SYNOPSIS

Trial identification and protocol summary

Company: JANSSEN PHARMACEUTICA N.V. **Finished product**: Reminyl® **Active ingredient**: Galantamine (R113675)		
Title: Placebo-controlled evaluation of galantamine in the treatment of Alzheimer's disease: Evaluation of safety and efficacy under a slow-titration regimen	**Trial no**.: GAL-USA-10 **Clinical phase**: III	
Investigator: Multicenter	**Country**: United States	
Reference: N/A		
Trial period: Start: September 3, 1998 End: August 30, 1999	**No. of investigators**: 54 **No. of patients screened**: 1178 **No. of patients randomized**: 979 **No. of patients treated**: 978	

Indication / objectives: Alzheimer's disease with mild-to-moderate symptoms/ to assess the safety and efficacy of 8, 16, and 24 mg/day (4, 8, and 12 mg bid) galantamine compared with placebo with a slow-titration regimen.

Trial design: Multi-center, randomized, double-blind, placebo-controlled trial with 4 parallel treatment groups: Placebo, GAL 8 mg/day (4 mg bid), GAL 16 mg/day (8 mg bid), GAL 24 mg/day (12 mg bid), with a ratio of 2:1:2:2.

Patient selection:

- Inclusion criteria:
  - Male or female outpatients with probable AD in accordance with National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) classification for probable AD.
  - Patients living at home (out-patients) or patients living in residential homes for the elderly and day patients with dementia of the Alzheimer's type. Patients living in residential homes could be included only if they had the opportunity to live there independently; i.e., the opportunity must be given to perform the activities of daily living the ADL scale comprises. If a patient lived in a residential home, the decision about inclusion was made only after discussing the case with a Janssen representative
  - Mild/moderate dementia as evidenced by a Mini-Mental State Examination score (MMSE) ranging from 10 to 22, inclusive, at screening and an Alzheimer's Disease Assessment Scale cognitive portion (ADAS/cog-11) score of at least 18 at screening
  - History of cognitive decline that had been gradual in onset and progressive over a period of at least 6 months
  - Patients had to live with or have regular daily visits from a responsible caregiver (preferably daily visits but at least 5 days/week).
  - Patient or patient's relative, guardian, or legal representative and caregiver signed the informed consent form.
- Exclusion criteria:
  - Neurodegenerative disorders
  - Cognitive impairment resulting from the following:
    - Acute cerebral trauma
    - Hypoxic cerebral damage
    - Vitamin deficiency states
    - Infection
    - Primary or metastatic cerebral neoplasia
    - Significant endocrine or metabolic disease
    - Mental retardation
  - Multi-infarct dementia or clinically active cerebrovascular disease as evidenced by:
    - History of a significant cerebrovascular event
    - Multiple focal signs
    - More than one infarct on a computed tomography or magnetic resonance imaging scan taken within the last 12 months

- Patients with the following co-existing medical conditions:
  - . Any history of epilepsy or convulsions
  - . Current clinically significant psychiatric disease
  - . Active peptic ulcer
  - . 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 5-month trial
- Approved, experimental and/or over-the-counter agents for treatment of dementia; previous treatment with M_1 agonists or cholinesterase inhibitors had to be stopped 2 months before trial entry
- History of drug or alcohol abuse within the last year or a prior prolonged history
- Female patients of childbearing potential not using adequate contraception
- Patients who, in the opinion of the investigator, were otherwise unsuitable for a trial of this type
- History of severe drug allergy or hypersensitivity
- Patients who had previously been enrolled in other galantamine trials or in this trial
- Patients who had received an investigational medication within the last 30 days or who were currently entered in another clinical trial
- Conditions that could interfere with the absorption of the compound or with the evaluation of the disease.

