EXTRA Dementia and Geriatric Cognitive Disorders

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Original Research Article

A 24-Week, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety and Tolerability of the Rivastigmine Patch in Japanese Patients with Alzheimer's Disease

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Key Words
Alzheimer's disease · Cholinesterase inhibitors · Japanese · Randomized clinical trial · Rivastigmine

Abstract
Background: As of 2010, the rivastigmine patch was licensed for the treatment of Alzheimer's disease (AD) in 64 countries. ***Methods:*** This 24-week, multicenter, randomized, double-blind, placebo-controlled study evaluated the efficacy, safety and tolerability of the 5-cm^2 (9-mg loading dose; 4.6 mg/24 h delivery rate) and 10-cm^2 (18-mg loading dose; 9.5 mg/24 h delivery rate) rivastigmine patch in Japanese patients with AD. ***Results:*** In the primary analysis population (intent-to-treat last observation carried forward) at week 24, delayed deterioration was seen with the 10-cm^2 patch versus placebo on the Japanese version of the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-J cog; $p = 0.005$) and the Japanese version of the Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC plus-J; $p = 0.067$). Participants receiving the rivastigmine patch showed numerically less decline versus placebo at week 24 on the CIBIC plus-J, although this did not reach statistical significance. Statistical significance for the CIBIC plus-J was met following adjustment for body weight and baseline Mini-Mental State Examination score as dynamic allocation factors ($p = 0.042$) and on the Disability

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Assessment for Dementia (DAD; p = 0.024) and Mental Function Impairment (MENFIS; p = 0.016) subscales. Serious adverse events were rare and were consistent with the known safety profile of the rivastigmine patch. ***Conclusion:*** The rivastigmine patch has a favorable efficacy and tolerability profile in Japanese patients with AD.

Introduction

There were an estimated 35.6 million people worldwide living with dementia in 2010, with numbers projected to nearly double every 20 years to 115.4 million persons in 2050 [1]. There were 1.8 million patients living with dementia in Japan in 2005, with a total cost of 34 billion USD [2]. Alzheimer's disease (AD) is the main cause of dementia and one of the most burdensome conditions of later life [3]. A 2009 prospective study of the general Japanese population aged 65 years or over reported that Japanese elderly are at high risk of developing dementia, with an AD incidence of 14.6 cases per 1,000 person-years [4].

The primary treatment option for AD is the cholinesterase inhibitor drug class, which act by inhibiting cholinesterases, the enzymes responsible for degrading acetylcholine in the synaptic cleft [5]. Globally, rivastigmine, donepezil and galantamine are widely used to treat patients with mild-to-moderate AD [5]. As of the end of 2010, the rivastigmine transdermal formulation had been licensed for the treatment of patients with mild-to-moderate AD in 64 countries worldwide, including those in the EU and the USA. However, at that time, donepezil was the only approved drug for the treatment of patients with AD in Japan.

Nausea and vomiting may be lessened by transdermal treatment due to reduced magnitude of peak plasma concentration (C_{max}) and slower rate of rise in the plasma concentration (t_{max}) [6–8]. In a multinational, double-blind, randomized, placebo-controlled study of rivastigmine patch versus capsule (IDEAL) [8], statistically significant differences versus placebo were seen for the 10-cm^2 (18-mg loading dose; 9.5 mg/24 h delivery rate) rivastigmine patch and 12 mg/day capsule on the primary efficacy outcomes: AD Assessment Scale-cognitive subscale (ADAS-cog) [9] and AD Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) [8, 10]. The 10-cm^2 rivastigmine patch demonstrated similar efficacy to the highest dose of the rivastigmine capsule (12 mg/day) and a superior tolerability profile [8].

The pharmacokinetic and pharmacodynamic profile of rivastigmine patch has been shown to be similar in healthy Japanese and Caucasian individuals [11]. However, drug exposure was slightly higher and cholinesterase inhibition slightly more pronounced in Japanese participants than Caucasians. This was attributed to the lower body weight (approximately 11% less on average) of Japanese participants. As a consequence, lower doses [e.g. the 5-cm^2 rivastigmine patch (9-mg loading dose; 4.6 mg/24 h delivery rate)] may offer efficacy.

The current study was designed to evaluate the efficacy, safety and tolerability of the 5-cm^2 (9-mg loading dose; 4.6 mg/24 h delivery rate) and 10-cm^2 (18-mg loading dose; 9.5 mg/24 h delivery rate) rivastigmine patch in Japanese patients with AD.

Methods

Trial Design

This was a 24-week, multicenter, randomized, double-blind, three-arm, placebo-controlled, parallel-group, dose-finding study (ClinicalTrials.gov Identifier: NCT00423085). Following assessments for eligibility during a 4-week screening period, participants were

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randomly assigned to one of three groups of equal size: the 5-cm^2 rivastigmine patch (9-mg loading dose; 4.6 mg/24 h delivery rate), the 10-cm^2 (18-mg loading dose; 9.5 mg/24 h delivery rate) rivastigmine patch or placebo.

Participants

The participants that met the inclusion criteria at randomization were 50- to 85-year-old male and female outpatients, not of child-bearing potential, had a diagnosis of dementia of the Alzheimer's type according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) criteria, 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) [12]. Participants required a Mini-Mental State Examination (MMSE) [13] score of $\geq$10 and $\leq$20 and sufficient education to read, write and communicate effectively during the premorbid state. They were required to be willing to cooperate and complete all aspects of the study and be capable of doing so, either alone or with the aid of a responsible caregiver. The participant was required to be residing with a caregiver throughout the study or, if living alone, in contact with the primary caregiver every day. The caregiver was required to be the primary caregiver and to be willing to accept responsibility for supervising the treatment, assessing the condition of the patient throughout the study and for providing input to efficacy assessments according to protocol requirements. The caregiver had to directly assess the condition of the patient during the day and night of 4 days or more per week.

Exclusion criteria at the time of randomization included any neurological or medical condition other than AD that could explain the participant's dementia, or an advanced, progressive or unstable disease that could interfere with study assessments or put the participant at special risk (e.g. vascular dementia, major depression, severe cerebrovascular disease or severe cardiovascular disease). Other exclusion criteria included the use of rivastigmine in the past, or the use of donepezil, other cholinesterase inhibitors, approved treatments for AD or centrally acting anticholinergic drugs during the 4 weeks prior to efficacy assessments at baseline.

Informed consent was obtained and the clinical study was designed, implemented and reported in accordance with applicable local regulations and with the ethical principles laid down in the Declaration of Helsinki.

