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Cessation versus Continuation of Galantamine Treatment after 12 Months of Therapy in Patients with Alzheimer's Disease: A Randomized, Double Blind, Placebo Controlled Withdrawal Trial

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Abstract. Galantamine improved symptoms in Alzheimer's disease (AD) patients after 5 to 6 months of treatment. To examine long-term outcomes, this study assessed if continuing of galantamine treatment beyond 12 months delayed further cognitive deterioration. It consisted of two phases: an open label (OL) phase (12 months), followed by a double blind, randomized, placebo controlled withdrawal phase (up to 24 months). Subjects with mild to moderate AD were included in the study and titrated up to 16 mg/day of galantamine. Subjects were eligible to enter the double blind phase if a cognitive decline of <4 points on AD Assessment Scale-cognitive subscale (ADAS-cog)/11 was recorded at the end of the OL phase. The differences between galantamine and placebo in time to dropout were estimated using the Cox proportional hazard model. 47.4% of galantamine and 31.7% of placebo subjects completed the double blind phase. Placebo subjects were more likely to discontinue prematurely than galantamine subjects for any reason (hazard ratio [HR] 1.76, 95% confidence interval [CI] 1.10–2.81, $p = 0.02$), or lack of efficacy (HR 1.80, 95% CI 1.02–3.18, $p = 0.04$); no statistically significant difference was seen for a change in ADAS-cog $\geq$4 between treatment groups (HR 1.66, 95% CI 0.78–3.54, $p = 0.19$). Subjects who responded to 12 months of galantamine treatment benefited from continued drug therapy for up to 36 months. Galantamine was effective in delaying time to cognitive deterioration in subjects with mild to moderate AD. Treatment was generally safe and well tolerated.

Keywords: ADAS-cog, Alzheimer's disease therapy, cognitive, galantamine, long-term treatment, withdrawal design

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INTRODUCTION

A systematic review of galantamine in Alzheimer's disease (AD) and mild cognitive impairment, including 10 randomized, placebo controlled trials with a duration of longer than 10 weeks and a total of 6805 subjects, confirmed a significant treatment effect of galantamine over placebo with regards to cognition, activities of daily living, and behavioral symptoms at doses between 16 to 24 mg per day [1].

Results from long-term open label extension trials suggest that a subgroup of AD patients treated with galantamine remained stable in the cognitive domain for up to 14 months [2] and that a third of treated patients showed very slow symptom progression up to 48 months [3]. However, most well controlled clinical trials present treatment outcomes at 5 to 6 months, therefore they are limited in the information that can be provided about long-term effects in a chronic disease such as AD. In addition, healthcare decision makers have acknowledged the beneficial outcomes of galantamine but raised doubts about long term effectiveness [4].

In order to examine long-term outcomes in more depth, a clinical trial was conducted to assess whether continuing treatment with galantamine for up to 24 months might result in delaying the cognitive deterioration associated with AD, compared with cessation of treatment after 12 months. At the time of designing the study, there were no placebo controlled long-term studies available to demonstrate efficacy, safety, and tolerability of galantamine over one year of treatment.

METHODS

Subjects

This multicenter study was conducted at 29 study sites in Italy between July 2001 (first subject in) and November 2005 (last subject out).

Subjects were eligible to participate if they were outpatients, aged ≥50 years, and had received a diagnosis of probable AD according to the National Institute of Neurologic and Communicative Disorders and Stroke and AD and Related Disorders Association (NINCDS-ADRDA), with mild to moderate cognitive impairment (Mini Mental State Examination [MMSE] score from 11 to 24). Key exclusion criteria were: presence of a neurodegenerative disorder other than AD, any serious and clinically significant illness, history of previous cerebral infarction, or the use of acetylcholinesterase inhibitors within 3 months before inclusion.

Subjects had to be withdrawn from the study if they showed a cognitive deterioration (≥4 points of the AD Assessment Scale-cognitive subscale [ADAS-cog]/11 score) at the end of the open label phase or during the double blind phase; they or their caregiver withdrew consent; or if the randomization code was broken. Subjects could also have been withdrawn from the study if a serious adverse event (SAE) occurred or if the investigator considered it to be in the best interest of the patient.

Anti-depressants, mood stabilizers, and cholinomimetics were not allowed during the trial. Anti-dementia agents other than study drug were not allowed during the trial: cholinesterase inhibitors (donezepil, tacrine, rivastigmine), nootropics.

