SYNOPSIS

Trial Identification

Company:	Ortho-McNeil Neurologics, Inc. (formerly Janssen Medical Affairs, L.L.C.)		
Finished product:	Razadyne™ ER		
Active ingredient:	galantamine HBr		
Title:	Galantamine ER Open Label Rapid Dose Escalation Trial in Alzheimer's Disease	**Trial No:**	GAL-ALZ-303
		Clinical Phase:	Phase IIIb
Investigator:	Multicenter	**Country:**	USA
Reference:	Not applicable		
Trial Period:	**Start:** The first subject was enrolled into the study on 22 May 2004.	**No. investigators:**	15
		No. subjects entered:	83
		No. subjects treated:	82
	End: The last subject completed the study on 15 April 2005.		

Protocol Summary

Indication / objectives:	The primary objective of this trial was to demonstrate the safety and tolerability of galantamine ER 16 mg daily when titrated from 8 mg daily after one week. Safety and tolerability of galantamine ER 16 mg daily is compared to the historical safety and tolerability data from a galantamine trial, GAL-INT-10, in which patients in one arm were maintained on galantamine ER 16 mg daily, following 4 weeks of treatment with galantamine ER 8 mg daily. The secondary objective was to evaluate the effect of galantamine ER on cognition as measured by the Mini Mental State Examination (MMSE). Additional secondary objectives were: to compare the safety and tolerability of galantamine ER 16 mg daily to the IR arm of GAL-INT-10 at 8 weeks of treatment and to the IR and ER arms of GAL-INT-10 at 12 weeks of treatment.
Trial design:	This was a 12-week, open-label, Phase IIIb trial, which evaluated the safety and efficacy of a rapid titration of galantamine ER dose from 8 mg daily to 16 mg daily after one week. The results are compared to historical safety and tolerability data (GAL-INT-10 trial) of galantamine ER 16 mg daily, following dose escalation from 4 weeks of treatment with galantamine ER 8 mg daily.

Main selection criteria:	• Male or female out-patients diagnosed with Alzheimer's disease based on NINCDS-ADRDA criteria. • Presence of mild to moderate dementia as evidenced by a Mini-Mental State Examination (MMSE) score of 10-24 inclusive at screening. • A history of cognitive decline that had been gradual in onset and progressive over a period of at least six months. • An age ≥60 years. • Caregiver involvement was recommended but not required. • Patient or patient's relative, guardian, or legal representative and caregiver had signed the informed consent form.

Treatment:	Galantamine HBr ER		
Form – dosing route	Capsules - Oral		
Medication	Galantamine Week 1-4 Kit		Galantamine Week 5-12 Kit
	8 and 16 mg galantamine		16 mg galantamine
Batch number	8 mg GAL Week 1-4 Kit	16 mg GAL Week 1-4 Kit	16 mg GAL Week 5-12 Kit
	Lot No. 02K27/F055	Lot No. 02K28/F056	Lot No. 02K28/F056
Dosage	8 mg galantamine HBr ER formulation once daily for one week followed by 16 mg galantamine HBr ER formulation once daily for 11 additional weeks		
Duration of treatment	12 weeks		
Disallowed medication	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, estrogens taken without medical need and chronic NSAIDs (30 consecutive days) should not be taken during the trial.		

Assessments:	Screening Visit 1	Baseline Visit 2	Interim Clinical Visit 3	Final/Early Termination Visit 4
Vital signs and weight	X	X	X	X
Medical history, demographics and height	X			
Physical exam	X	X		X
Neurologic exam	X			
Physician visit	X	X	X	X
MMSE	X	X	X	X
ECG	X	X	X	X
CT/MRI	X			
Laboratory samples	X	X	X	X
Adverse events	X	X	X	X
Concomitant medications	X	X	X	X
Drug accountability			X	X

Statistical methods:	The primary analysis end point is Week 8, which is the first visit in INT-10 after dose titration. The secondary end point is Week 12. The primary outcome measures are tolerability and safety. The secondary outcome measure is the change from baseline in total MMSE score. The percent of individuals with any AE and the percent of individuals with any specified AE (nausea, vomiting, diarrhea, anorexia, or weight loss) were compared to the historical adverse event data for galantamine ER group drawn from the 16 mg daily group of GAL-INT-10 for the first 8 weeks treatment using the 95% confidence interval approach, i.e. the conclusion will be drawn based on the overlapping of the two 95% confidence intervals for the AE rates from the current trial and historical data. The same comparisons were made with GAL-INT-10 IR 16 mg subjects for the first 8 weeks of treatment and the ER and IR 16 mg subjects for the first 12 weeks of treatment. The MMSE score is the secondary outcome measure of this study. Changes from baseline in MMSE scores were assessed using the paired t-test.