Interventions

Participants were titrated to their target patch dose at 4-week intervals over 16 weeks, followed by an 8-week maintenance period through weeks 17–24 (table 1). Four patch sizes were used in this study: 2.5-cm^2 (4.5-mg loading dose), 5-cm^2 (9-mg loading dose; 4.6 mg/24 h delivery rate), 7.5-cm^2 (13.5-mg loading dose) and 10-cm^2 (18-mg loading dose; 9.5 mg/24 h delivery rate). Participants in the rivastigmine treatment groups were titrated in 2.5-cm^2 steps from a starting patch size of 2.5 cm^2 to their target patch size of 5 or 10 cm^2. If the target dose was not reached during the titration period, the investigator could resume titration during the maintenance period. Dose adjustments and interruptions were permitted to allow the patient to continue on the study drug if any safety or tolerability aspects relating to the protocol-specified dosing schedule arose. The participants were maintained at their highest well-tolerated dose until the end of the study (week 24). The study drug was discontinued for a given patient if the investigator determined that continuing it would result in a significant safety risk for that patient.

Outcomes

Primary efficacy assessments were made at screening [Japanese version of ADAS-cog (ADAS-J cog) only], baseline (ADAS-J cog only), and weeks 8, 16 and 24. Primary efficacy

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Table 1. Study design and interventions

Treatment group	Loading dose	Delivery rate	Double-blind treatment phase				
			titration				maintenance
			W1–4	W5–8	W9–12[a]	W13–16[b]	W17–24
Rivastigmine							
10 cm^2	18 mg	9.5 mg/24 h	2.5 cm^2	5 cm^2	7.5 cm^2	10 cm^2	10 cm^2
5 cm^2	9 mg	4.6 mg/24 h	2.5 cm^2	5 cm^2	5 cm^2	5 cm^2	5 cm^2
Placebo			control patients maintained on equivalent placebo patch size				

[a] 5-/2.5- and [b] 7.5-/2.5-cm^2 patch size permitted for dose adjustment of decreased dose. W = Week.

assessments were the ADAS-J cog [14] and the Japanese version of the Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC plus-J) [15].

Primarily used to evaluate cognitive function in AD patients, ADAS-cog is the most popular cognitive assessment instrument used in AD clinical trials all over the world. Test scores range from 0 (best) to 70 (worst), and when performed multiple times on an ongoing basis, the change in the overall score can be used to measure the change in cognitive function.

CIBIC plus-J is the Japanese version of the New York University School of Medicine CIBIC plus, a semi-structured interview format including a 7-point CGIC rating scale. It comprises three subscales: Disability Assessment for Dementia (DAD), Behavioral Pathology in AD (BEHAVE-AD) and Mental Function Impairment (MENFIS), discussed further as secondary assessments.

Secondary efficacy assessments were baseline, week-8, -16 and -24 scores on the subscales of the CIBIC plus-J (DAD, BEHAVE-AD and MENFIS) and screening, baseline and week-24 scores on the MMSE [13].

DAD is a 46-item structured interview or questionnaire for the caregiver that is scored from 0 to 100 (least impairment); it evaluates activities of daily living. BEHAVE-AD was designed to assess potentially remediable behavioral symptoms in patients with AD as well as to evaluate treatment outcome. It consists of 22 symptoms grouped into 7 categories. Each symptom is scored by the caregiver on the basis of severity on a 4-point scale. MENFIS evaluates core symptoms of dementia including cognitive, motivational and emotional aspects based on interviews with the patient and information from the caregiver. Total scores range from 0 to 78; the higher the score, the greater the functional deficit.

Exploratory assessments included evaluation for inhibition of plasma butyrylcholinesterase (BuChE) activity, a questionnaire to evaluate caregiver experience of the rivastigmine patch compared with oral medication and scores on the Modified Crichton Scale from baseline to week 24. The Modified Crichton Scale includes a total of 7 items evaluated in 8 grades that assess basic activities of daily living, communication functions, psychiatric symptoms and quality of life [16].

Safety evaluations included recording all adverse events on Adverse Event Case Report Forms. Every serious adverse event occurring after the patient provided informed consent and until 28 days after the patient stopped the study was reported. Medical examination and monitoring, assessment of vital signs, ECG, laboratory assessments and measurement of body weight were conducted at every visit. Skin irritation was assessed by the investigator and the investigator queried the caregiver about impression of skin irritation during patch

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application according to a caregiver's rating scale. A rating of the patch adherence was provided and graded according to a patch adhesion score.

Sample Size

The sample size calculation was based on change from baseline at week 24 on the two primary efficacy variables (ADAS-J cog and CIBIC plus-J). In order for the 5-cm^2 (9-mg loading dose; 4.6 mg/24 h delivery rate) or 10-cm^2 (18-mg loading dose; 9.5 mg/24 h delivery rate) patch to demonstrate efficacy versus placebo, superiority needed to be demonstrated on both efficacy variables. The assumptions on delta (difference in means) and standard deviation (SD) for the change in ADAS-J cog and CIBIC plus-J were based on 24-week data from the IDEAL study [8], which used the ADAS-cog [9] and ADCS-CGIC [10]. For the 10-cm^2 rivastigmine patch to demonstrate superiority over placebo, estimated assumptions on delta (SD) were 3.1 (6.5) points for the ADAS-J cog and 0.37 (1.2) points for the CIBIC plus-J. For the 5-cm^2 patch, estimated assumptions were 2.1 (6.5) points on the ADAS-J cog and 0.37 (1.2) points on the CIBIC plus-J. A hierarchical testing procedure was set up according to which the superiority of the 10-cm^2 rivastigmine patch versus placebo was to be shown first, followed by the superiority of the 5-cm^2 patch versus placebo. Each of the two hypotheses was to be tested simultaneously for ADAS-J cog and for CIBIC plus-J. The α level for each test was 5%. Due to the hierarchical procedure with simultaneous testing of ADAS-J cog and CIBIC plus-J, no α correction was required. In order to reach an overall power of at least 76% for the two hypotheses, based on the above assumptions, 232 participants were required per treatment group for a total of 696 patients. Assuming 10% of the patients would not be available for inclusion into the primary analysis population, 774 participants (258/arm) were intended from randomization.

Randomization

On the day of randomization, the investigator confirmed that the first registered patient met all of the inclusion and exclusion criteria. The investigator ensured that all patients who met the inclusion and exclusion criteria were offered enrollment into the study. No additional exclusions were permitted to be applied by the investigator to ensure that the study population was representative of all eligible patients. Eligibility criteria were checked strictly on a rotating basis by a panel of 4 physicians. The Patient Registration Center provided a randomization number to the eligible participants and randomization lists were generated by a Study Drug Allocation Controller. A dynamic allocation was utilized for randomization. Only 2 allocation factors were utilized: body weight (<45, 45 to <55, ≥ 55 kg) and MMSE score (≤ 15 or >15 points).

