Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial

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Summary

Background  Vascular dementia is the second commonest form of dementia, and vascular factors contribute to the development of dementia in many patients with Alzheimer's disease. Galantamine amplifies the acetylcholine response by inhibiting acetylcholinesterase and modulating nicotinic receptors. It has shown broad, sustained benefits in patients with Alzheimer's disease. We investigated the effects of galantamine in patients with a diagnosis of probable vascular dementia or Alzheimer's disease combined with cerebrovascular disease.

Methods  Eligible patients were randomly assigned galantamine 24 mg/day (n=396) or placebo (n=196) in a multicentre, double-blind, 6-month trial. Primary endpoints were cognition (Alzheimer's disease assessment scale, cognitive subscale [ADAS-cog]) and global functioning (clinician's interview-based impression of change plus caregiver input [CIBIC-plus]). Secondary endpoints included assessments of activities of daily living and behavioural symptoms. Patients were monitored for adverse events. Analyses were on the basis of observed case or last observation carried forward.

Findings  Galantamine showed greater efficacy than placebo on ADAS-cog (galantamine change -1.7 [SE 0.4] vs placebo 1.0 [0.5]; treatment effect 2.7 points; p<0.0001) and CIBIC-plus (213 [74%] vs 95 [59%] patients remained stable or improved, p=0.001). Activities of daily living and behavioural symptoms were also significantly improved compared with placebo (p=0.002 and p=0.016, respectively). Galantamine was well tolerated.

Interpretation  Galantamine showed a therapeutic effect on all key areas of cognitive and non-cognitive abilities in this group of dementia patients.

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See Commentary page 1265

Introduction

In Europe, dementia is more common than stroke, in terms of both incidence and prevalence. Alzheimer's disease, primarily a neurodegenerative disorder, is the commonest cause of dementia, followed by the vascular dementias.

Vascular dementias are now known to extend beyond the traditional multi-infarct form. In addition to multiple stroke, the pathophysiology incorporates interactions between vascular processes (different types of cerebrovascular disease and vascular risk factors), changes in the brain (white-matter lesions and atrophy), host factors (age, education), and premorbid cognitive ability. The prevalence of mixed vascular dementia, Alzheimer's disease with cerebrovascular disease, has been underestimated, particularly in older populations. In addition to simple coexistence, Alzheimer's disease and vascular dementia have a closer association; they share several vascular risk factors (eg, cerebrovascular disease, arterial hypertension) and vascular pathology in the brain (eg, lacunae, white-matter lesions), which relate to the clinical manifestation of dementia. They also share common pathogenetic mechanisms such as neurotransmitter abnormalities.

One of the key symptoms of dementia is cognitive impairment. Whatever the underlying cause of the particular type of dementia, this impairment results from severe deficits in neurotransmission and degeneration of neuronal circuits in the brain. Therefore, a reasonable approach would be to study in other dementias the effects of drugs that have shown therapeutic benefit in Alzheimer's disease. In all cases studied so far, cognitive deficits involve lower than normal nicotinic cholinergic neurotransmission and numbers of nicotinic receptors.

Until now, there has been no widely accepted standard symptomatic treatment for vascular dementia, and management has focused mainly on preventive measures. Current research will improve the options for primary and secondary prevention of dementia and offers the promise of symptomatic treatment of the clinical manifestations of cerebrovascular damage. Furthermore, since differentiation between Alzheimer's disease and vascular dementia on clinical grounds can be difficult, a treatment that provides benefits to both groups of patients would be valuable. Treatment could be initiated early, to provide maximum benefit, while the results of diagnostic evaluations are awaited.

Galantamine, which inhibits acetylcholinesterase and modulates nicotinic receptors, has shown long-term benefits across several measures of efficacy (cognition, behaviour, and activities of daily living) in patients with dementia of the Alzheimer type. To explore further the therapeutic potential of galantamine, we examined its effects in a mixed population of patients diagnosed as having probable vascular dementia or Alzheimer's...
disease with cerebrovascular disease. Here, we report combined results of galantamine compared with placebo from the complete study population of a 6-month, randomised, placebo-controlled, double-blind study of galantamine. This study will be followed by a 6-month open-label trial, the results of which will be reported separately.

