CENA713DUS44 CTRD

Sponsor

Novartis Pharmaceutical Corporation

Generic Drug Name

Rivastigmine

Therapeutic Area of Trial

Severe dementia of the Alzheimer's type

Approved Indication

Indicated for the treatment of mild to moderate dementia of the Alzheimer's type and mild to moderate dementia associated with Parkinson's disease.

Protocol Number

CENA713DUS44

Title

A 24 week, prospective, randomized, parallel-group, double-blind, multi-center study comparing the effects of rivastigmine patch 15 cm^2 vs rivastigmine patch 5 cm^2 on ACTivities of daily living and cognitION in patients with severe dementia of the Alzheimer's type (ACTION)

Study Phase

Phase IIIb

Study Start/End Dates

22-Jul-2009 to 10-Jan-2012

Study Design/Methodology

This was a 24-week, prospective, randomized, parallel-group, double-blind, multi-center study comparing the efficacy and safety of rivastigmine 13.3 mg/24 hours (15 cm^2) patch with rivastigmine patch 4.6 mg/24 hours (5 cm^2) on activities of daily living and cognition in patients with severe dementia of the Alzheimer's type.

Centers

82 centers in the United States.

Publication

No publication to date. Primary manuscript is in progress.

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

Rivastigmine was provided in transdermal patches at doses of 4.6 mg/24 h (5 cm^2), 9.5 mg/24 h (10 cm^2), and 13.3 mg/24 h (15 cm^2).

Statistical Methods

The analyses of efficacy variables were performed for the MFAS which comprised all randomized patients with at least one post-baseline measurement of the primary efficacy variables. Tests for superiority were based on demonstration of differences between the rivastigmine patch 13.3 mg/24 h (15 cm^2) over rivastigmine 4.6 cm/24 h (5 cm^2) patch in changes from baseline to Week 24 in both the ADCS-ADL-SIV total score and SIB total score. Unless otherwise specified, all statistical tests were conducted against a 2-sided alternative hypothesis, employing a significance level of 0.05. The primary analysis endpoint was Week 24.

Mean changes from baseline for the co-primary efficacy variables were analyzed using an analysis of covariance (ANCOVA) model with treatment and pooled center as factors and baseline variable as a covariate. The value of "pooled center" was the site number with the largest number of randomized patients across all treatment groups. Missing data were imputed using the last observation carried forward (LOCF) approach in the MFAS. Least square (LS) means and LS mean difference, 95% confidence interval (CI) for treatment difference, and p-value for the comparison between treatment groups were reported. A paired t-test was performed to determine if significant changes from baseline occurred within treatment groups.

A longitudinal analysis of each of the co-primary efficacy variables was performed for the MFAS over the course of the study using the observed cases (OC) approach. An unstructured covariance matrix for the repeated measures within each patient was applied in the analysis. The explanatory variables
in the model included treatment, pooled center, week, treatment-by-week interaction, and corresponding baseline. Treatment groups were compared at each time point by reporting a point estimate, p-value, and 95% CI for the treatment difference based on LS means.

Sensitivity analyses were conducted for each of the co-primary efficacy variables using pattern mixture model considering missing data pattern (completers and non-completers).

Analyses of the secondary variables were performed at each post-baseline time point using LOCF. The ANCOVA model used for analyses of NPI total score was similar to the model used for the primary efficacy variables. ADCS-CGIC total scores were analyzed using the Cochran-Mantel-Haenzel test (CMH, van Elteren) with modified relative to an identified distribution integral transformation scores (RIDIT), adjusting for pooled center.

The exploratory efficacy variables were analyzed by a CMH test for general association at each post baseline time point using LOCF and adjusting for pooled center. A 95% CI for the difference between treatments was calculated based on a normal approximation. The percentage of responses in each variable was summarized by frequency counts and percentages for all post-baseline time points.

Adverse events were summarized for each treatment group by system organ class (SOC) and preferred term, presented alphabetically by primary SOC, and sorted in decreasing order of frequency of preferred terms within each primary SOC. The decreasing order of frequency of preferred terms was based on the total count. The number and percentage of patients with most frequent AE, i.e., ≥2% in either treatment regimen, were also presented. In a similar manner, SAEs and AEs leading to discontinuation were summarized by SOC and preferred term.

The summary tables of AEs were also presented regardless of study drug relationship, and separately by study drug. In addition, a summary of AEs by SOC, preferred term, and severity (mild, moderate, severe) of AE were provided, in which a particular AE was counted under its maximum severity rating only.

