SYNOPSIS

Trial identification and protocol summary

Company: JANSSEN PHARMACEUTICA N.V. **Finished product**: Reminyl **Active ingredient**: Galantamine (R113675)		
Title: Galantamine in the treatment of Alzheimer's Disease: Flexible dose range trial.	**Trial No.**: CR006028 **Clinical phase**: III	
Investigator: Multi-Center	**Country**: Multi-National	
Reference: JRF, Clinical Research Report CR006028, February 1998 (N 133910)		
Trial period: Start: 06 June 1997 End: 15 April 1998	**No. of investigators**: 43 **No. of patients randomized**: 386	
Indication / objectives: This trial evaluated the safety and efficacy of a "flexible" bid regimen of galantamine 12/16 mg bid in the treatment of Alzheimer's Disease.		
Trial design: Double blind, flexible dose, 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 or oligophrenia

Exclusion criteria (continued)

- 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 3-month trial
- Approved, experimental, and/or over-the-counter agents for treatment of dementia; previous treatment with cholinesterase inhibitors, and previous treatment with cholinomimetics was not allowed unless patient's previous participation in a cholinesterase inhibitor trial could clearly be shown to be in the placebo arm, or if patient had previously received tacrine and was discontinued before an effective dose was reached due to liver toxicity
- 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	8 mg	12 mg	16 mg
Batch numbers:	96K05/F4 96K04/F4	96F13/F5	96F18/F8	96K07/F9	96K08/F10 97B21/F10
Dosage	Galantamine or placebo (randomised 2:1) as two tablets daily; one with breakfast at approximately 8 AM and one with a meal at approximately 6 PM. Dose escalation as follows: Week 1: 4 mg bid or placebo Week 2: 8 mg bid or placebo Week 3: 12 mg bid or placebo Flexible dose: Week 4: 12 or 16 mg bid. or placebo Target dose: Weeks 5-12; 12 or 16 mg bid or placebo				
Duration of treatment	3 months				
Duration of trial	run-in period: 1 month; double-blind period: 3 months				
Disallowed medications	drugs for treating dementia (nootropic agents, estrogens); chronic use of nonsteroidal antiinflammatory drugs, vitamin E (>30 IU daily), or deprenyl				

	Run-in	Double-blind (W=Week; M=Month)				
Assessments	Screen	Baseline	W3	W4	M2	M3
Drug concentration		x	x[a]			x
Efficacy						
• Alzheimer's Disease Assessment Scale (ADAS)	x	x		x		x
• Clinician's Interview-Based Impression of Change (CIBIC)		x		x		x
• Disability Assessment in Dementia (DAD)		x		x		x
• Neuropsychiatric Inventory (NPI)		x		x		x
Safety						
• Adverse events			x	x	x	x
• Hematology, biochemistry, urinalysis	x	x	x		x	x
• Physical examination	x	x				x
• Vital signs	x	x	x	x	x	x
• Electrocardiogram	x	x		x		x
• Pittsburgh Sleep Scale		x		x		x
At the end of Week 1 and Week 2, patients were contacted by phone and adverse events and concomitant medications were collected. a: Predose and 1.5 hours post morning dose						

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 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
CIBIC-plus	Van Elteren test controlling for country
Responder (based on change in ADAS-cog/11 score at Month 3	Cochran-Mantel-Haenszel (CMH) test controlling for country
Adverse events	Number and % of patients with AE by treatment groups
Change from baseline in vital signs, ECG	Descriptive statistics, ANOVA as described above, % patients exceeding normal limits and the clinically important limits at each timepoint
Laboratory safety parameters	% patients exceeding normal limits and the clinically important limits at each timepoint
PSQI	Descriptive statistics, ANOVA as described above
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	Galantamine (12 mg bid or 16 mg bid)	Total
Number of patients screened			534
Number of patients randomized	125	261	386
Number of patients treated (M/F)	58/67	113/148	171/215
Age (mean ± SE)	74.6 ± 0.68	75.2 ± 0.45	75.0 ± 0.37
Patient years of exposure	30	52	
Premature discontinuations – reason			
Adverse events	5 (4.0%)	66 (25.3%)	71 (18.4%)
Ineligible to continue trial	2 (1.6%)	2 (0.8%)	4 (1.0%)
Noncompliant	0 (0%)	3 (1.1%)	3 (0.8%)
Withdrew consent	1 (0.8%)	1 (0.4%)	2 (0.5%)
Other	4 (3.2%)	14 (5.4%)	18 (4.7%)
Total number of discontinuations (%)	12 (9.6%)	86 (33.0%)	98 (25.4%)

Efficacy:

Patients treated with galantamine (24 or 32 mg/day when administered as 12 mg bid or 16 mg bid doses, respectively) were significantly improved when compared to placebo at Month 3 on both primary endpoints, the ADAS-cog/11 and the CIBIC-plus. The mean change in ADAS-cog/11 score from baseline to Month 3 were 0.5 points for the placebo group and -1.4 points for the combined galantamine groups. For the CIBIC-plus rating, 63% of patients in the placebo group and 79% of patients in the galantamine groups were rated as "improved" or "no change" at Month 3 from baseline. Significant differences between the placebo and galantamine groups were also found in the secondary endpoint DAD. The mean change in DAD scores from baseline to Month 3 were -4.2 for the placebo group and 0.1 for the galantamine groups. Additional analyses using three imputed datasets, classical ITT, traditional LOCF, and Observed Case + Retrieved Dropouts, also revealed statistically significant differences between the galantamine and placebo groups, suggesting that the treatment effect, although small, was robust. Treatment with galantamine was significantly more effective than placebo as measured by the secondary efficacy endpoints ADAS-cog/13, ADAS-cog/10 and responders analysis (0, 4, and 7 point cut-offs). No significant differences between the placebo and galantamine groups were found in the secondary efficacy endpoints ADAS-cog/mem or NeuroPsychiatric Index.

