SYNOPSIS

Trial identification and protocol summary

Company: JANSSEN PHARMACEUTICA N.V. **Finished product**: Reminyl **Active ingredient**: Galantamine (R113675)		
Title: Efficacy and safety of galantamine 12 mg bid and 16 mg bid compared with placebo in the treatment of Alzheimer's disease	Trial no.: CR006025 **Clinical phase**: III	
Investigator: Multicenter	**Country**: United States	
Reference: JRF, Clinical Research Report CR006025, November 1998 (N133909)		
Trial period: Start: 07 November 1996 End: 05 November 1997	**No. of investigators**: 33 **No. of patients screened**: 764 **No. of patients randomized**: 636 **No. of patients treated**: 636	
Indication / objectives: Alzheimer's disease with mild to moderate symptoms/ to assess the efficacy, safety and tolerability of galantamine 24 mg/day or 32 mg/day compared with placebo.		
Trial design: double-blind, placebo-controlled, parallel group, randomized		

Patient selection:

- Inclusion criteria:
  - Male or female outpatients with Alzheimer's disease, including 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. The diagnosis was established in accordance with the National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association classification for probable Alzheimer's disease.
  - Mild/moderate dementia as evidenced by a Mini-Mental State Examination score (MMSE) ranging from 11 to 24 (extremes included) at screening *and* an Alzheimer's Disease Assessment Scale cognitive portion (ADAS-cog) score of at least 12 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 6-month trial
- Approved and/or over-the-counter agents for treatment of dementia; previous treatment with cholinesterase inhibitors had to be stopped 3 months before trial entry, and previous treatment with cholinomimetics was not allowed
- 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
- 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	galantamine 16 mg
Batch numbers	96F10/F4 96J14/F4 96J15/F4	96F12/F5	96F17/F8	96J16/F9 96J17/F9 96J18/F9 96J21/F9 96F20/F9 96F21/F9 96F22/F9 96F24/F9	96H06/F10 96H07/F10 96H08/F10 96H09/F10 96J14/F10 96J15/F10 96J16/F10 96J17/F10
Dosage	Two tablets daily; one with breakfast at approximately 8 AM and one with a meal at approximately 6 PM. Four-week titration period as follows: Week 1: 4 mg bid (GAL 24 mg/day group and GAL 32 mg/day group) or placebo Week 2: 8 mg bid (GAL 24 mg/day group and GAL 32 mg/day group) or placebo Week 3: 12 mg bid (GAL 24 mg/day group and GAL 32 mg/day group) or placebo Week 4: 12 mg bid (GAL 24 mg /day group); 16 mg bid (GAL 32 mg/day group) or placebo Week 5 to Month 6: GAL 12 mg bid, GAL 16 mg bid or placebo				
Duration of treatment	6 months				
Duration of trial	single blind run-in: 1 month; double blind treatment: 6 months				
Disallowed medications	drugs for treating dementia (nootropic agents, estrogens); chronic use of nonsteroidal antiinflammatory drugs, vitamin E, or deprenyl				

	Run-in	Double-blind (W=Week; M=Month)							
Assessments	Screen	Baseline	W1,2,4	W3	M2	M3	M4	M5	M6
Efficacy									
• Alzheimer's Disease Assessment Scale (ADAS)	x	x		x		x			x
• Clinician's Interview-Based Impression of Change (CIBIC)		x				x			x
• Disability Assessment in Dementia (DAD)		x				x			x
• Resource use		x		x	x	x	x	x	x
• Psychological General Well-Being Index (PGWB)		x				x			x
Safety									
• Adverse events		x	x	x	x	x	x	x	x
• Hematology, biochemistry, urinalysis	x	x		x	x	x	x	x	x
• Physical examination	x	x				x			x
• Vital signs	x	x		x	x	x	x	x	x
• Electrocardiogram	x	x			x				x
Pharmacokinetics									
• Plasma sample		x			x		x[a]		x

a: Predose and approximately 1-2 hours and 4-5 hours postdose.

Statistical Methods	
Endpoint	**Method**
Change from baseline at Month 6 in ADAS-cog/11, ADAS-cog/13, ADAS-cog/10, ADAS-cog/mem, DAD scores	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); Dunnett's test procedure for comparisons with placebo; paired t-test
Change from baseline in ADAD-cog/11 at Week 3, Months 3 and 6	Mixed effects model
CIBIC-plus	Van Elteren test controlling for investigator effect; Holm's test procedure for comparisons with placebo
Responder (based on change in ADAS-cog/11 score at Month 6	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, ANOVA with treatment and investigator as factors, % patients exceeding the clinically important limits at each time point
Laboratory safety parameters	descriptive statistics, no. and % patients exceeding normal limits at each time point, no. of patients with potentially clinically important changes
Outcomes (PGWB)	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); Dunnett's test procedure for comparisons with placebo; paired t-test
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 24 mg/day	GAL 32 mg/day
Number of patients screened	764		
Number of patients randomized	213	212	211
Number of patients treated (M/F)	82/131	73/139	87/124
Age (mean ± SE)	75.3 ± 0.58	75.9 ± 0.51	75.0 ± 0.58
Patient years of exposure	95	83	72
Premature discontinuations – reason			
• Adverse event	16 (7.5%)	49 (23.1%)	67 (31.8%)
• Patient withdrew consent	19 (8.9%)	11 (5.2%)	13 (6.2%)
• Lost to follow up	1 (0.5%)	2 (0.9%)	1 (0.5%)
• Noncompliant	2 (0.9%)	3 (1.4%)	4 (1.9%)
• Other	3 (1.4%)	3 (1.4%)	4 (1.9%)
Total number of discontinuations (%)	41 (19.2%)	68 (32.1%)	89 (42.2%)

