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A six-month double-blind, randomized, placebo-controlled study of a transdermal patch in Alzheimer's disease—rivastigmine patch *versus* capsule

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SUMMARY

Objectives To compare the efficacy, safety and tolerability of a novel rivastigmine transdermal patch with conventional rivastigmine capsules and placebo in patients with Alzheimer's disease (AD).

Methods In this 24-week, multicenter, double-blind, double-dummy, placebo- and active-controlled trial, patients with probable AD were randomized to one of four treatment groups: 12 mg/day rivastigmine capsules; 10 cm^2 (9.5 mg/24 h) rivastigmine patch; 20 cm^2 (17.4 mg/24 h) rivastigmine patch; or placebo. Primary efficacy measures were the Alzheimer's Disease Assessment Scale—Cognitive subscale (ADAS-Cog) and Alzheimer's Disease Cooperative Study—Clinical Global Impression of Change (ADCS-CGIC).

Results One thousand one hundred and ninety five AD patients from 21 countries participated in the study. Treatment differences (*vs* placebo) on the ADAS-Cog at Week 24 in 10 cm^2 patch, 20 cm^2 patch and capsule groups were 1.6 ($p = 0.005$), 2.6 ($p < 0.001$) and 1.6 ($p = 0.003$). Treatment differences on the ADCS-CGIC were 0.3 ($p = 0.01$), 0.2 ($p = 0.054$) and 0.3 ($p = 0.009$). Comparison between the 10 cm^2 patch and the capsule revealed non-inferiority. Rates of nausea in the 10 cm^2 patch and capsule groups were 7.2% and 23.1%, respectively; rates of vomiting were 6.2% and 17.0%, respectively. Moderate or severe skin irritation occurred in $\leq$10% patients across the four patch sizes (5, 10, 15 and 20 cm^2).

Conclusions The target dose of 10 cm^2 rivastigmine patch provides efficacy similar to the highest doses of capsules with a superior tolerability profile. The transdermal patch with rivastigmine may offer convenience important to many caregivers and patients. Copyright © 2007 John Wiley & Sons, Ltd.

KEY WORDS — Alzheimer's disease; patch; rivastigmine; transdermal

INTRODUCTION

The most common cause of dementia is Alzheimer's disease (AD) (Fratiglioni *et al*., 1991), a chronic neurodegenerative brain disease that is characterized by progressive impairment in the cortically-projecting cholinergic system (Davies and Maloney, 1976) that contributes to the cognitive and functional impairment of this disorder. Cholinesterase inhibitors, which act by inhibiting the degradation of acetylcholine in the synapse, form the mainstay of therapy for mild to moderate AD.

Rivastigmine inhibits acetylcholinesterase and butyrylcholinesterase and is currently widely approved for the treatment of mild to moderate AD and mild to

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moderate Parkinson's disease dementia. Currently, rivastigmine is orally administered. A transdermal patch of rivastigmine (Exelon®, Novartis) has recently been developed. Rivastigmine is a small, potent molecule that is both lipophilic and hydrophilic—properties that make it well suited to transdermal therapy. A transdermal patch formulation may offer tolerability, convenience and therapeutic advantages for this patient population. By providing continuous delivery of drug with reduced fluctuation levels in the plasma, transdermal administration may improve tolerability and make optimal doses easier to achieve. The current objective was to evaluate the efficacy, safety, and tolerability of two rivastigmine patch sizes in patients with probable AD.

METHODS

Patients

Patients meeting the inclusion criteria for this study were women or men aged 50–85 years with a diagnosis of dementia of the Alzheimer's type according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (APA, 1994), and probable AD according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) (McKhann *et al*., 1984). The brain scan (magnetic resonance imaging or computed tomography) used for establishing these criteria must have been done within one year prior to randomization. Patients included in the study had Mini-Mental State Examination (MMSE) scores (Folstein *et al*., 1975) of 10–20 inclusive. Each patient had a comprehensive evaluation with a neurological examination and appropriate laboratory tests (Knopman *et al*., 2001). They were required to be living with someone in the community or, if living alone, in daily contact with a responsible caregiver.

Exclusion criteria included an advanced, severe, progressive, or unstable disease of any type that could interfere with study assessments or put the patient at special risk, and any condition other than AD that could explain the dementia. The use of any investigational drugs, new psychotropic or dopaminergic agents, cholinesterase inhibitors or anti-cholinergic agents during the 4 weeks prior to randomization also was prohibited.

Patients were recruited from 100 study centers that included hospitals, university research centers and neurology clinics in 21 countries. The protocol, informed consent form and other information given to patients and caregivers were reviewed by an Institutional Review Board in each country. The study was conducted according to the ethical principles of the Declaration of Helsinki, as revised in 2000.

Study design

This was a multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled, 24-week, parallel-group study. After assessments for eligibility during a 4-week screening period, patients underwent baseline efficacy and safety assessments. They were randomly assigned to four groups of equal size with target doses of: 10 cm^2 rivastigmine patch; 20 cm^2 rivastigmine patch; 12 mg/day rivastigmine capsules; or placebo.

The 10 cm^2 rivastigmine patch provides an equivalent drug delivery rate of 9.5 mg/24 h, based on drug load/residue calculations from pharmacokinetic studies, while the 20 cm^2 rivastigmine patch provides a delivery rate of 17.4 mg/24 h. The patch shows lower C_{max} and longer t_{max}, compared with a rivastigmine capsule dose of 12 mg/day, with markedly less fluctuation between peak and trough plasma levels. Average exposure with the 10 cm^2 patch is comparable to the highest dose of capsule (12 mg/day).