All subjects and their caregivers provided written informed consent. The trial was carried out in accordance with guidelines on good clinical practice from the International Conference on Harmonisation (ICH) of technical requirements for registration of pharmaceuticals for human use and was approved by the local ethics committee of each center.

Study design

Overall study duration was 36 months and encompassed two phases: a 12 month open label phase followed by a randomized, double blind, placebo controlled withdrawal phase that lasted for up to 24 months.

Open label phase

During the first four weeks of the open label phase, subjects were titrated from 4 mg bid (8 mg/day) of immediate release galantamine to 8 mg bid (16 mg/day). Tablets were taken in the morning and in the evening, preferably with a meal. Subjects whose cognitive deterioration was less than 4 points in ADAS-cog/11 score at the end of the open label phase compared with the baseline score were eligible to enter the double blind phase.

Double blind phase

During the double blind phase, subjects received galantamine tablets 8 mg bid (16 mg/day) or two placebo tablets, one in the morning and one in the evening. Drug accountability was checked at each visit.

The double blind phase lasted up to 24 months or until subjects met the withdrawal criteria (change in ADAS-cog score ≥4 points compared with the score at the end of the open label phase). If subjects had a

change in ADAS-cog score ≥4, the change had to be confirmed after one month; if subjects met the withdrawal criteria they were withdrawn from the study. If the change was not confirmed after one month, subjects continued their participation in the trial. The flow of participants through the study is shown in Fig. 1.

Randomization and blinding

At the beginning of the open label phase, subjects were given a subject number corresponding to a computer generated randomization code. Subjects were randomly allocated to treatment 1 : 1 (galantamine :

