

# Effects of galantamine in a 2-year, randomized, placebo-controlled study in Alzheimer's disease

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**Background:** Currently available treatments for Alzheimer's disease (AD) can produce mild improvements in cognitive function, behavior, and activities of daily living in patients, but their influence on long-term survival is not well established. This study was designed to assess patient survival and drug efficacy following a 2-year galantamine treatment in patients with mild to moderately severe AD.

**Methods:** In this multicenter, double-blind study, patients were randomized 1:1 to receive galantamine or placebo. One primary end point was safety; mortality was assessed. An independent Data Safety Monitoring Board monitored mortality for the total deaths reaching prespecified numbers, using a time-to-event method and a Cox-regression model. The primary efficacy end point was cognitive change from baseline to month 24, as measured by the Mini-Mental State Examination (MMSE) score, analyzed using intent-to-treat analysis with the 'last observation carried forward' approach, in an analysis of covariance model.

**Results:** In all, 1,024 galantamine- and 1,021 placebo-treated patients received study drug, with mean age ~73 years, and mean (standard deviation [SD]) baseline MMSE score of 19 (4.08). A total of 32% of patients (661/2,045) completed the study, 27% (554/2,045) withdrew, and 41% (830/2,045) did not complete the study and were discontinued due to a Data Safety Monitoring Board-recommended early study termination. The mortality rate was significantly lower in the galantamine group versus placebo (hazard ratio [HR] =0.58; 95% confidence interval [CI]: 0.37; 0.89) ( $P=0.011$ ). Cognitive impairment, based on the mean (SD) change in MMSE scores from baseline to month 24, significantly worsened in the placebo (-2.14 [4.34]) compared with the galantamine group (-1.41 [4.05]) ( $P<0.001$ ). Functional impairment, based on mean (SD) change in the Disability Assessment in Dementia score (secondary end point), at month 24 significantly worsened in the placebo (-10.81 [18.27]) versus the galantamine group (-8.16 [17.25]) ( $P=0.002$ ). Incidences of treatment-emergent adverse events were 54.0% for the galantamine and 48.6% for the placebo group.

**Conclusion:** Long-term treatment with galantamine significantly reduced mortality and the decline in cognition and daily living activities, in mild to moderate AD patients.

**Identification:** This study is registered at ClinicalTrials.gov (NCT00679627).

**Keywords:** cholinesterase inhibitors, cognition, long-term treatment, mortality, nicotinic

## Introduction

Alzheimer's disease (AD) is the sixth leading cause of death in the USA.<sup>1</sup> Although there is extensive literature showing that the currently available treatments can produce mild improvements in cognitive function, behavior, and activities of daily living in patients with AD,<sup>2-4</sup> the influence of antidementia drugs on long-term survival is not

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yet well established. Given that the mainstay of AD treatment remains cholinesterase inhibitors (ChEIs), determination of their impact on mortality remains important. The analyses examining the effect of ChEIs on survival have been largely retrospective or observational.<sup>2,5-7</sup> A recent retrospective, long-term observational study analysis showed decreased mortality with ChEIs in AD patients versus (vs) untreated patients.<sup>8</sup> However, controlled data to date do not suggest that any of the antidementia drugs improves long-term survival.<sup>5,9</sup>

Galantamine HBr (Reminyl®; called Razadyne® in the USA [Janssen Pharmaceuticals, Inc., Titusville, NJ, USA]) is a reversible, competitive ChEI and a positive allosteric modulator of nicotinic receptors.<sup>10</sup> It is approved for the treatment of mild to moderately severe dementia of Alzheimer type in the USA and for AD with cerebrovascular disease in certain other countries.<sup>11,12</sup> Galantamine's efficacy and safety have been documented in pivotal Phase III, double-blind, randomized controlled trials (RCTs) of ≤6 months duration; however, long-term RCTs have not been performed.<sup>13-16</sup>

A comprehensive post hoc analysis of a study for patients with mild cognitive impairment demonstrated no significant difference in survival for those on drug vs placebo, despite an initial impression of increased mortality in the galantamine group.<sup>17</sup> Considering the potential risk raised in this mild cognitive impairment trial, we designed a trial to prospectively assess the long-term survival of patients and efficacy of galantamine, in a 2-year placebo-controlled, randomized study in mild to moderately severe AD patients.

## Materials and methods

### Study design and participants

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study, conducted from May 19, 2008 to May 20, 2012, of galantamine vs placebo in patients with mild to moderately severe AD. The study was conducted at 127 centers in Czech Republic, Estonia, France, Germany, Greece, Italy, Latvia, Lithuania, Romania, Russia, Slovakia, Slovenia, and Ukraine.

The major inclusion criteria were: 1) men or women outpatients, aged 45 to 90 years (inclusive), with mild to moderate, probable or possible AD;<sup>18</sup> and 2) patient with or without cerebrovascular disease, having a computed tomography or magnetic resonance imaging of the head performed since the diagnosis of AD, and before inclusion in the study, a Mini-Mental State Examination (MMSE) score of 10–26, and a responsible caregiver.

