SYNOPSIS

Trial identification

Company: JANSSEN PHARMACEUTICA N.V. **Finished product**: Reminyl™ **Active ingredient**: galantamine (R113675)		
Title: The Safety and Efficacy of Galantamine in the Treatment of Vascular and Mixed Dementia (Double-Blind Part Only)	**Trial No.**: **CR006034** **Clinical phase**: 3	
Investigator: Multicenter	**Countries**: Canada, Denmark, Finland, France, Germany, Israel, Poland, The Netherlands, United Kingdom	
Reference: Erkinjuntti T, Kurz A, Gauthier S, Bullock R, Lillienfeld S, Damaraju CV. Efficacy of galantamine inprobable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomized trial. Lancet 2002; 359:1283-1290.		
Trial period: Start: 24 Nov 1998 End: 21 Jun 2000	**No. of investigators**: 66 **No. of patients entered/randomized**: 750/592	

Protocol summary

Indication / objectives: Vascular and mixed dementia / to evaluate the safety and efficacy of galantamine compared to placebo during the 6-month double-blind phase

Trial design: Double-blind placebo-controlled

Main selection criteria:

Inclusion criteria:

- 1A. Male or female outpatients with Vascular Dementia. The diagnosis should be established in accordance with the criteria proposed by the National Institute of Neurological and Communicative Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) International Workshop (as modified below):
  - Dementia (decline from previous higher level of functioning) established by clinical examination and documented by the Mini-Mental State Examination, Blessed Dementia Scale or similar examination:
    . deficits in 2 or more areas of cognition (memory, orientation, attention, language, visiospatial functions, executive functions, motor control, and praxis);
    . no disturbance of consciousness, delirium, psychosis, severe aphasia, or major sensorimotor impairment precluding neuropsychological testing;
    . absence of systemic disorders or other brain diseases such as Alzheimer's disease (AD) (EXCEPT CEREBROVASCULAR DISEASE) that could account for the dementia
  - Cerebrovascular disease:
    . focal neurologic signs consistent with previous stroke (even with negative stroke history)
    . evidence of relevant cerebrovascular disease by computed tomography (CT) or magnetic resonance imaging (MRI) scan (multiple large-vessel infarcts, single strategically placed infarct [angular gyrus, thalamus, basal forebrain, posterior or anterior cerebral artery territory], multiple basal ganglia and white matter lacunes, extensive periventricular white matter lesions, or combinations of these). Scan must be less than 12 months old.
  - A relationship must exist between the dementia and the cerebrovascular disease:
    . onset of dementia within 3 months of a recognized stroke or abrupt deterioration in cognitive functions or fluctuating, stepwise progression of cognitive deficits.

or:

- 1B. Male or female outpatients with Mixed Dementia (possible Alzheimer's disease with cerebrovascular disease). The diagnosis should be established in accordance with National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders (NINCDS-ADRDA) for **POSSIBLE** AD as MODIFIED below:
  - Dementia established by clinical examination and documented by the Mini-Mental Test, Blessed Dementia Scale or similar examination and confirmed by neuropsychological test
  - Deficits in 2 or more areas of cognition;

Protocol summary (continued)

- Progressive worsening of memory and other cognitive functions (the patient must show a history of cognitive decline that has been progressive over a period of at least 6 months. There must be evidence of sustained memory deterioration in an otherwise alert patient, plus additional impairment in at least 1 of the following 5 areas: orientation, judgment and problem solving, functioning in community affairs, functioning in home and hobbies, and functioning in personal care.);
- no disturbance of consciousness;
- absence of systemic disorders or other brain diseases (EXCEPT AD and CEREBROVASCULAR DISEASE) that could account for the dementia;
- Radiologic evidence (satisfying the NINDS-AIREN radiologic criteria) as documented on a CT or MRI scan less than 12 months old of:
  . Multiple (2 or more) basal ganglion/white matter infarcts or lacunes, and/or
  . Single strategically placed infarct in angular gyrus/thalamus/basal forebrain/anterior cerebral artery or posterior cerebral artery territory, and/or
  . Extensive periventricular white matter lesions.

