Janssen Research & Development

Clinical Research Report Synopsis
[GAL-INT-7; Phase IIIb]

JNJ-17335630-AAD (Galantamine)

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SYNOPSIS

Trial identification and protocol summary

Company: JANSSEN PHARMACEUTICA N.V. **Finished product**: Reminyl™ **Active ingredient**: Galantamine (R113675)		
Title: Long-term safety and efficacy of galantamine in the treatment of Alzheimer's disease	**Trial No.**: GAL-INT-7 **Clinical phase**: IIIb	
Investigator: Multicentre	**Countries**: Australia, Canada, New Zealand, Republic of South Africa, United Kingdom	
Reference: JRF, Clinical Research Report GAL-INT-7, October 1999 (N 141990)		
Trial period: Start: 12 November 1997 End: 23 June 1999	**No. of investigators**: 25 **No. of patients entered**: 144	
Indication / objectives: Mild to moderate Alzheimer's disease / assess the long-term safety and efficacy of galantamine 24 mg daily		
Trial design: long-term, open-label extension of double-blind trial GAL-INT-2		

Patient selection:

- Inclusion criteria:
  - Patients in Australia, New Zealand, Canada, the Republic of South Africa and the United Kingdom who completed trial GAL-INT-2. Patients were considered to have completed the trial if:
    . The patient completed 3 months of double-blind medication and completed visit 6 of trial GAL-INT-2, as scheduled; or
    . The patient discontinued the double-blind medication prematurely, at the investigator's recommendation, because of lack of efficacy or because of adverse events deemed not to be drug-related, but returned for all of the follow-up assessments specified in the protocol (GAL-INT-2, visit 6).
  - The patient and their primary caregiver gave informed consent for participation in the trial.
  - Patients remained in good health, as determined by medical history, complete physical examination, laboratory tests and ECG.
- Exclusion criteria:
  - Patients who prematurely discontinued the trial GAL-INT-2 due to lack of compliance or withdrawal of consent or due to adverse events deemed to be probably related to the trial medication.
  - Patients who developed, during the trial GAL-INT-2, symptoms of other neurological or psychiatric diseases that might contribute to dementia. This included patients developing neurodegenerative disorders such as Parkinson's disease, Pick's disease or Huntington's chorea, or Creutzfeldt-Jacob disease, and patients with cognitive impairment resulting from stroke, acute cerebral trauma, hypoxic cerebral damage, infection or primary or metastatic cerebral neoplasia.
    Additionally, patients could not be enrolled if they experienced significant loss of consciousness, transient ischaemic attack or 'drop attacks', other neurological signs or symptoms, stepwise deterioration, or had sustained head injury subsequent to entry into trial GAL-INT-2.
  - Patients with the following co-existing medical conditions:
    . Any history of epilepsy or convulsions except for febrile convulsions during childhood.
    . Peptic ulcer: if the ulcer was to be considered still 'active', i.e., if treatment for this condition started <3 months ago or if treatment was not successful (still symptoms present), the patient was not eligible.
    . Clinically significant hepatic, renal, pulmonary, metabolic or endocrine disturbances.

