# Supplementary materials

## Supplementary Methods

### Efficacy assessments

Mini-Mental State Examination (MMSE) was assessed during the screening visit (2–4 weeks before starting rivastigmine), baseline (day 1), and at weeks 8 and 24 (or discontinuation). MMSE comprises two parts, to assess language and performance. The highest possible score is 30, and lower scores indicate more severe impairment [1].

Japanese Clinical Global Impression of Change (J-CGIC) was assessed at Weeks 4, 8, 16 and 24 (or discontinuation). The J-CGIC is a 7-grade scale used by the investigator to judge the severity and change of the patient’s disease [2], where 1 = markedly improved, 2 = improved, 3 = slightly improved, 4 = no change, 5 = slightly aggravated, 6 = aggravated, and 7 = markedly aggravated.

Neuropsychiatric Inventory-10 (NPI-10) was assessed as baseline (Day 1), Week 8, and Week 24 (or discontinuation. NPI-10 is a tool used to assess behaviors of patients with dementia across 10 domains [3]: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, and aberrant motor behavior. The scale includes frequency and severity ratings for each domain, with a composite domain score (calculated as frequency × severity) and an overall composite score (sum of all 10 domains). Higher scores indicate more severe impairment.

Quality of life was assessed using the 13-item QOL-Alzheimer’s disease questionnaire on baseline (day 1) and Week 24 (or discontinuation). The questionnaire covers multiple aspects of QOL, including health status, mood, functional capacity, personal relationships and leisure, financial situation, and life as a whole [4]. Each item is scored on a 4-point Likert scale, ranging from 1 = poor to 4 = excellent. An overall score is also calculated, which ranges from 13 to 52.

The modified Crichton scale was used to assess the caregiver’s impression on baseline (day 1), and Weeks 4, 8, 16 and 24 (or discontinuation). The scale evaluates 7 items (orientation, conversation, cooperation with family and caregiver, restlessness, dressing and clothes, job and social activities/roles, and leisure activities), using an 8-point Likert scale for each item [5]. The total score ranges from 0 to 56, where higher scores indicate more severe impairment.

Efficacy assessments at discontinuation were not mandatory if the patient discontinued due to an adverse event (AE).

### Safety assessments

Safety was assessed in terms of AEs and serious AEs throughout the study. Laboratory evaluations were assessed at the screening visit and at Week 24 (or discontinuation), and at any time during the study as deemed necessary. Vital signs were assessed at each visit.

### Compliance

Compliance was assessed by the investigator who checked the number of patches left over at each visit, and was classified as poor (<25%), average (25%–50%), good (50%–75%) or very good (75%–100%).

### Usability assessment

Caregivers completed a usability questionnaire at Week 24 (or discontinuation) to examine their perceptions of the usability of rivastigmine transdermal patch relative to the prior oral therapy. The caregiver were offered 6 possible responses: Very easy to use, Easy to use, No change, Not easy to use, Not easy to use at all, or Unknown. The caregiver was then asked to explain the reason for their answer to this question.

### Statistical analyses

The sample size was calculated based on the change in MMSE score from baseline to Week 24. Briefly, 97 patients would ensure that the half-width of the 95% CI for the change from baseline in MMSE score would be 0.6, assuming a standard deviation of 3.0, which was estimated from studies 1301, 1303 and 1403 [6-8]. Assuming dropouts, a total of 120 patients were planned to be enrolled to achieve at least 97 evaluable patients.

Efficacy data were analyzed using the full analysis set (FAS), defined as all patients who received at least one dose of study treatment and had at least a baseline and any post-baseline assessment on treatment. The per-protocol set was defined as all patients in the FAS who had only 1 step titration without any major deviations from the protocol procedures. The Safety set included all patients who received at least one dose of drug and had at least one post-baseline safety assessment.

The change in MMSE from baseline to Week 24 (i.e. primary endpoint) was evaluated using a mixed-effects model with repeated measures (MMRM) with visit as a fixed effect, baseline MMSE score as a covariate and patient as a random effect. The unstructured covariance matrix was used for the modeling of within-patient errors. The Least Squares estimate of mean change at Week 24 was shown with two-sided 95% CIs and p-value. The p-value was descriptively used.

For the analysis of MMSE total score at Week 8 (i.e. secondary endpoint), we used the same MMRM model as that used in the primary analysis and showed estimated mean changes and two-sided 95% CIs.