Patients were titrated to their target dose in 4-week steps over 16 weeks, followed by an 8-week maintenance phase. Patients in the rivastigmine patch groups were up-titrated from a 5 cm^2 starting dose in 5 cm^2 steps to a maximum size of 20 cm^2. Those in the capsule group were up-titrated from 3 mg/day in steps of 3 mg/day to a maximum of 12 mg/day. Dose adjustments (interruptions or down-titrations) were permitted to address perceived safety or tolerability issues. If the target dose was not achieved during the titration period the investigator could resume titration during the maintenance period. Patients were maintained at their highest well tolerated doses until the end of the study.

The patch (rivastigmine or placebo) was applied by caregivers to clean, dry, hairless skin on the patient's upper back every morning and worn for 24 h, during which normal activities including bathing were allowed. To minimize possible skin irritation, patch placement on the upper back was alternated between the left and right sides, daily. All patients also took a capsule (rivastigmine or placebo) with breakfast and one with their evening meal.

Upon entry into the double-blind phase, patients were sequentially assigned the lowest available

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identification number at each center. Automated random assignment of treatment was performed using an interactive voice-response system. Blocking was done on a study center basis. All personnel directly involved in the conduct of the study remained unaware of the active treatment groups until all data had been retrieved and finalized for analysis.

Outcomes

Efficacy assessments were made at baseline and Weeks 16 and 24. Primary outcomes were the Alzheimer's Disease Assessment Scale-Cognitive subscale, (ADAS-Cog) (Rosen *et al*., 1984) and the Alzheimer's Disease Cooperative Study—Clinical Global Impression of Change (ADCS-CGIC) (Schneider *et al*., 1997) at Week 24. The ADAS-Cog assesses orientation, memory, language, visuospatial and praxis functions. The ADCS-CGIC provides a single global rating of change from baseline. The ADCS-CGIC was rated by an independent rater who had no access to the other efficacy or safety data. Prior to study initiation, investigators received training on administration of outcome measures.

Secondary efficacy outcomes were 24-week scores on the Alzheimer's Disease Cooperative Study—Activities of Daily Living (ADCS-ADL) scale (Galasko *et al*., 1997); Neuropsychiatric Inventory (NPI) for behavior and psychiatric symptoms (Cummings *et al*., 1994); MMSE (Folstein *et al*., 1975) for cognition; Ten Point Clock-drawing Test (Watson *et al*., 1993) for assessment of visuospatial and executive functions and the Trail Making Test Part A for assessment of attention, visual tracking and motor processing speed (Reitan, 1958; Corrigan and Hinkeldey, 1987).

Safety evaluations included recording all adverse events, which were coded using a standard glossary. Vital signs and body weight were recorded at every visit. Routine laboratory tests were performed at baseline; post-baseline laboratory tests were not routinely collected but if any abnormal clinical laboratory findings developed and induced clinical signs or symptoms, were considered clinically significant or required therapy, they were recorded as AEs. Skin irritation was evaluated at every visit by the investigator based on inspection of the skin at the site of application. Skin irritation also was assessed by the caregiver, who provided a summary irritation rating.

Skin adhesion was evaluated by the caregiver. A rating of the patch adherence was provided and graded according to a patch adhesion score.

Statistical analysis

A hierarchical testing strategy was applied to adjust for multiplicity. Study objectives were assessed according to four hypotheses tested in sequence. If any of the four tests failed to show statistical significance, testing of subsequent hypotheses would be stopped in order to control the type 1 error. These hypotheses were that, based on changes from baseline at Week 24: (1) on the ADAS-Cog and ADCS-CGIC, the rivastigmine 20 cm^2 patch would show superiority over placebo; (2) on the ADAS-Cog, the rivastigmine 20 cm^2 patch would show non-inferiority to 12 mg/day rivastigmine capsules; (3) on the ADAS-Cog and ADCS-CGIC, the rivastigmine 10 cm^2 patch would show superiority over placebo; (4) on the ADCS-ADL, the rivastigmine 20 cm^2 patch would show superiority over placebo. The second hypothesis, which tested for non-inferiority, was a one-sided hypothesis. The remaining three hypotheses were two-sided hypotheses.

In previous placebo-controlled trials of the rivastigmine capsule in AD patients, a treatment difference to placebo in the ADAS-Cog change from baseline of approximately 2.5 points was observed in the Intent-to-Treat (ITT) analysis (Schneider *et al*., 1998). In the current trial, a non-inferiority margin was pre-defined as 1.25 points on the ADAS-Cog to preserve 50% of this effect, which was considered the smallest value that could represent a clinically meaningful difference. To determine the power of this study, the assumptions on delta (difference in means) and standard deviation (SD) for the change in ADAS-Cog and ADCS-CGIC from baseline were based on 24 week data from the rivastigmine capsule studies that used the ADAS-Cog and CIBIC-plus. The ADCS-CGIC scale is comparable to the CIBIC-plus, which was used in previous rivastigmine capsule studies. To ensure that the study had adequate power, 1,040 evaluable patients were needed. In order to reach an overall power of 80% for all of the first three hypotheses (which is defined as the product of the individual powers), the sample size was 260 patients per treatment group. As a result, a total sample size of 1,040 patients with at least one post-baseline efficacy assessment on treatment was calculated.

Patients who had at least one dose of study medication, and at least one safety evaluation post-baseline, were considered for safety analysis (the 'safety population'). The main efficacy analysis was based on the ITT population using a Last Observation Carried Forward (LOCF) imputation. This ITT-LOCF population was pre-defined as all

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randomized patients who received at least one dose of study medication and had at least a pre- and post-baseline assessment for one of the primary efficacy variables on treatment (i.e. not more than 2 days after the last known date of study drug). Additional supportive analyses were included to confirm whether imputations and early discontinuations influenced the results. Among others, these included the ITT population without imputation (observed case, ITT-OC), the ITT-Retrieved Drop Out (ITT-RDO) population (all randomized patients who received at least one dose of study medication and had at least a pre- and post-baseline assessment for one of the primary efficacy variables, either under treatment or not), and a population that included all randomized patients.