To assess gastrointestinal-related AEs (nausea or vomiting) and skin irritations reported as AEs, the 2-sided 95% CI for the difference of incidence rate between treatment groups was presented using the normal approximation.

Serious adverse events, AEs leading to premature discontinuation, AEs requiring dose adjustment, nausea or vomiting, and skin irritation at the application site were listed separately in a similar manner. Episodes of skin irritation were captured as AEs on the CRF. The patch size related to the irritation was noted on the Skin Irritation Rating/Investigator's Rating page of the CRF.

Hematology, clinical chemistry, and urinalysis laboratory values and ECG results were summarized by treatment group for baseline and changes in baseline values by descriptive statistics. In addition, data were presented by shift tables with respect to normal ranges based on the extreme post-baseline values. The number and percentage of patients experiencing clinical notable laboratory abnormalities were also provided.

Summary statistics for baseline and change from baseline for vital signs, body weight, and ECG were summarized in a similar manner. Shift tables were also presented. The number and percentage of patients experiencing clinical notable abnormalities for these assessments were also provided by treatment group.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

- Diagnosis of probable Alzheimer's disease (AD) according to National Institute of Neurological Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria.
- A Mini-Mental State Examination (MMSE) score of ≥ 3 and ≤ 12.
- Be able to complete at least 1 item on the Severe Impairment Battery (SIB).

- Residing with someone in the community or in regular contact with the primary caregiver.
- Be ambulatory or ambulatory with aid.

Exclusion Criteria:

- An advanced, severe, progressive, or unstable disease of any type that may interfere with efficacy and safety assessments or put the patient at special risk.
- Patients currently residing in a nursing home.
- Any current medical or neurological condition other than AD that could explain the patient's dementia.
- A current diagnosis of probable or possible vascular dementia.
- A current diagnosis of severe or unstable cardiovascular disease.
- A current diagnosis of bradycardia (< 50 beats per minute [bpm]), sick-sinus syndrome, or conduction defects.
- Clinically significant urinary obstruction.
- History of malignancy of any organ system within the past 5 years unless patient is verified to be in stable condition with no active metastasis.
- Current diagnosis of an active skin lesion/disorder that would prevent the patient from using a transdermal patch every day.
- A known exaggerated pharmacological sensitivity or hypersensitivity to drugs similar to rivastigmine, or to other cholinergic compounds.
- Taken any of the following substances (at the time of the Baseline Visit [Visit 2]).
- Succinylcholine-type muscle relaxants during the previous 2 weeks.
- Lithium during the previous 2 weeks.
- An investigational drug during the previous 4 weeks.
- A drug or treatment known to cause major organ system toxicity during the previous 4 weeks.
- Rivastigmine (oral or transdermal patch), donepezil, galantamine, other cholinesterase inhibitors (eg, tacrine, physostigmine, or pyridostigmine), or other approved treatments for Alzheimer's disease during the previous 2 weeks, with exception of stable treatment with memantine for at least 3 months before study entry (Visit 1).
- Centrally acting anticholinergic drugs including tricyclic and tetracyclic antidepressants during the previous 4 weeks.
- Selegiline unless taken at a stable dose during the previous 4 weeks.
- Peripheral anticholinergics not taken at a stable dose during the previous 4 weeks.

Other protocol-defined inclusion/exclusion criteria applied to the study.

Participant Flow

	Rivastigmine patch		
	13.3 mg/24 h ($15\ cm^2$)	4.6 mg/24 h ($5\ cm^2$)	Total
	(N=356)	(N= 360)	(N= 716)
Disposition/Reason	**n (%)**	**n (%)**	**n (%)**
Total number of patients			
Screened			1014
Screened, not randomized			298
Randomized	356 (100.0)	360 (100.0)	716 (100.0)
Exposed to study medication	355 (99.7)	359 (99.7)	714 (99.7)
Completed	229 (64.3)	234 (65.0)	463 (64.7)
Discontinued from study	127 (35.7)	126 (35.0)	253 (35.3)
Primary reason for study discontinuation			
Adverse events	73 (20.5)	51 (14.2)	124 (17.3)
Abnormal laboratory values	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal test procedure results	0 (0.0)	0 (0.0)	0 (0.0)
Unsatisfactory therapeutic effect	13 (3.7)	14 (3.9)	27 (3.8)
Patient's condition no longer required study drug	0 (0.0)	0 (0.0)	0 (0.0)
Patient withdrew consent	27 (7.6)	46 (12.8)	73 (10.2)
Lost to follow-up	3 (0.8)	2 (0.6)	5 (0.7)
Administrative problems	2 (0.6)	2 (0.6)	4 (0.6)
Death	1 (0.3)	1 (0.3)	2 (0.3)
Protocol deviation	8 (2.2)	10 (2.8)	18 (2.5)

