Janssen-Ortho Inc., Canada
J&JPRD-Clinical Research

SYNOPSIS

Name of Sponsor/Company:	Janssen Ortho Inc.	Individual Study Table Referring to Part of the Dossier **n/a**	(for National Authority Use only)
Name of Finished Product:	[Pr]Reminyl*	Volume: n/a	
Name of Active Ingredient:	Galantamine bromide	Page: n/a	
Title of Study:		A pilot study to evaluate the safety and tolerability of galantamine HBr in the treatment of Pick Complex/Frontotemporal Dementia	
Investigators:		Dr Andrew Kertesz (London, ON)	
Study centre(s):			
Publication (reference)		TBD	
Studied period (years):		Phase of development:	Phase II
	(date of first enrolment)		30 April 03
	(date of last completed)		13 January 04
Objectives:		The primary objectives of this pilot study will to explore 1) the safety and tolerability of galantamine 8 and 12 mg BID treatment in subjects with PC/FTD, and 2) the efficacy of galantamine on the hallmark symptoms of PC/FTD during the randomized withdrawal period. Secondary study objectives will be to 1) confirm the safety of withdrawal of galantamine treatment in subjects with PC/FTD, and 2) use specific cognitive, behavioral, and language assessment tools to further explore the efficacy of galantamine treatment in study subjects.	
Methodology:		**STUDY DESIGN:** This pilot study of galantamine therapy in a maximum of 40 subjects with PC/FTD comprises an 18-week, open-label, galantamine-treatment phase followed by an 8-week, randomized, double-blind, placebo-controlled withdrawal phase. Subjects, upon completion of the open-label phase, will be randomly assigned to either galantamine (continued therapy) or placebo. In the study, the approved galantamine twice-daily (BID) tablets will be used for a total duration of 26 (=18+8) weeks. The placebo group will receive placebo daily for 8 weeks. During the withdrawal period, trial medication packaging and distribution will be identical for galantamine and placebo. Safety and efficacy assessments will be performed at Screening, Baseline and Weeks 12, 18 and 26; telephone contacts for safety will be made at Weeks 4, 8 and 22.	
Number of patients (planned and analyzed):		Planned: 40 enrolled, 40 randomized	Actual: 41 screened; 39 enrolled, 36 randomized.