Statistical analyses were performed using SAS software (Version 8). Changes from baseline on ADAS-Cog were assessed by analysis of covariance (ANCOVA), with baseline values as covariates and treatment groups and countries as factors. The main ADCS-CGIC analysis was the treatment comparison based on a stratified Wilcoxon rank sum test using country as a blocking factor. Robustness analyses using a proportional odds model were prospectively planned. Changes from baseline on secondary efficacy variables were analyzed using an ANCOVA model with treatment, country, and the corresponding baseline measurement as covariates, or a Cochran-Mantel-Haenszel (CMH) test. No interim analyses were performed.

Further, a prospective categorical analysis was conducted to determine percentages of patients demonstrating clinically significant improvements on the ADAS-Cog (defined as $\geq$4 point improvement over baseline at 24 weeks); a CMH test blocking for country was performed to compare treatment groups.

RESULTS

Study population

The first patient was screened in November 2003 and the last patient completed the study in January 2006. Of 1195 patients who were randomized, 1,190 received study drug. The safety population comprised 1,190 patients. The ITT-LOCF population comprised 1,053 patients. In total, 970 patients (81.2%) completed the study (Figure 1). Baseline demographic and background characteristics are summarized in

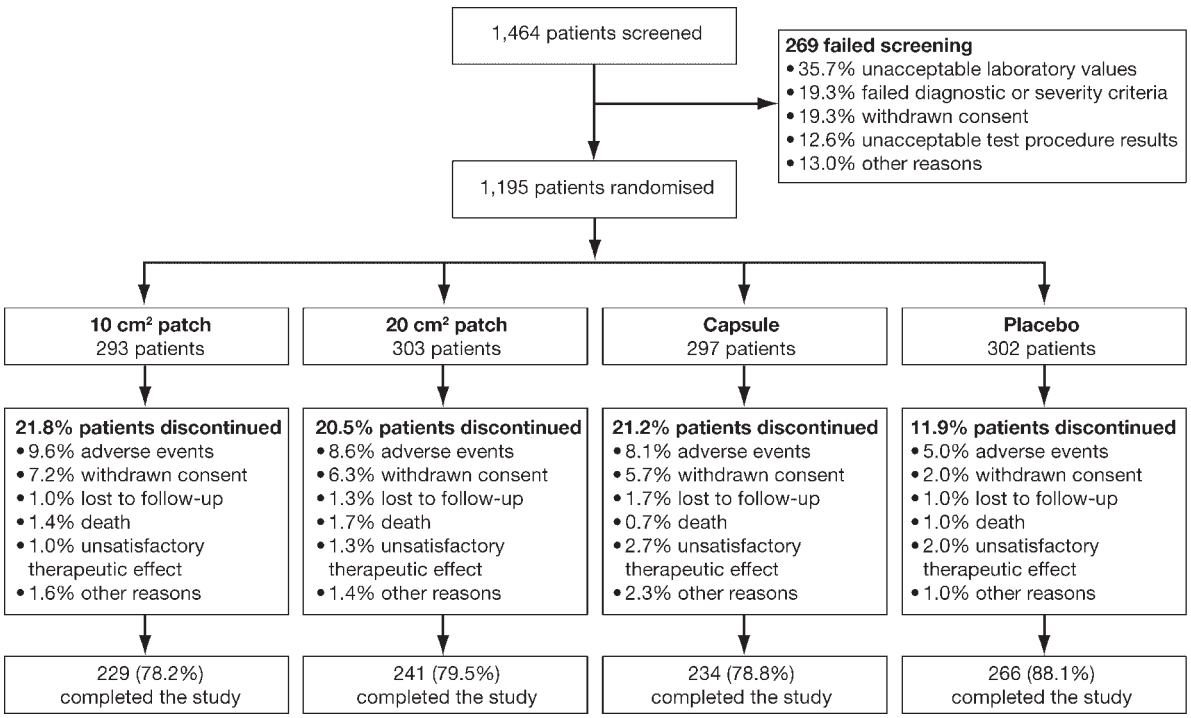

Figure 1. Study profile

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Table 1. Baseline characteristics and demographics of patients (safety population)

	Treatment group			
	Rivastigmine			Placebo ($n = 302$)
	10 cm^2 patch ($n = 291$)	20 cm^2 patch ($n = 303$)	Capsules ($n = 294$)	
Age, years				
Mean (SD)	73.6 (7.9)	74.2 (7.7)	72.8 (8.2)	73.9 (7.3)
Gender, %				
Male: Female	32.0: 68.0	34.0: 66.0	34.4: 65.6	33.4: 66.6
Ethnic origin, *n* (%)*				
Caucasian	220 (75.6)	227 (74.9)	219 (74.5)	227 (75.2)
Black	1 (0.3)	3 (1.0)	5 (1.7)	2 (0.7)
Oriental	25 (8.6)	27 (8.9)	29 (9.9)	27 (8.9)
Other	45 (15.5)	46 (15.2)	41 (13.9)	46 (15.2)
Years of formal education, years,				
Mean (SD)	9.9 (4.3)	9.9 (4.4)	9.9 (4.4)	9.9 (4.3)
Alzheimer's disease duration, years**				
Mean (SD)	1.1 (1.4)	1.1 (1.4)	1.1 (1.4)	1.1 (1.4)
Living situation, *n* (%)				
Alone	43 (14.8)	30 (9.9)	35 (11.9)	27 (8.9)
With caregiver	240 (82.5)	265 (87.5)	255 (86.7)	264 (87.4)
Assisted living	8 (2.7)	8 (2.6)	4 (1.4)	11 (3.6)
Baseline MMSE				
Mean (SD) scores	16.6 (3.1)	16.6 (2.9)	16.4 (3.1)	16.4 (3.0)

*Collected on the case report form using categories 'Caucasian', 'Black', 'Oriental', or 'Other'.
**Time since first diagnosis by a physician.