Treatment				
Form - dosing route	matching tablets - oral			
Medication	Placebo	Galantamine 4 mg	Galantamine 8 mg	Galantamine 12 mg
Batch numbers	98A12/F4 98A13/F4 98A14/F4 98A15/F4 98A16/F4	98I08/F5 97L02/F5 97L03/F5 98B25/F5 98D27/F5 98F23/F5 98F19/F5 98F18/F5 98F22/F5 98D28/F5	97L04/F8 97L05/F8 98B26/F8 98D29/F8 98D30/F8 98D14/F8 98D10/F8 98I09/F8	98A05/F9 97L08/F9
Dosage	Two tablets daily, one with breakfast at approximately 8 AM and one with a meal at approximately 6 PM. Titration period was as follows: Weeks 1-4: 4 mg bid (GAL 8 mg/day, GAL 16 mg/day, and GAL 24 mg/day groups) or placebo Weeks 5-8: 4 mg bid (GAL 8 mg/day group), 8 mg bid (GAL 16 mg/day and 24 mg/day groups) or placebo Weeks 9-21: 4 mg bid (GAL 8 mg/day group), 8 mg bid (GAL 16 mg/day), 12 mg bid (GAL 24 mg/day) or placebo			
Duration of treatment	5 months			
Duration of trial	Single-blind run-in: 1 month; double-blind treatment: 5 months			
Disallowed medications	Drugs for treating dementia (nootropic agents, estrogens); chronic use of nonsteroidal antiinflammatory drugs, vitamin E, or deprenyl			

	Run-in	Double-blind			
Assessments	Screening	Baseline Week 1	Week 4	Week 13	Week 21
Efficacy					
• Alzheimer's Disease Assessment Scale (ADAS)	X	X	X	X	X
• Clinician's Interview-Based Impression of Change (CIBIC-plus)		X	X	X	X
• Alzheimer's Disease Cooperative Study/Activities of Daily Living Inventory (ADCS/ADL)		X	X	X	X
• Neuropsychiatric Inventory (NPI)		X	X	X	X
Safety					
• Adverse events			X	X	X
• Hematology, biochemistry, urinalysis	X	X	X	X	X
• Body weight	X				X
• Physician visit	X	X	X	X	X
• Physical examination	X	X		X	X
• Vital signs	X	X	X	X	X
• Electrocardiogram	X	X	X	X	X
Pharmacokinetics					
• Plasma sample		X	X	X	X

Statistical Methods	
Endpoint	**Method**
Change from baseline at Month 5 in ADAS-cog/11, ADAS-cog/13, ADAS-cog/10, ADAS-cog/mem, ADCS/ADL, NPI	ANOVA model with treatment and investigator as factors (treatment-by-investigator interaction was tested and removed from the model when it was found not significant at the 10% level)*;* a step-down closed test procedure for comparisons with placebo; paired t-test for within group comparison with baseline.
Change from baseline in ADAS-cog/11 at Week 4, Month 3, and Month 5	Mixed effects model
CIBIC-plus at Month 3 and Month 5	Van Elteren test controlling for investigator effect; a step-down, closed test procedure for comparisons with placebo
Responder (based on change in ADAS-cog/11 score at Month 5)	Cochran-Mantel-Haenszel (CMH) test controlling for investigator effect
Adverse events	Number and % of patients with AE by treatment groups
Change from baseline in vital signs, body weight, ECG	Descriptive statistics of means and SE of means, ANOVA with treatment and investigator as factors, % patients exceeding the clinically important limits at each time-point
Laboratory safety parameters	Descriptive statistics of means and SE of means, no. and % patients exceeding normal limits at each time-point, no. of patients with potentially clinically important changes
Pharmacokinetics	Descriptive statistics per dose, per visit, per sampling time

Main features of the patient sample and summary of the results

Baseline characteristics: patient disposition	Placebo	GAL 8 mg/day	GAL 16 mg/day	GAL 24 mg/day
Number of patients screened	1178			
Number of patients randomized	286	140	279	273
Number of patients treated (M/F)	108/178	50/90	105/174	90/183
Age (mean ± SE)	77.1 (0.46)	76.0 (0.61)	76.3 (0.49)	77.7 (0.43)
Patient years of exposure	108.3	51.2	102.4	100.7
Premature discontinuations – reason				
• Adverse event	20 (7.0%)	9 (6.4%)	19 (6.8%)	27 (9.9%)
• Inefficacy	0 (0.0%)	1 (0.7%)	0 (0.0%)	2 (0.7%)
• Patient ineligible to continue	0 (0.0%)	0 (0.0%)	4 (1.4%)	2 (0.7%)
• Non-compliance	3 (1.0%)	4 (2.9%)	7 (2.5%)	10 (3.7%)
• Other reasons	23 (8.0%)	18 (12.9%)	30 (10.8%)	20 (7.3%)
Total number discontinuations	46 (16.1%)	32 (22.9%)	60 (21.5%)	61 (22.3%)

Efficacy: Treatment with galantamine 16 and 24 mg/day was found significantly more effective than placebo, as measured by both primary efficacy endpoints: (1) change from baseline in ADAS-cog/11 at Month 5 [redacted] and (2) the observed CIBIC-plus scores at Month 5 [redacted].

