Janssen Research & Development

Clinical Research Report Synopsis
[GAL-INT-3; Phase III]

JNJ-17335630-AAD (Galantamine)

Redaction and Removal of Information in This Document

- Information (including individual data listings, where applicable) has been removed or redacted to protect the privacy of patients, study subjects, and all named persons associated with the study. Names of companies other than Janssen Research & Development or Johnson & Johnson affiliates have been redacted, unless a contractual agreement is in place with those companies to disclose their names.
- Information has been removed or redacted to protect commercially confidential information.
- Aggregate data have been included, with any direct reference to an individual patient or study subject excluded.
- To disclose as much scientifically useful data as possible, no information other than that outlined above has been removed or redacted.

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-3 **Clinical phase**: III	
Investigator: Multicentre	**Countries**: Canada, Finland, France, Germany, Norway, Sweden, The Netherlands, United Kingdom	
Reference: JRF, Clinical Research Report GAL-INT-3, June 1999 (N 141565)		
Trial period: Start: 26 August 1997 End: 20 September 1998	**No. of investigators**: 76 **No. of patients entered**: 469	
Indication / objectives: Mild to moderate Alzheimer's disease / assess the long-term efficacy and safety of galantamine 24 mg daily		
Trial design: long-term, open-label extension of double-blind trial GAL-INT-1		

Patient selection:

- Inclusion criteria:
  - Patients completed trial GAL-INT-1. A patient was considered to have completed the trial if:
    - The patient completed 6 months of double-blind medication and completed visit 8 of trial GAL-INT-1 as scheduled; or
    - The patient discontinued double-blind medication at the investigator's recommendation due to lack of efficacy or due to adverse events that were deemed not to be drug related, but returned for all of the follow-up assessment visits specified in the protocol (GAL-INT-1, visits 5 and 8).
  - Patients and their primary caregiver gave informed consent for the patient's participation in the trial.
  - Patients remained in good health as determined by medical history, complete physical examination, laboratory tests, and ECG.
  - Patients were to enrol in this trial within one month after completing the final visit (visit 8) of trial GAL-INT-1.
- Exclusion criteria:
  - Patients who discontinued from trial GAL-INT-1 due to lack of compliance or withdrawal of consent or due to adverse events deemed to be probably related to trial medication.
  - Patients who developed, during trial GAL-INT-1, 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, Huntington's chorea, or Creutzfeldt-Jakob 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 had experienced significant loss of consciousness, transient ischaemic attack or 'drop attacks', other neurological signs or symptoms, stepwise deterioration, or had sustained head injury during trial GAL-INT-1.
  - 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 considered still 'active', i.e., if treatment for this condition started <3 months ago or if treatment was not successful (symptoms still present).
    - Clinically significant or unstable 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 6-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, that is, when symptoms occurred in a patient on stable medication during rest or light exercise (NYHA III and IV). If the only signs of decompensation were pretibial or malleolar oedema 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 per minute, atrioventricular block > first degree.
. Severe mitral or aortic valvular disease.
. Uncontrolled high blood pressure (systolic blood pressure greater than 170 mm Hg or diastolic blood pressure greater than 110 mm Hg).

- Patients taking any agent being used for the treatment of dementia (approved, experimental or 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 were not pregnant at screening and agreed 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 with 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	Galantamine 4 mg	Galantamine 8 mg	Galantamine 12 mg
Batch number	96F13/F5, H954	96F18/F8, I087	96F24/F9, 97B17/F9, 96F20/F9, I110, I298, I603
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. week 3		
Duration of treatment	6 months		
Duration of trial	6 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 6 GAL-INT-1)	weeks 1, 2, 3	month 1	month 2	month 3	month 6
Efficacy:						
• Alzheimer's Disease Assessment Scale (ADAS)	x				x	x
• Clinician's Interview-Based Impression of Change (CIBIC)	x				x	x