Table 1; no significant differences were observed between the four groups at baseline. The majority of patients were Caucasians, with a minority belonging to other ethnic groups; safety and efficacy analyses were performed on the full population comprising all ethnic groups.

Efficacy

At the end of the study, the mean (SD) dose of rivastigmine capsules taken by patients in the capsule group in Weeks 20–24 was 9.7 (3.4) mg/day. Mean (SD) patch sizes applied to patients in the 10 cm^2 and 20 cm^2 patch groups at the end of the study were 9.8 (1.0) cm^2 and 16.5 (5.3) cm^2, respectively. In the 20 cm^2 group, at the end of the titration and maintenance periods, about 61% and 62% of patients, respectively, reached the target patch size of 20 cm^2.

The results of the hierarchical statistical analysis are shown in Table 2.

Patients receiving rivastigmine patches or capsules showed significant benefits compared with placebo at Week 24 on the ADAS-Cog (ITT-LOCF; $p < 0.05$ *vs* placebo for all rivastigmine groups) (Table 3,

Table 2. Results of the hierarchical statistical analysis (ITT-LOCF)

Hypothesis	*p*-value
1) On the ADAS-Cog and ADCS-CGIC, the rivastigmine 20 cm^2 patch would show superiority over placebo	ADAS-Cog: <0.001 ADCS-CGIC: 0.054
2) On the ADAS-Cog, the rivastigmine 20 cm^2 patch would show non-inferiority to 12 mg/day rivastigmine capsules	CI: −2.06, 0.17*
3) On the ADAS-Cog and ADCS-CGIC, the rivastigmine 10 cm^2 patch would show superiority over placebo	ADAS-Cog: 0.005 ADCS-CGIC: 0.01
4) On the ADCS-ADL, the rivastigmine 20 cm^2 patch would show superiority over placebo	ADCS-ADL: 0.02

*Non-inferiority established, as the 95% Confidence Interval (CI) for the difference between treatment groups was entirely below the corresponding predefined non-inferiority margin of 1.25.

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Table 3. Mean efficacy scores at baseline and changes from baseline at Week 24 (ITT-LOCF patients with valid baseline and Week-24 scores)

	Mean (SD) baseline scores	Mean (SD) changes at Week 24	24-week difference (*p*-value*)
Primary efficacy variables			
ADAS-Cog scores			
Rivastigmine 10 cm^2 patch ($n = 248$)	27.0 (10.3)	−0.6 (6.4)	0.005
Rivastigmine 20 cm^2 patch ($n = 262$)	27.4 (9.7)	−1.6 (6.5)	<0.001
Rivastigmine 3–12 mg capsule ($n = 253$)	27.9 (9.4)	−0.6 (6.2)	0.003
Placebo ($n = 281$)	28.6 (9.9)	1.0 (6.8)	
ADCS-CGIC scores			
Rivastigmine 10 cm^2 patch ($n = 248$)	—	3.9 (1.2)	0.01
Rivastigmine 20 cm^2 patch ($n = 260$)	—	4.0 (1.3)	0.054
Rivastigmine 3–12 mg capsule ($n = 253$)	—	3.9 (1.3)	0.009
Placebo ($n = 278$)	—	4.2 (1.3)	
Secondary efficacy variables			
ADCS-ADL scores			
Rivastigmine 10 cm^2 patch ($n = 247$)	50.1 (16.3)	−0.1 (9.1)	0.01
Rivastigmine 20 cm^2 patch ($n = 263$)	47.6 (15.7)	0.0 (11.6)	0.02
Rivastigmine 3–12 mg capsule ($n = 254$)	49.3 (15.8)	−0.5 (9.5)	0.04
Placebo ($n = 281$)	49.2 (16.0)	−2.3 (9.4)	
NPI-12 scores			
Rivastigmine 10 cm^2 patch ($n = 248$)	13.9 (14.1)	−1.7 (11.5)	0.74
Rivastigmine 20 cm^2 patch ($n = 263$)	15.1 (13.4)	−2.3 (13.3)	0.69
Rivastigmine 3–12 mg capsule ($n = 253$)	15.1 (14.1)	−2.2 (11.9)	0.51
Placebo ($n = 281$)	14.9 (15.7)	−1.7 (13.8)	
NPI-Distress scores			
Rivastigmine 10 cm^2 patch ($n = 248$)	7.4 (7.1)	−1.0 (5.5)	0.37
Rivastigmine 20 cm^2 patch ($n = 263$)	8.4 (7.6)	−1.1 (6.4)	0.98
Rivastigmine 3–12 mg capsule ($n = 253$)	8.2 (7.6)	−1.1 (6.6)	0.12
Placebo ($n = 281$)	7.8 (7.7)	−1.1 (6.3)	
MMSE scores			
Rivastigmine 10 cm^2 patch ($n = 250$)	16.7 (3.0)	1.1 (3.3)	0.002
Rivastigmine 20 cm^2 patch ($n = 262$)	16.6 (2.9)	0.9 (3.4)	<0.001
Rivastigmine 3–12 mg capsule ($n = 256$)	16.4 (3.0)	0.8 (3.2)	0.002
Placebo ($n = 281$)	16.4 (3.0)	0.0 (3.5)	
Ten-point Clock-Drawing scores			
Rivastigmine 20 cm^2 patch ($n = 251$)	4.5 (3.6)	0.1 (3.1)	0.08
Rivastigmine 10 cm^2 patch ($n = 245$)	4.7 (3.8)	0.3 (3.4)	0.08
Rivastigmine 3–12 mg capsule ($n = 246$)	4.4 (3.6)	0.2 (2.9)	0.15
Placebo ($n = 269$)	4.3 (3.6)	−0.1 (3.2)	
Trail-making Test A scores			
Rivastigmine 10 cm^2 patch ($n = 241$)	183.3 (85.5)	−12.3 (55.1)	<0.001
Rivastigmine 20 cm^2 patch ($n = 238$)	176.5 (84.0)	−6.5 (55.9)	0.005
Rivastigmine 3–12 mg capsule ($n = 240$)	177.2 (86.2)	−9.8 (66.1)	<0.001
Placebo ($n = 258$)	178.3 (85.6)	7.7 (56.6)	

