

# SYNOPSIS

Document No.: EDMS-PSDB-7496559

<u>Name of Sponsor/Company</u>	Janssen-Cilag EMEA acting on behalf of Janssen-Cilag International	
<u>Name of Finished Product</u>	Reminyl®	
<u>Name of Active Ingredient(s)</u>	galantamine	
<b>Protocol No.:</b> GAL-ALZ-302		
<b>Title of Study:</b> Treatment of Severe Alzheimer's Disease in a Residential Home, Nursing Home, or Geriatric Residence Setting: Evaluation of Efficacy and Safety of Galantamine (Reminyl®) in a Randomised, Double-Blind, Placebo-Controlled Study.		
<b>International Principal Investigator:</b> Professor Alistair Burns, M.D. - Professor of Old Age Psychiatry, Psychiatry Research Group, University of Manchester, [REDACTED] UK		
<b>Publication (Reference):</b> Not applicable		
<b>Study Period:</b> 8 December 2003 - 4 September 2007		<b>Phase of Development:</b> III
<b>Objectives:</b> The <b>primary objective</b> of the trial was to assess the efficacy of galantamine in severe Alzheimer's disease (AD) subjects, as measured by 2 co-primary rating scales: <ul style="list-style-type: none"><li>• the Severe Impairment Battery (SIB) for the cognitive domain, and</li><li>• the Activities of Daily Living self-performance subscale from the Minimum Data Set (MDS-ADL[7]) for the assessment of basic activities of daily living.</li></ul> <b>Secondary objectives</b> were to assess: <ul style="list-style-type: none"><li>• The effect of galantamine on the emergence of behavioural symptoms, together with their disruptive effect on the professional caregivers as measured by the Neuro-Psychiatric Inventory – Nursing Home version (NPI-NH).</li><li>• Resource utilisation. This included effects on resources both within and external to the home/establishment. The level of staffing input needed was collected in the caregiver assistance subscale of the MDS-ADL, plus a time assessment.</li><li>• Social functioning, as measured by the psychosocial well-being subscale of the MDS.</li><li>• The cognitive function level of the subjects, measured by the Mini-Mental State Examination (MMSE).</li><li>• The safety and tolerability of galantamine, as measured by vital signs, physical examination, electrocardiogram (ECG), laboratory screening, adverse event (AE) reporting and concomitant medication.</li></ul>		

## SYNOPSIS (CONTINUED)

<u>Name of Sponsor/Company</u>	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	
<u>Name of Finished Product</u>	Reminyl®	
<u>Name of Active Ingredient(s)</u>	galantamine	
<p><b>Methodology:</b></p> <p>This was a multi-centre, randomised, 6-month double-blind (DB), placebo-controlled trial of galantamine treatment in subjects with severe AD with or without cerebrovascular disease (CVD). Subjects eligible for the trial were randomised in a 1:1 ratio to one of the two treatment groups, galantamine or placebo. In order to ensure both an equal balance of active and placebo medication across the range of dementia severity, and to ensure a reasonably equal spread of recruitment across the severity range, randomisation was stratified. Separate randomisation blocks were supplied for subjects with MMSE scores ranging from 5 to 8, and for subjects with scores from 9 to 12. The objective was to recruit approximately equal numbers in both these strata.</p> <p>A standard dose titration regimen was applied. A dose of 24 mg/day (12 mg b.i.d.) was set as the target (and maximum) dose. Subjects in the galantamine group received a standard dose escalation to a target dose of 24 mg/day, starting with 4 weeks of 8 mg/day (4 mg b.i.d.), followed by 4 weeks of 16 mg/day (8 mg b.i.d.). At Week 9, subjects were escalated to 24 mg/day (12 mg b.i.d.). At Week 13, subjects had to remain at 24 mg/day unless, based upon the investigator's evaluation of tolerability, subjects needed a dose reduction to 16 mg/day (8 mg b.i.d.). Subjects in the placebo group received corresponding placebo tablets, with similar appearance and packaging to ensure blindness.</p> <p>Primary efficacy measures of cognition and basic activities of daily living were assessed by the SIB and the MDS-ADL(7) self-performance, respectively, rated at the end of the 6-month double blind phase. Assessments were compared with baseline values.</p> <p>Secondary outcome measures were the NPI-NH, resource use (internal resource derived from a sub-scale of the MDS: "support provided" by staff to perform activities of daily living, a measurement of time spent providing support by staff, and external resource via a questionnaire of health and social service use), subject social functioning (using the "psycho-social well-being" subscale of the MDS-ADL), and cognition using the MMSE. Safety was also evaluated on the basis of AE reports, physical examination, vital signs, ECG and laboratory parameters. A Safety Board was set up to review blinded safety data during the course of the trial.</p> <p>Immediately after the DB phase, all completed subjects who, according to the investigator's impression, would benefit from galantamine medication were given the opportunity to be treated with galantamine in an optional follow-up 26-week open-label (OL) trial. The blind could not be broken at this time; therefore all subjects entering this phase had to have their dose re-escalated at standard 4-weekly intervals. The data of the OL extension study will be reported separately.</p>		
<p><b>Number of Subjects:</b></p> <p>Five hundred and five subjects were screened, of whom 407 subjects were randomised to galantamine (207 subjects) or placebo (200 subjects).</p>		
<p><b>Diagnosis and Main Criteria for Inclusion:</b></p> <p>Subjects had to satisfy the following criteria before entering the study:</p> <ol style="list-style-type: none"> <li>1. Male or female subjects diagnosed with dementia of the Alzheimer type as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM IV-TR).</li> <li>2. Progressive worsening of memory and other cognitive functions.</li> <li>3. Subjects needed to have severe dementia as evidenced by a MMSE score between 5 and 12, including these extremes.</li> <li>4. At inclusion, a brain computed tomography (CT) or magnetic resonance imaging (MRI) performed within the last 3 years had to be available.</li> <li>5. Subjects, aged 40 to 95 inclusive, had to be admitted at least 3 months previously to their current residential home, nursing home, or a geriatric residence for the elderly/subjects with dementia, providing long-term care by professional caregivers. Subjects needed to remain in this setting for the first 6 months of the study.</li> <li>6. Subjects had to be free of memantine or any cholinesterase-inhibitor (including galantamine) therapy for at least 3 months prior to randomisation.</li> </ol>		