**Methods**

**Patients**

Eligible patients met the clinical criteria of probable vascular dementia of the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) International Workshop (figure 1), or possible Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). They also showed significant radiological evidence of cerebrovascular disease on computed tomography or magnetic resonance imaging (ie, they had Alzheimer's disease and cerebrovascular disease). There was no attempt to favour recruitment of patients with either diagnosis; patients were accepted as they enrolled. The study ran between November 1998 and June 2000. Evidence of cerebrovascular disease on a recent (within 12 months) scan included multiple large-vessel infarcts or a single, strategically placed infarct (angular gyrus, thalamus, basal forebrain, territory of the posterior or anterior cerebral artery), or at least two basal ganglia and white-matter lacunae, or white-matter changes involving at least 25% of the total white matter. In addition, the patients had to meet the following criteria. They had to score 10–25 on the mini-mental state examination and 12 or more on the Alzheimer's disease assessment scale (ADAS-cog). Information had to be available from a carer on the patient's activities of daily living on the disability assessment in dementia scale. The onset of disease had to be between the ages of 40 and 90 years. We required evidence of relevant focal neurological signs consistent with previous stroke and of cerebrovascular disease. The patients had to have, on brain imaging (radiographic), lesions associated with dementia (meeting the NINDS-AIREN criteria); relations between cerebrovascular disease and dementia were defined by onset of dementia within 3 months of a recognised stroke, or abrupt deterioration in cognitive function, or fluctuating, stepwise progression of cognitive deficits.

![Diagram](http://www.elsevier.es, day 22/11/2018. This copy is for personal use. Any transmission of this document by any media or format is strictly prohibited.)
A patient who met the inclusion criteria for this study would not have satisfied those for galantamine studies in Alzheimer’s disease, and vice versa.

Patients were excluded from the study if they had: evidence of neurodegenerative disorders other than Alzheimer’s disease that may cause or contribute to dementia; cognitive impairment resulting from cerebral trauma; or manifest cerebral damage (other than that caused by cerebrovascular disease or cardiac causes of cerebral ischaemia), vitamin deficiency, infections, cerebral neoplasia, mental retardation, or oligophrenia; concomitant cardiovascular disease thought likely to prevent completion of the study; concomitant epilepsy or clinically significant psychiatric, hepatic, renal, pulmonary, metabolic, or endocrine disturbances; an active peptic ulcer; or any history of significant drug or alcohol abuse.

Patients who had received an investigational medication within the previous 30 days were also excluded. Any other antidementia medication (ie, nootropic agents, cholinomimetic agents, choline, or oestrogens prescribed for the treatment of dementia) had to be discontinued before entry to the study.

Patients were eligible only if they had a responsible carer who, in addition to the patient (or a legal representative), provided written informed consent to take part. The study was carried out according to the Declaration of Helsinki and subsequent revisions and was approved by the institutional review boards at each centre or centrally.

Design
This study was a multicentre, placebo-controlled, double-blind trial undertaken in ten countries. After a 4-week, single-blind, placebo-run-in period, patients were randomly assigned placebo or galantamine 24 mg/day for 6 months according to a randomisation code generated by the Janssen Research Foundation.

At the time the study was designed, the optimum dose-escalation scheme (now known to be 4-weekly dose increments of 8 mg/day) had not been confirmed; therefore, a 1-week dose-escalation scheme was used. Patients were started on galantamine 4 mg/day in the first week, with weekly increments of 4 mg/day until they reached 24 mg/day in week 6.

The randomisation ratio was two to one for galantamine versus placebo. Galantamine and placebo were administered as identical single tablets taken orally twice daily.

The primary efficacy measures were the standard 11-item ADAS-cog (ADAS-cog/11), which assesses cognitive ability,19 and the clinician’s interview-based impression of change plus caregiver input (CIBIC-plus).21 The CIBIC-plus scale provides an overall measure of the patient’s condition independently of other assessments. The ADAS-cog/11 was done at screening, baseline, week 6, month 3, and month 6. The CIBIC-plus was done at baseline, month 3, and month 6.

Secondary efficacy measures were the 13-item ADAS-cog (ADAS-cog/13), which includes two additional items (comprehension and concentration/distraction) that were originally part of the separate ADAS-cog behavioural subscale, the disability assessment in dementia,20 and the neuropsychiatric inventory.22 The disability assessment in dementia was developed to assess daily activities in patients with dementia, such as going on an outing, using the telephone, dressing, and eating. The neuropsychiatric inventory assesses the frequency and severity of symptoms in ten behavioural domains. These two instruments were applied at baseline, month 3, and month 6. The ADAS-cog/13 was done at each visit. In addition, the proportions of responders on ADAS-cog/11, defined as those patients with improved or maintained cognitive abilities (change 0 points or more), and the proportions who improved by at least 4 points were calculated at month 6.