Baseline Characteristics

Demographic variable	Rivastigmine patch 13.3 mg/24 h (15 cm^2) (N=356)	Rivastigmine patch 4.6 mg/24 h (5 cm^2) (N= 360)	Total (N= 716)	p-value
Age (years)				0.1040[a]
N	356	360	716	
Mean (SD)	77.6 (8.69)	76.5 (9.35)	77.0 (9.04)	
Median	78.0	78.0	78.0	
(Min, Max)	(52, 96)	(51, 96)	(51, 96)	
Age group (years) – n (%)				0.2553[b]
<65 years	33 (9.3)	45 (12.5)	78 (10.9)	
65–75 years	93 (26.1)	101 (28.1)	194 (27.1)	
> 75	230 (64.6)	214 (59.4)	444 (62.0)	
Gender – n (%)				0.7299[b]
Male	129 (36.2)	126 (35.0)	255 (35.6)	
Female	227 (63.8)	234 (65.0)	461 (64.4)	
Predominant Race – n (%)				0.5356[b]
Caucasian	306 (86.0)	319 (88.6)	625 (87.3)	
Black	28 (7.9)	19 (5.3)	47 (6.6)	
Asian	6 (1.7)	3 (0.8)	9 (1.3)	
Native American	2 (0.6)	2 (0.6)	4 (0.6)	
Pacific Islander	0 (0.0)	1 (0.3)	1 (0.1)	
Other	14 (3.9)	16 (4.4)	30 (4.2)	
Ethnicity				0.8383[b]
Hispanic/Latino	36 (10.1)	34 (9.4)	70 (9.8)	
Chinese	0 (0.0)	0 (0.0)	0 (0.0)	
Indian (Indian subcontinent)	1 (0.3)	3 (0.8)	4 (0.6)	
Japanese	2 (0.6)	1 (0.3)	3 (0.4)	
Mixed ethnicity	9 (2.5)	11 (3.1)	20 (2.8)	
Other	308 (86.5)	311 (86.4)	619 (86.5)	

AD=Alzheimer's Disease; SD= standard deviation

[a]From a 2-sample t-test comparing 2 treatment groups

[b]From a chi-squared test or Fisher's exact test (excluding missing values), comparing the 2 treatment groups

Outcome Measures

Efficacy: The co-primary efficacy variables were the change from baseline to Week 24 in the ADCS-ADL-SIV total score and the change from baseline to Week 24 in the SIB total score. The secondary efficacy variables were the change from baseline to Week 24 in NPI total score and changes from baseline to Week 24 in ADCS-CGIC total score.

Exploratory efficacy variables as defined by the protocol were:

1. No change or improvement in ADCS-ADL-SIV total score over 24 weeks (yes, no)
2. Improvement in ADCS-ADL-SIV total score over 24 weeks (yes, no)
3. At least 4 points improvement in ADCS-ADL-SIV total score over 24 weeks (yes, no)
4. No change or improvement in SIB total score over 24 weeks (yes, no)
5. Improvement in SIB total score over 24 weeks (yes, no)
6. At least 4 points improvement in SIB total score over 24 weeks (yes, no)
7. At least 10% improvement in NPI total score over 24 weeks for patients with at least one symptom present at Baseline (yes, no)
8. At least 20% improvement in NPI total score over 24 weeks for patients with at least one symptom present at Baseline (yes, no)
9. At least 30% improvement in NPI total score over 24 weeks for patients with at least one symptom present at Baseline (yes, no)

Safety: Safety assessments consisted of collecting all adverse events (AEs) and serious adverse events (SAEs) with evaluation of severity and relationship to study drug, including pregnancies, gastrointestinal events, and skin irritation. Regular monitoring of hematology, blood chemistry, and urine performed at a central laboratory, electrocardiograms (ECGs); measurement of vital signs and body weight; and evaluation of physical condition were also included in assessment of safety.