Main features of the subject sample and summary of the results

Baseline characteristics – subject disposition:				
		8-week analysis population		
	GAL-ALZ-303 ER Safety population	GAL-ALZ-303 ER	GAL-INT-10 ER	GAL-INT-10 IR
No. of subjects treated	82	77	306	313
Gender:				
Male	25 (30.5)	23 (29.9)	109 (35.6)	114 (36.4)
Female	57 (69.5)	54 (70.1)	197 (64.4)	199 (63.6)
Race:				
Caucasian	64 (78.0)	61 (79.2)	285 (93.1)	282 (90.1)
Hispanic	4 (4.9)	4 (5.2)	2 (0.7)	5 (1.6)
African American	9 (11.0)	7 (9.1)	8 (2.6)	12 (3.8)
Asian	4 (4.9)	4 (5.2)	9 (2.9)	4 (1.3)
Other	1 (1.2)	1 (1.3)	2 (0.7)	10 (3.2)
Age (years):				
Mean (± SE)	79.7 (0.81)	79.8 (0.85)	76.5 (0.44)	76.3 (0.44)
Median (min-max)	80.5 (57-96)	82.0 (57-96)	77.0 (55-93)	77.0 (49-92)
Weight (kg):				
Mean (± SE)	66.0 (1.61)	65.6 (1.66)	68.6 (0.81)	68.6 (0.90)
Median (min-max)	63.5 (42-99)	63.1 (42-99)	67.2 (36-121)	67.6 (37-136)
BMI:				
Mean (± SE)	24.9 (0.44)	24.8 (0.46)	25.4 (0.24)	25.9 (0.32)
Median (min-max)	24.5 (18-34)	24.4 (18-34)	24.8 (12-39)	25.1 (13-64)
Years since AD diagnosis:				
Mean (± SE)	0.8 (1.38)	0.8 (1.40)	1.2 (1.59)	1.2 (1.47)
Median (min-max)	0.2 (0.0-8.9)	0.2 (0.0-8.9)	0.6 (0.0-9.2)	0.6 (0.0-6.3)
MMSE:				
Mean (± SD)	18.9 (3.44)	18.7 (3.19)	18.1 (3.92)	17.8 (4.17)
Median (min-max)	19.0 (10.0-24.0)	19.0 (10.0-24.0)	18.0 (10.0-24.0)	18.0 (10.0-24.0)
Prior Rx for AD:				
Subjects with prior treatment	22 (26.8)	20 (26.0)	1 (0.3)	2 (0.6)
Donepezil	19 (23.2)	17 (22.1)	1 (0.3)	2 (0.6)
Tacrine	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rivastigmine	2 (2.4)	2 (2.6)	0 (0.0)	0 (0.0)
Metrifonate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Memantine	1 (1.2)	1 (1.3)	0 (0.0)	0 (0.0)
Galantamine	5 (6.1)	5 (6.5)	0 (0.0)	0 (0.0)

Baseline characteristics – subject disposition (Continued):			
12-week analysis population			
	GAL-ALZ-303 ER	GAL-INT-10 ER	GAL-INT-10 IR
No. of subjects treated	75	90	105
Gender:			
Male	23 (30.7)	26 (28.9)	31 (29.5)
Female	52 (69.3)	64 (71.1)	74 (70.5)
Race:			
Caucasian	60 (80.0)	81 (90.0)	94 (89.50
Hispanic	4 (5.3)	1 (1.1)	3 (2.9)
African American	7 (9.3)	2 (2.2)	5 (4.8)
Asian	3 (4.0)	6 (6.7)	1 (1.0)
Other	1 (1.3)	0 (0.0)	2 (1.9)
Age (years):			
Mean (± SE)	79.9 (0.88)	77.0 (0.84)	76.7 (0.78)
Median (min-max)	82.0 (57-96)	78 (55-92)	77 (53-92)
Weight (kg)			
Mean (± SE)	66.0 (1.68)	66.1 (1.40)	66.2 (1.48)
Median (min-max)	63.1 (42-99)	62.8 (40-95)	65.4 (39-135)
BMI:			
Mean (± SE)	24.9 (0.46)	25.0 (0.46)	25.3 (0.55)
Median (min-max)	24.5 (18-34)	24.5 (17-36)	24.6 (17-54)
Years since AD diagnosis:			
Mean (± SE)	0.8 (1.41)	1.4 (1.66)	1.4 (1.53)
Median (min-max)	0.2 (0.0-8.9)	0.7 (0.0-8.6)	0.7 (0.0-5.9)
MMSE:			
Mean (± SE)	18.7 (3.21)	17.5 (3.95)	18.0 (3.96)

