Sponsor– Novartis	**Web Page/Link to Prescribing/Label Information**– www.pharma.us.novartis.com/product/pi.jsp
Generic Drug Name– Rivastigmine	
Therapeutic Area of Trial– Neuroscience	
Approved Indication– Alzheimer's Disease (AD)	
Study Number– **CENA713IA07**	
Title– A Prospective, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Parallel-Group Study of the Effect of Rivastigmine on the Time to Clinical Diagnosis of Alzheimer's Disease in Subjects with Mild Cognitive Impairment (MCI)	
Phase of Development– IIIb	
Study Start/End dates– 25-May-1999 through 27-Apr-2004	
Study Design/Methodology– This was a prospective, randomized, multicenter, double-blind, placebo-controlled, 36-48 month study comparing neurocognitive decline and the length of time of progression from MCI to a clinical diagnosis of AD in subjects taking rivastigmine versus placebo. The dose of rivastigmine was optimized for each subject starting with a 0.5 mg b.i.d. regimen for two weeks followed by a series of one-step dose increases (1.5 mg bid, 3.0 mg bid, 4.5 mg, 6.0 mg bid), each occurring at a minimum of 4-week intervals. Subjects not tolerating the 1.5 mg b.i.d. regimen were discontinued. One-step dose decreases were permitted at any time to improve tolerability. Subjects with MCI were randomly assigned to treatment with either rivastigmine or placebo in an assignment ratio of 1:1. Subjects who progressed to dementia were given the option of receiving open-label rivastigmine for the remainder of the 36-48 month treatment period. Subjects who discontinued double-blind or open-label study drug treatment prematurely were encouraged to return to the clinic for efficacy assessments (retrieved dropout [RDO] visits) at regularly scheduled intervals for the remainder of the 36-48 month treatment period.	
Centres– A total of 69 centers in 14 countries were initiated: 4 in Argentina, 2 in Austria, 4 in Finland, 6 in France, 8 in Germany, 4 in Mexico, 3 in South Africa, 6 in Spain, 3 in Sweden, 2 in Switzerland, 1 in The Netherlands, 9 in the United Kingdom, 15 in the United States of America, and 2 in Uruguay. Seven centers did not participate in Protocol Amendment 5, which extended the treatment period from 36 to 48 months.	
Publication– Ongoing	
Objectives– *Primary outcome/efficacy objective(s)*– • Among subjects with Mild Cognitive Impairment (MCI) who are treated with rivastigmine as compared to placebo to demonstrate a prolongation in the time to clinical diagnosis of Alzheimer's disease (AD) and to evaluate the change from baseline on a neurocognitive test battery. *Secondary outcome/efficacy objective(s)*– To evaluate the effects of rivastigmine on the rate of volumetric changes in the brain, cognitive functioning, activities of daily living, and to determine the effect of APOE genotype on time to progression to AD and response to rivastigmine treatment; and to evaluate the safety and tolerability of rivastigmine treatment in subjects with MCI for up to 4 years.	
Test Product, Dose, and Mode of Administration– Double-blind phase: Capsules containing 0.5 mg, 1.5 mg, 3.0 mg, 4.5 mg, 6.0 mg rivastigmine Open-label phase: Rivastigmine capsules (market formulation) containing 1.5 mg, 3.0 mg, 4.5 mg, and 6.0 mg rivastigmine Medication was administered twice daily with morning and evening meals.	

Reference Product(s), Dose(s), and Mode(s) of Administration– Placebo capsules were identical in appearance to capsules containing rivastigmine. Placebo capsules were administered in the same way as the active drug.

Criteria for Evaluation–

Primary efficacy: The primary measures were time to clinical diagnosis of AD by NINCDS-ADRDA and DSM-IV criteria and change from baseline on cognitive function as measured by a single score summed from weighted scores on a series of individual cognitive tests.

Secondary efficacy: Other efficacy parameters measured during the study were volumetric changes in the brain, using Magnetic Resonance Imaging (MRI) imaging at selected study sites, Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog), Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL), and APOE genotype.

