SYNOPSIS

Company:	Ortho-McNeil Janssen Scientific Affairs, LLC		
Finished product:	No drug supplied for study subjects		
Active ingredient:	Not Applicable		
Title:	Review of Management Strategies in Dementia (REMIND)	**Trial No:**	GAL-OUT-065
		Clinical Phase:	Phase IV
Investigator:	Multicenter	**Country:**	USA
Reference:	Not Applicable		
Study Period:	**Start:** The first subject enrolled in the study on 7 July 2003.	**No. of Investigators:**	107
		No of Sites:	107
		No. subjects entered:	573
	End: The last subject completed the study on 31 January 2007.		
Objective:	In this large-scale observational study, sites collected data for 2 years on subjects with Alzheimer's disease (AD). Measured were: cognition, function, behavior, caregiver burden, time to institutionalization, and resource use. At baseline, subjects had been prescribed either galantamine or no AD treatment (i.e., neither an acetylcholinesterase inhibitor [AChEI] nor memantine); and their physicians had to have no intent of changing treatment in the following 90 days. However, physicians were allowed to change treatment when clinically warranted. Effectiveness analyses were based on original treatment groups, but safety analyses were also conducted based on treatment at time of event.		
Trial design:	This was a 2-year multicenter, prospective, longitudinal, observational study. All subjects enrolled in the study were intended to be prospectively followed for 2 years (the planned number of subjects was 600 [420 prescribed galantamine as the original treatment at baseline and 180 subjects receiving neither an AChEI nor memantine]). Data were collected at baseline and at month 6, 12, and 24 from the physician and at baseline and month 6, 12, 18, and 24 from the primary informal caregiver according to the Schedule of Assessments (Table 1).		

Main Criteria for Inclusion:	• Subjects with a physician-based diagnosis of AD according to the Diagnostic and Statistical Manual for mental disorders criteria and mild to moderate dementia as evidenced by a Mini-Mental State Examination (MMSE) score of 10 to 24 inclusive at screening. Subjects with existing diagnosis as well as newly diagnosed subjects were included in the study. • Subjects living at home or subjects living in a facility for the elderly (e.g., assisted living) and who lived with or had regular visits (at least 1 visit per week for nonresident caregivers) from a friend or relative. • Subjects must have met one of the following criteria: a) For subjects receiving neither an AChEI nor memantine, the current treatment plan was to keep the subject on no AChEI/no memantine therapy for at least 90 days after enrollment, provided there were no problems with tolerability or safety. b) For subjects receiving galantamine only, the current treatment plan was to keep the subject on galantamine only for at least 90 days after enrollment, provided there were no problems with tolerability or safety. • Subjects and caregivers were able to speak and read in English. • Subject or the subject's relative, guardian or legal representative and the primary informal caregiver had each signed the informed consent form.
Treatment:	For all subjects, inclusion was based on having a current treatment plan to maintain the subject on the original treatment strategy for at least 90 days after enrollment. However, as the study had a naturalistic design, duration, dosage and administration of the AD treatment were at the discretion of the physician treating the subject with AD.

Table 1. Schedule of Assessments

	Visit 1 Baseline	Visit 2 Month 6 (± 1 month)	Visit 3 Month 12 (± 1 month)	Mail questionnaire Month 18 (± 1 month)	Visit 4 Month 24 (± 1 month)
Physician					
Center characteristics	X				
Patient demographics	X				
Medical history	X				
History of AD	X				
Change in PIC		X	X		X
Permanent admission to ALF or NH		X	X		X
CGI	X	X	X		X
MMSE	X	X	X		X
AD tx of the patient	X	X	X		X
Con med	X	X	X		X
Adverse events	X	X	X		X
Primary Informal Caregiver					
Caregiver demographics	X	X*	X*	X*	X*
NPI-Q	X	X	X	X	X
DAD	X	X	X	X	X
Zarit Burden Interview	X	X	X	X	X
Service use of patient	X	X	X	X	X
Service use of caregiver	X	X	X	X	X
AD tx and con med use				X	

PIC = Primary Informal Caregiver; CGI = Clinical Global Impression; Con med = Concomitant Medication; AD tx = Alzheimer's Disease Treatment; NPI-Q = Neuropsychiatric Inventory Questionnaire; DAD = Disability Assessment in Dementia Scale; MMSE = Mini Mental State Examination; ALF = Assisted Living Facility; NH = Nursing Home

*new primary informal caregiver demographics will be obtained only if the primary informal caregiver has changed since the previous visit

