SYNOPSIS

Trial identification and protocol summary

Company: JANSSEN PHARMACEUTICA N.V. **Finished product**: Reminyl™ **Active ingredient**: Galantamine (R113675)		
Title: Efficacy, tolerability and safety of galantamine 12 and 16 mg b.i.d. versus placebo in the treatment of Alzheimer's disease	**Trial No.**: CR006031 **Clinical phase**: III	
Investigators: Multicentre	**Countries**: Canada, Finland, France, Germany, Norway, Sweden, The Netherlands, United Kingdom	
Reference: JRF, Clinical Research Report CR006031, January 1999 (N 134124)		
Trial period: Start: 24 January 1997 End: 9 March 1998	**No. of investigators**: 149 **No. of patients screened/randomized/treated:** 753/653/653	
Indication / objectives: Mild to moderate Alzheimer's disease / to assess the efficacy, tolerability and safety of galantamine 24 and 32 mg per day compared to placebo.		
Trial design: double-blind, placebo-controlled, parallel groups, randomized		

Patient selection:

- Inclusion criteria:
  - Male or female outpatients with Alzheimer's disease. This also included patients living in residential homes for the elderly and day patients with dementia of the Alzheimer's type. Patients living in residential homes could only be included 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 11-24 extremes included, at screening <u>and</u> an Alzheimer's Disease Assessment Scale cognitive portion (ADAS-cog) score of at least 12 at screening;
  - History of cognitive decline which had been gradual in onset and progressive over a period of at least six 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 <u>and</u> 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:
    - A history of a significant cerebrovascular event
    - Multiple focal signs
    - More than one infarct on a CT or MRI 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
  - . Peptic ulcer: if the ulcer was to be considered still 'active'
  - . 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 months trial;
- Approved and/or over the counter agents for treatment of dementia; previous treatment with cholinesterase inhibitors had to be stopped 3 months prior to entry into the trial and previous treatment with cholinomimetics was not allowed;
- History of drug or alcohol abuse within the last year or prior prolonged history;
- Female patient of childbearing potential without adequate contraception;
- Patients who, in the opinion of the investigator, were otherwise unsuitable for such a trial;
- 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 number:	96F09/F4 96J15/F4 96J14/F4	96E06/F5	96F17/F8 96F18/F8	96F19/F9 96K07/F9 96F25/F9 96J21/F9 96J22/F9	96K08/F10 96J18/F10
Dosage	2 tablets daily; one with breakfast around 8 AM and one with a meal around 6 PM; 4-week titration: 4 mg b.i.d. week 1, 8 mg b.i.d. week 2, 12 mg b.i.d. week 3, and 16 mg b.i.d. week 4 only for patients on 32 mg/d.				
Duration of treatment	6 months				
Duration of trial	single-blind placebo run-in period: ≤4 weeks, double-blind: 6 months				
Disallowed medication	drugs for treatment of dementia, such as nootropic agents, oestrogens, chronic use of NSAIDs, vitamin E, deprenyl				

	Run-in	Double-blind							
Assessments	screen	baseline	wks 1,2,4	wk 3	mo. 2	mo. 3	mo. 4	mo. 5	mo. 6
Drug concentration		x			x		x[a)]		x
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
Outcomes research									
• Resource use		x		x	x	x	x	x	x
• Psychological General Well-Being index		x				x			x

a) Samples taken pre dose and approximately at 1-2 h and 4-5 h post dose.

	Run-in	Double-blind							
Assessments	screen	baseline	wks 1,2,4	wk 3	mo. 2	mo. 3	mo. 4	mo. 5	mo. 6
Safety									
• Adverse events		x	x	x	x	x	x	x	x
• Haematology, 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
• ECG	x	x			x				x

Statistical Methods	
Parameters	**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 country as factors (treatment-by-country 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 ADAS-cog/11 at Week 3, Month 3 and 6	Mixed effects model
CIBIC-plus	Van Elteren test controlling for country 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 country effect
Adverse events	Number and % of patients with AE by treatment groups
Change from baseline in vital signs, body weight, ECG	Descriptive statistics, paired t-test, ANOVA with treatment and country 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 country as factors (treatment-by-country 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
Resource use	Descriptive statistics, Cochran-Mantel-Haenszel test controlling for country, ANOVA with factors treatment and country, Kaplan Meier test, Cox proportional hazards test, Wilcoxon signed rank test
Pharmacokinetics	Descriptive statistics per dose, per visit, per sampling time
Drug concentrations	
Bioanalysis	Galantamine : HPLC-method with fluorescence detection (LOQ : 1-2 ng/ml)
Statistics	Descriptive statistics were calculated per dose, per visit and per sampling time (for Month 4)

Main features of the patient sample and summary of the results

Baseline characteristics - patient disposition	Placebo (N=215)	GAL 24 mg/day (N=220)	GAL 32 mg/day (N=218)
Number of patients treated (M/F)	83/132	81/139	80/138
Age: mean (±SE), yrs	72.7 (±0.52)	71.9 (±0.56)	72.1 (±0.58)
Premature discontinuations- reason			
• Adverse events	19 (8.8%)	31 (14.1%)	48 (22%)
• Non-compliance	4 (1.9%)	4 (1.8%)	1 (0.5%)
• Other	3 (1.4%)	8 (3.6%)	4 (1.8%)
• Insufficient response	3 (1.4%)	1 (0.5%)	0
• Ineligibility	0	0	2 (0.9%)
Total no. of discontinuations	29 (13.5%)	44 (20%)	55 (25.2%)

