean (SEM) change from baseline	2.0 (0.7) (n = 262)	2.3 (0.7) (n = 234)	2.3 (1.0) (n = 129)	2.3 (1.1) (n = 106)	−0.1 (0.7)* (n = 255)	−0.1 (0.8)* (n = 211)	0.0 (0.8)* (n = 253)	−0.1 (0.9) * (n = 212)

* $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$ versus placebo; § $p < 0.05$, ¶ $p < 0.01$ versus galantamine 8-mg/day group.

ITT = intention-to-treat analysis; OC = observed case analysis; ADAS-cog = Alzheimer's Disease Assessment Scale—11-item cognitive subscale; CIBIC-plus = Clinician's Interview-Based Impression of Change plus Caregiver Input; ADCS/ADL = Alzheimer's Disease Cooperative Study Activities of Daily Living inventory; NPI = Neuropsychiatric Inventory.

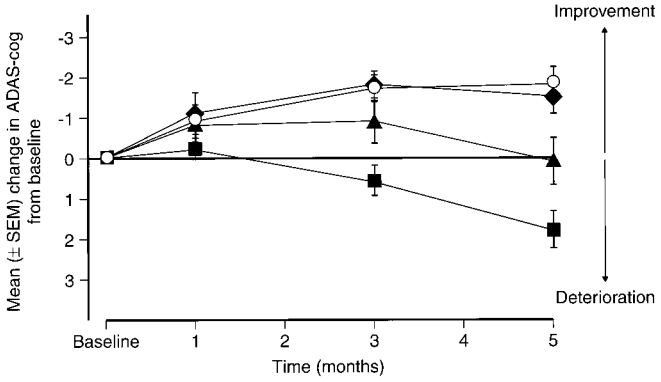

Figure 2. Mean change from baseline in AD Assessment Scale–cognitive subscale (ADAS-cog) scores over time (observed cases analysis). ■ *= placebo;* ▲ *= galantamine 8 mg/day;* ◆ *= galantamine 16 mg/day;* ○ *= galantamine 24 mg/day.*

The 16- and 24-mg/day doses of galantamine had favorable effects on patients' ADL at 5 months, as indicated by a significantly smaller decrease in the ADCS/ADL score than placebo ($p < 0.01$ for both doses versus placebo, OC and ITT analyses) (table 2, figure 3). There was no significant difference between the galantamine 16- and 24-mg/day groups on this measure. At 5 months, patients' ADL were preserved in the galantamine 16-mg/day group, as indicated by a mean change in the ADCS/ADL score from baseline that was not significant (confirmed on OC and ITT analyses). The galantamine 16-mg/day regimen was associated with a significantly smaller decrease in the ADCS/ADL score than the galantamine 8-mg/day regimen ($p < 0.05$ for OC analysis; $p < 0.01$, ITT analysis).

The results of the NPI indicate a significant beneficial effect of galantamine on behavioral symptoms (table 2, figure 4). At 5 months, both the 16- and 24-mg/day groups had significantly better NPI total scores than placebo (OC and ITT analyses; $p < 0.05$, all comparisons). For these two treatment groups, the NPI total scores at 5 months were not significantly different from baseline (confirmed on ITT analysis), whereas the NPI total scores of patients treated with placebo or galantamine 8 mg/day deteriorated compared with baseline ($p < 0.05$, both groups).

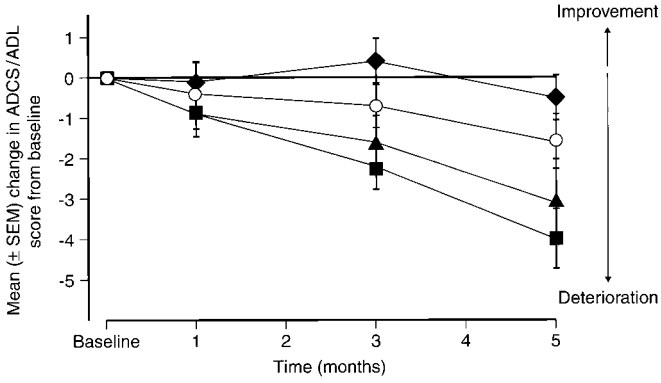

Figure 3. Mean change from baseline in AD Cooperative Study Activities of Daily Living inventory (ADCS/ADL) scores over time (observed cases analysis). ■ *= placebo;* ▲ *= galantamine 8 mg/day;* ◆ *= galantamine 16 mg/day;* ○ *= galantamine 24 mg/day.*