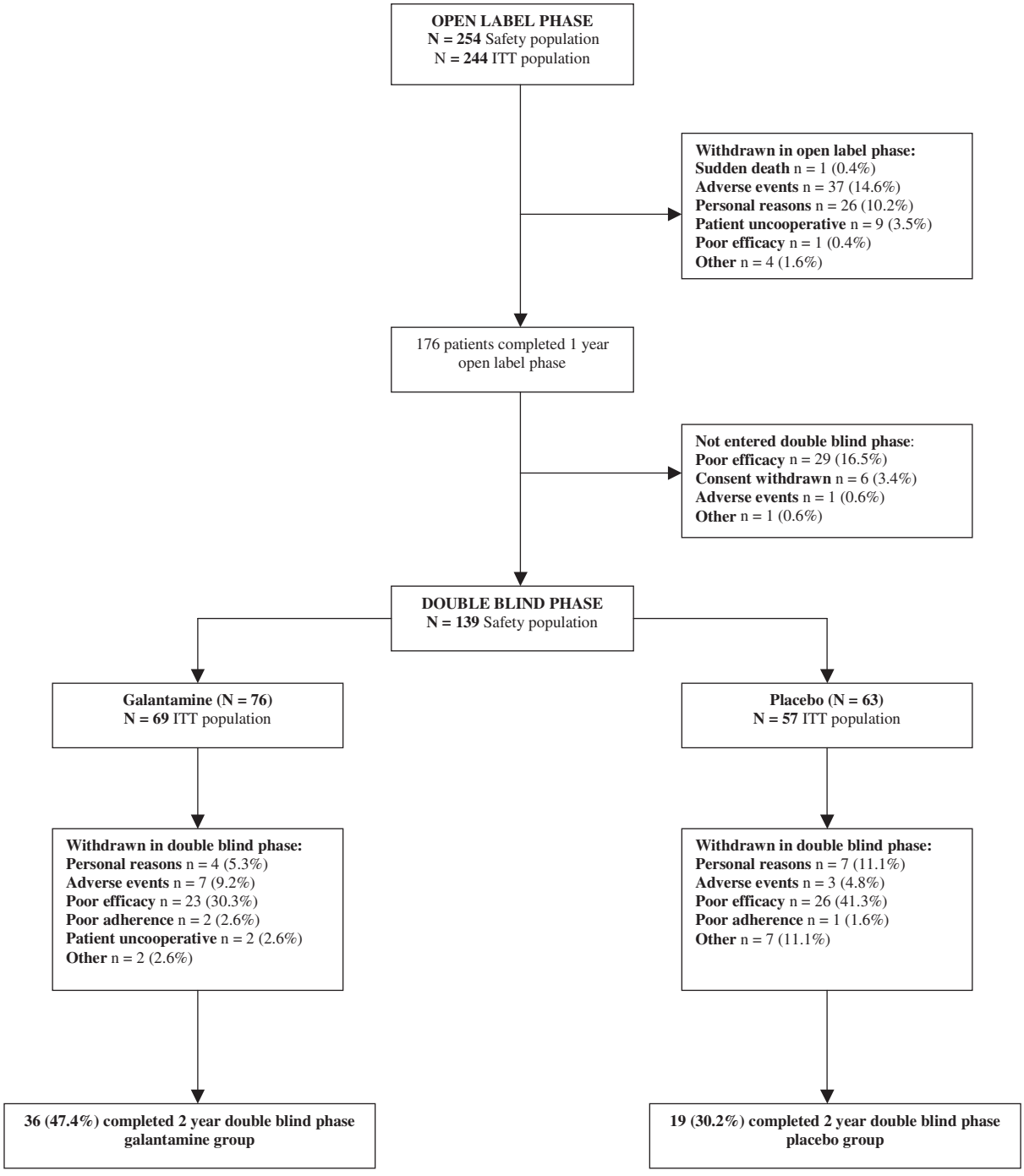

Fig. 1. Flow of participants through the study.

placebo). The randomization code was generated by Janssen Pharmaceutica, Beerse, Belgium. Randomization was balanced between the centers. Each study center received trial medication in blocks of 4 and assigned subject numbers consecutively starting with the lowest available number. Trial medication was provided by Janssen Cilag SpA.

For the double blind phase, centers received boxes containing 27 blisters of 14 tablets each. It was not possible to distinguish boxes containing active drug from those containing placebo. Galantamine and placebo tablets were identical in appearance, taste, and smell.

Assessments

During the open label phase, subjects were assessed at baseline, 1, 4, 7, and 12 months (end of open label phase). The double blind phase started at 12 months and subjects were also assessed at 18, 24, 30, and 36 months (end of double blind phase). The following assessments were conducted throughout the study:

- Cognitive functions measured using ADAS-cog/11 (total score ranging from 0 'no impairment' to 70 'severe impairment')
- Clinical Interview Based Impression of Changes-Plus Caregiver Input (CIBIC-plus; scores range from 1 'very much improved' to 7, 'very much worsened')
- Adverse events (AEs) were spontaneously recorded by subjects or their caregivers
- Hematology, biochemistry, and urinalysis clinical laboratory tests
- Vital signs, physical examination, body weight, and cardiovascular safety.

Statistical methods

Sample size calculation

The sample size was calculated based on an ability to have 90% power to detect a difference between the treatment groups at a significance level of 5% if the median deterioration time was 3 months and 6 months in the placebo and galantamine groups respectively, assuming a 2 year follow-up period. This required 100 patients (50 per group). To allow for an expected dropout rate of 40% during the open label phase of the study and similar numbers of losses to follow-up during the double blind phase, the study planned to recruit an initial total of 255 patients.

Statistical analysis

For the open label phase, the intent-to-treat (ITT) population for the efficacy analysis was defined as all enrolled subjects known to have taken at least one dose of study drug and who attended at least any post baseline visit. The safety population for the open label phase was defined as all enrolled subjects known to have taken at least one dose of study drug.

The analysis of ADAS-cog/11 for the open label phase was done according to an analysis of variance (ANOVA) with repeated measures. Multiple comparisons versus baseline values were done according to Bonferroni's correction and 95% confidence intervals (95% CIs) of the difference versus baseline mean were calculated.

The risk of showing a difference in ADAS-cog/11 score $\geq$4 points in comparison with the baseline value after one year of galantamine treatment was analyzed according to a logistic regression model, where ADAS-cog/11 score at baseline, gender, age, and MMSE were used as independent variables. The dependent variable was the endpoint variable: a difference of ADAS-cog/11 score $\geq$4 points in comparison with the baseline score.

For the double blind phase, the ITT population for the efficacy analysis was defined as all randomized subjects known to have taken at least one dose of blinded study medication and who completed at least one ADAS-cog/11 score. The safety population for the double blind phase was defined as all enrolled subjects known to have taken at least one dose of blinded study medication.