Safety/tolerability: Safety assessments consisted of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs); the annual monitoring of hematology, blood chemistry, and urine values; measurement of vital signs at every clinic visit (3 to 6 month intervals depending on study phase); the performance on annual electrocardiograms (ECGs); and data collected at the end-of-study physical examination.

Other: CSF and plasma biomarkers of AD, per Amendment 1.

Pharmacology: n.a.

Statistical Methods– The primary and secondary efficacy analyses were performed on the modified intent-to-treat population. Time to diagnosis of AD was analyzed using Cox's proportional hazards regression model and Kaplan-Meier estimates of the survivor function for each treatment group were presented. The composite standardized score of cognitive function was subjected to an analysis of covariance with the following explanatory variables: treatment, country, gender, race, age group (<75 years, ≥75 years), education level, and baseline composite score. The secondary efficacy variables were subject to analysis of covariance with the baseline score as covariate and treatment, country, age group, and education level as the main effects.

Study Population: Inclusion/Exclusion Criteria and Demographics– Eligible subjects were those aged 55-85 years, of either sex (females were either surgically sterilized, at least 1 year postmenopausal, or using adequate birth control), who showed evidence of MCI (Global CDR score = 0.5, NYU Delayed Paragraph Recall <9, 17-item HAM-D score <13, and HAM-D Item 1 for depressed mood score ≤1), had a suitable friend or family member who was willing to act as an informant, were cooperative, willing to complete all aspects of the study (MRI evaluations and pharmacogenetic testing were optional), able to ingest oral medical and provided written informed consent prior to their participation in the study. Excluded subjects were those with advanced, severe, and unstable disease of any type that could have interfered with primary and secondary evaluations, with signs or symptoms that warranted diagnosis of AD, and those with fewer than 4 years of formal education. Subjects were also ineligible if they had baseline MRI findings or CT-scan findings within a year of screening that were consistent with a neurodegenerative process other than AD, or a current diagnosis of any primary neurodegenerative disorder, e.g., Parkinson's disease, or a disability that may have prevented the subject from completing all study requirements (e.g., blindness, deafness, severe language difficulty).

Number of Subjects	**Rivastigmine**	**Placebo**
Planned N	450	450
Randomised n	508	510
Completed n (%) DB+DB-RDO	257 (50.6)	321 (62.9)
Withdrawn n (%) DB+DB-RDO	248 (48.8)	188 (36.9)
Included in the primary analysis n (%)	508 (100)	510 (100)
Withdrawn due to adverse events n (%)	120 (23.6)	65 (12.7)
Withdrawn due to lack of efficacy n (%)	8 (1.6)	11 (2.2)

Withdrawn for other reasons n (%)	120 (23.6)	112 (22)
Demographic and Background Characteristics		
N (ITT)	508	510
Females:males	270:238	262:248
Mean age, years (SD)	70.3 (7.4)	70.6 (7.6)
Mean weight, kg (SD)	72.5 (13.7)	72.6 (13.9)
Race White n (%) Black n (%) Asian n (%) Other n (%)	 494 (97.2) 4 (0.8) 0 10 (2.0)	 494 (96.9) 3 (0.6) 1 (0.2) 12 (2.4)

Subject disposition for entire study (All randomized population)

Disposition/Reason for discontinuation	Rivastigmine (N=508) n (%)	Placebo (N=510) n (%)
Completed study by phase at the end of the trial	**312 (61.4)**	**346 (67.8)**
Double-blind	179 (35.2)	219 (42.9)
Open-label	55 (10.8)	53 (10.4)
RDO	78 (15.4)	74 (14.5)
Discontinued study by phase at the end of trial	**193 (38.0)**	**163 (32.0)**
Double-blind	66 (13.0)	69 (13.5)
Open-label	9 (1.8)	17 (3.3)
RDO	118 (23.2)	77 (15.1)

Four randomized subjects did not take study medication and discontinued the study.