## SYNOPSIS (CONTINUED)

<u>Name of Sponsor/Company</u>	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
<u>Name of Finished Product</u>	Reminyl®
<u>Name of Active Ingredient(s)</u>	galantamine

**Test Product:** The treatment consisted of standard tablets, which contained 4 mg, 8 mg, and 12 mg of synthetic galantamine, or matching placebo.

**Dose:**

**DB controlled 6-month trial:**

**Galantamine:** The target dose was 24 mg/day, with a standard dose escalation of 4 weeks of 8 mg/day (4 mg b.i.d.), followed by 4 weeks of 16 mg/day (8 mg b.i.d.). At Week 9, subjects were escalated to 24 mg/day (12 mg b.i.d.). As of Week 13, subjects had to remain at 24 mg/day, unless based upon the investigator's evaluation of tolerability subjects needed to have their dose reduced to 16 mg/day (8 mg b.i.d.).

**Placebo:** Six months (i.e., 26 weeks) of placebo medication given twice daily, packaged in order to allow a "sham" dose escalation and adjustments to mirror the active galantamine group.

**Open Safety Study: Follow-Up to the 6-month controlled trial:** In order to retain blinding, all subjects needed to have their dose restarted from 4 mg b.i.d., in order to account for the subjects who had been receiving placebo before. Dose escalation was as described above, except that those subjects who finished the DB phase on 16 mg/day galantamine (or placebo equivalent) were permitted to escalate to a maximum dose of 16 mg/day. In addition, subjects were allowed to reduce the dose from 24 mg/day to 16 mg/day at any time after 8 weeks of OL treatment.

**Mode of Administration:** Standard tablets for clinical trial use, which contained 4 mg, 8 mg, or 12 mg of synthetic galantamine, or matching placebo.

**Batch No.:** 341888, 341896, 341897, 343443, 343893, 346093, 346691, and 346695

**Duration of Treatment:** Total treatment duration in the DB phase was 6 months. After completion of the DB trial, subjects had the option to enter a 6-month (i.e., 26 weeks) OL extension phase of the trial.

