Sponsor

Novartis Pharmaceuticals, Japan

Generic Drug Name

Rivastigmine

Therapeutic Area of Trial

Mild to moderate Alzheimer's disease

Approved Indication

Mild to moderate Alzheimer's disease

Study Number

Core study: CENA713D1301

Extension study: CENA713D1301E1

Title

Core study: A 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-finding evaluation of the efficacy, safety, and tolerability of the once-daily rivastigmine patch formulation in patients with probable Alzheimer's disease (MMSE 10-20)

Extension study: An open-label, 52-week extension to a 24-week, multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group evaluation of the efficacy, safety, and tolerability of the once-daily rivastigmine patch formulation in patients with probable Alzheimer's disease (MMSE 10-20)

Phase of Development

Phase IIb/III

Study Start/End Dates

Core study: 27 Jan 2007 to 31 Mar 2009

Extension study: 10 Jul 2007 to 30 Apr 2010

Study Design/Methodology

Core study: This was a multicenter, randomized, double-blind, 3-arm, placebo-controlled, 24-week, parallel-group study. After assessing eligibility during a pre-treatment period, patients were randomly assigned in a double-blind manner to one of the 3 treatment arms (placebo, rivastigmine 5 cm^2, and rivastigmine 10 cm^2) in a ratio of 1:1:1. Patients then entered a 16-week Double-blind Titration Period followed by an 8-week Maintenance Period.

Extension study: This study was a 52-week, prospective, multicenter, open-label, uncontrolled, single-arm extension study of rivastigmine patch in patients who have completed the preceding Double-Blind Treatment Phase. A starting dose of 2.5 cm^2 rivastigmine patch was applied to eligible patients who completed the Double-Blind Treatment Phase. The dose was titrated up to 5

cm^2, 7.5 cm^2, and a target dose of 10 cm^2 every 4 weeks in a stepwise manner. Because some patients, who were enrolled in the extension study, had received placebo during the Double-Blind Treatment Phase, all patients began the open-label treatment with DL1 (2.5 cm^2 patch formulation) for safety reasons, and were titrated thereafter.
Centres **Core study:** Healthcare corporation Sakuunkai Iizuka Hospital et al (a total of 174 study centres) **Extension study:** Nakamura Kinen Hospital et al (a total of 174 study centres)
Publication None

Objectives of the core study

Primary objectives: The primary objectives were to confirm the efficacy of rivastigmine patch in patients with probable AD (MMSE 10-20) by testing the following hypotheses:

1. Rivastigmine patch group (10 cm^2 group) is superior to the placebo group with respect to change from baseline (to 24 weeks of treatment with the study drug) for Alzheimer's disease assessment scale Japan-cognitive subscale (ADAS-J cog) and Clinician's interview-based impression of change-plus Japan (CIBIC plus-J) score after 24 weeks of treatment with the study drug.
2. Rivastigmine patch group (5 cm^2 group) is superior to the placebo group with respect to change from baseline (to 24 weeks of treatment with the study drug) for ADAS-J cog and CIBIC plus-J score after 24 weeks of treatment with the study drug.

Secondary objectives: To evaluate the efficacy, safety, tolerability, and pharmacokinetics of rivastigmine patch in patients with probable AD (MMSE 10-20):

- To evaluate whether rivastigmine patch groups (5cm^2 and 10cm^2, respectively) are superior to the placebo group with respect to change from baseline (to 24 weeks of treatment with the study drug) for subscale of CIBIC plus-J score (DAD, BEHAVE-AD, MENFIS) and MMSE after 24 weeks of treatment with the study drug.
- To evaluate the safety and tolerability of rivastigmine patch group for up to 24 weeks of treatment in patients with probable AD (MMSE 10-20).

3. To evaluate the adhesion and skin irritation of all four sizes of rivastigmine patches (2.5, 5, 7.5, 10 cm^2).
4. Pharmacokinetics (PK): To evaluate PK profile of rivastigmine by measuring plasma concentration in AD patients receiving various patch sizes (2.5, 5, 7.5, 10 cm^2).