Blinding

Patients, investigator staff, persons performing the assessments and data analysts were all blinded to the identity of the treatment from the time of randomization. Randomization data were kept strictly confidential by the Study Drug Allocation Controller until the time of unblinding and were not accessible by anyone else involved in the study. Pharmacokinetic and pharmacodynamic data were not reported to the sponsor (except for analytical personnel) and investigator prior to unblinding. Unblinding was only permitted in the case of patient emergencies and at the conclusion of the study.

Statistical Methods

Study participants who had at least 1 dose of study medication and at least 1 safety evaluation post-baseline were considered for safety analysis (the 'safety population'). The main efficacy analysis was based on the intent-to-treat (ITT) population using a last observation

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carried forward (LOCF) imputation. This ITT-LOCF population was pre-defined as all randomized patients who received at least 1 dose of study medication and had at least 1 assessment pre- and post-baseline for 1 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. These included the ITT population without imputation (observed case, ITT-OC), all ITT patients who completed the trial without any major deviations from the protocol procedures (per protocol, PP) and all randomized patients who received at least 1 dose of study drug and had at least 1 assessment at baseline and any 1 post-baseline for 1 of the primary efficacy variables [modified ITT (MITT)].

Statistical analyses were performed using SAS software (version 8.2). Changes from baseline to week 24 on the ADAS-J cog were assessed by analysis of covariance (ANCOVA), with baseline values as covariates and treatment groups as factors. Point estimates and 95% confidence intervals (CIs) for the treatment mean differences between each of the patch doses versus placebo were reported.

Treatment comparisons on the CIBIC plus-J were performed using the Wilcoxon rank sum test. The proportional odds regression model was used to determine whether participants treated with rivastigmine were more likely to have a favorable response on week 24 scores of the CIBIC plus-J. Supportive analyses were conducted on the dichotomized CIBIC plus-J variable (with levels 'improvement' and 'no response') using Fisher's exact test. Analyses for ADAS-J cog and CIBIC plus-J were carried out for the ITT-LOCF population and repeated for the ITT-OC, PP and MITT populations to assess the sensitivity of the results. No interim analyses were performed for this study.

All analyses were pre-specified in the statistical analysis plan with the exception of the secondary efficacy evaluations of CIBIC plus-J subscales (DAD, BEHAVE-AD and MENFIS), which were post-hoc analyses.

Results

Participants

The first participant was screened in January 2007 and the last participant completed the study in March 2009. Of 859 participants who were randomized, 284 were allocated to the 5-cm^2 (9-mg loading dose; 4.6 mg/24 h delivery rate) rivastigmine patch group, 287 to the 10-cm^2 (18-mg loading dose; 9.5 mg/24 h delivery rate) rivastigmine patch group and 288 to the placebo group. Of the patients who were randomized, 856 (99.7%) received the study drug and 690 (80.3%) completed the study (fig. 1). The safety population comprised 855 patients and the ITT-LOCF population comprised 810 patients.

Demographics and background/disease characteristics are summarized in table 2. The mean (±SD) age of the safety population was 74.6 (±7.22) years and the majority of patients (68.3%) were female. The overall mean (±SD) body weight at baseline was 50.7 (±9.39; range 31.0–87.1) kg. The mean (±SD) MMSE total score at baseline for the overall study population was 16.6 (±2.96) points. The majority (68.7%) had a baseline MMSE total score >15. The baseline demographics and background/disease characteristics were similar across all treatment groups (table 2).

Dosing

In the 5-cm^2 (9-mg loading dose; 4.6 mg/24 h delivery rate) and 10-cm^2 (18-mg loading dose; 9.5 mg/24 h delivery rate) rivastigmine patch groups, 91.5 and 83.7% of participants, respectively, reached their target dose at the end of the maintenance period in week 24.

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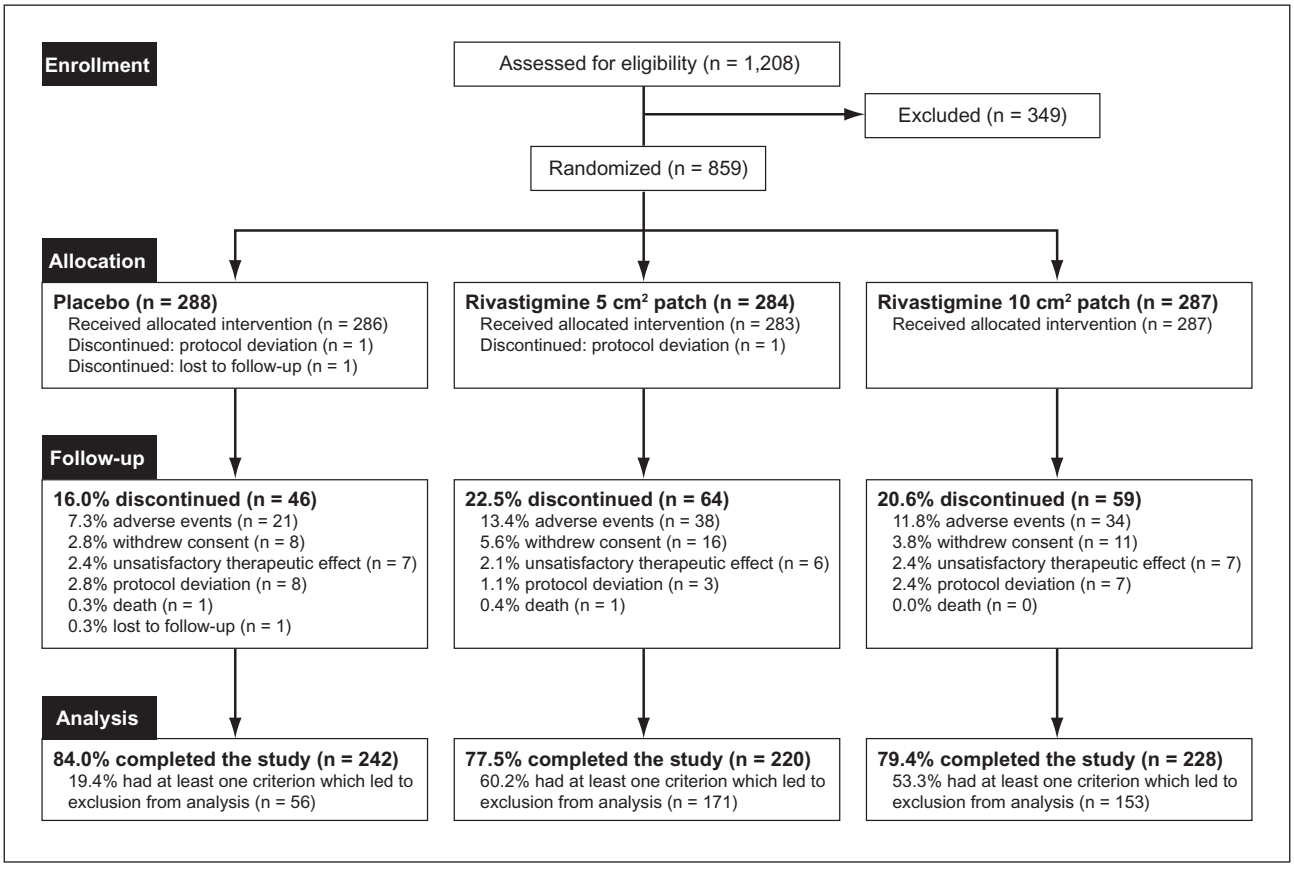