Efficacy:

There were significant differences between each galantamine dose and placebo as measured by both primary efficacy endpoints: (1) change from baseline in patients' ADAS-cog/11 at Month 6 and (2) the observed CIBIC-plus scores at Month 6. The mean change in ADAS-cog/11 score during the 6 months were 2.2, -1.7, and -1.6 points in the placebo, galantamine 24, and 32 mg/day groups, respectively. There were 55%, 70%, and 68% of patients with "improved" or "no change" in CIBIC-plus score with placebo, GAL 24 mg/day, and GAL 32 mg/day, respectively. Treatment effects were significant at Month 3 as measured by both primary efficacy endpoints. Results from the repeated measures analysis on ADAS-cog/11 score indicated that treatment effects increased significantly over time. Results from the analysis of the secondary efficacy endpoints, the responders analysis (based on the change in ADAS-cog/11 score), ADAS-cog/13, ADAS-cog/10, and ADAS-cog/mem, were consistent with that for the two primary efficacy endpoints. There was no significant difference between either galantamine dose and placebo in change from baseline at Month 6 in DAD scores. There was no difference among the three treatment groups at Month 6, but a significant difference at Month 6 between the GAL 32 mg/day and placebo groups was found for the overall PGWB score.

Primary efficacy parameters (observed case data)			
	Placebo	GAL 24 mg/day	GAL 32 mg/day
	Mean ± SE	Mean ± SE	Mean ± SE
Change from baseline in ADAS-cog/11 score at Month 6	(N=157) 2.2 ± 0.52	(N=131) -1.7 ± 0.45	(N=117) -1.6 ± 0.66
	—	($p \leq 0.001$)†	($p \leq 0.001$) †
	n/N (%)	n/N (%)	n/N (%)
CIBIC-plus at Month 6 Improved or no change	88/159 (55%)	95/135 (70%)	80/118 (68%)
	—	($p=0.023$)‡	($p=0.017$)‡

† Comparison with placebo using Dunnett's test procedure in ANOVA

‡ Comparison with placebo using Van Elteren test and Holm's test procedure based on the original 7-point scale.

Additional analysis of change from baseline at Month 6 in ADAS-cog/11 score (imputed data)			
	Placebo	GAL 24 mg/day	GAL 32 mg/day
	Mean ± SE	Mean ± SE	Mean ± SE
Classical intent-to-treat	(N=213) 2.2 ± 0.44	(N=212) -1.1 ± 0.39***	(N=211) -0.8 ± 0.45***
Traditional last observation carried-forward	(N=207) 2.0 ± 0.45	(N=202) -1.9 ± 0.36***	(N=197) -1.4 ± 0.44***
Observed case + Retrieved drop-out[a]	(N=164) 2.2 ± 0.51	(N=155) -1.4 ± 0.42***	(N=140) -1.3 ± 0.59***

Comparison with placebo using Dunnett's test procedure in ANOVA: *** $p \leq 0.001$
a: A retrieved drop-out was a patient who discontinued treatment but remained in the trial until next scheduled visit.

Secondary efficacy parameters (observed case data)			
	Placebo	GAL 24 mg/day	GAL 32 mg/day
Responder	n/N (%)	n/N (%)	n/N (%)
(based on ≤0 point change from baseline in ADAS-cog/11 score)	69/157(44%)	84/131(64%)***	68/117(58%)**
Change from baseline at Month 6 in	Mean ± SE	Mean ± SE	Mean ± SE
ADAS-cog/13	(N=155) 2.3 ± 0.57	(N=130) -2.2 ± 0.51***	(N=117) -1.8 ± 0.76***
ADAS-cog/10	(N=161) 2.1 ± 0.46	(N=134) -0.8 ± 0.38***	(N=118) -0.7 ± 0.49***
ADAS-cog/mem	(N=156) 0.4 ± 0.28	(N=132) -1.0 ± 0.30**	(N=118) -1.1 ± 0.43**
DAD total score	(N=164) -2.8 ± 1.23	(N=139) -2.9 ± 1.27	(N=117) -1.7 ± 1.40
PGWB overall score	(N=149) -1.8 ± 1.06	(N=126) -2.8 ± 0.99	(N=112) 1.1 ± 1.25*