Objectives of the extension study

Primary objective: To evaluate the safety and tolerability of rivastigmine for up to 52 weeks in patients with probable Alzheimer's disease (AD) who have completed the Double-Blind Treatment Phase

Secondary objective: To evaluate the efficacy of rivastigmine for up to 52 weeks of open-label treatment assessed by MMSE, DAD, modified Crichton scales in patients with probable AD (MMSE 10-20) who have completed the Double-blind Treatment Phase

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

Core study: The study drug was increased from DL1 to DL2, DL3, DL4 at 4-week intervals. DL3R and DL4R were the next lower doses of DL3 and DL4, respectively, and they were used only for dose adjustment of decreased dose. Study drug was applied once-daily. Dosing level in Double-Blind Treatment period is shown below.

- DL1: rivastigmine patch formulation or its placebo 2.5 cm^2
- DL2: rivastigmine patch formulation or its placebo 5 cm^2
- DL3R: rivastigmine patch formulation or its placebo 5 cm^2 and 2.5 cm^2
- DL3: rivastigmine patch formulation or its placebo 7.5 cm^2 and 5 cm^2

- DL4R: rivastigmine patch formulation or its placebo 7.5 cm^2 and 2.5 cm^2
- DL4: rivastigmine patch formulation or its placebo 10 cm^2 and 5 cm^2

Extension study: All patients started treatment with a 2.5 cm^2 patch (referred as dose level 1, DL1). After 4 weeks of treatment at DL1, the dose was increased to 5, 7.5, and 10 cm^2 (DL2 to DL4) after 4 weeks of treatment at each dose level. One patch was applied once daily. Treatment was started in the titration period on the day following Visit 9, after the intermediate period during which no treatment was administered, and a caregiver applied the transdermal patch on the back of the patient, alternating the application site between the right and left sides each day. Patches were applied at approximately the same time of the day. The DL reached by each individual patient at Visit 13 was maintained for the rest of the study duration (Maintenance Period). A predetermined ‘’allowed adjustment’’ scheme was followed in patients who required dose adjustment due to low tolerability. DL1 was not allowed as the maintenance dose; patients were discontinued if they were unable to tolerate DL2. Dosing level in Double-Blind Treatment period is shown below.

- DL1: rivastigmine patch formulation 2.5 cm^2
- DL2: rivastigmine patch formulation 5 cm^2
- DL3: rivastigmine patch formulation 7.5 cm^2
- DL4: rivastigmine patch formulation 10 cm^2

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

Core study: Placebo patch written in the test product, dose, and mode of administration section.

Extension study: None

Criteria for Evaluation- Core study

Primary variables

- The change from baseline to week 24 in the total sum score of the 11 items included in the ADAS-J cog
- The overall clinical rating of change from baseline to week 24 measured by the 7-point CIBIC plus-J scale

Secondary variables

The changes in subscale of CIBIC plus-J (DAD, BEHAVE-AD, MENFIS) and MMSE before and after treatment (at week 24)

Safety and tolerability

Adverse events, clinical laboratory values, vital signs, ECG, patch adhesion assessment, skin irritation assessment by Skin Irritation Rating Scale

Pharmacology

Plasma concentration of rivastigmine with 4 types of rivastigmine patch sizes (2.5, 5, 7.5, and 10 cm^2)

Other

None

Criteria for Evaluation- Extension study

Primary variables

There were no primary efficacy variables; safety and tolerability measures were the primary study outcomes.

Secondary variables

The changes in DAD, MMSE and modified Crichton Scale from Open-Label Baseline and after treatment (at week 52).

Safety and tolerability

Adverse events, clinical laboratory values, vital signs, ECG, skin irritation assessment by Skin Irritation Rating Scale.

Pharmacology

None

Other

Questionnaire about patch formulation

Statistical Methods

Core study: The confirmatory statistical testing on efficacy was assessed in the ITT (LOCF) population, which included all patients who had at least one assessment on the primary efficacy variables during the treatment (i.e. within 2 days from last dose). The primary analysis time point was Week 24. In case the value was missing, the last available observation was carried

forward to Week 24.