**Criteria for Evaluation:**

**Efficacy:**

**Primary efficacy criteria:**

- change versus baseline at Week 26 of SIB total score (40 items, 9 domains)
- change versus baseline at Week 26 of MDS-ADL(7) total self-performance score (7 items)

**Secondary efficacy criteria:**

- change in the emergence of behavioural symptoms, together with their disruptive effect on the professional caregivers (NPI-NH)
- change in resource utilisation (external resource use questionnaire, internal resource use: caregiver assistance subscale of the MDS-ADL[7] plus a time assessment)
- change in social functioning (psychosocial well-being subscale of the MDS)
- change in cognitive function level of the patients (MMSE)
- change in SIB domains

**Safety/tolerability:**

- AE reporting
- clinical laboratory tests
- vital signs
- ECG
- body weight
- physical and neurological examination

## SYNOPSIS (CONTINUED)

<u>Name of Sponsor/Company</u>	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.		
<u>Name of Finished Product</u>	Reminyl®		
<u>Name of Active Ingredient(s)</u>	galantamine		
<b>Statistical Methods:</b> Descriptive statistics, Van Elteren's test, Cochran-Mantel-Haenszel controlling, Intent-to-Treat analysis, analysis of covariance (ANCOVA) model, sensitivity analysis, paired t-test, parametric methods, repeated measurements model. All tests were performed at the 5% significance level.			
<b>SUMMARY - CONCLUSIONS</b>			
<b>STUDY POPULATION:</b>			
<p>This trial consisted of a DB and OL phase; this report presents the results of just the former phase.</p> <p>Four hundred and seven subjects were enrolled and treated in the DB phase. Two hundred and seven subjects were randomised to galantamine treatment, and 200 subjects to placebo treatment.</p> <p>All subjects were Caucasian, except for one subject of whom race was unknown. The population was mainly female (81%) with a median age of 84 years (range: 56-95 years) and a median BMI of 24.5 kg/m<sup>2</sup>. Most subjects (80%) were diagnosed with probable AD, the remaining 20% had possible AD with CVD. Mean (SD) duration of illness was 53.8 (30.01) months. Subjects were also stratified according to their MMSE score: 170 (42%) subjects had an MMSE score of 5 to 8; 237 (58%) subjects had a score of 9 to 12, where lower scores indicate higher disability.</p> <p>The baseline score of the SIB (scoring range: 0-100; higher scores indicating better performance), showed a mean (SD) of 67.3 (21.13). The baseline score of MDS-ADL(7) (scoring range: 0-28; lower scores indicating better performance), showed a mean (SD) of 12.2 (7.55). The MMSE (scoring range: 0-30; higher scores indicating better performance) resulted in a mean (SD) score of 8.9 (2.42) at baseline. The NPI-NH assessment (scoring range: 0-144; lower scores indicating better performance) resulted in a mean (SD) of 19.0 (16.79).</p> <p>Overall the treatment groups were well balanced for demographics and baseline disease characteristics.</p>			
<b>EFFICACY RESULTS:</b>			
<u>Primary efficacy parameters:</u>			
SIB Total Score and Total MDS-ADL(7) Self-Performance Score During the 26-Week Double-Blind Phase			
	Galantamine	Placebo	p-value <sup>b</sup>
SIB total score	N=162	N=149	
Actual score at baseline <sup>a</sup>			
Mean (SE)	67.1 (1.64)	69.9 (1.65)	0.835
Median	71.0	74.0	
Actual score at Week 26			
Mean (SE)	69.1 (1.84)	66.9 (1.93)	0.006
Median	75.0	72.0	
Change from baseline to Week 26			
Mean (SE)	1.9 (1.02)	-3.0 (1.29)	0.006
Median	3.0	-2.0	
p-value <sup>c</sup>	0.061	0.019	
Total MDS-ADL(7) self-performance score	N=166	N=151	
Actual score at baseline <sup>a</sup>			
Mean (SE)	11.8 (0.58)	12.0 (0.62)	0.448
Median	10.0	10.0	
Actual score at Week 26			
Mean (SE)	13.0 (0.60)	13.6 (0.65)	0.383
Median	13.0	13.0	
Change from baseline to Week 26			
Mean (SE)	1.2 (0.30)	1.6 (0.37)	0.383
Median	1.0	1.0	
p-value <sup>c</sup>	<0.001	<0.001	
N=number of subjects with data			
<sup>a</sup> This includes only baseline data for subjects with paired data at Week 26.			
<sup>b</sup> Comparison between the galantamine and placebo group using ANCOVA.			
<sup>c</sup> Within group change using a paired t-test.			