Exclusion criteria were: 1) other neurodegenerative or major psychiatric disorders or other causes of demen-

tia, including cerebral trauma, vascular dementia without AD, hypoxic cerebral damage, vitamin deficiency, central nervous system infections, transmissible diseases, primary or metastatic cerebral neoplasia, mental retardation, or significant endocrine or metabolic disease; and 2) epilepsy, hepatic, renal, or pulmonary disturbances, urinary outflow obstruction, or clinically significant cerebrovascular disease.

### Concomitant medications

Memantine and other cognition-affecting medications, including psychotropic drugs, sedatives/hypnotics, antidepressants, antipsychotics, cough and cold remedies, cholinergic agents (disallowed 2 weeks before screening), antiemetics, and antihypertensives with known cognitive side effects, were allowed during the study, but not <1 day before scheduled visits, whenever possible. Galantamine products other than the study drug, experimental agents, or other ChEIs were prohibited.

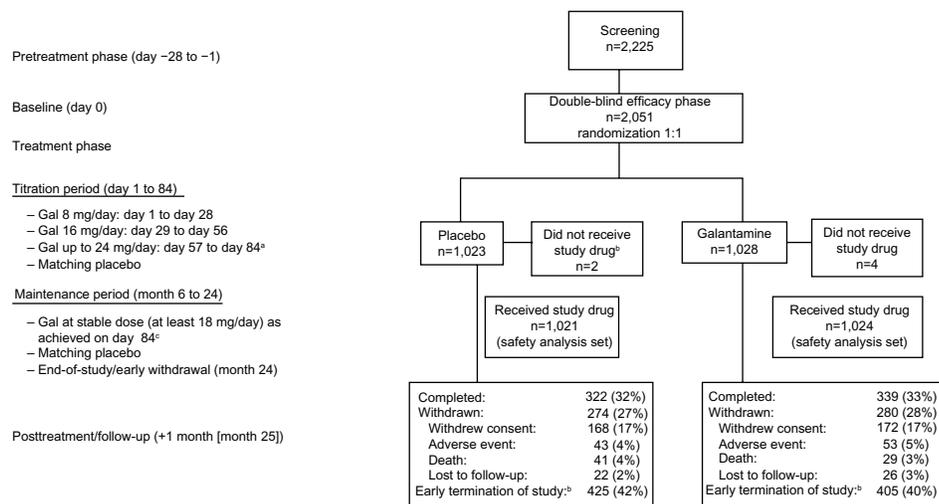
### Standard protocol approvals, registrations, and patient consents

The Independent Ethics Committee or Institutional Review Board at each study site approved the protocol, and the study was conducted in accordance with ethical principles having origin in the Declaration of Helsinki and consistent with Good Clinical Practice (GCP) and applicable regulatory requirements. All patients and caregivers (or legally acceptable representatives) provided written informed consent before entering the study.

### Randomization and blinding

The study consisted of a pretreatment phase of up to 4 weeks, including the screening period, followed by a treatment phase (24 months), which included a 12-week titration period and a maintenance period of approximately 21 months, and a posttreatment follow-up phase (30 days) (Figure 1). Patients were assigned in a 1:1 ratio to either a galantamine or placebo treatment group, based on a computer-generated randomization schedule prepared at Janssen Research and Development, LLC. The randomization was balanced by using randomly permuted blocks and was stratified by study center. An Interactive Voice Response System (IVRS) assigned patients to the study treatment; the assignment codes were maintained within the IVRS to ensure that investigators, patients, and caregivers were blinded.

Galantamine was supplied as oral extended release capsules equivalent to 8 mg, 16 mg and 24 mg with matching placebo, and dosed according to the product labeling.



**Figure 1** Patient disposition.

**Notes:** <sup>a</sup>Uptitration (from 16 mg/day to 24 mg/day) or downtitration (from 24 mg/day to 16 mg/day) of dose was allowed, based on tolerability and the investigator's judgment. Patients unable to tolerate a minimum of 16 mg/day dose were to discontinue treatment and were followed until the end of the maintenance and posttreatment period. The total number of patients included in the safety analysis set was n=2,045; <sup>b</sup>early study termination, per Data Safety Monitoring Board recommendation, when the prespecified number of deaths was ascertained and a significant imbalance favoring galantamine was observed; <sup>c</sup>a one-time dose titration to 16 or 24 mg/day was allowed, based on the investigator's judgment and patient tolerability.

**Abbreviation:** Gal, galantamine.

## Outcomes

### Safety

The primary safety analysis compared the rate of mortality between patients randomly assigned to receive galantamine or matching placebo over the 2-year study. Safety data were monitored during the study by a company-commissioned, external, independent, blinded Data Safety Monitoring Board (DSMB).

Secondary safety outcomes were the number of treatment-emergent adverse events (TEAEs), including serious TEAEs. Clinical laboratory test results, pregnancy tests, vital signs, body weight, physical and neurological examinations, and electrocardiograms were also assessed.