Assessments	Initial visit (final visit GAL-INT-1)	Weeks 1, 2, 3	Month 1	Month 2	Month 3	Month 6 (final)
• Disability Assessment in Dementia (DAD)	x				x	x
• Resource use	x				x	x
• Psychological General Well-Being index (PGWB)	x				x	x
Safety:	x	x	x	x	x	x
• Adverse events						
• Haematology, biochemistry, urinalysis	x		x		x	x
• Physical examination	x		x			x
• ECG	x		x			x
• vital signs	x		x	x	x	x

Statistical methods	
Variable	**Method**
Change at Month 6 in ADAS-cog/11, -cog/13, -cog/10, -cog/mem, DAD, PGWB	ANOVA, paired t-test, Dunnett's adjustment for multiple comparisons
CIBIC-plus	Cochran-Mantel-Haenszel, Van Elteren test
Adverse events	Number/% with AE
Change in vital signs, body weight, ECG	ANOVA, paired t-test, Fisher's LSD
Laboratory results	Tabulations of values outside normal and pathological limits

Main features of the patient sample and summary of the results

Baseline characteristics - patient disposition	PLA/ GAL24 mg/day (N=168)	GAL24/ GAL24 mg/day (N=155)	GAL32/ GAL24 mg/day (N=146)
Number of patients treated (M/F)	65/103	66/89	59/87
Age: mean ±SE, yrs	72.6 ± 0.56	72.3 ± 0.7	72.2 ± 0.73
Premature discontinuation - reason:			
• adverse events	25 (14.9%)	14 (9.0%)	11 (7.5%)
• insufficient response	2 (1.2%)	0	1 (0.7%)
• other	0	0	2 (1.4%)
• ineligibility	0	1 (0.6%)	0
• non-compliance	0	1 (0.6%)	0
• withdrawal of consent	2 (1.2%)	1 (0.6%)	1 (0.7%)
Total no. of discontinuations	29 (17.3%)	17 (11.0%)	15 (10.3%)

Efficacy: primary variables	PLA/ GAL24 mg/day	GAL24/ GAL24 mg/day	GAL32/ GAL24 mg/day	GAL24,32/ GAL24 mg/day
• ADAS-cog/11 change from baseline (GAL-INT-1) at month 6 (open)[a)], mean ±SE	(n=127) 2.2*** ± 0.53	(n=131) 1.8** ± 0.64	(n=122) 0.4 ± 0.55	(n=253) 1.2** ± 0.43
• ADAS-cog/11 change from initial visit (month 6 INT-1) at month 6 (open), mean ±SE	(n=124) -0.1 ± 0.48	(n=127) 2.8*** ± 0.52	(n=121) 2.8*** ± 0.49	(n=248) 2.8*** ± 0.36

Efficacy: primary variables	PLA/ GAL24 mg/day	GAL24/ GAL24 mg/day	GAL32/ GAL24 mg/day	GAL24,32/ GAL24 mg/day
• CIBIC-plus: improved or no change from initial visit (start INT-3) at month 6 (open), n/N assessed (%)	90/136 (66.2%)	75/136 (55.1%) p=0.050[a)]	68/134 (50.7%) p=0.008[a)]	143/270 (53%) p=0.007[b)]

Asterisks refer to within group differences
Levels of significance: ◊ p ≤ 0.1; * p ≤ 0.05; **p ≤0.01, ***p ≤0.001
a) change from baseline at month 6 corresponds to a 12-month change (6 months double-blind GAL-INT-1+ 6 months open)