Diagnosis and main criteria for inclusion:		STUDY POPULATION: A maximum of 40 subjects with PC/FTD will be enrolled. Subjects will have a clinical diagnosis of PC/FTD established by published consensus criteria and supported by neuroradiologic confirmation. Subjects will have a diagnosis of primary progressive aphasia or frontotemporal dementia. Main Inclusion Criteria: ▪ Outpatient, aged 30 to 80 years inclusive ▪ Documented (≥ 1 yr) primary progressive aphasia (including progressive nonfluent aphasia and semantic dementia) or frontotemporal dementia ▪ Recent MRI or CT scan (≤1 yr) confirming frontotemporal lobar atrophy consistent with PC/FTD ▪ MMSE > 5 and able to complete neuropsychometric tests ▪ Healthy based on medical history, physical examination, and ECG ▪ Responsible caregiver involved and opportunity to perform activities of daily living ▪ Signed informed consent (subject and caregiver) Main Exclusion Criteria: ▪ Other neurodegenerative disorders and causes of dementia ▪ Cognitive impairment resulting from: acute cerebral injury, cerebrovascular disease or hypoxic cerebral damage, vitamin deficiency states, infection, metastatic cerebral neoplasia ▪ Primary memory disturbance or an amnestic syndrome more compatible with Alzheimer's disease or other primary degenerative dementia ▪ Uncontrolled epilepsy or clinically significant psychiatric disease ▪ Clinically significant cardiovascular disease ▪ History of alcohol or drug abuse (≤1 yr) ▪ Treatment with agents for dementia or other cognitive impairment (during study)
Test product, dose and mode of administration, batch number:		The treatment will consist of oral BID administration of galantamine The active tablets will contain 4 mg, 8 mg, or 12 mg of synthetic, immediate-release galantamine hydrobromide. Galantamine hydrobromide; 4 mg numbers F24 (open-label) and F47 (double-blind): 8 mg numbers F25 (open-label) and F48 (double-blind): 12 mg numbers F26 (open-label) and F49 (double-blind).
Duration of treatment:		Total duration (open-label + double-blind phases): 26 weeks Using a flexible dosing regimen, subjects will be treated with galantamine up to 8 or 12 mg BID for 18 weeks. Subjects will then be randomly assigned (1:1) in a double-blind fashion to galantamine at the same dose or to placebo for an additional 8 weeks of treatment.
Reference therapy, dose and mode of administration, batch number		Placebo tablets will be identical in appearance, taste, and smell. F 4 (double-blind)
Criteria for evaluation:		
	Efficacy:	Efficacy variables: The main endpoint for efficacy is the Frontal Behavioral Inventory (FBI). Other efficacy measures are the following: the Aphasia Quotient (AQ) of the Western Aphasia Battery (WAB), the Mini Mental State Examination (MMSE), the Mattis Dementia Rating Scale (MDRS), the Frontal Assessment Battery (FAB), the Neuropsychiatric Inventory (NPI), the Alzheimer's Disease Cooperative Study - Activities of Daily living (ADCS-ADL) Scale, the Clinical Global Impressions (CGI) .
	Safety:	Safety and tolerability will be explored primarily by determining the incidence rates of (gastrointestinal) adverse events, and results from electrocardiograms, physical examination, blood pressure, heart rate, weight, and laboratory tests.
Statistical Methods:		Efficacy: This is a pilot study in an unexplored subject population. No hypotheses are specified for statistical testing. Efficacy assessments will be summarized. Changes will be calculated from the screening/baseline of the galantamine treatment period to Week 18 (open-label, galantamine-treatment period) and Week 26 (entire study for subjects randomized to galantamine for the 8-week withdrawal period). Comparisons between the placebo and galantamine treatment groups will use the changes in safety and efficacy parameters from Weeks 18 to 26 (the double-blind, placebo-controlled, randomized withdrawal period). The primary efficacy objective is to explore the effect of galantamine on behavior as measured by the FBI during the randomized withdrawal period. In addition, for subjects with primary progressive

	aphasia, the effects of galantamine on language will be explored using the AQ of the WAB, and for all subjects the CGI will be used to explore global change. Effects on the FBI, AQ, and CGI will be explored by comparing the changes between the placebo and galantamine treatment groups during the double-blind randomized withdrawal period (Week 18 to Week 26). **Analyses:** Open-label Phase: ITT-Efficacy population: all subjects who received open-label medication with ≥ 1 post-baseline efficacy assessment Double-blind Phase: all subjects who received double-blind medication with ≥ 1 one post-randomization efficacy assessment Primary and secondary efficacy parameters: between group analysis by ANCOVA (Wk 18 compared to Wk 26) **Safety:** This is a pilot study in an unexplored subject population. The primary variable of interest is the incidence of gastrointestinal events, which are the most frequently occurring drug-related adverse events. No hypotheses are specified for statistical testing. **Analyses:** Open-label Phase: ITT-population: all subjects who received open-label medication with ≥ 1 one post-baseline safety assessment Double-blind Phase: all subjects who received double-blind medication with ≥ 1 one post-randomization safety assessment Frequency tabulation of adverse events and neurological exam; descriptive statistics for: laboratory parameters, vital signs, and ECG.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS

Baseline Characteristics

	All subjects N=39	**Gal/Gal (N=18) (%)**	**Gal/Plc (N=18) (%)**
Age (yr) (mean ± SD)	63.3 ± 8.7	63.6 ± 10.7	63.1 ± 7.1
Age at onset (yr) (mean ± SD)	58.8 ± 8.7	58.9 ± 10.5	58.4 ± 7.1
MMSE (mean ± SD)	19.0 ± 7.1	18.2 ± 8.0	20.2 ± 6.1
Modified Hachinski (mean ± SD)	0.5 ± 0.7	0.5 ± 0.8	0.4 ± 0.6
Gender			
Male	24 (62)	16 (89)	8 (44)
Female	15 (38)	2 (11)	10 (56)
Diagnosis Type (stratified)			
Frontotemporal Dementia	17 (44)	8 (44)	8 (44)
Progressive Aphasia	22 (56)	10 (56)	10 (56)