### Efficacy

The MMSE scale (in which the maximum score is 30, with lower scores indicating greater impairment) was used for the primary efficacy variable;<sup>19</sup> assessment was conducted by trained site staff.

The secondary efficacy measures included the score on the Disability Assessment in Dementia (DAD),<sup>20</sup> a 20-item scale measuring activities of daily living (with a higher score representing better performance). The DAD was administered by the caregiver, who was trained in study processes.

## Analyses sets

The intent-to-treat (ITT) analysis set included all randomized patients who had at least one postbaseline MMSE

measure. The per protocol analysis set was a subset of the ITT analysis set and excluded patients with major protocol deviations. The safety analysis set included all randomized and treated patients. After the exclusion of patients from two sites with GCP noncompliance, the ITT data analysis set included 1,812 patients (906 patients in each group), and the per protocol analysis set included 1,729 patients (869 in the galantamine and 860 in the placebo group); all sites' data were included in the safety analyses.

## Statistical evaluations

### Safety analyses

The primary safety end point was the mortality data (all deaths) analyzed by the time-to-event (death) analysis method, using Cox proportional hazards regression model with treatment as covariate. A log-rank test was performed to compare the estimates of the hazard functions of the two groups.

Kaplan–Meier survival curves, relative risk (RR), confidence interval (CI), and summary statistics were also provided. A group sequential method was used to monitor mortality when the total number of deaths reached 16, 32, 48, 64, and 80. If <80 deaths occurred when all patients had completed the study, then the final analysis was to be based on <80 events. If ≥80 events occurred before all enrolled patients had completed the study, the study continued as planned unless the DSMB recommended stopping the study early. The final analysis was to be based on the total number

of events. Additional analyses of the mortality data included a survival analysis of death cases that occurred within 30 days of the last dose of study drug; a Cox proportional hazards regression model that provided a point estimate; and a 95% CI for the hazard ratio (HR) comparing mortality between the treatment groups. An analysis of deaths by baseline characteristics (age, MMSE, time-dependent covariates) was conducted. The TEAEs, vital signs and clinical examinations were monitored. The TEAE terms were coded using MedDRA<sup>®</sup> version 15.0.

### Efficacy analyses

The primary efficacy analysis used the change in MMSE score from baseline to month 24. The secondary end points included MMSE change from baseline to month 6 and change in the DAD scores from baseline to month 24.

An analysis of the ITT cohort with the last observation carried forward (LOCF) approach was used for the primary analysis. For MMSE scores, an analysis of covariance with a two-sided significance level of 0.05 was used to compare the two treatment groups, including treatment and study site as fixed factors and MMSE baseline values as covariates. A similar statistical approach was used for the DAD scores. A mixed-effect modeling analysis was used for the primary end point, as a sensitivity analysis to address missing data and the time course of treatment effect; analysis was based on the observed case data, with no imputation of missing values.

The MMSE scores were also analyzed by use vs nonuse of memantine.

### Sample size determination

Based on 6-month studies and with a two-sided logrank test and a proportional HR assumption, a 3% placebo mortality rate was estimated: a sample size of 1,000 patients per group was to be used to ensure  $\geq 80\%$  power to detect an RR of 2.0. A sample size of 1,000 patients per group would achieve a  $>99\%$  power to detect 0.8 point difference in MMSE between the two treatment groups.

### Results

A total of 2,225 patients were enrolled in the study, and 2,051 were randomized to galantamine or placebo. Of the 2,045 patients who received the study drug (galantamine [n=1,024] or placebo [n=1,021]), 32% (661/2,045) completed the study, while 27% (554/2,045) withdrew; 41% (830/2,045) did not complete the study and were discontinued as a result of the DSMB-recommended study termination

**Table 1** Demographic and baseline characteristics (safety analysis set)

Parameters	Placebo N=1,021 n (%)	Galantamine N=1,024 n (%)
Sex		
Women	654 (64.1%)	671 (65.5%)
Men	367 (35.9%)	353 (34.5%)
Race		
White	1,018 (99.7%)	1,024 (100.0%)
Multiple	1 (0.1%)	0
Other	2 (0.2%)	0
Age (years)		
Mean (SD)	73 (8.7)	73 (8.9)
<61 years	112 (11.0%)	112 (10.9%)
61 to <76 years	467 (45.7%)	466 (45.5%)
$\geq 76$ years	442 (43.3%)	446 (43.6%)
Mean (SD) age at time of probable AD diagnosis	72 (8.78)	71.9 (8.92)
Mean (SD) age at onset of cognitive problem	69.7 (8.96)	69.6 (9.17)
Mean (SD) years since diagnosis of cognitive problems	3.0 (2.69)	2.9 (2.69)
Mean (SD) years since probable diagnosis of Alzheimer-type dementia	0.8 (1.64)	0.8 (1.45)
Smoker		
Currently	54 (5.3%)	55 (5.4%)
In the past	183 (17.9%)	166 (16.2%)
Weight (kg), mean (SD)	70 (12.94)	70 (12.84)
MMSE score		
Mean (SD)	19.0 (4.04)	19.0 (4.12)
<18 group	378 (37.0%)	361 (35.3%)
$\geq 18$ group	643 (63.0%)	663 (64.7%)
DAD score, mean (SD)	60.9 (21.09)	61.8 (21.61)

**Abbreviations:** AD, Alzheimer's disease; DAD, Disability Assessment in Dementia; MMSE, Mini-Mental State Examination; SD, standard deviation.

when the prespecified number of deaths was reached and a significant difference in death rate between treatments was observed (Figure 1).