For primary analysis, the first hypothesis was composed of two comparisons (on ADAS-J cog and on CIBIC plus-J) between the rivastigmine 10 cm^2 patch and placebo treatment groups. In order to demonstrate superiority of the rivastigmine 10 cm^2 patch over placebo, superiority needed to be shown on both primary efficacy variables simultaneously. The second hypothesis composed of two comparisons (on ADAS-J cog and on CIBIC plus-J) between the rivastigmine 5 cm^2 patch and placebo treatment groups. In order to demonstrate superiority of the rivastigmine 5 cm^2 patch over placebo, superiority needed to be shown on both primary efficacy variables simultaneously.

The statistical hypotheses were tested sequentially according to the prospectively specified order at the alpha level of 5%. For change from baseline in ADAS-J cog, ANCOVA was conducted to compare treatment groups using baseline in ADAS-J cog as a covariate and the treatment group as a factor. The primary analysis for the CIBIC plus-J was the treatment comparison based on a Wilcoxon test. For secondary endpoints, the changes from baseline in the CIBIC plus-J subscales (DAD/BEHAVE-AD/MENFIS) were summarized by visits. For the changes from baseline in the subscales (DAD/BEHAVE-AD/MENFIS), ANCOVA was conducted to compare treatment groups including respective baseline as a covariate and treatment as a factor (Post hoc analysis). Wilcoxon rank-sum test was conducted to compare between treatment groups in MMSE.

The safety analyses were performed in the Safety population. Frequency and incidence of adverse events were summarized by severity, causal relationship with the study drugs, time of onset, and patch sizes as well as assessment of adverse events at application sites and skin irritation. Summary statistics were calculated for laboratory values, vital signs, and electrocardiography. The number of patients and its proportion were calculated for each of those who had clinically significant abnormal changes that met the pre-defined criteria.

For pharmacokinetics, summary statistics were obtained for trough plasma concentration of rivastigmine by patch sizes.

Extension study: The ITT population was used for efficacy, while MITT population was established to assess robustness of the results. Safety was assessed in the Safety population.
In light of the study objectives, efficacy was assessed descriptively, and did not conduct statistical hypothesis testing. Summary statistics were presented for MMSE, DAD, and modified Crichton Scale by visit for the ITT population by treatment group of Double-Blind phase, and summary statistics (including 95% confidence interval) in changes from baseline were provided. The changes were calculated for both Open-Label baseline and Double-Blind baseline (for reference). The above-mentioned analyses were also performed for MMSE and DAD using the MITT population. No imputation was applied for missing values.
For the safety evaluation, frequency counts and percentages of AEs were summarized by severity, relationship to the study drug, study period, and rivastigmine dose at onset, and application site AEs and skin irritation rating were assessed. Summary statistics for actual values and changes from baseline for laboratory tests, vital signs, and ECG (all continuous values) were provided. The number and percentages of patients were calculated for those who met the predetermined criteria of clinically notable abnormalities. The changes were calculated for both Open-Label baseline and Double-Blind baseline (for reference).

Study Population: Inclusion/Exclusion Criteria and Demographics

Core study: The major inclusion/exclusion criteria of the core study are listed below.

Inclusion criteria:

1. A diagnosis of dementia of the Alzheimer's type according to the DSM-IV criteria
2. A clinical diagnosis of probable AD according to NINCDS/ADRDA criteria
3. An MMSE score of > or = 10 and < or = 20

Exclusion Criteria:

1. A current DSM-IV diagnosis of major depression
2. Taken rivastigmine in the past
3. A score of > 5 on the Modified Hachinski Ischemic Scale (MHIS)

Extension study: The major inclusion/exclusion criteria of the extension study are listed below.

Inclusion criteria:

1. Patients who had completed the double-blind treatment phase on study.

Exclusion criteria

1. Patients who had any important protocol deviations until the completion of the Double-blind Treatment Phase

Number of Subjects

Core study:

Disposition/Reason	Placebo n (%)	Rivastigmine 5 cm^2 n (%)	Rivastigmine 10 cm^2 n (%)	Total n (%)
Total number of patients				
Screened				1208
Randomized	288 (100)	284 (100)	287 (100)	859 (100)
Exposed to study drug	286 (99.3)	283 (99.6)	287 (100)	856 (99.7)
Completed	242 (84.0)	220 (77.5)	228 (79.4)	690 (80.3)
Discontinued	46 (16.0)	64 (22.5)	59 (20.6)	169 (19.7)
Adverse Event(s)	21 (7.3)	38 (13.4)	34 (11.8)	93 (10.8)
Subject withdrew consent	8 (2.8)	16 (5.6)	11 (3.8)	35 (4.1)
Unsatisfactory therapeutic effect	7 (2.4)	6 (2.1)	7 (2.4)	20 (2.3)
Protocol deviation	8 (2.8)	3 (1.1)	7 (2.4)	18 (2.1)
Death	1 (0.3)	1 (0.4)	0 (0.0)	2 (0.2)
Lost to follow-up	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Abnormal laboratory value(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal test procedure result(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subject's condition no longer requires study drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Administrative problems	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Extension study:

Disposition/Reason	Total n (%)
Total number of patients	
Received OL Medication	637 (100)
Completed OL Extension	474 (74.4)
Discontinued	163 (25.6)
Adverse Event(s)	97 (15.2)
Subject withdrew consent	37 (5.8)
Unsatisfactory therapeutic effect	18 (2.8)
Protocol deviation	9 (1.4)
Death	2 (0.3)
Abnormal laboratory value(s)	0 (0.0)
Abnormal test procedure result(s)	0 (0.0)
Subject's condition no longer requires study drug	0 (0.0)
Lost to follow-up	0 (0.0)
Administrative problems	0 (0.0)

Demographic and Background Characteristics

Core study:

- Demographic summary by treatment group (Safety population)

Demographic variable	Placebo N=286	Rivastigmine 5 cm^2 N=282	Rivastigmine 10 cm^2 N=287	Total N=855
Age (years)				
Mean (SD)	74.5 (7.36)	74.3 (7.46)	75.1 (6.85)	74.6 (7.22)
Median (Range)	76.0 (49.0-85.0)	75.0 (53.0-85.0)	76.0 (55.0-85.0)	76.0 (49.0-85.0)
Age groups –n (%)				
< 65 years	32 (11.2)	34 (12.1)	26 (9.1)	92 (10.8)
>=65 years	254 (88.8)	248 (87.9)	261 (90.9)	763 (89.2)
< 75 years	116 (40.6)	125 (44.3)	116 (40.4)	357 (41.8)
>=75 years	170 (59.4)	157 (55.7)	171 (59.6)	498 (58.2)
Sex –n (%)				
Male	91 (31.8)	88 (31.2)	92 (32.1)	271 (31.7)
Female	195 (68.2)	194 (68.8)	195 (67.9)	584 (68.3)
Weight (kg)				
Mean (SD)	50.7 (9.75)	50.7 (8.95)	50.7 (9.48)	50.7 (9.39)
Median (Range)	49.0 (31.0-87.1)	50.4 (33.3-79.0)	50.0 (33.4-87.0)	50.0 (31.0-87.1)
Weight group –n (%)				
< 40 kg	35 (12.2)	34 (12.1)	37 (12.9)	106 (12.4)
40-<50 kg	113 (39.5)	99 (35.1)	105 (36.6)	317 (37.1)
50-<60 kg	87 (30.4)	110 (39.0)	99 (34.5)	296 (34.6)
>=60 kg	51 (17.8)	39 (13.8)	46 (16.0)	136 (15.9)

- Disease characteristics by treatment group (Safety population)

Background characteristic	Placebo N=286	Rivastigmine 5 cm^2 N=282	Rivastigmine 10 cm^2 N=287	Total N=855
Time since first symptoms of AD was noticed by patient/caregiver (years)				
Mean (SD)	3.8 (2.45)	3.5 (2.12)	3.6 (2.27)	3.6 (2.29)
Median (Range)	3.2 (0.1-15.8)	3.2 (0.1-9.7)	3.2 (0.1-16.9)	3.2 (0.1-16.9)
Time since first symptoms of AD was diagnosed by physician (years)				
Mean (SD)	1.7 (1.92)	1.6 (1.67)	1.7 (1.78)	1.7 (1.79)
Median (Range)	1.0 (0.0-9.6)	1.1 (0.0-7.6)	1.3 (0.0-9.1)	1.1 (0.0-9.6)
MMSE at baseline				
Mean (SD)	16.6 (2.91)	16.8 (2.92)	16.5 (3.07)	16.6 (2.96)
Median (Range)	17.0 (10-20)	18.0 (10-20)	17.0 (10-20)	17.0 (10-20)
<=15-n (%)	91 (31.8)	88 (31.2)	89 (31.0)	268 (31.3)
>15-n (%)	195 (68.2)	194 (68.8)	198 (69.0)	587 (68.7)
ADAS-J cog at baseline				
Mean (SD)	25.1 (9.68)	25.7 (9.96)	25.2 (10.00)	25.3 (9.87)
Median (Range)	23.0 (6.7-55.3)	23.9 (8.4-62.0)	23.5 (8.0-57.7)	23.5 (6.7-62.0)