- Mild/moderate dementia as evidenced by a Mini-Mental State Examination score (MMSE) ranging from 10-25, boundaries included at screening and an Alzheimer's Disease Assessment Scale cognitive portion (ADAS-cog) score of at least 12 at screening;
- Patients must have the opportunity to perform certain activities of daily living. Patients living in residential homes can only be included if they have the opportunity (but not necessarily the capability) to live there independently;
- Disease onset between ages 40 and 90;
- Patients who live with or have regular daily visits from a responsible caregiver (visit frequency: preferably daily but at least 5 days/week). This includes friends, relatives or paid personnel. The caregiver should be capable of assisting with the patient's medication, prepared to attend with the patient for assessments and willing to provide information about the patient;
- Patient or patient's relative, guardian or legal representative and caregiver have signed the appropriate informed consent forms.

Exclusion criteria:

- Neurodegenerative disorders such as Parkinson's disease, Pick's disease, Huntington's chorea, Down's syndrome, or Creutzfeldt-Jacob disease.
  Mild extrapyramidal signs, for which no treatment is required, do not exclude the patient.
- Cognitive impairment resulting from the following:
  - Acute cerebral trauma (caused by posttraumatic brain injury, subdural hematoma) or injuries secondary to chronic trauma (such as boxing);
  - Hypoxic cerebral damage due to diseases / conditions other than cerebrovascular disease or cardiac causes of cerebral ischemia, e.g., post resuscitation (cardiac arrest), post anesthesia, sequel to severe self-poisoning episode, secondary to severe hypovolemia. (orthostatic hypotension should not lead to exclusion). Stroke following an episode of cardiac arrest and a current acute stroke (within the last 6 weeks) are not acceptable.
  - Vitamin deficiency states such as folate, vitamin B12 and other B complex deficiencies, e.g., thiamine deficiency in Korsakoff's syndrome;
  - Infection such as cerebral abscess, neurosyphilis, meningitis or encephalitides such as acquired immune deficiency syndrome (AIDS);
  - Primary or metastatic cerebral neoplasia;
  - Significant endocrine or metabolic disease e.g., untreated or uncontrolled thyroid, parathyroid or pituitary disease, Cushing's syndrome, and severe renal failure. (Patients with uncontrolled diabetes mellitus or those requiring insulin are excluded.);
  - Mental retardation or oligophrenia.
- Patients with the following coexisting medical conditions:
  - Any history of epilepsy or convulsions except for febrile convulsions during childhood;
  - Current clinically significant psychiatric disease, as judged by DSM-IV criteria, in particular current major depression or schizophrenia. Patients with moderate to severe or uncontrolled behavioral disturbances are excluded. Patients with mild disturbances who are well controlled with stable use of medication may be included.

Protocol summary (continued)

- Peptic ulcer: if the ulcer is considered to be still 'active', i.e., if treatment for this condition started less then 3 months ago or if treatment is not successful (symptoms still present), the patient is not eligible;
- Clinically significant hepatic, renal, pulmonary, metabolic or endocrine disturbances;
- Clinically significant urinary outflow obstruction.

- Current, clinically significant cardiovascular disease that would be expected to limit the patient's ability to complete a 13-month trial. The following would usually be considered clinically significant cardiovascular disease:
  - Cardiac surgery or myocardial infarction within the past 6 months;
  - Unstable cardiac disease that required a change in medication within the last 3 months;
  - Decompensated congestive heart failure, i.e., when symptoms occur in a patient on stable medication during rest or light exercise New York Heart Association (NYHA) Class III and IV;
  - Cardiac arrhythmia or conduction disturbance potentially resulting in ventricular fibrillation, or causing syncope, near syncope or other alterations of mental status. Atrial fibrillation without prophylactic treatment to prevent thromboembolic stroke. Atrial fibrillation alone is NOT to be considered an exclusion criterion. Bradycardia less than 50 beats/min., atrioventricular block greater than first degree;
  - Severe mitral or aortic valvular disease;
  - High blood pressure despite adequate medication (systolic blood pressure greater than 170 mmHg or diastolic blood pressure greater than 105 mmHg).
- Any agent used for the treatment of dementia (approved, experimental, including over the counter agents), including, but not limited to nootropic agents, cholinomimetic agents, choline, oestrogens taken for dementia, chronic nonsteroidal anti-inflammatory drugs (NSAIDs; 30 consecutive days, regardless of indication), vitamin E more than 30 IU daily, and Deprenyl® (selegiline) may not be used after enrollment in this trial.
- History of drug or alcohol abuse within the last year or prior prolonged history.
- Female patient of childbearing potential without adequate contraception. Barrier, spermicidal and hormonal methods are considered adequate contraception. Females of childbearing potential must not be pregnant at screening and must agree not to become pregnant during the trial.
- History of severe drug allergy or hypersensitivity, including recorded hypersensitivity to cholinesterase inhibitors, choline agonists or similar agents or bromide.
- Patients who have previously been enrolled in other galantamine studies or in this trial. Patients who were screened for previous galantamine studies but not enrolled may be rescreened for this study.
- Patients who have received an investigational medication within the last 30 days.
- Conditions that could interfere with absorption of the compound or with evaluation of the disease.