The demographic and baseline characteristics were comparable between the galantamine and placebo groups (Tables 1 and S1), as were medical histories (Tables S2 and S3). The majority of patients were women (64.8%) and white (99.9%), and the mean (standard deviation [SD]) age of the patients was 73 (8.77) years. The mean (SD) baseline MMSE score was 19.0 (4.08) and DAD score was 61.4 (21.35), suggesting few disabilities in activities of daily living. The majority of patients ( $>80\%$ ) were on concomitant medications that were balanced between the groups. Less than 1% patients (n=8 [0.8%] placebo-treated and n=4 [0.4%] galantamine-treated patients) had received prior ChEIs. Memantine or memantine hydrochloride, was taken by 21.8% of galantamine- and 21.1% of placebo-treated patients.

**Table 2** Extent of exposure to galantamine and placebo

Duration of exposure	Placebo N=1,021 n (%)	Galantamine N=1,024 n (%)	Total N=2,045 n (%)
>24 months	345 (33.8%)	377 (36.8%)	722 (35.3%)
12 to 24 months	277 (27.1%)	248 (24.2%)	525 (25.7%)
6 to 12 months	187 (18.3%)	165 (16.1%)	352 (17.2%)
3 to 6 months	121 (11.9%)	131 (12.8%)	252 (12.3%)
<3 months	91 (8.9%)	103 (10.1%)	194 (9.5%)

The mean duration of study drug exposure was similar in patients receiving galantamine (16.1 months) and placebo (15.9 months). A total 1,247/2,045 (60.98%) patients received >12 months exposure to the study drug (Table 2).

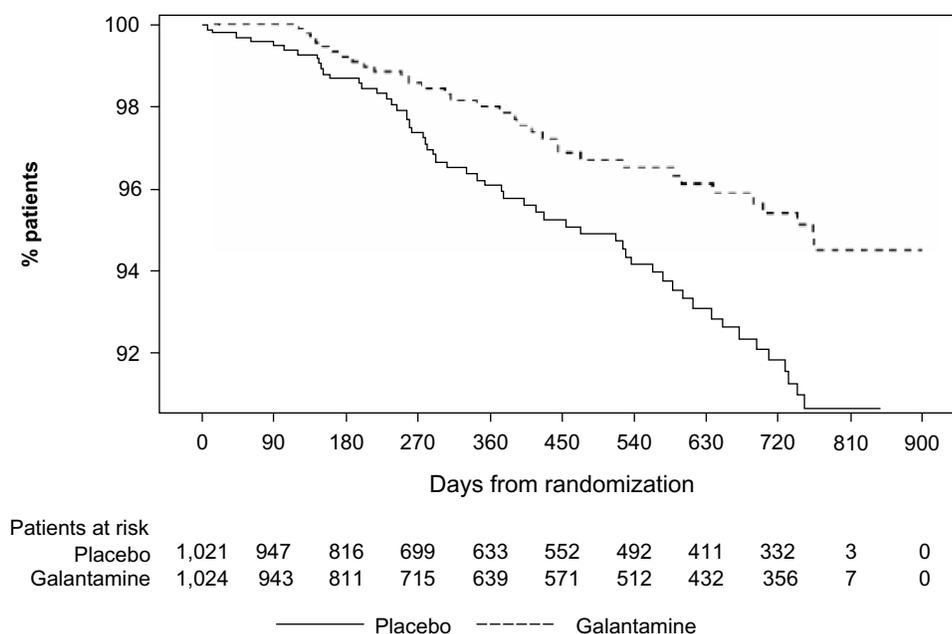
### Safety and tolerability findings

At the final interim mortality analysis (conducted when the study reached the prespecified milestone of 80 deaths), the DSMB recommended early termination due to a statistical difference in deaths between the blinded treatment groups. Subsequent unblinding revealed significantly lower mortality in patients treated with galantamine (3.1%) vs placebo (4.9%) ( $P=0.021$ ). The subsequent final analysis of 89 deaths showed that the 33 (3.2%) deaths in the galantamine group were significantly lower than the 56 (5.5%) deaths in the placebo group (HR =0.58; 95% CI: 0.37; 0.89) ( $P=0.011$ ). Patients receiving galantamine had a significantly higher survival rate than did the placebo-treated patients (Figure 2). Prespecified analyses of the

mortality data in the subgroups, defined by age ( $P=0.798$ ) and MMSE ( $P=0.341$ ), revealed no significant difference. However, the death rate (per 100 patient years) in patients with MMSE <18 was slightly higher (placebo: 7.01, galantamine: 4.82) than those with MMSE  $\geq$ 18 (placebo: 2.63, galantamine: 1.15), consistent with the primary analysis results.