Subject disposition for DB+DB-RDO phase (All randomized population)

Disposition/Reason for discontinuation in DB phase	Rivastigmine (N=508) n (%)	Placebo (N=510) n (%)
Completed DB phase (converted to dementia/AD or Month 36/48)	**257 (50.6)**	**321 (62.9)**
Diagnosed dementia (confirmed DMC)	72 (14.2)	99 (19.4)
Diagnosed AD (confirmed DMC)	71 (14.0)	97 (19.0)
Month 36 (no conversion)	41 (8.1)	41 (8.0)
Month 48 (no conversion)	139 (27.4)	175 (34.3)
Other (Amendment 3)**	5 (1.0)	6 (1.2)
Completed DB phase entered RDO	6 (1.2)	6 (1.2)
Discontinued in DB phase (No RDO)	68 (13.4)	69 (13.5)
Discontinued in DB phase entered RDO	180 (35.4)	119 (23.3)
Total Discontinued DB+DB-RDO phase (from phase completion form)	**248 (48.8)**	**188 (36.9)**
Adverse event(s)	120 (23.6) [1]	65 (12.7) [2]
Abnormal laboratory value(s)	0 (0.0)	1 (0.2)
Abnormal test value(s)	0 (0.0)	0 (0.0)
Unsatisfactory therapeutic effect	8 (1.6)	11 (2.2)
Subject condition no longer requires study drug	1 (0.2)	1 (0.2)
Protocol violation	8 (1.6)	9 (1.8)
Subject withdrew consent	87 (17.1)	74 (14.5)
Lost to follow-up	9 (1.8)	2 (0.4)
Administrative problems	6 (1.2)	11 (2.2)
Death	9 (1.8)[3]	14 (2.7)[4]
Not stated	0 (0.0)	0 (0.0)

**Classified as DB-DB-RDO phase completer by the investigator although conversion was not confirmed by DMC – refer to Protocol Amendment 3.

Four randomized subjects did not take study medication and discontinued the study; 3 in the Rivastigmine DB group and 1 in the placebo DB group; these subjects are not included in the tabulation.

[1] An additional 8 subjects had AEs leading to discontinuation, although the primary reason for discontinuation was not recorded as AE on the study outcome CRF page.

[2] An additional 10 subjects had AEs leading to discontinuation, although the primary reason for discontinuation was not recorded as AE on the study outcome CRF page.

[3] Total includes DB plus DB-RDO deaths (death checked by investigator as primary reason for discontinuation), 5 on treatment and 4 off-treatment (event occurred ≥2 days after last dose of DB study medication).

[4] Total includes DB plus DB-RDO deaths (death checked by investigator as primary reason for discontinuation), 7 on treatment and 7 off-treatment (event occurred ≥2 days after last dose of DB study medication).

Primary Efficacy Result(s)– Modified intent to treat population

Number (%) and time of DMC confirmed conversions to Alzheimer's disease

	Rivastigmine (N=508)	Placebo (N=510)	Total (N= 1018)
No Conversions to AD	420 (82.7%)	401 (78.6%)	821 (80.6%)
Conversions to AD	88 (17.3%)	109 (21.4%)	197 (19.4%)
Time to AD conversion			
Mean (SE) [1]	**1318.46 (15.08)**	**1289.45 (16.28)**	

[1] **The mean survival time and its standard error are underestimated because the largest observation is censored Quantiles cannot be estimated due to low conversion rate**

Treatment comparison for composite standardized Z score of cognitive function

	Rivastigmine		Placebo
Baseline			
N	507		509
Mean	-0.06		0.05
SD	6.87		6.78
Endpoint (1)			
N	507		509
Mean	-1.16		-0.98
SD	8.95		9.09
Change from baseline to endpoint			
N	507		509
Mean	-1.10		-1.03
SD	4.52		4.64
LS mean	-1.64		-1.55
Treatment difference (95% CI) (2)		-0.10 (-0.63, 0.44)	
p-value (3)		0.726	

- Only those subjects with both baseline and post-baseline measurement (imputation as needed) are included.
- (1) At time of investigator's diagnosis of AD confirmed by DMC (see details in Appendix 5).
- (2) Rivastigmine-Placebo
- (3) Treatment comparison based on ANCOVA adjusting for country, gender, age group, education (years), treatment and baseline value.