The primary endpoint was the time to deterioration, defined as deterioration in the ADAS-cog/11 score of $\geq$4 points relative to the start of the double blind phase, which had to be confirmed after one month. Patients meeting that criterion were withdrawn from the study. The difference between treatment groups in the time to deterioration was assessed using the Cox proportional hazards model. Patients who completed the study were censored at the time of study completion.

Patients who withdrew from the study prematurely were analyzed in three ways: by dropout for any reason, by dropout due to lack of efficacy, and by dropout due to the strict criteria of deterioration of $\geq$4 points in ADAS-cog/11. For dropout for any reason, all patients who withdrew from the study for any reason were considered to have deteriorated. Regarding dropout due to lack of efficacy, all patients who withdrew from the study for any lack of efficacy reason (including the subjective impression of the caregiver or general practitioner and deterioration of $\geq$4 points in ADAS-

cog/11) were considered to have deteriorated; dropouts for other reasons than lack of efficacy were censored at dropout. For dropout due to ADAS-cog/11 deterioration, all patients who withdrew from the study for confirmed deterioration of ≥4 points in the ADAS-cog/11 score were considered to have deteriorated, and patients who withdrew for other reasons were censored at the time of dropout.

RESULTS

Demographics

Two hundred and fifty four subjects entered the study. Demographic and clinical characteristics for all subjects are presented in Table 1. At baseline, mean MMSE score was 18.9 ± 3.6 and mean ADAS-cog/11 score was 24.7 ± 9.3. The most common co-morbidity was hypertension followed by diabetes.

During the open label phase, 75 subjects (29.5%) did not receive concomitant treatment other than study drug, while the remaining 179 subjects (70.5%) were treated with at least one concomitant drug. During the double blind phase, 23 subjects (30.7%) in the galantamine group and 20 subjects (31.7%) in the placebo group did not receive concomitant treatment other than the study drug. The most commonly administered concomitant medications during both phases of the study were antiinflammatory and analgesic agents. During the open label phase and for the galantamine group in the double blind phase, the second most common were antihypertensive drugs and the third most common were central nervous system agents. For the placebo group, the second most common were central nervous system agents and the third most common were antihypertensive drugs. During the double blind phase, the most commonly received central nervous system agents were atypical antipsychotics and benzodiazepines in the galantamine group and atypical antipsychotics and antidepressants in the placebo group. Antipsychotic use was comparable between the treatment groups (6 patients in the galantamine group and 9 patients in the placebo group). Anti-depressants were contraindicated during the study; however, very few patients received these medications (3 patients in each group).

Table 1
Demographic and clinical data at baseline (for all subjects who entered the open label phase) and at month 12 (for subjects who entered the double blind phase)

Characteristics	Open label phase (baseline)	Double blind phase (month 12)	
		Galantamine	Placebo
	(*n* = 254)	(*n* = 76)	(*n* = 63)
Demographic characteristics			
Age (mean, years)	74.2	74.5	74.4
Gender (% female)	61.4	64.5	54.0
Body mass index (mean)	24.6	24.8[a]	24.9[b]
Education (*n* [%])			
Primary school	180 (70.9)	54 (71.1)	45 (71.4)
Secondary lower school	28 (11.0)	9 (11.8)	8 (12.7)
Secondary upper school	33 (13.0)	12 (15.8)	8 (12.7)
University	13 (5.1)	1 (1.3)	2 (3.2)
Concomitant disease (%)	64.6	77.6	73.0
Clinical characteristics			
MMSE score			
Mean ± SD	18.9 ± 3.6	–	–
Median	19.6	–	–
ADAS-cog/11 score			
Mean ± SD	24.7 ± 9.3	20.4 ± 8.8[c]	23.0 ± 8.7[c]
Median	23.0	19.4[c]	22.3[c]

MMSE, Mini Mental State Examination; ADAS-cog, Alzheimer's Disease Assessment Scale-cognitive subscale; SD, standard deviation. [a] *n* = 75; [b] *n* = 62; [c]ADAS-cog/11 score at start of double blind phase. –, not applicable.

Reasons for withdrawal from both phases of the study are given in Fig. 1. During the open label phase, the majority of withdrawals were due to AEs (37 subjects [14.6%]) followed by personal reasons (26 subjects [10.2%]). During the double blind phase, the most common reason for withdrawal from the study was due to poor efficacy (i.e., the 'lack of efficacy' reason for withdrawal which included the subjective impression of the caregiver or general practitioner and confirmed deterioration of ≥4 points in ADAS-cog/11) for both the galantamine (23 subjects [30.3%]) and placebo (26 subjects [41.3%]) groups.