Treatment				
Form - dosing route	Medication (tablets – oral)			
	Placebo	Galantamine 4 mg	Galantamine 8 mg	Galantamine 12 mg
Batch number	98A12/F4, 98A13/F4, 98A15/F4, 98A16/F4	98H05/F5	98F15/F8	98A05/F9, 97L08/F9, 98A06/F9
Dosage	Run-in phase: placebo b.i.d. Double-blind phase: Week 1: 4 mg of galantamine or placebo o.d. (evening), Week 2: 4 mg or placebo b.i.d., Week 3: 4 mg or placebo morning + 8 mg or placebo evening, Week 4: 8 mg or placebo b.i.d., Week 5: 8 mg or placebo morning + 12 mg or placebo evening, Week 6 onwards: 12 mg or placebo b.i.d. Tablets were taken preferably with food around 8 AM and 6 PM.			
Duration of treatment	6 months			
Duration of trial	7 months: 1 month placebo run-in phase + 6 months double-blind phase			

Protocol summary (continued)

Disallowed medication	Drugs for treatment of dementia, including nootropic agents, cholinomimetic agents, choline, estrogens, chronic NSAIDs, vitamin E greater than 30 IU daily, Deprenyl® (selegiline)

Assessments	Screening	Baseline	Week 6	Month 3	Month 6
Efficacy					
• Primary variables					
- Alzheimer's Disease Assessment Scale-cog/11 (ADAS-cog/11)	x	x	x	x	x
- Clinician's Interview-Based Impression of Change-plus caregiver input (CIBIC-plus)		x		x	x
• Secondary variables					
- Response rate			x	x	x
- ADAS-cog/13, cog/10, cog/mem	x	x	x	x	x
- Disability Assessment in Dementia (DAD)		x		x	x
- Neuropsychiatric Inventory (NPI)		x		x	x
Safety					
• Adverse events			x	x	x
• Hematology, biochemistry, urinalysis	x	x	x		x
• Vital signs	x	x	x	x	x
• Electrocardiogram	x	x	x		x
• Weight	x				x

Statistical methods	
Change from baseline at Month 6 in ADAS-cog/11, ADAS-cog/13, ADAS-cog/10, ADAS-cog/mem, DAD, NPI	ANOVA model with treatment and country as factors (treatment-by-country interaction was tested and removed from the model when it was found not significant at the 10% level); paired t-test for within group comparison with baseline.
Change from baseline in ADAS-cog/11 at Week 6, Month 3, and Month 6	Mixed effects model
CIBIC-plus at Month 3 and Month 6	Van Elteren test controlling for country effect
Responder (based on change in ADAS-cog/11 score at Month 6)	Cochran-Mantel-Haenszel (CMH) test controlling for country effect
Adverse events	Number and % of patients with adverse events by treatment groups
Change from baseline in vital signs, body weight, ECG	Descriptive statistics of means and standard error (SE) of means, ANOVA with treatment and country as factors, % patients exceeding the clinically important limits at each time point
Laboratory safety parameters	Descriptive statistics of means and SE of means, number and % patients exceeding normal limits at each time point, number of patients with potentially clinically important changes

Main features of the patient sample and summary of the results

Baseline characteristics - patient disposition	Placebo	GAL 24 mg/day
Number of patients randomized (M/F)	105/91	207/189
Age: mean (± SE), yrs	75.2 ± 0.52	75.0 ± 0.34
Age: median (min-max), yrs	77.0 (52; 89)	76.0 (50; 90)
Diagnosis, n (%):		
• vascular dementia	81 (41.3%)	171 (43.2%)
• mixed dementia	97 (49.5%)	188 (47.5%)
• unknown	18 (9.2%)	37 (9.3%)
Discontinuation of treatment – reason[a]		
• other	6 (3.1%)	9 (2.3%)
• withdrawal of consent	1 (0.5%)	6 (1.5%)
• non-compliance	1 (0.5%)	4 (1.0%)
• insufficient response	2 (1.0%)	1 (0.3%)
• lost to follow-up	2 (1.0%)	0 (0%)
[a] Discontinuation for adverse events and number of deaths: see next page.		