Secondary efficacy result(s)–intent to treat population

Summary statistics for secondary efficacy variable – individual items from cognitive battery at endpoint time of conversion (MITT population)

			Baseline			Post-baseline Time of conversion			Change from baseline		
Month	**Treatment**	**N**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**
Delayed word list recall											
Baseline	Rivastigmine	507	6.0	2.6	6.0						
	Placebo	507	5.8	2.7	6.0						
Endpoint (2)	Rivastigmine	504	6.0	2.6	6.0	6.2	3.1	6.0	-0.2	2.3	0.0
	Placebo	502	5.8	2.7	6.0	5.8	3.3	6.0	-0.0	2.4	0.0
NYU paragraph recall test - immediate											
Baseline	Rivastigmine	507	4.0	2.3	4.0						
	Placebo	509	4.1	2.4	4.0						
Endpoint (2)	Rivastigmine	504	4.0	2.3	4.0	3.8	2.8	3.0	-0.3	2.4	0.0
	Placebo	505	4.1	2.4	4.0	3.7	2.7	3.0	-0.4	2.5	0.0
NYU paragraph recall test - delayed											
Baseline	Rivastigmine	507	3.6	2.6	3.0						
	Placebo	509	3.8	2.6	4.0						
Endpoint (2)	Rivastigmine	499	3.6	2.6	4.0	3.3	3.3	3.0	-0.3	2.3	0.0
	Placebo	504	3.8	2.6	4.0	3.5	3.3	3.0	-0.4	2.6	0.0

Buschke reminding text – total free recall											
Baseline	Rivastigmine	501	18.8	9.6	19.0						
	Placebo	504	19.9	9.9	21.0						
Endpoint (2)	Rivastigmine	477	19.0	9.5	20.0	18.3	11.9	19.0	-0.7	7.1	0.0
	Placebo	488	20.1	9.7	21.0	19.8	12.3	22.0	-0.3	7.1	0.0
Buschke reminding test – total cued recall											
Baseline	Rivastigmine	501	19.2	6.8	19.0						
	Placebo	504	19.0	6.3	19.0						
Endpoint (2)	Rivastigmine	477	19.2	6.8	19.0	16.2	7.7	16.0	-3.0	7.3	-2.0
	Placebo	488	19.1	6.2	19.0	15.8	7.3	16.0	-3.4	7.2	-2.0
Buschke reminding test – total free and cued recall											
Baseline	Rivastigmine	501	38.0	11.3	43.0						
	Placebo	504	38.9	10.9	44.0						
Endpoint (2)	Rivastigmine	478	38.2	11.2	43.0	34.4	14.8	42.0	-3.7	9.4	-1.0
	Placebo	488	39.3	10.6	44.0	35.6	14.6	43.0	-3.7	8.6	-1.0
Symbol digit modalities task – number correct											
Baseline	Rivastigmine	507	29.0	12.2	29.0						
	Placebo	508	29.0	11.8	29.0						
Endpoint (2)	Rivastigmine	499	29.0	12.1	29.0	28.5	14.1	29.0	-0.6	7.1	0.0
	Placebo	495	29.3	11.7	30.0	29.3	13.8	29.0	-0.0	8.0	0.0
Symbol digit modalities task – number of errors											
Baseline	Rivastigmine	507	1.1	1.7	1.0						
	Placebo	508	1.1	1.5	1.0						
Endpoint (2)	Rivastigmine	499	1.2	1.7	1.0	0.9	1.4	0.0	0.3	1.7	0.0
	Placebo	495	1.1	1.5	1.0	0.9	1.8	0.0	0.2	2.2	0.0
Digit cancellation task – number of target hits											
Baseline	Rivastigmine	507	19.9	7.0	20.0						
	Placebo	509	19.7	6.8	19.0						
Endpoint (2)	Rivastigmine	498	20.0	7.0	20.0	19.3	7.5	19.0	-0.7	5.3	0.0
	Placebo	501	19.7	6.8	19.0	19.1	7.5	19.0	-0.6	4.9	-1.0
Digit cancellation task – number of errors											
Baseline	Rivastigmine	507	0.2	1.0	0.0						
	Placebo	509	0.1	0.4	0.0						
Endpoint (2)	Rivastigmine	498	0.2	1.0	0.0	0.2	1.1	0.0	0.0	1.2	0.0
	Placebo	501	0.1	0.4	0.0	0.1	0.6	0.0	-0.0	0.7	0.0
Digit cancellation task – number of times reminded											
Baseline	Rivastigmine	506	0.2	2.0	0.0						
	Placebo	509	0.1	0.4	0.0						
Endpoint (2)	Rivastigmine	497	0.2	2.1	0.0	0.2	2.7	0.0	-0.1	3.4	0.0
	Placebo	501	0.1	0.4	0.0	0.1	0.4	0.0	-0.0	0.5	0.0
Maze – time to complete											
Baseline	Rivastigmine	506	43.7	34.1	35.0						
	Placebo	509	43.9	33.3	35.0						
Endpoint (2)	Rivastigmine	498	43.3	33.2	35.0	40.8	34.9	31.0	2.6	36.0	2.0
	Placebo	500	42.7	30.9	34.0	42.5	37.8	31.0	0.2	36.3	2.0
Letter numbering sequence											
Baseline	Rivastigmine	506	7.5	2.9	8.0						

