Sponsor

Novartis

Generic Drug Name

Rrivastigmine

Trial Indication(s)

Parkinson's Disease Dementia

Protocol Number

CENA713B2311

Protocol Title

A 24-week Prospective, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Parallel-Group Study of the Efficacy, Tolerability, and Safety of 3-12 mg/day of Exelon® (Rivastigmine) Capsules in Patients with Parkinson's Disease Dementia

Clinical Trial Phase

Phase III

Study Start/End Dates

10-Oct-2002 to 20-Jan-2004

Reason for Termination

Not applicable.

Study Design/Methodology

This was a 24-week, prospective, randomized, multicenter, double-blind, placebocontrolled, parallel group study in patients with PDD designed to evaluate the efficacy, safety, and tolerability of Exelon at doses of 3 to 12 mg/day in this patient population.

Centers

Sixty-eight (68) centers in 12 countries: Austria (1 center), Belgium (4), Canada (7), France (9), Germany (12), Italy (11), Netherlands (2), Norway (1), Portugal (1), Spain (8), Turkey (3), United Kingdom (9).

Publication

PMID: 1559

https://www.ncbi.nlm.nih.gov/pubmed/1559?dopt=Abstract

Objectives:

Primary objective(s)

The primary objective of this study was to evaluate the efficacy of Exelon (3 to 12 mg/day for 24 weeks) compared with placebo in patients with Parkinson's disease dementia (PDD), using the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and the Alzheimer's Disease Cooperative Study - Clinician's Global Impression of Change (ADCS-CGIC).

Secondary objective(s)

Secondary objectives included the evaluation of the effects of Exelon on activities of daily living, behavior, attention, executive functioning and health economic parameters including caregiver distress; to explore differences in the efficacy of Exelon depending on preexisting attentional deficits, the potential genetic factors related to PDD, potential biomarkers related to PDD; and the evaluation of the safety and tolerability of Exelon.

Test Product (s), Dose(s), and Mode(s) of Administration

Exelon capsules for oral administration (1 capsule b.i.d. with food) containing either 1.5 mg, 3.0 mg, 4.5 mg or 6.0 mg rivastigmine.

Statistical Methods

All patients who received at least one dose of study drug and who had a subsequent safety evaluation were included in the safety database. Primary efficacy variables included the ADAS-cog (analysis of covariance, ANCOVA, on mean change from baseline) and the CGIC(categorical analysis, Van Elteren test). ANCOVA analyses included country and baseline (when applicable) as stratification factor and covariates, respectively. All statistical tests were 2-tailed and performed at the 0.05 significance level. Analyses were performed on several analysis data set (ITT+RDO, LOCF, and OC) to assess the biasing effects of discontinuation. The primary population for comparing the treatment groups was the ITT+RDO population. This population included patients who discontinued study treatment early but continued to attend scheduled visits for efficacy evaluations (RDO patients).

The primary objective of this study required demonstration of a statistically significant difference at the two-sided 5% level of significance between the group of patients randomized to Exelon and the group randomized to placebo for each of the two primary efficacy variables.

No interim analyses were performed.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

• of either sex and aged 50 years or older

• having a clinical diagnosis of idiopathic PD according to the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria

• having a clinical diagnosis of PDD according to DSM IV criteria (Code 294.1), with onset of symptoms of dementia at least 2 years after the first diagnosis of idiopathic PD

• having a MMSE score of 10 to 24

• having had sufficient education to read, write, and effectively communicate during the premorbid stage

• being cooperative, able to ingest oral medication, and able to complete aspects of the study and capable of doing so, either alone or with the aid of a responsible caregiver according to judgment of the investigator.

• having a single, designated caregiver who was in contact with the patient a minimum of three days a week for a period sufficient to assess the patient, who was willing to accept responsibility for supervising the treatment and condition of the patient throughout the study and for providing input to efficacy parameters in accordance with all protocol requirements.

• written informed consent by the patient (or their legally authorized representative, as applicable) and by the caregiver.