## SYNOPSIS (CONTINUED)

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<u>Name of Finished Product</u>	Reminyl®		
<u>Name of Active Ingredient(s)</u>	galantamine		
<u>EFFICACY RESULTS, CONTINUED:</u>			
<p>During the DB phase, the mean total SIB score (co-primary parameter) of the galantamine group increased from 67.1 at baseline to 69.1 at the end of the DB phase (Week 26), resulting in an increase (improvement) of 1.9. For the placebo group the mean SIB score decreased (worsened) with 3.0 points. The difference between the changes in both groups was statistically significant (p=0.006).</p> <p>The mean total MDS-ADL(7) self-performance score (co-primary parameter) increased (worsened) from 11.8 at baseline to 13.0 at Week 26 in the galantamine group, and from 12.0 to 13.6 in the placebo group. The change from baseline was 1.2 for the galantamine group, and 1.6 for the placebo group, and was not statistically significantly different between the two groups (p=0.383).</p>			
<u>SAFETY RESULTS:</u>			
<u>Adverse Events (AEs)</u>			
<p>During the 6-month DB phase a similar proportion of subjects in the galantamine and placebo group had at least one treatment-emergent AE (TEAE), i.e., 183 (88%) and 177 (89%) subjects, respectively. The most common TEAEs were related to gastrointestinal disorders (vomiting, diarrhoea, and nausea). Apart from nausea (12% vs. 7% of subjects), which occurred more often in the galantamine group, these events were reported with a lower or similar incidence in the galantamine group compared to the placebo group. The majority of TEAEs were mild or moderate in severity.</p> <p>During the DB phase, fewer subjects died in the galantamine group (8 [4%] subjects) compared to the placebo group (21 [11%] subjects) (p=0.012). In the galantamine group, SAEs leading to death were reported in at most one subject, except for circulatory collapse and condition aggravated that were reported in 2 subjects each. The incidence of SAEs was similar in the galantamine group (18%) and placebo group (21%). The following SAEs were reported in more than 2 subjects: fall (6 subjects), cardiac failure, myocardial infarction, dehydration, and circulatory collapse (3 subjects each) in the galantamine group, and fall, hip fracture, cardiac failure, and pneumonia (4 subjects each), and femur fracture and anaemia (3 subjects each) in the placebo group. All other SAEs were isolated cases, occurring in at most 2 subjects. Thirty (15%) and 29 (15%) subjects in the galantamine and placebo group, respectively, permanently discontinued trial medication due to an AE.</p>			
Adverse Events During the Double-Blind Phase: Summary table			
	Galantamine (N=207)	Placebo (N=200)	p-value <sup>a</sup>
Parameter, n (%)			
Subjects with at least 1 AE	183 (88.4)	177 (88.5)	1.000
Subjects with at least 1 SAE	37 (17.9)	41 (20.5)	0.530
Subjects who died	8 (3.9)	21 (10.5)	0.012
Subjects who permanently discontinued treatment due to an AE	30 (14.5)	29 (14.5)	/
Subjects with a severe AE	37 (17.9)	47 (23.5)	/
Subjects with at least 1 AE that is thought to be at least possibly related to study medication	71 (34.3)	55 (27.5)	/
N=number of subjects with data; n=number of subjects with that observation; /=not calculated			
<sup>a</sup> Comparison between the galantamine and placebo group using ANCOVA.			