To investigate whether baseline severity of dementia affected treatment response at 6 months, ADAS-cog/11 scores at month 6 were further analysed according to baseline score on the mini-mental state examination (less than 18 vs 18 or more).

Safety assessments throughout the study comprised physical examinations, electrocardiography, vital signs, standard laboratory tests, and monitoring for adverse events (classified according to WHO preferred terms).

Statistical analyses
Data from an earlier international trial of galantamine20 indicated that 525 patients were needed (175 on placebo and 350 on galantamine 24 mg/day) for differences between the treatment groups to be detected on the two primary efficacy measures, ADAS-cog/11 and CIBIC-plus, at 5% significance with an overall power of at least 80%.

All randomised patients who received at least one dose of trial medication and had some follow-up data after baseline (the intention-to-treat population) were included in the analyses of baseline characteristics and safety data. The primary statistical assessment of efficacy was an observed-case analysis; it included results from all patients in the intention-to-treat population with observed data at each scheduled assessment visit. To confirm the robustness of the results of the observed-case analysis, a more conservative analysis—last observation carried forward—was done on data from the intention-to-treat population; it imputed missing data points in the post-baseline follow-up visits from the last observation available for each patient who received treatment.

The two primary efficacy measures were compared between treatments in terms of the changes from baseline. Scores on ADAS-cog/11, ADAS-cog/13, neuropsychiatric inventory, and disability assessment in dementia were compared by an a-priori-defined ANOVA model, with treatment and country as factors. Treatment by country interaction was tested and removed from the model, because it was not significant at p=0·05. To test for potential bias due to effects of assessment time and repeated measurements from the same patient on the primary efficacy outcome, a prespecified longitudinal analysis of ADAS-cog/11 was also done with a mixed-effects model (repeated measures with an unstructured variance-covariance matrix) incorporating treatment, country, and time as factors. CIBIC-plus scores were compared by the Van Elteren test24 (controlled for country). Responders on ADAS-cog/11 were analysed by the Cochran-Mantel-Haenszel test23 (controlled for country). As an a-priori-defined secondary analysis, the paired t test was used for within-treatment-group comparisons (baseline vs each visit). A subgroup analysis was done with an ANOVA model to assess consistency in treatment effects, as measured with the ADAS-cog/11, across the study population by baseline score on the mini-mental state examination score (less than 18 vs 18 or more).

Adverse events were summarised in terms of frequency (number of patients who experienced at least one episode during the study), and laboratory data were summarised by type of test. Descriptive statistics were used to assess changes in vital signs, electrocardiographic results, and laboratory data at each scheduled time point.
Analyses were done with standard statistical software (SAS version 6.12).

Role of the funding source
Janssen Research Foundation, in collaboration with the key investigators, participated in development of the study design, and in collection, analysis, and interpretation of data. Janssen Research Foundation and the authors agreed at the outset to publish the results of this study at the earliest available opportunity.

Results
Of the 592 patients who entered the study, 396 were assigned galantamine 24 mg/day and 196 were assigned placebo (figure 2); 74% and 83%, respectively, completed the study.

The two treatment groups were similar in terms of baseline demographic characteristics (table 1). Alzheimer’s disease with cerebrovascular disease was diagnosed in 48% of patients in the galantamine group and 50% of those in the placebo group. Probable vascular dementia was present in 43% and 41%, respectively. In each group, 9% of patients had intermediate diagnoses (these patients satisfied all inclusion criteria and were therefore included in the analyses). There were small differences in ADAS-cog/11 and scores on the mini-mental state examination between the treatment groups at baseline (table 1), but these were not judged clinically significant and did not affect the overall efficacy outcomes (in a secondary ANCOVA).