Fig. 1. Flow chart of the study design and patient participation.

Efficacy

Primary Efficacy Assessments

ADAS-J Cog. Participants receiving the rivastigmine patch showed less decline than those receiving placebo at week 24 on the ADAS-J cog (ITT-LOCF primary analysis population; fig. 2; table 3). Least-square (LS) means of the changes versus placebo were –0.8 points (95% CI, –1.7 to 0.0 points; p = 0.063) for the 5-cm^2 (9-mg loading dose; 4.6 mg/24 h delivery rate) rivastigmine patch and –1.2 points (95% CI, –2.1 to –0.4 points; p = 0.005) for the 10-cm^2 (18-mg loading dose; 9.5 mg/24 h delivery rate) rivastigmine patch. Results were similar with the supporting MITT, ITT-OC and PP populations (table 3). The significant delayed progression of worsening in week 24 ADAS-J cog scores with the 10-cm^2 rivastigmine patch remained when the ANCOVA model was adjusted for the dynamic allocation factors of body weight and MMSE (p = 0.004).

CIBIC Plus-J. Participants in the rivastigmine patch group tended to show less decline than those in the placebo group at week 24 on the CIBIC plus-J, although this did not reach statistical significance in the primary analysis ITT-LOCF population (table 4). Results were similar with the supporting MITT, ITT-OC and PP populations, though in the PP population the 10-cm^2 (18-mg loading dose; 9.5 mg/24 h delivery rate) rivastigmine patch group reached statistical significance versus the placebo group (p = 0.029; table 4). Proportional odds regression demonstrated that participants treated with rivastigmine were more likely to have a favorable response on week-24 scores of the CIBIC plus-J, with odds ratios (ORs) of

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Table 2. Baseline characteristics and demographics of the safety population

	Placebo	Rivastigmine patch		Total
		5 cm² (9-mg loading dose; 4.6 mg/24 h delivery rate)	10 cm² (18-mg loading dose; 9.5 mg/24 h delivery rate)	
	(n = 286)	(n = 282)	(n = 287)	(n = 855)
Mean age, years (± SD)	74.5 ± 7.4	74.3 ± 7.5	75.1 ± 6.9	74.6 ± 7.2
Female patients, %	68.2	68.8	67.9	68.3
Mean weight, kg (± SD)	50.7 ± 9.8	50.7 ± 9.0	50.7 ± 9.5	50.7 ± 9.4
Mean time since physician first diagnosed AD symptom, years (± SD)	1.7 ± 1.9	1.6 ± 1.7	1.7 ± 1.8	1.7 ± 1.8
Participants' living situation, %				
Living alone	1.7	1.4	2.1	1.8
Living with caregiver/other individual	96.5	94.7	95.8	95.7
Assisted living/group home	0.7	2.5	1.4	1.5
Nursing home/long-term institution	1.0	1.1	0.7	0.9
Other	0.0	0.4	0.0	0.1
Mean formal education, years (± SD)[a]	10.5 ± 2.8	10.7 ± 2.8	10.3 ± 2.7	10.5 ± 2.8
Mean baseline MMSE (± SD)	16.6 ± 2.9	16.8 ± 2.9	16.5 ± 3.1	16.6 ± 3.0
Mean baseline total ADAS-J cog (± SD)[b]	25.1 ± 9.7	25.7 ± 10.0	25.2 ± 10.0	25.3 ± 9.9

[a] Based on 285, 280, 285 and 850 patients in the placebo, 5- and 10-cm² patch and total groups.
[b] Based on 284, 280, 284 and 848 patients in the placebo, 5- and 10-cm² patch and total groups.

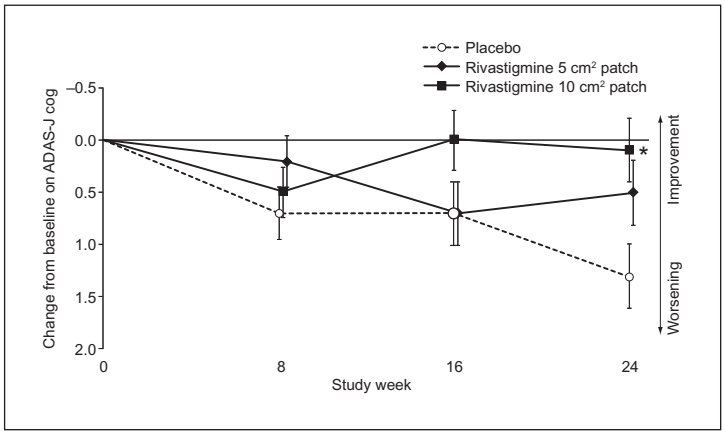

Fig. 2. LS mean (SEM) changes from baseline on the ADAS-J cog at 24 weeks (ITT-LOCF population). ANCOVA model, * p ≤ 0.01 vs. placebo.