## SYNOPSIS (CONTINUED)

<u>Name of Sponsor/Company</u>	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	
<u>Name of Finished Product</u>	Reminyl®	
<u>Name of Active Ingredient(s)</u>	galantamine	
<u>SAFETY RESULTS. CONTINUED:</u>		
<u>Clinical Laboratory Tests</u>		
<p>Changes from baseline in laboratory parameters were generally small and not considered clinically relevant. All treatment-emergent abnormalities in biochemistry and haematology parameters occurred with similar incidence in the galantamine and the placebo group, apart from neutrophils (%). The frequency of laboratory tests-related AEs was similarly low in both treatment groups (at most 2%). Most laboratory-related AEs were considered not or doubtfully related to the trial medication by the investigator, and were of mild or moderate severity.</p>		
<u>Vital Signs</u>		
<p>Average changes from baseline in vital signs parameters were small at all assessments. The incidence of AEs related to vital signs was lower in the galantamine (5%) and placebo (10%) group. Vital signs-related AEs reported were hypotension, hypertension and blood pressure increased. Apart from one case each of hypotension and hypertension in each treatment group, all these AEs were considered not related to trial medication.</p>		
<u>ECG</u>		
<p>Mean changes from baseline in ECG parameters were minor. The incidence of treatment-emergent ECG abnormalities was similar in both treatment groups, except for increases in QTcLD which tended to be somewhat more frequent in the galantamine group compared to the placebo group. The incidence of AEs related to ECG abnormalities were also similar. ECG-related AEs were reported in at most 2% of subjects and occurred in more than one subject for atrial fibrillation and bradycardia in each treatment group, and heart rate irregular in galantamine-treated subjects only. In one galantamine-treated subject, atrial fibrillation was reported as a mild SAE, considered probably related to study medication. Except for one subject in the placebo group who discontinued the trial due to the severe AE of bradycardia, none of the other ECG-related AEs were severe or led to discontinuation.</p>		
<u>Body Weight</u>		
<p>Mean body weight diminished slightly over time in both treatment groups. 'Weight decreased' was reported as an AE in 6 (3%) galantamine-treated and 3 (2%) placebo-treated subjects. This AE was considered related to trial medication for 5 subjects in the galantamine group, and for 1 subject in the placebo group. None of the AEs of 'weight decreased' were severe. For one galantamine-treated subject, 'weight decreased' was reported as a moderate SAE, considered probably related to study medication, for which trial medication was permanently stopped.</p>		
<u>Physical and Neurological Examination</u>		
<p>No clinically relevant abnormalities were observed after physical and neurological examination during the entire study period.</p>		
<u>CONCLUSION:</u>		
<p>Subjects with severe AD, with or without CVD, treated for 6 months with galantamine, showed an improvement in cognitive function (as measured by total SIB score) that was statistically significantly superior to placebo, but results failed to separate galantamine from placebo with regard to effects on activities of daily living (as measured by MDS-ADL[7] self-performance).</p> <p>Galantamine appeared safe in this very elderly population: mortality was lower than in the placebo group and galantamine was well tolerated, with no new safety-related information emerging during this trial.</p>		
<b>Issue Date of the Clinical Study Report:</b> 27 October 2008		

# SYNOPSIS

Document No.: EDMS-PSDB-9017950

<u>Name of Sponsor/Company</u>	Janssen-Cilag EMEA acting on behalf of Janssen-Cilag International	
<u>Name of Finished Product</u>	Reminyl®	
<u>Name of Active Ingredient(s)</u>	galantamine	
<b>Protocol No.:</b> GAL-ALZ-302		
<b>Title of Study:</b> Open-Label Phase (optional) of the SERAD study: Treatment of Severe Alzheimer's Disease in a Residential Home, Nursing Home, or Geriatric Residence Setting: Evaluation of Efficacy and Safety of Galantamine (Reminyl®) in a Randomised, Double-Blind, Placebo-Controlled Study.		
<b>International Principal Investigator:</b> Professor Alistair Burns, M.D. - Professor of Old Age Psychiatry, Psychiatry Research Group, University of Manchester, [REDACTED] UK		
<b>Publication (Reference):</b> Not applicable		
<b>Study Period:</b> 8 December 2003 – 4 March 2008		<b>Phase of Development:</b> III
<b>Objectives:</b> The <b>primary objective</b> of the open-label phase of the SERAD trial was to assess the tolerability and safety of galantamine, used 6 to 12 months in severe AD subjects with and without CVD. This was accomplished by measuring vital signs, ECG, physical examination, laboratory screening, AE reporting and concomitant medication recording. The <b>secondary objectives</b> of the open-label phase were to assess: <ul style="list-style-type: none"><li>• The cognitive function level of the subjects, measured by the MMSE.</li><li>• Resource utilisation. The external resource use questionnaire included questions on the use of health and social care services from service providers external to the establishment/home in which the subject was resident.</li></ul>		
<b>Methodology:</b> This was a multi-centre, randomised, 6-month double-blind and placebo-controlled trial of galantamine treatment, followed by a 6-month open-label extension phase, in subjects with severe AD, with or without CVD. Separate randomisation blocks were supplied for subjects with MMSE scores ranging from 5 to 8, and for subjects with scores from 9 to 12. The objective was to recruit approximately equal numbers in both these strata. A standard dose titration regimen was applied. A dose of 24 mg/day (12 mg b.i.d.) was set as the target (and maximum) dose, in order to optimise treatment effects. Standard dose escalation started with 4 weeks of 8 mg/day (4 mg b.i.d.), followed by 4 weeks of 16 mg/day (8 mg b.i.d.), and then escalation to the maximum dose of 24 mg/day. The dose could be reduced to 16 mg/day if needed for tolerability reasons at any point after Week 8. Thereafter, the dose had to remain fixed for the rest of the double-blind phase. Immediately after the double-blind phase, all completed subjects who, according to the investigator's impression, would benefit from galantamine medication were given the opportunity to be treated with galantamine in a 26-week open-label follow-up phase. The blind could not be broken at this time, therefore all subjects entering this phase had to have their dose re-escalated at standard 4 weekly intervals starting at 4 mg b.i.d., since some subjects would have received placebo in the first phase. Those subjects who had finished the double-blind phase on 16 mg/day were permitted to escalate to just 16 mg/day in the open-label phase. Subjects who had finished the double-blind phase on 24 mg/day were allowed to reduce the dose from 24 mg/day to 16 mg/day at any time after 8 weeks of open-label treatment. The primary objective of the open-label phase was to assess the tolerability and safety of galantamine, used 6 to 12 months in severe AD subjects with and without CVD, evaluated on the basis of AE reports, physical examination, vital signs, ECG and laboratory parameters. The secondary objectives of the open-label phase were assessment of 2 groups of efficacy parameters at the end of the open-label phase: cognitive function, as measured by the MMSE, and external resource use, as assessed by a questionnaire of any health and social service use.		
<b>Number of Subjects:</b> Four hundred and seven subjects were randomised to galantamine (207 subjects) or placebo (200 subjects) in the 6-month (26 weeks) DB phase, after which 303 continued into the 6-month OL phase.		