Efficacy results

Open label phase

One hundred and seventy six subjects completed the open label phase. Cognitive functions improved significantly (measured using the ADAS-cog/11 scale) with galantamine treatment at month 7 relative to baseline (from 24.1 ± 8.7 to 22.9 ± 9.6, difference = –1.2, 95% CI –2.3 to –0.1, $p < 0.01$). Scores were similar to baseline values at the end of the open label phase (month 12) (mean score at baseline = 24.1 ± 8.7, mean score at month12 = 24.7 ± 11.3, 95% CI –0.5 to 1.7, $p = 0.16$). At the end of the open label phase (month 12), CIBIC-plus score improved in 34.3% of subjects, was unchanged in 30.9%, and worsened in 34.9% compared with baseline.

Regression analysis of the risk of showing a difference in ADAS-cog/11 score ≥4 points in comparison with the baseline value after one year of galantamine treatment showed a significant influence ($p < 0.01$) of MMSE score on the probability of showing a difference in ADAS-cog/11 score ≥4. The higher the MMSE score, the lower the probability of cognitive decline (change in ADAS-cog score ≥4).

One hundred and forty one of the 176 subjects who completed the open label phase were responders.

Double blind phase

One hundred and thirty nine of the 141 responders entered the double blind phase of the study and were randomly allocated to galantamine (76 subjects) or placebo (63 subjects). 36 subjects (47.4%) in the galantamine group and 19 subjects (30.2%) in the placebo group completed the double blind phase without showing a change in ADAS-cog score ≥4 points.

One hundred and twenty six of the 139 subjects (69 galantamine subjects and 57 placebo subjects) who entered the double blind phase were included in the final efficacy analysis (ITT population). Thirteen subjects (9.4%) were not included in the ITT population because they dropped out before ADAS-cog/11 could be evaluated in the double blind phase. Reasons for dropout were: sudden death in one subject with myocardial infarction (not considered related to study treatment), SAEs in three subjects (acute lymphoma resulting in death, cerebral hemorrhage resulting in death, and endometrial cancer; none was considered related to study treatment), poor efficacy according to caregiver or private physician for one subject, an AE (depression, not considered related to study drug) in one subject, two subjects were not cooperative, four subjects withdrew owing to subjects reasons, and one subject was lost to follow-up.

Placebo treated subjects were more likely to discontinue the study prematurely than galantamine treated subjects for any reason (hazard ratio [HR] 1.76, 95% CI 1.10–2.81, $p = 0.02$, Table 2 and Fig. 2a) or due to lack of efficacy (HR 1.80, 95% CI 1.02–3.18, $p = 0.04$, Table 2 and Fig. 2b). No statistically significant dif-

Table 2
Cox regression analysis for dropout for any reason, owing to lack of efficacy, and owing to a change in ADAS-cog ≥4

Reason for dropout	Dropouts (*n*)	Hazard ratio	Lower 95% CI	Upper 95% CI	*p*
Any reason	71	1.76	1.10	2.81	0.02
Lack of efficacy	48	1.80	1.02	3.18	0.04
Change in ADAS-cog ≥4	27	1.67	0.78	3.54	0.19

ADAS-cog, Alzheimer's Disease Assessment Scale-cognitive subscale; CI, confidence interval.