Overall, 54% galantamine-treated patients and 49% placebo-treated patients reported one or more TEAEs, most of which were mild or moderate in severity. The most commonly reported TEAEs in the galantamine group vs the placebo group were nausea (8.4% vs 2.4%) and headache (5.7% in both the groups) (Table 3). Serious TEAEs occurred in similar proportions in both groups (galantamine: 12.6%, placebo: 12.0%), with 11% hospitalizations and 3.0% mortality in the galantamine group, and 8.6% hospitalizations and 4.6% mortality in the placebo group. The TEAEs leading to treatment discontinuation were higher in the galantamine- ( $n=87$  [8.5%]) vs placebo-treated patients (66 [6.5%]) and included nausea (2.0% vs 0.3%) and vomiting (1.0% vs 0.2%).

Of the total 89 deaths, 78 were due to TEAEs; the proportion of TEAEs leading to death tended to be lower in the galantamine ( $n=31$  [3.0%]) vs placebo group (47 [4.6%]). The remaining 11 deaths (two in the galantamine-treated and nine in the placebo-treated group) were due to events that occurred more than 30 days after last study drug intake and hence, not classified as TEAEs. The most frequent TEAEs (galantamine vs placebo) leading to death were cardiac failure

**Figure 2** Time from randomization to death (safety analysis set).

**Table 3** Treatment-emergent adverse events in at least 2% of patients in any treatment group (safety analysis set)

	Placebo N=1,021 n (%)	Galantamine N=1,024 n (%)
Total patients with TEAE	496 (48.6%)	553 (54.0%)
Nausea	24 (2.4%)	86 (8.4%)
Headache	58 (5.7%)	58 (5.7%)
Vertigo	48 (4.7%)	57 (5.6%)
Insomnia	29 (2.8%)	41 (4.0%)
Hypertension	37 (3.6%)	41 (4.0%)
Vomiting	11 (1.1%)	39 (3.8%)
Weight decreased	16 (1.6%)	33 (3.2%)
Decreased appetite	16 (1.6%)	31 (3.0%)
Diarrhea	29 (2.8%)	26 (2.5%)
Nasopharyngitis	20 (2.0%)	24 (2.3%)
Agitation	21 (2.1%)	23 (2.2%)
Fatigue	12 (1.2%)	23 (2.2%)
Anxiety	18 (1.8%)	21 (2.1%)

**Note:** TEAE terms were coded using MedDRA® version 15.0.

**Abbreviation:** TEAE, treatment-emergent adverse event.

(n=4 vs n=3, respectively), cardiopulmonary failure (n=3 vs n=4, respectively), Alzheimer-type dementia worsening (n=3 vs n=5, respectively), and pneumonia (n=3 vs n=2, respectively). Pulmonary or cardiovascular events occurred

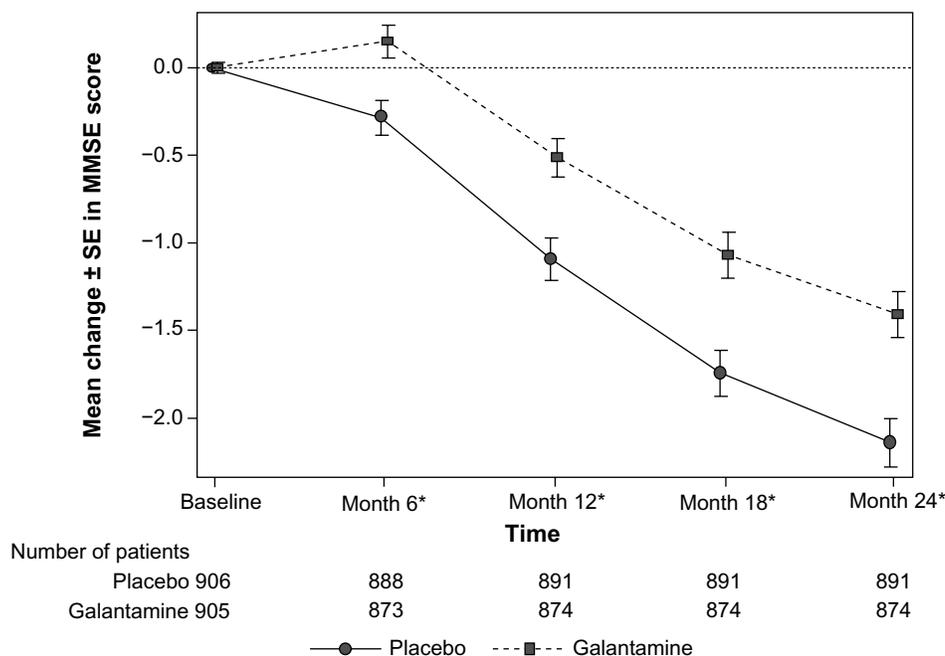
in 265 patients (n=139 in the galantamine-treated vs n=126 in the placebo-treated group). These resulted in the hospitalization of 27 galantamine- and 13 placebo-treated patients, with 17 deaths in galantamine-treated and 24 deaths in placebo-treated patients.