1.34 (95% CI, 0.98–1.83) for the 5-cm² (9-mg loading dose; 4.6 mg/24 h delivery rate) rivastigmine patch and 1.33 (95% CI, 0.98–1.82) for the 10-cm² (18-mg loading dose; 9.5 mg/24 h delivery rate) patch in the ITT-LOCF population. Similar results were seen in the MITT, ITT-OC and PP populations (table 4). Following adjustment for body weight and MMSE, ORs were 1.36 (95% CI, 1.00–1.86; p = 0.050) for the 5-cm² rivastigmine patch and 1.38 (95% CI, 1.01–1.88; p = 0.042) for the 10-cm² rivastigmine patch (table 4). In categorical analyses, improvement in the CIBIC plus-J (markedly, moderately or minimally) at week 24 was more often observed in patients receiving the rivastigmine patch. In the ITT-LOCF population, 57/269 (21.2%) of participants receiving the 5-cm² rivastigmine patch and 59/270 (21.9%) of participants receiving the 10-cm² rivastigmine patch had improved CIBIC plus-J scores

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Table 3. Mean and LS mean ADAS J-cog scores at baseline and changes from baseline at week 24 in the ITT-LOCF, ITT-OC, MITT and PP populations

	Placebo	Rivastigmine 5 cm^2 (9-mg loading dose; 4.6 mg/24 h delivery rate)	Rivastigmine 10 cm^2 (18-mg loading dose; 9.5 mg/24 h delivery rate)
ITT-LOCF			
N	268	269	273
n	265	266	268
Baseline (±SD)	24.8±9.46	25.2±9.62	25.0±9.93
Change at week 24 (±SD)	1.3±5.07	0.5±4.96	0.1±5.04
LS mean vs. placebo (±SE)	–	−0.8±0.43	−1.2±0.43
95% CI	–	−1.7, 0.0	−2.1, −0.4
p value	–	0.063	0.005**
ITT-OC			
N	268	269	273
n	235	214	218
Baseline (±SD)	24.6±9.36	25.1±9.67	25.0±9.95
Change at week 24 (±SD)	1.2±5.01	0.6±5.11	0.1±5.15
LS mean vs. placebo (±SE)	–	−0.6 (0.48)	−1.1 (0.47)
95% CI	–	−1.5, 0.3	−2.1, −0.2
p value	–	0.204	0.016*
MITT			
N	275	274	279
n	271	271	275
Baseline (±SD)	24.9±9.58	25.4±9.77	25.0±9.87
Change at week 24 (±SD)	1.3±5.17	0.6±4.95	0.0±5.15
LS mean vs. placebo (±SE)	–	−0.8 (0.43)	−1.3 (0.43)
95% CI	–	−1.6, 0.1	−2.1, −0.4
p value	–	0.083	0.004**
PP			
N	206	169	169
n	200	163	162
Baseline (±SD)	24.4±9.27	25.2±9.87	25.2±10.41
Change at week 24 (±SD)	1.2±4.90	0.7±5.22	0.1±5.19
LS mean vs. placebo (±SE)	–	−0.6 (0.53)	−1.2 (0.53)
95% CI	–	−1.6, 0.4	−2.2, −0.1
p value	–	0.263	0.026*

* $p < 0.05$; ** $p < 0.01$. Negative change scores on the ADAS-J cog indicate improvement from baseline. N = Overall efficacy population; n = number of participants with an evaluation at week 24. For descriptive mean baseline scores and changes from baseline at week 24, only patients with a valid baseline and post-baseline score were included (n). For the ITT-LOCF and MITT populations, last observation was carried forward to week 24 if appropriate. p values are derived from ANCOVA using treatment as factor and baseline score as covariate. 95% CIs are calculated for the treatment difference between LS means.

(table 4). While this was not statistically significant for either patch size versus placebo (41/267 of participants; 15.4%) in the ITT-LOCF population, the 10-cm^2 rivastigmine patch did reach statistical significance versus placebo in the ITT-OC population ($p = 0.034$) and borderline significance in the MITT population ($p = 0.049$).

Secondary Efficacy Assessments

The three subscales of the CIBIC plus-J are DAD, BEHAVE-AD and MENFIS. Participants receiving either rivastigmine patch size demonstrated efficacy versus placebo in week-

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Table 4. Mean CIBIC plus-J scores at week 24 in the ITT-LOCF, ITT-OC, MITT and PP populations

	Placebo	Rivastigmine 5 cm^2 (9-mg loading dose; 4.6 mg/24 h delivery rate)	Rivastigmine 10 cm^2 (18-mg loading dose; 9.5 mg/24 h delivery rate)
ITT-LOCF			
N	268	269	273
n	267	269	270
Mean at week 24 (±SD)	4.4 ± 0.94	4.2 ± 0.96	4.2 ± 0.96
p value	–	0.063	0.067
OR (95% CI)	–	1.34 (0.98, 1.83)	1.33 (0.98, 1.82)
p value[a]	–	0.050	0.042*
OR (95% CI)[a]	–	1.36 (1.00, 1.86)	1.38 (1.01, 1.88)
Markedly improved, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Moderately improved, n (%)	5 (1.9)	12 (4.5)	6 (2.2)
Minimally improved, n (%)	36 (13.5)	45 (16.7)	53 (19.6)
Unchanged, n (%)	111 (41.6)	109 (40.5)	109 (40.4)
Minimally worse, n (%)	84 (31.5)	82 (30.5)	78 (28.9)
Moderately worse, n (%)	29 (10.9)	21 (7.8)	22 (8.1)
Markedly worse, n (%)	2 (0.7)	0 (0.0)	2 (0.7)
ITT-OC			
N	268	269	273
n	239	218	223
Mean at week 24 (±SD)	4.4 ± 0.95	4.2 ± 0.98	4.2 ± 0.99
p value	–	0.031*	0.054
OR (95% CI)	–	1.44 (1.03, 2.01)	1.39 (0.99, 1.94)
OR (95% CI)[a]	–	1.46 (1.04, 2.04)	1.48 (1.06, 2.08)
MITT			
N	275	274	279
n	273	274	276
Mean at week 24 (±SD)	4.4 ± 0.94	4.2 ± 0.98	4.2 ± 0.96
p value	–	0.151	0.087
OR (95% CI)	–	1.25 (0.92, 1.70)	1.30 (0.96, 1.77)
OR (95% CI)[a]	–	1.26 (0.93, 1.71)	1.33 (0.98, 1.81)
PP			
N	206	169	169
n	199	165	165
Mean at week 24 (±SD)	4.4 ± 0.92	4.2 ± 0.97	4.2 ± 1.00
p value	–	0.065	0.029*
OR (95% CI)	–	1.42 (0.98, 2.07)	1.53 (1.05, 2.23)
OR (95% CI)[a]	–	1.45 (1.00, 2.12)	1.62 (1.10, 2.37)

* $p < 0.05$. N = Overall efficacy population; n = number of participants with an evaluation at week 24. ORs are from week 24 scores for treatment vs. placebo based on a proportional odds regression model; a score >1 represents an outcome in favor of rivastigmine. There are no baseline scores for the CIBIC plus-J because this is scored as a judgment of change and at baseline there is no comparison on which to base a judgment. For the ITT-LOCF and MITT populations, last observation was carried forward to week 24 if appropriate. p values are derived from the Wilcoxon test and are based on pairwise comparisons of the rivastigmine and placebo treatment groups.

