Sponsor:

Novartis

Generic Drug Name:

Rivastigmine

Therapeutic Area of Trial:

Mild to moderate dementia of the Alzheimer's type

Approved Indications

- Rivastigmine patch is indicated for the treatment of mild, moderate and severe Alzheimer's Disease (AD)
- Rivastigmine patch is indicated for the treatment of mild to moderate Parkinson's disease dementia (PDD)

Protocol Number

CENA713D2344

Title

A 24-Week, Randomized, Double-blind, Double-dummy, Parallel-group, Active-controlled Study to Assess the Efficacy, Safety, and Tolerability of the Once-daily Rivastigmine Patch Formulation in Patients with Probable Alzheimer's Disease (Mini-Mental State Examination (MMSE 10-20)

Study Phase

Phase III

Study Start/End Dates

05-Jul-2011 (first patient first visit) to 11-May-2013 (last patient last visit)

Study Design/Methodology

This was a 24-week, multi-center, randomized, double-blind, double-dummy, parallel-group and active controlled study in patients with mild to moderate AD. In order to assess the non-inferiority of rivastigmine patch compared to rivastigmine capsules, patients were randomized (1:1) to one of two blinded treatment groups: rivastigmine patch plus placebo capsules or rivastigmine capsules plus placebo patch. A double-dummy design was used in order to ensure blinding of the treatment groups, as the identity of the study drugs cannot be disguised due to their different formulations.

Centers

25 study sites in China

Publication

None

Objectives

The primary objective was to confirm the non-inferior efficacy of rivastigmine patch (target size of 10 cm2) compared with rivastigmine capsule (target dose of 6 mg bid) on the change from baseline at Week 24 on cognition, assessed by the Alzheimer's Disease Assessment Scale (ADAS-Cog) inpatients with probable AD (MMSE 10-20).

Secondary objectives

To compare the efficacy of rivastigmine patch (target size of 10 cm2) versus rivastigmine capsules (target dose of 6.0 mg bid) with respect to: change from baseline at Week 24 in

- global functioning, assessed by the Alzheimer's Disease Cooperative Study (ADCS)-Clinical Global Impression of Change (CGIC),
- caregiver-based activities of daily living (ADL)
- behavioral symptoms, assessed by the Neuropsychiatric Inventory (NPI),
- global cognitive function, assessed by the MMSE.

To compare the safety and tolerability of Exelon patch versus Exelon capsules with respect to:

- the incidence of adverse events, adverse events leading to discontinuation of study drug, and serious adverse events;
- the incidence of gastrointestinal (GI) adverse events (particularly nausea and vomiting), the degree of burden (severity x incidence) of GI adverse events (nausea and vomiting) and discontinuations due to GI adverse events;
- the incidence of application site reactions;
- changes in quantitative safety evaluations, such as vital signs, ECG and laboratory parameters.

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

Rivastigmine patches were provided in the following sizes:

- patch 5 cm^2 size, loaded with 9 mg of rivastigmine; the release rate is 4.6 mg per 24 hours
- patch 10 cm^2 size, loaded with 18 mg of rivastigmine; the release rate is 9.5 mg per 24 hours

Rivastigmine capsules were provided in the following strengths: 1.5 mg, 3.0 mg, 4.5 mg, and 6.0 mg.

Matching placebo 5 and 10 cm^2 patch sizes and matching placebo capsules were also provided.

Patients were assigned to one of the following treatment groups in 1:1 ratio:

- Group A: rivastigmine once-daily target patch size 10 cm^2 (loaded with 18 mg and providing 9.5 mg rivastigmine per 24 hrs)
- Group B: rivastigmine twice-daily target dose of 6 mg oral capsule (12 mg rivastigmine/day)