Primary efficacy parameters (observed case data)		
	Placebo	**Galantamine (24 and 32 mg/day)**
ADAS-cog/11 at Month 3		
Mean ± SE	25.0 ± 0.97 (n=108)	23.7 ± 0.81 (n=170)
Change from baseline	0.5 ± 0.42	-1.4 ± 0.40**
CIBIC-plus at Month 3	**n/N (%)**	**n/N (%)**
Improved or no change	70/111 (63%)	135/170 (79%)*

** $p \leq 0.01$, test for no difference between treatments from ANOVA model on change from baseline

* $p = 0.003$, comparison with placebo using Van Elteren test based on the original 7-point scale

Additional analyses of change from baseline at Month 3 in ADAS-cog/11 (imputed data)						
	Placebo			**Galantamine (24 and 32 mg/day)**		
	N	Mean ±SE	Mean Change ± SE	N	Mean ±SE	Mean Change ± SE
Traditional LOCF	120	25.0 ±0.90	0.6 ±0.45	239	24.7 ±0.72	-1.1 ±0.33**
Classical ITT	125	25.6 ± 0.92	0.7 ± 0.47	260	24.8 ± 0.68	-0.9 ± 0.31**
OC+Ret. D/O	110	25.2 ±0.96	0.8 ±0.46	197	24.2 ±0.77	-1.1 ±0.37**

**: p≤0.01, test for no difference between treatments from ANOVA model on change from baseline

Disability Assessment for Dementia at Month 3 (Total DAD)

Primary Efficacy	Placebo			Galantamine		
	N	Mean ± SE	Mean Change ± SE	N	Mean ± SE	Mean Change ± SE
Observed Case	110	68.3 ±2.18	-4.2 ±1.16	172	70.1 ±1.70	0.1 ±0.87**
Classical ITT	125	67.7 ±2.05	-5.3 ±1.17	261	67.9 ±1.46	-1.2 ±0.83**
Traditional LOCF	123	67.7 ±2.08	-5.2 ±1.18	241	68.9 ±1.50	-0.4 ±0.76***
OC+Ret. D/O	112	67.7 ±2.18	-4.8 ±1.24	197	68.9 ±1.62	-0.5 ±0.87**

** p≤ 0.01; *** p≤ 0.001 test for no difference between treatments from ANOVA model; analysis at baseline using actual value, at other timepoints, on change from baseline.

Safety:

The overall safety profile of galantamine is consistent with its presumed cholinomimetic/anticholinesterase pharmacology. Adverse events which occurred more frequently in the galantamine group compared to placebo were related to the gastrointestinal system, such as nausea, vomiting, and diarrhea. Serious adverse events were similar between galantamine ane placebo groups. There were no deaths in the galantamine group; 2 deaths occurred in the placebo group. There were no apparent clinically important laboratory findings, vital sign changes, or ECG findings in any of the treatment groups. Overall, galantamine was well tolerated by patients in this trial.

Summary of Adverse Events		
	Placebo (N=125)	Galantamine (N=261)
Most frequently reported AEs ≥ 10%		
Nausea	14 (11.2%)	84 (32.2%)
Dizziness	5 (4.0%)	39 (14.9%)
Diarrhea	13 (10.2%)	38 (14.6%)
Vomiting	5 (4.0%)	38 (14.6%)
Anorexia	3 (2.4%)	31 (11.9%)
Number (%) with one or more adverse event	79 (63.2%)	225 (86.2%)
Number (%) of deaths	2 (1.6%)	0 (0%)
Number (%) with one or more serious adverse event[a]	7 (5.6%)	22 (8.4%)
Number (%) treatment discontinued due to adverse event	5 (4.0%)	66 (25.3%)

a: during treatment or within 30 days after termination of trial medication.

Drug concentrations		
Bioanalysis*:* HPLC-method with fluorescence detection of galantamine (LOQ : 1-2 ng/ml)		
Results*:*		
Galantamine plasma concentrations, ng/ml	GAL 24 mg/day mean ± SD (n)	GAL 32 mg/day mean ± SD (n)
During dosing interval in Week 3: Predose (trough) >0hr - ≤3hr (near peak)	 49.6 ± 34.1 (194) 102 ± 42 (217)	 # #
Within 10 hours after the last drug intake Month 3	 93.1 ± 43.2 (61)	 125 ± 50 (89)

#: At Week 3 all patients received GAL 24 mg/day

Conclusions

Galantamine (24 and 32 mg/day) was significantly more effective than placebo in the treatment of patients with mild to moderate Alzheimer's disease. A significant improvement in galantamine treated groups as compared to placebo was consistently seen in both primary endpoints, the ADAS-cog/11 and the CIBIC-plus, at Month 3, as well as at Week 4, and also after adjusting for discontinuation rate. Patients discontinued treatment more frequently with galantamine than with placebo, primarily for dose-related gastrointestinal events predictable for an agent with cholinesterase-inhibiting pharmacology. Serious adverse events were similar between galantamine and placebo groups. No clinically important changes occurred in clinical laboratory, vital signs, or ECG findings. Therefore, galantamine treatment appears to be safe and effective, and its tolerability is consistent with that expected for a drug of its class. The flexible dose design of this trial revealed that, upon allowing clinical judgement, a subset of patients could be identified who tolerate galantamine up to 32 mg/day well, with a lower discontinuation rate in this subgroup (14.9%) than has been previously observed.

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