Extension study:

- Demographic summary by treatment group (Safety population)

Demographic variable	Total N=637 (100%)
Age (years)	
Mean (SD)	74.3 (7.34)
Age groups – n (%)	
< 65 years	74 (11.6)
>= 65 years	563 (88.4)
< 75 years	272 (42.7)
>= 75 years	365 (57.3)
Sex – n (%)	
Male	211 (33.1)
Female	426 (66.9)
Weight at OL baseline (kg)	
Mean (SD)	51.0 (9.64)
Weight group at OL baseline-n (%)	
< 40 kg	74 (11.6)
40 -<50 kg	259 (40.7)
50 -<60 kg	192 (30.1)
>=60 kg	112 (17.6)

- Disease characteristics by treatment group (Safety population)

Background characteristic	Total N=637 (100%)
Patients with relatives with AD-n (%)	
None	509 (79.9)
Mother	57 (8.9)
Father	33 (5.2)
Sibling	49 (7.7)
Other	4 (0.6)
Time since first symptoms of AD was noticed by patient/caregiver (years)	
Mean (SD)	3.6 (2.36)
Time since first symptoms of AD was diagnosed by physician (years)	
Mean (SD)	1.7 (1.80)
Patient's living situation-n(%)	
Living alone	14 (2.2)
Living with caregiver or others	609 (95.6)
Assisted living / group home	7 (1.1)
Nursing home or long term institution	7 (1.1)
Years of formal education	
Mean (SD)	10.6 (2.77)
MMSE at OL baseline	
Mean (SD)	16.5 (4.42)
Missing n (%)	5 (0.8)

<=15 n (%)	238 (37.4)
>15 n (%)	394 (61.9)
MMSE at DB baseline	
Mean (SD)	16.7 (2.95)
<=15 n (%)	200 (31.4)
>15 n (%)	437 (68.6)
ADAS-J cog at DB baseline	
Mean (SD)	25.1 (9.75)

Primary Objective Results

Core study:

- ADAS-J cog primary analysis at Week 24 (ITT, LOCF)

		Placebo N=268	Rivastigmine 5 cm^2 N=269	Rivastigmine 10 cm^2 N=273
	n	265	266	268
Baseline	Mean (SD)	24.8 (9.46)	25.2 (9.62)	25.0 (9.93)
Post-baseline	Mean (SD)	26.1 (11.49)	25.7 (11.70)	25.1 (11.25)
Change	Mean (SD)	1.3 (5.07)	0.5 (4.96)	0.1 (5.04)
	LSMean (SE)	1.3 (0.31)	0.5 (0.31)	0.1 (0.30)
Rivastigmine	LSMean (SE)	-	-0.8 (0.43)	-1.2 (0.43)
Placebo	95%CI	-	(-1.7,0.0)	(-2.1,-0.4)
	p-value	-	0.063(*)	0.005**

Negative change score indicates improvement and negative LSMean treatment difference indicates superiority of Rivastigmine versus Placebo.

p-values are derived from analyses of covariance (ANCOVA) and are based on comparison of each Rivastigmine treatment group with placebo.