Concomitant disorders were common (97% and 96% of patients in the galantamine and placebo groups, respectively). The most frequently taken classes of medication were analgesics (73% of galantamine patients and 71% of placebo patients) and antithrombotic agents (67% and 69%). Overall, 23% of patients were taking neuroleptics (24% and 20%) and 28% antidepressants (27% and 30%) at baseline. The intake of medications per class was mostly well balanced between the groups. However, greater proportions of patients in the galantamine group were taking antipsychotic and anticholinergic agents at baseline, particularly domperidone and metoclopramide (5% vs 1% and 3% vs none, respectively).

Of particular interest, 67% of patients in the galantamine group and 71% in the placebo group had concomitant cardiovascular disorders at baseline. As evidence of significant cerebrovascular disease, computed tomography, or magnetic resonance imaging at baseline revealed that 38·9% of patients assigned galantamine and 45·9% of those assigned placebo had territorial infarctions, 47·0% and 40·3% had lacunae, 63·9% and 64·3% had extensive white-matter lesions, and 6·8% and 8·2% had combined vascular lesions (territorial infarctions, lacunae, and extensive white-matter lesions). The proportions of major protocol deviations were low and slightly higher in the placebo group than in the galantamine group (10·2% vs 6·8%). The most frequent major deviation was non-compliance. The proportions of patients continuing in the trial were 84·6% (n=335) in the galantamine group and 92·9% (n=182) in the placebo group at 6 weeks, 79·0% (n=313) versus (89·3% (n=175) at month 3, and 74·2% (n=294) versus 83·2% (n=163) at month 6. Thus, more galantamine patients than placebo patients discontinued the trial, mostly as a result of adverse events (19·7% vs 8·2%). Other reasons for discontinuation were: death (1% vs 3%), withdrawal of consent (2% vs 1%), insufficient response (0% vs 1%), loss to follow-up (0% vs 1%), non-compliance (1% vs 1%), and other reasons (2% vs 3%). At 6 months, patients assigned galantamine had improved in cognitive function relative to baseline and compared with patients assigned placebo (both p<0.0001). At 6 months, the mean improvement in the galantamine group was 1·7 points (p<0·0001), whereas in the placebo group the mean change was deterioration by 1·0 points (p=0·045; table 2, figure 3). The superiority of galantamine over placebo in the whole study population was confirmed with similar significance by standard intention-to-treat analysis (p<0·0001). The robustness of

### Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=196)</th>
<th>Galantamine (n=396)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women/men</td>
<td>91 (46%)</td>
<td>105 (54%)</td>
</tr>
<tr>
<td>Age (mean, SD)</td>
<td>75-2 (7-32)</td>
<td>75-0 (6-84)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>195</td>
<td>395</td>
</tr>
<tr>
<td>Oriental</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Bodyweight (mean, SD)</td>
<td>68-8 (13-7)</td>
<td>71 (13-6)</td>
</tr>
<tr>
<td>Cognitive function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADAS-cog/11 score (mean, SD)*</td>
<td>24-1 (9-9)</td>
<td>22-3 (8-8)</td>
</tr>
<tr>
<td>Sum of MMSE (mean, SD)†</td>
<td>20-2 (3-5)</td>
<td>20-7 (3-7)</td>
</tr>
<tr>
<td>NPI score (mean, SD)‡</td>
<td>11-4 (11-27)</td>
<td>12-2 (12-98)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alzheimer’s disease with cerebrovascular disease</td>
<td>97 (50%)</td>
<td>188 (48%)</td>
</tr>
<tr>
<td>Probable vascular dementia</td>
<td>81 (41%)</td>
<td>171 (43%)</td>
</tr>
<tr>
<td>Intermediate diagnosis§</td>
<td>38 (9%)</td>
<td>37 (9%)</td>
</tr>
<tr>
<td>Concomitant cardiovascular disorders</td>
<td>140 (71%)</td>
<td>267 (67%)</td>
</tr>
<tr>
<td>MMSE=mini-mental state examination; NPI=neuropsychiatric inventory.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Baseline scores were available in 194 patients in placebo group and 388 in galantamine group; baseline scores were available in 186 patients in placebo group and 378 in galantamine group; *tpatients had either vascular dementia or Alzheimer’s disease with cerebrovascular disease—physician did not differentiate between the two conditions.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Trial profile**