	Placebo	509	7.5	2.9	8.0						
Endpoint (2)	Rivastigmine	496	7.5	2.9	8.0	7.3	3.3	8.0	-0.2	2.2	0.0
	Placebo	500	7.5	2.9	8.0	7.3	3.2	8.0	-0.2	2.3	0.0
Verbal fluency categories											
Baseline	Rivastigmine	506	17.3	6.0	17.0						
	Placebo	508	17.0	5.7	17.0						
Endpoint (2)	Rivastigmine	498	17.4	6.0	17.0	16.5	6.9	16.0	-0.9	4.8	0.0
	Placebo	502	17.0	5.7	17.0	16.9	7.0	17.0	-0.1	4.8	0.0
Clock Drawing											
Baseline	Rivastigmine	507	4.2	1.0	5.0						
	Placebo	509	4.2	1.0	5.0						
Endpoint (2)	Rivastigmine	504	4.2	1.0	5.0	4.1	1.3	5.0	-0.1	1.1	0.0
	Placebo	505	4.2	1.0	5.0	4.1	1.2	5.0	-0.1	1.1	0.0
Boston naming test (optional test)											
Baseline	Rivastigmine	29	7.2	2.8	8.0						
	Placebo	27	6.9	2.7	7.0						
Endpoint (2)	Rivastigmine	11	7.0	2.7	8.0	7.7	2.4	9.0	0.7	0.8	1.0
	Placebo	9	5.7	2.7	5.0	6.6	2.7	7.0	0.9	2.7	1.0
Warrington faces (optional test)											
Baseline	Rivastigmine	23	38.5	5.8	39.0						
	Placebo	21	38.0	5.9	38.0						
Endpoint (2)	Rivastigmine	4	39.0	7.5	38.0	41.5	5.4	40.0	2.5	3.3	1.5
	Placebo	3	32.3	4.0	33.0	34.3	8.7	32.0	2.0	12.2	-4.0
Benton judgement of line orientation (optional test)											
Baseline	Rivastigmine	22	22.3	4.9	23.0						
	Placebo	19	21.9	6.6	24.0						
Endpoint (2)	Rivastigmine	4	22.3	6.0	21.0	21.8	5.2	21.0	-0.5	1.0	0.0
	Placebo	3	21.7	2.5	22.0	19.7	4.5	20.0	-2.0	2.0	-2.0

Only those subjects with both baseline and post-baseline measurement (imputation as needed) are included.
- Endpoint (2) At time of investigator's diagnosis of AD confirmed by DMC.