This efficacy was also superior to that observed with 8 mg/day of galantamine. Galantamine treatment with 8 mg/day for 5 months maintained ADAS-cog/11 scores at baseline levels and was significantly different from patients who deteriorated with placebo [redacted] There was no significant difference between 16 mg and 24 mg/day galantamine in the change from baseline in ADAS-cog/11 and the CIBIC-plus scores at Month 5. However, patients in the 24 mg/day group were on their maintenance dose for one month less than the patients in the 16 mg/day group because of an additional titration step. Results from the analyses based on the last observation carried-forward (LOCF) and other imputed data corroborated these results.

Results from the analysis of the secondary efficacy parameters: the responders analysis (based on the change in ADAS-cog/11 score), ADAS-cog/13, ADAS-cog/10, ADAS-cog/mem, ADCS/ADL inventory scores, and NPI scores were consistent with those of the two primary endpoints. The percent of responders with improved or no change in ADAS-cog/11 score was significantly greater with 16 and 24 mg/day of galantamine compared with 8 mg/day or placebo. There were approximately 65% of patients with improvement or no change (change from baseline less than or equal to 0 at Month 5) at either 16 or 24 mg/day compared to 41.8% with placebo and 46.5% with 8 mg/day of galantamine. There was a statistically significant [redacted] benefit in ADCS/ADL inventory scores with 16 and 24 mg/day of galantamine after 5 months of treatment compared with placebo or 8 mg/day of galantamine. [redacted]

Primary efficacy parameters (observed case data) at Month 5				
	Placebo	GAL 8 mg/day	GAL 16 mg/day	GAL 24 mg/day
	Mean ± SE	Mean ± SE	Mean ± SE	Mean ± SE
Change from baseline in ADAS-cog/11 score at Month 5	(N=225) 1.8±0.43	(N=101) 0.1±0.58	(N=208) -1.5±0.40	(N=211) -1.8±0.44
	—	[redacted]	[redacted]	[redacted]
	n/N (%)	n/N (%)	n/N (%)	n/N (%)
CIBIC-plus at Month 5 Improved or no change	112/237 (47%)	54/106(51%)	143/212 (68%)	136/212 (64%)
			[redacted]	[redacted]

† Comparison of each galantamine group with placebo
‡Comparison with placebo using Van Elteren controlling for center effect based on the 7-point scale.

Primary efficacy parameters (last observed-case carried forward) at Month 5				
	Placebo	GAL 8 mg/day	GAL 16 mg/day	GAL 24 mg/day
	Mean ± SE	Mean ± SE	Mean ± SE	Mean ± SE
Change from baseline in ADAS-cog/11 score at Month 5	(N=255) 1.7±0.39	(N=126) 0.4±0.52	(N=253) -1.4±0.35	(N=253) -1.4±0.39
	—	—	[redacted]	[redacted]
	n/N (%)	n/N (%)	n/N (%)	n/N (%)
CIBIC-plus at Month 5 Improved or no change	128/263 (49%)	68/128 (53%)	169/255 (66%)	162/253 (64%)
			[redacted]	[redacted]

† Comparison of each galantamine group with placebo
‡Comparison with placebo using Van Elteren controlling for center effect based on the 7-point scale.

Secondary efficacy parameters (observed case data)				
	Placebo	GAL 8 mg/day	GAL 16 mg/day	GAL 24 mg/day
	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Responder (based on ≤0 point change from baseline in ADAS-cog/11 score)	94/225 (42%)	47/101 (47%)	136/208 (65%[redacted]	137/211 (65%[redacted]
Change from baseline at Month 5 for:				
ADAS-cog/13	(N=224) 1.8±0.48	(N=101) 0.1±0.65	(N=206) -1.7±0.45[redacted]	(N=209) -2.1±0.49[redacted]
ADAS-cog/10	(N=230) 2.2±0.37	(N=105) 0.4±0.47[redacted]	(N=209) -0.9±0.32[redacted]	(N=211) -0.9±0.35[redacted]
ADAS-cog/mem	(N=227) -0.2±0.21	(N=101) -0.1±0.34	(N=208) -0.9±0.24	(N=209) -1.2±0.24[redacted]
NPI total score	(N=234) 2.3±0.74	(N=106) 2.3±1.12	(N=211) -0.1±0.76[redacted]	(N=212) -0.1±0.86[redacted]
ADL overall score	(N=235) -4.0±0.59	(N=106) -3.1±0.91	(N=212) -0.5±0.55[redacted]	(N=212) -1.6±0.61[redacted]