Exclusion criteria

• a current diagnosis of any primary neurodegenerative disorder other than PD or any other causes of dementia (e.g., Alzheimer's disease, Frontotemporal dementia, Huntington's disease, Dementia with Lewy bodies, Parkinson-Plus-Syndromes other than PDD, e.g. progressive supranuclear palsy or olivopontocerebellar degeneration, vitamin B12 or folate deficiency, hypothyroidism, syphilis)
• a current diagnosis of probable or possible vascular dementia according to the NINDSAIREN criteria, i.e. clinical and brain imaging evidence of cerebrovascular disease (CVD) and a relationship between dementia and CVD
• a current diagnosis of a major depressive episode according to DSM IV criteria (Code 296), or any other DSM-IV Axis 1 diagnosis that may interfere with the response of the patient to study medication
• a current diagnosis of active, uncontrolled seizure disorder a disability that may prevent the patient from completing all study requirements and, in particular, interfere with the assessment of dementia
• a diagnosis of active, uncontrolled peptic ulceration within the last 3 months
• having a deep brain stimulation implant**.**

Participant Flow Table

Patient disposition for each treatment group

	Exelon		Placebo		Total	
Number (%) of patients						
Screened					650	
Randomized	362	(100)	179	(100)	541	(100)
Exposed	362	(100)	179	(100)	541	(100)
Completed	263	(72.7)	147	(82.1)	410	(75.8)
Discontinued	99	(27.3)	32	(17.9)	131	(24.2)
Main reason for discontinuation	n	(%)	n	(%)	n	(%)
Adverse event(s)	62	(17.1)	14	(7.8)	76	(14.0)
Subject withdrew consent	21	(5.8)	2	(1.1)	23	(4.3)
Death	4	(1.1)	7	(3.9)	11	(2.0)
Protocol violation(s)	5	(1.4)	2	(1.1)	7	(1.3)
Unsatisfactory therapeutic effect	2	(0.6)	4	(2.2)	6	(1.1)
Lost to follow-up	4	(1.1)	1	(0.6)	5	(0.9)
Administrative reasons	0	(0.0)	2	(1.1)	2	(0.4)
Abnormal test procedure result(s)	1	(0.3)	0	(0.0)	1	(0.2)

Baseline Characteristics

Demographic summary by treatment group – Safety population

		Exelon	Placebo	Total
		N = 362	N = 179	N = 541
Age (years)	Mean ± SD	72.8 ± 6.7	72.4 ± 6.4	72.7 ± 6.6
	Median	73.5	73.0	73.0
	Range	50 - 91	53 - 88	50 - 91
Age group – n (%)	< 65 years	49 (13.5)	19 (10.6)	68 (12.6)
	≥ 65 years	313 (86.5)	160 (89.4)	473 (87.4)
Gender – n(%)	Male	234 (64.6)	117 (65.4)	351 (64.9)
	Female	128 (35.4)	62 (34.6)	190 (35.1)
Race – n(%)	Caucasian	360 (99.4)	179 (100)	539 (99.6)
	Other	2 (0.6)	0	2 (0.4)

Summary of Efficacy

Primary Outcome Result(s)

ADAS-Cog change from baseline

		Exelon		Placebo			
	n	mean ± SD	n	mean ± SD	LS means difference	p-value	95% CI (Exelon – placebo)
ITT+RDO baseline	329	23.8 ± 10.2	161	24.3 ± 10.5			
Change at week 16	329	2.3 ± 7.3	161	0.3 ± 6.8	2.06	0.002 *	0.78 3.34
Change at week 24	329	2.1 ± 8.2	161	-0.7± 7.5	2.88	<0.001 *	1.44 4.31
LOCF baseline	287	24.0 ± 10.3	154	24.5 ± 10.6			
Change at week 16	287	2.8 ± 7.4	154	0.3 ± 6.7	2.74	<0.001 *	1.42 4.06
Change at week 24	287	2.5 ± 8.4	154	-0.8 ± 7.5	3.54	<0.001 *	2.05 5.04
OC baseline wk 16	284	23.9 ± 10.3	150	24.5 ± 10.6			
Change at week 16	284	2.8 ± 7.4	150	0.3 ± 6.8	2.78	<0.001 *	1.43 4.12
OC baseline wk 24	256	23.7 ± 10.4	139	23.4 ± 9.8			
Change at week 24	256	2.9 ± 8.3	139	-1.0 ± 7.6	3.80	<0.001 *	2.22 5.37

Higher change scores indicate greater improvement.