Negative change scores on ADAS-Cog, NPI and Trail-making Test A indicate improvement.
Negative change scores on ADCS-ADL, MMSE and Ten-point Clock-drawing indicate deterioration.
There are no baseline scores for the ADCS-CGIC because this is scored as a judgment of change and at baseline there was no comparison on which to base a judgment.
For ADAS-Cog, ADCS-ADL, NPI and Trail-making Test A, descriptive mean scores and changes from baseline are shown but *p*-values are derived from two-way ANCOVA (explanatory variables: treatment, country, and the baseline scores), and are based on least square means comparisons of each rivastigmine group *versus* placebo.
p-values for ADCS-CGIC, MMSE and Ten-point Clock-Drawing are derived from the CMH van Elteren test using modified ridit scores with country as the stratification variable, and are based on comparisons of each rivastigmine group *versus* placebo.

Figure 2). The 20 cm^2 rivastigmine patch showed non-inferiority to the capsule. Comparison between the 10 cm^2 patch and the capsule revealed non-inferiority. At Week 24, 27.4%, 32.8% and 28.5% of patients in the 10 cm^2 and 20 cm^2 patch groups and the capsule group, respectively, showed at least a four-point improvement over baseline on the ADAS-Cog, compared with 19.9% of patients in the placebo

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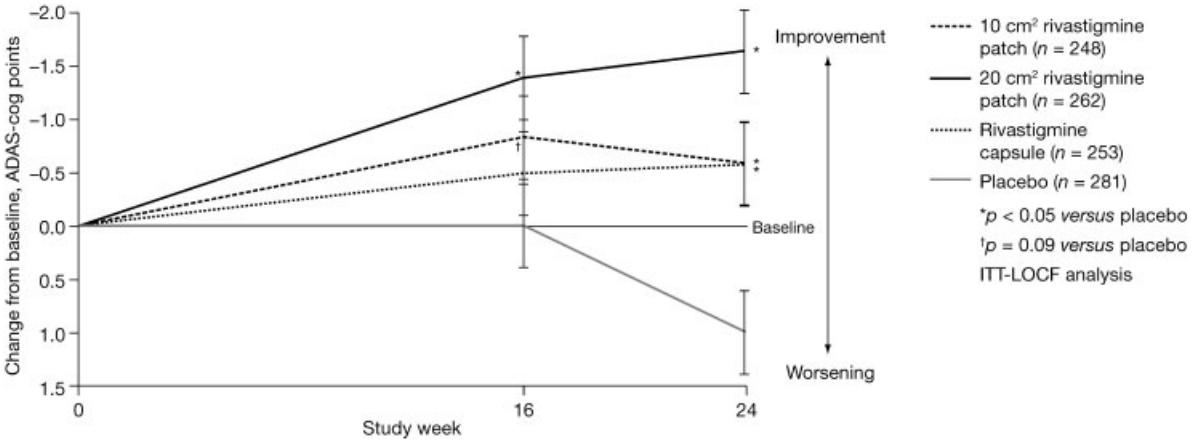

Figure 2. Mean (SEM) changes from baseline on the ADAS-Cog at 24 weeks (ITT-LOCF population)

group (ITT-LOCF; all $p < 0.05$ *vs* placebo). Results were similar in the ITT-RDO and OC populations.

Treatment differences on the ADCS-CGIC were statistically significant for the $10\,cm^2$ patch and capsule groups (ITT-LOCF; all $p < 0.05$ *vs* placebo) (Table 3, Figure 3). The $20\,cm^2$ patch did not achieve statistical significance *vs* placebo in the ITT-LOCF analysis (ITT-LOCF; $p = 0.054$). However, analyses in OC and ITT-RDO populations were statistically significant (both $p < 0.05$ for all rivastigmine groups *vs* placebo). The predefined proportional odds model also yielded statistically significant results across all three analysis populations ($p < 0.04$). Table 4 shows the ITT-LOCF categorical analysis of the change from baseline on the ADCS-CGIC. Results were similar in the ITT-RDO and OC populations.

Results for the secondary efficacy variables are shown in Table 3. Rivastigmine patches and capsule provided statistically significant benefits over placebo on the ADCS-ADL (Figure 4), MMSE and Trail-making Test A (ITT-LOCF; all $p < 0.05$ *vs* placebo). Changes from baseline on the NPI, NPI-distress subscale, and Ten-point Clock-drawing Test in the rivastigmine groups were not significantly different from those in the placebo group (Table 3).