Statistical methods:	The following statistical analyses were conducted with each of the outcomes (institutionalization, change in cognition [MMSE], change in global impression [CGI], change in activities of daily living [ADL], change in behavior [NPI-Q], change in caregiver burden [Zarit], and service utilization): 1. An unadjusted analysis using a two-sample t-test was performed for descriptive purposes. In every case, p-values comparing the galantamine and no AD treatment groups were provided, but these were also intended for descriptive purposes, as differences may reflect differences in the two groups at baseline as opposed to differences in the results of the two management strategies. 2. Risk adjusted analyses were performed as the preferred analyses for statistical inference. Models included initial baseline treatment, but not later treatments or the treatment at the time of the outcome assessment. 3. Both the unadjusted and risk adjusted analysis for each outcome was repeated for the subset of subjects who did not have any changes to their treatment between baseline and the 6 month, 12 month, and 24 month outcome assessments. 4. No single outcome was considered as primary outcome for this study. Institutionalization was given moderately greater emphasis then other outcomes assessed. Time to institutionalization was analyzed using Cox proportion Hazard modeling. Sample size was calculated based on time to institutionalization. 5. Adverse events (AEs) and serious adverse events (SAEs) were summarized by preferred term and original treatment groups as well as current treatment groups. The incidence of AEs was calculated as the number of individuals who experienced AEs divided by the total number of subjects at risk within each treatment group.

Table 2. Subject Demographics

	Galantamine	No AD Treatment
No. of subjects	414	159
Sex:		
Male	168 (40.6%)	63 (39.6%)
Female	246 (59.4%)	96 (60.4%)
Race:		
Caucasian	376 (90.8%)	132 (83.0%)
African American	30 (7.2%)	12 (7.5%)
Hispanic	5 (1.2%)	10 (6.3%)
Asian	2 (0.5%)	4 (2.5%)
Other	1 (0.2%)	1 (0.6%)
Age (years):		
Mean (± SD)	79.1 (8.02)	81.4 (8.26)
Median (min-max)	80.1 (42.8-98.2)	82.8 (50.2-97.9)
Education[a]:		
Less than High School	98 (24.0%)	60 (38.2%)
High School Degree/GED	171 (41.8%)	59 (37.6%)
Some College	71 (17.4%)	18 (11.5%)
College Degree	39 (9.5%)	7 (4.5%)
Graduate/Professional Degree	30 (7.3%)	13 (8.3%)
Years since AD Diagnosis[b]:		
Mean (± SD)	1.3 (1.66)	1.6 (2.06)
Median (min-max)	0.6 (0.0-10.0)	0.9 (0.0-11.2)
MMSE[c]:		
Mean (± SD)	19.7 (3.75)	19.0 (4.21)
Median (min-max)	21.0 (10.0-24.0)	20.0 (10.0-24.0)

[a] n = 409 for Galantamine and 157 for No AD Treatment
[b] n = 369 for Galantamine and 124 for No AD Treatment
[c] Higher scores indicate improvement.

Table 3. Subject Disposition

	Galantamine	No AD Treatment
6-Month Visit Received, n (%)	263 (63.5)	90 (56.6)
Termination Before 6-Month Visit, n (%)	55 (13.3)	34 (21.4)
No Data at 6-Month Visit	96 (23.2)	35 (22.0)
12-Month Visit Received, n (%)	205 (49.5)	60 (37.7)
Termination Before 12-Month Visit, n (%)	118 (28.5)	64 (40.3)
No Data at 12-Month Visit	91 (22.0)	35 (22.0)
24-Month Visit Received, n (%)	122 (29.5)	32 (20.1)
Termination Before 24-Month Visit, n (%)	184 (44.4)	89 (56.0)
No Data at 24-Month Visit	108 (26.1)	38 (23.9)

For subjects who had a 6-month visit, approximately 73% in the galantamine and 67% in the no AD treatment groups remained on the treatment associated with their original treatment group continuously from baseline to 6 months. During the course of the study, many subjects switched therapy and only 14.5% of subjects in the galantamine arm and 11.9% in the no AD treatment arm remained in the original regimen for the entire 24-month period. There was also a high loss to follow-up: 29.5% of subjects in the galantamine group and 20.1% in the no AD treatment group completed the study.

Outcomes:

Based on original treatment groups at 6 months, Kaplan-Meier estimates showed that 98.4% of subjects (n = 5 institutionalizations) in the galantamine group and 96.1% (n = 5 institutionalizations) in the no AD treatment group, respectively, were free of event (i.e., had not been placed in a nursing home) and at 12 months, these estimates were 96.4% (n = 10 institutionalizations) and 92.9% (n = 8 institutionalizations), respectively. At 24 months, these estimates were 92.1% (n = 17 institutionalizations) and 87.6% (n = 11 institutionalizations), respectively. No statistically significant difference was observed between these two groups (results from Cox regression: hazard ratio 1.01, 95% CI: 0.46 to 2.26, p = 0.9719).