* $p < 0.05$. p-value based on two-way analysis of covariance model using treatment and country as factors and baseline ADAS-cog as a covariate; 95% confidence interval calculated for the difference between Least Squares Means (LSMEANS).

ADAS-Cog categorical analysis - patients improving

		Exelon		Placebo		
Population	Visit	N	% improved	N	% improved	p-value
ITT+RDO	week 16	329	36%	161	25%	0.022*
	week 24	329	37%	161	29%	0.074
LOCF	week 16	287	39%	154	26%	0.005*
	week 24	287	40%	154	29%	0.015*
OC	week 16	284	39%	150	27%	0.006*
	week 24	256	42%	139	29%	0.008*

Improvement was defined as at least 4 points improvement.
p-values are based on CMH test blocking for country. * $p < 0.05$

ADCS CGI-C - categorical analysis at week 24

	ITT+RDO		LOCF		OC	
	Exelon	Placebo	Exelon	Placebo	Exelon	Placebo
N	329	165	289	158	252	145
Mean ± SD at week 24	3.8 ± 1.4	4.3 ± 1.5	3.7 ± 1.4	4.3 ± 1.5	3.7 ± 1.4	4.2 ± 1.5
Change	Exelon	Placebo	Exelon	Placebo	Exelon	Placebo
Markedly improved (1)	4%	2%	5%	2%	6%	2%
Moderately improved (2)	16%	12%	16%	12%	18%	12%
Minimally improved (3)	21%	15%	23%	16%	23%	15%
Unchanged (4)	26%	28%	25%	28%	25%	29%
Minimally worse (5)	21%	19%	20%	19%	19%	19%
Moderately worse (6)	11%	16%	9%	17%	8%	17%
Markedly worse (7)	2%	7%	2%	6%	2%	6%
p-value	0.007*		<0.001*		<0.001*	

p-value (Exelon vs. placebo) based on van Elteren test blocking for country. *: p<0.05

ADCS CGI-C —patients improving, and treatment effect

	Exelon		Placebo						
Population/ Visit	N	% impr.	N	% impr.	p-value	Treatment effect	p-value	Odds ratio	95% CI for odds ratio
ITT+RDO									
Week 16	318	42%	159	31%	0.028*	0.23 ± 0.11	0.027*	1.60	1.06 2.41
Week 24	329	41%	165	30%	0.025*	0.24 ± 0.11	0.023*	1.61	1.07 2.44
LOCF									
Week 16	282	46%	153	31%	0.007*	0.30 ± 0.11	0.006*	1.81	1.18 2.77
Week 24	289	44%	158	30%	0.006*	0.30 ± 0.11	0.006*	1.83	1.19 2.82
OC									
Week 16	282	46%	153	31%	0.007*	0.30 ± 0.11	0.006*	1.81	1.18 2.77
Week 24	252	46%	145	30%	0.002*	0.36 ± 0.12	0.002*	2.07	1.31 3.26

Improving (impr.) is defined as markedly, moderately, or minimally improved.

p-values are based on a CMH test blocking for country. * p < 0.05

The odds ratio denotes the likelihood of an Exelon patient experiencing improvement relative to the likelihood of a placebo - treated patient experiencing improvement. An odds ratio > 1 represents an outcome in favor of Exelon.