Tolerability and safety

There were no statistically significant differences between the $10\,cm^2$ rivastigmine patch and placebo groups with respect to the incidence of adverse events. Overall AE rates in the $20\,cm^2$ rivastigmine patch and

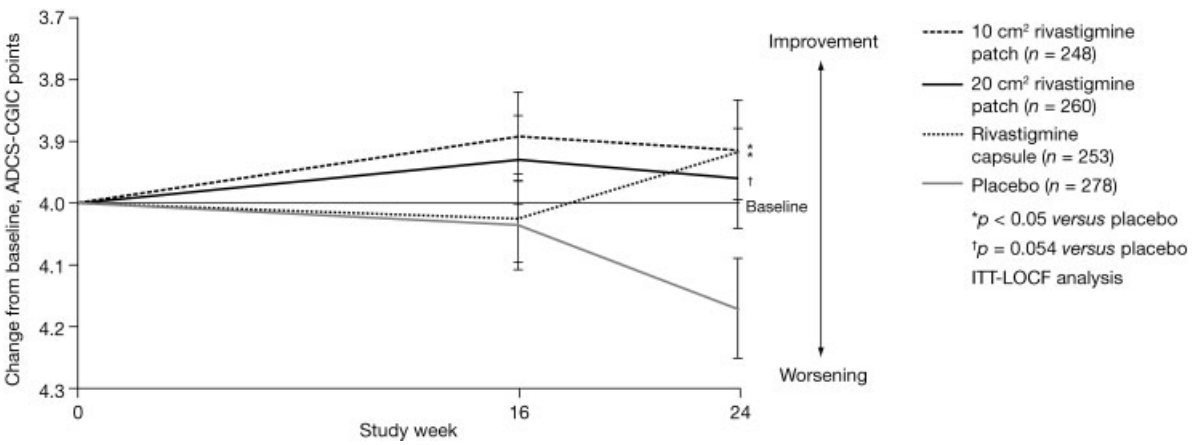

Figure 3. Mean (SEM) changes from baseline on the ADCS-CGIC at 24 weeks (ITT-LOCF population)

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Table 4. Categorical analysis change from baseline on the ADCS-CGIC at Week 24 (ITT-LOCF population)

ADCS-CGIC response	Rivastigmine 10 cm^2 patch ($n = 248$)	Rivastigmine 20 cm^2 patch ($n = 260$)	Rivastigmine 3–12 mg capsule ($n = 253$)	Placebo ($n = 278$)
Markedly improved, *n* (%)	5 (2%)	5 (2%)	3 (1%)	2 (1%)
Moderately improved, *n* (%)	29 (12%)	32 (12%)	29 (12%)	26 (9%)
Minimally improved, *n* (%)	43 (17%)	48 (19%)	60 (24%)	50 (18%)
Unchanged, *n* (%)	105 (42%)	94 (36%)	96 (38%)	91 (33%)
Minimally worse, *n* (%)	41 (17%)	50 (19%)	30 (12%)	65 (23%)
Moderately worse, *n* (%)	22 (9%)	27 (10%)	30 (12%)	36 (13%)
Markedly worse, *n* (%)	3 (1%)	4 (2%)	5 (2%)	8 (3%)

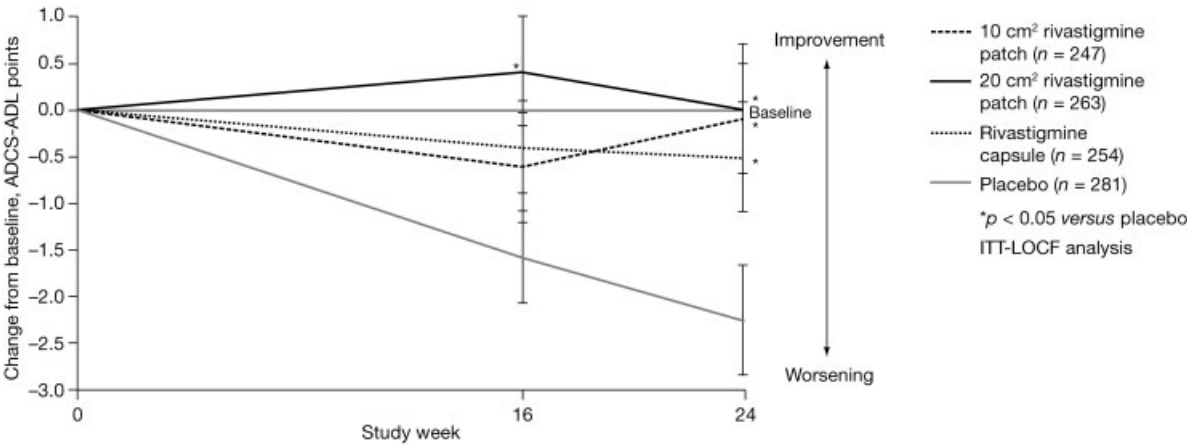

Figure 4. Mean (SEM) changes from baseline on the ADCS-ADL at 24 weeks (ITT-LOCF population)

capsule groups were generally higher than in the placebo group (Table 5). The most frequent AEs were nausea and vomiting (Table 5). Most AEs were mild or moderate. The occurrences of serious AEs (SAEs) were 8%, 12%, 7% and 9% in the 10 cm^2 patch, 20 cm^2 patch, capsule and placebo groups, respectively. Adverse events led to early discontinuations in 11% in the 10 cm^2 patch group, 10% of patients in the 20 cm^2 patch group, 9% in the capsule group, and 6% in the placebo group. The most common adverse

Table 5. Most frequently reported adverse events[†] (safety population)

Adverse event	10 cm^2 patch ($n = 291$)	20 cm^2 patch ($n = 303$)	Capsules ($n = 294$)	Placebo ($n = 302$)
Any adverse event	147 (51%)	200 (66%)***	186 (63%)***	139 (46%)
Nausea	21 (7%)	64 (21%)***	68 (23%)***	15 (5%)
Vomiting	18 (6%)	57 (19%)***	50 (17%)***	10 (3%)
Diarrhea	18 (6%)	31 (10%)***	16 (5%)	10 (3%)
Weight decreased	8 (3%)	23 (8%)***	16 (5%)**	4 (1%)
Dizziness	7 (2%)	21 (7%)*	22 (8%)**	7 (2%)
Decreased appetite	2 (1%)	15 (5%)**	12 (4%)*	3 (1%)
Headache	10 (3%)	13 (4%)	18 (6%)**	5 (2%)
Asthenia	5 (2%)	9 (3%)	17 (6%)***	3 (1%)

[†]Adverse events occurring in at least 5% of the patients in either group are reported.
*$p \leq 0.05$ *vs* placebo; **$p \leq 0.01$ *vs* placebo; ***$p \leq 0.001$ *vs* placebo.

