Janssen Research & Development

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

JNJ-17335630-AAD (Galantamine)

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- 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-USA-3 **Clinical phase**: III	
Investigator: Multicenter	**Country**: USA	
Reference: JRF, Clinical Research Report GAL-USA-3 **January 1999 N133911**		
Trial period: Start: 17 July 1997 End: 10 April 1998	**No. of investigators**: 33 **No. of patients**: 356 **(**353 treated)	
Indication / objectives: Alzheimer's disease with mild to moderate symptoms/ The primary objective was to evaluate the long-term safety and efficacy of galantamine in patients with Alzheimer's disease (AD). Secondary objective was to evaluate the impact of long-term treatment with galantamine on informal family caregiver quality of life and on health/social care resource use.		
Trial design: Long-term, open-label outpatient trial; continuation of double-blind trial GAL-USA-1		

Patient selection:

- Inclusion criteria:
  - Patients completed trial GAL-USA-1. Patients were considered to have completed the trial if they:
    - completed 6 months of double-blind medication and completed Visit 8 of trial GAL-USA-1, as scheduled;

    or

    - discontinued double-blind medication prematurely, at the investigator's recommendation, because of lack of efficacy or because of adverse events which were deemed not to be drug related, but returned for all of the follow-up assessment visits specified in the protocol (GAL-USA-1, Visits 5 and 8). Note: Patients who discontinued trial GAL-USA-1 were reviewed on a case-by-case basis with a Janssen representative prior to entry into trial GAL-USA-3.
  - Patients remained in good health, as determined by medical history, complete physical examination, laboratory tests and ECG.

- Exclusion criteria:
  - Patients who prematurely discontinued from trial GAL-USA-1 due to lack of compliance or withdrawal of consent or due to adverse events deemed to be probably related to trial medication were not eligible for the present protocol.
  - If a patient had developed, during trial GAL-USA-1, symptoms of other neurological or psychiatric diseases that might contribute to dementia, the investigator contacted a representative of Janssen Research Foundation before enrolling the patient. This applied to 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, the investigator was to contact a representative of Janssen Research Foundation before enrolling the patient if the patient experienced significant loss of consciousness, transient ischemic attack or 'drop attacks', other neurological signs or symptoms, stepwise deterioration, or sustained head injury during trial GAL-USA-1.
  - Patients with the following co-existing medical conditions:
    a. Any history of epilepsy or convulsions except for febrile convulsions during childhood.
    b. Peptic ulcer: 'active', i.e., if treatment for this condition started <3 months earlier or if treatment was not successful (still symptoms present), the patient was not eligible.

c. 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 six-month trial. The following would usually be considered clinically significant cardiovascular disease:

- a. Unstable angina; angina or coronary artery disease that required a change in medication (anti-angina or digitalis) within the last 3 months.
  b. Decompensated congestive heart failure, i.e., when symptoms occurred 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 edema and the exercise tolerance was still reasonable (absence of dyspnea) the patient was not to be excluded.
  c. Cardiac disease potentially resulting in syncope, near syncope or other alterations of mental status. In addition, the following conditions led to exclusion: atrial fibrillation, bradycardia < 50 beats/min., atrio-ventricular block > first degree.
  d. Severe mitral or aortic valvular disease.
  e. 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, estrogens taken without medical need, chronic NSAIDs (30 consecutive days), vitamin E more than 30 IU daily, and deprenyl.
- 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 must not be pregnant at screening and must 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 with conditions that could interfere with the absorption of the compound or with the evaluation of the disease.
- Possible pregnancy or lactation

Treatment			
Form - dosing route	matching tablets - oral		
Dose	4 mg	8 mg	12 mg
Galantamine batch number (expiration date)	970917P (5-99)	970920P (5-99)	970922P (5-99) 970921P (5-99) 97B17/F9 (2-99) 97B18/F9 (2-99) 97B19/F9 (2-99) 97B20/F9 (2-99)
Dosage	2 tablets daily (bid); with meals, at 8 AM and 6 PM		
Duration of treatment	6 months		
Duration of trial	6 months		
Disallowed medication	drugs for treating dementia (nootropic or cholinomimetic agents, estrogens, chronic NSAIDs, ≥30 IU vitamin E daily, deprenyl); sedatives given more than twice weekly		