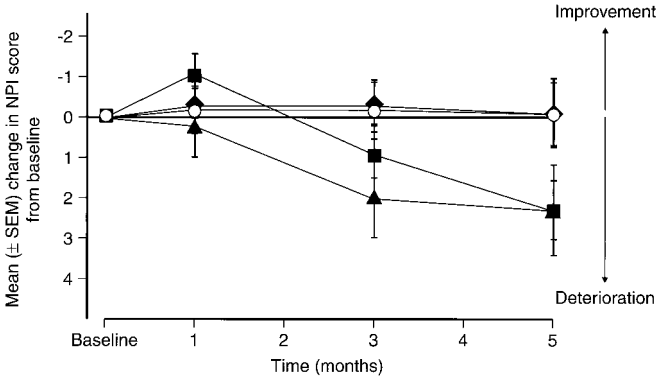

Figure 4. Mean change from baseline in total Neuropsychiatric Inventory (NPI) scores over time (observed cases analysis). ■ *= placebo;* ▲ *= galantamine 8 mg/day;* ◆ *= galantamine 16 mg/day;* ○ *= galantamine 24 mg/day.*

Safety. Galantamine was well tolerated. The rate of discontinuations due to adverse events was similar in galantamine-treated patients and those receiving placebo (10% in the 24-mg/day group, 7% in the 16-mg/day group, and 6% in the 8-mg/day group versus 7% in the placebo group) (see figure 1). The majority of adverse events, including gastrointestinal symptoms, were mild in severity. The proportions of serious adverse events were comparable across treatment groups (10 to 13%), as were deaths (0.7 to 1.4%) (table 3). Adverse events occurring at least 5% more often in any galantamine group than in the placebo group are listed in table 3. There were few reports of muscle weakness in patients receiving galantamine (0.4 to 1.1%) and the incidence was similar to that in the placebo group (1.0%).

There were no clinically relevant differences among treatment groups in any of the hematology, clinical chemistry, or other safety measures. The trends in changes in mean values were similar for the placebo and galantamine treatment groups, including indicators of liver function. There was a slight weight loss in all galantamine groups, which appeared to be dose-related (−1.3 kg with galantamine 24 mg/day; −0.5 kg with galantamine 16 mg/day; −0.5 kg with galantamine 8 mg/day; and −0.1 kg with placebo). In the 24-mg/day group, 11.0% of patients (30/273) lost >7% of body weight compared with 6% (18/279) in the 16-mg/day group, 7% (10/140) in the 8-mg/day group, and 3.5% (10/286) in the placebo group. Only small numbers of patients experienced weight loss of more than 15% of their baseline body weight (2 patients in the placebo group; 1 patient in the galantamine 8-mg/day group; 3 patients in the galantamine 16-mg/day group; and 3 patients in the galantamine 24-mg/day group).

Discussion. This study demonstrates that, relative to placebo, galantamine 16 and 24 mg/day significantly benefits the cognitive, functional, and behavioral symptoms of patients with mild to moderately severe AD. The CIBIC-plus results confirm galantamine's efficacy as judged by skilled clinicians' global impressions. In addition, galantamine is well tolerated when the dose is slowly escalated.

The performance on ADAS-cog of patients receiving galantamine 16 and 24 mg/day was significantly

Table 3 *Number (%) of patients with adverse events occurring at least 5% more often during treatment with any galantamine dose than with placebo*

Adverse event	Placebo (n = 286)	Galantamine 8 mg/day (n = 140)	Galantamine 16 mg/day (n = 279)	Galantamine 24 mg/day (n = 273)
Nausea	13 (4.5)	8 (5.7)	37 (13.3)	45 (16.5)
Vomiting	4 (1.4)	5 (3.6)	17 (6.1)	27 (9.9)
Anorexia	9 (3.1)	8 (5.7)	18 (6.5)	24 (8.8)
Agitation	27 (9.4)	21 (15.0)	28 (10.0)	22 (8.1)
Diarrhea	17 (5.9)	7 (5.0)	34 (12.2)	15 (5.5)
Any adverse event	206 (72.0)	106 (75.7)	206 (73.8)	219 (80.2)
Any serious adverse event	31 (10.8)	14 (10.0)	28 (10.0)	35 (12.8)
Deaths	4 (1.4)	1 (0.7)	3 (1.1)	3 (1.1)

superior to both placebo and galantamine 8 mg/day after 5 months' treatment. Furthermore, galantamine 16 and 24 mg/day produced a sustained improvement in cognitive function, as indicated by significant improvements from baseline on ADAS-cog at 5 months. Additional support for the robustness of this treatment effect came from the ADAS-cog responder analysis, which showed that the galantamine 16- and 24-mg/day groups had significantly more responders than the placebo group. Although patients in the 24-mg/day group received this maintenance dose for only the final 3 months of this study, these data are qualitatively similar to those of a 6-month study of comparable design, which also evaluated the efficacy of the 24-mg/day dose.[12]

Galantamine's positive effects on cognitive symptoms were associated with significant benefits on ADL. The groups of patients who received either the 16- or 24-mg/day dose of galantamine had a significantly better outcome on the ADCS/ADL relative to placebo. In addition, the group of patients who received 16 mg/day of galantamine maintained their baseline level of functional ability at 5 months, as indicated by a mean ADCS/ADL score that was unchanged from the baseline score.