Primary Outcome Result(s)

Summary statistics and treatment comparison in Alzheimer's Disease Cooperative Study-Activities of Daily Living-Severe Impairment Version (ADCS-ADL-SIV) total score (Modified Full Analysis set)

Visit / Statistics	Rivastigmine patch 13.3 mg/24 h (15 cm^2) (N=338) SIB	Rivastigmine patch 13.3 mg/24 h (15 cm^2) (N=338) Change from baseline	Rivastigmine patch 4.6 mg/24 h (5 cm^2) (N=335) SIB	Rivastigmine patch 4.6 mg/24 h (5 cm^2) (N=335) Change from baseline	13.3 mg vs. 4.6 mg
Baseline value (Up to Day 1)					
n	333		319		
Mean (SD)	29.7 (11.29)		29.1 (11.94)		
Median	31.0		31.0		
(Min, Max)	(0, 52)		(0, 52)		
Week 24 (Day 141 - [last dose date + 2 days])					
n	315	310	316	303	
Mean (SD)	27.4 (11.87)	-2.6 (6.82)	25.3 (12.22)	-3.6 (7.68)	
Median	29.0	-2.0	26.0	-3.0	
(Min, Max)	(0, 51)	(-26, 23)	(0, 53)	(-31, 18)	
p value[a]		<.0001		<.0001	
LS-mean (SE)[b]		-2.4 (0.41)		-3.6 (0.42)	
LS-mean difference					1.2
(95% CI)[b]					(0.16, 2.32)
p value[b]					0.0247

CI= confidence interval; LS= least squares; SE= standard error

Baseline was the last non-missing measurement on or prior to the day of first application of study medication.

Missing data were imputed using the last-observation-carried-forward (LOCF) method.

[a]From a paired t-test for mean change from baseline within each treatment group

[b]From an analysis of covariance (ANCOVA) model with treatment and pooled center as factors, and baseline as a covariate

Summary statistics and treatment comparison in Severe Impairment Battery total score (SIB) (Modified Full Analysis set)

Visit	Rivastigmine patch				13.3 mg vs. 4.6 mg
	13.3 mg/24 h (15 cm^2) (N=338)		4.6 mg/24 h (5 cm^2) (N=335)		
Statistics	SIB	Change from baseline	SIB	Change from baseline	
Baseline value (Up to Day 1)					
n	336		334		
Mean (SD)	69.3 (21.54)		68.3 (22.79)		
Median	75.0		76.0		
(Min, Max)	(3, 99)		(4, 99)		
Week 24 (Day 141 - [last dose date + 2 days])					
n	315	313	317	316	
Mean (SD)	68.3 (24.36)	-1.6 (13.54)	62.5 (26.22)	-6.4 (14.01)	
Median	75.0.	0.0	67.0	-4.0	
(Min, Max)	(2, 100)	(-68, 82)	(0, 100)	(-52, 50)	
p value[a]		0.0424		<.0001	
LS-mean (SE)[b]		-1.7 (0.79)		-6.6 (0.79)	
LS-mean difference (95% CI)[b]					4.9 (2.80, 6.95)
p value[b]					<.0001

CI= confidence interval; LS= least squares; SD= standard deviation; SE= standard error

Baseline was the last non-missing measurement on or prior to the day of first application of study medication.

Missing data were imputed using the last-observation-carried-forward (LOCF) method.

[a]From a paired t-test for mean change from baseline within each treatment group

[b]From an analysis of covariance (ANCOVA) model with treatment and pooled center as factors, and baseline as a covariate

Secondary Outcome Result(s)

Summary statistics and treatment comparison in Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) (Modified Full Analysis set)

	Rivastigmine patch		
	13.3 mg/24 h (15 cm^2)	4.6 mg/24 h (5 cm^2)	
Time point	(N=338)	(N= 335)	
Category	n (%)	n (%)	p-value[a]
Week 24 (Day 141 - [last dose date + 2 days])			0.0023
Marked improvement	3 (1.0)	4 (1.3)	
Moderate improvement	11 (3.5)	11 (3.5)	
Minimal improvement	63 (20.1)	36 (11.4)	
No change	107 (34.2)	92 (29.2)	
Minimal worsening	76 (24.3)	99 (31.4)	
Moderate worsening	44 (14.1)	60 (19.0)	
Marked worsening	9 (2.9)	13 (4.1)	

Note: Missing data were imputed using the last-observation-carried-forward (LOCF) method.

[a]From the Cochran-Mantel Haenszel Test (van Elteren test) with modified RIDIT (relative to an identified distribution integral transformation) scores (excluding missing values) adjusting for pooled center.