Efficacy	Placebo	GAL 24 mg/day	GAL 32 mg/day
Primary variables at month 6 (observed case):			
• ADAS-cog/11 change from baseline score, mean ±SE	(n=171) 2.4 ±0.44	(n=156) -0.7 ±0.48***	(n=152) -1.7 ±0.47***
• CIBIC-plus: improved or no change, n/N assessed (%)	86/174 (49.4%)	108/161 (67.1%) p=0.002[a)]	106/155 (68.4%) p<0.001[a)]
ADAS-cog/11 imputed data at end points:			
• Classical intent to treat	(n=215) 2.4 ±0.41	(n=220) -0.5 ±0.38***	(n=217) -0.8 ±0.43***
• Traditional last observation carried forward	(n=207) 2.2 ±0.40	(n=201) -0.6 ±0.40***	(n=205) -1.3 ±0.38***
• Observed case + retrieved drop-out[b)]	(n=178) 2.4 ±0.42	(n=168) -0.40 ±0.46***	(n=171) -1.0 ±0.51***

Asterisks refer to differences with placebo
Levels of significance: ◊ p ≤ 0.1; * p ≤ 0.05; **p ≤0.01, ***p ≤0.001
a) Comparison with placebo based on the original 7-point scale

b) A retrieved drop-out is a patient who discontinued treatment but remained in the trial

Efficacy	Placebo	GAL 24 mg/day	GAL 32 mg/day
Secondary variables at month 6			
• Response (improvement or no change in ADAS-cog 11 score), n/N assessed (%)	68/171 (39.8%)	102/156 (65.4%)***	97/152 (63.8%)***
• ADAS-cog/13, mean change ±SE	2.1 ±0.47	-1.0 ±0.53***	-1.9 ±0.52***
• ADAS-cog/mem, mean change ±SE	0.6 ±0.27	0.1 ±0.29	-0.8 ±0.29***
• ADAS-cog/10, mean change ±SE	1.8 ±0.36	-0.9 ±0.35***	-1.1 ±0.37***
• DAD total score, mean change ±SE	-5.2 ±1.21	-2.7 ±1.17	-1.4 ±1.32◊
• PGWB total score, mean change ±SE	-1.1 ±0.97	-1.3 ±1.12	-0.7 ±0.94

Asterisks refer to differences with placebo
Levels of significance: ◊ p ≤ 0.1; * p ≤ 0.05; **p ≤0.01, ***p ≤0.001

Safety (n = number of patients with data)	Placebo (n=215)	GAL 24 mg/day (n=220)	GAL 32 mg/day (n=218)
Adverse events (AE) Most frequently reported AE (≥10% of patients in any group):			
• nausea	26 (12.1%)	82 (37.3%)	87 (39.9%)
• vomiting	9 (4.2%)	45 (20.5%)	37 (17%)
• diarrhoea	16 (7.4%)	16 (7.3%)	29 (13.3%)
• dizziness	10 (4.7%)	24 (10.9%)	26 (11.9%)
• headache	7 (3.3%)	21 (9.5%)	25 (11.5%)
• abdominal pain	11 (5.1%)	18 (8.2%)	21 (9.6%)
• anorexia	0	22 (10%)	23 (10.6%)
• injury	24 (11.2%)	19 (8.6%)	20 (9.2%)
No. (%) with one or more AE	165 (76.7%)	182 (82.7%)	194 (89%)
No. (%) of deaths	2 (0.9%)	2 (0.9%)	0
No. (%) with one or more other serious AE	25 (11.6%)	29 (13.2%)	27 (12.4%)
No. (%) treatment discontinued due to AE	19 (8.8%)	31 (14.1%)	48 (22%)
Clinical laboratory parameters	There were no apparent clinically important changes		
Vital signs	There were no apparent clinically important changes		
Body weight, mean change at month 6 ±SE	0.2 ±0.30	-1.4 ±0.28***	-1.4 ±0.34***
ECG	There were no apparent clinically important changes		

Asterisks refer to differences with placebo
Levels of significance: ***p ≤0.001

Drug concentrations Galantamine plasma concentrations, ng/ml	GAL 24 mg/day mean ± SD (n)	GAL 32 mg/day mean ± SD (n)
Within a dosing interval of 10 hours :		
• Month 2	93.5 ± 33.8 (136)	126 ± 48 (131)
• Month 4	96.7 ± 34.1 (292)	125 ± 43 (279)
• Month 6	89.8 ± 34.6 (117)	117 ± 53 (122)
During a dosing interval at Month 4 :		
Predose (trough)	46.0 ± 24.4 (140)	57.4 ± 25.8 (136)
>0h - ≤3h (near peak)	106 ± 36 (145)	137 ± 44 (139)
>3h - ≤10h	89.8 ± 27.8 (138)	116 ± 34 (132)

Conclusions

The results of the present trial demonstrate that:

- Galantamine, at daily doses of 24 mg or 32 mg, was significantly more effective than placebo. This was consistently shown by both primary efficacy parameters, ADAS-cog/11 and CIBIC-plus at month 6 and at all imputed data at end points.
- More patients had adverse events with galantamine, mostly due to gastrointestinal adverse events. However, serious adverse events were not more frequent than with placebo. Galantamine treatment appears to be safe and its tolerability is in line with what is expected for a cholinomimetic agent.

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