Statistical Methods

The primary analysis variable was the change from baseline to Week 24 in the total score of the 11 items included in the ADAS-Cog.
For the non-inferiority hypothesis on ADAS-Cog, the two-sided 95% confidence interval for the difference in means between treatment groups was calculated, using the least square means derived by an analysis of covariance (ANCOVA) model with the following explanatory variables: treatment, region (geographic combination of single study centers), and the baseline total ADAS-Cog score. The strategy for region definition was defined in the statistical analysis plan prior to unblinding the treatment codes in order to ensure that an adequate number of subjects were available in the statistical analyses adjusted by region.
The non-inferiority of rivastigmine patch vs. rivastigmine capsules was demonstrated if the upper bound of the two-sided 95% confidence interval for the difference between treatment groups (rivastigmine patch minus rivastigmine capsules) was less than the pre-defined non-inferiority margin of 1.25.
The primary population for the confirmatory testing of the hypothesis was the Per-Protocol population using no imputation of missing data (i.e. with observed cases).
Analysis of secondary efficacy variables included comparison of treatment groups using statistical methods such as ANCOVA and Cochran-Mantel-Haenszel tests.

Study Population: Inclusion/Exclusion Criteria and Demographics

Ages Eligible for Study:	50 Years to 85 Years
Genders Eligible for Study:	Both
Accepts Healthy Volunteers:	No

Inclusion Criteria:

- had a diagnosis of dementia of the Alzheimer's type according to the DSM-IV criteria
- had a clinical diagnosis of probable AD according to NINCDS/ADRDA criteria
- had a brain scan (MRI or CT) consistent with the diagnosis of AD. The brain scan was to have performed within one year prior to randomization
- had an MMSE score of ≥ 10 and ≤ 20
- had sufficient education to be able to read, write, and communicate effectively during the premorbid state
- was residing with someone in the community throughout the study or, if living alone, in contact with the primary caregiver everyday

Exclusion Criteria:

- had an advanced, severe, progressive, or unstable infectious, metabolic, immune, endocrinologic, hepatic, hematological, pulmonary, cardiovascular, gastrointestinal, and/or urological condition that may have interfered with efficacy and safety assessments or put the patient at special risk
- had a history or current diagnosis of any medical or neurological condition other than AD that was identified as contributing cause of the patient's dementia

- had a current diagnosis of probable or possible vascular dementia according to the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria (NINDS-AIREN)
- had a score of > 4 on the Modified Hachinski Ischemic Scale (MHIS)
- had a current DSM-IV diagnosis of major depression, unless, in the opinion of the investigator, was in remission for at least 12 weeks

Other protocol-defined inclusion/exclusion criteria may have applied.

Participant Flow

Patient disposition by treatment group (Randomized population)

Disposition/Reason	Rivastigmine patch N=248 n (%)	Rivastigmine capsule N=253 n (%)	Total N=501 n (%)
Screened			601
Screening failure			100
Reason for screening failure			
Unacceptable past medical history/concomitant diagnosis			6 (6.0)
Intercurrent medical event Unacceptable			3 (3.0)
laboratory value Unacceptable test			27 (27.0)
procedure result(s) Did not meet			9 (9.0)
diagnostic/severity criteria Unacceptable			14 (14.0)
use of excluded medication/therapies			2 (2.0)
Subject withdrew consent			29 (29.0)
Unknown			1 (1.0)
Other			12 (12.0)
Randomized	248 (100.0)	253 (100.0)	501 (100.0)
Exposed to study drug	248 (100.0)	252 (99.6)	500 (99.8)
Completed	197 (79.4)	193 (76.3)	390 (77.8)
Discontinued	51 (20.6)	60 (23.7)	111 (22.2)
Reason for discontinuation			
Adverse Event(s)	32 (12.9)	30 (11.9)	62 (12.4)
Abnormal laboratory value(s)	0 (0.0)	1 (0.4)	1 (0.2)
Unsatisfactory therapeutic effect	0 (0.0)	4 (1.6)	4 (0.8)
Subject withdrew consent	5 (2.0)	8 (3.2)	13 (2.6)
Lost to follow-up	2 (0.8)	3 (1.2)	5 (1.0)
Administrative problems	7 (2.8)	11 (4.3)	18 (3.6)
Death	0 (0.0)	1 (0.4)	1 (0.2)
Protocol deviation	5 (2.0)	2 (0.8)	7 (1.4)

- Percentage (%) is calculated based on the Randomized population, except for the reasons for screening failure where percentage is based on the total number of screening failures.
- A patient with multiple reasons for screening failure is counted in each category.