(*) p < 0.10, * p < 0.05, ** p < 0.01, *** p < 0.001

- CIBIC plus-J primary analysis at Week 24 (ITT, LOCF)

		Placebo N=268	Rivastigmine 5 cm^2 N=269	Rivastigmine 10 cm^2 N=273
N'		267	269	270
Mean (SD)		4.4 (0.94)	4.2 (0.96)	4.2 (0.96)
Score-n (%)				
	Markedly improved (1)	0 (0.0)	0 (0.0)	0 (0.0)
	Moderately improved (2)	5 (1.9)	12 (4.5)	6 (2.2)
	Minimally improved (3)	36 (13.5)	45 (16.7)	53 (19.6)
	Unchanged (4)	111 (41.6)	109 (40.5)	109 (40.4)
	Minimally worse (5)	84 (31.5)	82 (30.5)	78 (28.9)
	Moderately worse (6)	29 (10.9)	21 (7.8)	22 (8.1)
	Markedly worse (7)	2 (0.7)	0 (0.0)	2 (0.7)
p-value		-	0.063 (*)	0.067 (*)

Last observation was carried forward to Week 24, if appropriate.

N': total number of patients with evaluation for that visit.

Percentages were calculated using the evaluable N' as denominator.

p-values are derived from Wilcoxon test and are based on comparison of each Rivastigmine treatment group with placebo.

(*) $p < 0.10$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Extension study:

None

Secondary Objective Results

Core study:

- Subscale for CIBIC plus-J:
  - DAD was used to assess levels of difficulty in activities of daily living, and had deteriorated in all treatment groups since baseline. The level of deterioration was, however, the smallest in rivastigmine 10 cm^2 group, with significant difference to placebo (p=0.024).
  - BEHAVE-AD was used to assess patient behavior and psychiatric symptoms, and had very slight changed in all treatment groups. There was no significant difference between treatment groups (placebo – 10 cm^2 p=0.795).
  - MENFIS was used to assess patient cognitive and psychiatric function, and had deteriorated in all treatment groups since baseline. The level of deterioration was, however, the smallest in rivastigmine 10 cm^2 group, with a significant difference to placebo (p=0.016).
- MMSE did not change considerably from baseline in all treatment groups. There were no significant differences between rivastigmine 5 cm^2 and 10 cm^2 groups and placebo group.

Extension study:

The efficacy results (MMSE, DAD, Modified Crichton Scale) are showed in the following tables.

- MMSE Change from Open-Label Baseline (ITT population)

			Total N=634
OL Week 52		n	466
	OL Baseline	Mean (SD)	16.6 (4.39)
	Post-baseline	Mean (SD)	14.8 (5.58)
	Change	Mean (SD)	-1.8 (3.34)
		95%CI for Mean	(-2.1,-1.5)
OL Endpoint		n	577
	OL Baseline	Mean (SD)	16.6 (4.43)
	Post-baseline	Mean (SD)	14.9 (5.58)
	Change	Mean (SD)	-1.7 (3.28)
		95%CI for Mean	(-2.0,-1.4)

OL Baseline: Last assessment after last dose of DB study drug but before OL study drug
OL Week 52: Only observed case at Week 52 is included
OL Endpoint: Last observation during OL phase is carried forward to Week 52

- DAD Change from Open-Label Baseline (ITT population)

			Total N=634
OL Week 52		n	460
	OL Baseline	Mean (SD)	63.16 (22.833)
	Post-baseline	Mean (SD)	53.08 (25.490)
	Change	Mean (SD)	-10.09 (14.205)

		95%CI for Mean	(-11.39, -8.78)
OL Endpoint		n	567
	OL Baseline	Mean (SD)	61.99 (22.939)
	Post-baseline	Mean (SD)	51.95 (25.407)
	Change	Mean (SD)	-10.04 (14.089)
		95%CI for Mean	(-11.20, -8.88)

OL Baseline: Last assessment after last dose of DB study drug but before OL study drug
OL Week 52: Only observed case at Week 52 is included
OL Endpoint: Last observation during OL phase is carried forward to Week 52

- Modified Crichton Scale Change from Open-Label Baseline (ITT population)

			Total N=634
OL Week 52		n	474
	OL Baseline	Mean (SD)	19.3 (9.73)
	Post-baseline	Mean (SD)	23.3 (11.09)
	Change	Mean (SD)	4.0 (6.76)
		95%CI for Mean	(3.4, 4.6)
OL Endpoint		n	634
	OL Baseline	Mean (SD)	20.0 (10.04)
	Post-baseline	Mean (SD)	24.0 (11.30)
	Change	Mean (SD)	4.0 (6.74)
		95%CI for Mean	(3.5, 4.5)