<u>Name of Sponsor/Company</u>	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	
<u>Name of Finished Product</u>	Reminyl®	
<u>Name of Active Ingredient(s)</u>	galantamine	
<b>Diagnosis and Main Criteria for Inclusion:</b>		
Subjects had to satisfy the following criteria before entering the study:		
<ol style="list-style-type: none"> <li>1. Male or female subjects diagnosed with dementia of the Alzheimer type as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM IV-TR).</li> <li>2. Progressive worsening of memory and other cognitive functions.</li> <li>3. Subjects needed to have severe dementia as evidenced by a MMSE score between 5 and 12, including these extremes.</li> <li>4. At inclusion, a brain computed tomography (CT) or magnetic resonance imaging (MRI) performed within the last 3 years had to be available.</li> <li>5. Subjects, aged 40 to 95 inclusive, had to be admitted at least 3 months previously to their current residential home, nursing home, or a geriatric residence for the elderly/subjects with dementia, providing long-term care by professional caregivers. Subjects needed to remain in this setting for the first 6 months of the study.</li> <li>6. Subjects had to be free of memantine or any cholinesterase-inhibitor (including galantamine) therapy for at least 3 months prior to randomisation.</li> </ol>		
<b>Test Product:</b> The treatment consisted of standard tablets, which contained 4 mg, 8 mg, and 12 mg of synthetic galantamine.		
<b>Dose:</b>		
In order to retain blinding, galantamine was retitrated at the start of the OL phase according to the standard dose escalation starting with 4 weeks of 8 mg/day (4 mg b.i.d.), followed by 4 weeks of 16 mg/day (8 mg b.i.d.), and then escalation to the maximum of 24 mg/day (12 mg b.i.d.). The dose could be reduced to 16 mg/day if needed for tolerability reasons at any point after Week 8, and those subjects who finished the DB phase on 16 mg/day were permitted to escalate to just 16 mg/day in the OL phase.		
<b>Mode of Administration:</b> Standard tablets for clinical trial use, which contained 4 mg, 8 mg, or 12 mg of synthetic galantamine.		
<b>Batch No.:</b> 341898, 341899, 341963, 343893, 346697, 346698, and 348218.		
<b>Duration of Treatment:</b> Total treatment duration in the OL phase was 6 months.		
<b>Criteria for Evaluation:</b>		
<b>Efficacy:</b>		
<ul style="list-style-type: none"> <li>• change in external resource utilisation (external resource use questionnaire)</li> <li>• change in cognitive function level of the patients (MMSE)</li> </ul>		
<b>Safety/tolerability:</b>		
<ul style="list-style-type: none"> <li>• AE reporting</li> <li>• clinical laboratory tests</li> <li>• vital signs</li> <li>• ECG</li> <li>• body weight</li> <li>• physical and neurological examination</li> </ul>		
<b>Statistical Methods:</b> Descriptive statistics, Van Elteren's test, Cochran-Mantel-Haenszel controlling, Intent-to-Treat analysis, analysis of covariance (ANCOVA) model, sensitivity analysis, paired t-test, parametric methods, repeated measurements model. All tests were performed at the 5% significance level.		