- Patients with current, clinically significant cardiovascular disease that would be expected to limit the patient's ability to complete a nine-month trial. The following would usually be considered clinically significant cardiovascular disease:
  . Unstable angina; angina or coronary artery disease that required a change in medication (anti-angina or digitalis) 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 (NYHA III and IV). Note: if the only signs of decompensation were pretibial or malleolar œdema and the exercise tolerance was still reasonable (absence of dyspnoea) the patient was not excluded.
  . Cardiac disease potentially resulting in syncope, near syncope or other alterations of mental status. In addition, the following conditions led to exclusion: atrial fibrillation without prophylactic treatment to prevent thrombo-embolic stroke, bradycardia < 50 beats /min., atrioventricular block > first degree.
  . Severe mitral or aortic valvular disease.
  . Uncontrolled high blood pressure (systolic blood pressure greater than 170 mmHg or diastolic blood pressure greater than 110 mmHg).
- Patients receiving 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 without medical need, chronic NSAIDs (30 consecutive days), vitamin E more than 30 IU daily, and deprenyl. Acetyl Salicylic Acid taken in doses up to 325 mg daily to prevent cardio- or cerebrovascular disease did not exclude the patient.
- Patients with a history of drug or alcohol abuse within the last year or prior prolonged history.
- Female patients of childbearing potential without adequate contraception.
  Females of childbearing potential could not be pregnant at entry and had to agree not to become pregnant during the trial.
- Patients who, in the opinion of the investigator, were otherwise unsuitable for a trial of this type.
- Patients with a history of severe drug allergy or hypersensitivity; including recorded hypersensitivity to cholinesterase inhibitors, choline agonists or similar agents or bromide.
- Patients who received an investigational medication other than galantamine within the last 30 days.
- Patients suffering from conditions that could interfere with the absorption of the compound or with the evaluation of the disease

Treatment						
Form - dosing route	tablets - oral					
Medication	Galantamine 4 mg		Galantamine 8 mg		Galantamine 12 mg	
Batch number	H954		I087		I128	
Dosage	2 tablets daily; one with breakfast around 8 AM and one with a meal around 6 PM; 3-week titration: 4 mg b.i.d. week 1, 8 mg b.i.d. week 2, 12 mg b.i.d. from week 3 onwards					
Duration of treatment	9 months					
Duration of trial	9 months					
Disallowed medication	drugs for treatment of dementia, such as nootropic agents, oestrogens, chronic use of NSAIDs, vitamin E more than 30 IU daily, deprenyl					
Assessments	Initial visit (month 3 GAL-INT-2)	weeks 1, 2, 3	month 1	month 3	month 6	month 9
Efficacy						
• Alzheimer's Disease Assessment Scale (ADAS)	x			x		x
• Disability Assessment in Dementia (DAD)	x			x		x
• Psychological General Well-Being index (PGWB)text	x			x	x	x

Assessments	Initial visit (month 3 GAL-INT-2)	weeks 1, 2, 3	month 1	month 3	month 6	month 9
Safety						
• Adverse events	x	x	x	x	x	x
• Haematology, biochemistry, urinalysis	x		x	x	x	x
• Physical examination	x		x			x
• ECG	x		x			x
• Vital signs	x		x	x	x	x
• Weight						x

Statistical methods	
Variable	**Method**
Change from baseline GAL-INT-2 and initial visit (month 3 GAL-INT-2) at month 12 in ADAS-cog/11, -cog/13, -cog/10, -cog/mem, DAD, PGWB	Two-way ANOVA with treatment and country as factors for between-group comparisons, paired t-test for within-group comparisons
Responder based on change in ADAS-cog/11 score at month 12	Number and percent of responders by treatment group
Adverse events	Number and % of patients with AE by treatment group
Change from baseline and initial visit in vital signs, body weight, ECG	Two-way ANOVA with treatment and country as factors for between-group comparisons, paired t-test for within-group comparisons
Laboratory results	Tabulations of values outside normal and pathological limits (potentially clinically important values)

Main features of the patient sample and summary of the results

Treatment group reflects treatment received in the preceding double-blind trial GAL-INT-2.

Baseline characteristics – patient disposition	PLA/GAL 24 mg/day	GAL/GAL 24 mg/day
Number of patients entered (M/F)	23/30	48/43
Age: mean ± SE, yrs	74 ± 1	73.3 ± 0.79
Premature discontinuations- reason		
• Adverse events	11 (20.8%)	13 (14.3%)
• Withdrawal of consent	3 (5.7%)	0
• Ineligibility	1 (1.9%)	0
• Insufficient response	1 (1.9%)	0
Total no. of discontinuations (%)	16 (30.2%)	13 (14.3%)