Efficacy **Primary variables**	Placebo	GAL 24 mg/day	GAL minus Placebo LS means (95% CI) p-value
Primary variables at Month 6 (observed case):			
• ADAS-cog/11 change from baseline score, mean ±SE	(n=162) 1.0 ±0.48	(n=290) -1.7 ±0.36	-2.7 (-3.87, -1.52) p<0.001
• CIBIC-plus: improved or no change, n/N assessed (%)	95/161 (59.0%)	213/289 (73.7%)	p=0.001
ADAS-cog/11 imputed data at end points:	(n=194)	(n=388)	
• Classical intent to treat (CITT)	1.3 ±0.43	-1.2 ±0.30	-2.5 (-3.51, -1.47) p<0.001
• Last observation carried forward (LOCF)	(n=186) 1.1 ±0.45	(n=357) -1.5 ±0.31	-2.5 (-3.58, -1.47) p<0.001

Efficacy results: Treatment with galantamine resulted in greater cognitive and functional improvement over placebo as measured by both primary efficacy parameters. At Month 6, there was a mean decrease (improvement) in ADAS-cog/11 score of 1.7 point in the galantamine group compared to an increase of 1.0 point in the placebo group ($p<0.001$). Similar statistically significant results were obtained in the analyses of the traditional last observation carried forward and classical intent to treat data. The results on the ADAS-cog/13, cog/10 and cog/mem, total DAD score and total NPI score also demonstrated that significantly better scores are associated with galantamine versus placebo.

In the mixed dementia subgroup, galantamine treatment was also of greater benefit to cognitive performance, activities of daily living, and global function than placebo, as demonstrated by both primary efficacy parameters, and in the mean total DAD score.

In the vascular dementia subgroup, scores for the galantamine group were consistently numerically higher than placebo for all 4 efficacy variables. The differences between the treatment groups in patients with vascular dementia did not reach statistical significance, although the p-value approached statistical significance for ADAS-cog/11 ($p=0.06$).

Safety	Placebo (n=196)	GAL 24 mg/day (n=396)
Adverse events, n (%)		
Most frequently reported adverse events (≥5% of patients in any group):		
• nausea	14 (7.1%)	93 (23.5%)
• vomiting	11 (5.6%)	51 (12.9%)
• dizziness	9 (4.6%)	37 (9.3%)
• fall	16 (8.2%)	25 (6.3%)
• diarrhea	10 (5.1%)	31 (7.8%)
• headache	12 (6.1%)	23 (5.8%)
• depression	12 (6.1%)	19 (4.8%)
• abdominal pain	11 (5.6%)	21 (5.3%)
• injury	10 (5.1%)	15 (3.8%)
• insomnia	2 (1.0%)	20 (5.1%)
n (%) with ≥1 adverse event	133 (67.9%)	330 (83.3%)
n (%) of deaths	5 (2.6%)	7 (1.8%)
n (%) with ≥1 serious adverse event	50 (25.5%)	76 (19.2%)
n (%) discontinued treatment due to adverse event	20 (10.2%)	82 (20.7%)
Clinical laboratory parameters	No clinically important changes	
Vital signs	No clinically important changes	
Electrocardiogram	No clinically important changes	
Body weight (kg), mean change at Month 6	0.5 ± 0.3	-0.8 ± 0.22

Conclusions

Treatment with galantamine 24 mg/day resulted in greater cognitive and functional improvement over placebo as measured by both primary efficacy parameters, ADAS-cog/11 and CIBIC-plus. In the mixed dementia subgroup, galantamine was also significantly more effective than placebo. In the vascular dementia subgroup, galantamine showed a numerical advantage over placebo but did not reach statistical significance. These findings indicated a consistent trend for observed case, LOCF and CITT analyses. More patients had adverse events with galantamine than placebo, mostly due to gastrointestinal events, which were related to the rapid dose escalation used in this trial. There were no laboratory, vital signs or ECG findings of clinical significance. Galantamine appears to be safe in this patient population.

Date of the report: 21 January 2004

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