Primary Efficacy Analysis:
Overall Study group

Test	Open Label			Double-blind			
	Baseline (n=37)	Week 12 (n=37)	Week 18 (n=36)	Group	Week 18 (n=17)	Week 26 (n=17)	p-value
	Mean ± SE	Mean ± SE	Mean ± SE		Mean ± SE	Mean ± SE	
FBI	26.0 ± 2.3	26.6 ± 2.4	27.5 ± 2.7	Galantamine	27.2 ± 4.3	30.4 ± 4.3	0.3975
				Placebo	28.4 ± 3.6	29.2 ± 3.0	
AQ	74.3 ± 3.0	72.9 ± 3.0	71.9 ± 3.4	Galantamine	75.1 ± 5.1	73.8 ± 5.1	0.0630
				Placebo	68.1 ± 4.9	64.2 ± 4.7	
CGI-S	2.6 ± 0.2	2.7 ± 0.2	2.7 ± 0.2	Galantamine	2.5 ± 0.2	2.5 ± 0.2	0.2479
				Placebo	2.8 ± 0.2	3.0 ± 0.2	

PPA Subgroup

Test	Open Label			Double-blind			
	Baseline (n=21)	Week 12 (n=21)	Week 18 (n=20)	Group	Week 18 (n=9)	Week 26 (n=10)	p-value
	Mean ± SE	Mean ± SE	Mean ± SE		Mean ± SE	Mean ± SE	
FBI	20.2 ± 2.8	19.0 ± 2.7	20.1 ± 3.3	Galantamine	17.6 ± 5.1	21.0 ± 5.4	0.6669
				Placebo	23.2 ± 4.2	25.0 ± 4.1	
AQ	68.8 ± 4.1	68.6 ± 4.2	66.4 ± 4.8	Galantamine	72.8 ± 7.6	72.0 ± 6.9	0.0465
				Placebo	61.2 ± 6.7	57.5 ± 6.3	
CGI-S	2.4 ± 0.2	2.4 ± 0.2	2.4 ± 0.2	Galantamine	2.2 ± 0.3	2.1 ± 0.2	0.0093
				Placebo	2.4 ± 0.2	3.0 ± 0.3	

FTD Subgroup

Test	Open Label			Double-blind			
	Baseline (n=16)	Week 12 (n=16)	Week 18 (n=16)	Group	Week 18 (n=8)	Week 26 (n=7)	p-value
	Mean ± SE	Mean ± SE	Mean ± SE		Mean ± SE	Mean ± SE	
FBI	33.7 ± 2.9	36.4 ± 2.7	36.8 ± 3.4	Galantamine	38.1 ± 5.0	41.0 ± 4.9	0.3372
				Placebo	35.7 ± 5.6	35.3 ± 3.4	
AQ	81.5 ± 3.7	78.7 ± 4.0	78.8 ± 4.3	Galantamine	77.6 ± 7.1	75.9 ± 8.0	0.3356
				Placebo	77.9 ± 5.4	73.9 ± 5.8	
CGI-S	2.8 ± 0.3	3.1 ± 0.3	3.1 ± 0.2	Galantamine	2.9 ± 0.4	3.0 ± 0.4	0.1770
				Placebo	3.4 ± 0.3	3.0 ± 0.3	

Secondary Efficacy Analysis

Overall Group

Test	Open Label			Double-blind			
	Baseline (n=37)	Week 12 (n=37)	Week 18 (n=36)	Group	Week 18 (n=17)	Week 26 (n=17)	p-value
	Mean ± SE	Mean ± SE	Mean ± SE		Mean ± SE	Mean ± SE	
MMSE	19.3 ± 1.3	18.1 ± 1.3	17.5 ± 1.4	Galantamine	20.0 ± 2.2	18.8 ± 2.1	0.8772
				Placebo	15.4 ± 1.8	14.4 ± 1.8	
DRS-2	91.8 ± 5.5	88.7 ± 5.7	85.7 ± 6.2	Galantamine	94.8 ± 9.7	91.6 ± 10.1	0.2656
				Placebo	76.7 ± 8.2	69.6 ± 8.1	
FAB	8.4 ± 0.8	8.4 ± 0.8	8.4 ± 0.8	Galantamine	9.3 ± 1.3	9.3 ± 1.4	0.1697
				Placebo	7.8 ± 1.1	6.8 ± 1.1	
NPI	19.4 ± 2.3	20.2 ± 2.5	19.8 ± 3.3	Galantamine	18.1 ± 4.1	25.4 ± 5.4	0.0664
				Placebo	22.5 ± 5.6	19.6 ± 3.9	
ADCS	53.2 ± 2.7	50.9 ± 3.0	49.8 ± 3.3	Galantamine	52.5 ± 4.9	51.2 ± 5.2	0.2745
				Placebo	47.6 ± 4.9	44.2 ± 5.3	