MRI assessments treatment comparisons at endpoint (Classical ITT population)

	Rivastigmine LS Mean	Placebo LS Mean	LS Mean Difference (CI)*	p-value
Rate of change from baseline (cm^3/year)				
- Left hippocampal volume (DIAL)	-0.06	-0.07	0.01 (-0.02, 0.04)	0.559
- Right hippocampal volume (DIAL)	-0.09	-0.08	0.00 (-0.04,0.03)	0.824
- Total hippocampal volume (DIAL)	-0.15	-0.16	0.00 (-0.06, 0.07)	0.890
- Whole Brain Volume (ION)	-9.75	-9.90	0.15 (-4.52, 4.83)	0.949
Absolute change per year (cm^3)				
- Ventricular Volume (ION)	2.08	2.25	-0.17 (-0.56, 0.21)	0.371
- Whole Brain Atrophy (ION)	-7.56	-8.19	0.62 (-1.04, 2.29)	0.463
Percent change per year (cm^3)				
- Brain Tissue Atrophy (DIAL)	-0.01	-0.01	-0.00 (-0.00, 0.00)	0.518

Only those subjects with both baseline and post-baseline measurements at end-point (imputation as needed) are included. Only reliable data were used for the analyses of ventricle rate and atrophy rate.
*Rivastigmine – Placebo

Summary statistics for secondary efficacy variables including ADAS-cog (11 item score) and ADL (18 item score and 23 item score) – (MITT population)

			Baseline			Post-baseline			Change from baseline		
Month	**Treatment**	**N**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**
ADAS-cog total score (items 1-3/5-12)											
Baseline	Rivastigmine	507	10.5	5.0	10.0						
	Placebo	509	10.2	4.9	9.0						
Endpoint (2)	Rivastigmine	507	10.5	5.0	10.0	12.3	8.6	10.0	-1.8	6.4	0.0
	Placebo	509	10.2	4.9	9.0	12.0	9.0	9.0	-1.8	6.6	-1.0
ADL total score (items 1-18)											
Baseline	Rivastigmine	503	45.6	6.2	48.0						
	Placebo	508	46.1	5.7	47.0						
Endpoint (2)	Rivastigmine	503	45.6	6.2	48.0	42.3	10.4	46.0	-3.3	8.7	-1.0
	Placebo	508	46.1	5.7	47.0	43.1	10.0	47.0	-3.0	8.2	-1.0
ADL total score (items 1-23)											
Baseline	Rivastigmine	503	57.7	8.5	60.0						
	Placebo	508	58.4	7.8	60.0						
Endpoint (2)	Rivastigmine	503	57.7	8.5	60.0	53.5	13.9	58.0	-4.2	11.3	-1.0
	Placebo	508	58.4	7.8	60.0	54.5	13.3	59.5	-3.9	10.6	-1.0

Only those subjects with both baseline and post-baseline measurement (imputation as needed) are included.
- Endpoint (2) At time of investigator's diagnosis of AD confirmed by DMC.
For ADAS-cog and ADL scores a positive change from baseline indicates improvement.

Summary statistics for APOE e4 genotype (MITT Population)

	Rivastigmine (N=508) n (%)	**Placebo (N=510) n (%)**
Evaluated	252 (49.6)	248 (48.6)
Carriers	92	115
Non-Carriers	160	133
Not Evaluated	256 (50.4)	262 (51.4)

p-value for testing treatment difference (CMH test) = 0.0148

Number of conversions to AD - Subpopulation APOE e 4 carriers and non-carriers (MITT Population - Subjects with APOE assessed)

	Rivastigmine		**Placebo**		
	N	**n (%)**	**N**	**n (%)**	**p-value**
Carriers	92	20 (21.7)	115	29 (25.2)	0.404
Non-carriers	160	16 (10.0)	133	20 (15.0)	0.226