- **750 patients assessed for eligibility**
- **158 excluded**
  - 126 did not meet inclusion criteria
  - 14 withdrew consent
  - 18 other reasons
- **592 randomised**
- **196 assigned placebo**
  - 33 lost to follow-up
  - 16 adverse events
  - 5 deaths
  - 1 withdrew consent
  - 1 non-compliance
  - 10 other reasons
- **396 assigned galantamine**
  - 102 lost to follow-up
  - 78 adverse events
  - 4 deaths
  - 6 withdrew consent
  - 4 non-compliance
  - 10 other reasons
- **196 analysed (ITT)**
  - 163 completed 6 months
- **396 analysed (ITT)**
  - 294 completed 6 months
this primary efficacy finding (based on an ANOVA analysis) was confirmed in a predefined secondary analysis (by a mixed-effects model), in which expected mean differences in mean ADAS-cog/11 between galantamine and placebo patients were similar to those observed in the primary analysis. The study was not powered to detect treatment differences in the subgroups; however, a subgroup analysis by diagnosis provided interesting results. In the subgroup of patients with probable vascular dementia, ADAS-cog scores improved from baseline by 2-4 points in those assigned galantamine (p<0.0001), whereas those patients assigned placebo did not differ significantly from baseline at 6 months (treatment difference 1-9 points, p=0.06; table 3). In the subgroup of patients with Alzheimer’s disease and cerebrovascular disease, ADAS-cog scores of galantamine-group patients significantly improved over those of patients assigned placebo (treatment difference 2-7 points, p=0.0006) and over baseline (p=0.024), whereas scores of patients assigned placebo deteriorated significantly below baseline (table 3). The proportion of ADAS-cog/11 responders, defined as those patients with improved or maintained cognitive abilities at 6 months, was significantly higher in the galantamine group than in the placebo group (63.8% vs 50.6%, p=0.006). The proportion of patients responding by at least 4 points on the ADAS-cog II scale was also higher in the galantamine group (35.3% vs 22.2%, p=0.005).

Galantamine was effective in mildly and moderately demented patients. In the subgroup of patients with a baseline score on the mini-mental state examination of less than 15 points, those assigned placebo deteriorated on the ADAS-cog/11 scale by 2-5 points, whereas those assigned galantamine improved by 0-8 points (treatment difference 3-3 points, p=0.019) at month 6. Similarly, in the subgroup of patients with a baseline score on the mini-mental state examination of 18 points or more, those assigned placebo deteriorated by 0-6 points and those assigned galantamine improved by 1-9 points (treatment difference 2-5 points, p=0.0002). As with the primary efficacy findings in the overall population, the significance of the changes in these subgroups was confirmed by testing the consistency of treatment effects across the study populations. In an ANOVA analysis, there was no significant interaction between baseline score on the mini-mental state examination and treatment.

ADAS-cog/13 also showed a significant improvement with galantamine treatment compared with placebo (p<0.0001, table 2). Scores of patients assigned galantamine improved compared with baseline by 2-4 points, while those assigned placebo were slightly below baseline (0-9 points). This superiority was confirmed by standard intention-to-treat analysis (p<0.0001).

Table 2: Efficacy outcomes in the total population after 6 months

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Placebo (n=196)</th>
<th>Galantamine (n=396)</th>
<th>Treatment difference</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SE) change from baseline</td>
<td>1-0 (0-5)</td>
<td>−1-7 (0-4)</td>
<td>2-7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ADAS-cog/11*</td>
<td>0-9 (0-6)</td>
<td>−2-4 (0-4)</td>
<td>3-2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ADAS-cog/13*</td>
<td>−4-4 (1-3)</td>
<td>0-2 (0-9)</td>
<td>4-6</td>
<td>0-0017</td>
</tr>
<tr>
<td>NIPI*</td>
<td>1-0 (0-9)</td>
<td>−1-2 (0-6)</td>
<td>2-2</td>
<td>0-0164</td>
</tr>
<tr>
<td>CIBIC-plus: patients improved or no change (number, %)</td>
<td>95 (59%)</td>
<td>213 (74%)</td>
<td>15%</td>
<td>0-001</td>
</tr>
</tbody>
</table>

DAD=disability assessment in dementia; NIPI=neuropsychiatric inventory.
*Negative changes indicate improvement; positive changes indicate improvement.

Figure 3: Mean change (with 95% CI) over time from baseline in cognitive abilities (as assessed with ADAS-cog/11), activities of daily living (as assessed with the disability assessment in dementia scale), and behavioural symptoms (as assessed with the neuropsychological inventory).