Secondary Outcome Result(s)

ADCS-ADL total score change from baseline

		Exelon		Placebo			
	N	mean ± SD	n	mean ± SD	LS means difference	p-value	95% CI (Exelon – placebo)
ITT+RDO baseline	333	41.6 ± 18.6	165	41.2 ± 17.7			
Change at week 16	333	-0.4 ± 11.2	165	-1.5 ± 8.3	1.09	0.262	-0.82 3.00
Change at week 24	333	-1.1 ± 12.6	165	-3.6 ± 10.3	2.51	0.023*	0.35 4.67
LOCF baseline	289	41.6 ± 18.5	158	40.9 ± 17.9			
Change at week 16	289	-0.2 ± 11.7	158	-1.3 ± 8.4	1.17	0.263	-0.88 3.22
Change at week 24	289	-0.8 ± 13.1	158	-3.5 ± 10.4	2.72	0.021*	0.41 5.04
OC baseline wk 16	283	41.5 ± 18.4	157	41.1 ± 17.9			
Change at week 16	283	-0.2 ± 11.8	157	-1.3 ± 8.4	1.19	0.261	-0.89 3.26
OC baseline wk 24	260	41.8 ± 18.5	142	42.4 ± 17.8			
Change at week 24	260	-0.3 ± 13.1	142	-3.5 ± 10.7	3.20	0.010*	0.77 5.62

p-value based on analysis of covariance model using treatment and country as factors and baseline ADCS-ADL as a covariate; 95% confidence interval calculated for the difference between Least Squares Means (LSMEANS). * : $p<0.05$

Higher scores indicate better performance.

NPI-10 total score change from baseline

Population/ Visit		Exelon		Placebo		Exelon vs. Placebo
		N	Mean ± SD	N	Mean ± SD	p-value
ITT+RDO	Baseline	334	12.7 ± 11.7	166	13.2 ± 13.0	
Week 16	Change	334	-1.6 ± 9.9	166	0.4 ± 10.7	0.018 *
Week 24	Change	334	-2.0 ± 10.0	166	0.0 ± 10.4	0.015 *
LOCF	Baseline	289	12.3 ± 11.7	159	13.0 ± 13.0	
Week 16	Change	287	-1.8 ± 10.3	157	-0.0 ± 10.1	0.038*
Week 24	Change	288	-2.1 ± 10.3	159	-0.4 ± 9.7	0.032 *
OC						
Week 16	Baseline	284	12.4 ± 11.8	157	12.8 ± 13.0	
	Change	284	-1.9 ± 10.3	157	-0.0 ± 10.1	0.038 *
Week 24	Baseline	262	12.4 ± 11.7	144	12.1 ± 11.8	
	Change	262	-2.5 ± 10.5	144	-1.1 ± 9.2	0.182

p-values are based on two-way analysis of covariance. * $p < 0.05$

Lower change scores indicate greater improvement

CDR - power of attention score change from baseline

Population/ Visit		Exelon		Placebo		Exelon vs. Placebo
		N	Mean ± SD	N	Mean ± SD	p-value
ITT+RDO	Baseline	328	2197.0 ± 1170.2	158	2490.5 ± 2134.8	
Week 16	Change	328	-26.5 ± 892.2	158	33.0 ± 1432.4	0.110
Week 24	Change	328	-30.5 ± 989.7	158	142.7 ± 1780.2	0.009*
LOCF	Baseline	283	2235.7 ± 1218.2	151	2519.2 ± 2362.3	
Week 16	Change	283	-26.9 ± 955.0	151	-26.2 ± 1223.8	0.276
Week 24	Change	283	-34.6 ± 1059.0	151	82.5 ± 1636.9	0.028*
OC						
Week 16	Baseline	261	2197.2 ± 1184.4	143	2469.4 ± 2369.4	
	Change	261	-29.2 ± 994.6	143	-27.7 ± 1257.8	0.287
Week 24	Baseline	249	2218.4 ± 1200.9	134	2326.9 ± 2164.7	
	Change	249	-63.9 ± 1106.0	134	139.7 ± 1709.5	0.025*

Lower change scores indicate greater improvement. p-values are based on two-way analysis of covariance. * $p < 0.05$