b) Comparison with placebo based on the original 7-point scale

Efficacy: Secondary variables	PLA/ GAL24 mg/day	GAL24/ GAL24 mg/day	GAL32/ GAL24 mg/day	GAL24,32/ GAL24 mg/day
Change from baseline (GAL-INT-1) at month 6 open-label (12-month change):				
• Response (improvement or no change in ADAS-cog 11 score), n/N assessed (%)	51/127 (40.2%)	58/131 (44.3%)	61/122 (50.0%)	119/253 (47.0%)
• ADAS-cog/13, mean change ±SE	2.0*** ± 0.59	1.9** ± 0.71	0.1 ± 0.63	1.0* ± 0.48
• ADAS-cog/mem, mean change ±SE	0.4 ± 0.30	0.7 ◊ ± 0.37	-0.3 ± 0.32	2.0 ± 0.25
• ADAS-cog/10, mean change ±SE	1.8*** ± 0.42	1.4** ± 0.50	0.7 ± 0.45	1.0** ± 0.34
• DAD total score, mean change ±SE	-6.2*** ± 1.78	-7.3*** ± 1.48	-6.8*** ± 1.51	-7.1*** ± 1.06
• PGWB total score, mean change ±SE	-1.9 ± 1.28	-5.9*** ± 1.40	-4.1** ± 1.26	not done
Change from initial visit (month 6 GAL-INT-1) at month 6 open-label:				
• ADAS-cog/13, mean change ±SE	-0.2 ± 0.51	3.1*** ± 0.58	2.7*** ± 0.58	2.9*** ± 0.41
• ADAS-cog/mem, mean change ±SE	-0.5 ◊ ± 0.28	0.8* ± 0.30	0.8* ± 0.35	0.8*** ± 0.23
• ADAS-cog/10, mean change ±SE	0.3 ± 0.39	2.6*** ± 0.45	2.0*** ± 0.43	2.3*** ± 0.31
• DAD total score, mean change ±SE	-1.9 ± 1.39	-5.4*** ± 1.44	-6.5*** ± 1.37	-5.9*** ± 0.99

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

Safety (N = number of patients with data)	PLA/ GAL24 mg/day (N=168)	GAL24/ GAL24 mg/day (N=155)	GAL32/ GAL24 mg/day (N=146)	GAL24,32/ GAL24 mg/day (N=301)
Adverse events (AE)				
Most frequently reported AE (≥10% of patients in any group)				
• Nausea	49 (29.2%)	32 (20.6%)	19 (13.0%)	51 (16.9%)
• Vomiting	20 (11.9%)	12 (7.7%)	9 (6.2%)	21 (7.0%)
• Bradycardia	6 (3.6%)	9 (5.8%)	14 (9.6%)	23 (7.6%)
• Headache	18 (10.7%)	8 (5.2%)	11 (7.5%)	19 (6.3%)
No. (%) with one or more AE	145 (86.3%)	121 (78.1%)	118 (80.8%)	239 (79.4%)
No. (%) of deaths	0	2 (1.3%)	1 (0.7%)	3 (1.0%)
No. (%) with one or more serious AE	19 (11.3%)	22 (14.2%)	13 (8.9%)	35 (11.6%)

Safety (N = number of patients with data)	PLA/ GAL24 mg/day (N=168)	GAL24/ GAL24 mg/day (N=155)	GAL32/ GAL24 mg/day (N=146)	GAL24,32/ GAL24 mg/day (N=301)
No. (%) treatment discontinued due to AE	25 (14.9%)	14 (9.0%)	11 (7.5%)	25 (8.3%)
Clinical laboratory parameters Changes	There were no apparent clinically important changes			
Vital signs	There were no clinically important changes			
ECG	There were no clinically important changes			
Body weight, mean change from screening at month 6 (open-label) ±SE (kg)	0.2 ±0.73	0.1 ±0.39	-1.1** ±0.37	-0.5 ±0.27

Asterisks refer to within group differences
Levels of significance: ◊ $p \leq 0.1$; * $p \leq 0.05$; **$p \leq 0.01$, ***$p \leq 0.001$

Conclusions

Treatment with galantamine for 12 months (6 months double-blind followed by 6 months open-label) reduces the gradual deterioration in cognitive function observed in the natural history of Alzheimer's disease. Delaying treatment by 6 months still adds a benefit but the treatment response is smaller, suggesting the need for early treatment. The tolerability of galantamine appears to improve with the duration of exposure, and 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 seven through twelve appeared to be better tolerated overall.