No clinically meaningful changes were observed in vital signs, weight, physical and neurological examination findings, or laboratory tests. No clear pattern or category of TEAEs or adverse events or TEAEs leading to mortality differentiated the galantamine and placebo groups.

### Efficacy findings

#### Primary efficacy

At 24 months, MMSE scores declined significantly less in the galantamine than in the placebo group (-1.41 vs -2.14) ( $P < 0.001$ ) (Figure 3). The analyses including the two noncompliant GCP sites also showed similar results; exclusion of the noncompliant GCP sites did not affect the results. Similar results were observed with analysis of the per protocol analysis set (MMSE scores at 24 months declined less in the galantamine vs the placebo groups [-1.39 vs -2.00;  $P < 0.001$ ]). The results of the sensitivity analysis were consistent with the primary LOCF analysis.



**Figure 3** Mean change in MMSE scores over time (LOCF) (ITT analysis set).

**Notes:** \*Significant difference between galantamine and placebo in MMSE score change from baseline. Two sites (049134 and 049137) were excluded from the analysis due to GCP noncompliance. Estimates of treatment differences (95% CIs) of MMSE using the repeated measures model (OC) were: -0.48 (-0.73 to -0.22) at month 6, and -1.10 (-1.67 to -0.52) at month 24.

**Abbreviations:** CI, confidence interval; GCP, Good Clinical Practice; ITT, intent-to-treat; LOCF, last observation carried forward; MMSE, Mini-Mental State Examination; OC, observed case; SE, standard error.

## Secondary efficacy

The mean (SD) change in MMSE from baseline at month 6 improved significantly in the galantamine (0.15 [2.73]) vs placebo group ( $-0.28$  [2.94]) ( $P < 0.001$ ). The mean (SD) change from baseline in DAD scores showed significant worsening in the placebo vs galantamine group at both prespecified secondary end points: at month 12 LOCF, was  $-6.50$  (16.17) vs  $-4.55$  (14.68) ( $P = 0.009$ ), and at month 24 LOCF, it was  $-10.81$  (18.27) vs  $-8.16$  (17.25) ( $P = 0.002$ ) (Figure 4).

## Additional analyses

In memantine nonusers, galantamine reduced MMSE decline by 1.03 points, nearly half of the decline in placebo patients (galantamine:  $-1.12$  [3.87], placebo:  $-2.15$  [4.41]). Galantamine did not appear to affect MMSE decline in memantine users (memantine + placebo:  $-2.10$  [4.12], memantine + galantamine:  $-2.35$  [4.48]). In placebo patients, the decline in the MMSE at 24 months was similar in memantine users and nonusers (memantine+placebo:  $-2.10$  [4.14], placebo:  $-2.15$  [4.41]) (Table 4).

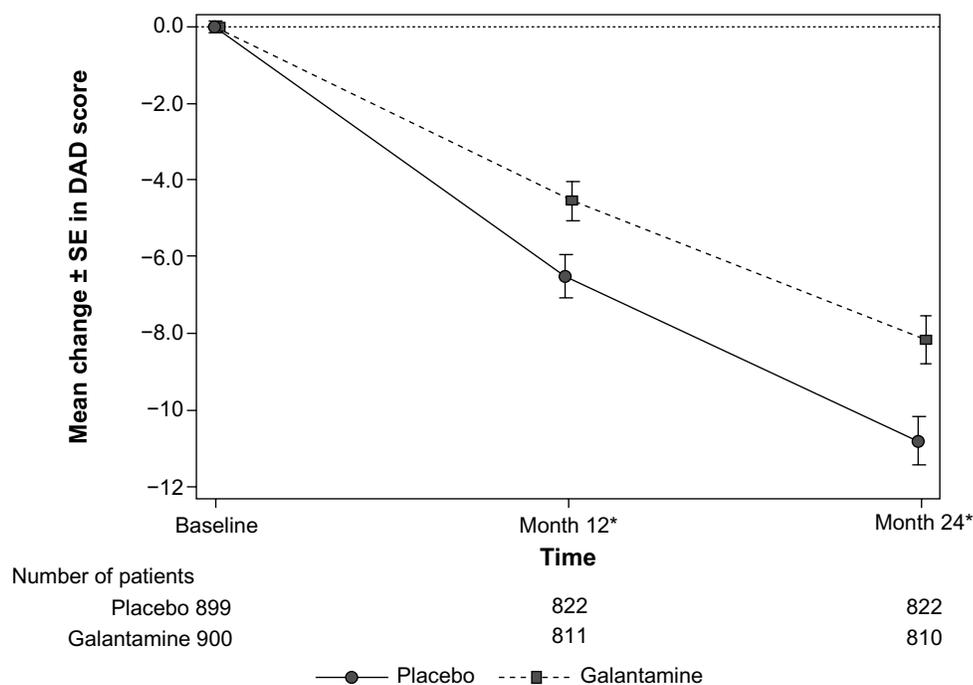
## Discussion

In patients with mild to moderate AD, 2-year treatment with galantamine resulted in a significantly lower mortality rate, a significant reduction of 34% from baseline in cogni-