OL Baseline: Last assessment after last dose of DB study drug but before OL study drug
OL Week 52: Only observed case at Week 52 is included
OL Endpoint: Last observation during OL phase is carried forward to Week 52

Safety Results

Core study:

- Adverse Events by System Organ Class (all patients / > 3% in any group) (Safety population)

System Organ Class	Placebo N=286 n (%)	Rivastigmine 5 cm^2 N=282 n (%)	Rivastigmine 10 cm^2 N=287 n (%)
At least one adverse event	222 (77.6)	243 (86.2)	248 (86.4)
General disorders and administration site conditions	85 (29.7)	123 (43.6)	128 (44.6)
Skin and subcutaneous tissue Disorders	60 (21.0)	94 (33.3)	83 (28.9)
Gastrointestinal disorders	53 (18.5)	35 (12.4)	55 (19.2)
Infections and infestations	49 (17.1)	39 (13.8)	52 (18.1)
Investigations	55 (19.2)	45 (16.0)	49 (17.1)

Musculoskeletal and connective tissue disorders	27 (9.4)	12 (4.3)	25 (8.7)
Nervous system disorders	16 (5.6)	9 (3.2)	23 (8.0)
Metabolism and nutrition disorders	8 (2.8)	11 (3.9)	21 (7.3)
Injury, poisoning and procedural complications	24 (8.4)	21 (7.4)	20 (7.0)
Renal and urinary disorders	5 (1.7)	9 (3.2)	8 (2.8)
Cardiac disorders	16 (5.6)	13 (4.6)	7 (2.4)
Psychiatric disorders	12 (4.2)	10 (3.5)	7 (2.4)
Respiratory, thoracic and mediastinal disorders	12 (4.2)	8 (2.8)	5 (1.7)

- Most Frequently Reported AEs Overall by Preferred Term (all patients / > 3% in any group) (Safety population)

Preferred Term	Placebo N=286 n (%)	Rivastigmine 5 cm^2 N=282 n (%)	Rivastigmine 10 cm^2 N=287 n (%)
Total no. of patients with AEs	222 (77.6)	243 (86.2)	248 (86.4)
Application site erythema	55 (19.2)	106 (37.6)	113 (39.4)
Application site pruritus	61 (21.3)	92 (32.6)	100 (34.8)
Dermatitis contact	40 (14.0)	69 (24.5)	68 (23.7)
Nasopharyngitis	32 (11.2)	22 (7.8)	33 (11.5)
Application site oedema	7 (2.4)	35 (12.4)	31 (10.8)
Vomiting	11 (3.8)	11 (3.9)	23 (8.0)
Nausea	9 (3.1)	3 (1.1)	20 (7.0)
Blood creatine phosphokinase increased	10 (3.5)	6 (2.1)	14 (4.9)
Application site exfoliation	4 (1.4)	14 (5.0)	11 (3.8)
Weight decreased	4 (1.4)	7 (2.5)	10 (3.5)
Diarrhoea	7 (2.4)	11 (3.9)	9 (3.1)
Contusion	6 (2.1)	9 (3.2)	8 (2.8)
Headache	10 (3.5)	2 (0.7)	8 (2.8)
Back pain	10 (3.5)	1 (0.4)	7 (2.4)
Blood urine present	10 (3.5)	7 (2.5)	7 (2.4)
Constipation	12 (4.2)	6 (2.1)	6 (2.1)
Application site pain	4 (1.4)	12 (4.3)	3 (1.0)
Eczema	7 (2.4)	9 (3.2)	2 (0.7)

- Serious Adverse Events and Deaths
  - Deaths, other serious or clinically significant adverse events or discontinuation due to adverse events - n (%) of patients (Safety population)

	Placebo N=286 n (%)	Rivastigmine 5 cm^2 N=282 n (%)	Rivastigmine 10 cm^2 N=287 n (%)
Patients with serious or significant AEs			
Death	1 (0.3)	1 (0.4)	0 (0.0)
SAEs	20 (7.0)	14 (5.0)	18 (6.3)
Discontinued due to AEs	22 (7.7)	39 (13.8)	34 (11.8)
Discontinued due to SAEs	12 (4.2)	8 (2.8)	4 (1.4)
Discontinued due to non-serious AEs	10 (3.5)	31 (11.0)	30 (10.5)

Adjusted/interrupted study drug due to AEs	33 (11.5)	54 (19.1)	63 (22.0)

A total of two patient deaths were reported in the core study; one (subarachnoid haemorrhage) in the placebo group and one (aspiration of food) in the 5 cm^2 patch group.