[a] Adjusted with allocation factors (weight and MMSE).

24 scores on DAD and less deterioration on MENFIS (table 5). Delayed progression of worsening was significant for the 10-cm^2 (18-mg loading dose; 9.5 mg/24 h delivery rate) rivastigmine patch on scores of MENFIS ($p = 0.016$) and DAD ($p = 0.024$; table 5), but significant efficacy was not demonstrated for BEHAVE-AD or MMSE scores.

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Table 5. Mean secondary efficacy scores at baseline and changes from baseline at week 24 (ITT-LOCF participants with valid baseline and post-baseline scores)

Efficacy variable	Baseline score (mean ± SD)	Changes at week 24 (mean ± SD)	24-week difference (p-value)
Secondary efficacy variables			
MMSE score			
Placebo (n = 251)	16.7 ± 2.87	−0.3 ± 2.82	–
Rivastigmine 5-cm^2 patch (n = 236)	16.9 ± 2.88	−0.3 ± 3.05	0.758
Rivastigmine 10-cm^2 patch (n = 246)	16.4 ± 3.09	0.0 ± 2.87	0.260
CIBIC plus-J DAD score			
Placebo (n = 267)	66.7 ± 19.90	−4.2 ± 12.44	–
Rivastigmine 5-cm^2 patch (n = 269)	64.2 ± 20.57	−3.0 ± 10.26	0.270
Rivastigmine 10-cm^2 patch (n = 269)	64.2 ± 21.92	−1.9 ± 10.66	0.024*
CIBIC plus-J BEHAVE-AD score			
Placebo (n = 267)	4.8 ± 4.50	−0.1 ± 3.76	–
Rivastigmine 5-cm^2 patch (n = 269)	4.7 ± 4.96	−0.1 ± 4.17	0.911
Rivastigmine 10-cm^2 patch (n = 270)	5.4 ± 5.15	−0.3 ± 4.70	0.795
CIBIC plus-J MENFIS score			
Placebo (n = 267)	23.2 ± 11.13	2.9 ± 6.18	–
Rivastigmine 5-cm^2 patch (n = 269)	24.3 ± 11.72	2.2 ± 5.86	0.192
Rivastigmine 10-cm^2 patch (n = 270)	24.6 ± 11.36	1.6 ± 5.82	0.016*
Exploratory efficacy variables			
Modified Crichton Scale score			
Placebo (n = 268)	17.3 ± 8.65	2.9 ± 7.40	–
Rivastigmine 5-cm^2 patch (n = 269)	17.3 ± 8.87	2.2 ± 7.44	0.256
Rivastigmine 10-cm^2 patch (n = 272)	18.2 ± 9.29	1.6 ± 7.43	0.040*

* $p < 0.05$. Negative change scores on BEHAVE-AD, MENFIS and the Modified Crichton Scale indicate improvement. Negative change scores on the MMSE and DAD indicate deterioration. For the CIBIC plus-J, descriptive mean scores and changes from baseline are shown but p values are derived from ANCOVA using treatment as factor and baseline score as covariate and are based on LS mean comparisons for each rivastigmine group [5-cm^2 patch (9-mg loading dose; 4.6 mg/24 h delivery rate) and 10-cm^2 rivastigmine patch (18-mg loading dose; 9.5 mg/24 h delivery rate)] vs. placebo. For the MMSE, p values are derived from the Wilcoxon test and are based on pairwise comparison of rivastigmine and placebo treatment groups.

Safety and Tolerability

The number and percentage of participants in each treatment group experiencing adverse events (AEs; at least 5% of participants, safety population) are summarized in table 6. The most common AEs were consistent with the known safety profile of the rivastigmine patch, i.e. application site reactions, nausea and vomiting. Other cholinergic effects occurred in <5% of patients in any study group, with the incidence of weight loss [placebo 1.4%; 5-cm^2 (9-mg loading dose; 4.6 mg/24 h delivery rate) rivastigmine patch 2.5%, and 10-cm^2 (18-mg loading dose; 9.5 mg/24 h delivery rate) rivastigmine patch 3.5%], diarrhea (2.4, 3.9 and 3.1%, respectively) and anorexia (0.7, 1.1 and 2.1%, respectively) slightly higher in rivastigmine treatment than placebo groups.

Serious AEs occurred in 5.0% of the 5-cm^2 rivastigmine patch group, 6.3% in the 10-cm^2 rivastigmine patch group and 7.0% in the placebo group. AEs led to early discontinuation in 13.8% of participants in the 5-cm^2 patch group, 11.8% in the 10-cm^2 patch group and 7.7%

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Table 6. Most frequently reported AEs regardless of the study drug relationship (occurring in ≥5% of patients in the safety population)

	Placebo	Rivastigmine patch	
	(n = 286)	5 cm^2 (9-mg loading dose; 4.6 mg/24 h delivery rate) (n = 282)	10 cm^2 (18-mg loading dose; 9.5 mg/24 h delivery rate) (n = 287)
Patients with an AE, n (%)	222 (77.6)	243 (86.2)	248 (86.4)
Application site erythema	55 (19.2)	106 (37.6)	113 (39.4)
Application site pruritis	61 (21.3)	92 (32.6)	100 (34.8)
Application site edema	7 (2.4)	35 (12.4)	31 (10.8)
Application site exfoliation	4 (1.4)	14 (5.0)	11 (3.8)
Dermatitis contact	40 (14.0)	69 (24.5)	68 (23.7)
Nasopharyngitis	32 (11.2)	22 (7.8)	33 (11.5)
Nausea	9 (3.1)	3 (1.1)	20 (7.0)
Vomiting	11 (3.8)	11 (3.9)	23 (8.0)

in the placebo group; among the most common were application site reactions and skin and subcutaneous tissue disorders.

There were 2 deaths during the study period. One participant in the 5-cm^2 rivastigmine patch group died of aspiration pneumonia and 1 participant in the placebo group died of subarachnoid hemorrhage. The deaths were not suspected to have a causal relationship with the study drug.

Patch Adhesion and Skin Irritability

When evaluating the total number of participants with an evaluation for each patch size, 491/522 (94.1%) of the 5-cm^2 (9-mg loading dose; 4.6 mg/24 h delivery rate) rivastigmine patches and 200/215 (93.0%) of the 10-cm^2 (18-mg loading dose; 9.5 mg/24 h delivery rate) rivastigmine patches remained completely or well attached.