tive decline, and less decline in activities of daily living by 24% vs placebo. Due to the significant mortality difference between treatment arms, the DSMB recommended early study termination. This is the largest placebo-controlled, randomized, prospective, 2-year study of a member of the class of anticholinesterases in AD to be reported and the first to establish a significantly lower mortality vs placebo.

The reduction in deaths was not attributable to any particular organ system. Except for gastrointestinal galantamine-associated adverse effects, the TEAE and serious TEAE incidences were similar to placebo, and the results corroborate those of other galantamine studies.<sup>5,13–16,21</sup> However, in this study, numerically more frequent hospitalizations were noted in galantamine- vs placebo- treated patients. The improved cognitive benefits, measured in part by the MMSE and DAD, possibly enabled patients to communicate their symptoms better and thus receive timely treatment and may underlie the improved survival that occurred with galantamine treatment. These results are also consistent with data suggesting that worsening functional abilities was the only time-dependent covariate detected that significantly decreased survival in AD patients.<sup>9</sup>

In a separate mild cognitive impairment study, galantamine reduced cortical atrophy by 34% in a subset of the patients who underwent magnetic resonance imaging (MRI)



**Figure 4** Mean change in DAD scores over time (LOCF) (ITT analysis set).

**Notes:** \*Significant difference between galantamine and placebo in DAD score change from baseline. Two sites (049134 and 049137) were excluded from the analysis due to GCP noncompliance.

**Abbreviations:** DAD, Disability Assessment in Dementia; GCP, Good Clinical Practice; ITT, intent-to-treat; LOCF, last observation carried forward; SE, standard error.

**Table 4** Analysis of MMSE at month 24 by concomitant use or nonuse of memantine medication (intent-to-treat analysis set)

	Placebo		Galantamine	
	Concomitant medications with memantine		Concomitant medications with memantine	
	Use	Nonuse	Use	Nonuse
Number of patients	223	683	214	692
Baseline				
N	223	683	213	692
Mean (SD)	18.39 (4.21)	19.20 (3.98)	18.05 (4.25)	19.29 (4.07)
Change from baseline to month 24 LOCF				
N	215	676	202	672
Mean (SD)	-2.10 (4.14)	-2.15 (4.41)	-2.35 (4.48)	-1.12 (3.87)

**Abbreviations:** LOCF, last observation carried forward; MMSE, Mini-Mental State Examination; SD, standard deviation.

scans at baseline and after 2 years, consistent with the reduced MMSE deterioration in the current study.<sup>22</sup> In the *in vitro* studies, galantamine, via positive allosteric modulation of nicotinic receptors, has been shown to protect neurons against amyloid- $\beta$  (A $\beta$ ) and glutamate toxicity, and to promote microglial uptake of A $\beta$  at therapeutic concentrations.<sup>23–25</sup> As late-onset AD, which affected the majority of patients in this study, is characterized by an A $\beta$ -clearance deficit, galantamine's nicotinic mechanism could have contributed to the observed effects.<sup>26</sup>

Our efficacy results corroborate those of previous shorter-term (up to 6 months) RCTs wherein galantamine treatment demonstrated significant improvement in cognitive and global function.<sup>13–16</sup> Although the change in MMSE (0.73) appears small in our study, it is significant and was persistent over 2 years. Galantamine patients' MMSE scores at 24 months were similar to placebo patients' interpolated scores at about 15 months. In memantine nonusers, galantamine MMSE scores at 24 months were approximately those of placebo patients at 13 months. In contrast, memantine appeared to oppose the effects of galantamine so that MMSE declined similarly to placebo in memantine users. Possibly, patients were on memantine in our study because they had failed on ChEIs previously and were not responsive to them. Only 0.4% of galantamine patients had previous ChEI treatment. Alternatively, as memantine is a powerful antagonist of  $\alpha_4\beta_2$  and  $\alpha_7$  nicotinic receptors, our findings may illustrate the importance of nicotinic enhancement in galantamine's mechanism of action.<sup>27,28</sup> In another study in moderate to severe AD, the effects of donepezil, a ChEI without nicotinic modulatory properties, were not reduced by concomitant memantine administration.<sup>29</sup>

The limitations of this study included a lack of information concerning medication compliance, an exclusively white European cohort, and a requirement for a responsible caregiver. As with all clinical trial results, these findings may not be broadly applicable to more diverse sets of patients or treatment conditions experienced in actual clinical practice settings.