At 6 months on MMSE, the mean change from baseline was 0.1 and -0.4 for galantamine and no AD treatment, respectively. The difference between the groups was 0.14 points (p = 0.7887), a positive change indicating improvement.

At 6 months on NPI-Q, the mean change from baseline was -0.1 and 1.5 for galantamine and no AD treatment, respectively. The difference between the groups was -1.81 points (p = 0.0113), a negative change indicating improvement.

The effectiveness results are summarized in Table 4.

Table 4. Change from Baseline at 6-Month Visit

	Galantamine	No AD Treatment	Difference in Change from Baseline, Multiple Linear Model (95% CI)
Total subjects with 6-Month Visit, n	263	90	
MMSE[a]			
Baseline, Mean (SD)	19.8 (3.64)	19.5 (4.39)	
6-Month Follow-up, Mean (SD)	19.9 (5.67)	19.1 (5.71)	
Change from Baseline, Mean (SD)	0.1 (4.37)	-0.4 (3.22)	0.14 (-0.85, 1.13)
CGI[b]			
Baseline, Mean (SD)	3.5 (0.84)	3.4 (1.11)	
6-Month Follow-up, Mean (SD)	3.5 (0.92)	3.6 (1.12)	
Change from Baseline, Mean (SD)	0.0 (0.86)	0.2 (0.87)	-0.06 (-0.25, 0.13)
DAD[a]			
Baseline, Mean (SD)	68.3 (23.85)	61.7 (26.68)	
6-Month Follow-up, Mean (SD)	64.3 (24.73)	54.2 (29.25)	
Change from Baseline, Mean (SD)	-4.1 (16.85)	-7.5 (15.60)	4.54 (0.22, 8.85)[c]
NPI-Q[b]			
Baseline, Mean (SD)	6.9 (6.21)	7.3 (5.84)	
6-Month Follow-up, Mean (SD)	6.8 (6.01)	8.8 (7.41)	
Change from Baseline, Mean (SD)	-0.1 (5.45)	1.5 (6.00)	-1.81 (-3.20, -0.42)[d]
Zarit[b]			
Baseline, Mean (SD)	24.1 (14.58)	26.5 (15.81)	
6-Month Follow-up, Mean (SD)	25.6 (15.05)	29.3 (16.56)	
Change from Baseline, Mean (SD)	1.5 (11.24)	2.7 (10.53)	-1.50 (-4.36, 1.37)

[a] Higher scores indicate improvement.
[b] Lower scores indicate improvement.
[c] p = 0.0402
[d] p = 0.0113

Safety:

Table 5. Adverse Events by Treatment Group at Time of Event

	Galantamine	Non-galantamine AChEI	Memantine	Galantamine and Memantime	No AD Treatment
Total Subjects	349	31	19	85	279
n (AE per subjects at Risk)					
Any Adverse Event	98 (28.1)	15 (48.4)	7 (36.8)	28 (32.9)	63 (22.6)
Serious Adverse Event	44 (12.6)	5 (16.1)	5 (26.3)	11 (12.9)	39 (14.0)
Fatal Adverse Event	12 (3.4)	3 (9.7)	2 (10.5)	3 (3.5)	11 (3.9)

NOTE: Subjects could switch treatment groups during the course of the study, thus some subjects could be included in more than one treatment column. Each event could only contribute one time based on the start date of the adverse event. Within each category, subjects within the same treatment and system-organ class were counted once.

Table 6. Most Commonly Reported AE(s) by Treatment Group at Time of Event

	Galantamine		Non-galantamine AChEI		Memantine		Galantamine and Memantime		No AD Treatment	
	Event	n (%)	Event	n (%)	Event	n (%)	Event	n (%)	Event	n (%)
All Adverse Events	Fall UTI NOS	9 (2.6)	Nausea	4 (12.9)	Abasia	2 (10.5)	UTI NOS	6 (7.1)	Fall Institution-alized	8 (2.9)
SAE	Fall	6 (1.7)	See footnote[a]	1 (3.2)	Abasia	2 (10.5)	UTI NOS	4 (4.7)	Institution-alized	6 (2.2)
Fatal AE	Fall	3 (0.9)	See footnote[a]	1 (3.2)	See footnote[b]	1 (5.3)	Dementia	2 (2.4)	Respirator y failure	3 (1.1)

[a] In the Non-galantamine AChEI group, the frequency of all reported SAEs and fatal AEs was 1 (3.2%).
[b] In the Memantine group, the frequency of all reported fatal AEs was 1 (5.3%).
UTI NOS = Urinary tract infection NOS
Dementia = Dementia of the Alzheimer's type NOS
Institutionalized = Living in Residential Institution

Termination due to AE

There were 10 subjects for whom an "Adverse Event" was the reason for study termination, 7 in the original galantamine group (2 at 6 months, 3 at 12 months, and 2 at 24 months) and 3 in the original no AD treatment group (1 at 6 months and 2 at 24 months). No further examination of these AEs was possible because the termination form did not capture the specific AE(s) leading to study termination.