NPI-10, QOL-AD, and modified Crichton scale were summarized descriptively, along with 95% CIs for the changes in scores from baseline to the indicated time-points. For J-CGIC, the number and proportion (with 95% CIs) were reported for each grade, and for the proportion of patients with an improvement (marked, moderate, or mild improvement) or no worsening (marked, moderate, or mild improvement or no change) in symptoms.

Usability was assessed in terms of the number (percent) of caregivers, with two-sided 95% CI.

As an exploratory analysis, changes in the MMSE total score were compared between before and after the switching of treatment from oral ChEIs to rivastigmine patch. In this analysis, the slope of the line that shows the time course of changes in the MMSE total score was estimated using mixed-effect models by setting durations before and after switching as different fixed effects and including random sections for each patient.

The MMRM model of subgroup analysis contained visit, subgroup (categories) and visit\*subgroup as fixed effects, baseline MMSE score as a covariate and subject as a random effect. An unstructured covariance matrix was used. The estimated mean change at Week 24 along with a two-sided 95% confidence interval and p-values are presented. P-values are used in descriptive manner.

Safety data were assessed descriptively in terms of the number (percent) of patients with each AE/SAE for the titration and maintenance periods separately and for the overall study period. AEs of special interest (skin-related and GI-related events) were also summarized separately.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

### References

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## Supplementary Tables

**Table S1.** Key eligibility criteria

|  |
| --- |
| **Main inclusion criteria** |
| Age 50–85 years |
| Outpatient status |
| Diagnosis of dementia of the Alzheimer’s type according to the DSM-IV criteria |
| Clinical diagnosis of probable AD according to NINCDS-ADRDA criteria |
| MMSE total score of 10–23 |
| Patients on donepezil or galantamine who are experiencing a lack or loss of efficacy (A) due to: |
| * ≥2-point decline of MMSE total score within the first 3 months with the previous medication (A-1)
 |
| * ≥2-point decline of MMSE total score within 6 months with the previous medication (A-2)
 |
| * Marked aggravation of ADL/BPSD during the first 3 months or the last 6 months with the previous medication (A-3)
 |
| Patients experiencing difficulty on donepezil or galantamine (B) due to: |
| * Poor compliance with the previous medication (B-1)
 |
| * Previous medication cannot be given adequately due to non-GI AEs (B-2)
 |
| * Difficulty with swallowing (B-3)

Patients residing with someone in the community throughout the study or, if living alone, were in contact with the primary caregiver every day |
| **Main exclusion criteria** |
| Patients with systemic or neurological disease, other than AD, that can explain the dementia symptoms |
| Patients with other neurodegenerative disorder, schizophrenia, bipolar disorder, etc. included in the first axis of the DSM-IV |
| Patients with a severe, active, progressive disease or a disease with unstable symptoms |
| Patients with an active skin lesion or a skin disorder  |

AD, Alzheimer’s disease; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association; MMSE, Mini-Mental State Examination; ADL, activities of daily living; BPSD, behavioral and psychological symptoms of dementia

**Table S2.** Results of the secondary efficacy endpoints (Neuropsychiatric Inventory 10, Quality of Life–Alzheimer’s disease, and modified Crichton scale) at baseline and change from baseline to the indicated visit

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Endpoint** | **Visit** | **N** | **Baseline score** | **Post baseline score** | **Change from baseline** |
| **NPI-10** | Baseline | 118 | 11.43 (11.15)  | – | – |
| Week 8 | 116 | 11.51 (11.19) | 9.70 (11.42) | −1.81 (8.81) [−3.43 to −0.19] |
| Week 24 | 102 | 10.97 (11.16) | 10.08 (12.38) | −0.89 (11.10) [−3.07 to 1.29] |
| **QOL-AD Patient assessment** | Baseline | 118 | 34.37 (5.78) | – | – |
| Week 24 | 102 | 34.43 (5.92) | 34.09 (6.71) | −0.34 (5.32) [−1.39 to 0.70] |
| **QOL-AD Caregiver assessment** | Baseline | 118 | 28.75 (5.74) | – | – |
| Week 24 | 103 | 28.79 (5.59) | 28.63 (6.52) | −0.16 (5.42) [−1.21 to 0.90] |
| **Modified Crichton scale** | Baseline | 118 | 18.38 (9.41)  | – | – |
| Week 4 | 117 | 18.39 (9.45) | 17.98 (9.41) | −0.41 (5.44) [−1.41 to 0.59] |
| Week 8 | 116 | 18.43 (9.48) | 17.88 (9.89) | −0.55 (6.58) [−1.76 to 0.66] |
| Week 16 | 108 | 18.29 (9.39) | 19.32 (10.65) | 1.04 (6.94) [−0.29 to 2.36] |
| Week 24 | 103 | 18.00 (9.14) | 20.23 (10.51) | 2.23 (6.69) [0.93 to 3.54] |