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<u>Name of Finished Product</u>	Reminyl®	
<u>Name of Active Ingredient(s)</u>	galantamine	
<b>SUMMARY - CONCLUSIONS</b>		
<b>STUDY POPULATION:</b>		
<p>This trial consisted of a DB and OL phase. <b>This report presents the results of the OL phase.</b></p> <p>All 303 subjects treated in the OL phase were Caucasian, except for one subject of whom race was unknown. The population was mainly female (80.5%) with a median age of 84 years (range: 56 to 95 years) and a median BMI of 24.4 kg/m<sup>2</sup> at study start. Most subjects (82.2%) had been diagnosed with probable AD, and the remaining 17.8% had possible AD with CVD. Mean (SD) duration of illness was 53.8 (30.6) months. Values of demographic and baseline characteristics of subjects in the OL phase are similar to those previously reported for the larger population included in the preceding DB phase, which suggests the absence of major biasing factors in the decision to move on from the DB phase into the OL phase of the study.</p> <p>Overall, treatment groups were well balanced for demographics and baseline characteristics.</p>		
<b>EFFICACY RESULTS:</b>		
<p>Two groups of secondary efficacy parameters were analysed at the end of the OL phase (i.e., Week 52 of the trial): cognitive function (assessed by MMSE) and external resource use (i.e., number of days hospitalised as in-patient, number of days hospitalised as out-patient, and number of services used).</p> <p>MMSE and external resource use showed a status quo or worsening at the end of the OL phase in relation to OL baseline for subjects who also had received galantamine in the DB phase. Changes vs. baseline were not statistically significantly different between subjects who had received galantamine or placebo during the DB phase, except for MMSE:</p> <ul style="list-style-type: none"> <li>• Subjects who had received galantamine during the DB phase showed a decrease (worsening) in mean MMSE score from 10.0 at OL-baseline (Week 26) to 9.1 at Week 52. No change in MMSE score was observed over the 6-month OL phase for subjects who had been receiving placebo in the DB phase (score at OL baseline and Week 52 was 9.6 each). The difference in change versus baseline between these groups was statistically significant (p=0.026). However, MMSE scores after one year treatment with galantamine were not different from values at study start, nor were MMSE scores after 6 months placebo plus 6 months galantamine treatment (mean changes in MMSE score were -0.1 and 0.4, respectively).</li> <li>• The mean number of days hospitalised as an in-patient during the last 6 months (Resource Use Questionnaire) increased slightly from OL-baseline (Week 26) to Week 52 for subjects who had previously (during the DB phase) received galantamine or placebo (from 0.8 to 1.5 days for the galantamine group, and 0.5 to 0.9 days for the placebo group). The mean number of visits as an out-patient during the last 6 months and number of services used over the past 4 weeks were virtually unchanged at Week 52 compared to Week 26, for both groups. No statistically significant difference between groups was observed.</li> </ul>		

<u>Name of Sponsor/Company</u>	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	
<u>Name of Finished Product</u>	Reminyl®	
<u>Name of Active Ingredient(s)</u>	galantamine	

**SAFETY RESULTS:**

**Adverse Events (AEs)**

During the 6-month OL phase the majority of subjects (85.8%) had at least one treatment-emergent AE (TEAE), with a similar proportion of subjects who had been treated with galantamine (130 [84.4%] subjects) or placebo (130 [87.2%] subjects) in the DB phase. In general, TEAEs were reported with a similar or lower incidence for subjects who had received galantamine in the DB phase compared to those who had received placebo. The most common TEAEs were urinary tract infection, fall, vomiting, and diarrhoea. The majority of TEAEs were mild or moderate in severity during the OL phase.

During the OL phase, 29 (9.6%) subjects died. This percentage is quite similar to the one found for placebo-treated subjects in the DB phase (10.5%) but higher than the one found for galantamine-treated subjects in the DB phase (3.9%). Specific SAEs leading to death were reported in at most 2 subjects, except for condition aggravated, pneumonia, cerebrovascular accident, and myocardial infarction. Sixty-five (21.5%) subjects reported at least one SAE. The most common SAEs were hip fracture (8 subjects), pneumonia and condition aggravated (7 subjects each), and fall (5 subjects). With the exception of hip fracture, these SAEs were less often reported for subjects who had received galantamine than those who had received placebo in the DB phase. Thirty-nine (12.9%) subjects permanently discontinued the OL phase due to an AE.