Safety Results

Patients with Adverse Events and Adverse Events by System Organ Class

	Rivastigmine DB (N=505) n (%)	Placebo DB (N=509) n (%)	Rivastigmine OL Previous Rivastigmine DB (N=79) n (%)	Rivastigmine OL Previous Placebo DB (N=97) n (%)	Rivastigmine OL Overall (N= 176) n (%)
Any Body System	483 (95.6)	472 (92.7)	65 (82.3)	87 (89.7)	152 (86.4)
Gastrointestinal disorders	377 (74.7)	251 (49.3)	36 (45.6)	59 (60.8)	95 (54.0)
Nervous system disorders	269 (53.3)	210 (41.3)	20 (25.3)	34 (35.1)	54 (30.7)
Infections and infestations	221 (43.8)	225 (44.2)	15 (19.0)	20 (20.6)	35 (19.9)
Psychiatric disorders	190 (37.6)	174 (34.2)	26 (32.9)	28 (28.9)	54 (30.7)
General disorders and administration site conditions	187 (37.0)	130 (25.5)	15 (19.0)	17 (17.5)	32 (18.2)
Musculoskeletal and connective tissue disorders	167 (33.1)	197 (38.7)	12 (15.2)	9 (9.3)	21 (11.9)
Cardiac disorders	91 (18.0)	98 (19.3)	8 (10.1)	10 (10.3)	18 (10.2)
Vascular disorders	91 (18.0)	110 (21.6)	4 (5.1)	5 (5.2)	9 (5.1)
Metabolism and nutrition disorders	84 (16.6)	77 (15.1)	8 (10.1)	12 (12.4)	20 (11.4)
Investigations	79 (15.6)	90 (17.7)	10 (12.7)	10 (10.3)	20 (11.4)
Injury, poisoning and procedural complications	77 (15.2)	98 (19.3)	12 (15.2)	10 (10.3)	22 (12.5)
Respiratory thoracic and mediastinal disorders	75 (14.9)	85 (16.7)	8 (10.1)	2 (2.1)	10 (5.7)
Skin and subcutaneous tissue disorders	75 (14.9)	78 (15.3)	8 (10.1)	5 (5.2)	13 (7.4)
Ear and labyrinth disorders	62 (12.3)	43 (8.4)	2 (2.5)	3 (3.1)	5 (2.8)
Eye disorders	57 (11.3)	80 (15.7)	8 (10.1)	6 (6.2)	14 (8.0)
Renal and urinary disorders	57 (11.3)	41 (8.1)	7 (8.9)	7 (7.2)	14 (8.0)
Reproductive system and breast disorders	47 (9.3)	53 (10.4)	1 (1.3)	2 (2.1)	3 (1.7)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	32 (6.3)	57 (11.2)	5 (6.3)	2 (2.1)	7 (4.0)
Blood and lymphatic system disorders	13 (2.6)	19 (3.7)	5 (6.3)	2 (2.1)	7 (4.0)

The table shows the most frequently affected system organ classes by descending order of frequency in the Rivastigmine DB group. The cut-off was set at 5% of subjects in any group.

10 Most Frequently Reported AEs Overall by Preferred Term

Preferred term	Rivastigmine DB (N=505) n (%)	Placebo DB (N=509) n (%)	Rivastigmine OL previous Rivastigmine DB (N=79) n (%)	Rivastigmine OL Previous Placebo DB (N=97) n (%)	Rivastigmine OL Overall (N=176) n (%)
Nausea	249 (49.3)	73 (14.3)	20 (25.3)	31 (32.0)	51 (29.0)
Vomiting	164 (32.5)	37 (7.3)	16 (20.3)	23 (23.7)	39 (22.2)
Dizziness	125 (24.8)	78 (15.3)	4 (5.1)	14 (14.4)	18(10.2)
Diarrhea	117 (23.2)	47 (9.2)	8 (10.1)	13 (13.4)	21(11.9)
Headache	108 (21.4)	77 (15.1)	2 (2.5)	6 (6.2)	8 (4.5)

Depression	62 (12.3)	63 (12.4)	3 (3.8)	7 (7.2)	10 (5.7)
Insomnia	62 (12.3)	43 (8.4)	5 (6.3)	3 (3.1)	8 (4.5)
Fatigue	59 (11.7)	31 (6.1)	4 (5.1)	5 (5.2)	9 (5.1)
Abdominal pain upper	56 (11.1)	36 (7.1)	4 (5.1)	4 (4.1)	8 (4.5)
Asthenia	52 (10.3)	15 (2.9)	1 (1.3)	2 (2.1)	3 (1.7)