Comparisons with placebo: CMH test for the responder analysis, ANOVA, and Dunnett's test procedure for change in scores for ADAS and DAD; Fisher's LSD for PGWB. * $p \leq 0.05$** $p \leq 0.01$; *** $p \leq 0.001$

Safety:
The most frequent dose-related adverse events were nausea, vomiting, diarrhea, anorexia, and weight loss. These events have previously been reported to be associated with other cholinesterase inhibitors. Although gastrointestinal events were frequent in galantamine-treated patients, they did not typically result in significant complications. Most GI-related adverse events in galantamine-treated patients were mild or moderate in severity. These event were the predominent cause for discontinuation with galantamine, although these events were not serious in nature. Bradycardia and syncope occurred more frequently with galantamine than with placebo. However, most of the affected galantamine-treated patients were asymptomatic for bradycardia, and the incidence of syncope was not increased in patients with galantamine 24 mg/day compared with placebo. There were no consistent differences in the incidence or pattern of serious adverse events with galantamine. The overall rate of discontinuation due to serious adverse events was similar for patients treated with galantamine compared with placebo. There were no clinically important laboratory test value, vital sign, or ECG changes (except a slowing of heart rate) in galantamine-treated patients. Although there was a mean weight loss with galantamine, this loss was not extreme or life threatening in individual patients. One death occurred in each treatment group but none were considered drug-related.

Safety			
	Placebo (N=213)	GAL 24 mg/day (N=212)	GAL 32 mg/day (N=211)
Adverse events (AE) Most frequently reported AE's ≥10%			
• Nausea	28 (13.1%)	80 (37.7%)	92 (43.6%)
• Vomiting	16 (7.5%)	44 (20.8%)	54 (25.6%)
• Anorexia	13 (6.1%)	30 (14.2%)	43 (20.4%)
• Dizziness	25 (11.7%)	30 (14.2%)	41 (19.4%)
• Diarrhea	21 (9.9%)	27 (12.7%)	41 (19.4%)
• Injury	30 (14.1%)	34 (16.0%)	25 (11.8%)
• Agitation	33 (15.5%)	24 (11.3%)	18 (8.5%)
• Weight decrease	10 (4.7%)	26 (12.3%)	26 (12.3%)
• Headache	16 (7.5%)	20 (9.4%)	24 (11.4%)
• Urinary tract infection	23 (10.8%)	24 (11.3%)	20 (9.5%)
• Abdominal pain	10 (4.7%)	15 (7.1%)	23 (10.9%)
No. (%) with one or more AE	175 (82.2%)	197 (92.9%)	197 (93.4%)
No. (%) of deaths	1 (0.5%)	1 (0.5%)	1 (0.5%)
No. (%) with one or more serious AE	27 (12.7%)	29 (13.7%)	34 (16.1%)
No. (%) treatment discontinued due to AE	16 (7.5%)	49 (23.1%)	67 (31.8%)
Clinical laboratory parameters	no clinically important values or changes		
Vital signs	no clinically important values or changes		
Body weight (kg), mean change±SE, Month 6	0.1 ± 0.33	-2.1 ± 0.37***	-2.5 ± 0.38***
ECG	no clinicially important values or changes		

***p<= 0.001, difference from placebo

Drug concentrations Galantamine plasma concentrations, ng/ml	GAL 24 mg/day Mean ± SD (n)	GAL 32 mg/day Mean ± SD (n)
Plasma samples were taken within the dosing interval of 10 hours between bid doses		
• Month 2	87.9 ± 31.7 (155)	113 ± 56.(133)
• Month 4	89.4 ± 31.2 (295)	114 ± 47.2 (243)
• Month 6	82.9 ± 31.4 (120)	117 ± 47.3 (103)
During a plasma sampling time period for Month 4:		
Predose (trough)	40.3 ± 22.3 (132)	53.1 ± 31.6 (107)
>0h - ≤3h (near peak)	96.5 ± 34.8 (148)	121 ± 51 (123)
>3h - ≤10h	82.2 ± 25.4 (147)	106 ± 43 (.120)

Conclusions

Galantamine at daily doses of 24 mg or 32 mg was significantly more effective than placebo in the treatment of patients with mild to moderate Alzheimer's disease. Testing of both primary efficacy endpoints, ADAS cog/11 and CIBIC-plus scores, showed consistent results for comparisons with placebo at Month 6, at earlier timepoints, and after adjusting for discontinuation rate. Patients discontinued treatment more frequently with galantamine than placebo, primarily for dose-related gastrointestinal events predictable for an agent with cholinesterase-inhibiting pharmacology. Serious adverse events were not more frequent or of different types than with placebo. No clinically important changes occurred in clinical laboratory, ECG, or vital signs findings, except for a minor decrease in heart rates. Therefore, galantamine treatment appears to be safe and effective, and its tolerability is consistent with that expected for a drug of its class.

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