With the CIBIC-plus as a measure of overall clinical response to therapy, 74% of galantamine-group patients remained stable or had improved after 6 months compared with 59% of those assigned placebo (p=0.0011,
The galantamine than in the placebo group (31% improved CIBIC-plus scores at 6 months was higher in patients with probable vascular dementia, the proportion with significant deterioration in patients in the placebo group and nine (2·3%) in the galantamine group died.

The treatment differences observed were of similar size to those seen in galantamine studies in patients with Alzheimer’s disease.13–15 In those studies, the benefits corresponded to a delay of disease progression for at least a year.14 Our double-blind study is being followed by a 6-month open-label phase, during which all patients will withdraws in the galantamine group and 3% in the placebo group. Most of the adverse events, including gastrointestinal symptoms, were mild to moderate and of short duration. The adverse events occurred at higher frequencies during the dose-escalation phase. Adverse events occurring at least 5% more frequently in patients of either group are listed in Table 4. The high rates of nausea and vomiting were probably due to the 1-week dose-escalation scheme (from 4 mg to 24 mg daily within 6 weeks). In the dose-escalation phase, the mean weekly proportion of patients having nausea was 3·2%, whereas in the maintenance phase the corresponding proportion was 0·5%. Similarly, the mean weekly proportion of patients having vomiting in the galantamine group during the escalation phase was 1·4%, compared with 0·3% during the maintenance phase.

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receive galantamine 24 mg/day. The results will be reported separately to provide an indication of the long-term effect of galantamine in these patients.

Although this study was not powered to detect treatment differences in the subgroups, analyses were undertaken to obtain data about the potential efficacy of galantamine in these groups. The subgroup of patients with Alzheimer’s disease combined with cerebrovascular disease showed significant improvements in cognition, compared with placebo and baseline, at 6 months. In this subgroup, galantamine also showed significant superiority over placebo on global functioning. These data suggest that cholinergic treatment of these patients is beneficial, and accord with findings of a study on rivastigmine, in which some benefit on cognition (versus placebo) was also seen with “high-dose” treatment in a subgroup of patients with Alzheimer’s disease and vascular risk factors at 6 months. Galantamine has shown broad, sustained efficacy in patients with mild to moderate Alzheimer’s disease, and this efficacy is not compromised by concomitant cerebrovascular disease.

The subgroup of patients with probable vascular dementia who were treated with galantamine in this study showed improvement in cognition, compared with baseline, at 6 months. The improvement over baseline was larger than that observed in the subgroup of patients with Alzheimer’s disease with cerebrovascular disease. Placebo-treated patients in this subgroup showed no cognitive deterioration, as would be expected, because an issue relevant to progression of cognitive symptoms in clinical trials of vascular dementia is that patients must have stable cerebrovascular disease—the inclusion of untreated patients with unstable disease may lead to a high rate of stroke. However, this precaution also means that the progressive deterioration seen in vascular dementia will not be as evident as in the clinical setting. In a small observational study of donepezil in patients with vascular dementia, cognitive abilities remained stable for 6 months (not significantly different from baseline). Therefore, the results observed with galantamine in our study represent an important finding for this subgroup of patients and provide evidence of efficacy further to those in previous trials with other cholinergic agents. The broad benefits of galantamine may reflect its novel mechanism of action.

Vascular dementia and Alzheimer’s disease are difficult to distinguish owing to overlaps in symptom pattern, pathophysiology, and comorbidity. Patients included in this study had to meet either the NINCDS-ADRDA or the NINDS-AIREN diagnostic criteria. The criteria for the diagnosis of Alzheimer’s disease from the NINCDS-ADRDA are generally agreed to be the best, and have been used in several randomised controlled trials in Alzheimer’s disease. Similarly, the NINDS-AIREN criteria have been used in several controlled clinical trials and seem to provide reliable diagnostic criteria for this disorder. Low sensitivity is the main weakness of all these criteria for the diagnosis of vascular dementia, but the NINDS-AIREN criteria are highly specific, excluding 91% of patients with Alzheimer’s disease. Therefore, identification of groups of people affected by typical Alzheimer’s disease or by vascular dementia is possible by the criteria used in this study. Furthermore, the NINDS-AIREN criteria are fairly sensitive in the diagnosis of Alzheimer’s disease, as postulated by concomitant cerebrovascular disease. The criteria were applied by attending physicians as described by NINDS-AIREN, and the scans were read by radiologists at each centre. There may have been some degree of variation between the centres, but the sensitivity of the criteria in making the correct diagnosis is supported by the separation of the placebo groups in the subgroup analysis. Placebo-treated patients in each subgroup followed a disease progression typical of that expected of patients with their respective diagnoses; those with Alzheimer’s disease and cerebrovascular disease experienced progressive deterioration, whereas those with probable vascular dementia did not.