D-KEFS Letter fluency test change from baseline – total correct responses

Population/ Visit		Exelon		Placebo		Exelon vs. Placebo
OC		N	Mean ± SD	N	Mean ± SD	p-value
Baseline		290	13.9 ± 9.5	158	14.5 ± 9.4	
Week 16	Change	280	0.6 ± 6.3	152	-1.2 ± 5.6	0.006*
Week 24	Change	258	1.7 ± 6.8	144	-1.1 ± 6.3	<0.001*

p-values are based on van Elteren test blocking for country. * $p < 0.05$

Higher change scores indicate greater improvement

Ten point clock test change from baseline

Population/ Visit	Exelon		Placebo		Exelon vs. placebo
OC	N	Mean ± SD	N	Mean ± SD	p-value
Baseline	62	3.5 ± 3.7	37	2.9 ± 3.8	
Change from baseline at week 24	50	0.6 ± 2.5	30	-0.6 ± 2.4	0.015*

Lower scores indicate worse cognitive performance. *: p-value <0.05

Summary of Safety
Safety Results

Serious adverse events – most frequently affected system organ classes and AE preferred terms (>1%)

	Exelon	Placebo
No. (%) of patients studied	362	179
No. (%) of patients with SAE(s)	47 (13.0)	26 (14.5)
System organ class	n (%)	n (%)
AE preferred term		
Cardiac disorders	3 (0.8)	3 (1.7)
Gastrointestinal disorders	9 (2.5)	4 (2.2)
Infections and infestations	5 (1.4)	7 (3.9)
Injury, poisoning and procedural complications	10 (2.8)	4 (2.2)
Investigations	4 (1.1)	0
Metabolism and nutrition disorders	7 (1.9)	2 (1.1)
Dehydration	5 (1.4)	2 (1.1)
Nervous system disorders	6 (1.7)	8 (4.5)
Syncope	0	2 (1.1)
Psychiatric disorders	7 (1.9)	6 (3.4)
Confusional state	2 (0.6)	2 (1.1)
Respiratory, thoracic and mediastinal disorders	1 (0.3)	2 (1.1)
Vascular disorders	4 (1.1)	1 (0.6)

Number (%) of patients with most frequent AEs, by preferred term and treatment group – Safety population

	Exelon	Placebo
No. (%) of patients studied	362	179
No. (%) of patients with AE(s)	303 (83.7)	127 (70.9)
AE preferred term	n (%)	n (%)
Nausea	105 (29.0)	20 (11.2)
Vomiting	60 (16.6)	3 (1.7)
Tremor	37 (10.2)	7 (3.9)
Diarrhea	26 (7.2)	8 (4.5)
Anorexia	22 (6.1)	5 (2.8)
Fall	21 (5.8)	11 (6.1)
Dizziness	21 (5.8)	2 (1.1)
Hypotension	19 (5.2)	14 (7.8)
Hallucination	17 (4.7)	17 (9.5)
Constipation	16 (4.4)	12 (6.7)
Confusion	13 (3.6)	10 (5.6)
Orthostatic hypotension	6 (1.7)	9 (5.0)

AEs are listed by descending order of frequency in the Exelon group. Shown are all AEs with an incidence of at least 5% in either group.

Number (%) of patients who died, had other serious or clinically significant AEs or discontinued because of them – Safety population

	Exelon	Placebo
No. (%) of patients studied	362	179
No. (%) of patients with AE(s)	303 (83.7)	127 (70.9)
Number (%) of patients with serious or other significant events	n (%)	n (%)
Death	4 (1.1)	7 (3.9)
SAE(s)	47 (13.0)	26 (14.5)
Clinically significant AE(s)		
Discontinued due to SAE(s)	20 (5.5)	14 (7.8)
Discontinued due to non-serious AE(s)	46 (12.7)	6 (3.4)

Treatment-emergent deaths and SAE(s) are reported.

Date of Clinical Trial Report

10-Nov-2004