Summary statistics and treatment comparison in Neuropsychiatric Inventory (NPI-12) total score (Modified Full Analysis set)

Visit / Statistics	Rivastigmine patch 13.3 mg/24 h (15 cm^2) (N=338) NPI-12	Rivastigmine patch 13.3 mg/24 h (15 cm^2) (N=338) Change from baseline	Rivastigmine patch 4.6 mg/24 h (5 cm^2) (N=335) NPI-12	Rivastigmine patch 4.6 mg/24 h (5 cm^2) (N=335) Change from baseline	13.3 mg vs. 4.6 mg
Baseline value (Up to Day 1)					
n	335		331		
Mean	17.3 (15.44)		16.8 (16.65)		
Median	13.0		13.0		
(Min, Max)	(0, 76)		(0, 114)		
Week 24 (Day 141 - [last dose date + 2 days])					
n	315	313	317	313	
Mean	16.7 (15.14)	-0.4 (14.01)	18.4 (18.81)	1.2 (16.79)	
Median	13.0	0.0	14.0	0.0	
(Min, Max)	(0, 70)	(-46, 46)	(0, 122)	(-80, 78)	
p-value value[a]		0.6409		0.2090	
LS-mean (SE)[b]		-0.1 (0.84)		1.5 (0.84)	
LS-mean difference					-1.6
(95% CI)[b]					(-3.84, 0.56)
p value[b]					0.1437

CI= confidence interval; LS= least squares; SE= standard error

Baseline was the last non-missing measurement on or prior to the day of first application of study medication.

Missing data were imputed using the last-observation-carried-forward (LOCF) method.

[a]From a paired t-test for mean change from baseline within each treatment group

[b]p-value from an analysis of covariance (ANCOVA) model with treatment and pooled center as factors, and baseline as a covariate

Safety Results

Number (%) of patients with adverse events by primary system organ class and treatment group (Safety set)

	Rivastigmine patch		
	13.3 mg/24 h (15 cm^2) (N=355) n (%)	4.6 mg/24 h (5 cm^2) (N= 359) n (%)	Total (N= 714) n (%)
Total number of patients with AEs	265 (74.6)	263 (73.3)	528 (73.9)
System organ class			
General disorders and administration site conditions	117 (33.0)	116 (32.3)	233 (32.6)
Psychiatric disorders	111 (31.3)	97 (27.0)	208 (29.1)
Gastrointestinal disorders	70 (19.7)	56 (15.6)	126 (17.6)
Infections and infestations	62 (17.5)	67 (18.7)	129 (18.1)
Nervous system disorders	57 (16.1)	59 (16.4)	116 (16.2)
Injury, poisoning and procedural complications	44 (12.4)	47 (13.1)	91 (12.7)
Investigations	44 (12.4)	30 (8.4)	74 (10.4)
Metabolism and nutrition disorders	42 (11.8)	30 (8.4)	72 (10.1)
Skin and subcutaneous tissue disorders	31 (8.7)	25 (7.0)	56 (7.8)
Renal and urinary disorders	29 (8.2)	28 (7.8)	57 (8.0)
Respiratory, thoracic and mediastinal disorders	24 (6.8)	21 (5.8)	45 (6.3)
Musculoskeletal and connective tissue disorders	23 (6.5)	21 (5.8)	44 (6.2)
Vascular disorders	23 (6.5)	20 (5.6)	43 (6.0)
Cardiac disorders	13 (3.7)	20 (5.6)	33 (4.6)
Blood and lymphatic system disorders	7 (2.0)	9 (2.5)	16 (2.2)
Eye disorders	5 (1.4)	2 (0.6)	7 (1.0)
Ear and labyrinth disorders	4 (1.1)	1 (0.3)	5 (0.7)
Hepatobiliary disorders	4 (1.1)	2 (0.6)	6 (0.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (1.1)	4 (1.1)	8 (1.1)
Reproductive system and breast disorders	2 (0.6)	1 (0.3)	3 (0.4)
Surgical and medical procedures	2 (0.6)	3 (0.8)	5 (0.7)
Immune system disorders	1 (0.3)	0 (0.0)	1 (0.1)
Endocrine disorders	0 (0.0)	4 (1.1)	4 (0.6)

System organ classes were by descending frequency, as reported in the rivastigmine patch 15 cm^2 column.

A patient with multiple occurrences of an adverse event was counted only once in the adverse event category.

Only adverse events occurring on or after the date of first application of study drug were included.