[redacted]

Safety results: The most common adverse events were evenly distributed across treatment groups except for events commonly associated with cholinomimetic agents. Of these events, nausea, vomiting and anorexia showed a mild dose-related occurrence. Most GI-related adverse events in galantamine-treated patients were mild or moderate in severity. There were no dose-related increases in GI-related serious adverse events. The four most frequent serious adverse events seen with galantamine and with an incidence of at least 1% of patients in any group were injury (24 mg/day, 1.8%), syncope (24 mg/day, 1.8%), fall (8 mg/day, 2.9%), and myocardial infarction (8 mg/day, 2.1%). In comparison with placebo, the incidence of these adverse events was 1.4%, 0.7%, 1%, and 0.7%, respectively. The incidence of discontinuation due to adverse events was low and similar across the four treatment groups. Compared to previous large placebo-controlled trials using a faster titration design, the discontinuation rates were much lower in this study. There were no clinically important laboratory test value, vital sign, or ECG changes in galantamine-treated patients. There was a slight decrement in pulse rate (2-3 beats per minute) which is consistent with the mechanism of action of galantamine. The magnitude of this effect was of doubtful clinical significance. Weight loss appeared evenly distributed among treatment groups. Only small numbers of patients (1 to 3 patients in any group) experienced weight loss in excess of 15% of their baseline body weight. A total of 11 deaths were evenly distributed across treatment groups and none were attributed to galantamine. One patient died of injuries sustained in an automobile accident, 5 patients died of cardiac-related causes, and 5 patients died of pulmonary-related causes.

Overall, the slower dose titration schedule that was used in this trial, compared with previous double-blind, placebo-controlled trials with galantamine sponsored by JRF, was associated with a lower rate of cholinergically mediated adverse events. There were no unexpected, dose-related adverse events.

Safety				
	Placebo (N=286)	GAL 8 mg/day (N=140)	GAL 16 mg/day (N=279)	GAL 24 mg/day (N=273)
Adverse events (AE) Most frequently reported AE's ≥10%				
• Nausea	13 (4.5%)	8 (5.7%)	37 (13.3%)	45 (16.5%)
• Agitation	27 (9.4%)	21 (15.0%)	28 (10.0%)	22 (8.1%)
• Diarrhea	17 (5.9%)	7 (5.0%)	34 (12.2%)	15 (5.5%)
No. (%) with one or more AE	207 (72.4%)	106 (75.7%)	207 (74.2%)	219 (80.2%)
No. (%) of deaths	4 (1.4%)	1 (0.7%)	3 (1.1%)	3 (1.1%)
No. (%) with one or more serious AE	31 (10.8%)	14 (10.0%)	28 (10.0%)	35 (12.8%)
No. (%) treatment discontinued due to AE	20 (7.0%)	9 (6.4%)	19 (6.8%)	27 (9.9%)
Clinical laboratory parameters	No clinically important changes or values			
Vital signs	No clinically important changes or values			
Body weight (kg), mean change ± SE, Month 5	-0.1 ± 0.18	-0.5 ± 0.31	-0.6 ± 0.24	-1.3 ± 0.24***
ECG	No clinically important changes or values			

***: p<= 0.001 based on a two-way ANOVA model comparing each galantamine-treatment group with placebo

Drug concentrations	To be provided in a separate report.

Conclusions: Galantamine was found to be safe and effective in the treatment of Alzheimer's disease patients. Treatment with 16 or 24 mg/day for 5 months was effective in improving cognitive and global performance while maintaining activities of daily living skills and preventing the emergence of neuro-psychiatric symptoms. In addition, tolerability and discontinuations due to adverse events appeared to be improved with the slower titration schedule employed in this trial.