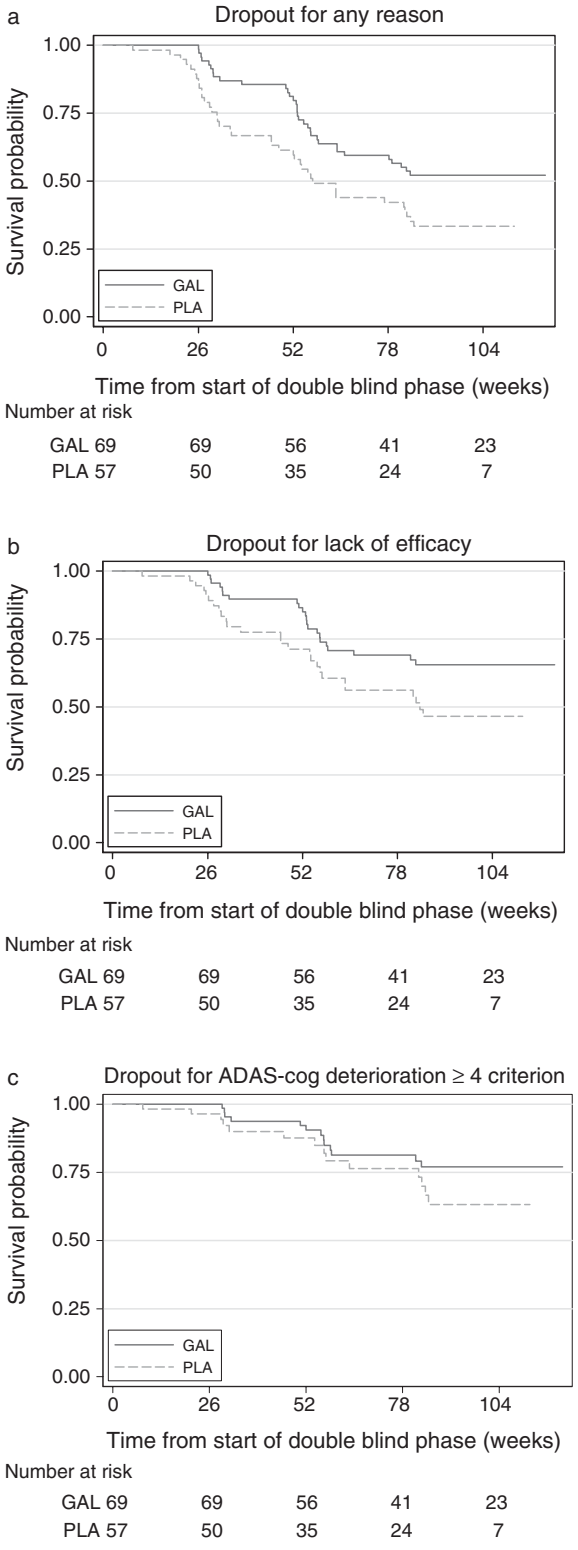

Fig. 2. a) Kaplan-Meier survival curve, dropout for any reason. b) Kaplan-Meier survival curve, dropout due to lack of efficacy. c) Kaplan-Meier survival curve, dropout due to a change in ADAS-cog ≥4.

ference was seen in the likelihood of premature study discontinuation due to a change in ADAS-cog ≥4 between placebo and galantamine treated subjects (HR 1.66, 95% CI 0.78–3.54, $p = 0.19$, Table 2 and Fig. 2c). Median time to dropout was 401 days and 589 days in the placebo group for dropout for any reason and dropout for lack of efficacy, respectively. Median time to dropout was not reached in the active group for either measure because less than 50% of subjects dropped out, therefore it was not possible to calculate median time to dropout. Median time to dropout was also not reached in either group for dropout owing to a change in ADAS-cog/11 score ≥4 points.

No difference was seen between treatment groups concerning mean values of the CIBIC-plus scale.

Safety and tolerability

Open label phase

A summary of AEs is presented in Table 3. One hundred and twenty eight subjects (50.4%) experienced 252 treatment emergent AEs (TEAEs). For 51 subjects (20.1%), the TEAE was considered to be treatment related, as judged by the investigator. Thirty one subjects (12.2%) experienced an SAE. The most frequent TEAEs, summarized by system organ class and individual TEAEs that occurred in > 2% of subjects, and their relationship to study drug are presented in Table 4. The most frequent TEAEs were: gastrointestinal disorders (21.3%), nervous system disorders (9.8%), and psychiatric disorders (19.7%).

Thirty eight subjects (15%) discontinued prematurely during the open label phase. A total of four deaths occurred during the open label phase, none was considered related to study drug. One subject was hospitalized due to acute dyspnea and diffuse lung edema and died due to bronchopneumonia and respiratory failure. Other reported causes of death were: serious scald complicated by bronchopneumonia, acute leukemia, and Creutzfeldt-Jakob disease (confirmed pathologically at autopsy). One subject, who was not eligible to enter the double blind phase (ADAS-cog/11 ≥4), died after completion of the open label phase due to a systemic infection and a concomitant history of prostatic cancer. This death was not included in the 38 subjects who discontinued the open label phase.

No clinically relevant changes were observed in electrocardiogram (ECG) or laboratory variables.