SAFETY RESULTS

Adverse Events

Treatment-emergent AEs were reported by 37 subjects (95%) during galantamine treatment (OL and DB phases for Gal/Gal group)

Most frequently reported AE's reported by >10% of subjects are:

Adverse Event	Galantamine (OL) (N=39) (%)	Galantamine (DB) (N=18) (%)	Placebo (DB) (N=18) (%)
Nausea	13 (33)	2 (11)	0 (0.0)
Diarrhea	10 (26)	0 (0.0)	1 (6)
Headache	10 (26)	1 (6)	1 (6)
Abdominal Pain	8 (21)	0 (0.0)	2 (11)
Dizziness	6 (15)	0 (0.0)	1 (6)
Fatigue	5 (13)	0 (0.0)	0 (0.0)
Dyspepsia	5 (13)	1 (6)	0 (0.0)
Vomiting	5 (13)	0 (0.0)	0 (0.0)
Agitation	5 (13)	0 (0.0)	0 (0.0)

- 2 subjects reported serious AEs during galantamine treatment; 1 report of moderate fever and dehydration and 1 of mild pancreatitis; 1 subject had a fatal myocardial infarction with accompanying urosepsis and dehydration 7 days following the start of placebo treatment in the DB withdrawal phase. All serious AEs were deemed unrelated to study medication.
- 4 subjects withdrew from the study prematurely due to: myocardial infarction; severe nausea; moderate headache and agitation and severe crying and tremor; moderate hyperkinesia, agitation and hallucination; and moderate fever and dehydration.
- Withdrawal of galantamine treatment at wk 18 (Gal/Plc group) did not show any difference in AEs as compared to those subjects who continued to receive galantamine.

Vital Signs

- There were no significant changes in during the open-label phase in: weight, pulse rate, and systolic and diastolic pressures. During the withdrawal period, there was a significant (p=0.001) difference between galantamine and placebo treatment in pulse rate. This was not deemed to be clinically significant.

ECG

- No clinically significant changes in ECGs were reported by the investigator during the study.

LABORATORY VALUES

- 2 subjects had hypercholesterlemia reported as an AE, the condition was present at baseline and either improved or stayed the same during galantamine tretament.
- No other laboratory values were reported as clinically significant.

Discussion:

Analysis of all the participants failed to show statistically significant differences in behaviour or language after the double-blind randomization phase of the study (between weeks 18 and 26. However the AQ (language scores) remained stable in the treated group with PPA, compared to placebo group, which showed continuing deterioration. Clinical Global Impression of Severity was in favor of galantamine in the overall group and in the PPA subgroup at p=0.009 in the placebo controlled withdrawal phase. Subgroup analysis showed no significant difference in the behavioural measure (FBI) in the FTD group. A downward trend confirmed the validity of the observation and the efficacy measures. For the secondary efficacy measures MMSE, MDRS, FAB, NPI and ADCS, in the withdrawal phase the placebo group appeared to be worse in all parameters, but the changes in scores were not significantly different. Galantamine was well tolerated.

CONCLUSION:

This first placebo-controlled, randomized, double-blind study of cholinesterase inhibitors in FTD/Pick complex suggest although glantamine is safe in FTD, it shows significant efficacy only in one of the primary efficacy measures, the Clinical Global Impression of Severity in the placebo-controlled withdrawal phase in the PPA subgroup. There was a trend for progressive aphasics to show less language deterioration on glantamine than on placebo.

Date of this report: January 17, 2006

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