Galantamine was well tolerated in this trial. Higher proportions of patients in the galantamine group than in the placebo group experienced nausea and vomiting, but this tolerability profile could probably be improved with use of a slower dose escalation of galantamine. In a previous 5-month study with a 4-week interval between dose escalations, rates of discontinuation owing to adverse events were similar to those in the placebo group, and there was a low rate of cholinergically mediated adverse events, particularly those involving the gastrointestinal system. This simple dose-escalation scheme results in patients receiving an effective dose of galantamine (16 mg/day) within 4 weeks of starting therapy. The physician then has the option of increasing the initial dose to 24 mg/day and, if the patient is likely to benefit from such an increase. This dose-escalation scheme has been well accepted in all countries where galantamine has been introduced. The rate of stroke was low, despite the vascular aetologies known to be present, as would be expected in a trial in which patients had to have adequate control of risk factors for cerebrovascular disease.

To avoid any potential unmasking of treatment allocation, an independent (masked to other components of the study), experienced, trained clinician undertook the CIBIC-plus assessments to provide an overall impression over the course of the trial. The investigator took care to elicit only factual information and refrained from asking the carer’s opinion about the condition of the patient.

Galantamine, being equally effective in dementia due to Alzheimer’s disease and in dementia due to cerebrovascular disease, provides a treatment option to a broad range of patients for whom little pharmacological help has been available. We found that galantamine provides an effective symptomatic treatment for patients with these disorders, offering a range of therapeutic effects that will give important benefits to patients with dementia.

Contributors
T Erkinjuntti was involved in protocol design, outcome assessment, planning and review of statistics, and writing and editing the manuscript; A Kurz was a principal investigator involved in data collection and outcome assessment, and was involved in writing, editing, and revising the paper; S Gauthier was a principal investigator and contributed to writing, editing, and revising the paper; B Bullock advised on the final stages of protocol, was a principal investigator involved in data collection and oversight of the study, and was involved in editing the paper; S Lilenfeld designed and wrote the protocol, was involved in data assessment and statistical review, and was involved in drafting the paper; C V Damaraju was the trial statistician.

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Conflict of interest statement

TE has given consultancy advice to Janssen-Cilag in planning the GAL-INT-6 trial; has had travel paid for as an invited speaker at medical conferences supported by Novartis, Janssen-Cilag, Pfizer, Eisai, and Merz; and has received honoraria from Janssen, Merz, Pfizer, Novartis, and Astra-Zeneca as an invited speaker. AK has provided consultancies on advisory boards for Janssen-Cilag, UCB, Novartis, Pfizer, and Eli Lilly; has had travel paid for as an invited speaker at symposia or advisory boards sponsored by Janssen-Cilag, UCB, Novartis, Pfizer, and Eli Lilly; and has received honoraria from Janssen, Pfizer, and Eli Lilly. SG has provided consultancies as an advisory board member for Janssen-Cilag and other special advisory boards on vascular dementia for Janssen-Cilag; has received research grants for clinical trials in vascular dementia and mild cognitive impairment from Janssen-Cilag and Pfizer-Biasi; has travel paid for by pharmaceutical companies when attending advisory boards, meetings, and symposia sponsored by pharmaceutical companies; and has received honoraria from Janssen, Novartis, and Pfizer. RB has provided consultancies on advisory boards for Pfizer, Novartis, Janssen-Cilag, Lundbeck, Shire, Eisai, and GlaxoSmithKline, and for clinical trials for all the above and Organon, Merz, and Elan; has been sponsored by all these companies to attend conferences and for talks and symposia; has received research grants for commercial clinical trial work by all the above companies, and for specific work by Novartis; has had travel paid for as a speaker at conferences sponsored by pharmaceutical companies; and has received honoraria from Janssen, Novartis, Pfizer, and Lundbeck; SL and CVD are employees of Janssen Research Foundation and have stock ownership in Johnson and Johnson.

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