Double blind phase

A summary of AEs is presented in Table 3. Twenty six subjects (34%) in the galantamine group experienced 35 TEAEs and 17 subjects (27%) in the placebo group experienced 30 TEAEs. TEAEs were considered to be treatment related by the investigator in 2 subjects (2.6%) in the galantamine group and 4 subjects (6.3%) in the placebo group. 11 subjects (14.5%) in the galantamine group and 4 subjects (6.3%) in the placebo group experienced an SAE. The most frequent TEAEs by system organ class and individual TEAEs that occurred in > 2% of subjects and their relationship to treatment are presented in Table 4.

Table 3
Summary of adverse events

	Open label	Double blind phase	
	phase n (%)	Galantamine n (%)	Placebo n (%)
Subjects with at least a treatment emergent AE	128 (50.4)	26 (34.1)	17 (27.0)
Subjects with a treatment related AE, as judged by the investigator	51 (20.1)	2 (2.6)	4 (6.3)
Subjects with an AE that led to study discontinuation	38 (15.0)	8 (10.5)	4 (6.3)
Proportion of subjects that experienced an SAE	31 (12.2)	11 (14.5)	4 (6.3)

AE, adverse event; SAE, serious adverse event.

Discontinuation due to an AE occurred in 8 subjects (10.5%) and 4 subjects (6.4%) in the galantamine and placebo groups, respectively. Seven subjects died and the following causes of death were reported in the galantamine group: sudden death in 2 subjects (1 patient with previous myocardial infarction and 1 patient with a recent hip fracture), cerebral hemorrhage in 1 patient, suspected lymphoid leukemia in 1 patient, and gastric carcinoma in 1 patient; causes of death in the placebo group were: cerebral hemorrhage in 1 patient and 1 patient had a cerebral ischemic event with aphasia and dysphasia. None of the deaths during the double blind phase was considered to be treatment related.

No clinically relevant changes in ECG or laboratory variables were observed.

DISCUSSION

The results of this study suggest that galantamine treated subjects stayed on treatment longer than placebo treated subjects and that galantamine was successful in maintaining patients on treatment for an additional 24 months without a significant decline in cognitive deterioration, as defined in this study. In fact, subjects treated with placebo were more likely to discontinue prematurely than subjects treated with galantamine, for any reason (HR 1.76, 95% CI 1.10–2.81, $p = 0.02$) or lack of efficacy (HR 1.80, 95% CI

Table 4
Most frequent adverse events in any system organ class and any individual adverse event that occurred in >2% of subjects with relationship to treatment

System organ class	Adverse event	Open label phase		Double blind phase			
		n (%)		Galantamine *n* (%)		Placebo *n* (%)	
		Not related	Related	Not related	Related	Not related	Related
Cardiac disorders	All	7 (2.8)	2 (0.8)	2 (2.6)	0	0	1 (1.6)
Gastrointestinal disorders	All	16 (6.3)	38 (15.0)	1 (1.3)	0	1 (1.6)	0
	Nausea	5 (2.0)	14 (5.5)	–	–	–	–
	Vomiting	2 (0.8)	15 (5.9)	1 (1.3)	0	–	–
General disorders and administration site conditions	All	11 (4.3)	3 (1.2)	3 (3.9)	0	2 (3.2)	0
Infections and infestations	All	10 (3.9)	1 (0.4)	3 (3.9)	0	2 (3.2)	0
Injury, poisoning, and procedural complications	All	8 (3.1)	0	1 (1.3)	0	–	–
Investigations	All	2 (0.8)	1 (0.4)	3 (3.9)	1 (1.3)	3 (4.8)	1 (1.6)
	Hyperglycemia	–	–	2 (2.6)	0	–	–
Metabolism and nutrition disorders	All	7 (2.8)	4 (1.6)	1 (1.3)	0	1 (1.6)	0
Musculoskeletal and connective tissue disorders	All	11 (4.3)	0	1 (1.3)	0	1 (1.6)	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	All	4 (1.6)	0	3 (3.9)	0	1 (1.6)	0
Nervous system disorders	All	17 (6.7)	8 (3.1)	5 (6.6)	0	7 (11.1)	0
Psychiatric disorders	All	28 (11.0)	22 (8.7)	4 (5.3)	0	5 (7.9)	3 (4.8)
	Anxiety	1 (0.4)	0	–	–	2 (3.2)	0
	Psychomotor agitation	2 (0.8)	5 (2.0)	1 (1.3)	0	0	2 (3.2)
Renal and urinary disorders	All	8 (3.1)	0	–	–	1 (1.6)	0
Respiratory, thoracic, and mediastinal disorders	All	10 (3.9)	0	2 (2.6)	0	–	–
Vascular disorders	All	10 (3.9)	0	3 (3.9)	0	–	–

–, not reported.