Investigator rating of skin tolerability (most severe rating) based on patch size and treatment (safety population) is summarized in figure 3. When evaluating the total number of evaluations for each patch size, 444/522 (85.1%) of participants who received the 5-cm^2 rivastigmine patch and 178/214 (83.2%) of participants who received the 10-cm^2 rivastigmine patch had no, slight or mild skin irritation. In the 5-cm^2 rivastigmine patch group, the most common severe skin irritation was erythema (8/522 participants; 1.5%). In the 10-cm^2 rivastigmine patch group, the most common severe skin irritation was pruritus (6/214 of participants; 2.8%).

Exploratory Assessments

The Modified Crichton Scale deteriorated in all treatment groups from baseline to week 24. However, there was less deterioration in scores on the Modified Crichton Scale and a significant treatment difference versus placebo at week 24 in participants treated with the 10-cm^2 (18-mg loading dose; 9.5 mg/24 h delivery rate) rivastigmine patch ($p = 0.040$).

The results of a survey conducted to investigate the usefulness of patch formulation compared with the existing oral formulation demonstrated that 510/842 (61%) of Japanese caregivers thought that the patch was 'easy' or 'considerably easy' to use.

The mean (±SD) trough plasma concentration of rivastigmine at week 24 was determined to be 2.61 (±1.74) ng/ml in the 5-cm^2 (9-mg loading dose; 4.6 mg/24 h delivery rate) rivastigmine patch group and 8.10 (±7.16) ng/ml in the 10-cm^2 (18-mg loading dose;

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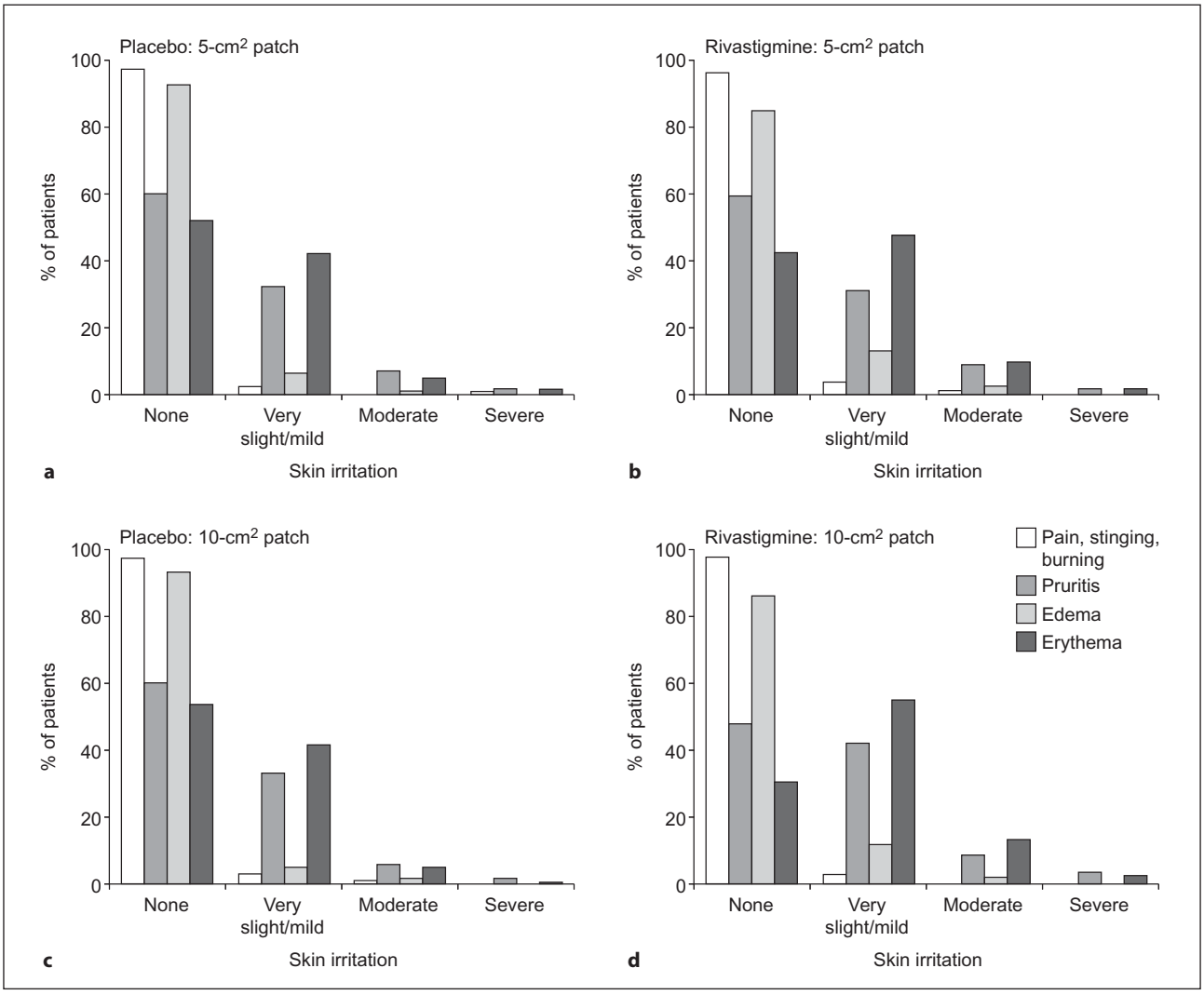

Fig. 3. Investigators' rating of skin tolerability (most severe rating) based on patch size and treatment (safety population). **a** Placebo: 5-cm^2 patch. **b** Rivastigmine: 5-cm^2 patch. **c** Placebo: 10-cm^2 patch. **d** Rivastigmine: 10-cm^2 patch.

9.5 mg/24 h delivery rate) rivastigmine patch group. The mean (±SD) plasma BuChE inhibition at week 24 was 21.2% (±30.1) in the 5-cm^2 rivastigmine patch group and 43.0% (±21.8) in the 10-cm^2 rivastigmine patch group.

Discussion

The results of this 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-finding study show that the rivastigmine transdermal patch may be effective at delaying symptomatic decline in Japanese patients with probable AD. Our findings support the clinical effectiveness, favorable tolerability and known safety profile of the rivastigmine patch for the treatment of patients with mild-to-moderately severe AD, and demonstrate its potential for the treatment of Japanese patients with probable AD.

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With respect to primary efficacy assessments, the 10-cm^2 (18-mg loading dose; 9.5 mg/24 h delivery rate) rivastigmine patch demonstrated significant benefit on the ADAS-J cog. The LS mean difference for the 10-cm^2 rivastigmine patch versus placebo was –1.2 points ($p = 0.005$), which was similar to that of the IDEAL study [–1.57; unpubl. data]. For the CIBIC plus-J, a trend for benefit with the 10-cm^2 rivastigmine patch just missed formal statistical significance in the ITT-LOCF population ($p = 0.067$). Even though the evaluated number of participants was decreased, statistical significance was reached in the PP population ($p = 0.029$). In addition, efficacy of the 10-cm^2 rivastigmine patch versus placebo at week 24 was more evident in the ITT-OC population ($p = 0.054$) than the ITT-LOCF population.