Baseline Characteristics

Patient demographic characteristics by treatment group (Randomized population)

Demographic Characteristic	Rivastigmine patch N=248	Rivastigmine capsule N=253	Total N=501
Sex – n (%)			
Male	108 (43.5%)	114 (45.1%)	222 (44.3%)
Female	140 (56.5%)	139 (54.9%)	279 (55.7%)
Race – n (%)			
Asian	248 (100%)	253 (100%)	501 (100%)
Age (years)[1]			
n	248	253	501
Mean	70.4	69.8	70.1
SD	8.02	8.20	8.11
Median	72.0	71.0	72.0
Min	50	50	50
Max	85	84	85
Age group – (years)[1] – n(%)			
< 65	60 (24.2%)	75 (29.6%)	135 (26.9%)
65 - <75	92 (37.1%)	97 (38.3%)	189 (37.7%)
75- <85	95 (38.3%)	81 (32.0%)	176 (35.1%)
≥ 85 years	1 (0.4%)	0 (0.0%)	1 (0.2%)
Height (cm)			
n	248	253	501
Mean	161.5	161.6	161.6
SD	8.44	8.49	8.46
Median	160.0	160.0	160.0
Min	130	143	130
Max	183	182	183
Weight (kg)			
n	248	253	501
Mean	58.7	58.9	58.8
SD	10.66	10.90	10.77
Median	57.3	57.0	57.1
Min	38	40	38
Max	91	100	100
Weight Category (kg)[1] – n (%)			
< 50	52 (21.0%)	52 (20.6%)	104 (20.8%)
50 – 70	158 (63.7%)	164 (64.8%)	322 (64.3%)
> 70	38 (15.3%)	37 (14.6%)	75 (15.0%)
BMI (kg/m^2)			
n	248	253	501
Mean	22.4	22.5	22.5
SD	3.11	3.35	3.23
Median	22.5	22.3	22.4
Min	15	16	15
Max	31	32	32

- Demographic characteristics are collected at screening visit.
- N: Number of patients in the Randomized population.
- n: Number of patients meeting the criterion (for categorical variables); number of patients with a non-missing assessment (for continuous variables).
- Body Mass Index (BMI) = weight (kg)/height(m)2.
- (1) Age and weight are reported at the baseline visit.

Summary of Efficacy

Outcome Measures

Primary Outcome Result(s)

Change from baseline in Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) by treatment group (PP (OC) population)

Visit		Rivastigmine patch N=192		Rivastigmine capsule N=188		Rivastigmine patch vs. Rivastigmine capsule		
		n	Mean	n	Mean	DLSM	95% CI	p-value
Week 8	Baseline	184	28.9	183	28.1			
	Post baseline	184	28.2	183	27.1			
	Change	184	-0.7	183	-1.0	0.4	(-0.7, 1.4)	0.495
Week 16	Baseline	179	28.9	181	28.2			
	Post baseline	179	27.5	181	26.7			
	Change	179	-1.4	181	-1.5	0.1	(-1.0, 1.3)	0.803
Week 24	Baseline	182	29.0	185	28.2			
	Post baseline	182	28.4	185	27.4			
	Change	182	-0.5	185	-0.7	0.1	(-1.2, 1.5)	0.834

- The baseline assessment corresponds to the last scheduled or unscheduled assessment prior to or on the first treatment date.
- A negative change indicates an improvement from baseline. A negative difference (DLSM) indicates greater improvement in Rivastigmine patch as compared to Rivastigmine capsule.
- Difference of least square means (DLSM), 95% confidence interval (CI), and p-value are based on an analysis of covariance (ANCOVA) model adjusted for region and baseline ADAS-Cog score.
- * $p < 0.05$
- n is the number of patients with an assessment at baseline and the corresponding visit.