Adverse Events During the Double-Blind and Open-Label Phase: Summary Table  
(Study GAL-ALZ-302: *All Subjects*)

Parameter, n (%)	Double-Blind Phase		Open-Label Phase		
	Galantamine (N = 207)	Placebo (N = 200)	Gal/Gal (N=154)	Pla/Gal (N=149)	Total (N=303)
Subjects with at least 1 AE	183 (88.4)	177 (88.5)	130 (84.4)	130 (87.2)	260 (85.8)
Subjects with at least 1 SAE	37 (17.9)	41 (20.5)	29 (18.8)	36 (24.2)	65 (21.5)
Subjects who died	8 (3.9)	21 (10.5)	13 (8.4)	16 (10.7)	29 (9.6)
Subjects who permanently discontinued treatment due to an AE	30 (14.5)	29 (14.5)	17 (11.0)	22 (14.8)	39 (12.9)
Subjects with at least 1 AE that is thought to be at least possibly related to study medication	71 (34.3)	55 (27.5)	31 (20.1)	35 (23.5)	66 (21.8)

N=number of subjects with data; n=number of subjects with that observation

**Clinical Laboratory Tests**

Overall, mean changes from OL baseline at Week 52 were small and comparable between subjects who had received galantamine or placebo treatment during the DB phase, except for AST and ALT. Aspartate amino transferase had increased with 4.59 U/L for subjects previously treated with galantamine, and with 0.56 U/L for subjects previously treated with placebo; for ALT these values were 6.49 U/L and 1.21 U/L, respectively. All treatment-emergent abnormalities in haematology parameters occurred with roughly similar incidence in subjects who had been treated with galantamine or placebo in the DB phase.

Apart from anaemia (2% of subjects), the frequency of specific laboratory test-related AEs was similarly low in both treatment groups (at most 1% for any specific laboratory deviation). Most laboratory-related AEs were considered not or doubtfully related to the trial medication by the investigator, and were of mild or moderate severity.

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<u>Name of Finished Product</u>	Reminyl®	
<u>Name of Active Ingredient(s)</u>	galantamine	
<b><u>SAFETY RESULTS, CONTINUED:</u></b>		
<u>Vital Signs</u>		
<p>Changes from baseline in vital signs were only minor and not of statistical significance except for the change in heart rate which was significantly different between the groups previously treated with placebo (mean -2.5 beats/min) as compared to galantamine (mean +1.5 beats/min, respectively).</p> <p>The incidence of vital signs-related AEs was similar for hypotension in subjects who had received galantamine or placebo during the DB phase, but was somewhat higher for hypertension in subjects who had previously received placebo. None of these AEs were serious or led to discontinuation of trial medication. All AEs were mild or moderate in severity and considered not or doubtfully related to trial medication by the investigator, except for 1 event of hypotension that was considered possibly related to trial medication by the investigator.</p>		
<u>ECG</u>		
<p>Changes from baseline in ECG parameters were generally minor. The incidence of treatment-emergent ECG abnormalities during the OL phase was similar for subjects that had been treated with galantamine or placebo during the DB phase, though an abnormally high QRS width was slightly less frequent, and QTc prolongation slightly more frequent in subjects treated with galantamine compared to placebo in the DB phase. The AEs of QT prolongation were all reported for subjects who already had received a 6-month galantamine treatment in the DB phase. In one subject, who had received placebo during the DB phase, ST segment abnormality was reported as a severe SAE, which led to permanent discontinuation of trial medication, but was considered not related to trial medication by the investigator. Except for this subject, none of the other ECG related AEs were severe or led to discontinuation.</p>		
<u>Body Weight</u>		
<p>Mean body weight diminished slightly over time. Weight reduction was reported as an AE for 7 (2.3%) subjects, i.e., for 3 (1.9%) and 4 (2.7%) subjects who had received galantamine or placebo during the DB phase, respectively. Neither of the body weight related AEs were reported as serious, nor led to permanent discontinuation of the trial medication, or were considered related to trial medication by the investigator.</p>		
<u>Physical and Neurological Examination</u>		
<p>No clinically relevant abnormalities were observed after physical and neurological examination during the entire study period.</p>		
<b><u>CONCLUSION:</u></b>		
<p>Subjects with severe AD, with or without CVD, treated for 6 months with galantamine after a 6 month double-blind treatment with either galantamine or placebo, showed a status quo or worsening in cognitive function (as measured by MMSE) and external resource use (as assessed by a questionnaire). Cognitive function after one year treatment with galantamine was not different from values at study start, nor was cognitive function after 6 months placebo plus 6 months galantamine treatment.</p> <p>Galantamine appeared safe in this very elderly population: mortality was similar to the one found for placebo-treated subjects during the double-blind phase, but higher than the one found for galantamine treated subjects in the double-blind phase. Galantamine was well tolerated, with no new safety related information emerging during this trial.</p>		
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