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events leading to early discontinuation were gastrointestinal disorders (1%, 3%, 4% and 1%, respectively) and nervous system disorders (3%, 3%, 3% and 1%).

No unexpected safety issues emerged. Five, five, two and four deaths occurred during the study period or in the 30-day follow-up in the 10 cm^2 rivastigmine patch, 20 cm^2 rivastigmine patch, rivastigmine capsule and placebo groups, respectively. Causes of death were as expected for an elderly population with AD, most commonly cardiac disorders (cardiac failure, congestive cardiac failure) and nervous system disorders (stroke). None were considered treatment-related. Two of the deaths occurred in the 30-day follow-up period after study drug discontinuation: one in the 10 cm^2 patch group and one in the placebo group.

There were no clinically significant changes from baseline in sitting or standing pulse rate, systolic or diastolic blood pressure, or in electrocardiogram recordings. Effects on body weight at the end of the study appeared to be dose-related, with the fewest reports of weight decreases reported in the 10 cm^2 patch (8%) and placebo (6%) groups. Weight loss was most frequently reported in the 20 cm^2 patch group (12%).

Skin tolerability of the rivastigmine patch was good. According to investigator assessments, the proportions of patients who experienced no, slight or mild skin irritation ranged from 90% to 98% across the four patch sizes (5, 10, 15 and 20 cm^2). The symptoms that were most frequently assessed as moderate or severe intensity were erythema (rivastigmine patch: 8%, placebo patch: 4%) and pruritus (rivastigmine patch: 7%, placebo patch: 3%). The percentages of patients who discontinued as a result of skin irritation were 2%, 2%, 1% and 0% in the 10 cm^2 rivastigmine patch, 20 cm^2 rivastigmine patch, rivastigmine capsule and placebo groups, respectively. Similar results were obtained from caregiver assessments of skin tolerability.

Skin adhesion

Most patches remained adherent to the body over the 24-h application period. Of 1,336 evaluations of the rivastigmine 10 cm^2 patch size, 96% remained completely attached or had the 'edges just lifting off' after 24 h, and the patch was described as 'mostly half off', 'just hanging on' or 'completely detached' in 4% of cases. Of 1,359 evaluations of the placebo 10 cm^2 patch size, respective attachment rates were 99% and 1%. Of 334 evaluations of the rivastigmine 20 cm^2 patch size, 94% remained completely attached or had the 'edges just lifting off', and 6% were described as 'mostly half off', 'just hanging on' or 'completely detached'. Of 1,359 evaluations of the placebo 20 cm^2 patch size, respective attachment rates were 99% and 1%, respectively.

DISCUSSION

In this study, the rivastigmine patch demonstrated superior efficacy over placebo in the treatment of AD. The efficacy of the rivastigmine 10 cm^2 patch was similar to that of the rivastigmine capsule, and showed statistically significant superiority over placebo on both primary efficacy assessments, as well as on secondary assessments of ability to perform activities of daily living, cognitive performance, attention, visual tracking and motor processing speed. Mean improvements on the ADAS-Cog were numerically higher in the 20 cm^2 patch group, compared with the 10 cm^2 patch group at Week 24.

The 20 cm^2 patch achieved statistically significant superiority over placebo in all pre-defined analysis populations and analysis methods except the ITT-LOCF analysis on the ADCS-CGIC. It is not known why the 20 cm^2 patch did not reach statistical significance in this analysis. One possible explanation may be that adverse events reported in these patients might have influenced their overall well-being, thus affecting a global clinical assessment of their condition. Nevertheless, the finding suggests that further research may be required to determine which subjects might benefit from titrating to a larger patch size beyond the target dose of 10 cm^2.

Statistically significant effects *vs* placebo were reported in all three rivastigmine groups on the ADCS-ADL. Similarly, all rivastigmine groups provided significant treatment differences *vs* placebo on the Trail-making Test A, indicating that rivastigmine improves attention in patients with AD. Emerging data provide new insights into the way the cholinesterase inhibitors might be working in the brains of demented patients, and how individual agents may affect different brain regions. In addition to enhanced neurotransmission in cholinergic neurons, acetylcholinesterase (AChE)-positive neurons in thalamic nuclei project diffusely to the cortex, modulating cortical processing and responses to new and relevant stimuli, while butyrylcholinesterase (BuChE)-positive neurons are found in thalamic nuclei that project specifically to the frontal cortex, and may have roles in attention (Darvesh & Hopkins, 2003). Rivastigmine is the only commonly used

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cholinesterase inhibitor that inhibits both AChE and BuChE, and this may explain its effects on attention. Importantly, beneficial effects on attention may have a secondary impact on other key symptom domains of AD, including cognitive performance and daily function. There were no statistically significant differences *versus* placebo on the NPI and Ten-point Clock-drawing.