Secondary Outcome Results

Van Elteren test results for Alzheimer's Disease Assessment Scale-Clinical Global Impression of Change (ADCS-CGIC) (PP (OC) population)

	Rivastigmine patch N=192 n (%)			Rivastigmine capsule N=188 n (%)		
	Week 8	Week 16	Week 24	Week 8	Week 16	Week 24
Marked improvement	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)
Moderate improvement	10 (5.2)	8 (4.2)	10 (5.2)	5 (2.7)	13 (6.9)	12 (6.4)
Minimal improvement	56 (29.2)	78 (40.6)	68 (35.4)	60 (31.9)	47 (25.0)	59 (31.4)
No change	97 (50.5)	64 (33.3)	67 (34.9)	96 (51.1)	81 (43.1)	74 (39.4)
Minimal worsening	26 (13.5)	35 (18.2)	38 (19.8)	22 (11.7)	39 (20.7)	35 (18.6)
Moderate worsening	1 (0.5)	4 (2.1)	7 (3.6)	2 (1.1)	2 (1.1)	6 (3.2)
Marked worsening	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	2 (1.1)	0 (0.0)
n	191	190	192	185	184	187
Mean	3.8	3.7	3.8	3.8	3.9	3.8
SD	0.81	0.90	0.98	0.74	0.94	0.95
Median	4.0	4.0	4.0	4.0	4.0	4.0
p-value of patch vs. capsule	0.990	0.047*	0.853			

- p-values are derived from CMH (van Elteren) test adjusted for region at the corresponding visit.
- * $p < 0.05$.

Change from baseline in Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL) total score by treatment group (PP (OC) population)

Visit		Rivastigmine patch N=192		Rivastigmine capsule N=188		Rivastigmine patch vs. Rivastigmine capsule		
		n	Mean	n	Mean	DLSM	95% CI	p-value
Week 8	Baseline	192	51.0	187	53.2			
	Post baseline	192	51.4	187	52.1			
	Change	192	0.4	187	-1.1	1.2	(-0.4, 2.8)	0.145
Week 16	Baseline	190	51.0	185	53.2			
	Post baseline	190	50.4	185	52.4			
	Change	190	-0.6	185	-0.8	-0.1	(-2.0, 1.8)	0.911
Week 24	Baseline	192	51.0	188	53.2			
	Post baseline	192	49.1	188	51.5			
	Change	192	-1.9	188	-1.7	-0.5	(-2.7, 1.7)	0.629

- The baseline assessment corresponds to the last scheduled or unscheduled assessment prior to or on the first treatment date.
- A positive change indicates an improvement from baseline. A positive difference (DLSM) indicates greater improvement in rivastigmine patch as compared to rivastigmine capsule.
- Difference of least square means (DLSM), 95% confidence interval (CI), and p-value are based on an analysis of covariance (ANCOVA) model adjusted for region and baseline ADCS-ADL score.
- * $p < 0.05$
- n is the number of patients with an assessment at baseline and the corresponding visit.

Change from baseline in Neuropsychiatric Inventory (NPI) total score by treatment group (PP (OC) population)

Visit		Rivastigmine patch N=192		Rivastigmine capsule N=188		Rivastigmine patch vs. Rivastigmine capsule		
		n	Mean	n	Mean	DLSM	95% CI	p-value
NPI-12: Total score (frequency x severity)								
Week 8	Baseline	192	11.4	187	9.9			
	Post baseline	192	11.0	187	8.7			
	Change	192	-0.4	187	-1.1	1.1	(-0.9, 3.1)	0.265
Week 16	Baseline	190	11.4	185	10.0			
	Post baseline	190	10.1	185	8.9			
	Change	190	-1.4	185	-1.0	0.2	(-1.6, 2.0)	0.833
Week 24	Baseline	192	11.4	188	9.8			
	Post baseline	192	10.1	188	8.5			
	Change	192	-1.3	188	-1.3	0.7	(-1.3, 2.6)	0.495
NPI-10: Total score (frequency x severity)								
Week 8	Baseline	192	10.0	187	8.5			
	Post baseline	192	9.7	187	7.3			
	Change	192	-0.3	187	-1.2	1.3	(-0.5, 3.1)	0.149
Week 16	Baseline	190	10.0	185	8.6			
	Post baseline	190	8.8	185	7.0			
	Change	190	-1.2	185	-1.6	1.0	(-0.5, 2.5)	0.207
Week 24	Baseline	192	10.0	188	8.5			
	Post baseline	192	8.8	188	7.1			
	Change	192	-1.2	188	-1.3	0.7	(-0.9, 2.4)	0.383
NPI-D: Distress score (frequency x severity)								
Week 8	Baseline	192	5.4	187	4.8			
	Post baseline	192	4.8	187	4.1			
	Change	192	-0.6	187	-0.7	0.3	(-0.7, 1.2)	0.572
Week 16	Baseline	190	5.4	185	4.9			
	Post baseline	190	4.9	185	4.2			
	Change	190	-0.5	185	-0.7	0.4	(-0.4, 1.3)	0.334