Values are expressed as the mean (standard deviation) or mean (standard deviation) [95% confidence interval]

SD, standard deviation; NPI-10, Neuropsychiatric Inventory 10, QOL-AD, Quality of Life–Alzheimer’s disease

**Table S3.** Changes in Neuropsychiatric Inventory 10 subdomains from baseline to Week 24
(N = 102)

|  |  |  |  |
| --- | --- | --- | --- |
| **Subdomain** | **Baseline** | **Week 24** | **Change from baseline** |
| Delusions | 0.69 (1.53) | 0.94 (2.23) | 0.25 (1.71) [−0.08 to 0.59] |
| Hallucinations | 0.15 (0.78) | 0.36 (1.38) | 0.22 (1.24) [−0.03 to 0.46] |
| Agitation/aggression | 1.18 (2.07) | 1.12 (2.39) | −0.06 (2.00) [−0.45 to 0.33] |
| Depression/dysphoria | 0.78 (2.00) | 0.77 (1.94) | −0.01 (2.08) [−0.42 to 0.40] |
| Anxiety | 1.40 (2.68) | 1.09 (2.42) | −0.31 (2.51) [−0.81 to 0.18] |
| Elation/euphoria | 0.10 (0.71) | 0.07 (0.60) | −0.03 (0.94) [−0.21 to 0.15] |
| Apathy/indifference | 3.29 (3.49) | 2.72 (3.31) | −0.58 (3.32) [−1.23 to 0.07] |
| Disinhibition | 0.33 (0.90) | 0.34 (1.15) | 0.01 (1.38) [−0.26 to 0.28] |
| Irritability/lability | 1.18 (2.31) | 1.00 (2.37) | −0.18 (2.81) [−0.73 to 0.38] |
| Aberrant motor behavior | 1.87 (3.68) | 1.67 (3.55) | −0.21 (3.89) [−0.97 to 0.56] |

Values are expressed as the mean (standard deviation) or mean (standard deviation) [95% confidence interval]

**Table S4.** Japanese Clinical Global Impression of Change

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Change** | **Week 4** **(N = 117)** | **Week 8** **(N = 116)** | **Week 16** **(N = 106)** | **Week 24** **(N = 103)** |
| Markedly improved | 1 (0.9) | 2 (1.7) | 2 (1.9) | 3 (2.9) |
| Improved | 8 (6.8) | 8 (6.9) | 7 (6.6) | 6 (5.8) |
| Slightly improved | 34 (29.1) | 40 (34.5) | 33 (31.1) | 39 (37.9) |
| No change | 69 (59.0) | 59 (50.9) | 52 (49.1) | 43 (41.7) |
| Slightly aggravated | 5 (4.3) | 7 (6.0) | 10 (9.4) | 11 (10.7) |
| Aggravated | 0 (0.0) | 0 (0.0) | 1 (0.9) | 1 (1.0) |
| Markedly aggravated | 0 (0.0) | 0 (0.0) | 1 (0.9) | 0 (0.0) |

Values are expressed as the number (%) of patients

**Table S5.** AEs leading to dose reduction

|  |  |
| --- | --- |
| **AE (by preferred term)** | **Study period (N = 118)** |
| Patients with AEs requiring dose reduction | 12 (10.2) |
|  Application site erythema  | 2 (1.7) |
|  Application site pruritus  | 2 (1.7) |
|  Application site rash  | 1 (0.8) |
|  Pneumonia  | 1 (0.8) |
|  Heat illness | 1 (0.8) |
|  Asterixis | 1 (0.8) |
|  Agitation | 1 (0.8) |
|  Irritability  | 1 (0.8) |
|  Dermatitis contact | 1 (0.8) |
|  Drug eruption  | 1 (0.8) |
|  Erythema | 1 (0.8) |
|  Rash | 1 (0.8) |
|  Rash generalized  | 1 (0.8) |