Efficacy: primary variables	PLA/GAL 24 mg/day	GAL/GAL 24 mg/day
• ADAS-cog/11 change from baseline (GAL-INT-2) at month 12 [a)], mean ±SE	(n=34) 1.5 ± 1.11	(n=72) 0.3 ± 0.66
• ADAS-cog/11 change from initial visit (month 3 INT-2) at month 12, mean ±SE	(n=34) 1.6 ± 1.06	(n=70) 1.9** ± 0.69

a) change from baseline at month 12 corresponds to a 12-month change (3 months double-blind GAL-INT-2 + 9 months open)

Asterisks refer to within group differences
Level of significance: **p ≤0.01

Efficacy: Secondary variables	PLA/GAL 24 mg/day	GAL/GAL 24 mg/day
Change from baseline (GAL-INT-2) at month 12:		
• Response (improvement or no change in ADAS-cog 11 score), n/N assessed (%)	16/34 (47.1%)	36/72 (50.0%)
• ADAS-cog/13, mean change ±SE	1.6 ± 1.26	0.6 ± 0.79
• ADAS-cog/mem, mean change ±SE	0.7 ± 0.75	-0.0 ± 0.46
• ADAS-cog/10, mean change ±SE	1.2 ± 0.81	0.7 ± 0.50
• DAD total score, mean change ±SE	-12.4*** ± 2.79	-5.9** ± 1.99
Change from initial visit (month 3 GAL-INT-2) at month 12:		
• Response (improvement or no change in ADAS-cog 11 score), n/N assessed (%)	15/34 (44.1%)	30/70 (42.9%)
• ADAS-cog/13, mean change ±SE	1.9 ± 1.19	2.4** ± 0.82
• ADAS-cog/mem, mean change ±SE	0.7 ± 0.67	0.9◊ ± 0.47
• ADAS-cog/10, mean change ±SE	1.2 ± 0.76	1.6** ± 0.57
• DAD total score, mean change ±SE	-7.5* ± 3.06	-5.5*** ± 1.64
• PGWB total score, mean change ±SE	-8.1** ± 2.43	-1.8 ± 1.78

Asterisks refer to within group differences
Levels of significance: * p ≤ 0.05; **p ≤0.01, ***p ≤0.001

Safety (n = number of patients with data)	PLA/GAL 24 mg/day (n=53)	GAL/GAL 24 mg/day (n=91)
Adverse events (AE) Most frequently reported AE (≥10% of patients in any group)		
• nausea	14 (26.4%)	13 (14.3%)
• diarrhoea	9 (17.0%)	10 (11.0%)
• dizziness	9 (17.0%)	8 (8.8%)
• depression	7 (13.2%)	3 (3.3%)
• vomiting	6 (11.3%)	5 (5.5%)
• somnolence	6 (11.3%)	5 (5.5%)
• injury	6 (11.3%)	3 (3.3%)
No. (%) with one or more AE	49 (92.5%)	77 (84.6%)
No. (%) of deaths	1 (1.9%)	2 (2.2%)
No. (%) with one or more serious AE	8 (15.1%)	10 (11.0%)
No. (%) treatment discontinued due to AE	11 (20.8%)	13 (14.3%)
Clinical laboratory parameters	No clinically important changes	
Vital signs	No clinically important changes	
ECG	No clinically important changes	
Body weight, change from screening at month 12, mean ±SE, kg	-2.1** ± 0.68	-0.0 ± 0.47

Conclusions

Treatment with galantamine 24 mg/day maintained cognitive performance at near baseline levels after 12 months of treatment (3 months double-blind followed by 9 months open-label). Delaying galantamine treatment by 3 months still reduced the gradual decline observed in the natural evolution of Alzheimer's disease, but the treatment benefit was smaller than when treatment was started earlier.

Galantamine treatment was found to be safe up to a year of exposure. No unexpected adverse events were seen in patients who received twelve months of treatment. Although there is an inevitable selection bias in open extension trials, treatment during months four through twelve appeared to be better tolerated overall.