Assessments	Initial (Final visit of GAL-USA-1)	Weeks 1,2,3	M 1	M 2	M 3	M 4,5	Final M6
Efficacy							
• ADAS	x				x		x
• CBIC-plus	x				x		x
• DAD	x				x		x
Safety							
• Vital signs	x		x	x	x		x
• Physical exam	x		x				x
• Adverse events	x	x	x	x	x	x	x
• Clinical laboratory	x		x		x		x
• ECG	x		x				x

ADAS= Alzheimer's Disease Assessment Scale; CIBIC=Clinician's Interview-based Impression of Change; DAD=Disability Assessment in Dementia; M=Month

Statistical Methods	
Variable	**Method**
Change at Month 6 in ADAS-cog/11, -cog/13, -cog/10, -cog/mem DAD, PGWB	ANOVA, paired t-test, Fisher's LSD ANCOVA (subgroup only)
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

	Group		
Baseline characteristics: patient disposition	PLA/GAL12 BID N=135	GAL12/GAL12 BID N=116	GAL16/GAL12 BID N=102
Number of patients treated (M/F)	50/85	46/70	49/53
Age: yrs; (mean±SE)	75.3±0.7	75.9±0.7	75.2±0.7
Premature discontinuations - reason			
• adverse event	40 (29.6%)	10 (8.6%)	8 (7.8%)
• noncompliant	3 (2.2%)	1 (0.9%)	3 (2.9%)
• other	6 (4.4%)	9 (7.8%)	5 (4.9%)
Total # of discontinuations	49 (36.3%)	20 (17.2%)	16 (15.7%)

Efficacy:

Patients treated with 12 mg bid of galantamine for the duration of 12 months were no different than baseline in their ADAS-cog/11 scores. However, patients treated with 16 mg bid of galantamine or placebo for 6 months and then switched to 12 mg bid of galantamine for an additional 6 months of treatment showed deterioration in cognitive function as was demonstrated by an increase in ADAS-cog/11 scores. The percentage of patients rated improved or unchanged from the initial visit on the CIBIC-plus was similar in all groups: 53.6%, 61.0% and 56.0% in the former placebo, 12 mg bid and 16 mg bid groups, respectively, and 58.6% in all patients treated with galantamine for 12 months. The group treated with 12 mg bid galantamine for 12 months showed relatively little change in secondary variables measuring change from baseline. Relative to baseline, there was no significant change in caregiver psychological well-being, as measured by the PGWB, over the twelve-month period.

	Group			
Primary efficacy parameters	PLA/GAL12 BID	GAL12/GAL12 BID	GAL16/GAL12 BID	GAL12,16/ GAL12 BID
• ADAS-cog/11: mean (±SE) change from baseline at Month 6	2.2** ±0.82	-0.2 ±0.61	1.8* ±0.86	0.7 ±0.52
• CIBIC-plus: % improved or unchanged from initial visit[a] to Month 6	53.6%	61.1%	56.0%	58.6%

[a]There were no statistically significant differences in distribution of CIBIC-plus ratings between PLA/GAL12 BID and GAL12/GAL12 BID and between PLA/GAL12 BID and GAL16/GAL12 BID.

* $p \leq 0.05$; ** $p \leq 0.01$, *** $p \leq 0.001$; two-sided paired t-test on change from timepoint indicated

Secondary efficacy parameters: change from baseline to Month 6	PLA/ GAL12 BID	GAL12/ GAL12 BID	GAL16/ GAL12 BID
• % Responders (based on >=0 change in ADAS-cog/11)	47%	60%	43%
	Mean ±SE	**Mean** ±SE	**Mean** ±SE
• ADAS-cog/13	2.6** ±0.88	-0.4 ±0.70	2.1 ±0.98
• ADAS-cog/mem	0.5 ±0.41	-0.9* ±0.38	1.0* ±0.48
• ADAS-cog/10	2.2** ±0.67	0.6 ±0.48	1.0 ±0.67
• DAD total	-8.1*** ±1.94	-1.7 ±1.78	-6.2*** ±1.71
• PGWB total score	-3.0 ±1.68	-1.3 ±1.19	0.4 ±1.70