Values are expressed as number (%) of patients

AE, adverse event; SAE, serious adverse event

**Table S6.** Application site skin-related or GI-related AEs in patients divided into body weight bands (<40 vs ≥40 kg and <50 vs ≥50 kg)

|  |  |
| --- | --- |
| **AE (by preferred term)** | **Body weight bands** |
| **<40 kg****N = 13** | **≥40 kg****N = 105** | **<50 kg** **N = 43** | **≥50 kg****N = 75** |
| Application site skin reactions and irritations | 2 (15.4) | 34 (32.4) | 15 (34.9) | 21 (28.0) |
|  Dermatitis contact | 1 (7.7) | 17 (16.2) | 9 (20.9) | 9 (12.0) |
|  Application site pruritus | 0 | 10 (9.5) | 2 (4.7)  | 8 (10.7) |
|  Application site erythema | 1 (7.7) | 8 (7.6) | 3 (7.0) | 6 (8.0) |
|  Application site rash | 1 (7.7) | 2 (1.9) | 2 (4.7) | 1 (1.3) |
|  Dermatitis allergic | 0 | 2 (1.9)  | 0 | 2 (2.7) |
|  Application site dermatitis | 0 | 1 (1.0) | 1 (2.3) | 0 |
|  Application site eczema | 0 | 1 (1.0) | 0 | 1 (1.3) |
| GI symptoms | 2 (15.4) | 7 (6.7) | 7 (16.3) | 2 (2.7) |
|  Nausea | 1 (7.7) | 4 (3.8) | 3 (7.0) | 2 (2.7) |
|  Diarrhea | 1 (7.7) | 3 (2.9) | 3 (7.0) | 1 (1.3) |
|  Vomiting | 1 (7.7) | 2 (1.9) | 3 (7.0) | 0 |

Values are expressed as the number (%) of patients

GI, gastrointestinal

## Supplementary Figures

**Figure S1.** Study design

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**Screening period:** 2–4 weeks (Week −4 [Day −28] to Week −2 [Day −14 to Day −1])

Oral cholinesterase inhibitor (ChEI; donepezil or galantamine) was continued during screening period until the night before starting rivastigmine transdermal patch. Day −1: oral ChEI discontinued. Day 1: start of rivastigmine transdermal patch treatment at starting dose of 9 mg/day.

**Titration period:** 8 weeks (Week 1 [Day 1] to Week 8 [Day 56])

After 4 weeks of treatment, the rivastigmine transdermal patch was increased to the maintenance dose of 18 mg/day. In patients with tolerability issues, the investigator or subinvestigator could temporarily interrupt the study treatment or reduce the dose. Investigators were permitted to switch to a three-step titration method in order to achieve the 18 mg/day dose or to explore the maximum tolerable dose in individual patients.

**Maintenance period:** 16 weeks (Week 9 [Day 57] to Week 24 [Day 168])

Treatment with rivastigmine transdermal patch was continued at 18 mg/day (or at the maximum tolerable dose) to evaluate the safety and efficacy according to the study protocol. In patients who did not achieved the 18 mg/day dose in the titration period, the investigators could attempt to increase the dose to 18 mg/day if tolerability was acceptable. If the dose of 18 mg/day was not tolerable, the patient could continue the study at the maximum tolerable dose.

AD, Alzheimer’s disease; AE, adverse event; ChEI, cholinesterase inhibitor; J-CGIC, Japanese Clinical Global Impression of Change; MMSE, Mini-Mental State Examination; NPI-10, Neuropsychiatric Inventory 10; QOL-AD, Quality of Life–Alzheimer’s Disease questionnaire

**Figure S2.** Changes in MMSE total scores from baseline (Week 0) to Weeks 8 and 24 in subgroups of patients. (A) By eligibility criteria (A only vs B only). (B) By age (≤60 vs >60 years old). (C) By use of skin moisturizer at baseline (yes vs no). (D) By compliance (<75% vs 75-100%). For all analyses, the mixed-effects model with repeated measures was used. Least-squared means of the changes are shown along with the 95% two-sided confidence interval. MMSE, Mini-Mental State Examination.