Extension study:

- Adverse Events by System Organ Class (all patients / > 3% in any group) (Safety population)

System Organ Class	Total N=637 n (%)
At least one adverse event	587 (92.2)
General disorders and administration site conditions	300 (47.1)
Skin and subcutaneous tissue disorders	239 (37.5)
Gastrointestinal disorders	190 (29.8)
Infections and infestations	178 (27.9)
Investigations	135 (21.2)
Injury, poisoning and procedural complications	109 (17.1)
Musculoskeletal and connective tissue disorders	92 (14.4)
Nervous system disorders	65 (10.2)
Metabolism and nutrition disorders	64 (10.0)
Respiratory, thoracic and mediastinal disorders	40 (6.3)
Cardiac disorders	39 (6.1)
Renal and urinary disorders	31 (4.9)
Vascular disorders	30 (4.7)
Psychiatric disorders	29 (4.6)
Eye disorders	27 (4.2)
Blood and lymphatic system disorders	17 (2.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	12 (1.9)
Ear and labyrinth disorders	11 (1.7)
Reproductive system and breast disorders	7 (1.1)
Hepatobiliary disorders	6 (0.9)
Immune system disorders	3 (0.5)
Endocrine disorders	2 (0.3)
Congenital, familial and genetic disorders	1 (0.2)

- Most Frequently Reported AEs Overall by Preferred Term (all patients / > 3% in any group) (Safety population)

Preferred Term	Total N=637 n (%)
Total no. of patients with AEs	587 (92.2)
Application site erythema	220 (34.5)
Application site pruritus	201 (31.6)
Dermatitis contact	162 (25.4)

Nasopharyngitis	95 (14.9)
Application site oedema	64 (10.0)
Vomiting	59 (9.3)
Constipation	44 (6.9)
Nausea	41 (6.4)
Contusion	39 (6.1)
Weight decreased	35 (5.5)
Diarrhoea	34 (5.3)
Decreased appetite	33 (5.2)
Application site exfoliation	30 (4.7)
Back pain	30 (4.7)
Blood creatine phosphokinase increased	23 (3.6)
Arthralgia	22 (3.5)
Eczema	21 (3.3)

- Serious Adverse Events and Deaths:
  - Deaths, other serious or clinically significant adverse events or discontinuations due to adverse events - n (%) of patients (Safety population)

	Total N=637 n (%)
Patients with serious or significant AEs	
Death	2 (0.3)
SAEs	74 (11.6)
Discontinued due to AEs	97 (15.2)
Discontinued due to SAEs	25 (3.9)
Discontinued due to non-serious AEs	73 (11.5)
Decreased/Interrupted study drug due to AEs	146 (22.9)

During the extension phase, 2 deaths were reported, both caused by myocardial infarction.

Other Relevant Findings

Core study:

- Investigator's rating of skin irritation (most severe rating) (Safety population)

  Overall, any severe rating was reported only in 3.5% of patients in the 5 cm^2 group, 6.6% of patients in the 10 cm^2 patch group, and 1.8% of patients in the placebo group

- Trough plasma concentration (ng/mL) of rivastigmine (PK population)

  The mean (SD) at Week 24 was 2.61 (1.74) in the 5 cm2 patch size [n=183], 8.10 (7.16) in the 10 cm2 patch size [n=167]

Extension study:

- Investigator's rating of skin irritation (most severe rating) (Safety population)

  According to the investigator's rating of skin irritation, more than 80% of skin irritation

scores were rated as none, slight or mild
Date of Clinical Trial Report **Core study:** 01 Oct 2009 **Extension study:** 25 Aug 2010
Date of Inclusion on Novartis Clinical Trial Results Database 26 Apr 2011
Date of Latest Update 26 Apr 2011