Conflicting views exist regarding the class of ChEIs in AD treatment; some favor their long-term use, while others question the clinically meaningful benefits. A recent retrospective observational study analysis from the Swedish Dementia Registry showed decreased mortality in AD patients with ChEI treatment for an average of 500 days, compared with untreated patients; the authors noted that it would be worthwhile if these results could be confirmed in RCTs.<sup>8</sup> Findings of RCTs like the AD2000 study have not confirmed long-term reduced mortality with ChEI-treated as compared with placebo-treated patients.<sup>30</sup> Due to limited controlled-data availability, more long-term ChEI placebo-controlled RCTs are warranted to focus on these outcomes, although ethical concerns are a challenge.

## Conclusion

This study represents the longest placebo-controlled RCT of a ChEI that addresses the issue of mortality. Conducted in over 2,000 patients with mild to moderate AD, it establishes that galantamine treatment resulted in a significantly decreased mortality rate and showed benefits in cognition and activities of daily living that persisted for 2 years.

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## Author contributions

KH was an investigator for this study. JSN and HRB were involved in the original study design and implementation. HMR and ASB were the (responsible) Medical Officers supervising the conduct of the study. JH was the study statistician. MS and BD contributed to the analysis and interpretation and critical revision of the manuscript for important intellectual content.

All authors contributed to the development of the manuscript and approved the final manuscript for submission. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors met the International Council of Medical Journal Editors' criteria for authorship, and anyone who met those criteria is listed as an author.

## Disclosure

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## Supplementary material

**Table S1** Demographic and baseline characteristics (completers analysis set)

Parameters	Placebo N=322 n (%)	Galantamine N=339 n (%)
Sex		
Women	196 (60.9%)	219 (64.6%)
Race		
White	321 (99.7%)	339 (100.0%)
Multiple	1 (0.3%)	0
Other	0	0
Age (years)		
Mean (SD)	72.5 (8.86)	72.5 (9.44)
<61 years	42 (13.0%)	48 (14.2%)
61 to <76 years	147 (45.7%)	145 (42.8%)
≥76 years	133 (41.3%)	146 (43.1%)
Smoker		
Currently	21 (6.5%)	14 (4.1%)
In the past	66 (20.5%)	57 (16.8%)
Weight (kg), mean (SD)	69.9 (13.04)	70.6 (12.77)
MMSE score		
Mean (SD)	19.4 (3.73)	19.3 (4.08)
<18 group	107 (33.2%)	110 (32.4%)
≥18 group	215 (66.8%)	229 (67.6%)
DAD score, mean (SD) <sup>a</sup>	60.5 (21.29)	60.5 (21.08)

**Notes:** <sup>a</sup>Placebo, n=320; galantamine, n=335.

**Abbreviations:** DAD, Disability Assessment in Dementia; MMSE, Mini-Mental State Examination; SD, standard deviation.

**Table S2** Medical history (safety analysis set)

	Placebo	Galantamine
Number of patients	1,021	1,024
Total number of patients with condition <sup>*</sup>	913 (89.4%)	921 (89.9%)
Allergic/immunologic	28 (2.7%)	34 (3.3%)
Cardiovascular	676 (66.2%)	690 (67.4%)
Dermatologic	62 (6.1%)	48 (4.7%)
Endocrine and metabolic	297 (29.1%)	326 (31.8%)
Eyes, ears, nose, and throat	339 (33.2%)	334 (32.6%)
Gastrointestinal	310 (30.4%)	315 (30.8%)
Genitourinary	259 (25.4%)	292 (28.5%)
Hemopoietic/lymphatic	48 (4.7%)	36 (3.5%)
Musculoskeletal	331 (32.4%)	333 (32.5%)
Neurologic	270 (26.4%)	270 (26.4%)
Psychiatric	188 (18.4%)	182 (17.8%)
Respiratory	132 (12.9%)	105 (10.3%)

**Note:** <sup>\*</sup>Medical history and/or currently active condition.

**Table S3** Medical history (completer analysis set)

	Placebo	Galantamine
Number of patients	322	339
Total number of patients with condition <sup>*</sup>	282 (87.6%)	295 (87.0%)
Allergic/immunologic	7 (2.2%)	13 (3.8%)
Cardiovascular	213 (66.1%)	211 (62.2%)
Dermatologic	25 (7.8%)	11 (3.2%)
Endocrine and metabolic	99 (30.7%)	103 (30.4%)
Eyes, ears, nose, and throat	94 (29.2%)	104 (30.7%)
Gastrointestinal	93 (28.9%)	87 (25.7%)
Genitourinary	62 (19.3%)	90 (26.5%)
Hemopoietic/lymphatic	11 (3.4%)	12 (3.5%)
Musculoskeletal	102 (31.7%)	113 (33.3%)
Neurologic	65 (20.2%)	71 (20.9%)
Psychiatric	54 (16.8%)	55 (16.2%)
Respiratory	33 (10.2%)	38 (11.2%)

**Note:** <sup>\*</sup>Medical history and/or currently active condition.

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