Subject disposition	
	GAL-ALZ-303 ER Safety Population
(n=number of subjects)	82
Total Discontinuation of treatment	16 (19.5%)
Reason	
Adverse events	9 (11.0%)
Non-compliant	4 (4.9%)
Other	3 (3.7%)

Safety: Primary endpoint: Week 8 analysis	GAL-ALZ-303 ER	GAL-INT-10 ER	GAL-INT-10 IR
(n = number of subjects)	(n = 77)	(n = 306)	(n = 313)
Individuals with any AE, n% [95% CI]	53 (68.8%) [58.49, 79.18]	168 (54.9%) [49.33, 60.48]	174 (55.6%) [50.09, 61.10]
Individuals with any specified AE n% [95% CI] (nausea, vomiting, diarrhea, anorexia, or weight decrease)	29 (37.7%) [26.84, 48.48]	43 (14.1%) [10.16, 17.95]	60 (19.2%) [14.81, 23.53]
Anorexia	6 (7.8)	11 (3.6)	12 (3.8)
Diarrhea	14 (18.2)	12 (3.9)	13 (4.2)
Nausea	9 (11.7)	26 (8.5)	32 (10.2)
Vomiting	2 (2.6)	10 (3.3)	18 (5.8)
Weight decrease	3 (3.9)	3 (1.0)	8 (2.6)
Secondary endpoint: Week 12 analysis			
(n = number of subjects)	75	90	105
Individuals with any AE, n% [95% CI]	55 (73.3) [63.33, 83.34]	61 (67.8) [58.12, 77.43]	66 (62.9) [53.62, 72.10]
Individuals with any specified AE n% [95% CI] (nausea, vomiting, diarrhea, anorexia, or weight decrease)	28 (37.3) [26.39, 48.28]	21 (23.3) [14.60, 32.07]	31 (29.5) [20.80, 38.25]
Anorexia	7 (9.3)	7 (7.8)	8 (7.6)
Diarrhea	14 (18.7)	4 (4.4)	7 (6.7)
Nausea	8 (10.7)	9 (10.0)	18 (17.1)
Vomiting	2 (2.7)	5 (5.6)	9 (8.6)
Weight decrease	3 (4.0)	3 (3.3)	3 (2.9)

Adverse events (AEs)	
	GAL-ALZ-303 ER Safety population
(n = number of subjects)	82
No. (%) of subjects with AEs	63 (76.8%)
AEs in ≥5%	
• Diarrhea	13 (15.9%)
• Nausea	10 (12.2%)
• Decreased Appetite	5 (6.1)
No. (%) of deaths	0
No. (%) with one or more serious AE	4 (4.88%)

In order to compare adverse event rates with the historical control study (GAL-INT-10), adverse events were coded using both the MedDRA and WHOART dictionaries. This lead to a few preferred terms having different rates in the two coding systems. For example, one case coded as "diarrhoea" in WHOART was coded as "loose stools" in MedDRA, resulting in 13 cases of diarrhoea in tables coded using MedDRA, but 14 in tables using WHOART.

Efficacy:	N	Mean (± SE)	Mean change from baseline (± SE)
Secondary endpoint (MMSE scores)			
Baseline	80	19.0 (3.46)	-
Week 4	80	20.8 (3.81)	1.8 (0.27)***
Week 12	67	20.6 (4.83)	1.9 (0.38)***
Endpoint	80	20.9 (4.67)	1.9 (0.34)***
***p. ≤0.001			

Conclusions:

This open-label, single-arm, rapid-titration trial provides no evidence of statistically significant differences in overall rates of individuals with incident AEs at 8 or 12 weeks when compared to the active arms of GAL-INT-10, a double-blind, placebo-controlled, trial with a standard titration regimen. For rates of individuals experiencing any of the specified gastrointestinal adverse events (nausea, vomiting, diarrhea, anorexia, or weight decrease), there were observed differences at Week 8, primarily due to differences in diarrhea rates, but not at Week 12. In addition, the MMSE results in the open label study were significantly increased from baseline by about 2 points, on average, at both follow-up visits. When interpreting these results, the imbalances at baseline between the patients in this study and those in the historic controls regarding age, gender, race, weight, and BMI may have influenced the tolerability results negatively in the rapid titration trial, warranting future post-hoc analysis. Years since AD diagnosis, MMSE, and prior history of treatment imbalances at baseline may have also impacted results. Additionally the timing of the diarrhea in relation to titration as well as characteristics of the individuals with diarrhea, such as prior history of or active gastrointestinal issues at baseline, requires additional post-hoc assessment. Less differences between the point estimates between the rapid titration trial and the IR arm of the standard titration trial (as opposed to the ER arm) either may be related to drug formulation or less imbalance between the groups on these variables.

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.