* p ≤ 0.05; **p ≤0.01, ***p ≤0.001; two-sided paired t-test on change from timepoint indicated

Secondary efficacy parameters: mean change (±SE) from initial visit to Month 6	PLA/ GAL12 BID	GAL12/ GAL12 BID	GAL16/ GAL12 BID
• ADAS-cog/11	0.4 ±0.79	2.6*** ±0.62	3.7*** ±0.73
• ADAS-cog/13	0.6 ±0.89	3.0*** ±0.70	4.1*** ±0.83
• ADAS-cog/mem	0.4 ±0.43	0.5 ±0.42	1.8*** ±0.43
• ADAS-cog/10	0.2 ±0.64	2.4*** ±0.45	2.3*** ±0.62
• DAD total	-4.2** ±1.49	-1.5 ±1.23	-5.2*** ±1.47

* p ≤ 0.05; **p ≤0.01, ***p ≤0.001; two-sided paired t-test on change from timepoint indicated
[a]There were no statistically significant differences in distribution of CIBIC-plus ratings between PLA/GAL12 BID and GAL12/GAL12 BID and between PLA/GAL12 BID and GAL16/GAL12 BID.

Safety:

The most common treatment-emergent adverse events were nausea, vomiting, dizziness and anorexia, all of which were more frequent in patients newly exposed to galantamine. Discontinuations due to adverse events were also more frequent in newly exposed patients (29.6%) than in those previously exposed to galantamine (8.3%). Cardiovascular adverse events were infrequent and only two cases of syncope were observed. The rate of serious adverse events was low and similar among groups. Eight deaths occurred during the trial or within 30 days after termination of study medication. They were evenly distributed among the groups. All were considered unrelated to study medication, with the exception of a fall which resulted in acute subdural hematoma. There were no clinically important changes in laboratory values, vital signs or ECG. There was a small (not statistically significant) weight loss from initial visit in patients newly exposed to galantamine.

Safety	PLA/ GAL12 BID N=135	GAL12/ GAL12 BID N=116	GAL16/ GAL12 BID N=102	GAL12,16/ GAL12 BID N=218
Treatment-emergent adverse events (AE)				
Most frequently reported AEs ≥10% [a]				
Nausea	49 (36.3)	13 (11.2)	10 (9.8)	23 (10.6)
Vomiting	25 (18.5)	5 (4.3)	5 (4.9)	10 (4.6)
Dizziness	20 (14.8)	9 (7.8)	6 (5.9)	15 (6.9)
Anorexia	19 (14.1)	9 (7.8)	3 (2.9)	12 (5.5)
Diarrhea	16 (11.9)	6 (5.2)	14 (13.7)	20 (9.2)
Somnolence	17 (12.6)	5 (4.3)	6 (5.9)	11 (5.0)
Agitation	12 (8.9)	14 (12.1)	8 (7.8)	22 (10.1)
Headache	16 (11.9)	8 (6.9)	5 (4.9)	13 (6.0)
Injury	15 (11.1)	7 (6.0)	6 (5.9)	13 (6.0)
Rhinitis	8 (5.9)	12 (10.3)	7 (6.9)	19 (8.7)
No. (%) with one or more AE	124 (91.9)	100 (86.2)	86 (84.3)	186 (85.3)
No. (%) of deaths	2 (1.5)	3 (2.6)	3 (2.9)	6 (2.8)
No. (%) with one or more serious AE	14 (10.4)	12 (10.3)	12 (11.8)	24 (11.0)
No. (%) treatment discontinued due to AE	40 (29.6)	10 (8.6)	8 (7.8)	18 (8.3)
• Clinical laboratory parameters • Vital signs • ECG	No clinically important values or changes			
Body weight (kg) Mean change from baseline to Month 6	-0.8 ±0.52	-1.9 ±0.51	-1.1 ±0.52	-1.5 ±0.36

[a]Frequency in any single group

Conclusions

This extension study supports the findings of the pivotal trials in demonstrating the safety and efficacy of galantamine. Despite retitration and medication gaps, patients treated with 24 mg/day of galantamine maintained cognitive benefits during the second six months of treatment. Gastrointestinal tolerability of the drug appears to improve during prolonged dosing of the drug. No unexpected, time-dependent adverse events were apparent during this trial.