1.02–3.18, $p = 0.04$). No statistically significant difference was seen in the likelihood of premature study discontinuation owing to a change in ADAS-cog/11 $\geq$4 between treatment groups (HR 1.66, 95% CI 0.78–3.54, $p = 0.19$). The HR was similar for each analysis; therefore, this shows consistency across analyses.

Deterioration of ADAS-cog/11 was based on just 27 subjects who dropped out owing to ADAS-cog/11 $\geq$4; therefore, the ADAS-cog analysis was underpowered. Forty five subjects withdrew before they reached a cognitive deterioration of ADAS-cog $\geq$4, so it was not possible to know if these subjects would have been eligible for the ADAS-cog/11 survival analysis. Thus, although the recruitment target was met, the number of subjects dropping out for other reasons was higher than expected, therefore affecting the power of the study.

Subjects with a higher MMSE score at baseline were more likely to respond to galantamine treatment and were less likely to show cognitive decline. Also, subjects who responded to treatment after 12 months benefited from continuing treatment with galantamine.

Delaying cognitive deterioration can delay time to nursing home placement (NHP) [5]. A recent study found that the length of treatment with galantamine was associated with a reduced risk of NHP; for each year of treatment with galantamine, the risk of NHP was reduced by 31% [5]. This, and the reduced burden of care for informal caregivers should reduce associated healthcare costs.

Measuring cognitive functions over prolonged periods of time in patients with AD is particularly challenging because of the declining health of subjects, which leads to a large number of dropouts. The present study accounted for this difficulty by using a withdrawal design and measuring time to dropout, which meant that there were no missing data. A weakness of this study was that it was not sufficiently powered for the ADAS-cog/11 survival analysis. Many subjects dropped out before they reached a difference in ADAS-cog/11 $\geq$4; only 27 subjects dropped out when

looking at measured cognitive decline (difference in ADAS-cog $\geq$4).

The withdrawal design of the trial could raise an ethical issue as some subjects positively responding to the drug were randomized to placebo treatment, hence effective treatment was stopped. However, in light of the lack of information in the literature at the time of trial planning, this approach was considered advisable in order to clarify the real efficacy of galantamine in a long-term treatment perspective. All local ethics committees of the 29 clinical centers gave their formal approval to the design in consideration of the importance of continuing the clinical development of galantamine.

It was an unusual design feature that randomization took place at the beginning of the open label phase rather than the double blind phase; however, this does not seem to have negatively affected the study, and the subjects were still well balanced.

In addition, neuropsychiatric and behavioral scales such as the Neuropsychiatric Inventory (NPI) and the Alzheimer's Disease Cooperative Study group – Activities of Daily Living (ADCS-ADL) scale were not included in this study; however, they might have been useful to include to assess the functional status of the patients.

Data from this study has provided supporting evidence that galantamine is well tolerated when used for long term treatment, as seen in other studies [6–8]. The tolerability of galantamine improved with the duration of treatment. Many of the AEs seen in this study were typical of those encountered after administration of cholinesterase inhibitors. There were more deaths in the galantamine group than in the placebo group, but no deaths were considered to be treatment related. These results should be interpreted with caution as data were obtained from a small sample size in a study with a withdrawal design. Therefore, definite conclusions on the safety profile of galantamine in this study cannot be made and data from other studies should be considered for safety and tolerability of galantamine. For example, a meta-analysis of mortality data from double blind, placebo controlled randomized trials and a recontact study to collect longer term mortality data found no evidence of increased risk of mortality associated with the use of galantamine in patients with AD [9].

On the basis of the evidence from this study, and in line with current guidelines [10], treatment should be continued in patients with AD who benefit from galantamine therapy, and interruption of therapy in specific patients should be undertaken with caution. Treatment should only be discontinued if the patient experiences untoward effects.

In conclusion, subjects who responded to 12 months of galantamine treatment benefited from continued drug therapy for up to 36 months. Galantamine was effective in delaying time to dropout due to any reason or for lack of efficacy in subjects with mild to moderate AD. Treatment was generally safe and well tolerated.

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