Serious Adverse Events and Deaths

	Double Blind		**Open-Label Rivastigmine**		**RDO or no drug**		
	Rivastigmine DB n (%)	**Placebo DB n (%)**	**Previous Rivastigmine DB n (%)**	**Previous Placebo DB n (%)**	**DB-RDO Previous Rivastigmine DB n (%)**	**DB-RDO Previous Placebo DB n (%)**	**OL-RDO Previous OL Rivastigmine n (%)**
Total no. of subjects studied (Safety)	505	509	79	97	186	125	42
SAEs, Discontinuations due to SAEs and ADOs							
SAEs (including deaths)	141 (27.9)	155 (30.5)	23 (29.1)	27 (27.8)	42 (22.6)	31 (24.8)	8 (19.0)
Discontinuations Due to SAEs (including deaths)	32 (6.3)	30 (5.9)	6 (7.6)	9 (9.3)	NA	NA	NA
ADOs+ (DB+DB-RDO or OL+OL-RDO phases & study completion CRFs = discontinuation due to AE)	120 (23.6)	65 (12.7)	7 (8.9)	24 (24.7)	NA	NA	NA
ADOs++ (AE action taken = study drug permanently discontinued)	128 (25.3)	75 (14.7)	10 (12.7)	25 (25.8)	NA	NA	NA

ADO+ tabulation based on reason for discontinuation = AE for DB and OL phase CRF

ADO++ tabulation based on if AE action taken code marked "study drug permanently discontinued due to this AE"

Statistical Analysis Population

		On Treatment				**Off Treatment (follow-up and RDO)**			
		Double Blind		**Open Label**		**Double Blind**		**Open Label**	
	Total n (%)	**Rivastigmine n (%)**	**Placebo n (%)**	**Previous Rivastigmine n (%)**	**Previous Placebo n (%)**	**Rivastigmine n**	**Placebo n**	**Previous Rivastigmine n**	**Previous Placebo n**
Total no. of subjects studied (safety population)	1014	505	509	79	97	187[+]	130[+]	16	30
Deaths*	48 (4.7)	5 (1.0)	7 (1.4)	2 (2.5)	0 (0)	9 (4.8)	17 (13.1)	3 (18.8)	5 (16.7)

* Death statistical analysis tabulation based on data on final outcomes assessment form (does not include 4 deaths that occurred outside the active study phases); Event is attributed to study medication (on-treatment) if it occurred within 2 days of last dose; off-treatment events include follow-up events occurring ≥2 days after last dose without an RDO

assessment, and RDO events occurring ≥2 days after last dose with an RDO assessment

[+]Increased overall N for DB off-treatment cases is due to subjects that discontinued during DB treatment and died during DB-RDO treatment.

All Inclusive Narrative Population

		Double Blind		Open-Label		RDO or no drug		
		Rivastigmine n (%)	Placebo n (%)	Previous Rivastigmine n (%)	Previous Placebo n (%)	DB-RDO Previous Rivastigmine n (%)	DB-RDO Previous Placebo n (%)	OL-RDO Previous OL Rivastigmine n (%)
Total no. of subjects studied (MITT)	1018	508	510	79	97	186	125	42
Deaths**	52 (0.05)*	7 (1.4)	13 (2.5)	4 (5.1)	2 (2.1)	8 (4.3)	11 (8.8)	6 (13.3)

*1 death that occurred during screening is counted in total, but not in study phases; event not in clinical database

**All inclusive narrative death tabulation includes mortality data on 41 subjects at study completion (reason for discontinuation = death, mortality data on 7 additional subjects collected on the final outcomes assessment at Month 36/48 and 1 case of death in the DB-RDO group (previously receiving Rivastigmine DB) and 2 cases of death in the OL-RDO group (previously receiving Rivastigmine OL randomized to Rivastigmine DB) reported ≥30 days after the final outcomes assessment: and 1 death during the screening period; (3 cases not in database).

Other Relevant Findings–		
Date of Clinical Trial Report–	25-Apr-2005	
Date Inclusion on Registry–	27-Apr-2005	
Date of Latest Update–	08-Mar-06	