The four hypotheses were tested in sequence, and if any of the four tests failed to show statistical significance, testing of subsequent hypotheses was to be stopped in order to control the type 1 error. The first hypothesis required the 20 cm^2 rivastigmine patch to show superiority over placebo on the ADAS-Cog and ADCS-CGIC, and the treatment difference on the ADCS-CGIC marginally missed statistical significance ($p = 0.054$). However, analyses in OC and ITT-RDO populations were statistically significant and the predefined proportional odds model also yielded statistically significant results across all three analysis populations. The effectiveness shown consistently by all pre-defined robustness analyses was considered sufficient to continue the hierarchical testing procedure, controlling the familywise error rate at a level of 0.054.

The adverse event profile was compatible with cholinergic stimulation. Acute cholinergic side effects, such as nausea and vomiting, have been associated with high maximum plasma concentrations (C_{max}) and short times to C_{max} (t_{max}) following oral administration (Jann *et al*., 2002). Transdermal administration prolongs t_{max} and lowers C_{max} for equivalent exposure. Furthermore, transdermal delivery reduces fluctuations of plasma drug levels and allows more continuous drug delivery over a 24-h period. Consistent with these observations, the side effect profile of the 10 cm^2 patch was much improved, compared with the capsule. Most patients in the rivastigmine 10 cm^2 patch group reached their target patch size, as demonstrated by a mean patch size of 9.8 cm^2 at the end of the study. Modeling of pharmacokinetic data collected in AD patients that accounted for inter-patient variability indicated that a 10 cm^2 patch produces average drug plasma concentrations provided by an oral dose of 12 mg/day (data on file, Novartis Pharma AG). Thus, these patients were receiving the equivalent of the highest recommended oral daily dose of rivastigmine, while experiencing relatively few side effects.

Individual responses to rivastigmine may vary and some patients may derive additional benefit from higher doses. In such cases, up-titration to the 15 cm^2 patch and then the 20 cm^2 patch may be made, although this should always be based on good tolerability of the current dose and should be considered only after a minimum of 4 weeks of treatment at previous dose levels. However, in the overall patient population there is little evidence of incremental efficacy benefit at higher doses and the tolerability benefit *versus* capsules is lost. Therefore, based on available efficacy and tolerability data, the recommended maintenance dose is the 10 cm^2 rivastigmine patch.

Effect sizes reported in this study with rivastigmine capsules or patches were more modest than those reported previously. For example, treatment differences as high as 4.9 on the ADAS-Cog were reported with rivastigmine capsules in early studies (Corey-Bloom *et al*., 1998). However, it is likely that the profile of patients entering clinical trials has changed since the late 1990s. For example, patients showing a particularly aggressive course of dementia and who have an urgent need for treatment may be less likely to enter placebo-controlled trials, now that approved drugs are available to treat them. Since it is thought that treatment effects on cholinesterase inhibitors are largely driven by placebo decline (Gauthier *et al*., 2006), it is feasible that patients entering more recent trials show less marked treatment effects due to slower placebo decline, compared with patients entering early studies.

The adverse events of cholinesterase inhibitors are well known and can usually be managed by clinicians by halting dose titration or decreasing the dose. This may explain why drop-outs due to adverse events were similar across treatment groups despite tolerability differences. In addition, although withdrawals due to gastrointestinal AEs were less frequent in the 10 cm^2 patch group than in the capsule group, there were very small (thought to be random) increases in other AEs leading to withdrawal (e.g. minimally greater withdrawal rate due to general disorders such as renal failure, asthenia or malaise in the 10 cm^2 patch group), and subsequently there was no overall difference between the rivastigmine groups.

The rivastigmine patch demonstrated good skin tolerability as well as good adhesion. This is particularly relevant when considering that this study was conducted in countries with a range of climates, including some that are hot and humid (e.g. Guatemala, Venezuela). Moreover, patients were allowed to bathe and perform normal activities while wearing the patches. The study gave no indication that patch use may interfere with normal daily activities.

As with any clinical study, there are some limitations for the extrapolation of the results to the

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AD population in general (Schneider, 2004). The dropout rate for the total current study population was approximately 19%, and the failure to obtain information at the final visit for some of the patients who discontinued the study prematurely may limit the interpretation of these results. Nevertheless, consistent results from other analysis populations as well as additional analyses on the impact of using LOCF to impute for missing data imply that attrition rate did not affect the interpretation of study outcomes. The patients taking part in this study were carefully selected, and their dementia profile was compatible with that typically seen in AD, as described in the criteria of both the DSM-IV (APA, 1994) and NINCDS/ADRDA (McKhann *et al*., 1984). A range of concomitant medications were permitted, as were various co-morbidities, to optimise applicability of the results to the clinical setting as far as possible.

The rivastigmine patch provided benefits across a range of symptoms and was well tolerated. The 10 cm^2 patch delivered equivalent efficacy to flexible titration to 12 mg/day capsules with improved tolerability. Both formulations were superior to placebo. The rivastigmine patch was associated with a low level of skin irritation and adhesion was good. The transdermal patch with rivastigmine may offer therapeutic benefits and may prove to be an optimal way to deliver this drug to treat AD.

DISCLOSURES

Study supported by Novartis Pharma AG, Basel, Switzerland. Data were collected by investigators and co-investigators, entered into a central database using electronic data capture software, and analyzed by Novartis Pharma AG, which vouches for the data and the analysis.

SZ, JN and RL are employees of Novartis. Remaining authors were investigators (BW, NA, GG, MO, CS) and/or Study Publication Committee members (BW, JC, NA, GG, MO, SZ, JN, RL). BW, JC, NA, GG, MO and CS have provided consultation services to many pharmaceutical companies that develop dementia drugs, including Novartis. A writing committee prepared an initial draft of the manuscript, based on a report provided by Novartis, and all authors contributed to its finalization through interactive review. Editorial assistance was provided by Sarah Clow; this assistance was funded by Novartis Pharma AG.

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