Conclusions:

Some treatment differences were detected at 6 month follow-up, but generally the results of this study are difficult to interpret due to insufficient follow-up data for a large proportion of subjects. Specifically 73% of subjects discontinued before the end of the study and a high percentage of subjects switching therapy, as only a small percentage of subjects (14.5% in the galantamine and 11.9% in the no AD treatment groups) remained in the original regimen for the entire 24-month period. In addition, the study had lower enrollment than initially planned, as the sample size of 1000 subjects was decreased to 600 because of difficulty in recruiting sites and AD subjects. More importantly, the overall event rate for institutionalization, irrespective of study arm, was much lower than anticipated, quite possibly reflecting selection bias in those who completed the study. Other contributing factors include the potential bias of the unmonitored non-randomized study design and the challenges with the underlying assumptions behind the power calculation.

Kaplan-Meier estimates of the time to institutionalization at 24 months were 92.1% for subjects initially treated with galantamine and 87.6% for subjects initially receiving no AD treatment. The results should be interpreted with caution, however, because of the issues described above.

Because of the non-randomized study design and the possibility of confounding data, risk adjustment was performed using multiple linear regression models for the outcomes. In the first ANCOVA model, only baseline score and treatment group were used. Because baseline score is almost always a strong predictor of follow-up scores and the original galantamine group had baseline scores indicative of a milder disease status for most of the secondary outcomes, the results from the analyses were expected and any true relationship to study drug may have been masked or distorted by failure to adjust for additional potentially confounding variables. Therefore, the results of the first ANCOVA model should be interpreted with caution.

In the multiple regression model, galantamine subjects had lower NPI-Q scores and higher DAD scores at 6 months compared to subjects initially receiving no AD treatment, suggesting improved behavior and less impaired ADL, respectively. For change in cognition, the analysis subset on subjects with no change in treatment was much closer to providing evidence of a treatment effect than the analysis of the full group, indicating that treatment switches, even in

the first 6 months, decreased the ability to identify treatment differences. There were no differences in any of the scale outcomes at 12 or 24 months. In summary, despite much drop out and switching, a positive galantamine effect was seen at 6 months for the DAD (ADL) and NPI-Q (behavior) for subjects who were part of ITT and those who stayed on therapy and a positive MMSE trend was seen for galantamine after restricting to subjects who stayed on therapy. No significant differences were seen on most outcomes at 6 months and all outcomes at 12 and 24 months.

The demographic characteristics of the subjects who completed the follow-up were similar to subjects who were lost to follow-up. However, the baseline DAD, NPI-Q and caregiver burden scores were indicative of more moderate disease at baseline in subjects who completed follow up. This imbalance could potentially have introduced bias into the Kaplan-Meier estimates and any analyses that excluded a large number of subjects (i.e., the 12-month and 24-month analyses). Specifically, these data suggest that the subjects who remained on study were not a representative sample of the full study population, and this may partially explain the lower than expected institutionalization rates. In addition, the bias appears to be stronger in the no AD treatment group. The imbalance in the bias between the two study groups reduces the chance of seeing treatment effects as more subjects with poor outcomes were omitted from the no AD treatment group.

The subjects enrolled in the original galantamine group were slightly younger and better educated than those subjects who were not prescribed any AD treatment. A larger proportion of galantamine subjects were treated by a neurologist and cared for by a partner or spouse compared to those subjects who had no AD treatment. Most of the subjects enrolled in the study were Caucasian, but the no AD treatment group had a larger proportion of Hispanic and Asian subjects. The galantamine subjects had slightly higher MMSE scores at baseline. The proportion of subjects that dropped out of the study (baseline data only) was 13.0% of subjects in the galantamine group and 10.1% of subjects in the no AD treatment group. The no AD treatment group had higher death rates, which may have contributed to less than expected nursing home placement (0.07 fatal AE per PYR).

The most common AEs by system-organ class involved the nervous system. Approximately 31% of subjects reported AEs during the 24-month study period. The proportion of subjects experiencing AEs was lower in the group initially treated with galantamine compared to the group initially receiving no AD treatment. When subjects were grouped by treatment at the time of the event, the AE incidence appeared to be somewhat lower for the galantamine group, although all treatment groups had AE incidence of 0.6 AE per PYR or lower. Furthermore, the galatamine and memantine group had an AE incidence that was similar to that of the no treatment group and lower than that for memantine alone. Due to the risk of selection bias in observational studies and the small number of PYR in some of the treatment groups, the differences in AE incidence should be interpreted with caution.

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.