The sensitivity of analyses may be improved by adjusting with MMSE at baseline, which is considered to be a factor for CIBIC plus-J evaluation. Indeed, the MMSE score at baseline may be inversely proportional to cognitive decline in clinical trials [17, 18]. Following adjustment for dynamic allocation factors (particularly baseline MMSE score), a statistically significant difference was observed in scores on the CIBIC plus-J versus placebo for the 10-cm^2 rivastigmine patch ($p = 0.042$, proportional odds model). The dynamic randomization was performed successfully and all treatment groups were generally comparable. It is not fully understood why statistical significance in scores on the CIBIC plus-J, one of the primary endpoints, was not fully met without adjustment.

With respect to the secondary efficacy assessments, the 10-cm^2 rivastigmine patch led to a significant delay in deterioration or improvement in scores on 2 of 3 CIBIC plus-J subscales (DAD and MENFIS), which could translate into improvements in functioning and cognition. No significant difference between rivastigmine and placebo was observed on the BEHAVE-AD. The overall global impression is judged based on changes in these 3 subscales. Hence, the inclusion of participants with mild-to-moderate AD that did not display measurable psychiatric symptoms would have impacted the performance of the BEHAVE-AD subscale and may have also influenced the overall sensitivity of the CIBIC plus-J evaluation.

Aside from body weight, the baseline patient characteristics of this study were comparable to IDEAL (mean age: 74.6 vs. 73.6 years; female gender: 68.3 vs. 66.5%; mean weight: 50.7 vs. 66.6 kg; formal education: 10.5 vs. 9.9 years; mean MMSE score: 16.6 vs. 16.5). Therefore, it was surprising that unlike IDEAL a statistically significant improvement was not seen in terms of change in MMSE score versus placebo at week 24. However, the MMSE is primarily used as a scale to stage AD and is not particularly sensitive for detecting treatment effects or tracking natural progression of the disease over a short period of time.

With respect to safety and tolerability, the 19.7% dropout rate may limit interpretation of the results, although this rate is consistent with other clinical trials using the rivastigmine patch (e.g. 20.5–21.8%) [8] and lower than clinical trials with high-dose oral rivastigmine (e.g. 22–35%) [8, 19–21]. The most common AEs were application site reactions (i.e. erythema and pruritus) and contact dermatitis. Other than skin reactions, nausea (7.0%) and vomiting (8.0%) were reported in the 10-cm^2 rivastigmine patch group. However, nausea and vomiting each lead to discontinuation in only 0.7% of those receiving the 10-cm^2 rivastigmine patch. Similarly, the IDEAL study demonstrated the most frequently reported AEs to be nausea and vomiting, and most AEs were mild or moderate [8]. Serious AEs were rare and correlated with the known safety profile of the rivastigmine patch [8].

A post-hoc analysis of the IDEAL trial has shown that the rivastigmine patch is generally well tolerated, regardless of patient body weight [22]. Among patients who received the rivastigmine patch, lower body weight, as stratified, was not associated with a higher AE rate. In contrast, there was an association between a higher AE rate and low body weight among patients receiving rivastigmine capsules. Therefore, transdermal delivery of rivastigmine

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may permit low-weight patients, such as Japanese, easier access to target doses than oral administration.

The current study found the rivastigmine patch to demonstrate good skin tolerability and adhesion. The proportion of participants who experienced no, slight or mild skin irritation with the rivastigmine patch ranged from 90.3 (10-cm^2 patch) to 91.6% (5-cm^2 patch). Patches were only alternated from the right to the left side of the upper back, and, at some dose levels, 2 patches of different size were administered at the same time. Consequently, skin irritation may have been lessened by greater rotation of the patch application site. In the IDEAL study, the proportion of participants who experienced no, slight or mild skin irritation with the rivastigmine patch ranged from 90 to 98% [8]. The results of our study are therefore consistent with earlier studies [8]. These results indicate the rivastigmine patch to show efficacy and to be well tolerated in Japanese patients with AD.

Rivastigmine is a dual inhibitor of acetylcholinesterase (AChE) and BuChE. Both AChE and BuChE can regulate the activity of acetylcholine in the human brain [23, 24]; BuChE may become more important as AD progresses [25–28], and BuChE is capable of compensating for AChE function when AChE is deficient [29]. There is a growing consensus among many experts that BuChE, as well as AChE, is a clinically relevant treatment target in AD [30–37]. A well-correlated inhibition of BuChE activity in plasma and in cerebrospinal fluid has been demonstrated in AD patients treated with rivastigmine, suggesting relevance of measuring plasma BuChE activity [35]. Our exploratory analyses have demonstrated that the degree of BuChE inhibition in plasma increases with rivastigmine dose.

Rivastigmine is the first and only approved transdermal patch for AD. In addition to a better tolerability profile when compared to oral rivastigmine (discussed above), transdermal delivery may allow better access to optimal therapeutic doses of cholinesterase inhibitors, encourage treatment compliance and offer convenience and emotional advantages to the patient and caregiver [38–40]. The rivastigmine patch provides visual reassurance that the medication is being taken and empowers the caregiver in the administration of treatment. Indeed, a substudy of the IDEAL trial previously showed that 72% of caregivers preferred patches to capsules for drug delivery, based on ease of use and ease following the schedule [40]. In this study, we found that 61% of Japanese caregivers thought the patch was 'easy' or 'considerably easy' to use compared with existing oral medications.

As with any clinical trial, there are some limitations relating to the extrapolation of results from our study to the general AD population. In particular, a main focus of this study is also a limitation in that our study was limited to patients with AD from Japan. Nevertheless, the results of our study suggest that the rivastigmine transdermal patch has a favorable efficacy and tolerability profile in Japanese patients with probable AD. Coupled with the potential practical and emotional benefits associated with transdermal administration of cholinesterase inhibitors, the rivastigmine patch may be considered a viable therapeutic option for the first-line treatment of patients with AD in Japan.

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Disclosure Statement

Yu Nakamura, Yukimichi Imai, Masahiro Shigeta and Akira Homma have no conflicts of interest to declare. Ana Graf, Toru Shirahase and Hyosung Kim are full-time employees of Novartis. Akifumi Fujii and Joji Mori are employees of ONO Pharmaceutical Co. Ltd.

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