Week 24	Baseline	192	5.4	188	4.8			
	Post baseline	192	4.9	188	4.2			
	Change	192	-0.4	188	-0.6	0.5	(-0.5, 1.5)	0.311

- The baseline assessment corresponds to the last scheduled or unscheduled assessment prior to or on the first treatment date.
- A negative change indicates an improvement from baseline. A negative difference (DLSM) indicates greater improvement in rivastigmine patch as compared to rivastigmine capsule.
- Difference of least square means (DLSM), 95% confidence interval (CI), and p-value are based on an analysis of covariance (ANCOVA) model adjusted for region and baseline NPI score.
- * $p < 0.05$
- n is the number of patients with an assessment at baseline and the corresponding visit.

Change from baseline in Mini-Mental State Examination (MMSE) total score by treatment group (PP (OC) population)

Visit		Rivastigmine patch N=192		Rivastigmine capsule N=188		Rivastigmine patch vs. Rivastigmine capsule		
		n	Mean	n	Mean	DLSM	95% CI	p-value
Week 8	Baseline	192	16.0	187	16.5			
	Post baseline	192	16.6	187	17.4			
	Change	192	0.6	187	0.9	-0.3	(-0.8, 0.3)	0.322
Week 16	Baseline	190	16.0	185	16.5			
	Post baseline	190	17.1	185	17.1			
	Change	190	1.1	185	0.6	0.6	(-0.0, 1.2)	0.060
Week 24	Baseline	192	16.0	188	16.5			
	Post baseline	192	16.7	188	17.2			
	Change	192	0.7	188	0.7	0.1	(-0.6, 0.7)	0.821

- The baseline assessment corresponds to the last scheduled or unscheduled assessment prior to or on the first treatment date.
- A positive change indicates an improvement from baseline. A positive difference (DLSM) indicates greater improvement in rivastigmine patch as compared to rivastigmine capsule.
- Difference of least square means (DLSM), 95% confidence interval (CI), and p-value are based on an analysis of covariance (ANCOVA) model adjusted for region and baseline MMSE score.
- * $p < 0.05$
- n is the number of patients with an assessment at baseline and the corresponding visit.

Summary of Safety

Safety Results

Adverse events by primary system organ class and treatment group (Safety population)

Primary system organ class	Rivastigmine patch N=247 n (%)	Rivastigmine capsule N=251 n (%)
Any primary system organ class	140 (56.7)	157 (62.5)
Blood and lymphatic system disorders	0 (0.0)	1 (0.4)
Cardiac disorders	4 (1.6)	6 (2.4)
Ear and labyrinth disorders	1 (0.4)	0 (0.0)
Eye disorders	2 (0.8)	3 (1.2)
Gastrointestinal disorders	39 (15.8)	72 (28.7)
General disorders and administration site conditions	50 (20.2)	28 (11.2)
Hepatobiliary disorders	1 (0.4)	2 (0.8)
Infections and infestations	12 (4.9)	10 (4.0)
Injury, poisoning and procedural complications	19 (7.7)	13 (5.2)
Investigations	14 (5.7)	20 (8.0)
Metabolism and nutrition disorders	20 (8.1)	40 (15.9)
Musculoskeletal and connective tissue disorders	2 (0.8)	4 (1.6)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (0.4)	1 (0.4)
Nervous system disorders	27 (10.9)	41 (16.3)
Psychiatric disorders	22 (8.9)	18 (7.2)
Renal and urinary disorders	5 (2.0)	2 (0.8)
Reproductive system and breast disorders	3 (1.2)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	4 (1.6)	9 (3.6)
Skin and subcutaneous tissue disorders	10 (4.0)	1 (0.4)
Vascular disorders	4 (1.6)	12 (4.8)

- Primary system organ classes are sorted alphabetically.
- A patient with multiple AEs within a primary SOC is counted only once.