Number (%) of patients with most frequent adverse events (at least 2% in any treatment group) by preferred term and treatment group (Safety set)

	Rivastigmine patch		
	13.3 mg/24 h (15 cm^2) (N=355) n (%)	4.6 mg/24 h (5 cm^2) (N= 359) n (%)	Total (N= 714) n (%)
Total number of patients with AEs	265 (74.6)	263 (73.3)	528 (73.9)
Application site erythema	47 (13.2)	42 (11.7)	89 (12.5)
Agitation	41 (11.5)	51 (14.2)	92 (12.9)
Urinary tract infection	29 (8.2)	34 (9.5)	63 (8.8)
Application site dermatitis	27 (7.6)	33 (9.2)	60 (8.4)
Fall	27 (7.6)	21 (5.8)	48 (6.7)
Insomnia	25 (7.0)	15 (4.2)	40 (5.6)
Vomiting	25 (7.0)	9 (2.5)	34 (4.8)
Diarrhea	23 (6.5)	19 (5.3)	42 (5.9)
Weight decreased	23 (6.5)	11 (3.1)	34 (4.8)
Nausea	22 (6.2)	10 (2.8)	32 (4.5)
Depression	17 (4.8)	15 (4.2)	32 (4.5)
Decreased appetite	17 (4.8)	5 (1.4)	22 (3.1)
Anxiety	16 (4.5)	16 (4.5)	32 (4.5)
Hypertension	13 (3.7)	9 (2.5)	22 (3.1)
Application site pruritus	13 (3.7)	8 (2.2)	21 (2.9)
Confusional state	12 (3.4)	13 (3.6)	25 (3.5)

	Rivastigmine patch		
	13.3 mg/24 h (15 cm^2) (N=355) n (%)	4.6 mg/24 h (5 cm^2) (N= 359) n (%)	Total (N= 714) n (%)
Somnolence	12 (3.4)	9 (2.5)	21 (2.9)
Constipation	11 (3.1)	12 (3.3)	23 (3.2)
Urinary incontinence	11 (3.1)	10 (2.8)	21 (2.9)
Application site irritation	11 (3.1)	9 (2.5)	20 (2.8)
Dehydration	11 (3.1)	8 (2.2)	19 (2.7)
Dizziness	11 (3.1)	5 (1.4)	16 (2.2)
Upper respiratory tract infection	9 (2.5)	9 (2.5)	18 (2.5)
Laceration	9 (2.5)	5 (1.4)	14 (2.0)
Fatigue	9 (2.5)	3 (0.8)	12 (1.7)
Edema peripheral	8 (2.3)	12 (3.3)	20 (2.8)
Hypokalemia	8 (2.3)	6 (1.7)	14 (2.0)
Asthenia	8 (2.3)	3 (0.8)	11 (1.5)
Rash	8 (2.3)	3 (0.8)	11 (1.5)
Hallucination	7 (2.0)	16 (4.5)	23 (3.2)
Abnormal behavior	7 (2.0)	10 (2.8)	17 (2.4)
Contusion	7 (2.0)	8 (2.2)	15 (2.1)
Syncope	7 (2.0)	8 (2.2)	15 (2.1)
Hypotension	4 (1.1)	8 (2.2)	12 (1.7)

AE=adverse event

Preferred terms were presented by descending frequency, as reported in the total column.

A patient with multiple occurrences of an AE was counted only once in the adverse events category.

Only adverse events occurring on or after the date of first application of study drug were included.

Number of patients who died or experienced other serious or clinically significant adverse events (Safety set)

	Rivastigmine patch		
Patients with AEs	13.3 mg/24 h (15 cm^2) (N=355) n (%)	4.6 mg/24 h (5 cm^2) (N= 359) n (%)	Total (N= 714) n (%)
Serious or other significant events	108 (30.4)	92 (25.6)	200 (28.0)
Deaths	1 (0.3)	1 (0.3)	2 (0.3)
SAEs	53 (14.9)	49 (13.6)	102 (14.3)
Clinically significant AEs	97 (27.3)	70 (19.5)	167 (23.4)
Discontinued due to SAEs	29 (8.2)	16 (4.5)	45 (6.3)
Discontinued due to non-serious AEs	48 (13.5)	39 (10.9)	87 (12.2)
Discontinued due to nausea or vomiting	9 (2.5)	4 (1.1)	13 (1.7)
Discontinued due to skin irritations at application site	6 (1.7)	9 (2.5)	15 (2.1)

AEs= adverse events; SAEs= serious adverse events

Date of Clinical Trial Report

08 November 2012

Date Inclusion on Novartis Clinical Trial Results Database

09 Jan 2013

Date of Latest Update