Several types of medication have been evaluated for the treatment of the behavioral and psychological symptoms of dementia. The majority of these studies have been exploratory in nature, and not of sufficient magnitude or rigor to define standards of practice.[23] However, large-scale randomized trials of the atypical antipsychotic risperidone have demonstrated efficacy and safety for the treatment of agitation and psychosis in patients with dementia.[24,25] These trials have typically enrolled patients with severe psychopathology. Similar to other AD studies, which have evaluated the effects of cholinergic treatments on cognition and daily activities, patients enrolled in the current study did not have a high level of behavioral disturbance at baseline. Nevertheless, the results of the NPI recorded in the current study indicate a significantly beneficial effect of galantamine on behavioral symptoms. Unlike the placebo group, the galantamine 16- and 24-mg/day treatment groups did not show a deterioration in behavioral symptoms, as indicated by NPI scores at 5 months that were not significantly different from baseline. These data suggest that cholinergic treatments, such as galantamine, may delay the expected emergence of psychopathology in patients with mild to moderate AD.

Deterioration in the ability to perform daily activities and behavioral symptoms contribute to caregiver burden, increase the utilization of health resources, and influence the decision to institutionalize a patient.[26-28] Therefore, to optimize clinical benefit for both the patient and carer, AD treatments should also improve these noncognitive domains of the illness. The current study indicates that galantamine produces this range of benefits. AChE inhibitors have consistently shown improvements in the cognitive symptoms of AD[29-31] and available data suggest that some members of this class of drug benefit daily activities.[29,30] Open-label studies suggest that tacrine and donepezil ameliorate behavioral symptoms[32,33] and in prospective, double-blind studies, metrifonate has also shown favorable effects on these symptoms.[30,34]

Central cholinergic deficits are thought to contribute to the development of cognitive impairment as well as some of the behavioral symptoms associated with AD.[1,35] Galantamine enhances cholinergic function by modulating presynaptic nAChR[7,8] and by competitively and reversibly inhibiting AChE.[5,6] The extent to which allosteric modulation of presynaptic nAChR contributes to galantamine's range of clinical benefits is uncertain. However, there is considerable evidence that targeting nAChR may be of therapeutic value in patients with AD.[9,36] Recently, presynaptic nAChR have been shown to control the release of ACh, glutamate, monoamines, and GABA.[8,9,36] Thus, direct agonists or allosteric modulators of nAChR may activate not only the cholinergic system, but also other, noncholinergic pathways that are impaired in AD and that contribute to both cognitive and noncognitive symptoms of the illness.[2,36,37] This raises the possibility that, compared with currently

available treatments for AD, galantamine may produce additional clinical benefits. Comparative studies between galantamine and more traditional cholinesterase inhibitors would help to clarify this issue.

This study provides some evidence of a dose–response effect. The 8-mg/day dose produced only modest benefit on cognitive function, which was not confirmed on ITT analysis, and was not associated with significant benefit on any other efficacy variable. Therefore, even if studied in a larger sample size, 8 mg/day is likely to be a subtherapeutic dose. In contrast, the 16- and 24-mg/day doses were clearly effective on all measures of efficacy. There were no clinically significant differences between these two doses on primary efficacy variables. However, at 5 months, the 24-mg/day group, compared with the 16-mg/day group, had more patients who improved by 7 points or more versus baseline on ADAS-cog. This difference in response rate between the two groups approached statistical significance. A longer trial might have detected clearer differences in efficacy between these two doses. Currently, only the long-term effects of the 24-mg/day dose of galantamine have been studied in AD.[12] After 12 months, patients treated with galantamine 24 mg/day had maintained their baseline level of cognitive and functional performance.

One of the main aims of the study was to investigate whether the tolerability of galantamine was improved with slow dose escalation. The slow introduction of galantamine was well-tolerated despite the fact that most patients in the current study had active comorbid conditions and were receiving concomitant medication. There was a low incidence of cholinergically mediated adverse events, particularly those involving the gastrointestinal system. The rates observed were lower than those reported in a previous double-blind trial of galantamine that used more rapid dose escalation.[12] The rates of discontinuations due to adverse events were similar in the galantamine and placebo groups, and the majority of events were mild in severity. Patients in the low-dose galantamine group experienced fewer adverse events than those receiving the 16- or 24-mg/day doses of galantamine. However, there appeared to be little difference in tolerability between the clinically effective doses of 16 and 24 mg/day. This latter finding may reflect the benefits of an 8-week dose escalation period for the 24-mg/day dose of galantamine.

The results of this study demonstrate that, compared with placebo, galantamine benefits the cognitive, functional, and behavioral symptoms of AD. The slow dose escalation enhanced the tolerability of galantamine, minimizing the incidence and severity of adverse events. Galantamine's range of therapeutic effects together with its favorable tolerability profile suggest that this drug will offer important benefits to patients with AD.

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Appendix

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