Most frequent adverse events (at least 3% in any treatment group), by preferred term and treatment group (Safety population)

Preferred term	Rivastigmine patch N=247 n (%)	Rivastigmine capsule N=251 n (%)
Total	140 (56.7)	157 (62.5)
Application site pruritus	27 (10.9)	7 (2.8)
Nausea	20 (8.1)	32 (12.7)
Vomiting	19 (7.7)	31 (12.4)
Decreased appetite	16 (6.5)	37 (14.7)
Dizziness	15 (6.1)	25 (10.0)
Medication error	10 (4.0)	7 (2.8)
Weight decreased	10 (4.0)	17 (6.8)
Insomnia	8 (3.2)	4 (1.6)
Somnolence	6 (2.4)	11 (4.4)
Diarrhea	5 (2.0)	8 (3.2)

- Preferred terms are sorted by descending frequency within the treatment group Rivastigmine patch.
- A patient with multiple occurrences of an AE within a preferred term is counted only once.

Number (%) of patients with adverse events of special interest and patient's mean daily degree of burden by treatment group (Safety population)

		Rivastigmine patch N =247	Rivastigmine capsule N = 251
Occurrence of nausea and/or vomiting and/or diarrhea and/or decreased appetite	n (%)	38 (15.4)	82 (32.7)
Discontinuation due to nausea and/or vomiting and/or diarrhea and/or decreased appetite	n (%)	4 (1.6)	11 (4.4)
Patient's mean daily degree of burden of nausea and/or vomiting and/or diarrhea and/or decreased appetite	Mean	0.302	0.343
	SD	0.3188	0.4191
	Median	0.157	0.132
	Min	0.01	0.01
	Max	0.96	1.71

- Adverse events of special interest include nausea and vomiting, diarrhea and decreased appetite.
- Only adverse events that started on or after the day of first dose of study medication and on or before the day of last dose of study medication are included.
- Mean daily degree of burden: mean severity of nausea and/or vomiting and/or diarrhea and/or decreased appetite during the course of study medication.

Number (%) of patients who died, had serious adverse events or discontinued due to adverse events, by treatment group (Safety population)

Patients with serious or significant AEs	Rivastigmine patch N =247 n (%)	Rivastigmine capsule N = 251 n (%)
Death	0 (0.0)	1 (0.4)
SAEs [(a)]	16 (6.5)	21 (8.4)
Discontinued due to AEs [(a)]	32 (13.0)	31 (12.4)
Discontinued due to SAEs [(a)]	6 (2.4)	11 (4.4)

(a) Deaths are included.

Conclusion

Concerning the primary endpoint, statistical non-inferiority of rivastigmine patch (target dose 10 cm^2) over rivastigmine capsule (target dose 6 mg bid) with respect to ADAS-Cog was not met at Week 24. The numerical difference between the two treatment groups was negligible (LSM mean 0.1 points on ADAS-Cog) at Week 24 and is not of clinical relevance. In addition, both treatment groups show a similar improvement versus baseline in ADAS-Cog. The similarity of treatment efficacy was apparent in the additional assessments: For the ADCS-CGIC (global assessment), the percentage of patients with improvement is higher for the rivastigmine patch group as compared to the rivastigmine capsule group. For ADCS-ADL, deterioration from baseline was observed in both treatment groups and the decline was similar in both groups.

The improvement in ADAS-Cog in both groups in the Chinese AD population in Study CENA713D2344 is comparable to what had been observed in the global pivotal Study CENA713D2320 at Week 24 in a mainly Caucasian AD population.

There are no new safety signals. Safety data of the two treatment groups in the Chinese study CENA713D2344 appear to be consistent with what has been observed in previous rivastigmine studies.

The overall benefit-risk in Chinese population for rivastigmine patch is similar to what had been observed in a rest of the population.

Date of Clinical Trial Report

12 September 2013

Date Inclusion on Novartis Clinical Trial Results Database

07-May-2014

Date of Latest Update